124° CONGRESSO NAZIONALE SIMI

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VOLUME COMUNICAZIONI ORALI E POSTER

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COMUNICAZIONI ORALI

1. CLINICAL FEATURES AND TREATMENT-RELATED OUTCOMES OF IGG4-RELATED DISEASE FROM A LARGE EUROPEAN STUDY COHORT

Lanzillotta M.[1], Overbeek KA.[2], Poulsen J.[3], Holmquist O.[4], Macinga P.[5], Lohr M.[6], Della Torre E.[1]
[1]San Raffaele Scientific Institute, Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS San Raffaele Scientific Institute, Milan, Italy, Milan, Italy; [2]Erasmus MC University Medical Center, Department of Gastroenterology & Hepatology, Erasmus MC University Medical Center, Department of Gastroenterology & Hepatology, Rotterdam, Netherlands; [3]Centre for Pancreatic Diseases, Department of Gastroenterology & Hepatology, Aalborg University Hospital, Aalborg, Denmark, ; [4]Akershus University Hospital, Loerenskog, Norway, Department of Digestive Surgery, , Loernskog, Norway,; [5]nstitute for Clinical and Experimental Medicine, Prague, Czech Republic, Department of Gastroenterology and Hepatology,, Prague; [6]Karolinska University Hospital, Stockholm, Sweden, Department of Upper Abdominal Diseases, Stockholm, Sweden

Background: IgG4-related disease is an increasingly recognized systemic fibro-inflammatory disorder involving almost any organ system. Most available data on treatment strategies and natural history of IgG4-RD are currently derived from large cohorts from the United States and Asian Countries. Real-life studies addressing the epidemiology, clinical manifestations, and treatment strategies of IgG4-RD in Europe are limited to smaller cohorts from single center experiences.
Objectives: To characterize the epidemiology, clinical manifestations, and response to treatment of IgG4-RD patients in Europe.
Methods: A pan-European registry (PrescrAIP) was set in place to retrospectively analyse adults diagnosed with IgG4-RD from 2005 and 2020 in 42 European university hospitals. Comprehensive diagnostic criteria and organ-specific criteria were used to diagnose IgG4-RD and central validation was applied. Data on disease epidemiology, clinical characteristics, treatment, and outcomes were retrospectively collected from the hospitals' medical records using a REDCap-based electronic case record form. The IgG4-RD responder index was used to assess response to therapy. Predictors of relapse were identified using multivariable logistic regression analysis after correcting for confounders.
Results: 1079 individuals with suspected IgG4-RD were screened but only 735 were diagnosed with IgG4-RD and considered for analysis (69% male; median age 57years; 85% Caucasian). 45% of patients had multiorgan (>=2) involvement (Table 1). Pancreas, salivary glands, and biliary tree were the most frequently involved organs. Steroid-treatment was started in 634 patients; 9 (1%) were lost to followup; 79% (496/625) had a complete response, 18% (111/625) had a partial response, and 3% (18/625) did not respond. 95 patients were not treated; 61% (58/95) had spontaneous complete response, 19% (18/95) had partial response, and 10% (9/95) did not respond. Higher daily steroid dose (>0.4mg/kg prednisone equivalent) was as effective as lower dose (<0.4mg/kg) (OR 0.428; 95%CI 0.054-3.387) for inducing disease response. Similarly, longer induction of remission treatment (> 2 weeks) was as effective as shorter therapy (<2 weeks) (OR 0.908; 95%CI 0.818-1.009). Elevated IgG4 levels were independently associated with a decreased chance of complete response (OR 0.639; 95%CI 0.427-0.955). Relapse occurred in 30% of patients. Relapse within 6 months of remission induction were independent of the steroid tapering duration, induction treatment duration, and total cumulative dose. Parenchymal enlargement (OR 0.390, 95%CI 0.167-0.910) and addition of maintenance therapy with immunosuppressive agents were independently associated with fewer relapses at 6 months (OR 0.299, 95%CI 0.120-0.740). No difference between maintenance therapy with glucocorticoids and rituximab was observed in maintaining disease response.
Conclusion: This is the first pan-European study addressing the epidemiological and clinical features of IgG4-RD in Europe. Our study indicates that patients with elevated IgG4 level may need closer monitoring during remission induction and that 0.4mg/kg/day of prednisone equivalent for at least 2 weeks represents the most effective strategy to induce IgG4-RD remission.

2. A RARE CASE OF MYOCARDIAL INFARCTION: WHEN MECHANICAL CAUSE MEETS CLINICAL CAUSE

Bagnato C.[1], Filoni D.[1], Urso F.A.[2], Galardo G.[2], Loffredo L.[1], Ettorre E.[1]
[1]Department of Clinical, Internal Medicine, Anesthesiology and Cardiovascular Sciences, Sapienza University of Rome, Italy. ; [2]Department of Emergency Urgency and Acceptance at the Policlinic Umberto 1 in Rome

Purpose of the work: The purpose of this work is to describe a rare clinical case of myocardial infarction. The aetiology of any acute cardiovascular event should always be carefully and rapidly investigated, as there may be unexpected differential diagnoses around the corner.
Materials and Methods: We describe the story of a 67-year-old man who entered to the emergency department with a code red for fainting, general weakness and widespread chest pain. A wake-up call was that his blood pressure was not measurable. History reported atrial fibrillation, hypertension and dyslipidaemia. An electrocardiogram was immediately performed, which showed STEMI with ST-segment elevation from V2 to V6. Urgent enzyme testing for myocardial necrosis was performed and showed: myoglobin of 5733 ng/mL, troponin t hs of 1.05 microg/L and CK-MB mass of 78.9 ng/mL. The patient's clinical status got worse and he was monitored in the emergency room and supported with oxygen therapy in consultation with anaesthesiologist and cardiologist. It was posed as a differential diagnosis between ACS-STEMI, aortic dissection and cardiac tamponade in the light of blood chemistry tests, highly unstable vital parameters and electrocardiographic tracing. To investigate the patient's clinical condition, an echocardiogram was performed showing an hypertrophic left ventricle with moderately depressed global systolic function (FE=35%) with akinesia of the medio-basal sectors of the anterior wall and SIV, a hypokinetic right ventricle and bi-atrial dilatation. Surprisingly, the exam showed an apparent left sinus Valsalva aneurysm of the tricuspid aortic valve. Considering this, the suspicion of a compression/occlusion of the coronary arteries provoked by the aneurysm of the sinus of Valsalva, capable of causing secondary cardiac ischemia, has been raised. An emergency chest-abdominal contrast-enhanced CT scan was performed which confirmed the presence of a giant aneurysm of the sinus of Valsalva measuring 6.6 x 5.8 cm, located below the ipsilateral coronary branch. The left coronary artery was in fact compressed in its course between the aneurysm itself and the main pulmonary trunk **(Figure 1).** Once the diagnosis was known, an indication for emergency cardiac surgery was made and the patient was immediately taken to the operating room. The timely diagnosis of aneurysm of the sinus of Valsalva has guaranteed a correct treatment, protecting the patient from the possible initiation of therapies with a dangerous outcome, such as antiplatelet drugs, anticoagulants and reperfusion therapy indicated in the first clinical suspicion of ACS-STEMI.In fact, thanks to the execution of this echocardiographic examination, it was possible to visualize the giant aneurysm of the sinus of Valsalva in a very short time. Treatment of Valsalva's aneurysm requires emergency cardiac surgery. Any reperfusion therapy would have irreparably precipitated the patient's clinical instability if it had been erroneously started before the echocardiogram was performed.
Results: The sinus of Valsalva aneurysm (SVA) is a rare cardiac abnormality that can be congenital or acquired through infection, trauma or degenerative disease (1). The treatment of this pathology is surgically challenging as it can spontaneously rupture into other cardiac chambers or into the pericardial space depending on its location (2). In the clinical case described the aneurysm of the sinus of Valsalva was about 6 cm long and the left coronary artery was compressed between the common trunk and the aneurysm itself, causing secondary cardiac ischemia and reduction of cardiac output with severe hypovolemia and hypotension. Patients with this disorder may be asymptomatic or have atypical cardiac symptoms or recurrent syncope; however, only a few cases are described in the literature, thus it is important to place this pathology in the differential diagnosis when faced with a clinic comparable to the one described. Missed or delayed diagnosis of sinus aneurysm of Valsalva can retard the initiation of therapy and further increase the mortality of a disease already at high risk of death.
Conclusion: This clinical case underlines the importance of performing an emergency echocardiogram in the face of a suspicious clinical picture to define the cardiovascular or mechanical cause that may have provoked it. Furthermore, the insidious and dangerous compression of the coronary arteries caused mechanically by a large aneurysm of the sinus of Valsalva should be counted among the possible causes of ACS-STEMI. Additionally, sinus of Valsalva aneurysm often coexists with ventricular septal defects, aortic valve dysfunction or other cardiac abnormalities and ASV rupture causes symptoms like those of acute myocardial infarction (3). In conclusion, the clinical status and the mechanical cause can coexist and must be investigated together to treat patients promptly and correctly.

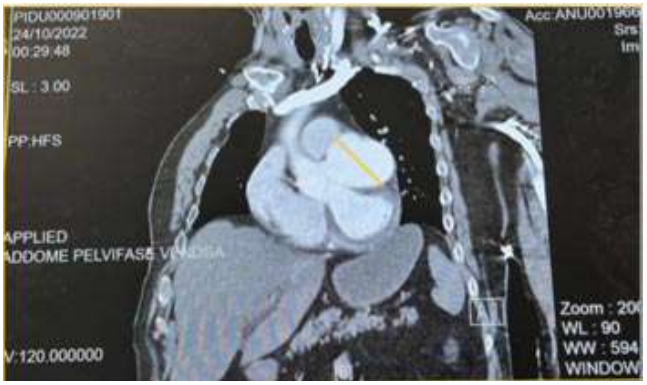


Figure 1.
Contrast-enhanced chest-abdomen CT image of the giant sinus of Valsalva aneurysm compressing the left coronary artery, highlighted with the yellow line.

SCAN ME : REFERENCES

3. A STORY OF UNEXPLAINED MULTIFOCAL THROMBOTIC COMPLICATIONS: FIND A WAY OUT IN THE TALL GRASS WITH A SICKLE

Polito G.[1], Cecchini A. L.[1], Biscetti F.[2], Rando M. M.[2], Scarpati R.[1], Nardella E.[2], Rossini E.[2], Nicolazzi M. A.[2], Pecorini G.[2], Massetti M.[3], Gasbarrini A.[4], Flex A.[2]
[1]Università Cattolica del Sacro Cuore, Largo Francesco Vito 1, 00168 Roma, Italy; [2]Cardiovascular Internal Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy ; [3]Department of Cardiovascular Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy; [4]Department of Medical and Surgical sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy

We report the case of a 68-year-old male admitted to the Emergency Department for high ventricular response Atrial Fibrillation (AF) associated with progressive dyspnea worsening in response to minimal efforts, epigastric pain radiating to the left shoulder and a single episode of vomiting. The patient has had a history of well-controlled permanent AF since 2013, hip prosthesis due to osteonecrosis of the right femoral head in 2001 and recurrent episodes of lower limbs thrombophlebitis and ulcers. On admission, the patient presented hypertension, tachycardia and dyspnea in room air. Physical examination revealed aching swelling of the left knee and the presence of extremely painful chronic perimalleolar ulcers. Laboratory tests showed normoglycemia, anemia (Hb 10 g/dL), leukocytosis (WBC count 10.34x10^9L) and signs of hemolysis (reticulocytes 4.9%, LDH 1118 UI/L, total bilirubin 1.3 mg/dL with 0.4 mg/dL of direct bilirubin). Emergent pneumo-cardiologic conditions were initially investigated with a 12-lead EKG, a double troponin determination and a chest x-ray resulted normal. Via an echocardiogram, the presence of macroscopic atrial/ventricular thrombi or acute right ventricular strain were also excluded. Rate control therapy was augmented and analgesics were administered.
A Rx scan of the knee showed diffuse morpho-structural alteration of the distal femur and proximal leg so an MRI was performed confirming femorotibial osteonecrosis.
In light of the thrombophlebitis history and the chronic perimalleolar ulcers, local macrovascular underlying causes were examined. However, ongoing deep vein thrombosis, thrombophlebitis, and/or venous insufficiency were ruled out by a venous Doppler-ultrasound. Due to the lack of supporting clinical and laboratory findings, also peripheral artery disease and diabetes were excluded as plausible causes. Furthermore, cardiac-embolism appeared unlikely as the patient reported that the first unexplained episode of osteonecrosis had occurred many years before the diagnosis of AF, while this second current episode, documented on MRI, occurred despite optimal anticoagulant therapy and without the involvement of other typical sites.
All of the above may support the consistency of microcirculation involvement and since macrovascular and embolic conditions of thrombosis were excluded, the hypothesis that a systemic disease could explain all the patient's multifocal thrombotic complications seemed more plausible. Therefore, patient's history was further investigated to obtain new clues to orient the diagnostic workup and a history of unexplained anemia was discovered in both parents. Therefore, given the suspect of congenital hemolytic anemia and possible presence of hemoglobinopathies, a screening test was performed. Hemoglobin electrophoresis and peripheral blood stream revealed a high percentage of HbS (HbS 69%) with sickle cells. Finally, a diagnosis of sickle cell syndrome was made.
In view of the high HbS levels, severe recurrent thrombotic complications, and ongoing symptomatic vaso-occlusive crises complicated by exacerbation of heart failure due to anemia, the hematologist was consulted and an erythro-exchange procedure was recommended.
Over the following days, a rise and stabilization of hemoglobin levels, a resolution of symptoms as well as a progressive improvement of the lower limb ulcer were registered. After discharge, the patient underwent periodic transfusion resulting in further improvement and healing of the ulcer.
Rare diseases (RD) are an emerging healthcare burden. Although individually rare, these disorders collectively affect 6–8% of the European population. Often the recognition of a key clinical sign leads to the diagnosis of RD. However, most of the cases people with RD present in emergency room with collateral symptoms that may cover the key symptom. In our case, patient's ulcers helped our diagnostic workup. Lower limb ulcers represent a major healthcare issue due to their frequency, resulting disabilities and morbidities, not to mention the high costs associated with the management and care of such lesions. Ulcers can result from multiple etiologies: up to 90% are due to chronic venous disease, peripheral arterial disease, and diabetic neuropathy. However there are many other less common causes including traumatic injuries, drugs, infections, autoimmune diseases, vasculitis, microvascular disorders and malignancies. Thus, the identification of a second key clinical sign allowed to narrow the differential diagnosis and determine the underlying cause to select the right management and the appropriate treatment.
Typically associated with high haemolysis levels, sickle leg ulcers (SLUs) are the result of a chronic vaso-occlusive condition leading to ischemic distress and tissue necrosis. The mainstays of SLU therapeutic approach include pain management, venous compression, local wound care and systemic therapy like hydroxyurea. Moreover, despite transfusion not being generally recommended for ulcer treatment, it can be considered on a case by case as an option being of most value to individuals with significant anemia.

4. EFFICACY OF VAGAL NEUROMODULATION IN ONE CASE OF POSTURAL TACHYCARDIA SYNDROME (POTS) ASSOCIATED WITH DYSAUTONOMIA

Ambrosecchia M., Carandina A., Montano N., Tobaldini E.
Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy; Department of Internal Medicine, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy

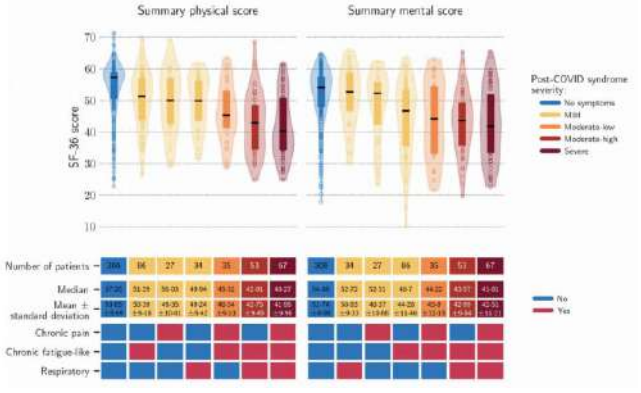
We report a case of a 24-year-old female affected by Ehlers-Danlos syndrome who presented to our outpatient clinic for postural tachycardia syndrome (PoTS). At the age of 14, after a head trauma, she had recurrent syncopes, but these episodes spontaneously disappeared within a year. She performed an ECG and a brain RMN, that resulted negative. At the age of 20 she had recurrent syncopes again. She performed a new EEG and a holter-ECG (that resulted negative) and a brain-RMN that showed cerebellar tonsil that surfaces in the foramen magnum and an arachnoid cyst. She performed a head up TILT-test too, which was conclusive for PoTS.
In 2021, after sever weight loss and intestinal dysmotility disorders, she performed an intestinal biopsy which showed small fiber neuropathy.
In March 2023, during a hospitalization for a new syncope in Neurology Unit (Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico), she was sent to our clinic for the evaluation of the cardiovascular autonomic profile for a re-evaluation of PoTS. We performed a complete head up tilt test, which consists in evaluating the cardiovascular response to the transition from supine to upright position by evaluating blood pressure at pre-established intervals and by monitoring heart rate. Furthermore, during the test the cardiovascular autonomic response to autonomic maneuvers (Valsalva maneuver and sinus arrhythmia) is evaluated.

In the transition from supine position to upright position there was an increase in heart rate (HR)>30 points without orthostatic hypotension. So the exam confirmed the diagnosis of PoTS (*Figure 1*). The test did not show pathological alterations of the cardiovascular response to autonomic maneuvers. The test was stopped after about 6 minutes of passive orthostatism due to orthostatic intolerance (dizziness, tremors in the lower limbs and hyperventilation).
We performed specific questionnaires in order to evaluate the presence and the severity of dysautonomic sympoms. The *Pittsburgh Sleep Quality Index (PSQI)*, that evaluate the sleep quality (the higher the score, the lower the quality of sleep) showed a global score of 15/21, indicating the presence of a serious sleep disorder; the *Patient Health Questionnaire-9 (PHQ-9)*, that scores each of the nine DSM-IV criteria for validated for use in primary care to monitor the severity of depression and response to treatment, showed a score of 8 (the cut-off for diagnosis of depression is 9). The *Orthostatic Hypotension Questionnaire (OHQ)*, showed a score of 8.5/10 indicating a severe hypotension disturb.
Considering the PoTS associated with dysautonomia possibly linked to an autonomic dysfunction with a shift of the sympathovagal balance towards a sympathetic predominance, we decided to start a preliminary 3 weeks treatment with transcutaneous auricular vagus nerve stimulation (tVNS).
tVNS was performed by the patient at home for 4 non-consecutive hours/day, with a stimulation frequency of 25 Hz and an intensity of 0.5-5 mA according to the personal daily skin sensitivity.
We evaluated the patient again after 27 days of tVNS. During the head up tilt test, she did not show either tachycardia during passive standing or symptoms attributable to orthostatic intolerance; the cardiovascular response to autonomic maneuvers was normal (*Figure 2*).
We repeated the questionnaires performed during the first evaluation to assess the subjective improvement of the symptoms. We performed the *PSQI*, the *PHQ-9* and the *OHQ* again. The results of the quesionnaires showed an improvement in the quality of sleep and a reduction of sympoms related to orthostatic intolerance compared to the period prior to tVNS.
So the head up tilt test indicates that after tVNS the patient obtained a better tolerance to passive standing. Moreover, as we can see from the results of the questionnaires, the patient reported subjective improvement in symptoms of orthostatic intollerance, such as dizziness.
The observed beneficial results could be due to a neuromodulatory effect of tVNS.
The transcutaneous stimulation of the auricular branch of the vagus nerve engages the nucleus tractus solitaries (NTS), which is the primary brainstem target of most afferent vagal projections.
We decided to continue the tVNS to our patient in order to evaluate the medium and long lasting neuromodulatory effect of tVNS.
Future studies will have to confirm the efficacy of tVNS as a therapeutic approach for POTS.

5. CLINICAL PHENOTYPES AND QUALITY OF LIFE TO DEFINE POST-COVID-19 SYNDROME: A CLUSTER ANALYSIS OF THE MULTINATIONAL, PROSPECTIVE ORCHESTRA COHORT

Canziani L.M.[1], Gentilotti E.[1], Gorska A.[1], Tami A.[2], Gusinow R.[3], Mirandola M.[1], Rodriguez-Baño J.[4], Palacios-Baena Z.[4], Rossi E.[5], Hasenauer J.[3], Lopes-Rafega I.[6], Righi E.[1], Carroccia N.[7], Cataudella S.[5], Pasquini Z.[8], Osmo T.[9], Del Piccolo L.[10], Savoldi A.[1], Kumar-Singh S.[11], Mazzaferri F.[1], Caponcello M. G.[4], de Boer G.[2], Levy Hara G.[12], De Nardo P.[1], Malhotra S.[11], Ghosn J.[13], Florence A.-M.[14], Lafhej N.[15], van der Gun B.T.F.[2], Giannella M.[16], Laouenan C.[17], Tacconelli E.[1]
[1]Infectious Disease, Department of Diagnostics and Public Health, University of Verona, Verona, Italy; [2]Department of Medical Microbiology and Infection Prevention, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; [3]LIMES Institute, University of Bonn; Institute for Computational Biology, Helmholtz Munich; Research Center for Environmental Health, Neuherberg, Germany; [4]Unidad Clínica de Enfermedades Infecciosas y Microbiología, Hospital Universitario Virgen Macarena, Departamento de Medicina, Universidad de Sevilla; Instituto de Biomedicina de Sevilla (IBiS)/CSIC, Seville; CIBERINFEC, Instituto de Salud Carlos III, Madrid, Spain; [5]CINECA Interuniversity Consortium, Bologna, Italy; [6]Barcelona Institute for Global Health (ISGlobal), Hospital Clínic, University of Barcelona, Spain; [7]Department of Medical and Surgical Sciences, "Alma Mater Studiorum" University of Bologna, Bologna, Italy; [8]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Infectious Diseases Unit, Bologna, Italy; [9]Centre Informatique National de l'Enseignement Supérieur CINES, France; [10]Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy; [11]Molecular Pathology Group, Cell Biology & Histology, and Laboratory of Medical Microbiology, Vaccine & Infectious Disease Institute, Faculty of Medicine, University of Antwerp, Antwerp, Belgium; [12]Instituto Alberto C. Taquini de Investigaciones en Medicina Traslacional, Facultad de Medicina, Universidad de Buenos Aires, Argentina; [13]Université Paris Cité, INSERM, Paris, France; AP-HP Nord, Hôpital Bichat, Department of Infectious and Tropical Diseases, Paris, France; [14]Université Paris Cité, INSERM, Paris, France; AP-HP Nord, Hôpital Bichat, Department of Epidemiology Biostatistics and Clinical Research, Paris, France; [15]AP-HP Nord, Hôpital Bichat, Department of Epidemiology Biostatistics and Clinical Research, Paris, France; [16]Department of Medical and Surgical Sciences, "Alma Mater Studiorum" University of Bologna, Bologna, Italy; IRCCS Azienda Ospedaliero-Universitaria di Bologna, Infectious Diseases Unit, Bologna, Italy; [17]Université Paris Cité, INSERM, Paris, France

Background: Lack of specific definitions of clinical characteristics, disease severity, and risk and preventive factors of post-COVID-19 syndrome (PCS) severely impacts research and discovery of new preventive and therapeutics drugs.
Methods: This prospective multicenter cohort study was conducted in 5 countries, enrolling SARS-CoV-2 out- and in-patients followed at 3-, 6-, and 12-month from diagnosis, with assessment of clinical and biochemical features, antibody (Ab) response, Variant of Concern (VoC), and physical and mental quality of life (QoL). Outcome of interest was identification of risk and protective factors of PCS by clinical phenotype, setting, severity of disease, treatment, and vaccination status. We used SF-36 questionnaire to assess evolution in QoL index during follow-up and unsupervised machine learning algorithms (principal component analysis, PCA) to explore symptom clusters. Severity of PCS was defined by clinical phenotype and QoL. We also used generalized linear models to analyse the impact of PCS on QoL and associated risk and preventive factors.
Findings: Among 1796 patients enrolled, 1030 (57%) suffered from at least one symptom at 12-month. PCA identified 4 clinical phenotypes: chronic fatigue-like syndrome (CFs: fatigue, headache and memory loss, 757 patients, 42%), respiratory syndrome (REs: cough and dyspnoea, 502, 23%); chronic pain syndrome (CPs: arthralgia and myalgia, 399, 22%); and neurosensorial syndrome (NSs: alteration in taste and smell, 197, 11%). Determinants of clinical phenotypes were different (all comparisons p<0·05): being female increased risk of CPs, NSs, and CFs; chronic pulmonary diseases of REs; neurological symptoms at SARS-CoV-2 diagnosis of REs, NSs, and CFs; oxygen therapy of CFs and REs; and gastrointestinal symptoms at SARS-CoV-2 diagnosis of CFs. A negative association (all comparisons p<0·05) was observed for early treatment of SARS-CoV-2 infection with monoclonal Ab (all clinical phenotypes), corticosteroids therapy for mild /severe cases (NSs), and SARS-CoV-2 vaccination (CPs). Highest reduction in QoL was detected in REs and CPs (43·57 and 43·86 vs 57·32 in PCS-negative controls, p<0·001). Female sex (p<0.001) and gastrointestinal symptoms (p=0.034) and renal complications (p=0.002) during the acute infection were likely to increase risk of severe PCS (QoL<50). Vaccination and early treatment with monoclonal Ab reduced the risk of severe PCS (p=0.01 and p=0.03, respectively).



Severity of post-COVID-19 syndrome by clinical phenotype and quality of life measured by SF-36.
Interpretation: Our study provides new evidence suggesting that PCS can be classified by clinical phenotypes with different impact on QoL, underlying

possible different pathogenic mechanisms. We identified factors directly and inversely associated to each clinical phenotype and to severe PCS. These results might help in designing pathogenesis studies and in selecting high-risk patients for inclusion in therapeutic and management clinical trials.
Funding: The study received funding from the Horizon 2020 ORCHESTRA project, grant 101016167; from the Netherlands Organisation for Health Research and Development (ZonMw), grant 10430012010023; from INSERM, REACTing (REsearch & ACtion emergING infectious diseases) consortium and the French Ministry of Health, grant PHRC 20-0424.
CT registration number: NCT05097677

6. REAL-WORLD EVIDENCE ON THE VACCINATION CAMPAIGN AGAINST SARS-COV-2 AMONG AUTOIMMUNE INFLAMMATORY RHEUMATIC DISEASE PATIENTS FROM A NETWORK OF 6 ITALIAN CLINICAL IMMUNOLOGY CENTERS

Murdaca G.[1], Amato R.[2], Noberasco G.[2], Ottanelli D.[2], Zanoni G.[3], Maule M.[3], Icardi G.[2], Sticchi L.[2], Orsi A.[2]
[1]Department of Internal Medicine, University of Genova, 16132 Genova, Italy. Ospedale Policlinico San Martino IRCCS", 16132 Genova, Italy; [2] Department of Health Sciences, University of Genova, 16132 Genova, Italy. Hygiene Unit, "Ospedale Policlinico San Martino IRCCS", 16132 Genova, Italy; [3] Immunology Unit, University Hospital of Verona, Verona, Italy. Department of Medicine, University of Verona, 37129 Verona, Italy

Systemic sclerosis (SSc) is a chronic immune-mediated disease characterized by a high mortality. It has been estimated that around 1-5 in 10,000 people are affected, worldwide, with a reported female/male ratio ranging from 3:1 to 8:1. In Italy, the incidence is estimated to be between 4 and 20 new cases per 1,000,000 population per year, while the prevalence is estimated to be between 30 and 450 cases per 1,000,000 population. SSc is a systemic autoimmune disease; its etiology is not yet fully defined, given the complex but some environmental factor (e.g. chemicals, chemotherapy and silicone implant) combined with genetic and epigenetic susceptibility (immune dysregulation and inflammation) play a role. SSc may present at any age, but the most frequent peak is between 20 and 50 years or even after, till 69 years. The disease is rare in children and teens below 15 years of age. Females tend to develop SSc at an earlier age compared to males.
Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with multisystemic involvement caused by several immunopathogenic pathways. SLE typically affects young women with a peak incidence between 15 and 40 years of age and a female-to-male ratio of 6-10:1. The global SLE prevalence in adults was 61.08 (22.18 to 151.87) per 100,000 persons, corresponding to approximately 3.17 million adults worldwide, while its incidence ranges from 0.3 to 23.2 per 100,000 person-years, with a trend to a constant increase and the highest prevalence reported in Brazil.The 10-year survival rate is about 70%. Etiology is unknown: genetic, immunological, endocrine, and environmental factors play a role in its etiopathogenesis.
Since the beginning of COVID-19 pandemic in December 2019, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), more than 6 million deaths have been recorded worldwide and the number of confirmed infections has risen to more than 242 million. Most people infected with the virus experience mild to moderate respiratory illness. People with chronical disease are more likely to develop serious illness, with an increased risk of hospitalization for pneumonia with multiorgan disease and the need of oxygen supplementation (in more than 75% of hospitalized patients). COVID-19 vaccination in patients with autoimmune disease had a major impact in reducing hospitalization and death by COVID-19.
We conducted a multicentric study between January 2021 and May 2023 involving six Italian Clinical Immunology Center: Ancona, Bari, Cagliari, Salerno, Verona, Messina. Data of followed-up patients, afflicted mainly by SSc, LES but also other autoimmune diseases, were collected and organized in a shared database.
The focus of this research was to start investigating vaccine coverage rate, and adverse effects of COVID-19 vaccination.
A cohort of 485 patients was gathered, 84% women. The main clinical condition was SSc with a percentage of 45% of all patients. Rheumatoid Arthritis was the second most represented group with the 33%. All further data are summarized in the table below.
The cohort was divided between vaccinated and not vaccinated. Patients were considered vaccinated seven days after completing the cycle of COVID-19 vaccine, patients were considered not vaccinated in absence of vaccination record or whether the test was collected prior to the eighth day after the completion of the vaccine schedule.
Among 485 patients, 324 (67%) were vaccinated; 86% (n. 278) of vaccinated patients were women. The group of vaccinated patients consists of the following distribution of diseases: systemic sclerosis 51% (N. 164), rheumatoid arthritis 27% (N. 88), systemic lupus erythematosus 11% (N. 34). The coverage rate was slightly higher among women (68% vs 60%).
90% (n. 292) of the vaccinated patients reported no symptoms or adverse reactions to the vaccine following vaccine administration. Only one patient (0.3%) reported a worsening of the clinical condition following vaccination. The remaining 10% of the vaccinated patients reported mild symptoms (e.g., arm pain, lymphadenopathy, asthenia, myalgias, arthralgias, headache, nausea, fever) and the most frequent was fever (44%). Local reaction was reported by 8 out of 32 people, while systemic reaction by 27 out of 32; 4 vaccinated patients experienced systemic and local reactions.
Our analysis shows that adverse events from anti-SARS-CoV-2 vaccination were mild in the patient category analyzed. This work provides data on the safety and reactogenicity of vaccination in a fragile patient category in a scenario of uncertainty; in fact, this population often falls victim to vaccination fear and adverse reactions. In addition, although vaccination effectiveness data show non-statistically significant differences between the vaccinated and unvaccinated, we noted that despite the occurrence of omicron in 2022 there were very few cases of serious infections.

Condition	Distribution of enrolled patients by disease (vaccinated and unvaccinated)	Sex	Vaccinated (%)	Distribution of the vaccinated population by sex
Systemic sclerosis	220 (45%)	Female 197 (90%) Male 23 (10%)	164 (75%)	Female 148 (90%) Male 16 (10%)
Lupus Erythematosus Systemic	52 (11%)	Female 43 (83%) Male 9 (17%)	34 (46%)	Female 28 (82%) Male 6 (18%)
Rheumatoid arthritis	163 (34%)	Female 130 (80%) Male 33 (20%)	88 (54%)	Female 73 (83%) Male 15 (17%)
Other condition	50 (10%)	Female 38 (76%) Male 12 (24%)	38 (76%)	Female 29 (76%) Male 9 (24%)

7. REMDESIVIR TREATMENT AND CLINICAL OUTCOME IN NON-SEVERE HOSPITALIZED COVID-19 PATIENTS: A PROPENSITY SCORE MATCHING MULTICENTER ITALIAN HOSPITAL EXPERIENCE

Caturano A.[1], Attena E.[2], Annunziata A.[3], Maraolo A.E.[4], De Rosa A.[5], Fusco F.M.[6], Halasz G.[7], Dell'Ospedale V.[8], Conte M.[9], Parisi V.[9], Galiero R.[10], Sasso F.C.[10], Fiorentino G.[3], Russo V.[11]
[1]Department of Advanced Medical and Surgical Sciences, University of Campania Luigi Vanvitelli, Naples, Italy; [2]Cardiology Unit, Monaldi Hospital - A.O.R.N. Dei Colli, Naples, Italy; [3]Sub-intensive Care Unit and Respiratory Pathophysiology Department, Cotugno Hospital - A.O.R.N. Dei Colli, Naples, Italy.; [4]First Division of Infectious Diseases, Cotugno Hospital - A.O.R.N. Dei Colli, Naples, Italy.; [5]Respiratory Infectious Diseases Unit, Cotugno Hospital - A.O.R.N. Dei Colli, Naples, Italy.; [6]Third Division of Infectious Diseases, Cotugno Hospital - A.O.R.N. Dei Colli, Naples, Italy; [7]Cardiology Department, Guglielmo Da Saliceto Hospital, Piacenza, Italy; [8]Cardiology Department, University of Parma, Parma, Italy; [9]Department of Translational Medical Sciences, University of Naples Federico II, Naples, Italy; [10]Department of Advanced Medical and Surgical Sciences, University of Campania Luigi Vanvitelli, Naples, Italy.; [11]Division of Cardiology, Department of Medical Translational Sciences, University of Campania Luigi Vanvitelli, Naples, Italy

Introduction: Remdesivir exerts positive effects on clinical improvement, even though it seems not to affect mortality among COVID-19 patients; moreover, it was associated with the occurence of marked bradycardia.
Methods: We retrospectively evaluated 989 consecutive patients with non-severe COVID-19 (SpO2 ≥ 94% on room air) admitted from October 2020 to July 2021 at five Italian hospitals. Propensity score matching allowed to obtain a comparable control group. Primary endpoints were bradycardia onset (heart rate < 50 bpm), acute respiratory distress syndrome (ARDS) in need of intubation and mortality.
Results: A total of 200 patients (20.2%) received remdesivir, while 789 standard of care (79.8%). In the matched cohorts, severe ARDS in need of intubation was experienced by 70 patients (17.5%), significantly higher in the control group (68% vs. 31%; $p < 0.0001$). Conversely, bradycardia, experienced by 53 patients (12%), was significantly higher in the remdesivir subgroup (20% vs. 1.1%; $p < 0.0001$). During follow-up, all-cause mortality was 15% (N = 62), significantly higher in the control group (76% vs. 24%; log-

rank p < 0.0001), as shown at the Kaplan-Meier (KM) analysis. KM furthermore showed a significantly higher risk of severe ARDS in need of intubation among controls (log-rank p < 0.001), while an increased risk of bradycardia onset in the remdesivir group (log-rank p < 0.001). Multivariable logistic regression showed a protective role of remdesivir for both ARDS in need of intubation (OR 0.50, 95%CI 0.29-0.85; p = 0.01) and mortality (OR 0.18, 95%CI 0.09-0.39; p < 0.0001).
Conclusions: Remdesivir treatment emerged as associated with reduced risk of severe acute respiratory distress syndrome in need of intubation and mortality. Remdesivir-induced bradycardia was not associated with worse outcome.

8. IMPACT OF COVID-19 AND VACCINATION CAMPAIGN ON 1,755 SYSTEMIC SCLEROSIS PATIENTS DURING THE FIRST THREE YEARS OF PANDEMIC. POSSIBLE RISKS FOR INDIVIDUALS WITH DISEASE-RELATED LUNG INVOLVEMENT, ONGOING IMMUNOMODULATING TREATMENTS, AND/OR IMPAIRED VACCINE IMMUNOGENICITY DURING THE NEXT PANDEMIC PHASE.

Ferri C.[1], Raimondo V.[2], Giuggioli D.[3], Gragnani L.[4], Lorini S.[5], Dagna L.[6], Bosello S.[7], Foti R.[8], Riccieri V.[9], Guiducci S.[10], Cuomo G.[11], Tavoni A.[12], De Angelis R.[13], Cacciapaglia F.[14], Zanatta E.[15], Cozzi F.[16], Murdaca G.[17], Cavazzana I.[18], Romeo N.[19], Codullo V.[20], Pellegrini R.[21], Varcasia G.[22], De Santis M.[23], Abignano G.[24], Caminiti M.[25], L'Andolina M.[26], Olivo D.[27], Lubrano E.[28], Spinella A.[29], Lumetti F.[29], De Luca G.[30], Ruscitti P.[31], Urraro T.[32], Bellando-Randone S.[10], Visalli E.[8], Bilia S.[33], Giannini D.[33], Masini F.[11], Pellegrino G.[34], Pigatto E.[16], Generali E.[23], Dall'Ara F.[35], Pagano Mariano G.[25], Pettiti G.[36], Zanframundo G.[20], Brittelli R.[37], Aiello V.[37], Dal Bosco Y.[8], Foti R.[38], Di Cola I.[31], Scorpiniti D.[37], Fusaro E.[39], Ferrari T.[22], Gigliotti P.[40], Campochiaro C.[30], Francioso F.[41], Iandoli C.[42], Balestri E.[43], Giusy E.[43], Caira V.[22], D'Angelo S.[24], Franceschini F.[18], Matucci-Cerinic M.[10], Giacomelli R.[44], Doria A.[45], Fallahi P.[46], Iannone F.[47], Antonelli A.[46]
[1]Rheumatology Unit, University of Modena & RE., School of Medicine, Modena, Italy;Rheumatology Clinic 'Madonna dello Scoglio' Cotronei, Crotone, Italy; [2]Rheumatology Clinic 'Madonna dello Scoglio' Cotronei, Crotone, Italy; [3]Rheumatology Unit, University of Modena & RE., School of Medicine, Modena, Italy; [4]Department of Translational Research of New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy; [5]University of Florence, Florence, Italy; [6]Ospedale S. Raffaele, Milano, Italy; [7]Institute of Rheumatology, Università Cattolica del Sacro Cuore, Rome, and Division of Rheumatology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy.; [8]AOU Policlinico Vittorio Emanuele, Catania, Italy; [9]Rheumatology, Sapienza-University of Rome, Roma, Italy.; [10]Rheumatology, University of Florence, Firenze, Italy; [11]University of Campania, Luigi Vanvitelli, Napoli, Italy; [12]linical Immunology, University of Pisa, Pisa, Italy; [13]Rheumatology Clinic, Department of Clinical & Molecular Sciences, Marche Polytechnic University, Ancona, Italy; [14]UO Reumatologia – DETO, Università di Bari, Italy; [15]Rheumatology, University of Padova, Padova, Italy; [16]Ospedale "Villa Salus", Mestre, Italy; [17]Ospedale Policlinico S. Martino-University of Genova, Genova, Italy; [18]Rheumatology, Spedali Civili di Brescia, Brescia, Italy; [19]ASO S. Croce e Carle, Cuneo, Italy.; [20]Rheumatology, Policlinico San Matteo, Pavia, Italy; [21]U.O.C. Medicina Interna 'M.Valentini" P.O. Annunziata, Cosenza, Italy; [22]U.O.S. Reumatologia, Ospedale Castrovillari, Cosenza, Italy; [23]Humanitas Clinical and Research Center IRCCS, Milano, Italy; [24]AOR San Carlo di Potenza, Potenza, Italy; [25]UOD Reumatologia- Grande Ospedale Metropolitano, Reggio Calabria, Italy; [26]Rheumatology Outpatient Clinic, ASP- Vibo Valentia-Tropea Hospital, Italy; [27]Rheumatology Outpatient Clinic, San Giovanni di Dio Hospital, Crotone, Italy; [28]Rheumatology, Università del Molise, Campobasso, Italy; [29]Rheumatology Unit, University of Modena and Reggio Emilia, School of Medicine, Modena, Italy; [30]Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS H San Raffaele, Milan, Italy; Vita-Salute San Raffaele University, Milan, Italy; [31]Rheumatology Unit, Department of Biotechnological & Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy; [32]Rheumatology Unit, M Scarlato Hospital, Scafati, Italy; [33]Clinical Immunology, University of Pisa, Pisa, Italy; [34]Rheumatology, Sapienza-University of Rome, Roma, Italy; [35]heumatology and Clinical Immunology, Department of Clinical and Experimental Sciences, Spedali Civili and University of Brescia, Italy; [36]SO S. Croce e Carle, Cuneo, Italy; [37]Rheumatology Clinic 'Madonna dello Scoglio' Cotronei, Crotone, Italy; [38]Rheumatology Unit, San Marco Hospital Policlinico, University of Catania, Catania, Italy; [39]Rheumatology Unit, Azienda Ospedaliero Universitaria Città della Salute e della Scienza, Torino, Italy; [40]U.O.T. Specialistica Ambulatoriale ASP 201, Cosenza, Italy; [41]Rheumatology Unit, Department of Clinical and Molecular Sciences, "Carlo Urbani" Hospital, Polytechnic University of Marche, Jesi, Italy; [42]Department of Precision Medicine, "Luigi Vanvitelli" University of Campania, 80138 Naples, Italy; [43]Department of Surgical, Medical and Molecular Pathology and Critical Area, University of Pisa, School of Medicine, Pisa, Italy; ; [44]Unità Operativa di Immunoreumatologia - Area Medicina Clinica Policlinico Universitario Campus Bio-Medico di Roma, Roma, Italy; [45]Rheumatology, University of Padova, Padova, Italy.; [46]Department of Translational Research & New Technologies in Medicine and Surgery, University of Pisa, School of Medicine, Pisa, Italy; [47]UO Reumatologia - DETO, Università di Bari, Bari, Italy

The impact of COVID-19 pandemic represents a serious challenge for different 'frail' patients' populations with inflammatory autoimmune systemic diseases such as systemic sclerosis (SSc). Here, we investigated the prevalence and severity of COVID-19, as well as the effects of COVID-19 vaccination campaign in a large series of SSc patients followed for the entire period (first 38 months) of pandemic.
This prospective survey study included 1,755 unselected SSc patients (186 M, 1,569F; mean age 58.7±13.4SD years, mean disease duration 8.8± 7.3SD years) recruited at 37 referral centers from February 2020 to April 2023. The following parameters were carefully evaluated: i. demographic, clinical, serological, and therapeutical features; ii. prevalence and severity of COVID-19; and iii. safety, immunogenicity, and efficacy of COVID-19 vaccines. The prevalence of COVID-19 recorded during the whole pandemic was significantly higher compared to Italian general population (47.3% vs 43.3%, p<.000), as well as the COVID-19-related mortality (1.91% vs 0.72, p<.001). As regards the putative prognostic factors of worse outcome, COVID-19 positive patients with SSc-related interstitial lung involvement (ILD) showed significantly higher percentage of COVID-19-related hospitalization compared to those without ILD (5.85% vs 1.73%; P<0.000), as well as of mortality rate (11/547, 2.01% vs 0.4%; p= 0.002).Over half of patients (56,3%) received the first two plus one booster dose of vaccine; while a fourth dose was administered to 35.6%, and only few of them (1.99%) had five or more doses of vaccine. Of note, an impaired seroconversion was recorded in 25.6% of individuals after the first 2 doses of vaccine, and in 8.4% of patients also after the booster dose. Furthermore, the absence of T-cell immunoreactivity was observed in 3/7 patients tested by QuantiFERON® SARSCoV-2 Starter Set (Qiagen). The efficacy of vaccines, evaluated by comparing the COVID-19-related death rate recorded during pre- and post-vaccination pandemic periods, revealed a quite stable outcome in SSc patients (*from* 2.54% to 1.76%; p=ns), despite the marked drop of mortality observed in the Italian general population (from 2.95% to 0.29%; p<.000). An increased COVID-19 prevalence and mortality rate was recorded in SSc patients; the efficacy of vaccines in term of improved outcomes was less evident in SSc compared to the Italian general population. A number of adverse prognostic factors may explain this discrepancy: high rate of non-responders to vaccine, low percentage of patients with four or more doses of vaccine, ongoing immunomodulating treatments, presence of SSc-related interstitial lung disease, and reduced preventive measures in the second half of pandemic. A careful monitoring of COVID-19 vaccine immunogenicity together with adequate preventive/therapeutical strategies are highly recommendable in the near course of pandemic in this frail patients' population.
(for the COVID-19 & ASD Italian Study Group)

9. HYPERGLYCEMIA AFFECTS FXR SIGNALING IN HUMAN INTESTINAL MUCOSA

De Vito F.[1], Facciolo A.[1], Marasco R.[1], Suraci E.[1], Melina M.[1], Monea G.[1], Succurro E.[1], Luzza F.[1], Andreozzi F.[1], Sesti G.[2], Fiorentino T.V.[1]
[1]Department of Medical and Surgical Sciences, University Magna Graecia of Catanzaro; [2]Department of Clinical and Molecular Medicine, University of Rome-Sapienza, Rome

Several evidence indicates the role of intestinal bile acids receptor farnesoid X receptor (FXR), in modulating energy homeostasis and maintaining intestinal mucosa barrier integrity. In the gut FXR, which is mainly expressed in the ileal mucosa, promotes the transcription of fibroblast growth factor-19 (FGF-19), a hormone having several beneficial effects on energy and glucose homeostasis, and expression of tight junction (TJ) proteins. Prior studies have demonstrated a link between type 2 diabetes (T2DM) and reduced circulating FGF-19 levels and augmented intestinal permeability, known to be implicated in the pathogenesis of several cardio-metabolic disorders. Moreover, hyperglycemia has been found to directly induce intestinal barrier dam-

age in animal models. However, it is currently unknown whether hyperglycemia may affect FXR/FGF-19/TJ pathway in human intestinal mucosa. To address this issue, we enrolled 53 subjects who underwent to a complete clinical characterization including OGTT. Based on their glucose tolerance, study subjects were categorized as having normal glucose tolerance (NGT) (n=26), prediabetes (n=12), or T2DM (n=15). All participants underwent to a colonoscopy with terminal ileum endoscopy and collection of ileum mucosa biopsies. We assessed ileal levels of FXR, FGF-19 and the TJ proteins Zonulin (ZO)-1 and Occludin by western blot and RT-PCR. Additionally, serum levels of FGF-19 were evaluated by ELISA assay. In order to investigate the effect of high glucose (HG) exposure on the FXR-FGF19-TJ signaling, we performed intestinal organ culture experiments by culturing ileal mucosa specimens collected from subjects with NGT in presence of HG (25 and 50 mM) for 8 hours. Ileal mucosa specimens cultured in presence of mannitol (25mM) were used as a control of hyperosmolarity. The three study groups were well matched for gender and anthropometric measures. Conversely, subjects with T2DM were significantly older than those with NGT. After adjusting for age, we found that subjects with prediabetes and T2DM have progressively reduced levels of FXR protein (-20% and -25%, respectively, P=0.002) and mRNA (-43% and -49%, respectively, P=0.02) as compared to NGT group. The decrease in ileal FXR abundance observed in subjects with prediabetes and T2DM was paralleled by a reduction in ileal mRNA (-56% and -69% in prediabetes and T2DM groups, respectively, P=0.03) and serum levels of FGF-19 (-34% and -40% in subjects with prediabetes and T2DM, respectively, P=0.007). Additionally, we found a progressive reduction of mRNA and protein levels of the TJ ZO-1 and Occludin in ileal mucosa of subjects with prediabetes and T2DM as compared to those with NGT ($p<0.05$ for all). Next, we assessed FXR/FGF-19/TJ pathway in ileal mucosa specimens of subjects with NGT exposed to HG levels. We found that HG treatment resulted in a significant reduction of FXR expression, with HG 50 mM concentration having the maximal effect inducing a 20% decrease in FXR mRNA and protein levels (P=0.01). HG induced FXR downregulation was mirrored by a significant decrease of FGF-19 mRNA levels (-33% as compared to control, P=0.026). Additionally, in ileal mucosa biopsies exposed to HG we observed a 35% decrease of the TJ ZO-1 protein levels (P=0.011) and a 20% reduction of Occludin protein levels (P=0.001) as compared to the control. In conclusion, our results demonstrate that subjects with T2DM or prediabetes have a down-regulation of intestinal FXR/FGF-19/TJ pathway, and hyperglycemia may directly affect ileal FXR signaling and induce intestinal mucosa dysfunction.

10. ASSOCIATION BETWEEN CARDIAC AUTONOMIC NEUROPATHY AND ONE-HOUR POST-LOAD GLUCOSE IN SUBJECTS WITH DIFFERENT GLUCOSE TOLERANCE

Monea G.[1], Jiritano R.[1], Salerno L.[1], Varano Y.[1], Natale M.R.[1], Melina M.[1], Abramo E.[2], Mannino GC.[1], Andreozzi F.[1]
[1]Department of Medical and Surgical Sciences, University Magna Graecia of Catanzaro, 88100 Catanzaro, Italy; [2]Azienda Ospedaliero-universitaria Renato Dulbecco, Catanzaro, Italy

Background: Several clinical evidences reported that normo-glucose tolerant (NGT) subjects with a 1 h postload glucose ≥155 mg/dL (NGT-1h-high) have an increased risk of type 2 diabetes (T2DM) and subclinical organ damage, all independent predictors of subsequent cardiovascular events. Cardiac autonomic neuropathy (CAN) is a serious complication of T2DM that can predispose patients to postural hypotension, exercise intolerance, severe arrythmias, painless myocardial ischemia and thus to higher risk for cardiovascular death. Despite its significant negative impact on survival and quality of life, CAN remains a poorly recognized and understood clinical condition. The initial signs of CAN are linked to parasympathetic dysfunction and reduction of heart rate variability (HRV) parameters. With the progression of CAN, sympathetic nervous function and its effects on blood pressure control are also affected. At this time, the potential role played by the early post prandial glucose variability on the development of CAN has not been elucidated.
Methods: To address this issue, we analyzed a cohort of 39 well-characterized individuals: 20 NGT of which 10 wereNGT-1h-high , 9 with impaired glucose tolerance (IGT) and 10 newly diagnosed with T2DM. To evaluate the presence of CAN we used the Ewing test score (range 0-5) as a standard for diagnosis of autonomic dysfunction. It is a composite score combining expiratory-to-inspiratory ratio (E:I); Valsalva ratio; HR response to standing (30:15 ratio); postural blood pressure change; handgrip test. Ewing Score of 1.5 has been reported as the cut-off for diagnosis of mild-to-moderate CAN. All patients underwent electrocardiography (ECG) monitoring for 24 hours by a three-channel.
Results: Our exploratory analysis showed that the prevalence of CAN was significantly increased in NGT-1h-high compared to the other NGT subjects ($p<0.001$) and it was similar to the prevalence found for IGT and T2DM . Consistent with this observation HRV resulted similar in NGT-1h-high, IGT and T2DM groups and significantly lower than plain NGT individuals. Moreover, similar findings were observed in Standard Deviation of NN intervals (SDNN) and Triangular Index values ($p<0.001$). The partial correlation analysis between 1-h Plasma Glucose values and Ewing Score, corrected for age, sex and body mass index (BMI), confirmed the existence of a positive association ($r = 0.737$, $p < 0.001$). Multivariable linear regression analysis confirmed that 1-h Plasma Glucose levels are independent contributors of Ewing Score ($\beta=0.646$, $p<0.001$), after correcting for age, sex and BMI, with a stronger standardized effect than fasting plasma glucose (FPG) ($\beta=0.514$, $p<0.001$) and fasting plasma insulin ($\beta=0.248$, $p<0.05$). Nevertheless, the association was attenuated when the homeostasis model assessment-estimated insulin resistance index (HOMA-IR) was included in the model ($\beta=0.548$, $p<0.001$).
Conclusion: Our results support the hypothesis that the early post prandial glucose variability may contribute to the development of CAN. We highlighted that individuals with how NGT 1-h high are significantly more affected by CAN compared to their NGT counterpart, manifesting a risk pattern similar to IGT and newly diagnosed T2DM patients Our data support the hypothesis that subjects with 1-h PLPG ≥ 155 mg/dL should be particularly monitored for the arrhythmic risk stratification. Prospective studies and larger numbers are needed to elucidate the effects on cardiac mortality.

11. JAK2 GERMLINE VARIANTS IN IDIOPATHIC ERYTHROCYTOSIS

Benetti A., Bertozzi I., Cosi E., Randi M.L.
First Medical Clinic, Department of Medicine – DIMED, University of Padova, Padova, Italy

Background and Aims: Absolute erythrocytosis is a clinical condition characterised by an increased red cells production, resulting in haemoglobin and haematocrit levels above the reference range. Polycythemia vera (PV) is a primary acquired erythrocytosis characterized by the presence of the somatic mutation *JAK2*V617F in exon 14 (95% of cases) and, rarely, the gain-of-functions mutations in exon 12 of *JAK2 (*3%). Secondary acquired erythrocytosis occur due to appropriate or inappropriate production of erythropoietin. Rare congenital erythrocytosis forms are classified as primary when erythropoietin receptor gene is altered and secondary when the defects are present in genes involved in the oxygen sensing pathway or in globin genes. In 70% of patients no cause is recognized and they are considered Idiopathic Erythrocytosis (IE). We searched in patients with IE possible new variants with a Next Generation Sequencing (NGS) custom gene panel.
Methods: An ad hoc NGS panel comprehending genes known to cause or to be frequently altered in erythrocytosis was used to search germline molecular variants in 118 sporadic IE patients (M/F =101/17; mean age 53.7±17.2 years). The approach used for library preparation was multiplexing PCR and data were analysed using bioinformatics tools to obtain the variants. All NGS data obtained were confirmed by Sanger Sequencing.
Results: We report here 11 patients out of the 118 evaluated with NGS (9,3%) carrying various germline variants of *JAK2*. These variants are located in different exons and are almost not described at all in literature. Only two of these patients, both males respectively of 60 and 82 years of age, had a thrombotic event (1 deep vein thrombosis - DVT and pulmonary embolism - EP and one stroke and DVT). The genetic alteration found were respectively *JAK2*G571S and *JAK2*N1108S. All others were asymptomatic. Three patients with *JAK2*L393V variant belong to the same family (Table 1).
Conclusions: One patient who suffered for a DVT with EP, carries *JAK2*G571S variant in exon 13 close to the somatic *JAK2*V617F mutation and located in the same protein pseudokinase domain. Thus, we hypothesize that the *JAK2*G571S variant may result in constitutive activation of *JAK2*, inducing high and constant erythrocytes production, similar to the *JAK2*V617F mutation. The *JAK2*N1108S germline variant, found in a stroke patient, involves the tyrosine kinase domain. This area of the protein, following its activation by trans-phosphorylation of two tyrosine residues, is responsible for the phosphorylation of specific substrates. Four of our IE patients carry *JAK2*L393V alteration that has been hypothesized to precede the acquisition of *JAK2*V617F mutation. In conclusion, germline *JAK2* variants in patients with IE represent an intriguing group of molecular gene alterations that may improve the knowledge of IE etiology. An appropriate functional evaluation

of such alterations, hypothetically linked to thrombosis development, could help in reducing the number of unexplained erythrocytosis.

Table 1: Descriptions of JAK2 variants found in our IE patients.

Pats	Sex/Age	HB (g/L)	HT (%)	Thrombotic events	Protein Change	EXON	rs code	Describe in literature	ACMG Classification
1	M/54	166	55	-	p.Leu393Val / L393V	9	[illegible]	1 paper	Likely Benign
2	M/34	173	49.8	-	p.Leu393Val / L393V	9			
3	F/31	143	44.6	-	p.Leu393Val / L393V	9			
4	F/57	140	40.40	-	p.Leu393Val / L393V	9			
5	M/60	174	52.5	DVT + EP	p.Gly571Ser / G571S	13	[illegible]	NO	Uncertain Significance
6	M/50	-	-	-	p.Gly571Ser / G571S	13			
7	M/38	178	58	-	p.Gly48Glu / G48E	3	[illegible]	NO	Benign
8	F/73	172	48.4	-	p.Leu113Val / L113V	4	[illegible]	NO	Benign
9	M/68	183	59.1	-	p.Thr78Ile / T78I	4	Not available	NO	Uncertain Significance
10	M/21	-	-	-	p.Arg923Cys / R923C	21	[illegible]	NO	Uncertain Significance
11	M/62	184	54.4	Stroke + DVT	p.Asn1108Ser / N1108S	25	[illegible]	NO	Benign

12. MAIN FEATURES OF ISCHEMIC STROKE IN PATIENTS WITH ACUTE IMMUNE-MEDIATED THROMBOTIC THROMBOCYTOPENIC PURPURA

Truma A.[1], Agosti P.[1], Mancini I.[1], Artoni A.[2], Semproni E.[1], Giannotta J.A.[2], Ferrari B.[2], De Leo P.[2], Peyvandi F.[3]
[1]Università degli studi di Milano, Department of Pathophysiology and Transplantation, Milan, Italy; [2]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Milan, Italy; [3]Università degli studi di Milano, Department of Pathophysiology and Transplantation, Milan, Italy Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Milan, Italy

Background: Immune-mediated thrombotic thrombocytopenic purpura (iTTP) is a lifethreatening thrombotic microangiopathy often characterized by acute neurological involvement. However, neuroimaging patterns, epidemiology and risk factors of ischemic stroke (IS) in iTTP are largely unknown.
Aims: To evaluate neuroimaging patterns and main related risk factors of ischemic stroke in acute iTTP.
Methods: We performed a cross-sectional study of patients from the Milan TTP Registry who presented with neurological signs/symptoms and underwent a brain imaging during their first acute iTTP episode. Patients with history of IS were excluded.
Results: Seventy-four patients were enrolled, most of patients were women (72%) and of Caucasian ethnicity (98%), with a median age of 45 years. Computed tomography (CT) was performed in all patients, whereas magnetic resonance imaging (MRI) in 20 patients (27%). IS was confirmed by CT and/or MRI in 17 patients (23%), the majority (70%) showed a nonlacunar pattern. In patients who underwent both CT and MRI (n=12), MRI detected an IS in 5 patients with negative CT scans and multiple ischemic lesions in 3 patients with one single lesion on CT. The median age was slightly higher in patients with IS (44 vs 48 years), whereas the prevalence of cardiovascular risk factors and iTTP-associated parameters were comparable between the two groups.
Conclusion: We found a 23% prevalence of imaging-proven ischemic stroke in patients presenting with neurological manifestations at their first acute iTTP episode. Cardiovascular risk factors and iTTP-laboratory parameters were not associated with an increased IS risk. The unexpected high prevalence of non-lacunar and bilateral stroke patterns needs further investigation. The higher sensitivity of MRI than CT in detecting ischemic lesions might suggest the usefulness of this technique in the setting of acute iTTP.

13. MIRNA-21 AND SUBOPTIMAL RESPONSE TO ASPIRIN IN PATIENTS AT HIGH CARDIOVASCULAR RISK

Liani R[1], Simeone P.[2], Tripaldi R.[1], Ciotti S. [1], Boccatonda A.[3], D'Ardes D.[2], Recchiuti A.[4], Romano A.[4], Pulcinelli F.M.[5], Cipollone F.[2], Santilli F.[2]
[1]Department of Medicine and Aging, and Center for Advanced Studies and Technology (CAST), "G. d'Annunzio" University of Chieti-Pescara, Chieti, Italy; [2]Department of Medicine and Aging, and Center for Advanced Studies and Technology (CAST), "G. d'Annunzio" University of Chieti-Pescara, Chieti, Italy; Internal Medicine – Chieti University, Chieti, Italy; [3] Internal Medicine – Chieti University, Chieti, Italy; [4]Department of Medical and Oral Sciences and Biotechnologies, and Center for Advanced Studies and Technology (CAST), Chieti, Italy; [5]Department of Experimental Medicine, Sapienza-University of Rome, Rome, Italy

Background: The variable turnover of aspirin's target, platelet COX-1, is the most compelling determinant of interindividual variability in aspirin response. Overexpression of platelet multidrug resistance protein 4 (MRP4) reduces aspirin-induced COX-1 inhibition by its ability to extrude this drug from platelets. Aspirin is known to modulate platelet miR-21 expression levels in platelets, and this translates into altered platelet levels of MRP4.
Objectives: To identify the relationship between miR-21/MRP4 system and suboptimal aspirin (ASA) response in patients at high cardiovascular risk.
Methods: We evaluated the changes in MRP4 protein and miR-21 expression in high CV risk patients (100 with and without type 2 diabetes mellitus (T2DM)) in chronic treatment with ASA (100 mg/day), for cardiovascular prevention. Blood sampling was performed at 10 (T10) and 24 hours (T24) after a witnessed administration of ASA. Patients were stratified into tertiles based on the slope of serum TXB2. The first and third tertiles were compared.
Results: Third tertile patients, with accelerated recovery of COX-1, tended to be more obese (p=.053) and a higher weight (p=.015), BMI (=.011), waist circumference (p=.002), WHR (p=0.01) than the patients of first tertile. We observed reduced levels of platelet miRNA-21-5p (p=.024) and increased levels of circulating miR-21-5p (p=.017) with inverse correlation between them (rho=-.217, p=.040) in the third vs first tertile, (**Figure 1**). Platelet protein MRP4 increased in third tertile patients (p<.000) with inverse (rho=-.665, p<.000) and direct (rho=.471, p=.003) correlation with platelet and circulating miR21 respectively (**Figure 2**). To corroborate the relationship with accelerated recovery of COX-1, both miR-21-5p (platelet: rho=-.216 p=.020, circulating: rho=.191, p=.066) and MRP4 (rho=.369 p=.064), were correlated with sTXB2 slope (**data not shown**).
Conclusions: MRP4 and both platelet and circulating miR-21, contribute to interindividual variability in aspirin response. Inhibition of platelet cyclooxygenase 1 activity by standard once-daily aspirin may be incomplete due to elevated MRP4 levels, responsible for aspirin extrusion. Antithrombotic drugs such as aspirin plus prasugrel are able to reduce the levels of circulating miRNAs in healthy subjects after one week of treatment, possibly through inhibition of their release during platelet activation. Consistently, in our cohort, patients with accelerated COX-1 recovery display lower platelet miR21 and higher circulating levels of the miR21. Altered levels of platelets and circulating miR-21 may be a potential biomarker to predict response to ASA treatment in high-risk cardiovascular patients.

Figure 1

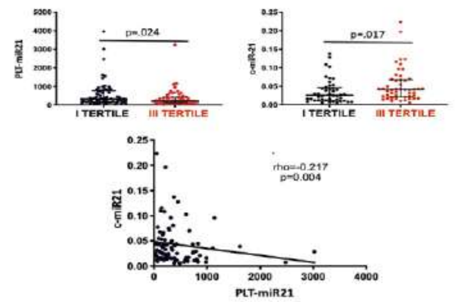
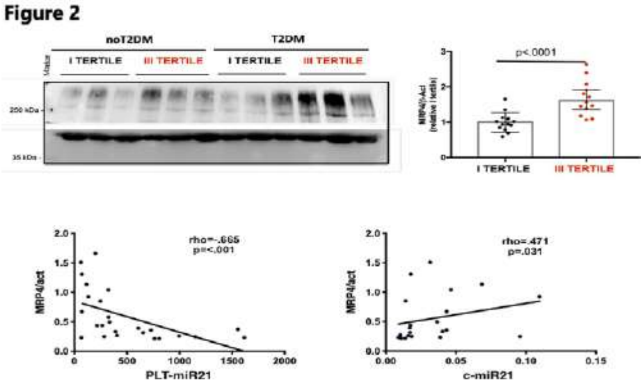


Figure 2

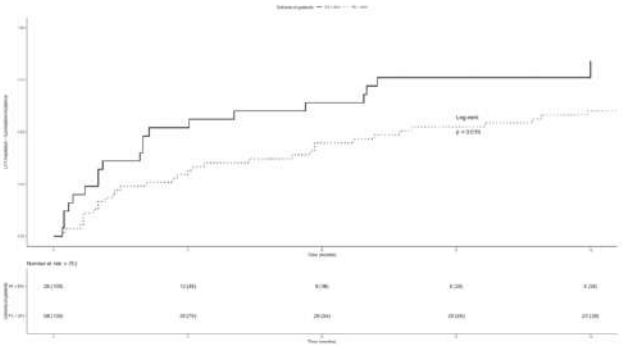


14. LONG-TERM VITAMIN K ANTAGONIST IN PATIENTS WITH LEFT VENTRICULAR THROMBOSIS

Valeriani E.[1], Pastori D.[2], Astorri G.[2], Menichelli D.[2], Ageno W.[3], Donadini M.P.[3], Santagata D.[3], Becattini C.[4], Satula K.[4], De Candia E.[5], D'Innocenzo L.[5], Tufano A.[6], Marcucci R.[7], Berteotti M. [7], Pignatelli P.[2]
[1]Department of General Surgery and Surgical Specialty Paride Stefanini, Sapienza University of Rome; Infectious Disease Department, Umberto I Hospital, Rome; [2]Department of Clinical Internal, Anesthesiological and Cardiovascular Sciences, Sapienza University of Rome; [3]Department of Medicine and Surgery, University of Insubria, Varese, Italy; [4]Internal Vascular and Emergency Medicine - Stroke Unit, University of Perugia, Perugia; [5]Department of Diagnostic Imaging, Radiotherapy, Oncology and Haematology, Hemorrhagic and Thrombotic Diseases Center, Fondazione Policlinico Universitario A. Gemelli IRCCS; [6]Department of Clinical Medicine and Surgery, Federico II University of Naples, Naples, Italy; [7]Department of Clinical and Experimental Medicine, University of Florence and Careggi Hospital, Florence, Italy

Background and aims: The optimal duration of anticoagulant therapy in patients with left ventricular thrombosis (LVT) is unknown. The aim of our study is to evaluate the effectiveness and safety of a vitamin K antagonist (VKA) therapy up to 12-months in patients with LVT.Methods: Consecutive patients were retrospectively included from 2011 through 2021 if they received anticoagulant therapy with VKA until LVT resolution or up to 12-months and data on relevant baseline characteristics and outcomes were available. Primary effectiveness outcome comprehended on-treatment LVT resolution while secondary effectiveness outcomes comprehended on-treatment acute ischemic stroke, acute myocardial infarction, and acute peripheral embolism during 12-months follow-up. Safety outcomes comprehended on-treatment major and clinically relevant non-major bleedings. The frequency of thrombus resolution was expressed as cumulative incidence with 95% confidence intervals (CIs). The frequency of other outcomes was descriptively reported. Cox proportional hazards model with stepwise (both backward and forward) elimination by the akaike's information criterion was used to identify potential predictors for thrombus resolution. RStudio (version 3.6.3, R Core Development Team, Vienna, Austria) was used for the analysis.Results: A total of 83 patients were included. Median age was 68 year and 78.3% of patients were male. A total of 28.4% of patients received VKA monotherapy and median time in therapeutic range was 59%. The 3- and 12-months cumulative incidences of LVT resolution were, respectively, 36% (95% CI, 26%-46%) and 66% (95% CI, 54%-75%). A left-ventricular ejection-fraction < 50% appeared to be associated with a lower hazard of LVT resolution (Hazard Ratio 0.51; 95% CI, 0.29 to 0.89; p = 0.02). During follow-up, one patient (1.2%) developed an on-treatment acute ischemic stroke, one (1.2%) an on-treatment acute myocardial infarction, and no patients an on-treatment acute peripheral embolism. Three patients (3.6%) developed an on-treatment major bleeding (one cerebral, one in the upper and one in the lower gastrointestinal tract) and 3 patient (3.6%) developed an on-treatment clinically relevant non-major bleeding (one in the genitourinary tract and two epistaxis). Two major and two clinically relevant non-major bleeding occurred beyond the first three months of therapy.Conclusion: A VKA treatment course up to 12-months was effective and safe in patients with LVT and was responsible for higher cumulative incidence of LVT resolution than a VKA therapy up to 3-months.

Figure. Cumulative incidences of left ventricular thrombus resolution sorted by baseline left ventricular ejection fraction (i.e., ≥ 50% vs < 50%)



15. EFFICACY AND SAFETY OF STATIN THERAPY IN SECONDARY PREVENTION OF ISCHEMIC STROKE IN PATIENTS WITH NVAF

Marvardi M.
Medicina Interna Vascolare - Stroke Unit, Perugia

Background: In patients with non-valvular atrial fibrillation (NVAF) on oral anticoagulant therapy (OAC) with DOACs, hyperlipidemia represents a significant risk factor for both ischemic and bleeding events, but the efficacy and safety of statins in secondary prevention in cardioembolic stroke patients remain unclear. We analyzed statins' role in the secondary prevention of cardioembolic acute ischemic stroke (AIS).
Methods: We combined the databases of RAF and RAF-NOACs studies, which were prospective observational studies carried out between January 2012 and March 2014 at 29 Stroke Units and between April 2014 and June 2016 at 35 Stroke Units, respectively, across Europe, the United States and Asia. We included patients with AIS and NVAF who were prospectively followed up for 90 days. The primary outcome was the composite of stroke, transient ischemic attack, symptomatic systemic embolism, symptomatic cerebral bleeding, and major extracranial bleeding within 90 days from acute stroke.
Results: A total of 1.742 patients were included (46% male), and 898 (52%) were on statins. Out of these, 1380 (79.2%) were on OAC therapy, 396 (22.7%) and 575 (33%) had type 2 diabetes mellitus and hyperlipidemia, respectively. The use of statin was statistically associated with age (OR 0.98, p 0.001), male sex (OR 1.35, p 0.013), OAC therapy (OR 2.53, p <0.0001), hyperlipidemia (OR 5.52, p <0.0001), paroxysmal AF (OR 1.40, p 0.003), leukoaraiosis (OR 1.39, p 0.004) and heart failure (OR 0.72, p 0.034). Diabetes mellitus type 2 (OR 1.59, p 0.014) and peripheral arterial disease (OR 1.97, p 0.009) were significantly associated with the combined outcome, whereas OAC therapy was protective against the combined outcome. (OR 0.53, p 0.001). Regarding statins, we observed a protective trend (OR 0.81) for the combined outcome and protective against bleeding (symptomatic intracranial plus major extracranial bleeding, OR 0.49, p 0.016).
Conclusions: Our data show that statins seem to protect against global bleeding events in cardioembolic stroke patients; this may be due to the pleiotropic effect of statins. More data are warranted to confirm these findings.

16. THROMBOTIC AND BLEEDING EVENTS IN VACCINE-INDUCED IMMUNE THROMBOTIC THROMBOCYTOPENIA (VITT) - A SYSTEMATIC REVIEW

Clerici B., Pontisso E. , Peroni B. , Aloise C., Birocchi S., Podda G.
Struttura Complessa di Medicina Generale II, ASST Santi Paolo e Carlo, Dipartimento di Scienze della Salute, Università degli Studi di Milano, Milan, Italy

Background and Aims: Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a highly prothrombotic reaction to COVID-19 adenoviral vector vaccines characterized by thrombocytopenia and thrombosis. Similarly to heparin-induced thrombocytopenia (HIT), antibodies against Platelet Factor 4 (PF4) are involved in its pathogenesis, albeit in the absence of previous heparin exposure. In HIT, the ratio of venous and arterial thrombotic events is 4.1, the bleeding rate in hospitalized patients is 5.7% and the mortality rate ranges from 6.3 to 15.9%. On the contrary, the ratio of venous and arterial thrombosis, the pattern of associated thrombotic events and bleeding rates in VITT are unknown. Thus, we aimed to describe thrombotic and bleeding events in patients with VITT.
Methods: We carried out a systematic review of the literature up to July 31st, 2022, including case reports and case series providing non-aggregate data of VITT patients. PubMed and Embase were searched by C.A. and B.P. with a pre-defined research string. Our research was restricted to articles written in English. VITT diagnosis was considered accurate if supported by the authors, vaccine type (adenoviral vector vaccines only) and timing (symptom onset 4-42 days after vaccination) were consistent, thrombocytopenia (defined as platelet count below 150x109/L) and thrombosis were present, and anti-PF4 antibodies were detected (either by enzyme-linked immunosorbent assays or platelet activation tests). We excluded studies or single patients of eligible studies if: (i) diagnosis of VITT was not supported by all the criteria listed above, (ii) patients' clinical features were absent, unclear or presented in aggregate, (iii) diagnostic test results were unclear, (iv) patients had already been described in other eligible studies, and (v) diagnostic tests were performed on biological specimens collected *post-mortem*. Eligibility assessment was performed

at the title and/or abstract level by two reviewers (C.A. and B.P.); disagreements were solved by consensus or by a third reviewer (S.B.). Relevant data from eligible studies regarding study site, patients' characteristics and diagnostic tests were collected by C.A., B.P., E.P. and B.C. Thrombotic events were categorized into two types (venous and arterial) and four categories: classic venous thrombo-embolism (VTE, including deep vein thrombosis – DVT, and pulmonary embolism – PE), venous thrombosis at unusual sites (including cerebral venous sinus thrombosis – CVST, splanchnic vein thrombosis – SVT, jugular vein thrombosis, and other sites of venous thrombosis), cardio/cerebral arterial thrombosis, and aortic/peripheral artery thrombosis. 95% Confidence Intervals (CI) were calculated using the exact binomial method.
Results: We retrieved 2157 studies through our literature search. Following the exclusion of 887 duplicates and of 1127 ineligible studies, we included 143 studies describing 366 VITT patients, 647 thrombotic events and 140 bleeding events. Among eligible patients, there was a slight prevalence of females (54%, 95% CI 48-59), and 80% of patients were under 60 years of age. With respect to vaccine type, 88% (95% CI 84-91) had received ChAdOx1 nCoV-19 and 12% (95% CI 9-16) Ad26.COV.2. Of 647 thrombotic events (see **Table**), most events were venous (521/647, 81%, 95% CI 77-84). Classic VTE events accounted for 28% (95% CI 25-32) of all thrombotic events, with 59 DVTs and 122 PEs. On the other hand, 53% (95% CI 49-56) of all thrombotic events were venous thromboses at unusual sites. Of these, the most common sites were CVST (30% of all thrombotic events, 95% CI 27-34) and SVT (14%, 95% CI 12-17). PEs, SVTs and Central Nervous System (CNS) arterial thromboses accounted for 19% (95% CI, 16-22), 14% (95% CI 12-17), and 7% (95% CI 5-9) of all thrombotic events. The ratio of arterial and venous events was 4.1 (521/126). Most thrombotic events occurred in association with others, with the exception of CVST [isolated in 49% (95% CI 42-56) of cases]. The frequency of association of arterial thrombotic events with venous thrombotic events ranged from 14% (95% CI 3-36) for aortic thrombosis to 53% (95% CI 27-79) for myocardial infarction, whereas venous thrombotic events were less frequently associated with arterial thrombotic events (frequency ranging from 3 to 8%). Bleeding occurred in 36% (95% CI 31-41) of patients; 68% (95% CI 59-75) of bleeding events were intracranial hemorrhages (ICHs), in association with CVST in 83% of cases. Among bleeding events, ICHs were followed at a distance by skin bleeding (11% of all bleeding events, 95% CI 6-17) and adrenal gland hemorrhage (9%, 95% CI 5-14). Overall mortality was 24% (95% CI, 19-29), but increased up to 77% (95% CI 58-90) in patients with isolated CVST complicated by ICH.
Conclusions. In VITT, the ratio of venous and arterial thrombosis is 4.1, as in HIT, but with a higher prevalence of venous thromboses at unusual sites, in particular CVST. It is likely that the high prevalence of CVST and ICH in VITT drives bleeding and mortality rates, which are both higher than in HIT.

Table. Thrombotic events in eligible patients with Vaccine-induced Immune Thrombotic Thrombocytopenia

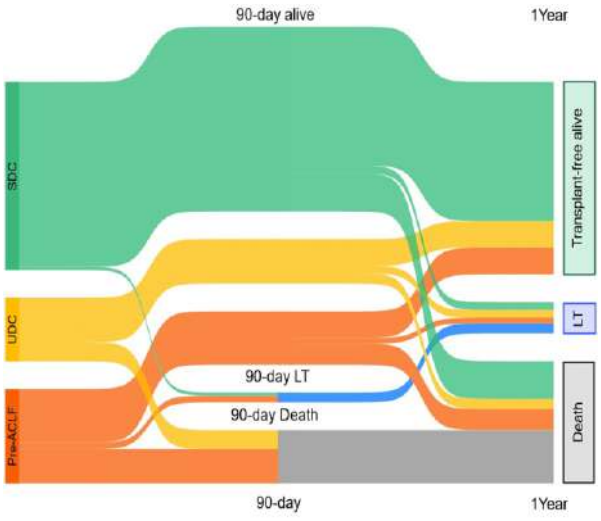
Thrombosis according to site	Total number of events, N=647	95% CI*
Venous thrombosis, n/N (%)		
DVT	59/647 (9)	7-12
PE	122/647 (19)	16-22
Total Classic VTE events	181/647 (28)	25-32
CSVT	196/647 (30)	27-34
SVT	93/647 (14)	12-17
JVT	33/647 (5)	4-7
Others	18/647 (3)	2-4
Total venous thrombosis events at unusual sites	340/647 (53)	49-56
Total venous thrombotic events	521/647 (81)	77-84
Arterial thrombosis, n/N (%)		
CNS	46/647 (7)	5-9
AMI	15/647 (2)	1-4
Peripheral artery	22/647 (3)	2-5
Aorta	21/647 (3)	2-5
Others	22/647 (3)	2-5
Total arterial events	126/647 (19)	16-23

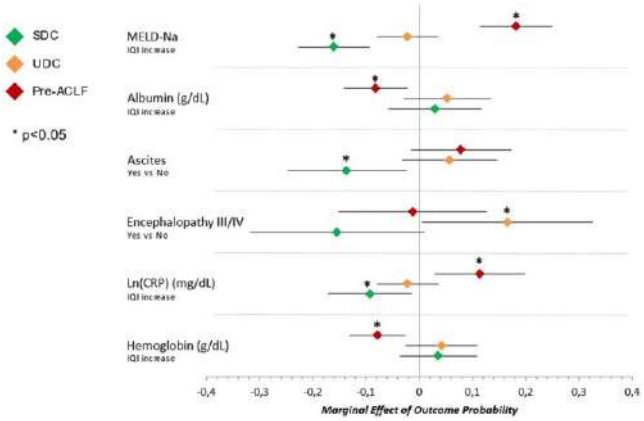
Abbreviations: CI, confidence interval; DVT, deep vein thrombosis (upper and lower extremities); PE, pulmonary embolism; VTE, venous thrombo-embolism; CVST, cerebral venous sinus thrombosis; SVT, splanchnic vein thrombosis; JVT, jugular vein thrombosis; CNS, central nervous system; AMI, acute myocardial infarction.
*95% Confidence Intervals were calculated using the exact binomial method.

17. CLINICAL TRAJECTORIES OF ACUTELY DECOMPENSATED PATIENTS WITH CIRRHOSIS

Pompili E.[1], Baldassarre M.[1], Bedogni G.[1], Zaccherini G.[1], Iannone G.[1], De Venuto C.[1], Pratelli D.[1], Palmese F.[2], Domenicali M.[2], Caraceni P.[3]
[1]Dipartimento di Scienze Mediche e Chirurgiche, Università di Bologna; [2]U.O. Medicina Interna 1 ad indirizzo Invecchiamento e Fragilità, AUSL Romagna, Ravenna; [3]U.O. Semeiotica Medica, IRCCS Azienda Ospedaliero-Universitaria di Bologna

Background and Aims: Acute decompensation (AD) is a major cause of hospitalization and mortality in patients with liver cirrhosis and is defined by the development of at least one of the main complications of the disease (hepatic encephalopathy (HE), ascites, gastrointestinal bleeding or bacterial infections). Recently, the multicentric European PREDICT study showed that patients presenting AD without ACLF at admission can have 3 possible clinical trajectories with different clinical trajectories and mortality rates at 3 and 12 months: pre-ACLF, Unstable Decompensated Cirrhosis (UDC) and Stable Decompensated Cirrhosis (SDC). Pre-ACLF is defined as patients who develop ACLF within 90 days; UDC is defined as patients who are readmitted within 90 days or die without prior ACLF; SDC is defined as patients who are alive without ACLF or readmission within 90 days. Up to now, external validation of the clinical trajectories of these three cohorts is still lacking. This study aimed to i) validate the existence of three distinct trajectories in AD patients and compare their 1-year mortality rate in a real-life cohort; and ii) identify potential predictors of the occurrence of each clinical phenotype.
Method: We performed a secondary analysis in a cohort of patients with prospectively collected data admitted to hospital for AD. Laboratory and clinical data at admission, development of ACLF and readmission up to 3 months and 1-year mortality were recorded. Patients were classified as pre-ACLF, UDC or SDC according to the PREDICT criteria. A multinomial multivariable model (MNM) and binary logistic regressions were used to evaluate the association between baseline features and the occurrence of pre-ACLF, SDC or UDC. Results are shown as marginal estimates of the probability of pre-ACLF, SDC or UDC calculated though the MNM.
Results: Of the 311 patients included, 169 (55%) met the criteria for SDC, 57 (18%) for UDC, and 85 (27%) for pre-ACLF. The 1-year mortality was significantly different between the three groups: pre-ACLF 65%, UDC 46% and SDC 21% ($p < 0.001$). Sankey Plot (figure 1) shows clinical trajectories of SDC, UDC and pre-ACLF at 90 days and 1 year. At baseline SDC and UDC patients were similar in clinical and laboratory features (except for HE) and prognostic score. Contrariwise pre-ACLF groups presents significant differences in presence of ascites, MELD score, CLIF-C AD score, markers of systemic inflammation. Marginal changes of the probability of pre-ACLF, SDC and UDC attributable to the predictors are reported in Figure 2 for 1 IQI interval increase for continuous variables or for presence vs absence for categorial variables. Among clinical parameters, the presence of hepatic encephalopathy was associated to UDC ($p = 0.043$), while the absence of ascites to SDC ($p = 0.017$). Among laboratory parameters, the increase in MELD-Na ($p = 0.000$) and C-Reactive Protein ($p = 0.009$) and the decrease in hemoglobin ($p = 0.004$) and albumin ($p = 0.008$) levels were associated to pre-ACLF. Biomarkers of systemic inflammation (IL-6) and oxidative stress (Human non-mercaptoalbumin-1) were also associated to pre-ACLF phenotype (respectively $p=0.043$ and $p=0.003$).
Conclusion: The present study confirms that patients with AD have 3 different clinical trajectories associated to different mortality rates. Besides severity of cirrhosis, the association with CRP, IL-6 and HNA-1 supports the predominant role of systemic inflammation and oxidative stress in ACLF development. Finally, although UDC present basal features similar to SDC, they had a relevant 1-year mortality, and HE was associated to these trajectories. UDC trajectory highlighting the need of a better management of this complication after discharge.





18. DEVELOPMENT AND VALIDATION OF A SCORE FOR THE PREDICTION OF BIOCHEMICAL RESPONSE IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS TREATED WITH OBETICHOLIC ACID.

De Vincentis' A.[1], Ampuero' J.[2], Terracciani' F.[1], D'Amato D.[3], Invernizzi P.[4], Morgando A.[3], Vanni E.[3], Viganò M.[5], Alvaro D.[1], Venere R.[1], Lleo A.[5], Colapietro F.[5], Degasperi E.[5], Viganò R.[5], Giannini E.G. [6], Labanca S.[6], Feletti V.[7], Mussetto A.[7], Cozzolongo R.[8], Losito F.[8], Pompili M.[1], Ponziani F.R.[1], Niro G.A.[9], Cotugno R.[9], Pozzoni P.[10], Chessa L.[11], Cuccorese G.[12], Pace Palitti V.[13], Gómez-Dominguez E.[14], Montero J.L.[15], Molina E.[16], Garcia-Buey L.[14], Casado M.[17], Berenguer M.[18], Conde I.[18], Simon M.A.[19], Fuentes J.[19], Costa-Moreira P.[20], Macedo G.[20], Jorquera F.[21], Morillas R.M.[22], Presa J.[23], Sousa J.M.[24], Gomes D.[25], Santos L.[25], Olveira A.[14], Hernandez-Guerra M.[26], Aburruza L.[27], Santos A.[25], Carvalho A.[25], Uriz J.[28], Gutierrez M.L.[14], Perez E.[14], Russello M.[29], Cannavò M.[29], Frazzetto E.[29], Bertino G.[29], Marzioni M.[30], Terreni N.[31], Zolfino T.[11], Saitta C.[32], Pellicelli A.[1], Coco B.[33], Brunetto M.[33], Cazzagon N.[34], Floreani A.[34], Muratori L.[35], Floriano[36], Distefano M.[37], Scifo G.[37], Baiocchi L.[1], Grassi G.[1], Sacco R.[38], Izzi A.[39], Crocè S.L.[40], Fiorini C.[41], Marra F.[41], Simone L.[42], Morelli O.[43], Abenavoli L.[44], Pizzolante F.[1], De Matthaeis N.[1], Gimignani G.[1], Boano V.[45], Manfredi G.F.[46], Marignani M.[1], Fanella S.[1], Giacchetto M.[1], Castellaneta A.[8], Poggi G.[46], Buzzanca V.[43], Scivetti P.[47], Tortora A.[1], Casella S.[48], Bellia V.[31], Omazzi B.F.[49], Alagna G.[50], Ricci C.[35], Poisa P.[51], Rigamonti C.[52], Calvaruso[53], Fernandez-Rodriguez C.^[14], Vespasiani Gentilucci U.^[1], Carbone M.^[4]

[1]Roma; [2]Siviglia; [3]Torino; [4]Monza; [5]Milano; [6]Genova; [7]Ravenna; [8]Bari; [9]S Giovanni Rotondo; [10]Lecco; [11]Cagliari; [12]Barletta; [13]Pescara; [14]Madrid; [15]Coruna; [16]Cordoba; [17]Almeria; [18]Valencia; [19]Zaragoza; [20]Porto; [21]Leon; [22]Badalona; [23]Douro; [24]Seville; [25]Coimbra; [26]Tenerife; [27]Donosti; [28]Pamplona; [29]Catania; [30]Ancona; [31]Valduce; [32]Messina; [33]Pisa; [34]Padova; [35]Bologna; [36]Rosina; [37]Siracusa; [38]Foggia; [39]Napoli; [40]Trieste; [41]Firenze; [42]Ferrara; [43]Perugia; [44]Catanzaro; [45]Asti; [46]Pavia; [47]Biella; [48]Gardone; [49]Bo; [50]Sassari; [51]Brescia; [52]Vercelli; [53]Palermo

Background: Obeticholic acid (OCA) is the only approved second-line treatment for patients with primary biliary cholangitis (PBC), and has been shown to provide an effective biochemical response in around ~40% of patients, according to POISE criteria. The aim of the present study was to derive the OCA response score (ORS) for predicting response to OCA therapy at 12 and 24 months.
Methods: The Italian RECAPITULATE (N 441, women 88%, mean age 57.8, cirrhosis 34%; Italy) and the IBERIAN (N 244, women 93%, mean age 56.6, cirrhosis 23%; Spain-Portugal) OCA real-world cohorts were used to derive and validate a scoring system including only widely available pre-treatment variables (ORS), or also the change of alkaline phosphatase(ALP)/upper limit of normal(ULN) and total bilirubin after 6 months' therapy (ORS+). Multivariable Cox's regressions with backward selection method were applied to obtain parsimonious predictive models for the prediction of biochemical response to OCA according to either POISE (ALP/ULN<1.67 with a reduction of at least 15%, and normal bilirubin), or ALP/ULN<1.67, or NORMAL RANGE criteria (NR, ALP/ULN<1 and alanine aminotransferase (ALT) /ULN<1 and normal bilirubin).
Results: In the Italian RECAPITULATE, we derived the ORS including the following variables: age at OCA start, pruritus, cirrhosis, ALP/ULN, ALT/ULN, GGT/ULN and total bilirubin (for predicting POISE response); pruritus, cirrhosis, ALP/ULN, GGT/ULN and total bilirubin (for ALP/ULN<1.67 response); and pruritus, ALP/ULN and total bilirubin (for NR response). The ORS+ was also derived by including the relative changes of ALP/ULN and of total bilirubin at 6 months. Good discriminative properties for both ORS and ORS+ in the derivation cohort (c-statistics: POISE criteria= 0.77 and 0.84; ALP/ULN<1.67= 0.79 and 0.88; NR criteria=0.73 and 0.82, respectively) were also confirmed in the IBERIAN validation cohort (c-statistics: POISE criteria= 0.70 and 0.81; ALP/ULN<1.67= 0.72 and 0.82; NR criteria=0.71 and 0.86, respectively). Bootstrap validation evidenced modest overfitting (calibration slopes>0.90). Mean absolute errors <0.08 were observed in the IBERIAN cohort, indicating adequate models' calibration.
Conclusions: We derived and externally validated the ORS, that accurately predicts OCA response at 12 and 24 months. This could enhance allocation of second-line therapies in PBC with a personalised medicine approach.
' co-first authors; ^co-last authors

19. COMPARISON OF COAGULATION PARAMETERS AS PROGNOSTIC MARKERS OF DECOMPENSATION AND LIVER-RELATED DEATH IN ADVANCED CHRONIC LIVER DISEASE

Pallozzi M.[1], Giuli L.[1], Santopaolo F.[1], Gasbarrini A.[2], De Cristofaro R.[3], Pompili M.[2], Ponziani F.R.[2]

[1]Internal Medicine and Gastroenterology-Hepatology Unit, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy; [2]Internal Medicine and Gastroenterology-Hepatology Unit, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy, Translational Medicine and Surgery Department, Catholic University, Rome, Italy; [3]Translational Medicine and Surgery Department, Catholic University, Rome, Italy, Hemorrhagic and Thrombotic Diseases Service, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

Background and aims: Liver cirrhosis has long been considered an acquired bleeding disorder but recent studies have demonstrated that the coagulation balance is associated with disease progression. In patients with advanced chronic liver disease (ACLD) plasma levels of many procoagulant factors (factor VIII [FVIII], von Willebrand Factor [VWF]) are reduced but also the levels of anticoagulant factors (a disintegrin and metalloprotease with thrombospondin 1 repeats number 13 [ADAMTS-13], protein C [PC]) are markedly decreased. A recent study demonstrated that FVIII/PC ratio correlates with the severity of liver disease and with worse liver outcomes [1]. We recently reported that ADAMTS-13/VWF ratio is useful to predict the development of portal vein thrombosis (PVT), but little is known about its role as marker of decompensated ACLD. Based on these previous results, we investigated the prognostic role of ADAMTS13/VWF ratio on the development of dACLD and compared it with FVIII/PC ratio [2]
Materials and Methods: Consecutive outpatients with ACLD underwent clinical evaluation and were subjected to blood sampling for the assessment of laboratory tests and coagulation parameters. Data from ultrasound examination and upper endoscopy were also recorded. We compared the FVIII/PC ratio and ADAMTS13/VWF ratio between patients with compensated and decompensated ACLD and their correlation with the other variables. We finally analyzed survival probability of remaining free of decompensation/liver-related death, stratifying patients according to FVIII/PC ratio or ADAMTS-13/VWF ratio by using the median value of each index in decompensated patients as cut-off.
Results:We included 86 patients with ACLD (median age 66 (59-72.70) years; 65.47% male; etiology viral/nonviral 50%/50%; Child Pugh A/B/C 80.2%/15.1%/4.7% and median model for end-stage liver disease (MELD) 8 [7-9.20]), 20 (23.25%) developed dACLD after a median follow-up of 48.8 (48-57.30) months. Those patients showed a significantly higher FVIII/PC ratio and a lower ADAMTS-13/VWF ratio compared to their counterparts maintaining cACLD (FVIII/PC 2.62 [1.87-3.81] vs 1.44 [1.13-1.77], p< 0.0001 Figure 1A); ADAMTS-13/VWF 0.26 [0.22-0.41] vs 0.52 [0.16-0.62], p< 0.0001 Figure 1B). Both the indices correlated with liver disease severity according to Child Pugh score and MELD score (Figure 1C). FVIII/PC ratio showed the strongest correlation with clinical and coagulation parameters. Both FVIII/PC ratio or ADAMTS13/VWF ratio had a good prognostic ability for ACLD decompensation/liver-related death (p < 0.0001, Figure 1D-E); however, when ADAMTS-13/VWF ratio was used the survival curves crossed after 40 months, underlining a limitation in the identification of patients with early events. Finally, the four patients who developed PVT during follow-up showed a lower ADAMTS-13/VWF ratio (0.23 [0.22-0.25] vs 0.58 [0.45- 0.73], p = 0.004) or a higher FVIII/PC ratio (2.62 [2.45-2.82] vs 1.57 [1.2-2.09], p = 0.02) compared to their counterparts who did not experience PVT.

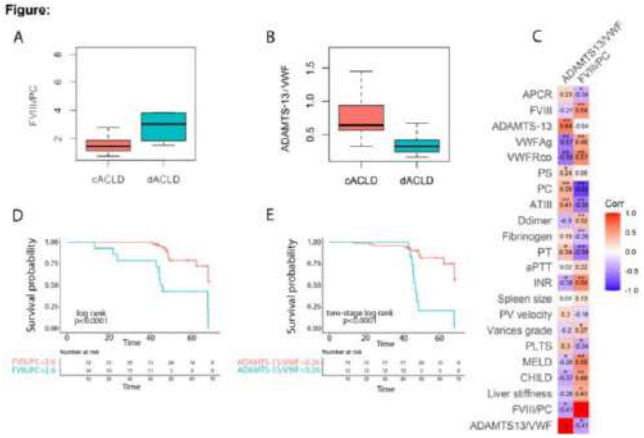
Conclusion: Coagulation parameters, historically used only for assessing bleeding risk in patients with ACLD, are instead harbingers of important prognostic information. Indeed, ADAMTS13/VWF ratio and FVIII/PC ratio correlate with liver disease severity and can predict liver-related death or decompensation in patients with ACLD.

References

[1]Scheiner B. et al. "Factor VIII/protein C ratio independently predicts liver-related events but does not indicate a hypercoagulable state in ACLD." Journal of hepatology vol. 76,5 (2022): 1090-1099

[2]Sacco M. et al. "ADAMTS-13/von Willebrand factor ratio: A prognostic biomarker for portal vein thrombosis in compensated cirrhosis. A prospective observational study." Digestive and liver disease vol. 54,12 (2022): 1672-1680.

Figure:



(A,B) FVIII/PC ratio and ADAMTS-13/VWF ratio in patients with cirrhosis, with new or further episodes of decompensation during the study. (C) Spearman's correlations between FVIII/PC ratio and ADAMTS-13/VWF ratio with coagulation, liver disease severity and portal hypertension parameters. [1]p <0.05; [2]p <0.001. (D,E) Patients' survival according to FVIII/PC ratio and ADAMTS-13/VWF ratio. In the case of ADAMTS-13/ VWF ratio, a two-stage log-rank test was used due to non-proportional hazards.

ADAMTS-13, a disintegrin and metalloprotease with thrombospondin 1 repeats number 13; APCR, activated protein C resistance; aPTT, partial thromboplastin time; ATIII, antithrombin III; FVIII, factor VIII; INR, international normalized ratio; MELD, model for end-stage liver disease; PC, protein C; PLT, platelet count; PS, protein S; PT, prothrombin time; PV, portal vein; VWF, von Willebrand factor; VWFAg, von Willebrand factor antigen; VWFRco, von Willebrand factor ristocetin cofactor.

20. PERFORMANCE OF NON-INVASIVE FIBROSIS TESTS FOR LONG-TERM LIVER, HEART AND KIDNEY OUTCOMES IN EUROPEANS WITH METABOLIC RISK FACTORS FROM THE UK BIOBANK

Tavaglione F.[1], De Vincentis A.[2], Jamialahmadi O.[3], Antonelli Incalzi R.[4], Picardi A.[1], Romeo S.[5], Vespasiani-Gentilucci U.[1]

[1]Clinical Medicine and Hepatology Unit, Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy; Department of Medicine and Surgery, Università Campus Bio-Medico di Roma, Rome, Italy; [2]Internal Medicine Unit, Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy; Department of Medicine and Surgery, Università Campus Bio-Medico di Roma, Rome, Italy; [3]Department of Molecular and Clinical Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [4]Department of Medicine and Surgery, Università Campus Bio-Medico di Roma, Rome, Italy; Internal Medicine Unit, Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy; [5]Department of Molecular and Clinical Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; 5Cardiology Department, Sahlgrenska University Hospital, Gothenburg, Sweden; 6 Clinical Nutrition Unit, Department of Medical and Surgical Sciences, University Magna Graecia, Catanzaro, Italy

Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease in Western countries. NAFLD is associated with both liver-related and extrahepatic complications, including cardiovascular disease (CVD) and chronic kidney disease (CKD). Non-invasive tests (NITs) for advanced fibrosis are increasingly used to identify individuals with NAFLD who are at risk for liver-related complications. Their performance for extrahepatic complications has been recently tested in tertiary care settings and found to be limited. Herein, we investigated the performance of NITs for predicting long-term liver, heart and kidney outcomes in individuals with dysmetabolism from the large prospective UK Biobank.

Method: To assess the performance of NITs for liver, heart and kidney outcomes, we selected 1) 305,745 Europeans with overweight/obesity and/or type 2 diabetes, without any liver disease at baseline, 2) 194,236 Europeans with overweight/obesity and/or type 2 diabetes, without chronic viral hepatitis and CVD at baseline, and 3) 203,522 Europeans with overweight/obesity and/or type 2 diabetes, without chronic viral hepatitis and CKD at baseline, respectively. Then, we estimated the performance of NITs for predicting incident severe liver disease (SLD: cirrhosis, decompensated liver disease, hepatocellular carcinoma, liver transplantation), incident CVD (angina, myocardial infarction, stroke, transient ischemic attack) or incident CKD (eGFR<60 ml/min/1.73m2, chronic renal failure, kidney transplant status) by Cox proportional hazards models. Follow-up length was calculated from the date of baseline assessment visit up to the first date of target outcome diagnosis, the date of death, or the date of end of follow-up at the assessment center (July 1st, 2022), whichever occurred first. The following NITs were tested: fibrosis-4 index (FIB-4), NAFLD fibrosis score (NFS), fibrotic NASH index (FNI), AST to platelet ratio index (APRI), BARD.

Results: After a median follow-up of 9 years, FNI was the best score for predicting liver outcomes (area under the curve [AUC] 0.77, $p < 0.05$ vs all the other NITs). After a median follow-up of 13 years, NFS was the best score for predicting heart outcomes (AUC 0.60, $p < 0.05$ vs all the other NITs). After a median follow-up of 13 years, NFS was the best score for predicting kidney outcomes (AUC 0.73, $p < 0.05$ vs all the other NITs). All NITs showed a worse and limited performance for heart and kidney outcomes compared to liver outcomes, except for a slightly better performance of NFS for kidney outcomes compared to liver outcomes (Table 1).

Conclusion: NITs showed a satisfactory performance for predicting liver outcomes, but a rather modest performance for predicting heart and kidney outcomes in individuals with dysmetabolism from the general population.

Table 1: Performance of NITs for incident liver, heart and kidney outcomes in the UK Biobank.

	SLD (N=305,745)		CVD (N=194,236)		CKD (N=203,522)	
Score	AUC	P value	AUC	P value	AUC	P value
FIB4	0.75 (0.73-0.77)	0.03	0.59 (0.59-0.60)	< 0.001	0.64 (0.62-0.66)	< 0.001
NFS	0.72 (0.70-0.74)	< 0.001	0.60 (0.60-0.61)	reference	0.73 (0.71-0.75)	reference
FNI	0.77 (0.75-0.79)	reference	0.59 (0.58-0.60)	0.001	0.62 (0.60-0.64)	< 0.001
APRI	0.75 (0.73-0.77)	0.01	0.58 (0.53-0.54)	< 0.001	0.52 (0.50-0.54)	< 0.001
BARD	0.62 (0.61-0.64)	< 0.001	0.55 (0.54-0.55)	< 0.001	0.65 (0.62-0.67)	< 0.001

Abbreviations: APRI, AST to platelet ratio index; AUC, area under the curve; CVD, cardiovascular disease; CKD, chronic kidney disease; FNI, fibrotic NASH index; FIB-4, fibrosis-4 index; NFS, NAFLD fibrosis score; SLD, severe liver disease.

21. IMPACT OF CLONAL HEMATOPOIESIS OF INDETERMINATE POTENTIAL ON HEPATOCELLULAR CARCINOMA IN INDIVIDUALS WITH FATTY LIVER DISEASE

Pelusi S.[1], Marchetti A.[2], Marella A.[3], Malvestiti F.[1], Ricchiuti A.[4], Ronzoni A.[1], Bianco C.[1], Cherubini A.[1], Margarita S.[1], Bugianesi E.[5], Miele L.[6], Vespasiani Gentilucci U.[7], Petta S.[8], Fracanzani A.L.[9], Russo F.P.[10], Federico A.[11], Soardo G.[12], Borroni V.[13], D'Ambrosio R.[14], Vaira V.[15], Lionetti M.[2], Prati D.[1], Bolli N.[2], Valenti L.[1]

[1]Department of Transfusion Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [2]Hematology Division, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [3]Hematology Division, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Mialn, Italy; [4]Università degli Studi di Milano, Milan, Italy; [5]Department of Medical Sciences, University of Torino, Torino, Italy; [6]Department of Medical and Surgical Sciences, Policlinico Universitario A. Gemelli IRCCS Rome, Università Cattolica del S. Cuore, Rome, Italy; [7]Clinical Medicine and Hepatology Unit, Campus Bio-Medico University, Rome, Italy; [8]Section of Gastroenterology and Hepatology, University of Palermo, Italy; [9]Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy; [10]Department of Surgery, Oncology and Gastroenterology, University of Padua, Padova, Italy; [11]Department of Precision Medicine, Hepato-Gastroenterology Unit, University of Campania "Luigi Vanvitelli", Naples, Italy; [12]University of Udine, Department of Medicine; Italian Liver Foundation, AREA Science Park - Basovizza Campus- Trieste; [13]Department of Medical Division,

Ospedale L. Sacco, ASST Fatebenefratelli Sacco, Milan, Italy; [14]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Gastroenterology and Hepatology, Milan, Italy; [15]Department of Medicine, Surgery and Dentistry, Division of Pathology, University of Milan, Milan, Italy

Fatty liver disease (FLD) is now the leading cause of liver disease worldwide and encompasses a range of disease severity, from simple steatosis to steatohepatitis, which can lead to liver fibrosis and HCC. Recently, clonal hematopoiesis of indeterminate potential (CHIP) has been linked to increased susceptibility to FLD and severe liver disease. CHIP is the presence of somatic mutations in hematopoietic stem cells with a variant allele frequency (VAF) ≥2% and located in genes involved in hematologic cancers. CHIP prevalence increases with age and is associated with the predisposition to hematologic cancers, cardiovascular and other ageing-related disorders.
The association of CHIP with liver inflammation and fibrosis seems to depend on the presence of acquired CHIP-related gene mutations (especially in *TET2*) in myeloid cells homing to the liver. However, it is not yet known whether CHIP can facilitate the progression of liver disease to HCC independently of liver fibrosis.
The aim of this study was therefore to examine whether CHIP is associated with HCC independently of cirrhosis and the major clinical determinants in a case-control multi-center cohort of patients with NAFLD-HCC and controls (EPIDEMIC-NAFLD cohort).
European patients with HCC related to FLD (n=179) and two groups of controls: patients with advanced fibrosis without HCC (n=263), and individuals with simple FLD without advanced FLD (n=38) and locally and ethnically matched healthy individuals (n=50) were enrolled. Age, sex, presence of type 2 diabetes (T2D), advanced liver fibrosis, AST and ALT levels at the time of study enrolment were available in all patients. DNA was extracted from peripheral blood and sequencing was subsequently by the HiSeq 4000/NextSeq2000 platforms (Illumina). Somatic mutations were identified accepting a minimum variant coverage of 20, a minimum alternative allele count of 3 and a variant allele frequency (VAF) between 0.02 and 0.46. Variants with a population mean allelic frequency higher than 1 in a 1000 were treated as polymorphisms. Variants were then curated to include only variants known to be somatic and associated to either malignancy or CHIP with the use of a semi-automatic pipeline. CHIP-defining genetic lesions were identified in 92 out of 530 participants (17.3%).
CHIP was found in 43 (24.0%) of patients with HCC, 41 (15.6%) of those with advanced fibrosis without HCC, and in 8 (9.1%) of those without advanced fibrosis (p=0.006).
As expected, the prevalence of CHIP was age-dependent and increased consistently across diagnosis groups, with the spike in CHIP incidence being observed after the age of 65. Expectedly, the most frequently mutated gene was *DNMT3A*, followed by *TET2, TP53* and *ASXL1*. Presence of CHIP with VAF ≥10% was associated with higher AST levels corrected for cirrhosis (p=0.02). No significant association was observed with ALT, consistent with a greater contribution of CHIP to inflammation and tissue fibrosis rather than steatosis. A relevant proportion of patients with HCC carried CHIP. The association between CHIP and HCC was independently of sex, diabetes, polygenic risk score of FLD and cirrhosis (OR 1.81, 95%CI 1.10-2.98; p=0.018) but not significant when correcting for age (p>0.05). A sub-analysis of the different CHIP lesions revealed an association between *TET2* and *TP53* mutations with HCC. *TET2* mutations were enriched in the HCC cohort with respect to patients affected by advanced fibrosis without HCC. The association between HCC and *TET2* remained statistically significant at multivariate regression when correcting for known contributing variables such as age, gender, diabetes, polygenic risk of FLD and cirrhosis (OR 4.35, 95%CI 1.18-16.01; p=0.029). In conclusion, our work suggests a possible role of CHIP in the progression of FLD to HCC and *TET2* mutations showed the strongest enrichment in HCC subjects. Further studies are needed to better clarify the mechanisms by which the different CHIP lesions contribute to hepatic carcinogenesis modulating inflammation and immune phenotypes.

22. CHANGES IN MEAN ARTERIAL PRESSURE ARE INADEQUATE TO GUIDE TREATMENT WITH TERLIPRESSIN AND ALBUMIN IN PATIENTS WITH HEPATORENAL SYNDROME – ACUTE KIDNEY INJURY

Calvino V.[1], Barone A.[1], Tonon M.[1], Gambino C. G.[1], Incicco S.[1], Gagliardi R.[2], Zeni N.[1], Angeli P.[1], Piano S. S.[1]
[1]Dipartimento di Medicina - DIMED - UOC Clinica Medica 5 - Medicina Interna ad Indirizzo Epatologico ; [2]Dipartimento di Medicina - DIMED - UOC Clinica Medica 5 - Medicina Interna ad Indirizzo Epatologico

Background: Hepatorenal syndrome acute kidney injury (HRS-AKI) is a life-threatening complication of cirrhosis characterized by a rapidly progressive but potentially reversible form of acute kidney injury. The treatment with terlipressin and albumin is recommended for the management of the HRS-AKI and continuous infusion (CI) is the most feasible administration route. Treatment is titrated according to changes in serum creatinine on day 3 of treatment. Some studies showed that an increase in mean arterial pressure (MAP) is associated with resolution of HRS-AKI in patients treated with terlipressin and albumin as intravenous boluses, leading some experts to suggest titration of terlipressin and albumin according to MAP changes. However, the optimal MAP target and factors associated with response to the therapy remain unclear.
Aim: The aim of the study was to evaluate the association between the increase in MAP on day 3 and response to treatment with terlipressin and albumin as CI in patients with HRS-AKI. Other outcomes of interests were side effects and 90-day survival.
Methods: We conducted a retrospective study in patients with cirrhosis and HRS-AKI treated with terlipressin and albumin as CI. Clinical and biochemical data were collected at day 0 (D0), day 3 (D3), and at the end of treatment (final). We followed patients until death, liver transplantation or the end of follow-up (90 days). The primary endpoint was response to treatment (defined as serum creatinine < 133 umol/l at the end of treatment). Secondary endpoints were early response (defined as reduction of serum creatinine > 25% vs D0 on D3) and survival at day 90 and adverse events. Death and liver transplantation were considered competing events for the resolution of HRS-AKI.
Results: We enrolled 108 patients (mean age=59 ± 9 years; male=70%; MELD=29 ±7) . The most prevalent cirrhosis etiology was alcohol (58%) followed by HCV (27%) and HBV (11%). A precipitating event of HRS-AKI was found in 57 patients (53%), the main one being bacterial infections (49%). The median creatinine at the start of treatment was 242 µmol/L (IQR 203.5 – 306.8 µmol/L), the median MAP 76.3 mmHg (IQR 69.6 – 86.7 mmHg). On D3 most of patients had an increase in MAP (delta MAP = 5.6±11.5 mmHg; p<0.001). Response to treatment was found in 56 patients (52%). No difference was found in baseline MAP between responders and nonresponders (76 vs 76 mmHg; p=0.668). Delta MAP on D3 was not significantly different between responders and non-responders (7.8 vs 4.4 mmHg; p=0.218). Only mild negative correlation was found between delta MAP on D3 and delta serum creatinine on D3 (r=-0.188; p=0.051). Delta MAP on D3 was not significantly different between patients classified as early responders or early non-responders (5.3 vs 6.0 mmHg; p=0.751). Even after stratifying patients according to delta MAP changes on D3 (<0 mmHg; >0-10 mmHg; >10 mmHg) no difference was found in rate of early response and resolution of HRS-AKI. As expected, early responders were more likely to achieve a resolution of HRS-AKI (73 vs 33%; p<0.001). In the univariable analysis responders had lower baseline serum creatinine (2.91 vs 2.51 µmol/L, p=0.016), higher rate of precipitating factor of HRS-AKI (61 vs 38%; p=0.007). In multivariable competing risk analysis adjusted for age, precipitating events, baseline serum creatinine and ACLF grade, delta MAP on D3 showed no significant association with response to treatment (sHR= 1.00; p= 0.870). Lower baseline serum creatinine (sHR= 0.75 ; p= 0.012) and precipitating factor of HRS-AKI (sHR= 1.89; p=0.014) were independent predictors of response to treatment. Survival at 90 days of follow-up was significantly higher in responders than in non-responders to treatment (sHR 0.45, IC 0.26-0.78, p-value 0.004).
Conclusion: We found no significant association between the increase in MAP from D0 to D3 and response to treatment with terlipressin and albumin in patients with cirrhosis and HRS-AKI. Considering the potential risk of serious adverse events with terlipressin, the titration of terlipressin should not be based on MAP changes during treatment, but only on changes of serum creatinine.

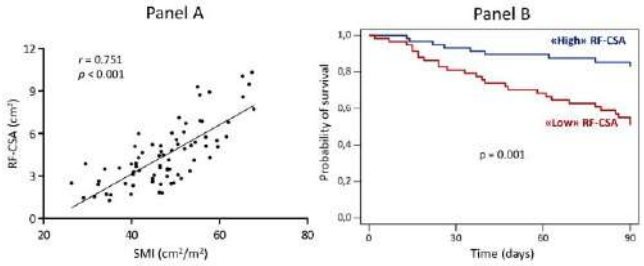
Multivariate analysis: predictors of renal recovery			
	HR	IC 95%	p-value
Age	0.98	0.96 – 1.01	0.081
Precipitating event	1.89	1.14 – 3.15	**0.014***
Creatinine	0.75	0.60 – 0.94	**0.012***
ACLF (Grade ≥ 2 VS Grade ≤ 1)	1.08	0.58 – 2.04	0.791
Delta MAP (at Day 3)	1.00	0.98 – 1.02	0.870

23. RECTUS FEMORIS ULTRASOUND IDENTIFIES SARCOPENIA AND PREDICT A POOR CLINICAL COURSE IN PATIENTS WITH AN ACUTE DECOMPENSATION OF CIRRHOSIS

Gagliardi R.[1], Campadello P.[1], Brocco S.[1], Incicco S.[1], Calvino V.[1], Sikadi B.[1], Tonon M.[1], Brocca A.[1], Gambino C.G.[1], Zeni N.[1], De Conti G.[2], Giraudo C.[2], Angeli P.[1], Piano S.[1]

[1]Unit of Internal Medicine and Hepatology, Department of Medicine, University and Hospital of Padova, Padova, Italy; [2]Radiology Unit, Department of Medicine, University and Hospital of Padova, Padova, Italy

Background and aims: sarcopenia is common and associated with poor outcomes in patients with cirrhosis. The gold standard for assessing sarcopenia is the CT scan, with the measurement of skeletal muscle index (SMI) at L3. However, CT scan is expensive, exposes patients to radiations and SMI assessment requires a specific software. We evaluated: a) the accuracy of ultrasound measurement of rectus femoris cross sectional area (RF-CSA) in the assessment of sarcopenia; b) the prognostic value of RF-CSA in hospitalized patients with cirrhosis.
Methods: phase 1: abdominal CT scan and thigh ultrasound were performed in 77 patients with cirrhosis. RF-CSA was measured at two-thirds of the distance from the anterior superior iliac spine to the superior patellar border. Intraclass correlation coefficient (ICC) was used to evaluate intra- and inter-operator reliability. Sarcopenia was defined by SMI (<39 cm2/m2 in women and <50 cm2/m2 in men). Predictors of sarcopenia were evaluated.
Phase 2: RF-CSA was measured at bedside in 120 consecutive patients hospitalized for an acute decompensation of cirrhosis. Patients were classified in two groups according to the median values of RF-CSA for males and females ("low" vs "high"). Patients were followed up until death, liver transplant or 90 days.
Results: RF-CSA showed a strong correlation with SMI (r = 0.751; p<0.001; Fig. Panel A) outperforming BMI and mid arm muscle circumference. RF-CSA was an independent predictor of sarcopenia (aOR=0.28; p=0.002) and showed a high discrimination ability for ruling out sarcopenia (AUROC=0.90 in male and 0.92 in female).
Among inpatients (mean age: 64 ± 11 years, mean MELD-Na: 20±7), those with "low" RF-CSA had a higher incidence of hepatic encephalopathy (63% vs 39%; p=0.010), sepsis (36% vs 10%; p=0.001), transfer to ICU (17% vs 5%; p=0.042) and in-hospital mortality (27% vs 8%; p=0.014), and a lower probability of 90-day survival (51% vs 83%; p=0.001; Fig. Panel B) than those with "high" RF-CSA. In multivariable analysis (adjusted for age, sex, MELD-Na and leukocytes), a "low" RF-CSA was an independent predictor of 90-day mortality (aHR=4.13; p<0.001). Inter- and inter-operator reliability was high (ICC=0.983 and 0.942, respectively, p<0.001 for both).
Conclusions: ultrasound measurement of RF-CSA is an easy, reliable bedside tool for the assessment of sarcopenia in patients with cirrhosis. Low RF-CSA values independently predict poor outcomes in hospitalized patients with cirrhosis.



24. THE DIAGNOSTIC ACCURACY OF NON-INVASIVE TESTS OF FIBROSIS IN PATIENTS WITH METABOLIC ASSOCIATED FATTY LIVER DISEASE. A MULTICENTRIC COMPARATIVE STUDY BETWEEN LIVER BIOPSY AND NON-INVASIVE SCORES OR FIBROSCAN

Cespiati A.[1], Lombardi R.[1], Carvalhana S.[2], Smith D.[1], Cinque F.[1], Santomenna F.[1], Currà J.[1], Bertelli C.[3], Pisano G.[3], Cortez-Pinto H.[2], Fracanzani A.L.[1]
[1]SC Medicina ad Indirizzo Metabolico, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy; Department of Pathophysiology and Transplantation, University of Milan, Italy; [2]Departamento de Gastroenterologia, Centro Hospitalar Universitário Lisboa Norte, Departamento de Dietética e Nutrição, Lisbon, Centro Hospitalar Universitário Lisboa Norte Portugal; [3]SC Medicina ad Indirizzo Metabolico, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy

Background and Aims: Metabolic dysfunction-associated fatty liver disease (MAFLD) is characterized by liver steatosis and at least one metabolic comorbidity. Conversely to NAFLD, MAFLD can also include other causes of liver disease, so the two terms are not interchangeable. Both NAFLD and MAFLD may progress towards advanced form of liver disease as hepatic fibrosis, the latter being the main determinant of long-term adverse outcomes and mortality. Liver biopsy is the gold standard for fibrosis staging but due to its invasiveness several non-invasive tests (NITs) of fibrosis have been proposed. The most widely used are fibrosis-4 (FIB-4), NAFLD fibrosis score (NFS) and the liver stiffness measurement (LSM) by Fibroscan, which to date have been validated only in NAFLD but not in MAFLD. Therefore, the aims of our study are 1) to evaluate the diagnostic accuracy of NITs in MAFLD 2) to evaluate their performance specifically in diabetic and obese subjects 3) to identify new thresholds for scores NITs in MAFLD.
Method: We enrolled 223 consecutive patients who underwent liver biopsy for diagnostic purpose or for staging liver fibrosis in Milan and Lisbon Liver Clinic. Of these, 164 patients fulfilled the diagnostic criteria of MAFLD and were finally included in the analysis. Clinical, laboratory and Fibroscan data were collected within 6 months from biopsy. According to 2021 EASL clinical practice guidelines, FIB-4<1.3, NFS<-1.455 and LSM<8 kPa ruled out advanced fibrosis (>F3), FIB-4>3.25, NFS>0.675 and LSM≥8 kPa ruled in advanced fibrosis.
Results: Mean age was 56±12 ys, and 62% were males. 59% of patients was obese, 47% diabetic. The prevalence of fibrosis >F3 was 24% at histology, whereas only 7% and 8% by FIB-4>3.25 and NFS>0.675, respectively. Conversely, 62% of patients was diagnosed with advanced fibrosis by LSM ≥8 kPa. The scores showed a high percentage of indeterminate values (43% for FIB-4, 49% for NFS). All NITs showed a lower accuracy for both identification (AUROCs FIB-4 0.62; NFS 0.57; LSM 0.72) and exclusion (AUROCs FIB-4 0.65; NFS 0.68; LSM 0.72) of advanced fibrosis at biopsy compared to those reported for NAFLD in literature.
For ruling-in advanced fibrosis, FIB-4 and LSM performed worst in diabetic vs non-diabetic (AUROCs FIB-4 0.58 vs 0.69 p<0.001; LSM 0.66 vs 0.71 p<0.001) and in obese vs non-obese MAFLD (AUROCs FIB-4 0.59 vs 0.65 p<0.001; LSM 0.68 vs 0.75 p<0.001). NFS accuracy did not significantly differ between diabetic and non-diabetic (AUROCs 0.58 vs 0.50 p=0.06), whereas it seemed to perform better in obese vs non-obese (AUROCs 0.58 vs 0.55 p=0.01). For the exclusion of fibrosis, all NITs performed worst in diabetic vs non-diabetic (AUROCs FIB-4 0.59 vs 0.67 p=0.001; NFS 0.58 vs 0.63 p=0.003; LSM 0.68 vs 0.69 p=0.06) and in obese vs non-obese (AUROCs FIB-4 0.66 vs 0.69 p=0.002; NFS 0.65 vs 0.70 p=0.003; LSM 0.68 vs 0.74 p<0.001). The Youden indexes of current cut-offs for FIB4 and NFS were <0.5 for both ruling in and ruling out advanced fibrosis, whereas new thresholds as FIB-4>1.63/NFS>-1.09 and FIB-4<1.22/NFS<-1.23 had the best Youden indexes to rule in and rule out fibrosis, respectively. As for Fibroscan, LSM>10.4 kPa seemed to better identify MAFLD patients with advanced fibrosis compared to the established cut-off of 8kPa even though to a small extent, whereas a cut-off of 8.4 kPa showed the better performance in excluding fibrosis.
Conclusion: In MAFLD, either FIB4, NFS or Fibroscan performed worse compared to NAFLD, with LSM having the higher accuracy. The presence of metabolic comorbidities such as diabetes and obesity impaired the accuracy of NITs for both the identification and exclusion of advanced fibrosis. In MAFLD lower cut-offs for both FIB-4 and NFS might be used to avoid misdiagnosis, whereas no change seems to be needed for LSM.
The presence of obesity and diabetes should be carefully evaluated in patients with steatosis in order to better estimate the risk of advanced fibrosis until more accurate NITs will be developed specifically for MAFLD patients.

25. PIVKA-II IS AN EARLY PREDICTOR OF RESPONSE TO TRANSARTERIAL CHEMOEMBOLIZATION IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

Caspanello AR.[1], Caccamo G.[2], Cacciola I.[1], Filomia R.[2], Franzè MS.[1], Maimone S.[2], Pitrone C.[2], Raimondo G.[1], Saitta C.[1]
[1]Department of Clinical and Experimental Medicine, Unit of Medicine and Hepatology, University of Messina; [2]Department of Medical Sciences, Unit of Medicine and Hepatology, University Hospital of Messina

Introduction and aims: Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and a leading cause of cancer related death worldwide. Its management is guided by the Barcelona Clinic Liver Cancer (BCLC) staging system. Transarterial chemoembolization (TACE) is the first line therapy in unresectable, intermediate-stage HCC (BLCL B). Response to TACE is usually evaluated radiologically at least 1 month after the procedure and is based on the modified Response Evaluation Criteria in Solid Tumors (mRECIST). Nowadays, there are no early predictors of TACE response, which might be instead very useful in order to early identify patients candidate to subsequent treatments without further delays. In recent

years, prothrombin induced by the absence of vitamin K II (PIVKA-II), has been identified as a serum diagnostic biomarker in HCC and an increasing amount of data indicates that it is more sensitive than alpha-fetoprotein (aFP) for discriminating HCC at all stages from cirrhosis. However, limited data are available about its utility as possible biomarker of response to HCC treatments. The aim of this study was to evaluate the possible role of PIVKA-II as early predictor of response to TACE and its possible prognostic value in these patients.

Patients and Methods: We prospectively enrolled 67 patients [43 males (64.2%) and 24 females (35.8%), median age 71.6 years (± 10.1 DS)] with HCC who underwent TACE at the Unit of Medicine and Hepatology of Messina University Hospital between January 1st2017 and December 31st 2021. HCC was diagnosed in all patients by standard radiological and/or pathological methods. Demographic and clinical characteristics were recorded for all patients. All of them underwent blood sampling the day before TACE procedure and 48 hours after TACE, and the corresponding serum samples were aliquoted and stored at -80 °C until testing for PIVKA-II. Similarly, routine biochemical laboratory tests were performed one day before and two days after TACE. All patients underwent contrast enhanced radiological examination [computed tomography (CT) or magnetic resonance (MR)] one month after TACE for the assessment of radiologic response, according to mRECIST criteria. No patient was under treatment with vitamin K or warfarin. PIVKA-II serum levels were measured on a Lumipulse® G1200 (Fujirebio Inc.). All tests were performed in duplicate. Univariate logistic regression analysis was used to identify predictors of HCC response after TACE. Variables with p value < 0.05 at univariate analysis were then subjected to multivariate analysis and included in the logistic model. A 2-tailed p value < 0.05 was used to determine statistical significance.

Results: The underlying liver disease was HCV-related in 33 cases (49.2%), associated to metabolic diseases in 8 cases (11.9%), alcohol-related in 6 cases (9%), HBV-related in 5 cases (7.5%), due to mixed etiology in 4 cases (6%), while in 11 cases (16.4%) liver disease was classified as cryptogenic. 52/67 patients (77.6%) were in Child-Pugh class A and 15/67 (22.4%) were in Child-Pugh class B. The BCLC stage was 0 in 5 patients (7.5%), A in 23 patients (34.3%) and B in 39 patients (58.2%). The mean survival follow-up was 23.5 months (± 17.6 DS). In 21/67 cases (31.3%), TACE was performed as first HCC treatment, while in the remaining 46 (68.7%) TACE was performed as treatment of a tumor recurrence. The radiological responses after TACE procedure - evaluated according to the mRECIST criteria - were the following: complete response in 10 cases (14.9%), partial response in 19 patients (28.4%), stable disease in 22 cases (32.8%), progressive disease in 16 subjects (23.9%). Comparing the pre- and post-TACE values of the biochemical variables analyzed, a significant increase in GOT (p = 0.04), GPT (p < 0.0001) and gammaglobulin (p = 0.018) levels was observed, together with a significant reduction of aFP (p = 0.031) and alkaline phosphatase (p = 0.001) values. After stratification of the patients according to the radiological response, a statistically significant increase of the median PIVKA-II values from pre-TACE to post-TACE (p < 0.05) was observed in patients with progressive disease, while there were no significant differences in pre- and post-TACE PIVKA-II values in patients without progressive disease. Comparing patients with complete response vs. patients without complete response, the former had lower pre- and post-TACE PIVKA-II values than the latter (p < 0.05, and p = 0.04, respectively). Uni- and multivariate logistic regression analyses showed that increased post-TACE PIVKA-II values (p = 0.04), and progressive neoplastic disease (p = 0.03) were independent predictors of mortality.

Conclusions: This study showed that PIVKA-II may be a useful early predictor of progressive disease after TACE, thus potentially allowing a timing decision making for subsequent treatments in these patients. These data also revealed a possible prognostic role of PIVKA-II values after TACE, probably reflecting the progressive neoplastic disease.

26. HEPATIC STEATOSIS EVALUATION USING ARTIFICIAL INTELLIGENCE ON ULTRASOUND IMAGES: PERFORMANCE COMPARISON WITH MAGNETIC RESONANCE PROTON DENSITY FAT FRACTION AND HEPATORENAL INDEX

Santoro S.[1], Khalil M.[2], Abdallah H.[2], Farella I.[2], Lanza E.[2], Bonfrate L.[2], Di Ciaula A.[2], Portincasa P.[2]
[1]Clinica Medica "A. Murri", Department of Preventive and Regenerative Medicine and Ionian Area (DiMePrev-J), University of Bari Aldo Moro, Piazza Giulio Cesare 11, 70124, Bari, Italy; R&D resp. - Eurisko Technology Srl, Modugno, Bari, Italy; ; [2]Clinica Medica "A.Murri", Department of Preventive and Regenerative Medicine and Ionian Area (DiMePrev-J), University of Bari Aldo Moro, Piazza Giulio Cesare 11, 70124, Bari, Italy;

Introduction: Hepatic steatosis, characterized by excessive fat accumulation in the liver, is a prevalent condition and a leading cause of chronic liver diseases. Magnetic resonance imaging (MRI) with the proton density fat fraction (PDFF) technique is the current gold standard for assessing liver fat content. However, ultrasound (US) imaging offers a more accessible and cost-effective alternative. The Hepatorenal Index (HRI) is considered efficient in determining the liver steatosis level on US images. In this study, we developed an artificial intelligence (AI)-based algorithm to evaluate automatically hepatorenal index (HRI) using ultrasound images and we compared its performance using MRI-PDFF as reference.

Materials and methods: The algorithm was trained on a dataset of 370 annotated ultrasound images divided into training (70%), test (15%) and validation (15%) subsets. After training we enrolled a total of 134 volunteers (50 Males/84 females) older than 18 years (Male age 55.5 IQR 19.25, Female age 63.0 IQR 16). For each patient we collected US scan consisting in a parasagittal scanning plane showing the right lobe of the liver and adjacent right kidney. During the US examination we evaluated the steatosis grade based on standard ultrasound evaluation of liver steatosis. Within 6 hours from the US scan (E2 Sonoscape by Fujifilm) each patient has undergone MRI scan (3 Tesla Siemens) from which we obtained the MRI-PDFF and calculated the average percentage of fat in liver. Four trained researchers evaluated manually the HRI in a blind test. The HRI has also been evaluated by the AI algorithm. Significance in revealing steatosis has been assessed using logistic regression. Finally, we compared manual HRI with AI calculated HRI and used MRI-PDFF has reference dataset.

Results: Steatosis prevalence in males was 44%, in females 56%. The average time needed to evaluate HRI was 20s for the AI algorithm. The findings demonstrated that the AI-based algorithm had better correlation with MRI-PDFF (Pears. 0.75 p<0.00001) respect the manual HRI (Pears. between 0.21 and 0.75). AI-aided HRI also had no variability whereas manual HRI had a coefficient of variability equal to 15%. The ROC analysis of AI algorithm reported AUC = 0.83 in revealing presence of liver steatosis (grade 1) and AUC = 0.93 in revealing grade 2 steatosis.

Conclusion: The results suggest that the AI algorithm can provide a reliable and fast assessment of hepatic steatosis using ultrasound images, comparable to the gold standard techniques of MRI-PDFF and with better performances than manual evaluated HRI. This approach has the potential to facilitate early detection and management of hepatic steatosis, contributing to improved patient outcomes. Further research is warranted to validate these findings and explore the algorithm's applicability in diverse clinical settings.

27. PLATELETS BEHAVIOR IN METABOLIC PATIENTS AFFECTED BY HEPATIC STEATOSIS/STEATOHEPATITIS AND LIVER CIRRHOSIS

Zoncapè M.[1], Castelli M.[1], Sacerdoti D.[2], Minuz P.[1], Dalbeni A.[3]
[1]Division of General Medicine C, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy.; [2]Liver Unit, University and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy.; [3]Division of General Medicine C, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy

Background and aims. Non-alcoholic fatty liver disease (NAFLD) is the most prevalent liver disease worldwide, with an incidence of approximately 25% in the general population, particularly in Western countries. NAFLD can progress to liver cirrhosis. Non-alcoholic steatohepatitis (NASH) typically develops in individuals with metabolic syndrome, which itself is a pro-thrombotic and pro-atherogenic condition where platelets may play a significant role.

Although a few studies have investigated the role of platelets in NAFLD and its progression to cirrhosis, it is well established that platelets can exhibit pro-inflammatory and pro-fibrotic activities. This pilot study aimed to explore the potential involvement of platelets in the development and progression of NAFLD/NASH to cirrhosis, as well as their interaction with coagulation factors, by comparing them to healthy subjects.

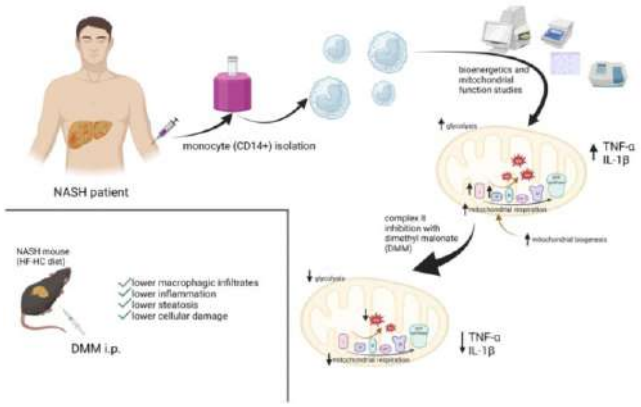
Methods. Microfluidic and Flow Cytometry techniques were employed to investigate the presence of a pre-activation state and the *in vitro* level of platelet activation in patients with NAFLD/NASH and cirrhosis, in comparison to healthy subjects. Additionally, we examined potential procoagulant and pro-fibrotic alterations of platelets by studying their interaction with coagulation factors. Experimental combinations were conducted using platelet-poor plasma from healthy controls, along with washed platelets from patients with

NAFLD/NASH or cirrhosis, and vice versa.
Results. Platelet adhesion was significantly higher in the NAFLD group compared to controls and cirrhotic subjects (p<0.01), suggesting increased platelet reactivity to stimuli. Cirrhotic patients exhibited a lower number of circulating platelets, but with normal adhesion capacity compared to controls. Furthermore, although high concentrations of von-Willebrand Factor (vWF) were found in cirrhosis (cirrhotic vs controls and NAFLD/NASH subjects: p<0.01), the efficiency of vWF-mediated collagen binding was relatively low. Flow cytometry analysis revealed that cirrhotic patients had reduced capacity for heteroaggregation and expression of PAC-1 and P-selectin compared to controls (p<0.05, p<0.01, and p<0.01, respectively).
Moreover, we observed no significant contribution of platelets to their interaction with coagulation factors. Any alterations in coagulation factor levels we observed in our study, were consistently reflected in plasma and not attributed to platelet involvement.
Conclusions. This study highlights the pivotal role of platelets in NAFLD and its progression to cirrhosis. The presence of "reactive" platelets in NAFLD patients suggests an inflammatory and pro-fibrotic role. Conversely, platelets in metabolic cirrhosis appear to exhibit reduced responsiveness, possibly indicating a state of "exhaustion" where platelets have already undergone degranulation in vivo and may exhibit limited reactivity to in vitro stimuli.

28. PECULIAR BIOENERGETIC PROFILE IN MONOCYTES: A POTENTIAL TARGET IN NONALCOHOLIC STEATOHEPATITIS (NASH).

Sangineto M.[1], Ciarnelli M.[1], Kanwal H.[1], Frisoli I.[1], Duda L.[2], Villani R.[1], Romano A.D.[1], Di Gioia G.[1], Serviddio G.[1]
[1]U.O.C. di Epatologia, Dipartimento di Scienze Mediche e Chirurgiche, Università di Foggia; [2]Anatomia Patologica, Dipartimento di Medicina Clinica e Sperimentale, Università di Foggia

Nonalcoholic steatohepatitis (NASH), the inflammatory subform of nonalcoholic fatty liver disease (NAFLD) is characterised by several pathogenetic mechanisms as explained by the "multiple hit pathogenesis". Inflammation in NASH is orchestrated by the innate immunity. Kupffer cells are triggered by PAMPs and DAMPs, and recruit monocytes (Mo), which repopulate the liver with new macrophages crucial for perpetuating inflammation and liver injury.The recent biology field of immunometabolism showed that myeloid cells reprogram cellular bioenergetics to sustain the pro-inflammatory activity, suggesting novel immunosuppressive approaches in oncological and autoimmune diseases. However, some evidence is emerging in chronic diseases such as heart failure or diabetes. On the contrary, very few has been shown in hepatology, and in NASH the field is unexplored. Here, we dissected the immunometabolic profile of circulating Mo in NASH patients. To do this, 20 NASH patients (histologically determined) and 10 healthy controls were enrolled for isolation of circulating CD14+ Mo from peripheral blood. Mo were used for analysis of bioenergetics and mitochondrial function, and RNA/protein isolation. In particular, glycolysis and mitochondrial respiration (MR) were quantified with extracellular acidification rate and oxygen consumption rate, respectively, by using a Seahorse HS Mini analyser (Agilent). Respiratory chain (RC) complexes enzymatic activities and H2O2 production rate were assessed. In a second step, the effect of succinate dehydrogenase (SDH) inhibition was investigated *in vitro* by exposing patient Mo to dimethyl malonate (DMM), and *in vivo* by using a preclinical model of NASH. Therefore, wild-type (C57BL/6) mice were fed with high-fat and high-cholesterol (HF-HC) diet for 8 weeks. From week 6 to week 8 mice were treated by injecting DMM (160 mg/kg), or vehicle (PBS) intraperitoneally every second day.
NASH Mo presented a peculiar bioenergetic profile characterized by a significant increase of both glycolysis and MR compared to controls, with a preponderant change of glycolysis. Basal respiration was higher in NASH Mo, and the injection of the uncoupler FCCP permitted to appreciate a significant increase of maximal respiration as well. The higher respiration observed in NASH Mo was partially addressed to ATP production, while a large part was devoted to create proton leak. In accordance with this, we found that NASH Mo presented a considerable enzymatic activity of RC complex I and complex II. However, using pyruvate/maleate or succinate as substrates we found that complex I and II activities produced high levels of hydrogen peroxide with consequent mitochondrial oxidative stress. Taken together these results highlighted that Mo in NASH have a bioenergetic reprogramming with increase of glycolysis and mitochondrial dysfunction, which are associated with cytokine expression (i.e. IL-1β and TNF-α). The mRNA expression of 78 targets included in the PrimePCRTM array "*mitochondria energy metabolism plus*" showed a preponderant up-regulation of this pathway as only 7 genes were significantly down-regulated in NASH Mo, while 32 genes resulted up-regulated. Most of these genes encoded for RC complex subunits, and in particular, 3 out of 4 SDH subunits were more expressed. SDH is an enzyme complex also known as RC complex II, whose role in driving the metabolic rewiring in macrophages has been recently demonstrated. Therefore, considering the higher activity and expression of RC complexes, and in particular the SDH, we tried to expose NASH Mo to DMM, a SDH inhibitor with demonstrated immunomodulatory properties. Interestingly, DMM normalized glycolysis and MR levels, abrogating Il-1β and TNF-α expression.
Moreover, mice were fed with HF-HC diet for 8 weeks and, from week 6 to week 8 treated with DMM or vehicle Interestingly, the administration of DMM in HF-HC fed mice significantly reduced liver injury, steatosis and inflammation as indicated by serum ALT levels, hepatic fat, number of macrophages and expression of inflammatory cytokines (i.e., IL-1β and TNF-α). In particular, the number of crown-like macrophagic aggregates was significantly lower in DMM-treated mice, highlighting an important effect of DMM in inhibiting Mo infiltration in the liver.
In conclusion, Mo immunometabolism might be targeted in NASH.



29. INAPPROPRIATE PRESCRIBING ACCORDING TO STOPP/START IN PATIENTS ACCESSING INTERNAL MEDICINE DEPARTMENTS: EXPERIENCE OF A TERTIARY CARE HOSPITAL

Pata G.[1], Festorazzi C.[1], Leoni L.[1], Farina F.[1], Montagna M.[1], De Lorenzo R.[1], Lucini A.[2], Castellani J.[3], Ramirez G.A.[2], Tresoldi M.[2], Rovere Querini P.[4]

[1]Vita-Salute San Raffaele University, Milan, Italy; [2]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy; [3]Unit of Medical Specialties and Healthcare Continuity IRCCS Ospedale San Raffaele, Milan, Italy; [4]Vita-Salute San Raffaele University, Milan, Italy; Unit of Medical Specialties and Healthcare Continuity IRCCS Ospedale San Raffaele, Milan, Italy

Introduction. Potentially inappropriate prescribing (PIP) — i.e. the prescription of drugs that hold a higher risk of causing harm than benefit in a specific patient — is highly prevalent in all clinical settings, especially among elderly people with multiple comorbidities and polypharmacy. Besides its substantial, yet avoidable, economic burden on healthcare systems, PIP is a major contributor to patient morbidity and mortality. The Screening Tool of Older Persons' Prescriptions (STOPP) and the Screening Tool to Alert the Right Treatment (START) are widely recognized criteria used to identify PIP in clinical practice. They were developed based on the revision of the Beers Criteria by the American Geriatric Society in 2011 and have been thereafter extensively adopted to scrutinize medical prescriptions and avoid therapeutic inappropriateness. Here we evaluated PIP based on STOPP/START criteria among patients referring to Internal Medicine Departments of a tertiary care hospital, and investigated whether in-hospital therapeutic adjustments have an impact on PIP.
Methods. This study is part of the more extensive prospective observational study Med-Cli, aimed at characterizing the clinical phenotype of patients accessing Internal Medicine Departments of San Raffaele University Hospital in Milan, Italy. All patients enrolled in the Med-Cli study from November 2022 to April 2023 were included. STOPP and START criteria were used to assess the presence of potentially inappropriate medications (PIMs) and potentially prescribing omissions (PPOs), respectively, at both hospital admis-

sion and discharge. Chi-square test and Mann-Whitney U test were used to compare patients with ≥1 PIM or ≥1 PPO and those without any inappropriate prescription in terms of categorical and continuous variables, respectively. Logistic regression analyses were employed to identify risk factors for the presence of ≥1 PIM or ≥1 PPO at admission. Paired differences in the prevalence of ≥1 PIM or of ≥1 PPO between admission and discharge were investigated using McNemar test. Linear regression was used to investigate predictors of the degree of change in the number of PIMs and PPOs from admission to discharge.
Results. 304 patients were included. 168 (55%) patients were males and median (interquartile, IQR) age was 76 (68-83) years. 87% of patients were on ≥5 chronic medications, with a median (IQR) number of 10 (7-12) ongoing therapies per patient. Patients had a median (IQR) number of 3 (2-5) comorbidities each. 218 (72%) patients had cardiovascular diseases, 66 (22%) respiratory diseases, 88 (29%) neurologic diseases, 32 (10%) psychiatric disorders, 110 (36%) endocrinological diseases, 104 (34%) gastrointestinal or liver diseases, 93 (31%) renal or urogenital disorders, 77 (25%) musculoskeletal diseases, and 115 (38%) had cancer. The most common PIMs at admission concerned drugs for the cardiovascular system (26%), drugs that increased the risk of falls (24%), and neurological and psychotropic drugs (22%). PPOs at admission mostly involved drugs for the cardiovascular system (36%), for the musculoskeletal system (14%), drugs for the respiratory system (12%), analgesics (12%), and neurological drugs (12%). No difference was found between patients with ≥1 PPO at admission and those without in terms of demographics, comorbidities, or number of chronic therapies. Patients with at ≥1 PIM at admission more frequently suffered from psychiatric disorders than those without any PIM (19% vs. 8%, p 0.014), history of psychiatric disorders being a significant predictor of the presence of ≥1 PIM at admission (odds ratio 2.76 [CI 95% 1.26-5.90], p 0.0093). We found no significant change in the prevalence of PIMs between admission and discharge (22% vs. 20%, p>0.05). However, a history of cancer significantly predisposed to lower reductions in PIMs from admission to discharge at linear regression (p 0.020). The prevalence of PPOs decreased significantly from admission to discharge (51% vs. 20%, p<0.0001), indicating an increased appropriateness of prescriptions following hospitalization. A history of psychiatric disorders emerged as a significant predictor of the degree of reduction of the number of PPOs from admission to discharge, such that patients with a psychiatric disorder show more prominent decrease in PPOs following hospital stay (p 0.0090).
Conclusion. Potentially inappropriate prescribing (PIP) is frequent among patients accessing Internal Medicine departments. We found that at hospital discharge the prevalence of PIP is reduced compared to time of admission, pointing to the importance of critically reviewing ongoing therapies during hospital stay, regardless of the reason of the hospitalization. Further studies are needed to unravel the long-term benefits of improved prescribing appropriateness and to investigate the usefulness and applicability of START/STOPP criteria in routine clinical practice.

30. HOME-BASED REHABILITATIVE EXERCISE IMPROVES LONG-TERM CLINICAL OUTCOMES IN FEMALES WITH PERIPHERAL ARTERY DISEASE: A SINGLE CENTER, 7-YEAR OBSERVATIONAL STUDY

Savriè C.[1], Traina L.[2], Tsolaki E.[2], Rinaldo N.[3], Boari B.[1], De Giorgi A.[1], Tiseo R.[1], Guerzoni F.[4], Napoli N.[4], Straudi S.[3], Lamberti N.[3], Manfredini F.[3], Gasbarro V.[2], Manfredini R.[5]
[1]Clinica Medica Unit, University Hospital of Ferrara; [2]Vascular and Endovascular Surgery Unit, University Hospital of Ferrara; [3]Department of Neuroscience and Rehabilitation, University of Ferrara; [4]Health Statistics Unit, University Hospital of Ferrara; [5]Clinica Medica Unit, University Hospital of Ferrara & University Center for Studies on Gender Medicine, Department of Medical Sciences, University of Ferrara

Background: Cardiovascular (CV) diseases are the leading cause of death, taking an estimated 18 million lives each year (Roth, JACC 2020). Vascular atherosclerosis may affect mobility, and this is associated to higher rates of CV death and major cardiovascular events (Tsao, Circulation 2023). With reference to peripheral artery disease (PAD), females exhibit differences either in terms of presentation (absent or atypical lower limb symptoms) and post-invasive treatment outcome (more adverse events, higher in-hospital mortality) (McDermott, Circulation 2000; Lee, J Vasc Surg 2022).
Aims: We aimed to investigate whether sex differences in clinical outcomes and rate of survival are observable at 7-year follow up in two cohorts of PAD patients, one followed by a structured home based program, and one not exposed to rehabilitation.
Methods
This study retrospectively analyzed a prospectively collected database of PAD patients, diagnosed at the Vascular Surgery or Clinica Medica units, and partly referred at the Rehabilitation Medicine unit for a training program (years 2012-2015). The follow-up period lasted for seven years from recruitment. The final sample consisted of 200 PAD patients (Leriche-Fontaine's stage II) enrolled in the rehabilitation program (exclusion criteria: lower limb ischemia, foot ulcers, cardiovascular conditions contraindicating exercise) and 200 PAD patients (identical inclusion/exclusion criteria), not referred to the rehabilitation program. According to study objectives, patients were categorized into four subgroups: males (M) and females (F) that underwent the exercise program (MEX and FEX), and control (MCO and FCO). All patients received the "test in–train out" home-based exercise program (Manfredini F, Circ J 2008; Malagoni, Circ J 2011). Patients in the control group were treated with optimal medical therapy, advise to adhere to the current guidelines of healthy and active lifestyle. The primary outcome was survival probability, and secondary outcomes included all-cause hospitalizations and amputations, assessed since the date of enrollment for the following 7 years. Statistical analyses, as appropriate, included: Shapiro-Wilk test, Chi-squared test, Student's t-test, Mann-Whitney test, Kruskal-Wallis test, Kaplan–Meier curves and log-rank test for trend, multivariate Cox proportional hazards (MedCalc Statistical Software 20.216 (MedCalc Software, Ostend, Belgium).
Results: The final sample included 400 patients, 113 F (51 FCO, 62 FEX) and 287 M (149 MCO, 138 MEX). At baseline, the four subgroups did not differ for demographic or clinical characteristics, nor for PAD severity. All patients included in the Exercise group completed the program, that lasted a median of 253 (interquartile range 187-322) days, with a median of 6 (interquartile range 4-9) serial visits. Adherence was high (mean value of completed exercise sessions: 85%), with no sex differences of compliance (M 85 *vs.* F 86%, respectively; p=0.80).
Primary outcome. Along a median follow-up of 6.3 years (interquartile range 4.8-7.0), there were 143 deaths, 34 F (30%) and 109 M (38%). Thirty-one patients deceased in the EX group and 112 in the CO group. The survival rate was 94% in FEX, 82% in MEX, 45% in FCO and 44% in MCO. Kaplan–Meier analyses (Figure) showed a significantly lower mortality risk for FEX subgroup compared to all the other subgroups, including MEX.
Secondary outcomes. Hospitalization occurred in 312 patients: 66% FEX, 68% MEX, 88% FCO and 89% MCO, with a significantly lower hospitalization risk (Logrank p<0.001) for FEX (HR: 0.62; 95% CI 0.45-0.87) and MEX (HR: 0.62; 95% CI 0.47-0.80) respect to MCO. A similar pattern was observed for amputations, occurring in 3% of FEX and MEX, 4% of FCO and 10% of MCO (Logrank p=0.016), with a significant between group difference for FEX (HR: 0.26; 95% CI 0.08-0.90) and MEX (HR: 0.24; 95% CI 0.09-0.64) when compared to MCO.
Conclusion: In a PAD population, at 7-year follow-up and compared to usual care, participation and adherence to a home rehabilitation program were associated to a lower rate of mortality, with active F showing greater benefit than M. In addition, better long term rate of hospitalizations and amputations were observed after rehabilitation program, in both sexes, compared to subjects not undergoing rehabilitation.

31. SMALL BOWEL CARCINOMAS IN COELIAC DISEASE SHOW HYPOMETHYLATION OF LINE-1

Bianchi P.I.[1], Guerini C.[2], Libera L.[3], Vanoli A.[4], Arpa G.[4], Aronico N.[5], Furlan D.[3], Grillo F.[6], Nesi G.[7], Sampietro G.[8], Fociani P.[9], Fiocca R.[6], Latella G.[10], Sessa F.[11], D'Errico A.[12], Malvi D.[12], Mescoli C.[13], Rugge M.[13], Ferrero S.[14], Poggioli G.[15], Rizzello F.[16], Macciomei M.C.[17], Santini D.[12], Volta U.[18], De Giorgio R.[19], Caio G.[19], Calabrò A.[20], Ciacci C.[21], D'Armiento M[22], Rizzo A.[23], Solina G.[24], Tonelli F.[25], Villanacci V.[26], Cannizzaro R.[27], Canzonieri V.[28], Florena A.M.[29], Biancone L.[30], Monteleone G.[30], Caronna R.[31], Ciardi A.[32], Elli L.[33], Caprioli F.[33], Vecchi M.[33], D'Incà R.[34], Zingone F.[34], D'Odorico A.[34], Oreggia B.[35], Reggiani Bonetti L.[36], Astegiano M.[37], Cantoro L.[38], Papi C.[39], Sandri G.[40], Silano M.[41], Usai P.[42], Perfetti V.[43], Quaquarini E.[44], Giannone AG.[29], Orlandi A.[45], Barresi V.[46], Ardizzone S.[47], Ciccocioppo R.[48], Amodeo G.[48], Biletta E.[49], Lenti M.V.[50], Corazza GR.[50], Di Sabatino A.[50]
[1]Department of Medicine, San Matteo Hospital Foundation, Pavia, Italy; [2]Anatomic Pathology Unit, Department of Molecular Medicine, San Matteo Hospital Foundation, University of Pavia, Pavia, Italy ; [3]Unit of Pathology, Department of Medicine and Surgery and Research Center for the Study of Hereditary and Familial Tumors, University of Insubria, Varese, Italy; [4]Anatomic Pathology Unit, Department of Molecular Medicine, San Matteo Hospital Foundation, University of Pavia, Pavia, Italy; [5]First Department of Medicine, San Matteo Hospital Foundation, Pavia, Italy; [6]Pathology Unit,

Department of Surgical and Diagnostic Sciences, University of Genoa and Policlinico San Martino University Hospital, Genoa, Italy; [7]Division of Pathological Anatomy, Department of Surgery and Translational Medicine, University of Florence, Florence, Italy; [8]Unit of General Surgery, ASST Rhodense, Rho Hospital, University of Milan, Milan, Italy; [9]Anatomic Pathology Unit, ASST Ovest Milanese, Milan, Italy; [10]Gastroenterology Unit, Department of Life and Environmental Sciences, University of L'Aquila, L'Aquila, Italy; [11]Pathology Unit, Department of Medicine and Surgery, University of Insubria, Varese, Italy; [12]Department of Experimental, Diagnostic and Specialty Medicine (DIMES), Institute of Oncology and Transplant Pathology, St. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy; [13]Pathology Unit, Department of Medicine, University of Padua, Padua, Italy; [14]Division of Pathology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy; [15]Surgery of the Alimentary Tract, Department of Medical and Surgical Sciences, Sant'Orsola—Malpighi Hospital, University of Bologna, Bologna, Italy; [16]ntestinal Chronic Bowel Disease Unit, Department of Medical and Surgical Sciences, Sant'Orsola—Malpighi Hospital, Alma Mater Studiorum University of Bologna, Bologna, Italy; [17]Pathology Unit, San Camillo-Forlanini Hospital, Rome, Italy; [18]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy; [19]Department of Morphology, Surgery and Experimental Medicine, University of Ferrara, Ferrara, Italy; [20]Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence, Italy; [21]Department of Medicine and Surgery, University of Salerno, Salerno, Italy; [22]Public Health Department, Federico II University of Naples, Naples, Italy; [23]Unit of Pathology, Cervello Hospital, Palermo, Italy; [24] Unit of General Surgery, Cervello Hospital, Palermo, Italy; [25]Surgery and Translational Medicine, University of Florence, Florence, Italy; [26]Institute of Pathology, Spedali Civili Hospital, Brescia, Italy; [27]Department of Gastroenterology, Centro di Riferimento Oncologico (CRO) di Aviano IRCCS, Aviano, Italy; [28]Pathology Unit, Centro di Riferimento Oncologico (CRO) di Aviano IRCCS, Aviano, Italy and Department of Medical, Surgical and Health Sciences, University of Trieste, Trieste, Italy; [29]Pathologic Anatomy Unit, Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, University of Palermo, Palermo, Italy; [30]Department of Systems Medicine, University of Tor Vergata, Rome, Italy; [31]Department of Surgical Sciences, La Sapienza University, Rome, Italy; [32]Department of Radiological, Oncological, Pathological Sciences, Umberto I Hospital, La Sapienza University, Rome, Italy; [33]Gastroenterology and Endoscopy Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [34]Gastroenterology Section, Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy; [35]General Surgery Unit, Ca' Granda-Ospedale Maggiore Policlinico, Milan, Italy; [36]Section of Pathology, Department of Diagnostic Medicine and Public Health, University of Modena and Reggio Emilia, Modena, Italy; [37]General and Specialistic Surgery, Città della Salute e della Scienza-Molinette Hospital, Turin, Italy; [38]Gastroenterology Unit, USL Umbria 1, Perugia, Italy; [39]IBD Unit, San Filippo Neri Hospital, Rome, Italy; [40]Clinical Nutrition Unit, Sant'Eugenio Hospital, Rome, Italy; [41]Unit of Human Nutrition and Health, Istituto Superiore di Sanità, Rome, Italy; [42]Department of Internal Medicine, University of Cagliari, Cagliari, Italy; [43]Internal Medicine Unit, S.S. Annunziata Hospital, ASST-Pavia, Varzi, Italy; [44]Medical Oncology Unit, IRCCS ICS Maugeri and Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy; [45]Department of Biopathology and Image Diagnostics, University of Tor Vergata, Rome, Italy; [46]Section of Anatomical Pathology, Department of Diagnostics and Public Health, University and Hospital Trust of Verona, Verona, Italy; [47]Gastroenterology Unit, Luigi Sacco University Hospital, Milan, Italy; [48]Gastroenterology Unit, Department of Medicine, AOUI Policlinico G.B. Rossi, University of Verona, Verona, Italy; [49]Anatomic Pathology ASL Biella, Biella, Italy; [50]University of Pavia, First Department of Medicine, San Matteo Hospital Foundation, Pavia, Italy

Background and aim: Small bowel carcinoma (SBC) is an uncommon neoplastic condition affecting the gastrointestinal tract. It occurs more frequently not only in genetic syndromes but also in coeliac disease (14-fold) and Crohn's disease (8-fold), compared to the general population.
SBC, especially in early-stage disease, has been associated with high rates of mismatch repair deficiency/microsatellite instability. Long interspersed nucleotide element-1 (LINE-1) is an interspersed repetitive DNA retrotransposon that makes up approximately 17% of the human genome. LINE-1 methylation can serve as a global surrogate marker for assessing genomic DNA methylation level. In normal cells, LINE-1 is mainly methylated, while hypomethylation can lead to genomic instability and abonrmal expression of LINE-1 retrotransposon.

Material and methods: We collected biopsies from 25 sporadic SBC cases, 25 SBC cases in patients with Crohn's disease, and 38 SBC cases in patients with coeliac disease through the Small Bowel Cancer Italian Consortium. The methylation level of LINE-1 was assessed and measured as a percentage using bisulfite pyrosequencing. LINE-1 methylation was also evaluated in small intestinal biopsies of 10 untreated coeliac disease patients and 12 non-SBC normal small bowel mucosa samples for comparison.
Results: The LINE-1 methylation level was significantly lower (55.3%) in SBCs associated with coeliac disease (median patient age: 54 years (43.75-65.25); M:F =1) compared to the other SBC cases (62.4%, p=0.002). Similarly, LINE1 methylation in duodenal mucosa of cancer-free patients with newly diagnosed coeliac disease (59.8%; median age: 35 years (27.25-52.75); M:F =0.11) was significantly lower compared to normal small bowel mucosa (65.3%; median age:62.5-years (56.50-70.75); M:F =2).
Conclusions: The observed hypomethylation of LINE-1 in both in SBC and non-neoplastic mucosa of coeliac patients may suggest the presence of an epigenetic field defect in the non-cancerous small bowel mucosa of coeliac patients, which may contribute to carcinogenesis.

32. IDENTIFICATION OF POSSIBLE BIOMARKERS FOR NON-CELIAC GLUTEN SENSITIVITY: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, TWO-ARMS, MULTICENTER STUDY

Seidita A.[1], Sapone A.[2], De Magistris L.[3], Soresi M.[4], Amato M.R.[5], Andriulli A.[6], Bossa F.[6], Caio G.[7], Camhi S.[2], Casolaro V.[8], Catassi C.[9], Giaquinto G.[10], Kenyon V.[2], Leonetti E.[11], Mansueto P.[4], Mazzarella G.[12], Napolitano V.[13], Riegler G.[3], Rotondi Aufiero V.[12], Ruocco E.[14], Santora D.[15], Fasano A.[2], Carroccio A.[1]
[1]Unit of Internal Medicine, "V. Cervello" Hospital, Ospedali Riuniti "Villa Sofia-Cervello", 90120 Palermo, Italy. Department of Health Promotion Sciences, Maternal and Infant Care, Internal Medicine and Medical Specialties (PROMISE), University of Palermo, 90127 Palermo, Italy; [2]Massachusetts General Hospital, Center for Celiac Research &Treatment, Boston, USA.; [3]Department Precision Medicine, University of Campania Luigi Vanvitelli, 81100 Caserta, Italy.; [4]Department of Health Promotion Sciences, Maternal and Infant Care, Internal Medicine and Medical Specialties (PROMISE), University of Palermo, 90127 Palermo, Italy; [5]Dipartimento Assistenziale Integrato di Medicina Interna e Specialistica, AOU, University of Campania Luigi Vanvitelli, 81100 Caserta, Italy; [6]Division of Gastroenterology, Fondazione IRCCS-Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy.; [7]Department of Translational Medicine, University of Ferrara, 44121 Ferrara, Italy; [8]Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", University of Salerno, 84081 Baronissi, Italy ; [9]Polytechnic University of Marche, Department. of Pediatrics, Ancona, Italy.; [10]Gastroenterology Department, San G. Moscati Hospital, 83100 Avellino, Italy; [11]Department of Specialized Clinical Sciences and Odontostomatology, Ancona, Italy; [12]Institute of Food Sciences-CNR, Immuno-Morphology, Avellino, Italy; [13]Department of Translational Medical Sciences, University of Campania "Luigi Vanvitelli", 80138 Naples, Italy; [14]Department of Dermatology, University of Campania Luigi Vanvitelli, Naples, Italy; [15]University of Maryland, Baltimore, MD 21201, USA

Introduction: During the last decade several reports identified Non-Celiac Gluten Sensitivity (NCGS) as part of spectrum of Gluten-Related Disorders. However, its etiopathogenesis remain still unknown because the lack of reliable biomarkers, so it is preferred to consider this new clinical entity, as a sensitivity to wheat (NCWS) rather than gluten. Its diagnosis is still based on exclusion criteria of other gluten related disorders (celiac disease and wheat allergy), presence of compatible symptoms that resolve following the implementation of a gluten/wheat-free diet (GFD/WFD) and their reappearance following a Double-Blind, Placebo-Controlled (DBPC) gluten/wheat challenge.
We report the results of a large randomized, DBPC, two-arms, multicenter study which aimed to: 1) evaluate the gluten dependency of the clinical symptoms claimed by the patients identified as affected by NCGS; 2) identify possible biomarkers specific for the diagnosis of NCGS.
Materials and Methods: Patients identified as NCGS by the 2010 Munich criteria and on a strict GFD, were recruited in 7 different centers in Italy and United States from November 2011 to November 2015. Subjects were randomly assigned to a 14-days DBPC challenge, with envelopes containing 10g of either gluten (Glu group) or rice starch (Plb group). Before the challenge (T0), at the end of the challenge (T1) and after further 14 days of strict GFD (T2), gastrointestinal (GIS) and extraintestinal (EIS) symptoms and quality of life (QoL) questions were assessed respectively with Gastrointestinal Symptoms Rating Scale (GSRS), Extraintestinal Symptoms Rating Scale (ESRS)

and the State Anxiety Inventory-Form Y1 (STAI-Y1) questionnaire. The Gluten Challenge was considered positive when an increase >30%, in one or more scores was reported. At T1 patients underwent endoscopy with duodenal biopsies to assess histological pattern, gene mucosal expression of inflammatory/allergic cytokines of the innate and/or adaptive immune response. Finally, at each timepoints patients were assessed for serological biomarkers directed vs gluten, ATIs-related immune activation, and/or intestinal permeability impairment.
Results: 712 patients were initially interviewed; 110 of them (84.3% female, mean age 36.84±9.95 years) fulfilled the inclusion/exclusion criteria and were recruited and equally randomized to the Glu or Plb group. Nineteen patients dropped-out from the study (17.3%). Out of 42 patients who completed the challenge in Glu group, 26 were considered positives (61.9%) (true NCGS) and 16 negatives (38.1%). Conversely, out of 49 patients who completed the challenge in Plb group, 16 tested positive (32.7%) and 33 negative (67.3%). A significative difference was provided between the Glu group compared to Plb group when exposed to the challenge (P=0.05), with a RR of symptom's worsening=1.90 (95% CI 1.19-3.02, P=0.007) and an Odds Ratio of 3.35 (95 % CI: 1.41-7.94, P=0.006). Most of the patients in Glu group complained worsening of GSRS alone or in association with ESRS, but over a quarter (26.9%) complained exclusively ESRS worsening. To notice, most of the patients (75.0%) reported a QoL worsening due to GIS reappearance. Finally, at T2, approximately 50% of patients reported equal or better scores compared to the values registered at T0.
Related to the serum biomarkers, the mean values of both anti-gliadin antibodies (AGA) IgA and IgG significantly increased (T0 *vs* T1, P=0.005 and P<0.0001, respectively) after challenge, reducing at T2 (T1 *vs* T2, P=0.018 and P=0.04, respectively) in trueNCGS. ROC analysis showed that AGA IgA provided the best diagnostic performance, with a sensitivity of 91.03% and a specificity of 54.17%. No significant alterations were found in immunological response to ATIs, intestinal permeability and inflammatory cytokines pattern, excluding IL-8 values which showed a significant increase after gluten challenge (P<0.0001) in trueNCGS patients.
On the histology specimens no differences were found in CD3+ IELs infiltration, Marsh degree and villi/crypts ratio between true-NCGS and no-NCGS, whereas eosinophils (P=0.008), tryptase+ cells (P=0.027) and CD177+ cells (P=0.003) were significantly elevated in the true-NCGS patients. Of a large panel of mucosal gene expression, we found higher values of IgG1 (P=0.042), IgG4 (P=0.043), GATA-3 (P=0.003), and TBX-21 (P=0.001) in true-NCGS compared to no-NCGS.
Conclusion: Our study demonstrates that gluten is responsible of worsening of both GIS and EIS as well as of QoL, in a subgroup of NCGS patients. Our data seem to indicate that, even if a clear increase in proinflammatory cytokines cannot be proven, the increased IL-8 serum levels, the simultaneous activation of the Th1 and Th2 response suppression mechanisms (TBX-21 and GATA-3), the high presence of mucosal eosinophils and tryptase+ cells, the hyperexpression of the IgG1 and IgG4 genes, as well as the absence of a clear IgE-mediated response, may underlie the existence of a non-IgE-mediated hypersensitivity mechanism linked to the activation of innate immunity.

33. DONOR SCREENING AND STOOL BANKING FOR FECAL MICROBIOTA TRANSPLANTATION: RESULTS FROM A PUBLIC ITALIAN CENTER.

Marasco G., Marangoni A., Cremon C., Cogliandro R.F., Capelli E., Ciuffi B., Foschi C., Barbara M.R., Barone M., Trapani F.F.
University of Bologna

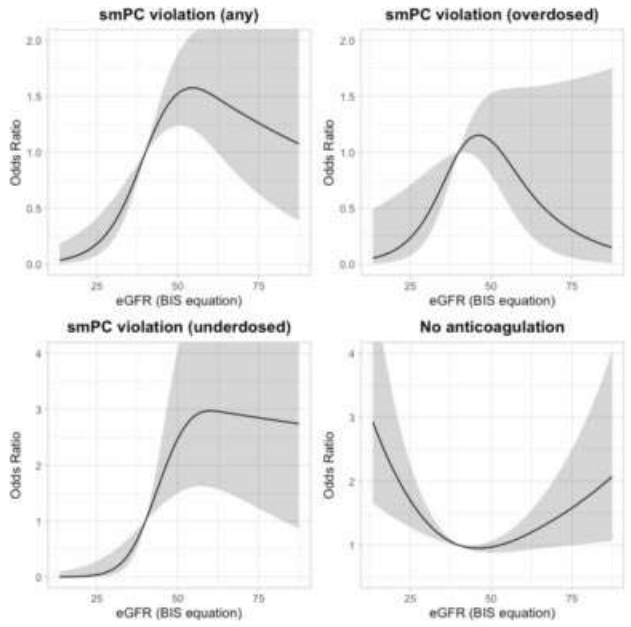
Introduction: Fecal microbiota transplantation (FMT) is an effective therapy for recurrent Clostridioides difficile infection. A pool of healthy stool donors is essential for any FMT program. However, donor recruitment is not easy due to screening failures and the commitment requested.
Aims & Methods: We aimed to report data from the first two years of stool donor screening, recruitment, and stool banking from the first public Italian FMT center. We prospectively collected data from donor screening questionnaires, laboratory evaluations, and donations. Donor screening has been performed according to the Italian Health Ministry regulation and the FMT European consensus FMT (1): potential donors, all aged below 50 years old, were initially screened for the presence of concomitant gastrointestinal and systemic diseases or for the anamnestic drugs intake or recent antibiotic intake. The subsequent clinical evaluation aimed at excluding at-risk conditions for infectious diseases, while the microbiological screening evaluated the colonization by potential pathogens. Bacterial counts in terms of aerobes and anaerobes concentration [colony forming unit (CFU)/mL] from aliquots of each frozen fecal material after aerobic samples preparation were assessed after 1 week and subsequently monthly until 18 months from the donation.
Results: Two hundred and 12 patients completed screening questionnaires. Of these, 29 (13.7%) were excluded for concurrent gastrointestinal symptoms (altered bowel habits) or diseases, 50 (23.6%) for concomitant systemic diseases, and 8 (3.8%) for antibiotic intake in the previous 6 months. Finally, of the 120 donors clinically evaluated, 79 (37.3%) were excluded for at-risk conditions for infectious disease (e.g., use of illegal drugs, risky sexual behavior, recent body tattoo, piercing, travel in tropical countries, healthcare workers, etc.). Among the remaining 41 donors microbiologically screened, 19 (9%) were excluded for pathogens or potential pathogens presence (6 pathogenic Escherichia coli, 1 Vancomycin-resistant Enterococci, 2 Helicobacter pylori, 1 Rotavirus, 1 Giardia, and 8 for other reasons). Finally, 22 subjects (10.4%) were suitable for donation. Among the 10 healthy donors actively donating stools (50% females), 6 were excluded for pathogens infections diagnosed during donation screenings after a median of 3 donations (3 pathogenic Escherichia coli, 1 Salmonella enterica, 1 Campylobacter jejuni, 1 Cryptosporidium). Among the remaining 4 subjects, 2 discontinued the donation program due to the commitment requested. Finally, 22 subjects (10.4%) were suitable for donation. Ten healthy donors actively donated stools (50% females), but 6 were excluded for pathogens/potentially pathogenic bacteria diagnosed during donation screenings after a median of 3 donations. Among the remaining 4 subjects, 2 discontinued the donation program due to the commitment requested. Aliquots evaluation showed no differences in aerobic counts until 18 months, while significant differences were found for anaerobic counts already after 1 month (1.33x10^10 CFU/mL vs 7.6x10^9 CFU/mL at donation and after 1 month, respectively, p=0.028).
Conclusion: Only one in ten potential healthy donors is finally eligible for stool donation. Frozen stool samples showed a significant decrease in anaerobic concentration already after 1 month from storage, compared to fresh material.
References:
1. Cammarota G., et al. Gut. 2017 Apr;66(4):569-580.

34. PRESCRIPTIVE APPROPRIATENESS OF DIRECT ORAL ANTICOAGULANTS IN OLDER SUBJECTS WITH ATRIAL FIBRILLATION DISCHARGED FROM ACUTE MEDICAL WARDS

Arena E.[1], De Vincentis A.[1], Soraci L.[2], Aucella F.[3], Sciacqua A.[4], Armentaro G.[4], Corsonello A.[5], Antonelli Incalzi R.[1]
[1]Dipartimento di Medicina Interna e Geriatria, Fondazione Policlinico Campus Biomedico, Roma; [2]Dipartimento di Geriatria, RCCS INRCA, Cosenza; [3]Dipartimento di Nefrologia, Fondazione Casa Sollievo della Sofferenza, San Giovanni Rotondo, Foggia; [4]Dipartimento di Geriatria, Ospedale Mater Domini -Università Magna Graecia, Catanzaro; [5]Unità di Laboratorio di Farmacoepidemiologia Geriatrica, INRCA, Cosenza

Background: With the advancement of medical treatments, people's life expectancy is increasing, but they are also facing a higher incidence of chronic illnesses. This, in turn, often results in the prescription of many medications (polypharmacy), which can increase the risk of adverse drug events. This is especially relevant in the acute care setting, where prescribed medications tend to proliferate, often with a suboptimal consideration of their appropriateness. Direct oral anticoagulants (DOACs) are often prescribed to older patients with prothrombotic conditions, but they can be subject to prescribing errors, particularly overdosing, and in minor proportion drug-drug interactions (DDIs). The aim of the present study was to evaluate the prevalence and appropriateness of DOAC prescriptions in older hospitalized patients with atrial fibrillation.
Methods: Data were extracted from an observational, retrospective, cross sectional study of patients aged 65 years old or more discharged from twenty-four geriatrics and fifteen nephrology units across Italy within the first half of 2018 (total N=2,202) funded by the Italian Society of Nephrology and the Italian Society of Gerontology and Geriatrics (SIN-SIGG). After excluding subjects without available data on serum creatinine and on prescribed drugs at discharge, 2,054 subjects were analyzed. The evaluation for prescriptive appropriateness was carried out using European Medical Agency (EMA) Summary of Products Characteristics (SmPC), STOPP v2 criteria and 2019 updated American Geriatric Society (AGS) Beers criteria and drug-drug interactions, either pharmacodynamic or pharmacokinetic as defined by the SmPC.
Results: Out of 2,054 eligible subjects, 609 individuals (52% women, mean age 85.1 years) presented with atrial fibrillation at hospital discharge, accounting for 204 of total DOACs prescriptions. In total, 31% of DOAC prescriptions in the sample were considered inappropriate based on smPC indications, with

13% of prescriptions being for higher doses and 17% being for lower doses than recommended. Additionally, 48% of subjects had potentially inappropriate medication involving DOAC according to STOPP/Beers criteria while 18% had a pharmacokinetic drug-drug interaction. Interestingly, we found a sizable number of patients (N=247, 41%) with AF who were discharged without an anticoagulant therapy. Body mass index (BMI, OR 1.05, 95%CI 1.01-1.10), chronic obstructive pulmonary disease (OR 1.97, 95%CI 1.15-3.36), coronary artery disease (OR 0.38, 95%CI 0.14-0.84), anaemia (OR 0.34, 95%CI 0.19-0.58) and eGFR (OR 1.02, 95%CI 1.01-1.04) were associated with smPC violations in subjects with AF. Consistent associations were confirmed at multivariable analyses for BMI (aOR 1.09, 95%CI 1.02-1.16), being admitted in a nephrology unit (aOR 0.32, 95%CI 0.10-0.86), anaemia (aOR 0.5, 95%CI 0.25-0.99) and eGFR (aOR 1.02, 95%CI 1.00-1.05). Finally, by means of restricted cubic splines, a non-linear relationship was disclosed between eGFR and the risk of smPC. In particular, the risk of smPC violations increased with eGFR values with a plateau starting from values of 50 ml/min/m2 and above (Figure, upper left panel). This was mainly explained by an increasing risk of DOAC underdosage at higher eGFR (Figure, lower left panel), while the risk of overdosage peaked at eGFR values 30-50 ml/min/m2, leaning down at lower (<30 ml/min/m2) and higher (>60 ml/min/m2) ranges (Figure, upper right panel).
Conclusions: Around a third of older subjects with AF was discharged from acute care wards with an inappropriate DOAC prescription. Moreover, nearly half were discharged without any anticoagulant therapy, even when indicated. In addition, DOAC inappropriate underdosing was more frequent than overdosing. Overall, this suggests that physicians may be overly concerned about the bleeding risk in older and frailer patients with AF, leading to the exclusion of those at higher risk of thromboembolic events from proper anticoagulant therapy. Further investigation is needed to determine the risk-benefit balance of anticoagulant therapy in this specific population.



35. FECAL MICROBIOTA TRANSPLANTATION FOR RECURRENT CLOSTRIDIOIDES DIFFICILE INFECTION IN FRAIL AND VERY OLD PATIENTS.

Agnitelli M. C.[1], Pellegrino S.[1], Pero E.[1], Ibba F.[1], Gallo A.[1], Gasbarrini A.[2], Landi F.[1], Cammarota G.[2], Ianiro G.[2], Montalto M.[1]
[1]Medicina Interna Geriatrica, Università Cattolica del Sacro Cuore, Fondazione Policlinico Gemelli IRCCS, Roma; [2]Medicina Interna e Gastroenterologia, Università Cattolica del Sacro Cuore, Fondazione Policlinico Gemelli IRCCS, Roma

Introduction: The incidence of Clostridioides difficile infection (CDI) is significantly growing over the past decades, mainly in hospitalized older patients undergoing prolonged courses of antibiotic therapy. Currently, the hardest challenge in the management of CDI is the sustained cure of recurrent infection. In recent years, fecal microbiota transplantation (FMT) has emerged as a highly effective treatment, widely recommended for the treatment of recurrent CDI (rCDI) or refractory CDI, with high efficacy also in severe and fulminant forms of CDI, and an overall high safety level. However, there is still concern about its real applicability in the elderly. Our study aims to evaluate the efficacy and safety of FMT in a group of very old subjects with rCDI, and to identify patient features potentially associated with clinical outcomes.
Patients and methods: This is a retrospective single-center study performed in a tertiary care center (Fondazione Policlinico Gemelli, Rome, Italy), including patients aged over 85 years old, treated with FMT for rCDI. Primary outcomes included efficacy of FMT, defined as cure of CDI at 8 week-follow-up, and safety evaluation. We retrospectively evaluated the baseline functional status by the Charlson Comorbidity Index (CCI), and frailty through the Clinical Frailty Scale (CFS) and correlated these variables with clinical outcomes of FMT. We recorded for each patient minor and major FMT-related adverse events occurring within the 8 weeks, by regular visits or phone interview, eventually with care-givers, in those subjects unable to perform a regular outpatient assessment.
Results: Records relative to 50 patients fitting inclusion criteria between January 2014 and May 2022 were recorded. Seven incomplete records were excluded. Thus, our final study cohort included 43 patients with a median age of 88 years [range 85-90]. Median CCI was 7 [6-8] and median CSF was 7 [5-7]. According to the CSF, none of the patient (0%) was classified as fit, 20 (46.5%) were classified as vulnerable, and 23 (54.5%) were classified as frail. All patients received at least one FMT, and 33 of them were cured after a single FMT (77.0%). Among the ten remaining patients, eight received further fecal infusions, including six patients who presented with pseudomembranes at first FMT and were treated with early repeat FMT per our previous protocol, and two patients who recurred 7-10 days after the first FMT. Finally, the other two patients failing the first FMT did not undergo repeat FMT, being treated respectively with fidaxomicin and tapered vancomycin. Five of the eight patients undergoing repeat FMT achieved the CDI cure, increasing the overall cure rate of FMT in our cohort to 88.0% (38 of 43 patients). Of the three patients who failed the FMT, the first, aged 86 years old, was unsuccessfully treated with pulsed vancomycin and fidaxomycin and finally achieved cure after tapered vancomycin, the second and the third, aged 93 and 87 years old respectively, were successfully treated with a long-term tapered scheme of vancomycin therapy. The CFS was able to discriminate those patients achieving cure, both after the first FMT and after multiple infusions, and those patients that did not ($p<0.01$). Three patients (7.0%) were re-hospitalized for recurrence of CDI, while four patients were re-hospitalized for other causes than CDI. Eleven (25.0%) patients experienced mild adverse events related or possibly related to FMT, including abdominal pain (4 patients, 9.3%), constipation (1 patient, 9.0%), dyspnea (4 patients, 9.3%) and fever with TC >37.5°C (2 patients, 4.7%). All these symptoms disappeared within the following 48-72 h. Only one patient (2.3%) died within 7 days from the first FMT. He suffered from decompensated hepatic cirrhosis (Child-Pugh B10, MELD 10) and died of respiratory failure related to massive pleural effusion.
Discussion: Our study shows that FMT is effective and safe in very old patients and that frailty assessment at baseline may correlate with FMT outcomes. While chronological age and comorbidities do not always truly reflect the overall health status of older patients, frailty assessment is growing as one of the most relevant methods in defining the real complexity of these subjects. Frailty is usually associated with a higher prevalence of adverse health outcomes and, encouraging a multidisciplinary approach, may be useful for risk stratification and decision-making in different clinical settings.

36. MUTUAL EFFECT MODIFICATION BETWEEN INSULIN-RESISTANCE AND ENDOTHELIAL DYSFUNCTION IN PREDICTING INCIDENT HEART FAILURE IN HYPERTENSIVES

Perticone M.[1], Maio R.[2], Gigliotti S.[3], Shehaj E.[4], Toscani A.F.[5], Marincola L.[5], Severini G.[5], Potenza G.[5], Fabiani G.[6], Capomolla A.[7], Macrì P.G.[8], Sciacqua A.[5], Perticone F.[5]

[1]Dipartimento di Scienze Mediche e Chirurgiche, Università Magna Graecia di Catanzaro; [2]UOC di Geriatria, AOU Renato Dulbecco di Catanzaro; [3]Dipartimento di Scienze della Salute, Università Magna Graecia di Catanzaro; [4]UOC di Cardiologia-UTIC, Ospedale Giovanni Paolo II, Lamezia Terme; [5]Dipartimento di Scienze Medico-Chirurgiche, Università Magna Graecia di Catanzaro; [6]Dipartimento di Medicina Sperimentale e Clinica, Università di Firenze; [7]Don Mottola Medical Center, Drapia; [8]UOC Medicina Legale e responsabilità sanitaria ASL Toscana Sud Est, Arezzo

Introduction: Heart failure (HF) is a complex clinical syndrome characteri-

zed by diminished quality of life, high mortality, and recurrent and expensive hospital admission. Both ischemic heart disease and type-2 diabetes mellitus represent the major clinical conditions involved in the appearance and progression of HF. Thus, early identification of possible predictor of incident HF may be considered an interesting and important strategy to reduce morbidity and mortality HF-related as well as healthcare costs.
The vascular endothelium is an active autocrine, paracrine, and endocrine organ that is essential for the regulation of vascular tone and the maintenance of vascular homoeostasis. Endothelial activation, also known as endothelial dysfunction, is a principal determinant of microvascular dysfunction by shifting the physiological vascular equilibrium towards more vasoconstriction with subsequent organ ischemia, inflammatory and procoagulant state, and proliferation of smooth muscle cells. Endothelial dysfunction is considered the earliest pathophysiologic step in the atherosclerotic process, and it is an established independent and powerful prognostic factor for adverse cardiovascular outcomes in different setting of patients, appearance of new diabetes and incident HF. Several evidences demonstrate that endothelial dysfunction participates to HF pathogenesis with different mechanisms, such as the reduction of vasoreactivity of epicardial and small coronary vessels, the cardiac post-load increase, myocardial oxidative stress and fibrotic process. Endothelial dysfunction is present in patients with chronic HF, both in those with reduced and preserved ejection fraction.
Thus, the aim of this study was to investigate the possible interaction between endothelium-dependent vasodilation, tested by pharmacologic stimulation of muscarinic receptor, and insulin-resistance state, evaluated by the HOMA-index, in predicting incident HF in a very large and well characterized group of hypertensive patients.
Materials and Methods: We recruited a total of 705 Caucasian patients [358 men and 347 women aged 22-73 years (mean age 48.4+10.5 years), with *SBP* >140 mmHg and/or *D*BP >90 mmHg. Vascular function was evaluated through strain-gauge plethysmography, with arterial infusion of sodium-nitroprusside and acetylcholine (ACh).
Results: During the follow-up [median 117 months (range 31–211)], there were 223 new cases of HF (3.3 events/100 patient-years). Stratifying the study population in progressors and non-progressors, progressors were older and had a higher prevalence of females, baseline glucose, insulin, HOMA, creatinine, and hs-CRP mean values, while estimated glomerular filtration rate and endothelium-dependent vasodilation were lower. In the multiple Cox regression analysis, serum hs-CRP (HR=1.362,(95% CI=1.208-1.536), HOMA (HR=1.293, 95% CI=1.142-1.465), maximal ACh-stimulated FBF (100% of increase, HR=0.807,(95% CI=0.697-0.934) and e-GFR (10 ml/min/1.73m2 increase, HR=0.552, 95% CI=0.483-0.603) maintained an independent association with incident HF. HOMA and endothelial dysfunction interact between them in a competitive manner (HR = 6.548, 95% CI = 4.034-10.629), showing also a mutual effect modification.
Conclusions: The major finding obtained in the present study, conducted in a very large population of well-characterized never treated hypertensive patients, is the demonstration, for the first time, of a possible competitive interaction between maximal ACh-stimulated forearm blood flow and HOMA in the appearance of incident HF. The biological plausibility of this evidence is based on the fact that our data demonstrate that HOMA significantly modifies the prognostic effect of ACh-stimulated FBF on incident HF and vice versa. On this basis, it is evident that the less favorable median value of one of the two variables significantly reduces the risk of HF attributable to the other variable. Thus, our findings reinforce the causative role of endothelial dysfunction in the cardiovascular continuum, from hypertension to clinical outcomes, as already demonstrated by our group [12] in the same population. Secondly, for the first time, we demonstrated that also insulin resistance, evaluated by HOMA, is an independent and strong predictor of incident HF; this finding, obtained in a very well-characterized population, represents an additional step in the comprehension of the pathophysiological mechanisms shared by both HF and insulin resistance, in the continuum of cardio-metabolic diseases. In conclusion, it is possible to affirm that both endothelial dysfunction, evaluated by strain-gauge plethysmography, and insulin-resistance, measured by HOMA, are independent and strong predictors of incident HF in never treated hypertensive patients. In addition, our data demonstrate that these two conditions interact between them with a competitive mechanism.

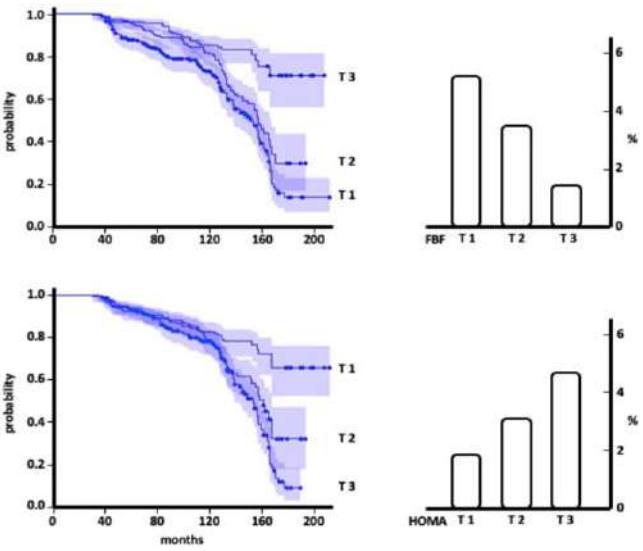
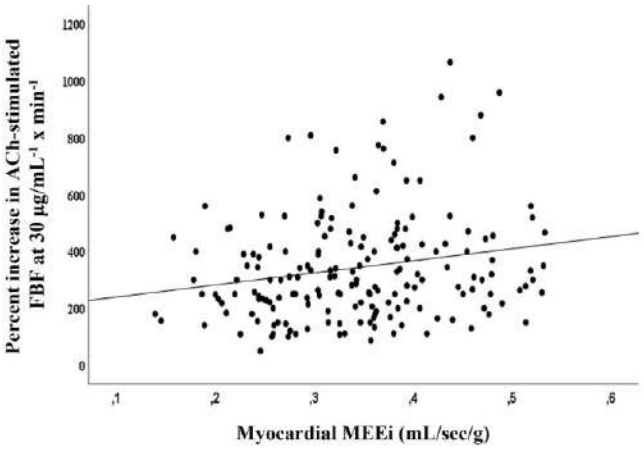


Figure 1. Survival curves for incident heart failure in hypertensive patients by tertiles of both maximal ACh-stimulated forearm blood flow (FBF) and HOMA (**a**), and crude (**b**) incident of events by tertiles of endothelium-dependent vasodilation and HOMA.

37. ENDOTHELIAL DYSFUNCTION IS ASSOCIATED WITH REDUCED MYOCARDIAL MECHANO-ENERGETIC EFFICIENCY IN DRUG-NAÏVE HYPERTENSIVE INDIVIDUALS

Cefalo C.M.A.[1], Riccio A.[1], Fiorentino T.V.[2], Rubino M.[2], Mannino G.C.[2], Succuro E.[2], Perticone M.[2], Sciacqua A.[2], Andreozzi F.[2], Sesti G.[1]
[1]Dipartimento di Medicina Clinica e Molecolare, Università Roma La Sapienza ; [2]Dipartimento di Scienze Mediche e Chirurgiche, Università Magna Graecia di Catanzaro

Background: Impaired myocardial mechano-energetics efficiency (MEEi) was shown to predict incident heart failure, but pathophysiological mechanisms linking impaired MEEi with heart failure have not been elucidated. Endothelial dysfunction is a plausible candidate because it has been associated with heart failure. This study aims to investigate the association between MEEi and endothelium-dependent vasodilation, among drug-naïve hypertensive individuals.
Methods: 199 drug-naïve hypertensive individuals participating in the CATAnzaro MEtabolic RIsk factors (CATAMERI) study were included. All participants underwent to an oral glucose tolerance test and to an echocardiogram for myocardial MEEi measurement. Endothelial-dependent and endothelial-independent vasodilatation were measured by strain-gauge plethysmography during intra-arterial infusion of acetylcholine and sodium nitroprusside, respectively. A multivariate linear regression analysis was conducted to investigate the independent association between maximal endothelial-dependent vasodilation and MEEi.
Results: Maximal ACh-stimulated forearm blood flow (FBF) was associated to decreased myocardial MEEi (β =0.205, P=0.002) independently of well-established cardiovascular risk factors including age, sex, BMI, waist circumference, smoking status, total and HDL cholesterol, triglycerides, hsCRP, glucose tolerance status, and HOMA-IR index of insulin resistance. Conversely, no association was observed between SNP-stimulated vasodilation and MEEi.
Conclusions: We found that endothelium-mediated vasodilation contributed to reduced myocardial MEEi independently of several potential confounders. Because diminished myocardial MEE has been previously associated with incident heart failure, a non-invasive assessment of myocardial MEEi may improve the identification of individuals at higher cardiovascular risk who may benefit from the initiation of pharmacological treatments ameliorating the endothelial dysfunction.



Correlation between ACh-stimulated FBF and myocardial MEEi

38. EFFECTS OF INTRAVENOUS FUROSEMIDE PLUS SMALL-VOLUME HYPERTONIC SALINE SOLUTIONS ON INFLAMMATORY, REMODELLING MARKERS AND EPIGENETICS SIGNATURES OF PATIENTS WITH CONGESTIVE HEART FAILURE.

Daidone M.[1], Del Cuore A.[1], Casuccio A.[2], Soldano J.[1], Puleo M.G.[1], Di Chiara T.[1], Di Raimondo D.[1], Clemente G.[1], Tuttolomondo A.[1]
[1]U.O. C di Medicina Interna con Stroke Care, Dipartimento di Promozione della Salute, Materno-Infantile, di Medicina Interna e Specialistica di Eccellenza "G. D'Alessandro"(PROMISE), University of Palermo, Italy.; [2]Dipartimento di Promozione della Salute, Materno-Infantile, di Medicina Interna e Specialistica di Eccellenza "G. D'Alessandro"(PROMISE), University of Palermo, Italy.

Background: Heart failure (HF) is a leading cause of death in industrialized nations, especially in an ageing population. In strong contrast to the therapeutic developments in cardiac revascularization therapy, novel conceptual approaches in the clinics to treat the heart at the wound healing phase and to improve cardiac remodelling processes remain scarce. HF involves micro- and macro-structural changes, each involving the activation of inflammatory and neuro-hormonal systems that release several biomolecules to compensate for the failing heart. Consequently, a storm of cytokines and regulatory molecules is released. The abundance of dysregulated molecules makes it difficult to identify biomarkers that can specifically aid in HF prognosis.
Aims: We sought to compare the effects of furosemide + HSS treatment in patients with acute decompensated heart failure in comparison to furosemide alone and the response in a compensated state after an acute saline load with regard to serum levels of heart failure biomarkers. We also aimed to further address the yet actual knowledge gap concerning the role of miRNA not only as a pathogenetic factor but also as possible therapeutic efficacy markers. Thus, we investigated the effects of treatment with high dose furosemide + HSS on fold changes of circulating miRNAs potentially involved in structural alterations of the failing heart.
Materials and Methods: All consecutive patients aged >18 years with a diagnosis of acute decompensated congestive heart failure due to HF with reduced ejection fraction (HFrEF) admitted to our Internal Medicine ward enrolled from 03/2017 to 11/2019. Enrolled patients were randomly assigned to undergo treatment with moderate/high doses of i.v. furosemide plus hypertonic saline solution or i.v. furosemide alone (1:1). Patients were randomly assigned to undergo treatment with i.v. furosemide plus HSS or i.v. furosemide alone (1:1). Patients underwent three different evaluations at T0 *(at admission before treatment)*, T1 *(after six days of treatment))*, and *T2 (after a saline load)* by venipuncture to obtain venous blood samples for the determination of serum concentrations of NT-proBNP, hsTnT, s-ST2, galectin-3, IL-6, and CRP and of some microRNA fold increase as markers of epigenetic modifications induced by the two different treatments.
Results: We enrolled 200 patients with acute decompensated HFrEF. 107 patients randomized to treatment with i.v. high-dose furosemide plus HSS, 93 patients were randomized to i.v. high-dose furosemide alone. Patients treated with furosemide plus HSS compared to controls showed a comparable degree of reduction in the serum levels of IL-6, sST2, and NT-proBNP in the "between-group" analysis. Nevertheless, patients treated with high-dose furosemide + HSS showed significantly higher absolute delta values of IL-6, sST2, hsTnT, NT-proBNP and galectin-3. After acute saline load, a lower increase in the serum concentrations of IL-6, sST2 and NT-proBNP**.** At "*between-group*" analyses, between T0 and T1, patients treated with intravenous furosemide plus HSS showed a more significant degree of reduction in the serum levels of IL-6, sST2, NT-proBNP and galectin-3. At "*between-group*" analyses, between T1 and T2, controls treated with i.v. furosemide alone compared to patients treated with intravenous moderate/high-dose furosemide plus HSS showed a more significant degree of increase in the serum levels of IL-6, hsTnT, sST2, NT-proBNP and galectin-3. Nevertheless, in the "*in-group*" analyses, no significant difference in the degree of reduction in the serum levels of IL-6, hsTnT, NT-proBNP, ST2, galectin-3, and SST2 between patients treated with i.v. furosemide plus HSS. With regard to MIRNA fold change, we observed at "between-group" analysis only a higher reduction of MIR181b*1* fold change in subjects treated with i.v. furosemide plus HSS, at T1 and of MIR365, whereas we observed a reduction of MIR125a5p at T2 in subjects treated with furosemide alone and a reduction of MIRNA 181b fold in subjects treated with furosemide plus HSS. At "in-group" analysis, we observed a change at T0 vs T1 with regard to MIR214**,** MIR181, MIR1505p, MIR125a5p and at T1 vs T2 with regard of MIR214, MIR365, MIR181b, MIR1505p, MIR125a5p**.**
Discussion: Our findings concerning a higher degree of modulation of biomarkers of heart failure after combined treatment with intravenous furosemide and HSS, and this finding has also an epigenetic feature indicating a possible genetic modulation of treatment with i.v furosemide plus HSS. This issue may have possible benefits on clinical practice concerning its therapeutic effects over and beyond the simple amelioration of clinical congestion signs and symptoms. Nevertheless, our findings of higher delta values after treatment with i.v. furosemide plus HSS indicate a possible higher efficacy by means of modulation of the stretching and fibrosis mechanisms.

39. "CHOOSING WISELY" IN PULMONARY ARTERIAL HYPERTENSION: REDEFINING CURRENT SCREENING, FOLLOW-UP AND PROGNOSTIC PROCEDURES IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION

Valente V.[1], D'Agostino A.[2], Crisci G.[3], Giardino F.[3], Rainone C.[3], Argiento P.[4], Romeo E.[4], D'Alto M.[4], Gargani L.[5], Bossone E.[6], Salzano A.[7], Cittadini A.[3], Marra A.M.[3]
[1]Department of Translational Medical Sciences,University of Naples Federico II ,Naples ,Karolinska Institutet Department of Medicine, Solna, Sweden; [2]IRCCS SYNLAB SDN; [3]Department of Translational Medical Sciences,University of Naples Federico II, Naples ; [4]Department of Cardiology, Second University of Naples, Monaldi Hospital, Naples; [5]Institute of Clinical Physiology, National Research Council, Pisa; [6]Department of Public Health,University of Naples Federico II , Naples; [7]AORN Antonio Cardarelli-Cardiology ,Naples /University of Leicester: Leicester, Leicestershire, GB

Background: Pulmonary arterial hypertension (PAH) is a progressive condition characterized by high pulmonary arteriolar resistance, eventually leading to right heart failure and death.
Although the prevalence of the disease is increasing in individuals over the age of 65, the diagnosis often remains unrecognized due to the lack of a non-invasive diagnostic tool of choice and the poor specificity of the clinical presentation.
Aim of the study is to establish a clinical-instrumental score capable of estimating the probability of Pulmonary Arterial Hypertension to facilitate the diagnosis of PAH and reduce the number of right heart catheterizations (RHC) performed, currently, the only recognized diagnostic method.
Methods: 200 patients with the desired inclusion criteria (age ≥ 18 years, belonging to one of the high-risk PAH categories such as connective tissue disease, congenital heart disease, HIV infection and portal hypertension) were enrolled at Ospedale dei Colli and at Policlinico 'Federico II' between October 2017 and October 2020 and underwent a protocol of diagnostic techniques for PAH according to the 2015 ESC/ERS guidelines. An RHC was then performed to confirm or reject the hypothetical diagnosis of PAH.
Correlations between clinical-instrumental data and the diagnosis of PAH, were assessed by univariate logistic regression model, and regression coefficient, odds ratio, and 95% confidence intervals were calculated for each variable. Subsequently, the evaluation of significant parameters in the univariate analysis was performed using multivariate logistic regression models. The multivariate statistical was adjusted with the estimates for the different confounding factors, providing adjusted odds ratios for the various covariates. The score on the general population was composed based on the multivariate variables taking into account the odds ratios obtained. An alpha error of 0.05

has been used as the cutoff for significance.
Results: Out of 200 patients,147 were female (73.5%) who showed better left ventricular systolic function parameters (EF 57.3 ± 4.9 vs 48.1 + 14.6 p<0.0001) e right ventricular arterial coupling (TAPSE\PASP 0.42 ±0.19 vs 0.35 ±0.18 p 0.04). A total of 66 patients (55 female,11 male) tested positive for RHC and were effectively diagnosed with PAH.
In the subgroup of PAH patients, female gender (univariate odds ratio 0.44 CI 0.21 – 0.92 *p* 0.03; multivariate odds ratio 0.33 CI 0.14 – 0.79 *p* 0.01) echocardiography-estimated PAPS greater than 45 mmHg(2.60 CI 1.11 – 6.00 *p* 0.0; 4.24 CI 1.68 – 10.71 *p*. 0.002), ejection fraction greater than 60% (1.90 CI 1.02 – 3.50, *p* 0.04; 2.10 CI 1.10 – 4.21 *p* 0.04) and normal spirometric pattern (2.10 CI 1.10 – 4.10 *p* 0.03; 3.10 CI 1.45 – 6.70 *p* 0.004) are significantly associated with the diagnosis of PAH.
With these parameters, a clinical-echocardiographic score for the diagnosis of PAH in the general population was constructed.
Considering the odds ratios obtained in the multivariate analysis, we assigned: 1 point to female patients, 2 points to patients with echocardiographic PAPs > 45 mmHg, 1 point to patients with LVEF>60%, and 1 point to patients with normal spirometry. The final score was obtained from the sum of the above scores ranging from a minimum of 0 to a maximum of 5
Only 1% of the study population scored 0. The highest prevalence of PAH was found in the group of patients with a score of 5 (64%), followed by patients with a score of 4 (40%). In patients with a score of 2, the prevalence of PAH was 14%.
Using a univariate logistic regression model, a score value ≥ 4 has been shown to predict a final diagnosis of PAH using only the clinical data of the patients (odds ratio 3.81 CI 1.98-7.13 p <0.0001).
Conclusion
Our score was developed to provide physicians with a simplified method of risk calculation that can be routinely applied in clinical practice to choose wisely which patients to submit to RHC and which not.

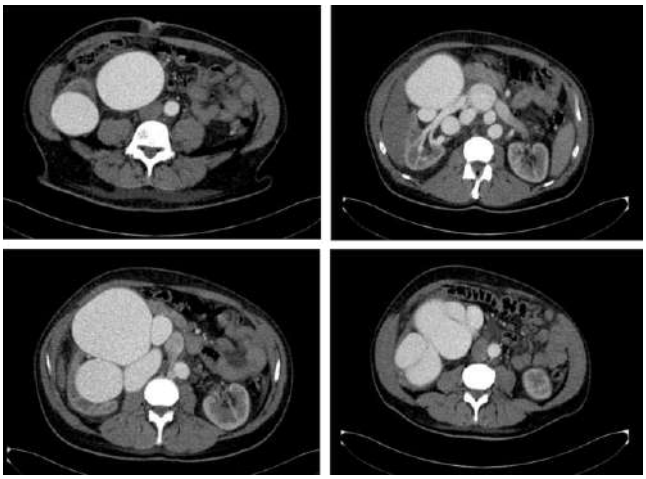
Table 1. Univariate and multivariate odds ratio for the subgroup of PAH patients.

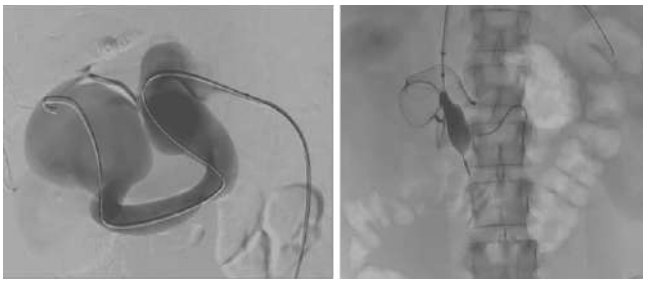
	Univariate			Multivariate			
	B	Odds ratio	95 % CI	p	B	Odds ratio	95% CI	p
Sex female (0,1)	-0.83	0.44	0.21 – 0.92	0.03	-1.10	0.33	0.14 – 0.79	0.01
PASP > 45 mmHg (0,1)	0.95	2.60	1.11 – 6.00	0.03	1.45	4.24	1.68 – 10.71	0.002
LV EF > 60 % (0,1)	0.64	1.90	1.02 – 3.50	0.04	0.74	2.10	1.10 – 4.21	0.04
PFR Normal pattern (0,1)	0.74	2.10	1.10 – 4.10	0.03	1.13	3.10	1.45 – 6.70	0.004

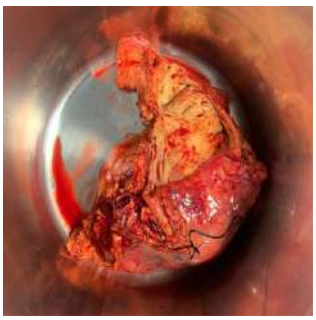
40. THE LAST DROP MAKES THE CUP RUN OVER: EXPLORING A RARE ETIOLOGY OF RIGHT VENTRICULAR FAILURE"

Di Francesco P.[1], Della Torre A.[2], Miglio M.[2], Montano N.[2]
[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico; [2]Università degli studi di Milano Statale

Right ventricular failure is a complex phenomenon that can result from various initiating factors, including increased afterload, decreased contractility, volume overload, and/or RV outflow obstruction. Symptoms of RVF can resemble those of other conditions such as portal hypertension and liver failure.
We present a case of a 55-year-old male who presented to the emergency room with exertional dyspnea and edema. The symptoms had started six months prior to admission and had improved with diuretic therapy, but rapidly recurred upon discontinuation. An echocardiogram revealed mild tricuspid regurgitation with bi-atrial enlargement. During a subsequent relapse of symptoms, follow-up tests showed increased bilirubin levels and nt-proBNP. Abdominal ultrasound revealed dilation of the inferior vena cava, initial ascites, absence of bile duct dilation, and a right polycystic kidney.
The patient was referred to the emergency room, where a complete blood test showed mild renal insufficiency, worsening signs of cholestasis, absence of inflammation, normal white blood cell count, and normal electrolyte levels. A comprehensive echocardiography demonstrated severe right atrial dilation (55 cm^2), tricuspid regurgitation, and dilation of the main pulmonary artery trunk and its major branches. Dynamic parameters were consistent with a hyperdynamic circulation. Chest CT scan ruled out primary pulmonary diseases causing pulmonary hypertension or signs of chronic pulmonary embolism.
After admission to the internal medicine department, diuretic therapy was initiated, leading to a rapid improvement in symptoms. An abdominal CT scan was performed to investigate the causes of the hyperdynamic circulation, revealing a high-flow arteriovenous fistula (HFAVF) involving the right renal artery and vein, along with multiple large collaterals, the largest exceeding 10 cm in diameter. These findings were previously misinterpreted as renal cysts in the ultrasound exams. The diagnosis was confirmed through an angiographic study, and multiple attempts to correct the fistula with endovascular stents were made but proved unsuccessful. Eventually, the patient underwent open surgery, including fistulectomy and right nephrectomy. Following the procedure, the hyperdynamic state was rapidly resolved, and there was a gradual restoration of normal pressure values in the right atrium and ventricle. The hospitalization was prolonged due to several complications, including pulmonary embolism, intestinal ischemia necessitating a colostomy, and septic shock. Finally, the patient was discharged after receiving rehabilitation. This case highlights a rare cause of right ventricular failure, likely of congenital origin, which went undetected until fluid overload began affecting the patient's well-being. The management of such a complex situation required a multidisciplinary team involving cardiologists, internists, ICU specialists, interventional radiologists, and surgeons from various backgrounds, including urologists, vascular surgeons, and abdominal surgeons.
It is interesting to reflect on the fact that the vascular anomaly was initially mistaken for a polycystic kidney, a common finding in abdominal ultrasound. The use of Doppler technology, while not commonly used to study renal cysts, could potentially have led to a faster diagnosis.







41. EXPLORATORY ANALYSES FROM APOLLO-B, A PHASE 3 STUDY OF PATISIRAN IN PATIENTS WITH ATTR AMYLOIDOSIS WITH CARDIOMYOPATHY

Perlini S.[1], Kale P.[2], Maurer M.S.[3], Fontana M.[4], Grogan M.[5], Fernandes F.[6], Palecek T.[7], Taylor M.[8], Hung R.R.[9], González-Duarte A.[10], Poulsen S.[11], Donal E.[12], Perfetto F.[13], Tsujita K.[14], Yu W-C.[15], Sarswat N.[16], White M.T.[17], Yureneva E.[17], Jay P.Y.[17], Vest J.[17],Gillmore J.D.[18]

[1]Dipartimento Medicina Interna, Medicina Urgenza, Università degli Studi di Pavia, Pavia, Italy; [2]Advanced Heart Failure and Transplant Department, Baylor University Medical Center, Dallas, TX, USA; [3]Columbia University Medical Center, New York, NY, USA; [4]Division of Medicine, University College London, Royal Free Hospital, London, UK; [5]Division of Cardiovascular Diseases, Mayo Clinic College of Medicine, Rochester, MN, USA; [6]Instituto do Coração – HCFMUSP, São Paulo, Brazil; [7]2nd Department of Medicine - Department of Cardiovascular Medicine, First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Prague, Czech Republic; [8]Department of Clinical Immunology and Allergy, Westmead Hospital and Westmead Clinical School, University of Sydney, Sydney, Australia; [9]Division of Cardiovascular Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA; [10]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México D.F., México; [11]Aarhus University Hospital, Aarhus, Denmark ; [12]Inserm, LTSI - UMR 1099, Centre Hospitalier Universitaire de Rennes, Rennes, France; [13]Department of Clinical and Experimental Medicine, Careggi University Hospital, Firenze, Italy; [14]Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Kumamoto-shi, Japan; [15]Taipei Veterans General Hospital, Taipei, Taiwan, Province of China; [16]Department of Medicine, University of Chicago, Chicago, IL, USA; [17]Alnylam Pharmaceuticals, Cambridge, MA, USA; [18]UCL Medical School, Royal Free Hospital, National Amyloidosis Centre, London, UK

Introduction: Transthyretin-mediated (ATTR) amyloidosis is a progressive and fatal disease caused by TTR amyloid accumulation in organs and tissues. Patients with hereditary or wild-type ATTR amyloidosis frequently develop cardiomyopathy, as demonstrated by cardiac biomarkers and imaging. Patisiran, an IV RNAi therapeutic that inhibits synthesis of wt and variant TTR, is approved for the treatment of hATTR amyloidosis with polyneuropathy. Hypothesis: Patisiran can benefit a range of disease-relevant measures in patients with ATTR amyloidosis with cardiomyopathy.
Methods: Patients were 18–85 yrs old with evidence of cardiac amyloidosis by echocardiography, either ATTR amyloid deposition on tissue biopsy or fulfilling nonbiopsy diagnostic criteria for ATTR amyloidosis with cardiomyopathy, and with prior hospitalization for heart failure due to ATTR amyloidosis or clinical evidence of heart failure. Patients were randomized (1:1) to receive patisiran IV 0.3 mg/kg or placebo Q3W for 12 months. The primary endpoint was change from baseline in 6-MWT at Month 12 (M12) with patisiran vs placebo. Exploratory parameters at M12 included changes in cardiac biomarkers, echocardiographic parameters of cardiac structure and function, and Tc scintigraphy parameters.
Results: APOLLO-B enrolled 360 patients (patisiran, n=181; placebo, n=179): median age (range) age, 76.0 (41, 85) yrs; male, 89%; wtATTR, 80%; on tafamidis at baseline, 25%. Patisiran showed a significant benefit compared with placebo in the 6-MWT (median [95% CI] change from baseline: patisiran, -8.15 [-16.42, 1.50]; placebo, -21.35 [-34.05, -7.52]; Hodges-Lehmann estimate of median difference: 14.69 [0.69, 28.69]; p=0.0162). Patisiran demonstrated favorable trends in change from baseline of NT-proBNP (adjusted geometric mean fold change ratio [95% CI]: 0.80 [0.73, 0.89]; nominal p=1.825 × 10–5) and troponin I (adjusted geometric mean fold change ratio [95% CI]: 0.87 [0.80, 0.95]; nominal p=0.0011) at M12 vs placebo. Patisiran also demonstrated a trend towards benefit in change from baseline of most evaluated echocardiographic parameters at M12 vs placebo. Patisiran-treated patients who were evaluable for scintigraphy (n=37) experienced a reduction (37.8%) or no change (62.2%) in Perugini grade at M12 compared with baseline (3 [8.1%] patisiran patients reduced from baseline by ≥2 Perugini grades). Among evaluable placebo patients (n=28) at M12, none experienced a reduction from baseline in Perugini grade, and 1 (3.6%) increased in grade. Patisiran demonstrated an acceptable safety profile; AEs were mostly mild or moderate in severity, and there were no cardiac safety concerns.
Conclusions: Exploratory analyses after 12 months provide further evidence for the potential benefit of patisiran treatment on cardiac biomarkers and manifestations of cardiac amyloid involvement in patients with ATTR amyloidosis. The long-term impact of patisiran on these measures will be assessed in the ongoing APOLLO-B open-label extension (NCT03997383).

42. URINARY HYALURONIDASE ACTIVITY IN SPONTANEOUSLY HYPERTENSIVE RATS (SHR): RELATIONSHIP WITH ACTIVATION OF THE VASOPRESSINERGIC SYSTEM AND SUSCEPTIBILITY TO ESSENTIAL HYPERTENSION

Bongrani A.[1], Verzicco I.[1], Tedeschi S.[1], Graiani G.[2], Cavazzini S.[3], Dancelli S.[1], Vicini V.[1], Calvi A.[1], Coghi P.[1], Montanari A.[1], Cabassi A.[1]

[1]Clinica Medica Generale e Terapia Medica, Dipartimento di Medicina e Chirurgia, Università degli Studi di Parma; [2]Unità di Istologia e Istopatologia, Laboratorio di Biologia Molecolare, Dipartimento di Medicina e Chirurgia, Università degli Studi di Parma; [3]Servizio Medicina Preventiva dei Lavoratori, Dipartimento di Medicina e Chirurgia, Università degli Studi di Parma

INTRODUCTION: Water-sodium homeostasis plays a key role in blood pressure regulation and kidney is one of the main players in this process. In particular, water reabsorption in the collecting duct is strictly dependent on the activation of vasopressin (or antidiuretic hormone, ADH), which stimulates the translocation of Aquaporin 2 to the tubule apical membrane via interaction with V2 receptors on principal cells. The process of urine concentration and dilution also appears to be related to the content of hyaluronic acid in the renal interstitial medullary, which in turn is regulated by several hormones involved in water homeostasis. The aim of our study was therefore to assess hyaluronidase activity in the urine of spontaneously hypertensive rats (SHR), an experimental model of essential hypertension in humans, treated or not with vasopressinergic antagonists.
MATERIAL AND METHODS: The study included female SHR (n=28) and Wystar Kyoto (WKY, n=12, normotensive control group) rats, evaluated between 3 and 27 weeks of age. Considering that SHR rats develop essential hypertension from 6 weeks of age, 20 of them were treated from day 25 to day 49 of life with a vasopressin antagonist selective for V1 or V2 receptors (OPC 21268, n=10, and OPC 41061, n=10, respectively). At the age of 3, 8, 15 and 27 weeks, hyaluronidase activity was measured by turbidimetry on urine from two consecutive days.
RESULTS: Although hyaluronidase activity decreased with age in all groups, SHR rats showed significantly higher values than WKY rats, from the pre-hypertensive stage ($p<0.05$) to the stage of established hypertension with organ damage ($p<0.001$). Furthermore, while treatment with the V1 vasopressinergic antagonist induced an increase in urinary hyaluronidase activity ($p<0.01$ vs. untreated SHR rats), SHR rats receiving the V2 antagonist showed comparable levels to WKY rats ($p<0.05$ vs. untreated SHR rats). In both cases, treatment withdrawal was accompanied by a progressive return to the values found in untreated rats. Additionally, urinary hyaluronidase activity resulted to be closely correlated to the urinary Aquaporin-2/creatinine ratio at every stage of the study ($p<0.0001$).
CONCLUSION: Since subjects genetically predisposed to essential hypertension seem to have higher renal sensitivity to vasopressin action, assessed as urinary Aquaporin-2/creatinine ratio, our results suggest the existence of a strong correlation between urinary hyaluronidase activity and activation of the vasopressinergic system, which, at least in this animal model, could play a key role in the early stages of essential hypertension pathogenesis.

43. TREATMENT OUTCOMES WITH REZAFUNGIN AND CASPOFUNGIN IN PEOPLE AGED 65 YEARS AND ABOVE WITH CANDIDAEMIA AND/OR INVASIVE CANDIDIASIS: INTEGRATED ANALYSIS OF POOLED PHASE 2 AND PHASE 3 DATA

Merelli M.[1], Cornely O.A.[2], Thompson G. R.[3], Soriano A.[4], Kullberg BJ.[5], Kollef M.[6], Vazquez J.[7], Honore P.M.[8], Bassetti M.[9], Pullman J.[10], Dignani C.[11], Das A.F.[12], Sandison T.[12], Pappas P.J.[13]

[1]Clinica di Malattie Infettive di Udine; [2]University of Cologne, Faculty of Medicine and University Hospital Cologne; [3]University of California Davis Medical Center - Sacramento, California; [4]Hospital Clínic de Barcelona, IDIBAPS, University of Barcelona - Barcelona (Spain); [5]Radboud University Medical Center - Nijmegen (Netherlands); [6]Washington University - St. Louis, Missouri ; [7]Augusta University - Augusta, Georgia ; [8]Brugman University Hospital - Brussels; [9]University of Genoa - Genoa ; [10]Mercury Street Medical - Butte, Montana ; [11]PSI-CRO - Durham, North Carolina (United States); [12]Cidara Therapeutics, Inc. - San Diego, California (United States); [13]University of Alabama at Birmingham - Birmingham, Alabama (United States)

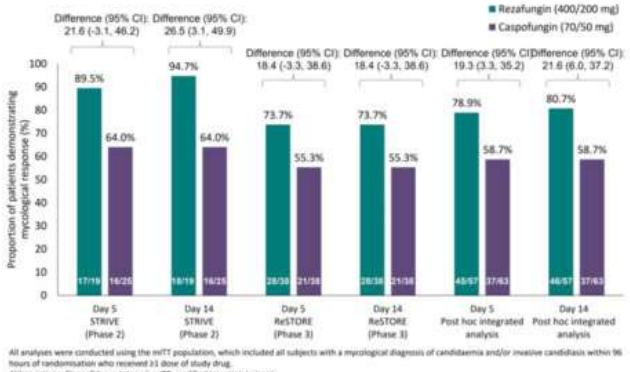
Background: Factors including frailty and multimorbidity can affect candidaemia and/or invasive candidiasis (C/IC) treatment in older people (1). The current analysis explored data from C/IC patients aged ≥65 years who were treated with rezafungin or caspofungin in the STRIVE (Phase 2: NCT02734862) and ReSTORE (Phase 3: NCT03667690) clinical trials (2,3).
Methods: STRIVE and ReSTORE were double-blind, randomised studies. Adults with C/IC, diagnosed by systemic signs and mycological confirmation, received rezafungin once-weekly (Week 1: 400 mg; Weeks 2–4: 200 mg) or once daily caspofungin (Day 1: 70 mg; Days 2–28: 50 mg) by intravenous injection for ≥14 days (≤4 weeks). Post hoc analysis examined pooled STRIVE/ReSTORE data for subjects aged ≥65 years. Safety outcomes included treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) in subjects who received ≥1 dose of study drug (safety population). Day 30 all-cause mortality (ACM) and mycological response at Days 5 and 14 were examined for the modified intention-to-treat (mITT) population (subjects with mycological C/IC diagnosis within 96 hours of randomisation who received ≥1 study drug dose).
Results: The safety population included 132 subjects (rezafungin arm: 64; caspofungin arm: 68). The mITT population included 120 subjects (rezafungin arm: 57; caspofungin arm: 63). The most common TEAEs with rezafungin were hypokalaemia, diarrhoea, vomiting and anaemia (Table 1). Eight subjects reported rezafungin-related TEAEs and 7 had caspofungin-related TEAEs. SAEs comprised one case each of first degree atrioventricular block (rezafungin arm) and acute liver injury (caspofungin arm). Day 30 ACM rate was 14.0% (rezafungin arm) and 31.7% (caspofungin arm). The between-group difference (95% confidence interval [CI]) was -17.6 (-32.5, -2.8). Day 5 mycological response was 78.9% (rezafungin arm) and 58.7% (caspofungin arm; difference [95% CI]: 19.3 [3.3, 35.2]; Figure 1).
Conclusions
Integrated analysis of pooled STRIVE/ReSTORE study data revealed similar incidence of drug-related TEAEs and SAEs in patients aged ≥65 years treated with rezafungin or caspofungin. Further analyses are required to understand underlying factors influencing between-group differences regarding treatment outcomes.

Table 1. Safety data for candidaemia/invasive candidiasis patients aged ≥65 years treated with rezafungin (400 mg/200 mg) or caspofungin (70 mg/50 mg) (safety population)

	Rezafungin (400/200 mg) (N=64)	Caspofungin (70/50 mg) (N=68)
Subjects with at least 1 TEAE, n (%)	59 (92.2)	62 (91.2)
Subjects with TEAEs leading to study discontinuation, n (%)	7 (10.9)	19 (27.9)
Subjects with at least 1 drug-related TEAE, n (%)	8 (12.5)	7 (10.3)
Subjects with at least 1 SAE, n (%)	37 (57.8)	38 (55.9)
Subjects with at least 1 drug-related SAE, n (%)	1 (1.6)	1 (1.6)
TEAEs affecting at least 10% of safety population		
Hypokalaemia	11 (17.2)	7 (10.3)
Diarrhoea	10 (15.6)	9 (13.2)
Vomiting	8 (12.5)	2 (2.9)
Anaemia	7 (10.9)	5 (7.4)
Septic shock	6 (9.4)	8 (11.8)
Acute kidney injury	4 (6.3)	8 (11.8)
Urinary tract infection	1 (1.6)	7 (10.3)

The safety population included all subjects who had received ≥1 dose of study drug.
Abbreviations: SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Figure 1. Analysis regarding mycological response at Days 5 and 14 in candidaemia/invasive candidiasis patients aged ≥65 years included in the STRIVE (Phase 2) and ReSTORE (Phase 3) clinical trials and integrated analysis of STRIVE/ReSTORE data (mITT population)



All analyses were conducted using the mITT population, which included all subjects with a mycological diagnosis of candidaemia and/or invasive candidiasis within 96 hours of randomisation who received ≥1 dose of study drug.
Abbreviations: CI, confidence interval; mITT, modified intention to treat.

44. WHEN A FORGOTTEN DISEASE KNOCKS AT OUR DOOR: THE OUTBREAK OF TRICHINOSIS IN APULIA REGION, ITALY

Mansueto C.L.[1], D'Agruma A.[1], Pacilli G.[1], Antonaccio M.[2], Corritore M.[2], Vendemiale G.[1], Minonne R.[2], Caccio' S.M.[2], Gomez Morales M.A.[2], De Cata A.[2], Varriale A.[2], De Cosmo S.[2], Piscitelli P.[2], Mirijello A.[2]
[1]SC di Medicina Interna, Policlinico Riuniti-Università degli studi di Foggia; [2]SC di Medicina Interna, IRCCS Casa Sollievo della Sofferenza

Introduction: Trichinosis, also known as Trichinellosis, is a zoonotic infection caused by the nematode Trichinella. This infection is widespread across the globe, with the exception of Antarctica, although the distribution of the various Trichinella species may vary among continents. The primary way of transmission is through the consumption of undercooked or raw meat containing Trichinella's cysts. Two distinct patterns of transmission are known: the domestic cycle and the sylvatic cycle, which can function independently or interactively. In Europe, the majority of human infections are attributed to wild animals.
Clinically, Trichinosis shows two phases: the intestinal stage and the muscle stage. The intestinal stage develops within the first week after the ingestion of encysted larvae and may result in symptoms such as diarrhea and abdominal pain. The muscle stage occurs when the adult larvae exit the intestine and migrate into muscle cells. During this stage, individuals may experience symptoms such as myalgia (muscle pain) and urticarial rash. Here we report the occurrence of a Trichinella outbreak in Apulia Region.
Case Series Description: A total of 10 patients (age 8 to 71 y.o.), all of them living in the same village in Apulia Region, Southern Italy, came to our attention due to a non-specific symptomatology characterized by myalgia with muscle weakness, arthralgia, fatigue, fever, diarrhea, maculopapular pruritic rash and angioedema.
Laboratory tests showed hypereosinophilia (100% of patients); raised creatine phosphokinase (CPK) or lactate dehydrogenase (LDH) levels (90% of patients); raised CK-MB (80%) with high HS-troponin levels in 2 cases and increased alanine aminotransferase (ALT) and/or aspartate transaminase (AST) (90% of patients with the exception of the pediatric case).
A total of 5 (50%) patients were admitted to our Internal Medicine inpatients Unit for further examinations: the diagnostic workup included blood cultures (all negatives), smear tests (revealed no parasites, ova, nor cysts), autoimmune markers (slightly increased ANA title in 1 case), low levels of serum protein according with low levels of albumin (100% of the hospitalized patients), inflammatory markers (i.e. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)) raised in 4 of the 5 hospitalized patients. A mild IGM-lambda monoclonal serum component was found in two patients.
Two patients performed a routine abdominal US-scan revealing hepatomegaly. One patient underwent total body CT-scan due to a suspicious paraneoplastic syndrome, resulting only in splenomegaly.
Serological ELISA test for the diagnosis of trichinella spp. antibodies and subsequent identification of specific IgG-recognized proteins by Western blotting resulted positive in all patients.
Retrospective medical history collection revealed that some patients had consumed uncooked pork meat during New Year's Eve dinner, while others within their domestic setting.
All of the patients received anthelmintic treatment with Mebendazole.
Conclusion: richinosis is classified as a rare disease. The diagnosis may result difficult due to the presence of non-specific signs and symptoms. Differential diagnosis includes immunological diseases such as selective IgA deficiency, hyper-IgE syndrome, Graft-versus-host disease (GVHD), vasculitis, eosinophilic pneumonia or the most common atopic syndromes such as asthma and rhinitis, besides other human parasitosis that need to be considered.
If not treated trichinosis can lead to neurological manifestation (i.e. encephalopathy, neuromuscular disturbances, and ocular involvement), myocarditis, thrombotic complications and hepatic involvement (which was observed in 90% of our patients).
The aim is to increase the level of awareness and consciousness towards a pathological disease that can negatively affect the quality of life if not properly/promptly diagnosed, mainly because of the non-specific findings which can lead to delays in the diagnosis. An accurate medical history in presence of hypereosinophilia, fever, myalgia angioedema and diarrhea should be carefully taken in order to not miss the diagnosis.

45. MANAGEMENT AND PROGNOSIS OF OLDER ADULTS WITH SUSPECTED INFECTIVE ENDOCARDITIS ADMITTED TO THE INTERNAL MEDICINE DEPARTMENT

Tonelli F.[1], Masseroli M.[1], Tedeschi Polmonari P.[2], Casella F.[1], Ceriani E.[1], Torzillo D.[1], Cogliati CB.[1]
[1]Department of Internal Medicine, L. Sacco Hospital, University of Milan, Milan, Italy.; [2]Università degli Studi di Milano, Milan, Italy

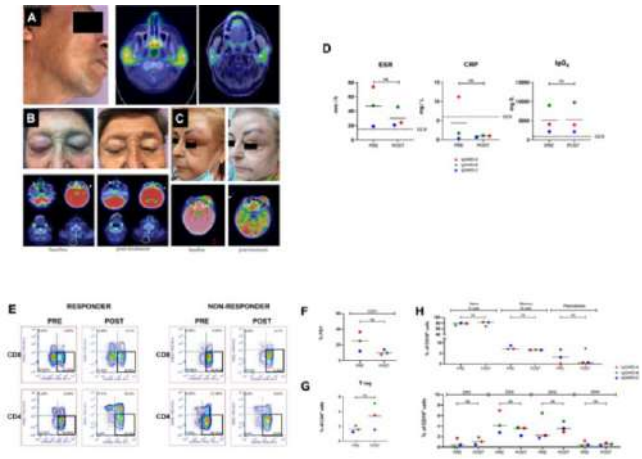
Background: Infective endocarditis (IE) has an annual incidence of 3-10 per 100,000 and a 30% mortality rate at 30 days. The epidemiological landscape of IE has changed due to an aging population and increased prevalence of intracardiac devices and prosthetic heart valves. Staphylococcus is currently the pri-

mary cause of infective endocarditis, followed by viridans streptococci and enterococci. Clinical presentation varies, and the modified Duke criteria have an 80% sensitivity, which decreases in the presence of intracardiac devices (prosthetic valves, Pacemakers, and Implantable Cardioverter Defibrillators – ICDs). Diagnostic and therapeutic management of endocarditis is particularly challenging in the elderly population due to multiple comorbidities and frailty. Transthoracic echocardiography (TTE) has limited diagnostic accuracy in elderly patients due to valve fibro-calcifications, valvular defects, and the presence of intracardiac devices, making it difficult to satisfy the Strict Negative Criteria. Additionally, many elderly patients may not tolerate second-level methods such as transesophageal echocardiography (TEE), making it impractical in numerous cases. Treatment can also be problematic, as there is no validated surgical scoring system to guide decisions in cases requiring surgery, particularly in older and frail adults. Furthermore, older patients are at an increased risk of adverse events due to high doses of antibiotics and potential drug-drug interactions.
The objective of this study was to describe the clinical characteristics, evaluate the diagnostic-therapeutic management, and assess the prognosis of patients admitted to the Internal Medicine Department with suspected IE.
Methods: In this retrospective observational study, 124 consecutive patients with suspected IE attending the echocardiography laboratory at L. Sacco Hospital in Milan were enrolled. TTE results were categorized as positive, inconclusive or non-diagnostic, or negative for IE based on echocardiography reports. Strict Negative Criteria were assessed retrospectively. The Charlson Comorbidity Index (CCI) and Clinical Frailty Scale (CFS) were used to evaluate comorbidities and frailty, respectively.
Results: Between September 2021 and December 2022, 124 TTEs were performed for suspected endocarditis. The median age of the patients was 78 years (IQR: 64-83), with 45 (36%) being women. The median CCI and CFS scores were 4 (IQR: 3-7) and 4 (IQR: 2-6), respectively. Among these patients, 22 (18%) were discharged with a diagnosis of IE, with 20 patients (91%) having a "definite" diagnosis according to the modified Duke criteria and 2 (9%) having a "possible" diagnosis. Enterococci (35%) and streptococci (35%) were the most common causative pathogens. There were 8 cases (36%) of native mitral valve EI, 4 (18%) of native aortic valve EI, 1 case (4%) of both mitral and aortic EI, 7 cases (32%) of prosthetic valve EI and 1 case (4%) involving pacemaker leads. TTE identified valve vegetation in 11 patients (50%), while 14 TEE were performed and identified valve vegetation in 9 cases. 4 patients underwent surgical intervention and none of them died within 30 days. All of these patients had a CFS score < 3. Among the 102 patients discharged with a different diagnosis, 31 had a "possible" diagnosis of IE according to the modified Duke criteria. Of these 31 patients, 29 (93%) had positive blood cultures and in 18 cases (58%), no alternative infectious focus was found. Only 3 out of 31 patients received four weeks of antibiotic therapy. Among these 31 patients, 19 had a negative TTE, but only in 4 cases the Strict Negative Criteria were met. Only 3 out of these 19 patients underwent a TEE. Among the 12 patients with an inconclusive or non-diagnostic TTE, 5 underwent a TEE. The mortality rate among patients discharged with a diagnosis of IE was higher compared to those with an alternative diagnosis, with rates of 27% vs. 10% ($p = 0.080$) at 30 days and 32% vs. 20% ($p = 0.158$) at 90 days, although the difference did not reach statistical significance. There were no significant differences in terms of CCI and CFS scores between the two populations. A significant difference was observed in the presence of intracardiac devices (59% vs. 10%, $p < 0.001$) and significant valve disease (64% vs. 26%, $p < 0.001$) between patients discharged with a diagnosis of EI and those discharged with an alternative diagnosis, respectively.
Conclusion: EI is associated with high mortality in frail elderly patients. TTE often yields inconclusive results and Strict Negative Criteria are rarely met. In some cases, considering the patient's comorbidities and frailty, TEE is not performed, and patients are empirically treated in the absence of a "definite" diagnosis. Factors associated with the presence of IE include the presence of intracardiac devices (prosthetic valves, pacemakers and ICD), significant valvular disease and the absence of a known infectious focus.

46. EFFICACY AND SAFETY OF ABATACEPT IN IGG4-RELATED DISEASE: A CLINICAL AND IMMUNO-PATHOLOGICAL PILOT STUDY

Mahajne J.[1], Minici C.[2], Lanzillotta M.[1], Batani V.[1], Dagna L.[1], Della Torre E.[1]
[1]Unit of Immunology, Rheumatology, Allergy and Rare Diseases, Ospedale San Raffaele, Milano, Italy; [2]Università Vita-Salute San Raffaele, Milano, Italy

Background: IgG4-related disease (IgG4-RD) is a relapsing-remitting fibroinflammatory condition clinically characterized by fibrous lesions and often elevated serum IgG4 levels. The pathogenesis of IgG4-RD remains largely unknown but likely relies on co-stimulatory and activating signals between antigen-specific B and T lymphocytes. Glucocorticoids and B-cell depleting therapies (e.g. rituximab) are highly effective in patients with IgG4-RD but represent an untenable treatment option in the long term due to intrinsic metabolic and infectious complications. Personalized and targeted therapies with fewer side effects represent, therefore, an important unmet need in this condition.
Objectives. In the present work we aimed to evaluate the efficacy and safety of abatacep – a selective inhibitor of B-T cell co-stimulation – in patients affected by IgG4-RD. In particular, the primary aim of the study was to assess the clinical, serological, and radiological response of patients with IgG4-RD to abatacept therapy. The secondary aim of the study was to assess the effects of abatacept on circulating B and T lymphocyte subsets and on their activation profile.
Methods: This prospective, open-label, single-arm pilot study was carried out in San Raffaele Hospital (HSR), Milan, Italy. Three patients with active untreated disease (IgG4- RD responder index (RI) > 3 at baseline) who poorly tolerated steroid therapy and experienced hypersensitivity reactions to rituximab were recruited at the IgG4-RD Outpatient Clinic. Participants fulfilled the 2019 American College of Rheumatology and European League Against Rheumatism classification criteria for IgG4-RD. At the time of abatacept administration patients were not on glucocorticoids or other immunosuppressive drugs. Two patients received rituximab one year prior to abatacept infusion. All patients received 10 mg/kg of intravenous abatacept (Orencia®) at baseline, 2 and 4 weeks after the first infusion, and then every 4 weeks for a total of 7 doses. Peripheral venous blood samples were drawn at baseline and before each abatacept infusion. Flow cytometry was used to assess the effects of abatacept on B and T immune cell populations. Disease activity and response to abatacept were assessed by measuring plasma levels of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), IgG4, and soluble IL2-receptor (sIL2R), as well as by means of the IgG4-RD RI and 18F-Fluorodeoxyglucose Positron Emission Tomography/ Computed Tomography scan. The primary outcome was the rate of disease remission at 6 months and the incidence of adverse events. Disease remission was defined by an IgG4-RD RI < 3 off glucocorticoid therapy.
Results: After six months of abatacept therapy, two patients achieved disease remission. One patient showed no response to abatacept. (Fig. A, B, C). ESR and CRP decreased in responder patients and remained unchanged in the non-responder patient. Serum IgG4 at baseline were above normal values in all patients and were unaffected by abatacept treatment (p value > 0.05) (Fig. D). Soluble IL-2R was also unaffected by abatacept treatment (p value > 0.05). Circulating T and B cell subsets were generally unaffected by abatacept therapy (p value > 0.05 for all the comparisons), yet differential effects on T and B cell subsets were observed between responder and non-responder patients. Specifically, putative pathogenic SLAMF7+ CD4+ and CD8+ effector memory T cells decreased in responder patients, and did not change after treatment in the non-responder patient (Fig. E). Activated PD- 1+ CD4+ T cells also decreased in responder patients but increased in the non-responder patient (Fig. F). Conversely, T-regulatory cells increased in responder patients and remained unchanged in the non-responder patient (Fig. G). Circulating follicular T helper cells decreased in all three patients. No difference was observed before and after abatacept in the percentage of circulating naïve, memory, plasmablasts, regulatory B cells, and double negative B cell regardless of the treatment outcome (p values > 0.05 for all the comparisons) (Fig. H). Of note, surface expression of BAFF-R on CD19+ cells increased in all three patients after treatment with abatacept although to a not statistically significant extent (p value > 0.05 compared to baseline).
Conclusions. A six months treatment with intravenous abatacept lead to variable responses in patients affected by biopsy-proven IgG4-RD. In particular, response to abatacept was associated with consistent modifications of specific circulating T and B cell subsets suggesting that inhibition of B-T cell co-stimulation may be effective in a selected population of patients with a specific genetic and immunological background. A better understanding of this background will be pivotal to the identification of personalized and safer targeted therapies for patients with IgG4-RD.



47. OLIPUDASE ALFA FOR ADULTS WITH ACID SPHINGOMYELINASE DEFICIENCY: IMPROVEMENTS IN CROSSOVER PLACEBO PATIENTS AND FURTHER IMPROVEMENTS IN ORIGINAL OLIPUDASE ALFA PATIENTS AFTER 2 YEARS IN ASCEND TRIAL

Barbato A.[1], Gallagher R.C.[2], Giugliani R.[3], Guelbert N.B.[4], Hennermann J.B.[5], Hollak C.[6], Ikezoe T.[7], Lachmann R.[8], Lidove O.[9], Mabe P.[10], Mengel E.[11], Scarpa M.[12], Senates E.[13], Tchan M.[14], Villarrubia J.[15], Armstrong N.M.[16], Thurberg B.T.[16], Yarramaneni A.[17], Kim Y.[18], Kumar M.[17], Wasserstein M.P.[19]

[1]Dept of Clinical Medicine and Surgery, Federico II University Hospital, Naples, Italy; [2]Dept of Pediatrics, University of California San Francisco, San Francisco, CA, USA; [3]UFRGS, HCPA, INAGEMP, DASA and Casa dos Raros, Porto Alegre, Brazil ; [4]Reina Fabiola University Clinic, Córdoba, Argentina; [5]Villa Metabolica, University Medical Center, Dept of Pediatric and Adolescent Medicine, Mainz, Germany ; [6]Amsterdam UMC, University of Amsterdam, Dept of Endocrinology and Metabolism, Amsterdam, The Netherlands; [7]Dept of Hematology, Fukushima Medical University, Fukushima, Japan; [8]Charles Dent Metabolic Unit, National Hospital for Neurology and Neurosurgery, London, UK; [9]La Croix St Simon Hospital, Paris, France; [10]Clinica Santa Maria, Santiago de Chile; [11]SphinCS, Institute of Clinical Science for Lysosomal Storage Disorders, Hochheim, Germany ; [12]Regional Coordinating Center for Rare Diseases, University Hospital of Udine, 33100 Udine, Italy; [13]Istanbul Medeniyet University, Istanbul, Turkey; [14]Dept of Genetic Medicine, Westmead Hospital, Sydney, Australia; [15]Hematology Dept, Hospital Universitario Ramón y Cajal, Madrid, Spain; [16]Sanofi, Cambridge, MA, USA; [17]Sanofi, Bridgewater, NJ, USA; [18]Sanofi, Paris, France; [19]Children's Hospital at Montefiore, Albert Einstein College of Medicine, Bronx, NY, USA

Background: Acid sphingomyelinase deficiency (ASMD) is a rare debilitating lysosomal storage disease characterized by pulmonary dysfunction, hepatosplenomegaly and dyslipidemia. Olipudase alfa, intravenous recombinant human ASM (Sanofi) was recently approved as the first treatment for the non-central-nervous-system manifestations of ASMD. The ASCEND study (NCT02004691), a phase 2/3 placebo-controlled trial in 36 adults with ASMD, completed its primary analysis. At Year 1, olipudase alfa patients compared to placebo patients (1:1 randomization) had statistically significant increases in %-predicted diffusing capacity for carbon monoxide in lung (DLCO) and decreases in spleen and liver volume.Thirty-five patients continued in an open-label trial extension. One placebo patient withdrew during Year 1.
Methods: We report the year 2 results for the former placebo group after 1 year of olipudase alfa (crossover group) and for the original olipudase alfa group patients after 2 years of olipudase alfa. Patients underwent gradual dose-escalation to 3.0 mg/kg/2-weeks. Change from baseline results are presented as least-square (LS) mean ANCOVA % change ±standard error of the mean for %-predicted DLCO, spleen volume, liver volume, platelet count, liver function, and lipid profile. Change in lung high-resolution computed tomography (HRCT) scores for ground glass appearance is presented as LS mean ANCOVA absolute change from baseline.
Results: Of 35 patients who completed Year 1, 33 completed Year 2. In Year 2, improvements in crossover group paralleled the original olipudase alfa group (Table): DLCO increased 28.0±6.2% (n=10); spleen volume decreased 36.0±3.0% (n=11); liver volume decreased 30.7±2.5% (n=11). In the 2-year olipudase alfa group, %-predicted DLCO increased by 22.2±3.4% (n=17) at Year 1 and 28.5±6.2% at Year 2 (n=10); spleen volume decreased by 39.5±2.4% (n=17) at Year 1 and 47.0±2.7% (n=14) at Year 2; liver volume decreased by 27.8±2.5% (n=17) at Year 1 and 33.4±2.2% (n=14) at Year 2. HRCT ground glass appearance score decreased 0.30±0.5 (n=14) at Year 2 for the crossover group and decreased 0.45±0.13 (n=18) at Year 1 and 0.48±0.07 (n=16) at Year 2 for 2-year olipudase alfa group. Improvements in dyslipidemia, liver function, platelet count, liver sphingomyelin clearance, and plasma lyso-sphingomyelin in crossover patients paralleled those seen in the 2-year olipudase alfa patients in Year 1; 2-year olipudase alfa patients maintained these benefits in Year 2. Overall, 99% of treatment-emergent adverse events (AEs) were mild or moderate, with 1 treatment-related serious AE. No patient discontinued due to an AE.
Conclusion: In summary, during Year 2 of ASCEND, crossover patients improved to a similar extent as olipudase alfa patients in Year 1 and patients continuing on olipudase alfa showed sustained or further improvements.

48. HELIOS-A: IMPACT OF VUTRISIRAN ON QUALITY OF LIFE AND FUNCTIONAL STATUS IN HEREDITARY TRANSTHYRETIN-MEDIATED AMYLOIDOSIS

Ajroud-Driss S.[1], Berk J.L.[2], Adams D.[3], Gillmore J.[4], Lin K.[5], Kale P.[6], Koike H.[7], Aldinc E.[8], Chen C.[8], Vest J.[8], Obici L.[9]

[1]Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [2]Boston Medical Center, Boston, MA, USA; [3]Neurology Department, Université Paris-Saclay, U1195, INSERM, Neurology Department, AP-HP, CHU Bicêtre, Le Kremlin Bicêtre, France; [4]National Amyloidosis Centre, University College London, Royal Free Hospital, London, UK; [5]Department of Neurology, Taipei Veterans General Hospital, Taipei, Taiwan; [6]Baylor University Medical Center, Dallas, TX, USA; [7]Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya, Japan; [8]Alnylam Pharmaceuticals, Cambridge, MA, USA; [9]Amyloidosis Research and Treatment Centre; IRCCS Fondazione Policlinico San Matteo, Pavia, Italy

Introduction: Hereditary transthyretin-mediated (hATTR) amyloidosis, also known as ATTRv amyloidosis, is associated with significant disability, worsening quality of life (QOL), and loss of function. The effects of treatment with vutrisiran, an investigational RNA interference therapeutic, on QOL and functional status were evaluated in HELIOS-A (NCT03759379).
Methods: Patients with hATTR amyloidosis with polyneuropathy were randomized (3:1) to vutrisiran (25 mg subcutaneous [SC] injection q3m) or patisiran (0.3 mg/kg intravenous infusion q3w), a reference comparator. The APOLLO placebo group (n=77) provided an external control. HELIOS-A primary endpoint was change from baseline in modified Neuropathy Impairment Score +7 (mNIS+7) at 9 months vs. external placebo. Secondary and exploratory endpoints at 18 months included change from baseline vs. external placebo in measures related to QOL (Norfolk QOL-diabetic neuropathy [Norfolk QOL-DN], EuroQoL-Visual Analog Scale [EQ-VAS]) and functional status (Rasch-built Overall Disability Scale [R-ODS], gait speed [10-meter walk test; 10-MWT], Karnofsky Performance Status [KPS]).
Results: HELIOS-A enrolled 164 patients (vutrisiran, n=122; patisiran, n=42). The primary endpoint was met. At 18 months, vutrisiran significantly improved Norfolk QOL-DN (least squares [LS] mean difference: –21.0; p=1.844 x10–10) and EQ-VAS (13.7; p=2.214–7) vs. external placebo. Significant improvement was observed across all Norfolk QOL-DN domains vs. external placebo. Additionally, total score alongside the large-fiber function, symptoms, and autonomic domains improved vs. baseline. At 18 months, vutrisiran improved R-ODS (LS mean difference: 8.4; p=3.541 x10–15) and 10-MWT (0.239; p=1.207 x10–7) vs. external placebo. The majority of vutrisiran-treated patients (71.3%) had stable or improved KPS at 18 months vs. baseline.
Conclusions: In HELIOS-A, vutrisiran q3m SC significantly improved multiple measures of QOL and functional status at 18 months vs. external placebo. Continued worsening of these measures was observed on placebo, highlighting the importance of effective treatment. The long-term effect of vutrisiran will be confirmed in an open-label extension study.

49. PRIMARY RESULTS FROM APOLLO-B OPEN-LABEL EXTENSION STUDY OF PATISIRAN IN PATIENTS WITH TRANSTHYRETIN CARDIAC AMYLOIDOSIS

Mussinelli R. (on behalf of the authors)[1], Maurer M.S.[2], Berk J.L. [3], Hanna M.[4], Gillmore J.D.[5], Schwartzmann P.V.[6], Lairez O.[7], Hatano M.[8], Cho H-J.[9], Van der Meer P.[10], White M.T. [11], Yureneva E.[11], Sweetser M.T.[11], Jay P.Y.[11], Vest J.[11], Fontana M.[5]

[1]Centro per lo Studio e la Cura delle Amiloidosi Sistemiche, Fondazione IRCCS Policlinico San Matteo, Pavia; [2]Columbia University Irving Medical Center, New York, NY, USA; [3]Boston University School of Medicine, Boston, MA, USA; [4]The Cleveland Clinic Foundation, Cleveland, OH, USA; [5]National Amyloidosis Centre, University College London, Division of Medicine, Royal Free Hospital, London, UK; [6]Advanced Research Centre (CAPED) and Unimed Hospital, Ribeirão Preto, São Paulo, Brazil; [7]Hôpital de Rangueil, Toulouse, France; [8]The University of Tokyo Hospital, Tokyo, Japan; [9]Seoul National University Hospital, Seoul, South Korea; [10]Universitair Medisch Centrum Groningen, University of Groningen, Groningen, The Netherlands; [11]Alnylam Pharmaceuticals, Cambridge, MA, USA

Introduction: The Phase 3, placebo-controlled APOLLO-B study (NCT039 97383) is evaluating the efficacy and safety of patisiran in patients (pts) with ATTR cardiac amyloidosis in a 12-month (M) double-blind (DB) period followed by an open-label extension (OLE) period when all pts receive patisiran. During the DB period, patisiran demonstrated statistically significant differences vs placebo in change from baseline (CFB) to M12 in 6-minute walk test (6MWT) and KCCQ-OS, and nominal significance in NT-proBNP and troponin I. Patisiran preserved functional capacity, health status and quality of life (QoL), while placebo was associated with steady worsening. Here, we describe data during the APOLLO-B OLE period.
Hypothesis: TTR reduction by RNAi therapeutic patisiran provides long-term benefit in pts with ATTR cardiac amyloidosis.
Methods: Eligible pts (18–85 yrs) had echocardiographic evidence of cardiac amyloidosis and either ATTR amyloid detected in tissue biopsy or diagnosed by nonbiopsy criteria. Medical history of heart failure (HF) due to ATTR amyloidosis with ≥1 prior HF hospitalization or current clinical evidence of HF was required. Pts were randomized 1:1 to patisiran 0.3 mg/kg or placebo every 3 weeks for 12M. All pts completing the 12M DB period were eligible to receive patisiran in the OLE for up to 36M. Pts are summarized based on DB treatment assignment. Assessments in the OLE include CFB in 6MWT, KCCQ-OS, NT-proBNP, and troponin I, among other endpoints.
Results: At baseline, 359 pts (placebo, n=178; patisiran, n=181) received study drug in DB period: median (range) age, 76.0 (41, 85) yrs; male, 89%; wtATTR, 80%; receiving tafamidis, 25%. Of these, 334 (93%) pts entered the OLE. Preliminary data show that CFB to M18 in the patisiran arm were similar to results at M12 for 6MWT, KCCQ-OS, NT-proBNP, and troponin I. In the placebo arm, patisiran initiation was associated with a slower rate of worsening (6MWT) or relative stability (KCCQ-OS, NT-proBNP, troponin I) in each endpoint from M12 to M18 vs DB period. Differences between patisiran and placebo groups at M12 persisted at M18 (Table). Patisiran demonstrated an acceptable safety profile, with no new safety concerns. Data collection during the OLE and their analyses are ongoing.
Conclusions: Preservation of functional capacity, health status and QoL by patisiran has been observed to date to be sustained through 18M of treatment in pts with ATTR cardiac amyloidosis. Placebo-treated pts initiating patisiran at M12 appear to show stabilization in these endpoints at M18. Early treatment initiation is important, as differences across evaluated endpoints persisted between patisiran and placebo arms after placebo-treated pts initiated patisiran. Data collection in the study is ongoing.

For 6MWT, baseline is defined as the last non-missing value available prior to first dose of study drug in the DB period. For the other parameters, baseline is defined as the last non-missing value available on or before the date of first dose of study drug in the DB period.All pts received patisiran after M12.

50. THE VALUE OF THE "INTERNISTIC METHOD" IN THE DIAGNOSIS OF AN ULTRA-RARE INHERITED METABOLIC DISORDER

Chesini F.
Dipartimento di Medicina Generale d'Urgenza di Verona

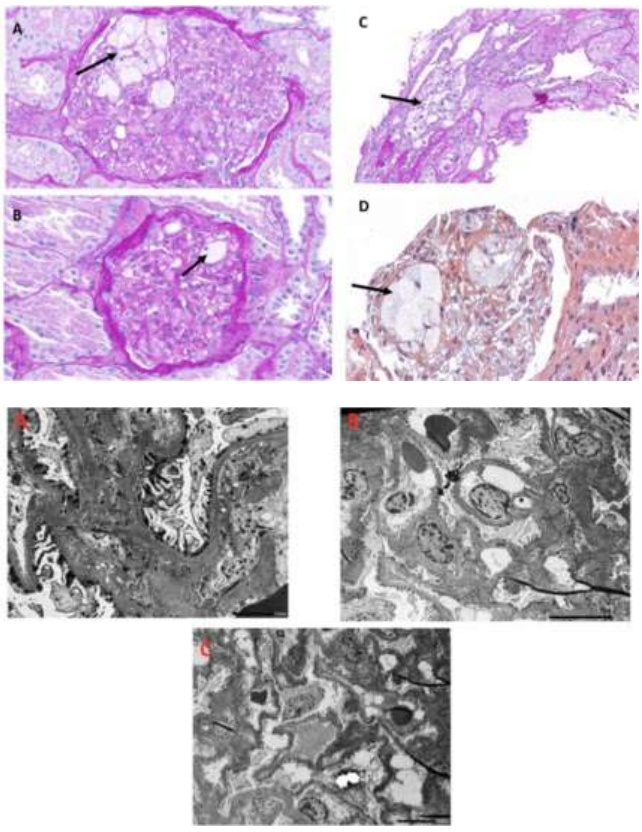
Presentation: An 18-years old Tunisian boy was referred to our EuroBlood-Net tertiary centre for Iron Disorders at University Hospital of Verona because of an unexplained hyperferritinemia. Since 2002 the patient underwent a long list of hospitalizations and investigations. Splenomegaly, thrombocytopenia, anaemia and hyperferritinemia were first detected during a hospitalization in a paediatric clinic when he was two. Peripheral blood smear and bone marrow analysis were not diagnostic. In the following years the patient suffered from recurrent upper respiratory tract infections with severe otitis (perforation of the eardrum in 2008 and subsequent tympanoplasty), sinusitis and a bilateral bronchopneumonia in 2007. Remarkably, he had recurrent hospitalizations for infected skin ulcers, especially of the lower limbs. For an elephantiasis-like scrotal oedema, he underwent bilateral hydrocele drainage in the first years of life without benefit. The US revealed a scrotal sac thickening rather than hydrocele. Skin thickening, initially interpreted as "oedema", was also described in cheeks, lips and hands since childhood. He underwent several exams to exclude an atopic disorder or a hereditary angioedema, including the C1-INH which was normal. Cycles of steroids and anti-histaminic agents were ineffective. For eyelid redness he had regular oculistic examinations with recurrent finding of corneal opacity, attributed to a "dry eye" and treated with lubricant eye drops.
At our observation, we detected multiple dysmorphic features (hypertelorism, depressed nasal bridge, thin vermilion of the upper lip, camptodactily), telangiectasias, scrotal and skin thickening, axillary suppurative adenitis, skin ulcers of the legs, palpable spleen almost in left iliac fossa, mild hepatomegaly and overweight (80 kg x 166 cm, BMI 29). He had a normal growth for age, no apparent mental retardation and no bone and vertebral column disorder. Laboratory exams showed Hb 14,3 g/dl, MCV 78,1 fl, GR 5.200.000/mmc, PLTs 130.000/mm3, polyclonal hypergammaglobulinemia (IgG 21 g/l, IgA 8 g/l), non-selective mild proteinuria (230 mg/l), ferritin 1037 mcg/l with normal transferrin saturation. CRP, transaminases and renal function were within the limits. ANA were 1:160 speckled.
Differential diagnosis: An abdomen-MRI was performed: 3-axis calculated volumes were 1069 ml for spleen (n.v. <480 ml) and 1476 ml for liver (n.v. <1600 ml); no nodular lesions were detected. No iron accumulation was observed in liver or spleen and a disorder of iron metabolism was easily ruled out. Considering the syndromic dysmorphic features and splenomegaly, we suspected an inherited metabolic disorder. Dosage of urinary mucopolysaccharides, oligosaccharides, enzymatic assay for MPS (type I, II, IVa, IVb and VI) and Gaucher disease were negative. However, the clinical presentation was atypical for most of lysosomal storage disorders. After discussion with experts in this field, a next generation sequencing (NGS) like whole exome sequencing (WES) was suggested.
Diagnosis: Before WES, we performed the plasmatic amino acid profile, which showed a marked reduction of hydroxyproline. After a literature review, we found that prolidase deficiency could have explained the clinical scenario. A very low prolidase activity in erythrocytes (2,6% compared to a control sample) confirmed the diagnosis. Genetic test identified a pathogenetic homozygous mutation in *PEPD* gene: c.977G>A. The patient has a sister, who reports no clinical issue. Prolidase deficiency is an inherited autosomal recessive disorder due to mutations in the *PEPD* gene (19q13.11), encoding prolidase, a Xaa-Pro dipeptidase, playing a crucial role in the biosynthesis and degradation of collagen. Less than 100 cases are described worldwide, mostly in pediatric patients and with a NGS approach. Clinical manifestations are mainly due to impaired collagen synthesis and wound healing. Severe chronic skin ulcers of the lower extremities and telangiectasias, recurrent infections (particularly of the skin and respiratory tract), dysmorphic facial features, variable intellectual disability, hepatomegaly with elevated liver enzymes and splenomegaly are typical manifestations of this metabolic disorder. Anaemia, thrombocytopenia, hypergammaglobulinemia and hypocomplementemia are also common. Hyperferritinemia has never been described at best of our knowledge but is known to occur in other storage disorders like Gaucher disease. Prognosis is variable but patients often have a decreased life-expectancy and quality of life because of severe and sometimes fatal infections.
Therapy: No specific treatment is currently available for prolidase deficiency. The care of these patients relies on the optimization of supportive treatments, like on demand courses of antibiotics. We used a galenic 5% proline and 5% glycine ointment, as described in the literature, with no result in reducing

the severity and relapse of skin ulcers. Further studies and therapeutic research are desirable for this highly invalidating multi-organ "internistic" disorder.

51. KIDNEY DISEASE IN FAMILIAL CHYLOMICRONEMIA SYNDROME, A NEW POSSIBLE HALLMARK OF FCS PHENOTYPE

Tramontano D., Bini S., Di Costanzo A., Minicocci I., Carosi M., Covino S., Arca M., D'Erasmo L.
Dipartimento di Medicina Traslazionale e di Precisione, Università di Roma La Sapienza

Background: Hypertriglyceridemia (HTG) is one of the most common lipid disturbances in clinical practice. HTG has been recognized as a risk factor for atherosclerotic cardiovascular disease (ASCVD) and acute pancreatitis (AP) depending on the triglycerides levels (TGs). The risk for AP progressively increases with serum TG levels >500mg/dl and is markedly elevated with levels >1000mg/dl (severe hypertriglyceridemia, sHTG). The typical monogenic disorder causing sHTG is Familial Chylomicronemia Syndrome (FCS). FCS is a rare, autosomal recessive disease, caused by the presence of biallelic (homozygous or compound heterozygous) mutations in lipoprotein lipase (LPL) gene as well as in the other genes encoding proteins required for LPL activity. Patients with FCS have a high risk of developing severe recurrent AP, a potentially life-threatening complication, resulting in increased morbidity and mortality. Recently, many studies are focusing on the possible kidney impairment linked to HTG. Indeed, although it is though that HTG is a consequence of kidney dysfunction, several lines of evidence support that HTG may contribute to the onset and progression of kidney disease. It has been reported also kidney complication in FCS, but the data are sparse. To this aim, we have retrospectively evaluated the Kidney impairment in a cohort of patients with FCS and we report clinical cases series, with images of histological slides of our FCS patients undergoing renal biopsy.
Methods: The population comprises 21 FCS patients (17 index cases) equally distributed among sex (F/M 12/9). The median observational period was 6,5 ± 5,6 years (min 1-max 22). Most were Caucasian (95%) and carrying homozygous mutation in LPL (81%). The median age at enrolment was 51 years (20-78) and 18 patients (85%) had experienced cumulatively 68 episodes of acute pancreatitis (AP). None had history of atherosclerotic cardiovascular disease, but one patient has had Tako-Tsubo. Overall, 81% have hepatic steatosis. Chronic pancreatitis was observed in 8 patients while diabetes in 5. History of hypertension was present in 33% of FCS patients. Glomerular filtration rate (eGFR) was estimated with CKD-EPI and diagnosis of CKD was performed based on the more recent Kidney Disease Improving Global Outcomes (KDIGO) guideline. Hyperfiltration was defined as an increase in eGFR greater than 75° percentile. Proteinuria was defined as protein in the urine spot ≥30 mg/dl or ≥ 150 mg/day in the 24-hour urine sample. Kidney impairment has been defined as a composite of hyperfiltration, proteinuria and eGFR<90 ml/min.
Results: Across the study population, the median GFR values was 99.5 ml/min (IQR 93.8-113.7). Overall, 7 (34%) have had proteinuria in at least one occasion. Four (20.0%) patients had hyperfiltration whereas 5 (24.0%) were exhibiting an eGFR below 90 ml/min. Among hyperfiltrating, two had also proteinuria in at least one occasion during life. Two patients experienced nephrotic syndrome with severe proteinuria (>3.5 g/24h) and sHTG (>13,000 mg/dl in one case) for which they underwent renal biopsy. One patient showed focal segmental glomerulosclerosis (Figure 2), while in the other case the biopsy showed the presence of foam cells with initial interstitial fibrosis (Figure 1). Similar cases in FCS syndrome are not reported in the literature. Overall, the impairment in kidney function occurred in 48% of patients and it results independent from age, diabetes, median TGs, acute pancreatitis and sex (Table 1).
Conclusions: The present analysis confirmed that kidney impairment might be a clinical characteristics of FCS phenotype. Similar cases of glomerulopathy associated with FCS have not yet been reported in the literature. Further studies in larger cohort are needed to better clarify if kidney disease might be a hallmark of FCS in broader population and understand the potential patho-physiological mechanism link sHTG to kidney impairment.



48% have evidence of kidney impairment	
Kidney impairment	**FCS patients N 21 (%)**
Proteinuria > 150 mg/24h	1 (5)
Proteinuria >150 mg/24h + eGFR < 90 ml/min	4 (19)
Hyperfiltration	2 (9)
Hyperfiltration + Proteinuria > 150 mg/24h	2 (10)
eGFR < 90 ml/min	1 (5)
Total	10 (48)

52. ROLE OF TRIGLYCERIDE-GLUCOSE INDEX IN METABOLIC ASSESSMENT OF SARCOIDOSIS PATIENTS

Rizzi L., Coppola C., Cocco V., Hbaidi Y., Suppressa P.
Department of Internal Medicine and Rare Diseases Centre "C. Frugoni", Lipigen Centre, University of Bari "Aldo Moro"

Sarcoidosis is a chronic granulomatous inflammatory disease of unknown etiology that can affect any organ, especially lungs. It is a rare disease, with a ranging incidence from 1 to 71 cases per 100000 individuals per year. Symptoms include cough, chest discomfort, dyspnea, fatigue, weight reduction, and night sweats. Diagnosis is reached with histological evidence of non-necrotizing granulomas of the involved organs, upon exclusion of other granulomatous diseases. The milestone of pharmacological treatment is represented by oral corticosteroids, while second-line therapy includes azathioprine, methotrexate, and hydroxychloroquine; a third-line therapy comprises anti-tumor necrosis factor-α antibodies (TNF-α), such as infliximab. Sarcoidosis can lead to several metabolic comorbidities such as metabolic syndrome, arterial hypertension, diabetes, dyslipidemia and thus to an increase of cardiovascular risk. This could be explained considering that sarcoidosis and metabolic syndrome partially share common pathogenetic mechanisms such as an overexpressed pro-inflammatory cytokines pathway that includes interleukin (IL)-6, IL-8, IL-12, and TNF-α. For these reasons, a metabolic assessment of sarcoidosis patients is mandatory.

The aim of our retrospective observational study has been to investigate the role of triglyceride-glucose index (TyG index) in metabolic assessment of sarcoidosis patients; TyG index is a novel and reliable surrogate marker of insulin resistance calculated from serum fasting blood glucose and triglycerides, that also behaves as a good predictor of cardiovascular events.
68 sarcoidosis patients (32 males, 36 females; age 55,42±10,14) and 48 healthy persons without any rheumatological or neoplastic disease (20 males, 28 females; age 54,04±8,27) were enrolled. Among sarcoidosis patients, 47,1% of them was under therapy for the disease; diabetes was found in 19,1% of cases, metabolic syndrome in 54,4%, arterial hypertension in 45,6% and dyslipidemia in 42,6%. Among controls, 8 of them (16,7%) suffered from metabolic syndrome; no one of them suffered from diabetes, dyslipidemia or arterial hypertension. T-test, one-way Anova, Pearson test, receiver operating characteristics (ROC) curve analysis and binary logistic regression were used for statistical analysis; a p value less than 0,05 was considered statistically significant.
Results showed that TyG index was higher in sarcoidosis group than in controls (8,64±0,40 vs 8,28±0,49, p=0,000), even when comparison was made after exclusion of metabolic syndrome in both groups and diabetes in the first one (8,42±0,36 vs 8,14±0,36, p=0,003).
Among sarcoidosis group, TyG index values did not show significative differences among GenPhenReSa clinical phenotyping groups (p=0,377), neither among the treated and not-treated groups (8,72±0,36 vs 8,56±0,42, p=0,107) or in relation to radiological stages (p=0,550).
Moreover, TyG index showed a statistically significative direct correlation with Framingham score (r=0,268, p=0,030); ROC curve analysis highlighted a TyG index cut-off value of 8,10 (96% sensitivity, 85% specificity) in predicting Framingham score equal or greater than 10 (equivalent to an almost moderate cardiovascular risk), with an area under the curve (AUC) of 67% (95% CI 54-80; figure 1).
Referring to metabolic syndrome, TyG index values were higher in the metabolic subjects than in non-metabolic ones (8,80±0,38 vs 8,45±0,35, p=0,000); ROC curve analysis showed that a TyG index cut-off value of 8,04 (97% sensitivity, 87% specificity) was useful to predict metabolic syndrome in sarcoidosis cohort (AUC 74%, 95% CI 62-86; figure 2). Binary logistic regression analysis, in which metabolic syndrome was the dependent binary categorical outcome, confirmed the role of TyG index in determining metabolic syndrome (OR=13,76; 95% CI 2,83 – 66,9, p=0,001).
Finally, TyG index showed a statistically significant positive correlation with waist circumference (r=0,257, p=0,035) and diastolic arterial pressure (r=0,280; p=0,021); no significant correlations were found between TyG index and systolic arterial pressure (r=0,206; p=0,092), age (r=0,090; p=463) or disease duration expressed by months (r=-0,187; p=0,127).
At our knowledge, this study represents the first investigation about the usefulness of TyG index in metabolic assessment of sarcoidosis patients. First, our study suggests that sarcoidosis could act as an independent trigger for insulin resistance: even excluding subjects with diabetes and metabolic syndrome, analysis showed TyG index values significantly higher in sarcoidosis group than in the controls one.
Results also highlighted that TyG index can be considered an easy-to-use tool that can help physicians to quickly identify patients with metabolic syndrome and so at a higher risk of insulin resistance; TyG index also gives clear information about cardiovascular risk, being directly correlated with Framingham score.
Concluding, TyG index should be implemented in the clinical practice for the metabolic management of sarcoidosis patients, to promptly identify patients at higher risk of developing metabolic comorbidities and cardiovascular disease.

53. INVESTIGATING THE EFFICACY OF FX06 IN RESTORING ENDOTHELIAL BARRIER FUNCTION IN IDIOPATHIC SYSTEMIC CAPILLARY LEAK SYNDROME

Wu M.A.[1], Locatelli L.[2], Colombo R.[3], Cogliati C.B.[4], Maier J.A.[2]
[1]Division of Internal Medicine, ASST Fatebenefratelli Sacco, Luigi Sacco Hospital – Polo Universitario, University of Milan, Milan, Italy; [2]Department of Biomedical and Clinical Sciences, University of Milan, Milan Italy; [3]Division of Anesthesiology and Intensive Care, ASST Fatebenefratelli Sacco, Luigi Sacco Hospital – Polo Universitario, University of Milan, Milan, Italy; [4]Division of Internal Medicine, ASST Fatebenefratelli Sacco, Luigi Sacco Hospital – Polo Universitario, University of Milan, Milan, Italy; Department of Biomedical and Clinical Sciences, University of Milan, Milan Italy

Background: Idiopathic systemic capillary leak syndrome (ISCLS) is a life-threatening disorder characterized by recurrent hypovolemic shock caused by excessive plasma extravasation. Current treatment options for acute flares are limited to supportive care.
Objective: This study aimed to investigate the impact of FX06, a Bβ15-42 fibrin-derived peptide that binds to VE-cadherin, on the barrier function of endothelial cells exposed to intercritical and acute sera from ISCLS patients.
Methods: We employed the Transwell Permeability Assay to assess the permeability of human umbilical vein endothelial cells (HUVECs). The Griess method was used to measure nitric oxide (NO) metabolites in collected sera. Additionally, a three-dimensional microfluidic device was utilized to evaluate the permeability induced by acute ISCLS serum, with changes in fluorescence intensity measured by confocal fluorescent microscopy. Western Blot analysis was conducted on cell lysates.
Results: Both in two-dimensional (2D) and three-dimensional (3D) systems, sera from ISCLS patients increased endothelial permeability, leading to alterations in VE-Cadherin localization and cytoskeletal organization. Intercritical sera also induced similar albeit less pronounced effects. The alteration of endothelial permeability was independent of NO involvement. FX06, administered with varying time schedules, effectively restored the endothelial barrier function by acting solely on the cellular localization of VE-Cadherin rather than its quantity.
Conclusion: This study presents the first report of preliminary yet highly promising findings regarding the effectiveness of a drug that targets the underlying pathophysiological mechanisms of ISCLS. FX06 demonstrates the potential to restore the compromised endothelial barrier function during critical ISCLS crises, providing a significant breakthrough in the management of this life-threatening condition.

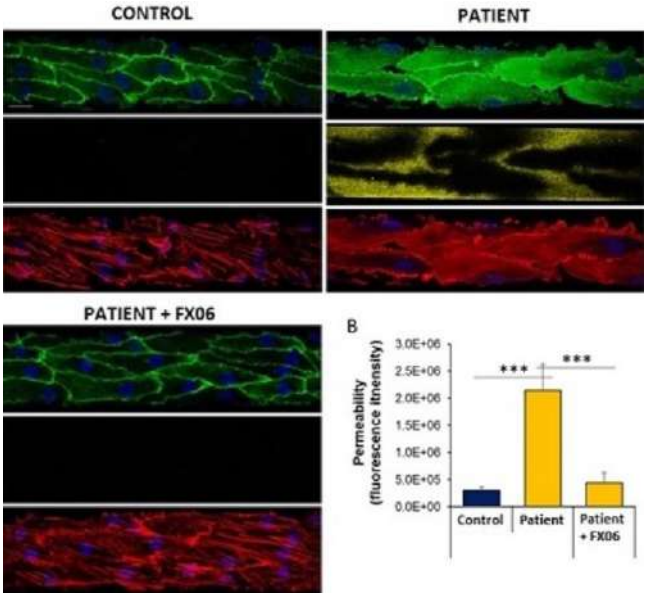


Figure. The effect of acute ISCLS serum and FX06 on VE-Cadherin localization and cytoskeletal organization in HUVECs cultured in 3D and treated for 24h.

54. GENETIC HETEROGENEITY IN FIVE ITALIAN FAMILIES WITH AUTOSOMAL DOMINANT AUTOINFLAMMATORY DISEASES

Sangiorgi E.[1], Verrecchia E.[2], Sicignano L.L.[2], Gerardino L[2], Murace C.A.[3], Massaro M.G.[3], Gurrieri F.[4], Manna R. [3]
[1]Department of Genetics, Università Cattolica del Sacro Cuore, Rome, Italy; [2]Department of Geriatrics, Università Cattolica del Sacro Cuore, Rome, Italy; [3]Periodic Fever Research Center, Università Cattolica del Sacro Cuore, Rome, Italy; [4]Operative Research Unit of Medical Genetics, Fondazione Policlinico Universitario Campus Biomedico, Rome, Italy

Periodic fever syndromes are rare conditions in which patients experience recurrent episodes of fever with multiple inflammatory symptoms, in the absence of infection, malignancy, immunodeficiency or autoimmunity. These diseases may recur with varying intervals between attacks and they have a significant impact on the quality of life of patients/caregivers and on the healthcare system.

These conditions can be categorized in monogenic disorders and multifactorial polygenic disorders, but in many cases it is difficult to identify a molecular base, because they present as sporadic without any variants in genes commonly mutated in autoinflammatory diseases. Systematic studies exploring their molecular causes are lacking.
In order to identify new causative genes involved in undifferentiated periodic fever syndromes, suspected autoinflammatory disorders and PFAPA syndrome, for which no common genetic cause has ever been defined, we started a small exome sequencing project on five families with an undefined autoinflammatory condition with a presumed autosomal dominant segregation. All five families had slightly different symptoms, onset of the disease and periodicity of their symptoms and they were negative to an NGS panel testing the most commonly mutated genes in these diseases. After exome sequencing we validated through genetic segregation different variants in different families and using bioinformatics tools we restricted the predisposing variant in each family to a single one.
In this study, we focused our attention on five familial cases of AID presenting with classical autosomal dominant transmission. To identify the probable monogenic cause, we performed exome sequencing. Through prioritization, filtering, and segregation analysis, we identified few variants for each family. Subsequent bioinformatics evaluation and pathway analysis helped to narrow down the best candidate genes for each family to *FCRL6*, *PKN1*, *STAB1*, *PTDGR*, and *VCAM1 (Table 1)*. Future studies on larger cohorts of familial cases will help confirm the pathogenic role of these genes in the pathogenesis of these complex disorders.
All five genes in the five families have a role in different aspects of the innate immune pathways. Given the genetic heterogeneity discovered in these five families it is of paramount importance to test a larger cohort of families and sporadic cases in order to extend and validate the preliminary findings of this project.

Genes	Variant	Frequency gnomAD	CADD score	
MROH9	p.Leu671Ser	6/179018	23.6	family R
CRP	p.Arg206Trp	77/282680	19.27	
FCRL6	p.Gly350Arg	23/282834	**14.48**	
KIF26B	p.Ala277Val	47/269910	14.42	
NUBP1	p.Pro5Arg	46/208086	32	family G
SLC15A1	p.Ile631Thr	313/282220	25.9	
PKN1	p.Gly884Ser	-	**23.6**	
GBP3	p.Glu457Asp	223/282744	14.52	
CCNG2	p.Ala67Val	-	23.7	family C
STAB1	p.Arg1305Gln	19/250642	21.6	
GNAI2	p.Thr11Lys	-	6.59	
PTGDR	p.Met228Ile	2/245746	**29.3**	family V
PNN	p.Ala74Pfs*43	-	28.6	
TCTEX1D4	p.Gly115Glu	-	11.28	
PNN	p.Asp680Gly	1/251262	28.6	family A
VCAM1	p.Thr49Ile	-	**23.6**	
PBK	p.Asp178Asn	7/279908	23	

Table 1. List of the variants identified in different family segregating among the affected individuals

55. COMPARISON BETWEEN CAPILLARY AND SERUM LACTATE LEVELS IN PREDICTING SHORT-TERM MORTALITY OF SEPTIC PATIENTS IN THE EMERGENCY DEPARTMENT

Guarino M.[1], Perna B.[1], Cesaro A. E.[1], Spampinato M. D.[1], Previati R.[2], Costanzini A.[1], Maritati M.[3], Contini C.[3], De Giorgio R.[1]
[1]Dipartimento di Medicina Traslazionale, Università degli Studi di Ferrara; [2]Dipartimento di Emergenza, Azienda Ospedaliero-Universitaria di Cona, Ferrara; [3]Dipartimento di Infettivologia, Università degli Studi di Ferrara

Background: Sepsis is a time-dependent and life-threating condition. The cytokine cascade, responsible for its manifestations, compromises both macro- and micro-circulation leading to anaerobic metabolism and an increase of lactate levels. The available evidence suggests that capillary lactates (CLs) can reflect micro-circulation damages. The aims of this study were to assess the prognostic accuracy of CLs *vs*. serum lactates (SLs) on 48-hour (primary endpoint) and 7-day mortality (secondary endpoint) in patients with suspected sepsis.
Methods: This was an observational, prospective, single-centre study conducted between October 2021 and May 2022 at the Emergency Department (ED) of Ferrara, where the following inclusion criteria were applied: *i*) clinical suspect of infectious disease; *ii*) qSOFA ≥2; *iii*) age ≥18 years; *iv*) a signed informed consent from recruited patients. CLs were assessed as soon as patients arrived in the ED with LactateProTM2®.
Results: A total of 203 patients met the inclusion criteria. Among them 19 (9.3%) died within 48 hours from admission to the ED, while 28 (13.8%) within 7 days. Patients dead in the first 48 hours had higher CLs (19.3 *vs*. 5 mmol/L, $p<0.001$) and SLs (6.5 *vs*. 1.1 mmol/L, $p=0.001$). The best CLs predictive cut-off for the primary outcome (48-hour mortality) was 16.8 mmol/L (72.22% sensitivity, 94.02% specificity, 12.08 +LR, 0.3 -LR, 54.2% PPV and 97.2% NPV). A multivariable analysis demonstrated CLs (OR 22.9, 95% CI 4.7-111.5, $p<0.001$) and SL (OR 13.8, 95% CI 1.4-132.9, $p=0.023$) as strong independent predictors of negative outcome (death) within 48 hours. Patients who underwent death in the first 7 days had higher CLs (11.5 *vs*. 5 mmol/L, $p=0.020$) and SLs (2.75 *vs*. 1.1 mmol/L, $p<0.001$). The multivariate analysis confirmed that both CLs (OR 6.09, 95% CI 1.78-20.88, $p=0.004$) and SLs (OR 3.88, 95% CI 1.25-12.05, $p=0.019$) were strong independent predictors of negative outcome within 7 days.
Conclusions: Our data indicate that CLs can be a reliable tool for identifying septic patients at a high risk of mortality within 48 hours and 7 days. Further confirmatory results on larger series are eagerly awaited to aid emergency physicians in establishing timely outcome of septic patients.

Figure 1. Fagan's nomograms illustrating the effect of CLs ≥16.8 mmol/L and SLs ≥2 mmol/L on 48-hour mortality.

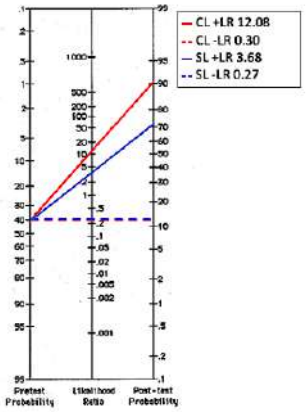


Figure 2. Fagan's nomograms illustrating the effect of CLs ≥16.8 mmol/L and SLs ≥2 mmol/L on 7-day mortality.

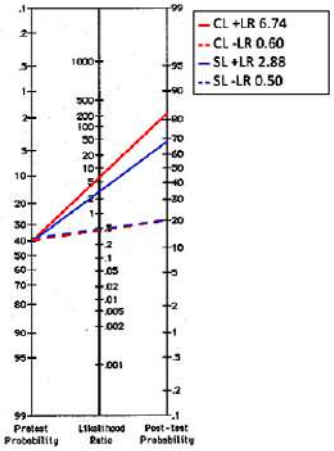
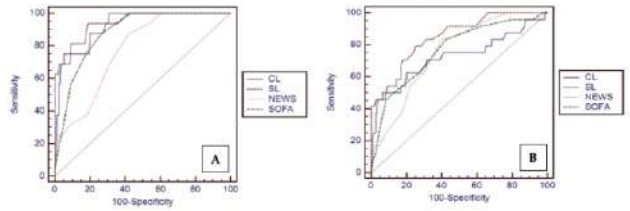


Figure 3: ROC curves illustrating the discrimination ability of CL, SL, NEWS and SOFA in assessing 48-hour (panel A) and 7-day mortality (panel B).



Footnotes. Panel A: CL AUC 0.924, 95%CI 0.875-0.958; SL AUC 0.941, 95%CI 0.896-0.970; NEWS AUC 0.773, 95%CI 0.707-0.832; SOFA AUC 0.879, 95%CI 0.823-0.923. Panel B CL AUC 0.724, 95%CI 0.8652-0.788; SL AUC 0.848, 95%CI 0.787-0.898; NEWS AUC 0.751, 95%CI 0.681-0.812; SOFA AUC 0.766, 95%CI 0.697-0.826.

56. NOVEL ANGPTL3-PCSK9 INTERACTION AND THEIR INVOLVEMENT IN LIPID METABOLISM IN HEPG2 CELLS

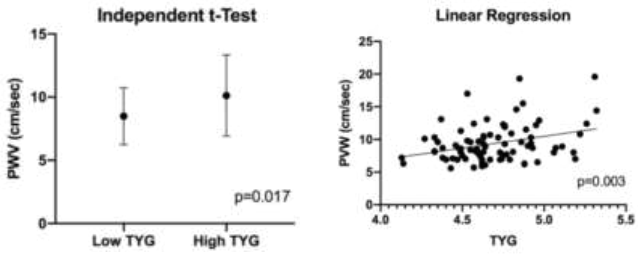
Bini S., D'Erasmo L., Pomanti G., Di Costanzo A., Minicocci I., Covino S., Tramontano D., Arca M., Pecce V.
Dipartimento di medicina Traslazionale e di Precisione, Sapienza Università di Roma

Aim: ANGPTL3 and PCSK9 are known regulators of lipoprotein metabolism. Patients harboring homozygous loss-of-function mutations in the ANGPTL3 gene show reduced levels of circulating PCSK9, indicating a possible coordinate regulation of these two proteins. This study aimed to establish whether the two proteins can cross-regulate in different conditions of nutritional availability.
Method: HepG2 cell models (HepG2 OE) transiently overexpressing ANGPTL3, PCSK9, or both were generated and grown in nutrients rich (feeding) or poor (fasting) conditions. Co-immunoprecipitation (CoIP) was performed to verify protein-protein interaction and western blotting to quantify relative protein expression and ApoB secretion both intracellularly and extracellularly in the culture medium. Intracellular lipid content in the different experimental conditions was measured using Oil-Red-O staining. LDL-receptor expression was quantified using flow cytometry.
Results: The Co-IP in basal growth conditions showed a direct interaction between ANGPTL3 and PCSK9 both intracellularly and in the culture media.In HepG2 OE model ANGPTL3 and PCSK9 showed intense metabolic regulation: at the steady-state ANGPTL3 accumulated in the medium in feeding, while PCSK9 levels were lower in experimental conditions presenting higher levels of ANGPTL3. Intracellular lipid accumulation and ApoB-containing lipoprotein metabolism were investigated in the HepG2 OE models. Cells overexpressing ANGPTL3 showed moderate intracellular lipid accumulation, increased ApoB secretion, and reduced expression of LDL-receptor. Surprisingly, cells overexpressing PCSK9 or ANGPTL3 and PCSK9 showed a consistent reduction in intracellular lipid accumulation (-50%) and increased intracellular ApoB catabolism while LDL-receptor membrane expression was moderately reduced.
Conclusions: A novel direct protein-protein interaction between ANGPTL3 and PCSK9 has been identified. The two proteins show post-translational regulation based on nutrient availability in the culture medium. ANGPTL3 is secreted in feeding conditions, it determines an increase in intracellular lipid accumulation and ApoB secretion. Conversely, PCSK9 is secreted in fasting conditions, it reduces intracellular lipid content and determines enhanced catabolism of ApoB.

57. ASSOCIATION OF TRIGLYCERIDES-GLUCOSE INDEX (TYG) WITH MECHANICAL VASCULAR IMPAIRMENT IN SUBJECTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE

Spampinato S., Bosco G., Di Giacomo Barbagallo F., Lanzafame L., Coppolino G., Di Pino A., Purrello F., Piro S., Scicali R.
Department of Clinical and Experimental Medicine, University of Catania, Internal Medicine, Garibaldi Hospital, Catania, Italy

Background: Non-Alcoholic Fatty Liver Disease (NAFLD) is the most common cause of chronic liver disease in the western countries and its prevalence will grow in the next decades. Increasing evidences showed that NAFLD is a multisystem disease strongly associated with insulin resistance, type II diabetes mellitus, dyslipidemia, chronic kidney disease and cardiovascular diseases. Recent studies showed that the Triglyceride and Glucose index (TYG) - a simple and cost-effective marker of insulin resistance – was associated with atherosclerotic cardiovascular disease (ASCVD) risk in patients with metabolic disorders. In this study we aimed to investigate the potential role of TYG on mechanical vascular impairment, evaluated by pulse wave velocity (PWV) in patients with NAFLD.
Methods: In this observational study we evaluated 80 middle-aged (40–70 years) NAFLD subjects without secondary causes of fatty liver or history of major adverse cardiovascular events (MACE). All subjects performed a routine medical examination from the Internal Medicine outpatient clinic of the A.R.N.A.S. Garibaldi-Nesima (Catania). Fatty liver was diagnosed by ultrasonography. PWV was measured by SphygmoCor CvMS (AtCor Medical, Sydney, Australia). The study population was divided into two groups according to the median value of TYG (high TYG group, TYG ≥ 4.64, n=40; low TYG group, TYG < 4.64, n=40). To test differences of clinical and biochemical characteristics between the two groups, we used Student's t test. Simple linear regression analysis was performed to assess the relationship between TYG and PWV.
Results: High TYG group exhibited a significant higher PWV compared to the low TYG group (10.11 ± 3.28 vs 8.58 ± 2.22 cm/s, $p < 0.05$) (*Figure 1*). A simple linear regression analysis showed that PWV was significantly associated to TYG (β=0.324, $p < 0.01$), indicating that higher TYG values were associated with increased arterial stiffness (*Figure 2*).
Conclusions: In our study we observed that high TYG group exhibited a higher PWV than low TYG group; moreover, PWV was significantly associated to TYG. NAFLD patients with elevated TYG values showed an increased cardiovascular risk compared to NAFLD patient with low TYG values. In this context, TYG could be considered a useful clinical biomarker to predict the mechanical vascular impairment in patients with NAFLD.



58. AARPRI [(AST TO ALT RATIO)-TO-PLATELET RATIO INDEX] PREDICTS CANCERS: A SINGLE CENTER 8-YEARS FOLLOW-UP STUDY IN 653 WOMEN

Crudele L.[1], De Matteis C.[1], Graziano G.[2], Novielli F.[1], Petruzzelli[1], Piccinin E.[3], Gadaleta R.M.[1], Cariello M.[1], Moschetta A.[1]
[1]Department of Interdisciplinary Medicine, University of Bari "Aldo Moro", Bari, Italy; [2]Center for Outcomes Research and Clinical Epidemiology (CORESEARCH), Pescara, Italy; [3]Department of Translational Biomedicine and Neuroscience (DiBraiN), University of Bari "Aldo Moro", Bari, Italy

Background: Non-alcoholic fatty liver disease (NAFLD), specifically liver steatosis and fibrosis with steatohepatitis (NASH), represents a clinical manifestation that is often associated with visceral adiposopathy, whose pathogenetic features have been proposed as tumorigenic triggers. Gender medicine is now focusing on those sex-specific metabolic and hormonal features that might explain the different cancer incidence in men and women despite identical risk factors and the different sensitivity to the same treatment, with the aim of reaching a more personalized clinical approach between males and females. Thus, in this observational prospective study, we followed-up a cohort of 653 metabolic women without previous oncological history for 8 years to find any baseline specific parameters or conditions of risk or prediction that could drive their susceptibility for cancer development.
Methods: Anthropometric, bio-humoral, and clinical parameters were recorded at the index day and comparisons were carried out by Student-T test. ROC analysis was performed to assess variables cut-off values and calculating the associated Odds Ratios (OR) for cancer development. Non-invasive liver fibrosis scores were calculated as follows: AARPRI= (AST to ALT ratio) to platelet count x 150; APRI= AST/Upper limit of normal values/platelet count x 100; FIB-4= (age x AST)/(platelet count x √ALT); mFIB-4=(10 x age x AST)/(platelet count x ALT).
Results: During the 8 years, 62 (9.5%) out of 653 women developed cancer.

Specifically, 16 patients developed endometrial cancer, 11 breast cancer, 10 thyroid cancer, 9 ovarian cancer, 5 colon and 5 stomach cancer, 6 other types of cancer.
Women who developed cancer showed no significant different biochemical and clinical parameters at baseline, except for AST levels. Intriguingly, all non-invasive liver fibrosis scores were significantly higher (p<0.001) in cancer-developer compared to women who did not develop cancer. Subsequently, we performed ROC and cut-off analysis of non-invasive liver fibrosis indexes to eventually differentiate patients who developed gynecological cancers (breast, uterus, ovary) from those who did not develop any kind of cancer. To all, AARPRI score showed the best Youden's Index and the larger AUC with strong significant power. (AUC= 0.75 for AARPRI, AUC= 0.74 for APRI, AUC= 0.74 for FIB-4, and AUC=0.73 for mFIB-4, all p<0.001). We then calculated OR for these indexes and for BMI, waist circumference, FPG and HDL levels, finding that AARPRI values above the ROC cut-off ≥ 0.7 were associated with a OR of 6 (p-value <0.001) for gynaecological cancers development. We further validated these cut-off values in women who had developed non-gynaecological cancers, confirming that AARPRI also identified risk for cancer development with a OR of 5 (p <0.001).
Discussion: These data underscore the *bona fide* predictive power of non-invasive liver fibrosis scores and the impact of NAFLD-associated dysmetabolic conditions in sex-female specific cancers development. The finding that, among all indexes, AARPRI shows the best strength in the assessment of cancer risk in women may depend on the variables that it considers. Differently from APRI, AARPRI considers AAR instead of AST, thus reducing the weight of AST elevation that occurs in severe hepatic inflammation. Furthermore, AARPRI does not consider age, differently from FIB-4 and mFIB-4, reducing the influence related to aging and associated chronic diseases. Our findings support the hypothesis that NAFLD, more than obesity *per se*, is directly associated with the clinical and pathogenic metabolic scenario of gynaecological cancers and encourage the use of liver fibrosis indexes to detect risk of cancer onset in women. Thus, preventing adiposopathy and NAFLD through lifestyle and therapies may represent an instrumental strategy for gynaecologycal cancer prevention and/or co-treatment in oncology.

59. THE EFFICACY OF VERY LOW CALORIE KETOGENIC DIET (VLCKD) ON CARDIO-METABOLIC PROFILE IN PATIENTS WITH OBESITY

Trapanese V., Natale M.R., Vatalaro C., Giofrè F., Melina M., Cosentino F., Donato U., Armentaro G., Sciacqua A., Arturi F.
Dipartimento di Scienze Mediche e Chirurgiche, Università degli Studi "Magna Graecia" di Catanzaro, Catanzaro, Italia

Background: Very low calorie ketogenic diet (VLCKD) has been proposed as an effective intervention for obesity. Hyperketonemia induced by VLCKD is associated with beneficial cardiovascular effects. In addition, ketogenic diet is able to prevent mitochondrial fission, improve mitochondrial function, suppress oxidative stress and attenuate cardiac myocytes apoptosis in the heart of mice.
Aim: To evaluate the role of VLCKD on cardio-metabolic risk factors, cardiac dysfunction and myocardial remodelling in obese patients.
Materials and methods: Ten obese patients treated with VLCKD were enrolled. All patients were characterized from an anthropometric, cardio-metabolic and echocardiographic point of view at baseline and 8 weeks after VLCKD treatment. In addition, each patient underwent measurement of global myocardial work efficiency (GWE), a novel indicator that accounts for deformation and afterload, which may provide additional value for assessment of myocardial function. The insulin resistance was evaluated by HOMA-IR.
Results: As expected, all the patients experienced a significant reduction in body weight and an overall improvement of body composition parameters after VLCKD. Weight (kg) (from 105.1 ± 18.2 to 83.7 ± 16.7, P <0.05), BMI (kg/m2) (from 40.1 ± 4.7 to 31.8 ± 4.8, P= 0.002) and waist circumference (cm) (from 115 ± 13.6 to 101.8 ± 12.4, p < 0.05) were significantly lower after VLCKD treatment. VLCKD treatment improved also significantly fasting glucose (P <0.05), fasting insulin (P =0.004), HOMA IR (P <0.001), lipid profile and blood pressure. In addition, we observed an improved in left ventricular end-diastole volume, left ventricular end-systole volume, left ventricular mass and left ventricular mass index. Interestingly, a significantly changes in GWE was observed (P<0.05).
Conclusion: Although preliminary, our data suggest that VLCKD treatment is able to reduce cardio-metabolic risk factors and to improve cardiac dysfunction and myocardial function.

60. DO HDL LIPOPROTEIN QUALITY AND FUNCTIONALITY CONTRIBUTE TO CARDIOVASCULAR RISK OF PATIENTS AFFECTED BY FAMILIAL HYPERCHOLESTEROLEMIA?

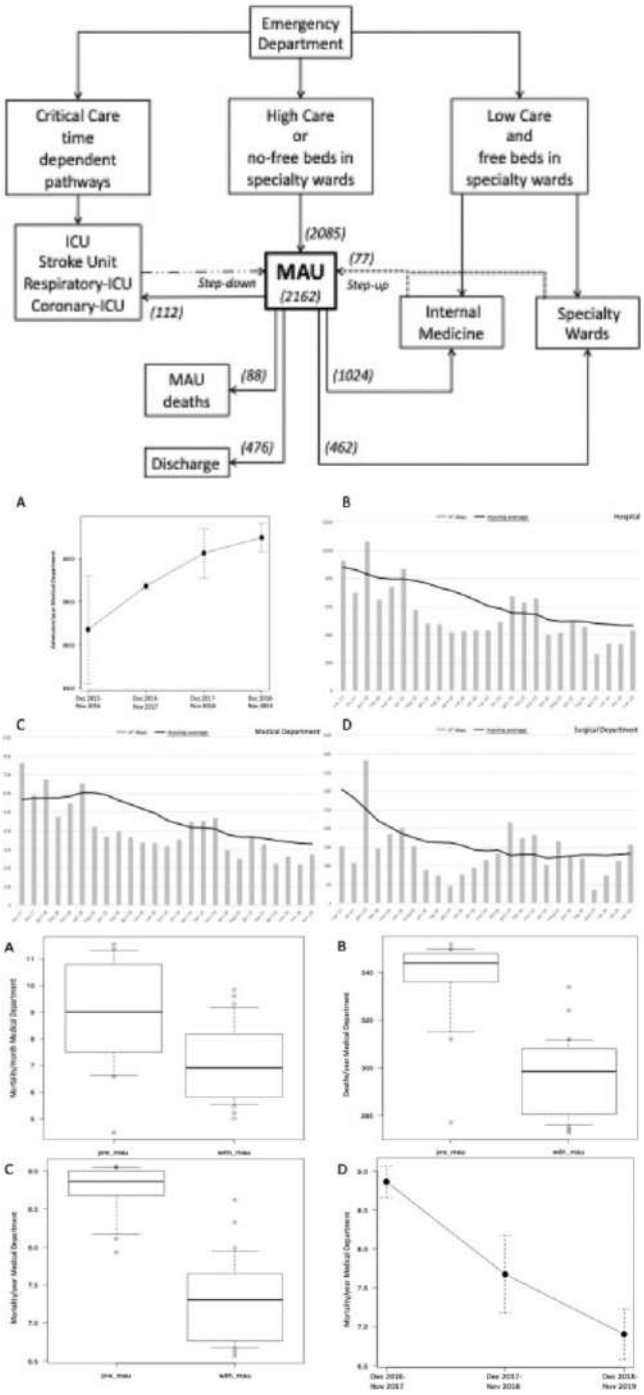
Spaggiari R.[1], Sanz J.M.[2], D'Amuri A.[3], Sergi D.[1], Angelini S.[1], Fortunato V.[1], Favari E.[4], Vigna G.[5], Zuliani G.[6], Dalla Nora E.[3], Passaro A.[7]
[1]Department of Translational Medicine, University of Ferrara, Ferrara, Italy; [2]Department of Chemical and Pharmaceutical Sciences, University of Ferrara, Ferrara, Italy; [3]Medical Department, University Hospital of Ferrara Arcispedale Sant'Anna, Ferrara, Italy; [4]Department of Food and Drug, University of Parma, Parma, Italy; [5]General Medicine, Trecenta Hospital, Trecenta (RO), Italy; [6]Department of Translational Medicine, University of Ferrara, Ferrara, Italy; Medical Department, University Hospital of Ferrara Arcispedale Sant'Anna, Ferrara, Italy ; [7]Department of Translational Medicine, University of Ferrara, Ferrara, Italy; Research and Innovation Section, University Hospital of Ferrara Arcispedale Sant'Anna, Ferrara, Italy

Introduction: Familial Hypercholesterolemia (FH) is an autosomal dominant severe form of dyslipidemia leading to an increase in the levels of circulating LDL cholesterol (LDL-C) thereby increasing cardiovascular risk. The main therapeutic goal in FH patients is the reduction of LDL-C, whereas less is known about the involvement of HDL cholesterol (HDL-C) in the pathogenesis of this lipid metabolism disorder. HDLs are involved in mediating reverse cholesterol transport (RCT), which, in turn, make these lipoproteins a pivotal player in protecting against the development of atherosclerosis. RCT can be estimated by measuring the cholesterol efflux capacity (CEC). HDLs represent a highly heterogeneous class of lipoproteins in terms of size and function, with features potentially impacting upon RCT. The aim of this study was to evaluate the distribution and the function of the HDL subfractions in a group of patients affected by FH.
Materials and Methods: Forty patients affected by FH attending the "Center for the Study of Metabolic Diseases and Atherosclerosis" were compared with eighty metabolically healthy subjects matched for sex, age and body mass index (BMI). Anthropometric data, blood pressure and fasting venous blood samples were obtained for each study participant. CEC was estimated through the analysis of two different pathways: the passive aqueous diffusion (aq-CEC) and the active efflux mediated by the cholesterol transporter ATP-binding cassette A1 (ABCA1-CEC). Cholesterol distribution over 10 HDL subfractions was assessed using the Lipoprint System. The 10 subfractions were grouped according to their size into large HDLs (l-HDL: HDL1-3), intermediate (m-HDL: HDL4-7) and small (s-HDL: HDL8-10). Comparisons among the two cohorts were performed using parametric and non-parametric tests for continuous variables, according to the distribution of each variable, whereas Fisher's exact test was used for categorical variables.
Results: The study cohort included adult patients (age: 53±12 years; BMI: 25.3±3.9 Kg/mq for the controls and 25.9±3.9 Kg/mq for FH patients; females were 60%). Thirty-three FH patients (82.5%) were on a lipid-lowering therapy and eleven (27.5%) had a previous cardiovascular event. Compared to controls, FH subjects displayed a more atherogenic lipid profile, with elevated levels of total cholesterol (TC) (p<0.001), LDL-C (p<0.001) and triglycerides (TG) (p<0.01). Despite HDL-C values being similar among the two groups, FH patients were characterized by an increase in aq-CEC (p<0.01) and ABCA1-CEC (p<0.001). However, when these values were normalized for LDL-C levels, aq-CEC resulted significantly lower in FH patients compared to the controls (p<0.001) whereas no differences were observed for ABCA1-CEC. No associations between CEC and previous cardiovascular events were detected. Furthermore, on the whole cohort, aq-CEC correlated positively with TC (p<0.001), TG (p<0.001) and LDL-C (p<0.001) but no relationship was observed with HDL-C. To a similar extent, ABCA1-CEC correlated positively with TC (p=0.001) and LDL-C (p=0.002). Regarding the HDL-C distribution, higher levels of s-HDL (p=0.039) and lower amount of l-HDL (p=0.037) were detected in FH patients compared to controls.
Conclusion: The cardiovascular burden due to high LDL-C levels in patients with FH is related both to the amount in the circulation and to the time of exposure, whereas when dealing with HDL-C, its concentrations in the blood are not strictly suggestive of HDL function and cardiovascular risk. In fact, despite similar HDL-C, FH patients present an altered HDL function, when focusing on CEC, and a different HDL subfraction distribution compared to their healthy counterparts.

61. THE PROACTIVE ROLE OF AN ACUTE MEDICAL ADMISSION BUFFER UNIT IN A FIRST LEVEL ED HOSPITAL IN LOMBARDY

Accordino S.[1], La Boria E.[2], Formagnana P.[2], Masotti M.[2], Cacco S.[2], Provini S.[3], Arosio G.[2], Passera S.[2], Canetta .[1]
[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano; [2]Ospedale Maggiore di Crema, ASST Crema; [3]Ospedale Civico di Codogno, ASST Lodi

Background: In the last years the rise of acute complex (elderly, frail and poli-pathological) patients that access to Emergency Departments (ED) and require hospitalization has entailed prolonged boarding in ED and hospital overcrowding (especially in medical area), with a secondary increasing of bed occupancy rate and the outlying phenomenon. Moreover, about one-fifth of patients normally admitted in hospitals require a higher clinical and nursing monitoring than provided in ordinary wards, even if less than in Intensive Care Unit (ICU), resulting in a noticeably high clinical risk. These issues highlight the need for new adequate patients' flow logistic strategies and judicious healthcare resources' management. The aim of this study is to analyse the effects on clinical governance of a buffer high-technology and time-limited Medical Admission Unit (MAU), 12 beds and a time of stay ≤ 72 hours. MAU is a dedicated facility located in proximity to ED, Intensive Care Unit (ICU), radiology and laboratory services, designed as a logistically and functionally more intensive care section of the Internal Medicine Unit (IMU) and conceived to focus on acute medical care for patients who have presented in ED or who have developed clinical instability while in-hospital.
Methods: all consecutive patients admitted to MAU from December 2017 to November 2019 have been included considering data regarding inflow (ED or other wards) and outflow status (discharges, transfers, or deaths) and high care needs as continuous multiparameter monitoring and non-invasive ventilation. Clinical patients' characteristics as age, NEWS at admission and output diagnoses and key indicators of unit's workflow as patients' income provenience, in MAU time of stay and outcomes (the direct discharge or transfer rate and the destination wards) have been considered. The number of admissions from ED and the overall in-hospital mortality rate in medical department, the total days of hospitalization and the overall outliers bed days, separated into medical and surgical area, have been compared to those from the previous two years, December 2015 - November 2017.
Results: 2162 patients have been admitted, 2085 (96.5%) from ED, 77 (3.5%) from other wards for clinical instability. After a median time of stay of 64.5 [0.2-344.2] hours, 476 (22.0%) patients were directly discharged while 88 (4.1%) died in MAU and 1598 (73.9%) were transferred to other wards. Among transferred patients, 112 (7.0%) were addressed to Critical Care (CC) units, primarily to the Respiratory Intensive Care Unit, followed by the Coronary Care Unit, the Stroke Unit and ICU. Unlike no-CC transfers, these patients were statistically younger (78 [31-94] vs 81 [18-100], p = 0.002), with a higher NEWS (4 [0-13] vs 2 [0-13], p < 0.001), a shorter time of stay (29.0 [1.0-160.0] vs 52.2 [2.5-295.5], p < 0.001) and a considerably higher in-hospital mortality rate (14.4% vs 5.0%, p < 0.001). 1486 (93.0%) non-critical patients, according to NEWS, main diagnosis and clinical judgement were transferred to other inpatients wards, first IMU which has received 1024 patients (64.1%), the older (82 [18-100] vs 77 [21-99] years, p < 0.001) and more complex, in a higher number compared to what would have been only established by the specialistic criterion of the main diagnosis. By comparison with previous 24 months, despite the increase in admissions/year from ED in medical area (3842 ± 106 in Dec 2015-Nov 2017 vs 4062 ± 100 in Dec 2017-Nov 2019, p < 0.001), the high turn-over in MAU has ensured a constant beds availability significantly reducing overall outlier bed days (from 9.82 ± 2.37% in Dec 2015-Nov 2017 to 6.69 ± 2.07% in Dec 2017-Nov 2019, p < 0.001), especially in surgical department (from 11.46 ± 6.25% in Dec 2015-Nov 2017 to 6.39 ± 3.08% in Dec 2017-Nov 2019, p = 0.001). Lastly and most relevantly, the overall in-hospital mortality in medical area has been reduced, from 8.74 ± 0.37% to 7.29 ± 0.57% (p < 0.001), with fewer 40 deaths/year before and with MAU, respectively.
Conclusions: over two years, a proactively managed acute medical admission buffer unit, strictly interconnected with the hospital macro-organization as the main interface between primary services (ED) and the downstream specialty wards, has demonstrated a positive effect on quality and safety of care. It has been designed as a monitored, well-equipped and well-managed waiting area, whose activity is effective when it ensures availability of free beds, with high technology and standardized in- and out-flow criteria, according to right place, right time and right professional concept. MAU workload with a patient-centred and problem-oriented clinical approach to complex patients' management had a significant effect either on IMU, centralising clinically unstable patients, or on the entire hospital organization. Despite the increase in admissions from ED in medical area, MAU ensured a constant flow of acute medical patient, reducing the outlying phenomenon, especially in surgical department, and the in-hospital mortality.



62. ASSOCIATION BETWEEN CAUSATIVE MUTATIONS AND RESPONSE TO PCSK9 INHIBITOR THERAPY IN SUBJECTS WITH FAMILIAL HYPERCHOLESTEROLEMIA: A SINGLE CENTER REAL-WORLD STUDY

De Ruberto F.[1], Iannuzzo G.[1], Calcaterra I.[1], Stanzione C.[1], Schiano N.[1], Di Taranto M.D.[2], Cardiero G.[2], Tufano A.[1], Fortunato G.[2], Di Minno M.N.D.[1]
[1]Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy; [2]Department of Molecular Medicine e Medical Biotechnologies, Federico II University, Naples, Italy

Background and Aims: Familial hypercholesterolemia (FH) is an autosomal dominant disease that leads to cardiovascular (CV) disease. Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9-I) demonstrated efficacy in low-density lipoprotein cholesterol (LDL-C) reduction and in prevention of CV events. The aim of our study is to evaluate the relationship between LDL receptor (*LDLR*) mutations and response to PCSK9-I therapy. Methods and Results: We evaluated total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) in consecutive patients with FH before PCSK9-I treatment and after 12 (T12w) and 36 (T36w) weeks of treatment. We evaluated LDL-C target achievement according to different mutations in *LDLR*. Eighty FH subjects (mean age:54±13.3 years), 39 heterozygous (He) with defective *LDLR* gene mutations, 30 He with null mutations and 11 compound-He or homozygotes (Ho) were recruited. At baseline, 69 subjects were under maximal lipid lowering therapy (MLLT) and 11 subjects had statin-intolerance. From baseline to T36w we observed an overall 51% reduction in LDL-C. We found no difference in LDL-C changes between subjects with He-defective mutation and He-null mutations both at T12w (p=1.00) and T36w (p=0.538). At T36w, LDL-C target was achieved in 59% of He-defective mutations subjects and in 36% of He-null mutations subgroup (p=0.069), whereas none of compound-He/Ho-FH achieved LDL-C target.
Conclusions: After 36 weeks there were no differences in response to PCSK9-I therapy between different groups of He-FH subjects. Response to PCSK9-I was significantly lower in carriers of compound-He/Ho mutations.

63. CANCER IMMUNOTHERAPY ADVERSE EVENTS AS MISSING LINK BETWEEN POLYARTHRITIS AND WORSENING DIABETES: CASE REPORT

Criscuolo L.[1], Nasta C.[1], Facciuto A.I.[1], Di Sisto A. [1], Brunelli V. [2], Giordano M. [3], Paolisso G. [1]
[1]Dipartimento di Scienze Mediche e Chirurgiche Avanzate, Università degli Studi della Campania "Luigi Vanvitelli"; [2]UOC Medicina e Pronto Soccorso, Ospedale "A. Guerriero", Marcianise; [3] Dipartimento di Scienze Mediche e Chirurgiche Avanzate, Università degli Studi della Campania "Luigi Vanvitelli"

Background: Monoclonal Ab against immunological checkpoints, called immune checkpoint inhibitor (ICI), represents a novel class of cancer immunotherapy. Molecular targets include cytotoxic T lymphocyte-associated protein 4, programmed cell death-1 (PD-1), PD-1 ligand, which normally downregulate T-cell activation. Tumor cells exploit these T-cell tolerance mechanisms to evade detection and proliferate. ICI block inhibitory signaling so T cells can mount effective antitumor response. Interfering with these pathways, however, also causes immune-related adverse events (irAEs).
Case report: A 63-year-old man was admitted in emergency room with decompensated diabetes, swollen left knee and polyarthralgias. Two weeks earlier, the patient had suffered from febrile urinary tract infection (UTI) caused by E.Coli, treated with cotrimoxazole . Few days after the resolution of UTI, he reported onset of the joint symptoms and worsening of glycemic control, that required switch to insulin basal bolus therapy from metformin. His past medical history was significant for bladder cancer with pelvis lymph nodes metastasis, for which the patient had undergone radical cystectomy and he had been taking pembrolizumab, an ICI against PD-1, for 3 months. The man was also affected by peripheral arterial disease, hypertension and T2DM, diagnosed in the previous year, and he was currently on treatment with dual antiplatelet therapy, statin, ARB and PPI. At admission he was apyretic, with normal vital signs. Physical examination revealed fine bilateral basal pulmonary crackles, systolic murmur over aortic area and the presence of ureterostomy on right flank. Joint examination detected warm, tender and swollen left knee, left shoulder functional limitation, bilateral positive squeeze test, tender proximal interphalangeal (PIP) joint of 2nd toe of the left foot. ECG showed sinus rhythm at 75 b.p.m. ABG demonstrated a normal AG metabolic acidosis plus respiratory alkalosis, hyperglycemia (427 mg/dL) with hyponatremia and hypokalemia. A prompt correction of electrolytes and glycemia with i.v. insulin and fluids was set up. Laboratory studies highlighted: WBC 7500/μL (PMN 80%), Hb 14 g/dL, urea 78 mg/dL, eGFR 50.2 ml/min, CRP 7.3 mg/dL, Na+ 134 mmol/L, K+ 3.6 mmol/L, ESR 55 mm, normal liver function, glycemia 280 mg/dL, HbA1c 8.5%, elevated glycosuria without chetonuria, uric acid 5.0 mg/dL, lipase 100 UI/L. Chest X-Ray exhibited coarse bronchovascular markings bilaterally. Abdominal US revealed hepatic steatosis and calcifications of aorta. Our diagnostic work-up continued with the search of etiology of arthritis: X-ray of knees evidenced bilateral gonarthrosis and soft tissue swelling of left knee, while musculoskeletal US showed joint effusion and synovial hypertrophy of left knee, bursitis of left shoulder, minimal effusion without synovitis of both PIP joint of 2nd toe of the left foot and 3rd metacarpophalangeal joint of the hands. Rheumatoid factor and anti-CCP Ab resulted negative; ANA were present at low titer. Left knee arthrocentesis demonstrated yellow fluid of inflammatory type (WBC 5000/mm3 – PMN 50%); neither crystals nor bacteria were detected. All possible differential diagnosis were considered: asymmetric joint distribution and negative serology made the diagnosis of rheumatoid arthritis unlikely; features of synovial fluid were not consistent with septic arthritis or crystal arthropathy; absence of urethritis and nucleic acid amplification test for enteric pathogens on stool excluded reactive arthritis. ICI therapy, time of onset of symptoms after first drug dose and seronegative type suggested diagnosis of ICI-induced arthritis; so, prednisone 20 mg/die was started. At the same time we focused on worsening diabetes: very low levels of c-peptide and poor glycemic control despite intensified insulin therapy supported the hypothesis of insulin dependent diabetes related to ICI. Two weeks after discharge, improvement in joint symptomatology and glycemic control was observed, allowing continuation of pembrolizumab.
Discussion: Musculoskeletal manifestations (arthralgia, arthritis, myalgia, myositis, polymyalgia rheumatica) are the most common rheumatic irAEs. ICI-induced arthritis usually presents with seronegative polyarticular type. Guidelines recommend NSAIDs for grade 1 arthritis, low dose prednisone for grade 2 and high dose for grade 3 arthritis. sDMARDS and/or bDMARDs are recommended for steroid refractory cases. A multidisciplinary discussion between rheumatologist and oncologist is essential for the optimal management of rheumatic irAEs. The continuation or discontinuation of ICIs should be guided by their effectiveness, the severity of irAEs and the intensity of immunosuppressive therapy. Immune checkpoint inhibitor induced diabetes mellitus (ICI-DM) is another significant irAE. This condition is characterized by exposure to ICI, presentation in diabetic ketoacidosis or very low C-peptide levels, insulin dependence. ICI-DM can occur despite pre-existing T2DM, but it is difficult to recognize unless the pre-existing T2DM is well controlled without insulin.

64. A REAL-WORLD SNAPSHOT OF END-OF-LIFE MANAGEMENT OPINIONS IN INTERNAL MEDICINE WARDS IN PIEDMONT-LIGURIA-AOSTA VALLEY: RESULTS FROM THE EOLO SURVEY

Stabile M.[1], Ghinatti M.[2], Migliore E.[3], Elia F.[4], Riccardi F. [2], Ferrando L.[2], Ravera F.[1], Penso M.[1], Dotta D.[1], Biffa G.[2], Aprà F.[4], Fenoglio L.[3], Ballestrero A.[5], Girtler N.[6], Pontremoli R.[5], Bracco C.[3], Zoppoli G.[5]
[1]Dipartimento di Medicina Interna e Specialità Mediche (DiMI) - Università degli Studi di Genova, Genova; [2]IRCCS Ospedale Policlinico San Martino, Genova; [3]U.O. Medicina Interna - Azienda Ospedaliera Santa Croce e Carle, Cuneo; [4]U.O. Medicina e Chirurgia d'Accettazione e Urgenza (MeCAU 2) - Ospedale San Giovanni Bosco, Torino; [5]Dipartimento di Medicina Interna e Specialità Mediche (DiMI) - Università degli Studi di Genova e IRCCS Ospedale Policlinico San Martino, Genova; [6]Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili (DINOGMI) - Università degli Studi di Genova e IRCCS Ospedale Policlinico San Martino, Genova

Background: Patient care at the end of life (EOL) is a daily issue for the internist. It is clinically relevant and has social, ethical, and psychological implications.[1] The SARS-CoV-2 pandemic highlighted the lack of training on EOL management by medical specialists and residents in Internal Medicine.[2,3] The lack of evidence on this issue is also a likely cause of heterogeneity in EOL management between Internal Medicine departments and between physicians of the same unit.[4,5] Under the auspices of the Italian Society of Internal Medicine (SIMI), a task force of internists from several hospitals in Liguria and Piedmont was established to tackle the issue and propose solutions aimed to increase the quality of patient care at the EOL. The project was assisted by a team of fellow psychologists. The joint effort led to the creation of a survey about EOL opinions (EOLO) in internal medicine wards.
Objectives: The main goal of the present project was to design and conduct a pilot survey to collect data on unmet needs in health care service management related to end-of-life.
Methods: We designed an easy-to-use questionnaire consisting of 25 closed-ended questions to assess epidemiological, pharmacological, psychological, practical, and clinical training issues related to EOL. The questionnaire was presented at the SIMI Piedmont-Liguria-Aosta Valley (PLAV) congress and then emailed to all SIMI members of the PLAV section. The answers were

collected and compared using the Chi-squared test where appropriate, without multiple testing correction due to the exploratory nature of our work. All hypothesis testing was two-sided, and a p-value of less than 0.05 was considered statistically significant. All analyses were performed using R software.
Results: A sample of 119 SIMI members volunteered to participate in the survey. Of these, 60 were females (50.4%) and 59 were males (49.6%). Sixty-seven (57.3%) were training residents, almost all of them in internal medicine. One hundred two subjects (85.5%) worked in a low- or medium-intensity clinical ward, and seventeen (14.5%) in a high-intensity one. In their daily clinical activity, all subjects faced the problem of terminality and terminal sedation at least once a month; 99 (93.2%) more than twice a month, and 51 (42.8%) more than five times a month. Sixty-nine (58.0%) used the advice of a specialized figure for the assessment and/or management of the patient at the end of life in more than 25% of cases; those who did not answer "never" indicated the specialist to whom they would turn, in most cases a palliative care physician. Ninety-eight subjects (82.4%) did not receive specific training in EOL patient management through master or postgraduate courses, ten (8.4%) did, but felt their training as inadequate. Twenty-nine (24.4%) considered their preparation in EOL management to be inadequate overall, 88 (73.9%) partially adequate, and only 2 (1.7%) entirely adequate. Difficulty in EOL communication to the hospitalized patient was found to be significantly associated with difficulty in communication with the patient's family members at the EOL (p-value < 0.001). The lack of dedicated training in EOL patient management through master or postgraduate courses was found to be significantly associated with being in training as a resident (p-value = 0.001) and with the perception of suboptimal preparation in EOL management (p-value = 0.035).
Conclusions: The present survey represents one of the first joint efforts to address unmet needs related to EOL management in internal medicine wards. Despite the small sample size, the results are relevant and highlight the lack of and demand for specific training. The survey could be extended to a larger sample of internists to offer a more comprehensive landscape of EOL care. Our intention is to implement strategies to improve EOL management based on the survey results, which could be included in a dedicated training program.
References
1. Sallnow, L. et al. Report of the Lancet Commission on the Value of Death: bringing death back into life. Lancet, 2022.2. Fadul, N. et al., E. Integration of palliative care into COVID-19 pandemic planning. BMJ Support. Palliat. Care 2021.
3. Ersek, M. et al. End-of-life care in the time of COVID-19: Communication matters more than ever. J. Pain Symptom Manage, 2021.4. Lendon, J. P. et al. Measuring experience with end-of-life care: A systematic literature review. J. Pain Symptom Manage, 2015.
5. Leung, D. Y. P. et al. Palliative and End-of-Life Care: More Work is Required. Int. J. 5. Environ. Res. Public Health 2020.

65. GUT-DERIVED LIPOPOLYSACCHARIDES IN PANS/PANDAS

Totè C. M.[1], Salvatori F.[2], Capponi M.[2], Magna A.[1], Pannunzio A.[1], Palumbo I. M.[1], Carnevale R.[3], Nocella C.[4], Bartimoccia S.[4], Zicari A. M. [5], Violi F. [6], Spalice A.[5], Loffredo L.[4]
[1]Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy; [2]Department of Maternal Infantile and Urological Sciences, Division of Pediatric Allergology and Immunology, Sapienza University of Rome, Rome, Italy.; [3]Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy; [4]Department of Clinical Internal, Anesthesiology and Cardiovascular Sciences, Sapienza University of Rome, Rome, Italy; [5]Department of Maternal Infantile and Urological Sciences, Division of Pediatric Allergology and Immunology, Sapienza University of Rome, Rome, Italy; [6]Sapienza University of Rome, Rome, Italy

Background: Paediatric acute-onset neuropsychiatric syndrome (PANS) is defined as a wide spectrum of disorders characterized by sudden onset of obsessive-compulsive disorder (OCD) or severely restricted food intake in children. Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections syndrome (PANDAS) identifies patients with acute onset of obsessive-compulsive and tic disorders; PANDAS is considered a particular subtype of PANS. Recent studies showed that PANDAS have changes of the gut microbiota that could favor the neuro-inflammation. Thus, low grade endotoxemia could represent a trigger for NADPH oxidase activation that could favor neuroinflammation in PANDAS. There is currently no data available on PANS. Considering the different etiopathogenetic cause, there may be differences between PANS and PANDAS in terms of dysbiosis and oxidative stress.
The objective of this study: this study aims to explore possible differences in oxidative stress and LPS concentration between PANS and PANDAS subjects.
Methods: In this study we wanted to compare serum levels of soluble NOX2-dp (sNOX-2-dp), iso-PGF2α and LPS in 70 consecutive subjects, including 30 children affected by PANDAS and 30 controls (CT) and 10 PANS matched for age and gender. Serum zonulin was used as intestinal permeability assay.
Results: Compared with CT, PANDAS children had increased serum levels of sNOX-2-dp, 8-iso-PGF2α and LPS. Compared to PANS, PANDAS subjects have statistically significant higher levels of LPS and zonulin (Figure). Compared to PANS, increased levels, but not statistically significant, of sNOX-2-dp, 8-iso-PGF2α were found in PANDAS (20.4±8.1 vs 15.8±2.2, P=0.090 and 176±84 vs 123±34, P=0.062, respectively).

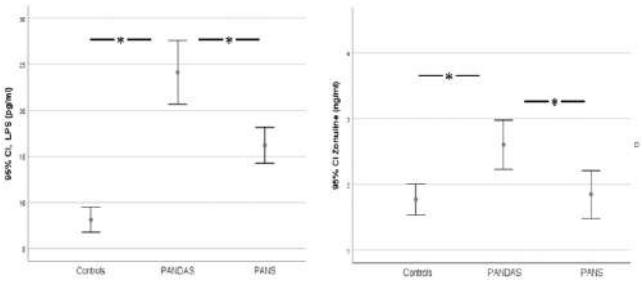


Figure. *p<0.05
Bivariate analysis showed that serum sNOX2-dp was significantly correlated with LPS (R= 0.504; p<0.001), zonulin (R=0.583; p < 0.001) and 8-iso-PGF2α (Rs = 0.724; p < 0.001). Serum LPS significantly correlated with zonulin (Rs = 0.479; p<0.001), and 8-iso-PGF2α (R=0.443; p<0.001). Finally, a multiple linear regression analysis showed that serum 8-iso-PGF2α and zonulin were the only independent variables associated with LPS (R2 = 57%).
Conclusion: This study shows that children affected by PANDAS have higher low grade endotoxemia than PANS.

66. THE VALUE OF THE HISTOLOGICAL CLASSIFICATIONS OF ANCA-ASSOCIATED VASCULITIS IN PREDICTING LONG TERM KIDNEY SURVIVAL

Stella M.[1], Locatelli L. [2], Sala F. M. [3], Reggiani F. [1], Calatroni M.[1], Moroni G.[4], Sinico R.A.[5]
[1]Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini 4, 20090 Pieve Emanuele – Milan, Italy IRCCS Humanitas Research Hospital, Via Manzoni 56, 20089 Rozzano – Milan, Italy; [2]IRCCS Humanitas Research Hospital, Via Manzoni 56, 20089 Rozzano – Milan, Italy; [3]Nephrology unit, ASST Vimercate, Vimercate Hospital, Vimercate, Italy.; [4]Department of Biomedical Sciences, IRCCS Humanitas Research Hospital, Rozzano, Lombardia, Italy; [5]Nephrology and Dialysis Unit, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy

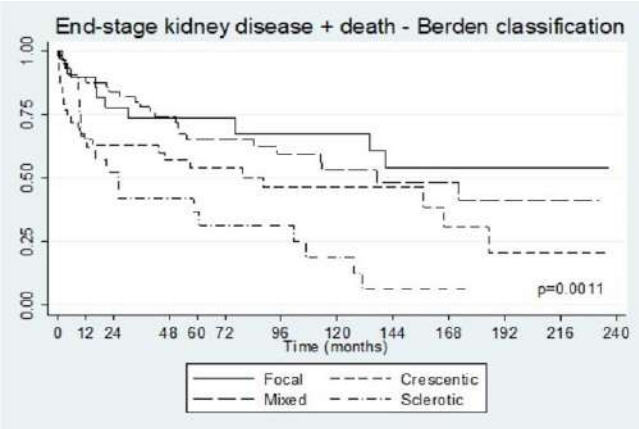
Characteristics	All (n=152)	ESKD (n=59)	no ESKD (n=93)	p
Male, n (%)	84 (55.3)	33 (55.0)	51 (55.4)	0.89
Age	63.8 (51.3-70.8)	66 (53.7-74.8)	62.0 (47.9-70.0)	0.03
Serum creatinine mg/dL	3.9 (2.45-7.0)	6.0 (4.0-8.2)	3.1 (2.0-4.7)	0.001
Proteinuria g/die mean (SD)	1.53 (1.66)	2.05 (1.96)	1.24 (1.29)	0.005
Hemoglobin g/dL, median (IQR)	9.00 (8.1-10.4)	8.7 (8.2-9.8)	9.3 (8.1 - 10.7)	0.048
eGFR ml/min/1.73 m2 mean (SD)	21.32 (24.0)	12.1 (12.8)	27.1 (27.4)	0.0001
eGFR at diagnosis <30 mL/min/1.73 m2, n (%)	121 (79.6)	55 (93.2)	66 (70.9)	0.0009
GPA, n (%)	55 (36.1)	20 (33.8)	35 (37.6)	0.64
MPA, n (%)	66 (43.4)	25 (42.3)	41 (44.0)	0.72
Renal-limited vasculitis, n (%)	30 (19.7)	14 (23.7)	16 (17.2)	0.32
Churg-Strauss, n (%)	1 (0.6)	0	1 (1.1)	
MPO - ANCA n (%)	77 (50.6)	28 (47.4)	49 (52.6)	0.39
PR3 - ANCA n (%)	49 (32.2)	20 (33.8)	29 (31.1)	0.72
MPO - ANCA and PR3- ANCA n (%)	3 (1.9)	1 (1.7)	2 (2.1)	
BVAS, median (IQR)	15.0 (13.0-19.0)	15 (12.5-19.0)	15.0 (13.0-19.0)	0.95
Hypertension n (%)	80 (52.6)	39 (66.1)	41 (44.5)	0.008
Follow-up months	46.9 (12.8-119.0)	11.3 (3.3-51.9)	74.1 (33.4-140.9)	<0.00001

Background and Aims: Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) are a group of multisystemic autoimmune diseases characterized by necrotizing inflammation of small vessels, with a predilection for the kidney. The prognostic value of histological classification of

ANCA-glomerulonephritis (ANCA-GN) is discussed. In 2010, Berden and colleagues [1] proposed a prognostic classification based on glomerular involvement; in 2018, Brix et al. [2] introduced the ANCA Renal Risk Score, which includes histological features and glomerular filtration rate; in 2017 the Mayo Clinic Chronicity Score, [3] that considers chronic histological lesions, was designed and assessed in ANCA-GN. We aimed to identify which score is the best tool to predict end-stage kidney disease or death in a cohort of ANCA-GN patients.

	Pure kidney survival rate at 5 years	P
BERDEN's HISTOPATHOLOGICAL CLASSIFICATION		
Focal	76.70%	0.0013
Crescentic	57.20%	
Mixed	72.80%	
Sclerotic	44.10%	
RRS		
Low	85.90%	0.0001
Medium	74.20%	
High	39.70%	
MCCS		
Minimal	73.70%	0.14
Mild	73.00%	
Moderate	57.50%	
Severe	45.80%	

Method: Patients who underwent kidney biopsy in two Italian centers within 32 years were retrospectively collected. Inclusion criteria: age >18 years, and at least one year of follow-up. A minimum of 10 glomeruli was considered adequate for a biopsy. Renal biopsies were classified according to Berden's classification, Renal Risk Score and Mayo Clinic Chronicity Score. The primary end point of the study was the development of end-stage kidney disease (ESKD) at 5 years, defined as the chronic need of renal replacement therapy (RRT) or glomerular filtration rate (GFR) <15 ml/min. The secondary endpoint was a composite endpoint of ESKD or death for all causes.The predictive accuracy of the three classification tools was assessed for the two different outcomes (renal survival alone and composite outcome of ESKD and death). Area under the curve (AUC) values and their corresponding 95% confidence interval (95% CI) were calculated.



Results: Of the 152 patients 84 were male, the median age was 63.8 years (Figure 1). Mean eGFR at diagnosis was 21.32 ml/min/1.73 m2. 32.2% of patients were PR-3 positive, 50.6% were MPO positive, 17.2% were ANCA-negative. After a median follow-up of 46.9 (12.8-119.0) months, 59 patients (38.8%) were on chronic dialysis or with a GFR <15 ml/min; among them, 20 patients died. The pure kidney survival rate (without ESKD or GFR<15 ml/min) was 79% at 1 year, 65% at 5 years, 59.8% at 10 years. Figure 2 reported the pure kidney survival rates of the patients assigned to every class of the three scores that we considered in this study.

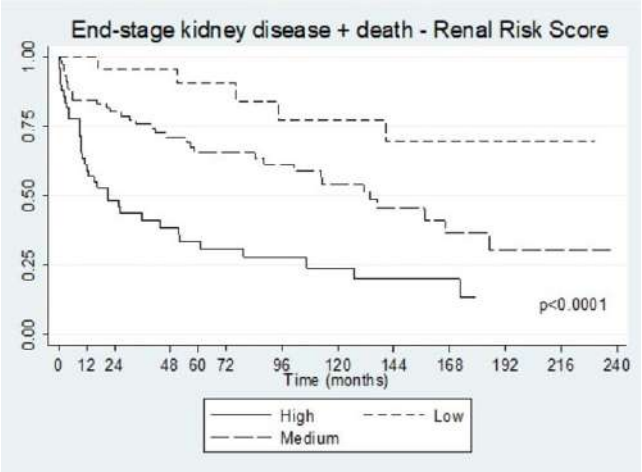
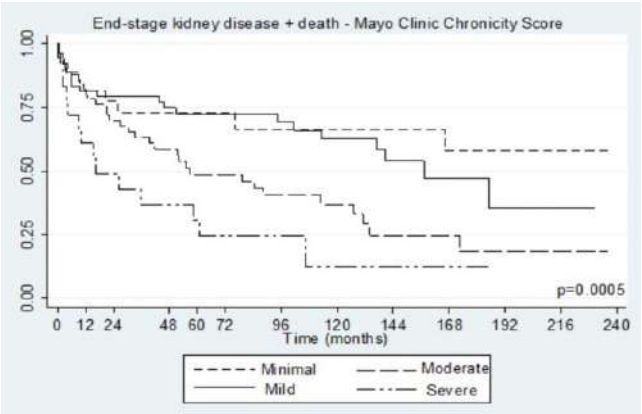
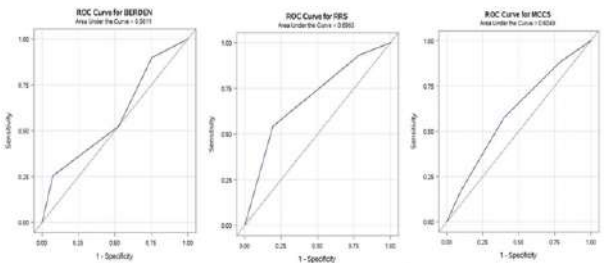


Fig. 3, Fig. 4, Fig. 5. Show Kaplan-Meyer curves for the secondary outcome (ESKD+death); patients are classified according to the Berden's score (Fig. 3), the Renal Risk Score (Fig. 4) and Mayo Clinic Chronicity Score (Fig. 5). The predictive accuracy of the three classification tools was assessed by ROC curves (Fig. 6) for overall adverse outcomes (ESKD and death) and renal survival alone (ESKD). Figure 7 shows the comparison of accuracy among the three classification methods.



Conclusions: Berden histopathological classification and Renal Risk Score are predictive of prognosis both when we consider the primary outcome (ESKD or eGFR<15 ml/min) and when we consider the composite outcome (ESKD + death). The Mayo Clinic Chronicity Score allows a reliable stratification of the patients only when we consider the composite outcome (ESKD and death). The Renal Risk Score showed the best accuracy in defining prognosis, as it remained acceptable both when assessing renal prognosis alone and the composed outcome of death and ESKD.



	ESKD	ESKD + death
	AUC (95% CI)	AUC (95% CI)
Berden	0.581 (0.491-0.672)	0.599 (0.513-0.685)
RRS	0.696 (0.618-0.775)	0.680 (0.603-0.756)
MCCS	0.605 (0.517-0.693)	0.662 (0.580-0.744)

References
[1] A. E. Berden *et al.*, "Histopathologic classification of ANCA-associated glomerulonephritis," *Journal of the American Society of Nephrology*, vol. 21, no. 10. American Society of Nephrology, pp. 1628–1636, 2010. doi: 10.1681/ASN.2010050477.
[2] S. R. Brix *et al.*, "Development and validation of a renal risk score in ANCA-associated glomerulonephritis," *Kidney Int*, vol. 94, no. 6, pp. 1177–1188, Dec. 2018, doi: 10.1016/j.kint.2018.07.020.
[3] S. Sethi *et al.*, "A proposal for standardized grading of chronic changes in native kidney biopsy specimens," *Kidney Int*, vol. 91, no. 4, pp. 787–789, Apr. 2017, doi: 10.1016/j.kint.2017.01.002.

67. NEW POTENTIAL BIOMARKERS FOR EARLY CHRONIC KIDNEY DISEASE DIAGNOSIS IN PATIENTS WITH DIFFERENT GLUCOSE TOLERANCE STATUS

Cassano V.[1], Miceli S.[1], Armentaro G.[1], Rosa M.[1], Scarcelli M.R.[1], Cuda P.[1], Fiorentino T.V.[1], Succurro E.[1], Hribal M.L.[1], Condoleo V.[1], Maio R.[1], Perticone M.[1], Andreozzi F.[1], Sesti G.[2], Sciacqua A.[1]
[1]Department of Medical and Surgical Sciences, University Magna Græcia of Catanzaro, Italy; [2]Department of Clinical and Molecular Medicine, University Rome-Sapienza, Rome, Italy

Introduction: Patients with renal dysfunction present increased risk for cardiovascular (CV) events and dysfunction in hemostatic system, in particular bleeding disorders and thrombosis. In this contest, oxidative stress has a central role in the pathophysiology, development, and complications of Chronic kidney disease (CKD). In addition, recent studies highlighted that endothelial dysfunction plays a significant role in CKD, in particular endocan, a soluble proteoglycan secreted by endothelial cells, and considered a novel biomarker of endothelial dysfunction. Subjects with 1-hour plasma glucose values ≥ 155 mg/dl (NGT≥155), detected during oral glucose tolerance test (OGTT), are at increased risk to develop type 2 diabetes mellitus (T2DM) among subjects with normal glucose tolerance test (NGT). Recent observation highlighted that these subjects have a worse cardiometabolic risk profile and an increased risk for CKD.
Purpose: Based on evidences present in literature, the aim of the current study was to test the role of oxidative stress, platelets activation and endocan levels in renal dysfunction, in NGT<155, NGT≥155, impaired glucose tolerance (IGT) and T2DM individuals.
Materials and methods: We enlisted 233 Caucasian newly diagnosed hypertensive patients (132 men and 101 women, mean age 58.4±11.0) referring to Catanzaro Metabolic Risk Factors (CATAMERI) Study. Plasma glucose was measured by the glucose oxidation method and plasma insulin concentration was determined by a chemiluminescence-based assay. Insulin sensitivity was evaluated using the Matsuda index (Matsuda/ISI). Renal function was tested by measurement of estimated glomerular filtration rate (e-GFR) with CKD-Epi formula. The serum levels of platelets activation (Glycoprotein-VI and sP-selectin) oxidative stress biomarkers (8-isoprostane and Nox-2), and endocan were evaluated with ELISA test. ANOVA test was used to test the differences between groups. A linear correlation analysis was performed in the entire study population, with the aim to evaluate the possible correlation between e-GFR, considered as dependent variables, and different covariates. Variables reaching statistical significance were inserted in a stepwise multivariate linear regression model.
Results: According to plasma glucose value during OGTT, subjects were divided into 4 groups: NGT<155, NGT≥155, IGT and T2DM. Among the four study groups, no significant differences were observed regarding age and gender distribution, anthropometric indicators, DBP, PP, total, LDL and HDL cholesterol. By contrast, among the study groups, there was a significant increase of SBP (p=0.031), triglyceride (p<0.0001), fasting plasma glucose (FPG) (p<0.0001), 1-h glucose (p<0.0001), 2-h glucose (p<0.0001) during OGTT, as well as fasting insulin (p<0.0001), 1-h insulin (p<0.0001) and 2-h insulin (p<0.0001). As awaited, there was a worsening of insulin sensitivity accounting for the decrease of MATSUDA/ISI (p<0.0001). Moreover, we observed a worsening of the inflammatory profile with the deterioration of glucose tolerance, as attested by hs-CRP values (p<0.0001). In addition, with the deterioration of metabolic status, there was a decrease in renal function, as demonstrated by e-GFR values (p<0.0001), in addition there was a statistically significant rise in creatinine (p<0.0001) and azotemia (p=0.002). Of interest, from NGT<155 to T2DM group, there was a statistically significant increase in 8-isoprostane (p<0.0001), Nox-2 (p<0.0001), Glycoprotein-VI (p<0.0001), sP-selectin (p<0.0001) and endocan (p<0.0001) serum levels. Specifically, NGT≥155 patients presented higher serum endocan values compared to NGT<155 (p<0.0001). From the linear correlation analysis, e-GFR resulted significantly and negatively correlated with 1-h glucose (r=-0.489, p<0.0001), 8-isoprostane (r= -0.473, p<0.0001), Nox-2 (r= -0.479, p<0.0001), endocan (r= -0.476 p<0.0001), Glycoprotein-VI (r=-0.238, p<0.0001), sP-selectin (r=-0.368, p<0.0001), hs-CRP (r=-0.171, p=0.005) and positively correlated with MATSUDA/ISI (r=0.418, p<0.0001). Variables reaching statistical significance were included in a stepwise multivariate linear regression model to detect the independent predictors of e-GFR; 1-h glucose resulted the major predictor of e-GFR justifying 23.6% of its variation (p<0.0001), 8-isoprostane and Nox-2 added respectively another 6.0% (p<0.0001) and 3.2% (p=0.001). **Conclusions:** In conclusion, our study confirmed the link between 1-hour post-load glucose ≥155 mg/dl during OGTT and the possible increased risk for CKD, in newly hypertensive diagnosed patients. The novelty of the present study is that we demonstrated a progressive increase in oxidative stress, platelets activation and serum endocan levels with the worsening of metabolic profile, which becomes evident early during the progression of CKD.

68. ROLE OF EXTRACELLULAR VESICLES IN THE PHYSIOPATHOLOGY OF PRE-ECLAMPSIA

Smirne C.[1], Grossini E.[2], Crobu M.G.[3], Quaglia M.[4], Cantaluppi V.[4], Remorgida V.[5], Libretti A.[5], Venkatesan S.[2], Aquino C.I.[5], Colangelo D.[6], Surico D.[5], Pirisi M.[1]
[1]Internal Medicine Unit, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy; [2]Laboratory of Physiology, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy; [3]Laboratory of Molecular Virology, Maggiore della Carità Hospital, Novara, Italy; [4]Nephrology Unit, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy; [5]Obstetrics and Gynecology Unit, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy; [6]Laboratory of Pharmacology, Department of Health Sciences, University of Piemonte Orientale, Novara, Italy

Background and aims: Among hypertensive disorders, pre-eclampsia (PE) is a frequent cause of maternal death and of complications for the newborns. At the basis of PE there would be a placentation defect resulting into an altered perfusion with consequent placental hypoxia, ischemic damage, syncytiotrophoblast apoptosis and release in the maternal circulation of antiangiogenic and vasoconstrictive factors, reactive oxygen species (ROS) and inflammatory cytokines. These changes would lead to the onset of the second stage of PE that occurs after 20 weeks of gestation and is characterized by systemic endothelial dysfunction in many organs including the kidneys. Among other various factors released by the placenta, extracellular vesicles (EVs), which modulate the crosstalk between different cell types, may play a crucial role in the onset of renal damage, probably through pro-inflammatory and pro-oxidant actions, and endothelial dysfunction.
Based on the above considerations, the aim of the present study was to shed light on some of the possible mechanisms involved.
Methods: In 36 PE patients and 17 healthy controls, clinical variables were thoroughly examined at different time points (T0: diagnosis; T1: delivery; T2: one month after delivery). At the same times plasma samples were collected for the characterization of EVs. The latter ones were then used to stimulate human renal glomerular endothelial cells (HRGEC) and human primary podocytes, where we examined viability, ROS and specific markers release, and the permeability to albumin.
Results: EVs isolated from PE patients and healthy controls were CD63, CD9, CD81, PLAP and TF positive, which demonstrated their exosomal nature and placental origin. In PE patients, the size of EVs was higher in comparison with healthy controls at all time points. The EVs concentration correlated with some important clinical variables (i.e., systolic blood pressure, diastolic blood pressure, proteinuria, pulsatility index of the umbilical arteries, soluble fms-like tyrosine kinase-1 (sFlt-1) levels, liver enzymes, uricemia) at T0. Moreover, EVs concentration was higher in severe PE in comparison with mild PE both at T0 and T1. Compared to healthy subjects, at all time points EVs of PE patients had a higher expression of markers of inflammatory, platelet and endothelial origin (CD3, CD4, CD8, CD19, CD20, CD42b, CD105, HLA-1, CD14, CD178, CD190). Similarly, significant differences were observed between severe and mild PE patients for all the markers of inflammatory derivation, and for most of endothelial and platelet origin. *In vitro* experiments showed that PE EVs were able to damage both HRGEC and podocytes, as shown by the reduction of cell viability and the increase of ROS release; additionally, HRGEC displayed features of endothelial to mesenchymal transition. Damage of both cell lines was also confirmed by the

analysis of permeability to albumin and by the quantification of the release of specific markers (respectively, endothelin-1 concerning HRGEC, nephrin and VEGF-A concerning podocytes). Co-culture experiments with the aforementioned cell types showed similar results to those found with the direct stimulations. In the presence of an endothelin-1 antagonist, the harmful effects on podocytes by the co-stimulation with HRGEC were reduced.
Conclusions: In this study we highlighted for the first time a specific pattern of circulating EVs that could account for the renal damage associated with PE as early as the time of diagnosis. Those EVs demonstrated to play a role in the early onset of changes in HRGEC and podocytes function, both as a direct effect and through the modulation of the crosstalk between the two cell lines. These results may be useful for the identification of new early markers with prognostic significance in the management of PE.

69. CLINICAL AND HISTOPATHOLOGICAL FINDINGS IN BIOPSY-PROVEN NEPHROANGIOSCLEROSIS IN PATIENTS WITH AND WITHOUT ARTERIAL HYPERTENSION: ANALYSIS FROM RETROSPECTIVE STUDY

Gigante A.[1], Lai S.[1], Sorato G.[1], Acquaviva E.[1], Ciarniello C.[1], Rosato E.[1], Giannakakis K.[2], D'Amati G.[2], Ferri C.[3], Cianci R.[1], Muscaritoli M.[1]
[1]Department of Translational and Precision Medicine, Sapienza University of Rome, Sapienza, Italy.; [2]Department of Radiological, Oncological and Pathological Sciences, Sapienza University of Rome, Sapienza, Italy.; [3]Department of Clinical Medicine, Public Health, Life and Environmental Sciences, Internal Medicine and Nephrology Unit, ESH Excellence Center for Hypertension and Cardiovascular Prevention, San Salvatore Hospital, University of L'Aquila, L'Aquila, Italy

Background: Nephroangiosclerosis (NAS), hypertensive nephrosclerosis, and benign nephrosclerosis are commonly used to describe the same clinical condition characterized by changes in the kidneys usually attributed to the effects of arterial hypertension (AH). In course of chronic kidney disease (CKD) of any cause, including patients without history of AH, in the elderly or in diabetic patients, the same histopathological changes can be found. Thus, NAS in clinical practice is a diagnosis of exclusion and the real prevalence has been overestimated and varies among different countries. According to European Renal Association/ European Dialysis and Transplant Association (ERA-EDTA) Registry annual Report, hypertensive nephrosclerosis is responsible for end stage renal disease in 16% of patients starting dialysis while NAS, biopsy proven, ranges from 2.7% to 20% in native kidney biopsy registry.
Aims: to describe the prevalence and clinical presentation of NAS in hospitalized patients who required renal biopsy; to evaluate the association of NAS with AH; to evaluate the association of NAS with other glomerulonephritis; to evaluate the relationship between NAS and renal resistive index (RRI).
Methods: renal native biopsies from 837 consecutive patients examined in 18 years (2003–2021) at the Policlinic Umberto I of Rome, were collected. Specimens from pediatric patients, kidney transplants and cancers were excluded from the study. For each patient history, complete physical examination, proteinuria, urinalysis, serum creatinine level (sCr), blood urea nitrogen were recorded and inserted into a database at the time of biopsy. History of AH and antihypertensive drugs were recorded prior to performing the procedure. Every participant underwent renal ultrasonographic assessment immediately before kidney biopsy, within 1 hour of the procedure. RRI was calculated as: (peak systolic frequency shift- minimum diastolic frequency shift)/peak systolic frequency shift. The average of three measurements for each Doppler parameter of arcuate and interlobar arteries in both kidneys was calculated. RRI > 0.7 was considered abnormal. Renal tissue was obtained by percutaneous needle biopsy. Tissue cores were received within 10 min of biopsy and divided in three portions for immunofluorescence and light and electron microscopy. For vascular lesions, if the changes are focal, the most severe lesion present gives the final grade (0 = absent; 1 + = increased wall thickness but to a degree that is less than the diameter of the lumen; 2 + = wall thickness that is equal or slightly greater to the diameter of the lumen; 3+=wall thickness that far exceeds the diameter of the lumen with extreme luminal narrowing or occlusion).
Results: The histological diagnosis of NAS was present in 80 (10.5%) patients. Patients with NAS had significantly higher sCr [2.07 mg/dl (IQR 1.13–5.2) vs 1.1 mg/dl (IQR 0.8–2.1), p<0.001] and lower eGFR than patients without NAS [28.3 ml/min/1.732 (IQR 11.3–53.4) vs 57.6 ml/min/1.732 (IQR 27.6–93), p<0.001]. We performed a sub-analysis on stages of NAS as follows: the stage was mild in 25 (31.3%), moderate in 20 (25%), and severe in 35 (43.7%) patients. Serum creatinine was significantly higher in severe NAS compared to patients with mild-moderate NAS [4.3 mg/dl (IQR 1.9–6.6) vs 1.7 mg/dl (IQR 1–3.47), p < 0.001]. Estimated GFR was significantly lower in patients with severe NAS with the respect to patients with mild- moderate NAS [14.4 ml/min/1.732 (IQR 7.3–36.7) vs 33.6 ml/min/ 1.732 (IQR 16.4–70.5), p < 0.01]. Proteinuria was significantly higher in patients with mild-moderate NAS compared to patients with severe NAS [2.6 g/die (IQR 1–5) vs 1.5 g/die (IQR 0.86–2.3), p < 0.05]. Arterial hypertension was found in 36 (45%) NAS patients and disease duration was 7 (5–13) years. We did not find any significant differences, including histological features, in NAS patients with AH and NAS patients without AH (p > 0.05). In 43 (53.8%) patients, NAS was associated with glomerulonephritis (GN): the most frequent were IgA nephropathy (IgAN, 34.9%), focal segmental glomerulosclerosis (FSGS, 27.9%) and membranous nephropathy (MN, 23.3%). Renal resistive index ≥ 0.70 (54.4% vs 33.7%, p < 0.01) and AH (45% vs 26.8%, p < 0.001) were more frequently in patients with NAS compared to patients without NAS. Patients with severe NAS had more frequently RRI ≥ 0.70 than patients with mild-moderate NAS (70% vs 45.9%, p < 0.05).
Conclusions: Patients with NAS showed a worsening of renal function and high RRI, mainly in patients with severe grade of arteriolosclerosis, than patients without NAS. No significant differences, including specific histological features, are reported in NAS with and without AH. More information on the phenotype, clinical presentation and biomarkers are needed to improve histological and clinical diagnostics.

70. RISK FACTORS FOR CANCER IN A COHORT OF HEART TRANSPLANT RECIPIENTS

Patauner F.[1], Masini S.[1], Autiero G.[1], Boccia F.[1], Bertolino L.[2], Mattucci I.[3], Amarelli C[3], Zampino R.[1], Durante Mangoni E.[2]
[1]Dipartimento di Scienze Mediche e Chirurgiche Avanzate, Università della Campania Luigi Vanvitelli; [2]Dipartimento di Medicina di Precisione, Università della Campania Luigi Vanvitelli; [3]AORN Ospedali dei Colli, Ospedale Monaldi, Napoli

Background. Cardiac transplantation is the treatment of choice for advanced heart failure. Heart transplant (HTx) recipients are immediately exposed to high-intensity immunosuppressive regimens, that reduce the incidence of acute rejection but, on the other hand, lead to an increased risk of adverse events related to long-term cumulative exposure. Among these, malignancy occurs in an estimated 15.3% of cases. Skin cancer, post-transplant lymphoproliferative disorders (PTLD) and lung cancer are the most common malignancies after HTx. Reduction of immunosurveillance, reactivation of oncogenic viruses, carcinogenic effects of immunosuppressants together with comorbidities are considered as the major risk factors. However, data are sparse. Accordingly, we studied the clinical characteristics and cancer occurrence in a single center, large cohort of HTx recipients.
Methods. This was a retrospective observational analysis of data obtained from 335 HTx recipients. Included were patients who received the graft and were followed up in our Hospital between January 2005 and December 2019. Data were collected from electronic charts, available to each patient's hospitalizations or outpatient visits. Data analyzed included information regarding full medical history, exposure to known cancer risk factors, immunosuppressive therapy, clinical course after transplantation and viral reactivations. According to the diagnosis of neoplasia after HTx, patients were divided in two groups and studied for the collected variables in a univariable and multivariable model. A Kaplan-Meier curve was drawn for survival analysis. This study was approved by our University Ethics Committee and was compliant with the 1975 Declaration of Helsinki and its later amendments.
Results. During the study period, 335 eligible patients were enrolled. Clinical features of the cohort are reported in Table 1. Among patients with cancer the median time interval between HTx and malignancy diagnosis was 2013 days [IQR:1413-2929]. Median time interval between diagnosis and clinical status at the end of follow-up was 703 days [IQR:270-1591]. The most common malignancies were non-melanoma skin cancer (NMSC) (29.4%) and lung cancer (23.5%). According to the occurrence of malignancy, patients were divided in two groups and studied for the collected variables. At univariable analysis, patients who developed cancer were older at HTx (p=0.011), and had positive family history for cancer (p=0.032). Cancer onset was also associated with smoking (p=0.006), alcohol consumption (p=0.002) and occupational exposure (p=0.013) before HTx. Patients with a diagnosis of cancer had a longer length of follow-up (p<0.001). Immunosuppressive agents used differed between the two groups, everolimus was prescribed more frequently among patients with neoplasia (p<0.001). However, we did not collect data on the timing of each immune suppressor initiation/switch

or whether these were used prior to or after cancer diagnosis. Due to the low number of patients in the index group (cancer group = 34 patients), we entered only four variables in the multivariable analysis. Alcohol consumption (p=0.027) and length of follow-up (p=0.011) were the independent predictors of cancer occurrence. All results are shown in Table 2. After excluding patients with a follow-up period lower than one year, Kaplan Meier curves showed a significant impact of post-HTx neoplasia on survival (log rank p=0.044) Figure 1.

Discussion. In this single centre experience, we described clinical characteristics and risk factors for cancer of heart transplanted patients followed up in our hospital. The overall prevalence of neoplasia considering a follow up time in our cohort shorter than previous studies was in line with the literature. In accordance with such data, our patients with cancer were older, had a more frequent family history of cancer, smoke history and occupational risk exposure. The length of follow-up independently associated with cancer occurrence and together with Kaplan-Meier analysis showed that HTx recipients who live longer have higher risk of developing cancer; also, when this complication occurs, it leads to lower survival. Alcohol consumption relation with cancer is well known although the association with NMSC and lung cancer (52.9% of our cancer patients) is still controversial. Therefore, after HTx, alcohol may act enhancing chronic immunosuppression and reducing immune system control of cancer transformation.

In conclusion, although there are, to date, no differences in oncology screening programs between HTx and the general population, our data suggest efforts should be focused on patients with alcohol exposure and in those who lived long since transplantation.

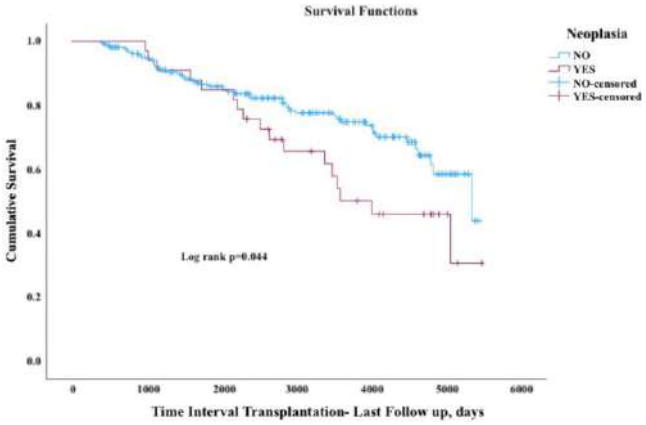


Table 1. Clinical features of the 335 heart transplant patients studied

Parameter	
Age at HT, *years*	53 [42-59]
Sex, male	260 (77.6)
Neoplasia	34 (10.1)
Death	153 (45.7)
Family history of cancer	56 (16.7)
Reason for HT	
Ischemic heart disease	123 (36.7)
Dilative cardiomyopathy	139 (41.5)
Hypertrophic cardiomyopathy	25 (7.5)
Valvular heart disease	25 (7.5)
Others	21 (6.3)
Smoking history	172 (51.3)
Alcohol use	84 (25.1)
Occupational risk factors exposure	26 (7.8)
Previous cancer history	16 (4.8)
Systemic inflammatory disease	70 (20.9)
Metabolic Syndrome	90 (26.9)
Cyclosporin	253 (75.5)
Tacrolimus	70 (20.9)
Mycofenolic acid	257 (76.7)
Everolimus	129 (38.5)
Acute cell-mediated rejection	77 (23)
Antibody-mediated rejection	42 (12.5)
CAV	50 (14.9)
Graft dysfunction	164 (49.0)
Time Interval Transplantation-Last Follow up, days	2177 [316-3833]
CMV reactivation	212 (63.3)
EBV reactivation	118 (35.2)
Cancer site	
NMSC	10 (29.4)
PTLD	3 (8.8)
Lung cancer	8 (23.5)
Kidney cancer	1 (2.9)
Breast cancer	1 (2.9)
CRC	1 (2.9)
Bladder cancer	3 (8.8)
Pancreatic cancer	2 (5.9)
Prostate cancer	3 (8.8)
Cerebral cancer	1 (2.9)
Gastric cancer	1 (2.9)
Time Interval Cancer occurrence-Last Follow-up, days	703 [270-1591]
Time Interval HT-Cancer occurrence, days	2013 [1413-2929]

Data are N (%) or median [IQR]
CAV, Cardiac allograft vasculopathy; CMV, Cytomegalovirus; CRC, Colorectal cancer; EBV, Epstein-Barr virus; HT, Heart transplantation; NMSC, Non Melanoma Skin Cancer; PTLD, post-transplant lymphoproliferative disorders;

Table 2. Analysis of factors associated with cancer occurrence in heart transplant patients

	Univariable analysis			Multivariable analysis	
	Cancer N=34	Non-cancer N=301	p value	O.R. [95% C.I.]	p value
Sex,					
Male	30(88.2)	230(76.4)	0.133		
Female	4(11.8)	71(23.6)			
Age at HT, year	57[51-62]	52[40-59]	**0.011**	1.04 [0.98-1.10]	0.127
Mortality	18(52.9)	135(44.9)	0.468		
Family history of cancer	12(35.3)	44(14.6)	**0.032**		
Heart transplant indication					
Ischemic heart disease	21 (61.8)*	102 (33.9)*	**0.076**		
Dilative cardiomyopathy	10 (29.4)	129 (42.9)			
Hypertrophic cardiomyopathy	1 (2.9)	24 (8.0)			
Valvular heart disease	2 (5.9)	23 (7.6)			
Others	0 (0.0)	23 (7.6)			
Smoking history	28(82.4)	144(47.8)	**0.006**	1.49 [0.38-5.80]	0.565
Alcohol consumption	18(52.9)	66(21.9)	**0.002**	3.02 [1.13-8.09]	**0.027**
Occupational exposure	7(20.6)	19(6.3)	**0.013**		
Previous cancer history	2(5.9)	14(4.7)	0.700		
History of systemic inflammatory disease	7(20.6)	63(20.9)	0.487		
Metabolic syndrome	12(35.3)	78(25.9)	0.681		
Cyclosporine	31(91.2)	222(73.8)	0.163		
Tacrolimus	3(8.8)	67(22.3)	**0.050**		
Mycophenolic acid	26(76.5)	231(76.7)	0.357		
Everolimus	26(76.5)	103(34.2)	**<0.001**		
Graft rejection					
Acute cellular rejection	11(32.4)	66(21.9)	0.285		
Antibody-mediated rejection	3(8.8)	39(13.0)	1.000		
Cardiac allograft vasculopathy	3(8.8)	47(15.6)	0.277		
Graft dysfunction	17(50.0)	147(48.8)	1.000		
Length of follow-up, days	3285(2268-4717)	1800(168-3676)	**<0.001**	1.00[1.00-1.01]	**0.011**
CMV reactivation	26(76.5)	186(61.8)	1.000		
EBV reactivation	10(29.4)	108(35.9)	0.801		

Data are N (%) or median [IQR]
CMV, Cytomegalovirus EBV, Epstein-Barr virus; HT, Heart transplantation;

71. CLINICAL MANIFESTATIONS AND SEROLOGICAL PROFILE OF CANCER-ASSOCIATED MYOSITIS IN A MONOCENTRIC COHORT OF PHENOTYPED PATIENTS

Tonutti A.[1], Ceribelli A.[1], Isailovic N.[2], Lleo A.[3], De Santis M.[1], Selmi C.[1]
[1]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy; Rheumatology and Clinical Immunology, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy; [2]Rheumatology and Clinical Immunology, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy; [3]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy; Hepatology and Internal Medicine, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy

Background: Among idiopathic inflammatory myopathies (IIM), cancer-associated myositis (CAM) remains a clinical challenge and established risk factors include older age, male sex, and the presence of skin manifestations (i.e. dermatomyositis). Specific serum autoantibodies have been associated to CAM, including anti-MJ/NXP2 and anti-TIF1-γ. Recent reports have however suggested a lower risk of malignancy in definite subgroups of anti-TIF1-γ positive patients with other concurrent autoantibodies, whereas the protective role against malignancy of antisynthetase or anti-Mi-2 antibodies (traditionally not associated to cancer) is being questioned.

Objectives.: We aimed at describing the demographic, clinical, and serological characteristics of a cohort of pheno- and endotyped patients with CAM.
Methods: We performed a retrospective cohort analysis. Clinical data were derived from electronic clinical charts. Serum autoantibody analysis was performed with indirect immunofluorescence on HEp-2 cells, protein and RNA immunoprecipitation, and ELISA.
Results: From our cohort of 73 patients with IIM, malignancy was observed in 17/73 (23%) cases, of whom 2/17 (12%) were men, with a median age of 56 years. In 13/17 (76%) patients cancer occurred within 5 years before or after IIM diagnosis, and in 7/17 (41%) cases malignancy relapse or progression was observed. Breast cancer was the most frequent (6/17), followed by lung (3/17), thyroid (2/17), ovarian (2/17), and lymphoma (2/17). Four patients died: three for cancer-related complications and one for severe refractory myositis.
Clinical presentation of CAM included myopathy in 13/17 (76%) and skin lesions in 14/17 (82%) patients. Dysphagia (2/17 – 12%), ILD (4/17 – 24%) and arthritis (3/17 – 18%) rarely occurred, and no cases of myocardial involvement were described.
Anti-Ro52 was the most common antibody (5/17 – 29%) in our cohort, detected as the only specificity in 2/5 cases. Anti-TIF1-γ was described in 4/17 (24%, in one case with concurrent anti-Ro52), followed by antisynthetase (3 – 18%), anti-Mi-2 (2 – 12%), anti-MJ/NXP2, anti-SAE1, anti-SRP (1 each – 6%). Combined anti-E2/E3 pyruvate dehydrogenase (antimitochondrial antibodies – AMA) and anti-Ro52 positivity was found in a patient who developed both lymphoma and cholangiocarcinoma within two years from IIM.
No statistically significant difference was found by comparing CAM patients with (n=4) and without (n=13) serum anti-TIF1-γ. However, dysphagia and skin disease were more frequently observed with anti-TIF1-γ, whereas arthritis, Raynaud's phenomenon, and capillaroscopy alterations were rarer in such group. Prevalence of early-stage cancers seemed more frequent with anti-TIF1-γ. 3/13 patients without anti-TIF1-γ died due to cancer-related causes, while the only death observed in the anti-TIF1-γ positive group was due to progressive IIM and occurred in a patient with complete cancer remission.
Conclusions: In our cohort, CAM accounted for nearly one-fourth of patients with IIM, and most cancers occurred within 5 years before or after the onset of rheumatological manifestations. We observed that dermatomyositis remains the most common clinical subset of CAM, even if other IIM phenotypes can be observed (e.g. antisynthetase syndrome). Along with anti-Ro52, anti-TIF1-γ is the most prevalent autoantibody in CAM, and in our cohort seemed to correlate with a better oncological prognosis but more severe rheumatological manifestations. The clinical and pathogenic significance of AMA warrants further investigation, particularly in patients with otherwise seronegative CAM.

72. CHANGE OVER TIME OF LIPID PROFILE RELATES TO STEROID TREATMENT BUT NOT TO AN INFLAMMATORY STATE IN GRANULOMATOSIS WITH POLYANGIITIS (GPA)

Marozzi M.S.[1], Cicco S.[1], Panebianco T.[2], Dipaola V.[2], Noviello S.[2], Cirulli A.[2], Solimando A.G.[2], Ria R.[2]
[1]UOC Medicina Interna "G. Baccelli" and Unit of Hypertension "A.M. Pirrelli", Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), University of Bari Aldo Moro, AUOC Policlinico di Bari, Italy; [2]UOC Medicina Interna "G. Baccelli", Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), University of Bari Aldo Moro, AUOC Policlinico di Bari, Italy

Aim: Granulomatosis with polyangiitis (GPA) is a small vessel vasculitis that causes multiple vascular damages including accelerated atherosclerosis. Accordingly, cardiovascular atherosclerotic disease (CAD) is a risk factor for the patients' outcome. However, metabolic profile and cardiovascular risk are far to be determined in these patients. The CAD risk was thus evaluated during the GPA follow-up.
Methods: We retrospectively evaluated 37 patients (22 Females) aged 51.45±17.15 at diagnosis (T0) and at 1 (T1) and 2 (T2) year follow-up. All patients were treated with high steroid dose (0,5-1 mg/Kg/die) followed by a one-year tapering, associated to another immunosuppressant. Lipid profile included total cholesterol, HDL, LDL and Triacylglycerol. The erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and neutrophil to lymphocyte ratio (NLR) were evaluated at the same time points to score the inflammatory status. ANOVA for repeated values followed by Tukey's multiple comparisons were used to calculate the trend over time.
Results: Total cholesterol increased at T1 vs T0 ($p<0.05$) and at T2 vs T1 ($p<0.05$). LDL presented the same trend (T1vsT0, $p<0.05$), while Triacylglycerol increased in T1 vs T0 ($p<0.05$), but no differences were seen in T2 vs T0. No difference was found in HDL between the all time points. CRP was only marginally reduced. On the contrary, ESR was lower at T2 vs T0 ($p<0.05$) whereas the NLR increased in T2 but not in T1 vs T0 ($p<0.05$).
Conclusions: Our data suggest that a change in lipid profile is not related to better control of inflammation. On the contrary, the increase in the first year of follow-up is consequent to the steroid treatment. These data may be helpful for evaluation of both cardiovascular disease and lipid metabolism being both conditions linked to vessel inflammation. Further studies are needed to better evaluate the cardiovascular effect of vasculitis and of specific treatment.

POSTER

ALLERGOLOGIA, IMMUNOLOGIA CLINICA

1. HUGHES SYNDROME: CASE REPORT

Curione M., Ciammaichella M.M., De Paola G., Marzano M.A., Ulissi A., Di Castri C., Pignata D., Fanfarillo F.
UOC Medicina Interna ad Alta Intensità di Cure, Dipartimento di Medicina Interna, A.O. S. Giovanni-Addolorata, Roma

INTRODUCTION: We describe the case of a 28-year-old woman who came to our observation for dyspnoea and chest pain that had started for a few days and turgor of the left lower limb. No noteworthy data emerged from the anamnestic collection.
PURPOSE OF THE WORK: We have the following objectives: 1) present the case report of Hughes syndrome associated with complete venous thromboembolism.; 2) to analyze the association of the syndrome with complete venous thromboembolism.
CASE REPORT: The onset clinical picture was characterized by severe respiratory insufficiency (arterial blood gas value of pO2 <60 mmHg) associated with chest pain, confusional state, hemodynamic instability (SBP <90 mmHg) according to the Evidence-Based American College of Chest Physicians Clinical Practice Guidelines (2019 Edition). The patient underwent: Thoraco-abdomino-pelvic CT with contrast medium which documented thrombosis of the inferior lobar branch of the left pulmonary artery and of the segmental branches of the right pulmonary artery, numerous areas of "ground glass" bilaterally, patency of the inferior vena cava, thrombosis occluding the left iliac-femoral axis. The patient was treated with LMWH in association with oral anticoagulants after daily monitoring of INR, as required by the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (2019 Edition); pre-discharge echocardiography (within limits) with measurement of pulmonary arterial pressure (PAP) within limits; venous color Doppler ultrasound of the lower limbs (occluding thrombosis of the left popliteal-femoral-iliac axis) and elastic compression; spirometry (restrictive ventilatory deficit with DLCO within limits); search for neoplastic markers (negative); research thrombophilic markers (positive).
DISCUSSION: The illustrated case of venous thromboembolism is pathogenetically related to the thrombophilic condition, of which the patient was unaware, represented by the positivity of the LAC, of the anticardiolipin and anti-betaglicoprotein antibodies that configure Hughes syndrome.
CONCLUSIONS: The Authors presented a case of Hughes syndrome (positive LAC, anti-cardiolipin and anti-β2GPI antibodies) associated with complete venous thromboembolism and baseline aPTT values persistently greater than 85 sec. for which therapy with LMWH was undertaken since the aPTT could not be monitored if sodium heparin had been chosen. The patient was discharged on treatment with oral anticoagulants.

2. A SENSATIONAL LIBMAN-SACKS ENDOCARDITIS IN LES

Rosellini V., Mattei M., Ciurleo G., Martini L., Morettini A., Iozzia M., Simonetti V., Hennig M., Rossi Ferrini G., Puma A., Abatangelo S., Coppola A., Giovangnini E.
Dipartimento di Medicina Interna 2, AOUC

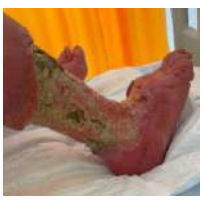
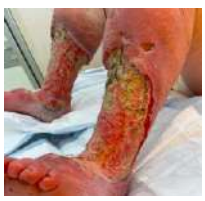
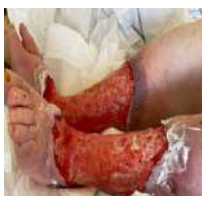
Introduction: we present the case of G.M., a 58-year-old female patient, who was brought to the emergency department for finding palm-plantar skin lesions associated with fever (up to 40°C) arising a week earlier. In particular, some flame-like hemorrhages were noted on the toenails, some hemorrhagic-nodular areas suggestive of Osler nodules, further nodules found purplish in the pretibial site suggestive of erythema nodosum. Cold blood cultures were collected and routine examinations were performed, finding normocytic and normochromic anemia (values unchanged from usual), mild elevation of myoglobin and CPK values, PCR <5, procalcitonin negative. She was admitted to the Internal Medicine 2 department of Careggi Hospital to continue the diagnostic-therapeutic procedure. On suspicion of endocarditis and in agreement with infectivology colleagues, empiric broad-spectrum antibiotic therapy with Daptomycin and Ceftriaxone was introduced.
Background: the patient presented past medical history of gastro-oesophageal reflux disease, treated with pantoprazole; hepatitis B, treated with lamivudine; vertebral and femoral osteopenia, treated with calcium carbonate and bisphosphonates; systemic lupus erythematosus diagnosed since 2005, associated with erythema nodosum, arthritis/atralgias, coombs-positive hemolytic anemia, treated with low-dose steroid therapy, Methotrexate, Colchicine, and Rituximab (Hydroxychloroquine not tolerated).
Differential diagnosis: initially, infectious evaluation was acquired in the suspicion, albeit modest, of hand-foot-mouth syndrome, which was not supported by the specialist and therefore no specific therapy was indicated.
Far higher was the clinical probability of endocarditis, for which collection of blood culture sets from cold peripheral venous access was repeated (patient persistently apiretic during hospital stay) and subsequently acquired cardiologic evaluation with performance of cardiac echocolordoppler, at which were described: mitral leaflets normal in morphology, not thickened, with mobile image at the base of the papillary muscle implant suspected for rupture of order II chord or small endocardial vegetation. Serologies were performed for the main pathogens responsible for endocarditis at negative blood cultures, such as HACEK group forms, Brucella, and Coxiella (all were negative). Serology for Treponema Pallidum and HIV, as well as CD4+/CD8+ quantiferon stimulation and pharyngeal swab for hemolytic Streptococcus B were also negative.
Through thoracic-abdomen CT with contrast mediunm and encephalic-trunk MRI, systemic hemobolizations were excluded. Finally, a transesophageal echocardiogram was performed, which confirmed the presence of minimal echoreflective spicules on the free leaflets of the mitral valve, suggestive, given the clinical and anamnestic history, for a form of Libman-Sacks endocarditis. Therefore, on the basis of this report and the persistence of persistently normal indices of inflammation and consistently negative hemocultures, antibiotic therapy was discontinued and home steroid dosage increased with subsequent clinical benefit. Given the close association between Libman-Sacks endocarditis in the course of SLE and APS (antiphospholipid antibody syndrome) and the consequent risk of valve emboligenic events, in the absence of contraindications, an indication for anticoagulant therapy is placed in the literature. Therefore, therapy with therapeutic-dose heparin s.c was initially set, later replaced by DOAC once antiphospholipid antibody positivity was ruled out.
In addition, to rule out a possible vasculitic/autoimmune form, the following were performed: venous echocolordoppler of the upper and lower limbs, negative for thrombosis in the explored districts; arterial echocolordoppler of the upper and lower limbs, negative for hemodynamically significant stenosis; fondus oculi examination, with retinal inflammatory foci found in a vitritis picture to be rechecked at a later date. Repeated assays of C3 (reduced, 0.39 g/L) and C4 (at lower limits, 0.14 g/L), consistent with SLE picture, were repeated. Performed ENA screen, assay of ANCA autoantibodies, cryoglobulins, antiphospholipid antibodies (all results within limits). Skin biopsy of the lesions at the plantar level was also performed, which showed large area of coagulative necrosis and presence of microembolic phenomena at the level of the superficial dermis at the periphery of the necrotic area.
Conclusions: cardiac imaging (echotransesophageal) together with the negativity of blood cultures, serologies, and quantiferon allowed the diagnosis of non-bacterial thrombotic endocarditis (Libman Sacks') in the absence of peripheral embolization to be made, which was treated with steroid and anticoagulant therapy to prevent possible embolic complications. The result was complete regression of the known lesions and resolution of the endocarditis.

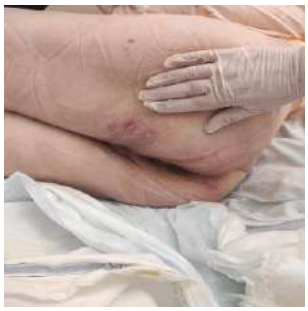
3. WHO KNOWS THE REASON OF THESE TERRIBLE LEGS?

Rosellini V.[1], Mattei M.[1], Morettini A.[2], Menicacci L.[1], Martini L.[1], Ciurleo G.[1], Iozzia M.[1], Giovagnini E.[1], Coppola A.[1], Simonetti V.[1], Hennig M.[1], Rossi Ferrini G.[1], Puma A.[1], Abatangelo S.[1]
[1]Dipartimento di Medicina Interna 2, AOUC; [2]Direttore del Dipartimento di Medicina Interna 2, AOUC

Introduction: we present the case of M.V., a 71-year-old female patient who

was brought to the emergency department for head trauma reported as a result of an accidental fall without loss of consciousness. On examination, as a collateral finding, extensive skin lesions of the lower extremities with considerable loss of substance and sleeve-like extension, covered with fibrin and exudation; numerous ulcerations also at the level of the fingers and toes and in the gluteal area were evidenced. The patient reported presence of these lesions, albeit minor in extent, for several years, clinically worsened following Sars-COV2 infection (contracted 1 month before admission), without important impact on daily activities until the date of admission. The patient never presented fever or other accompanying clinic. In addition, newly detected high-frequency atrial fibrillation was evidenced, treated with lanoxin and anticoagulant therapy, scaled to prophylactic dosing for anemia. On examinations microcytic anemia was detected (Hb 7.5), creatinine 1.62, PCR 265, pct 0.85, cold blood cultures taken (later found negative), empirical antibiotic therapy with daptomycin and tazocin was also set.
Background: the patient presented with partial Reynaud's phenomenon (red and white phase). Onset of lower extremity ulcers about 12 years earlier self-medicated at home without ever medical supervision. No chronic therapy, only ibuprofen as needed. No allergies.
Differential diagnosis: the etiologic study of the lower extremity lesions led first to consider an autoimmune inflammatory picture. The following were performed: ANA panel, ENA-screen, ANCA, anti-phospholipid antibodies and cryoglobulins, all negative; capillaroscopy, not suggestive of specific capillaroscopic patterns. AngioTC of the lower extremities, found negative, was also excluded osteomyelitis. In addition, serologies of major viruses and HIV and Quantiferon assay were requested, which were negative. High-dose corticosteroid therapy was undertaken ex-adiuvantibus, resulting in clinical benefit given by the progressive improvement of the known lesions. The lesions found at the gluteal level (roughly rounded with a subminiated margin) raised the suspicion of pyoderma gangrenosum, for which skin biopsy was performed and a search for occult primary tumor was undertaken through second-level examinations, since this lesion could be also a paraneoplastic manifestation. For the picture of anemia with positive SOF, colonoscopy was performed, which was negative. On the other hand, gastroscopy showed grade C esophagitis and erosive-hemorrhagic gastritis, duodenal ulcer magna with active oozing-type bleeding (Forrest 1B), treated with Argon Plasma, and two additional nonbleeding bulbar ulcers. Therefore, Zollinger Ellison syndrome from gastrinoma was ruled out by gastrinoma assay and 18-FDG PET scan was performed, which showed no areas of glucose hypermetabolism at the gastro-duodenal-pancreatic level, but rather focus with marked hypermetabolism at the uterine body level. Therefore, the patient underwent transvaginal pelvic ultrasonography, which showed a nodular image with sharp margins and oval morphology, referable to intramural uterine myoma, but in consideration of PET uptake, deserving of evolutionary control. On CT chest with MdC, the presence of pulmonary micropacities of nonspecific significance, skin thickening of the right breast region and edematous imbibition of the mammary gland with apparent nipple retraction was noted. Therefore, breast ultrasonography was performed, which showed no solid-type nodular lesions of suspicious appearance. CT abdomen with MdC showed ovoid formation in the context of myometrium with homogeneous enhancement imprinting the endometrial profile. Neoplastic markers: negative CEA (5.6 ng/mL), positive Ca-125 (102). Collaterally, the patient presented with an episode of severe desaturation with finding of submaximal pulmonary thrombo-embolism, associated with extensive thrombosis at the level of the right great saphenous vein and thrombosis in right basilic vein site of Vygon.
Conclusions: Histologic examination of the gastric mucosa revealed circumscribed expressions of intestinal metaplasia in the absence of frank neoplastic lesion, while the gluteal skin biopsy showed picture compatible with scleroderma, a finding that, in specialist opinion, did not collide with the clinical data. In conclusion, the hypothesis of a seronegative autoimmune pathology, possibly evolved as a result of superimposed infectious event (bacterial or viral, given the poor hygiene and care of the leg lesions and the recent Sars-Cov2 infection) or from systemic paraneoplastic cause, was highly suggestive, given the aggressiveness and extent of the lesions and the concomitant finding of multi-district thrombosis as a likely prothrombotic manifestation of the underlying pathology.

4. DEVELOPMENT OF AN IGG4-RELATED DISEASE SPECIFIC QUALITY OF LIFE QUESTIONNAIRE

Lanzillotta M.[1], Batani V.[1], Brombin C[2], Cugnata F.[2], Mazzetti M[3], Dagna L.[1], Della Torre E.[1]
[1]Unit of Immunology, Rheumatology, Allergy and Rare Diseases, UnIRAR, IRCCS San Raffaele Scientific Institute, Milan, Italy; [2]University Centre for Statistics in the Biomedical Sciences (CUSSB), Vita-Salute San Raffaele University, 20132 Milan, Italy; [3]Clinical and Health Psychology Unit, IRCCS San Raffaele Scientific Institute

Introduction. IgG4-related Disease (IgG4-RD) is an increasingly recognized fibro-inflammatory disorder that can involve almost any organ system and lead to end-stage organ damage if left untreated. IgG4-RD typically responds well to high-dose glucocorticoids (GCs), but long-term maintenance treatment is required to avoid disease relapses. Patients are exposed to IgG4-RD related complications and to untenable side effects associated to long-term GCs therapies. Yet, despite these potentially debilitating consequences on patients' health care, patient reported outcomes (PROMs) in IgG4-RD have never been established and a tool for exploring patients' quality of life in this condition is lacking. Objective. We herein report the development of the first IgG4- RD specific Quality of Life (QoL) questionnaire from a derivation cohort of patients with IgG4-RD Methods. 4 rheumatologists and 2 professional nurses experienced in IgG4-RD, 4 European patients' representatives of rare connective tissue disease associations, and 2 psychologists trained in QoL questionnaires nominated items that they felt were important determinants of QoL for IgG4-RD patients. The explored domains included items related to IgG4-RD diagnosis, treatment, and symptoms of the four disease clinical phenotypes, as well as social, working, and family relations. Moreover, questions explored items related to pain, social stigma, and psychological burden. Items were formulated as a questionnaire and administered during outpatient visits to patients with active and inactive disease. A total of 30 IgG4-RD patients were asked to fill in the questionnaire, to assess the relevance of each item, and to suggest additional items that were not listed in the first version of the questionnaire. Results. 67 items covering a wide range of QoL concerns were identified. Of the 30 participants,22 were males, median age 65(IQR 59-75). Most patients showed pancreato-biliary disease, followed by systemic phenotype (9), head/neck limited disease (6), and aortitis/retroperitoneum involvement (3). Patients with active disease (41%) reported a higher impact of IgG4-RD on QoL in terms of reduced social and daily living activities ($p < 0.05$). Moreover, active IgG4-RD determined an increased psychological burden compared to patients in remission. Of note, almost 50% of the patients reported increased fatigue, weight gain, and suboptimal sexual activity. Moreover, 45% of the patients expressed concerns on GCs side effects and disease relapse. No differences were observed in terms of QoL between the four IgG4-RD clinical phenotypes. Finally, after the first cohort of patients returned the questionnaire, 10 additional items exploring the impact of IgG4-RD on family relations and economic issues were added. Discussion. We have developed a new 67-items questionnaire for capturing PROMs and QoL of patients with IgG4-RD. An international effort with an adequately sized population of patients with active untreated disease is required to optimize and validate the IgG4-RD QoL questionnaire, as well as to assess its performance longitudinally in treated patients.

5. EFFICACY OF TOCILIZUMAB IN A CASE OF IGG4-RELATED AORTITIS

Batani V.[1], Mahajne J.[1], Lanzillotta M.[1], Dagna L.[1], Venturini E.[2], Sanvito F.[3], Della Torre E.[1]
[1]1San Raffaele Hospital, Unit of Immunology, Rheumatology, Allergy and Rare Diseases, Milano, Italy; [2]San Raffaele Hospital, Radiology Unit, Milano, Italy,; [3]San Raffaele Hospital, Clinical Pathology Unit, Milano, Italy

Background: IgG4-related disease (IgG4-RD) is a relapsing-remitting fibroinflammatory condition of unknown pathogenesis with a wide range of clinical presentations. Glucocorticoids and rituximab currently represent the treatments of choice for IgG4-RD patients but are burdened by metabolic and infectious complications. Alternative DMARDs have been used with unclear efficacy. Tocilizumab is an anti IL-6 receptor monoclonal antibody approved for the treatment of large vessel vasculitis and its efficacy has never been tested in IgG4-RD.
Objectives: To describe the efficacy of tocilizumab in a patient with biopsy-proven IgG4-related aortitis.
Methods: Tocilizumab was administered subcutaneously with 162 mg weekly injections. No additional steroid therapy or immunosuppressive agent was concomitantly administered. The IgG4-RD Responder Index (RI) along with monitoring of symptoms was used to assess clinical response to treatment. Peripheral blood venous samples were drawn at baseline and every 3 months to monitor IgG4 serum titers, Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) levels. Radiological response was assessed via magnetic resonance angiography (MRA) at baseline and after 6 months of treatment. Complete and partial responses were considered in case of IgG4-RD RI normalization (=0) or decrease ≤3, respectively. Side effects were recorded for safety assessment.
Results: A 60 years old woman with a history of recurrent episodes of myocardial infarctions was diagnosed in June 2013 with ascending aorta and coronary arteries aneurisms and underwent surgical replacement of the aortic valve and ascending aorta. Pathology was diagnostic for IgG4-related aortitis and the patient was referred to our Unit. From 2013 to 2018 the patient was treated with corticosteroids but only periodical increase of steroid dose allowed optimal control of angina and dyspnea. Methotrexate failed as a steroid sparing agent. In June 2018, due to persistent disease activity on MRA and increased inflammatory markers the patient was treated with rituximab with prompt clinical improvement. In June 2021 IgG4-RD relapsed with recurrence of angina, and increase of serum IgG4, ESR and CRP, and rituximab was administrated. Yet, after immediate improvement, angina progressively early recurred and in January 2022 ESR and CRP rose again, and MRA showed increased disease activity with restricted diffusion and contrast enhancement at the aortic arch and subrenal aorta. In situ immuno hibridization and immuno histo chemistry revealed high density of interleukin 6 positive fibroblasts. Therefore, tocilizumab was therefore started leading to rapid clinical, radiological and serological response with normalization of inflammatory markers and resolution of angina within the first month of treatment. An MRA after 6 months of treatment showed a complete resolution of the findings at the level of the aortic arch and a marked decrease in contrast enhancement at the abdominal aorta. The IgG4-RD RI dropped from 6 to 2 indicating a nearly complete response to the treatment. No adverse effects were reported so far.
Conclusion: This is the first report of a patient with IgG4-RD resistant to rituximab successfully treated with
tocilizumab. Further studies are needed to confirm the efficacy of anti-IL6 therapy in IgG4-RD,
especially for the treatment of retroperitoneal fibrosis/aortitis phenotype of disease.

6. STILL'S DISEASE AND RELAPSING MACROPHAGE ACTIVATION SYNDROME: ANY RELEVANCE OF COVID 19?

Bassanello E.[1], Goldin M.[2], Tinazzi E.[1], Senna G.[3], Caminati M.[1], Maiolini F.[1], Friso S.[1]
[1]Unit of Internal Medicine B, Department of Medicine, School of Specialization in Allergology and Clinical Immunology, University of Verona School of Medicine; [2]Unit of Internal Medicine B, Department of Medicine, School of Specialization in Internal Medicine, University of Verona School of Medicine; [3]Unit of Allergology and Asthma Center, Department of Medicine, School of Specialization in Allergology and Clinical Immunology, University of Verona School of Medicine

INTRODUCTION: Adult-onset Still's disease (AOSD) is a rare multi-systemic auto-inflammatory disorder. Macrophage activation syndrome (MAS) represents a potentially life-threatening complication of AOSD. Viral infections might trigger AOSD and MAS. Furthermore, a common immunological background in COVID-19, AOSD and MAS was described. Several cases of AOSD or disease flare post SARS-CoV-2 infection has been reported. Only a few cases of AOSD following other vaccinations were known.
CASE PRESENTATION: We report the case of a healthy 41 y.o. woman, who developed Fever of Unknown Origin (FUO) after the second SARS-CoV-2 vaccine dose (mRNA vaccine, BioNTech/Pfizer). She was successfully treated with prednisone 25 mg/die, but 4 months later she experienced fever relapse, pharyngodynia, arthralgias, skin rash, splenomegaly and lymphadenopathy. The patient was diagnosed with AOSD according to Yamaguchi's criteria and treated with prednisone 1mg/kg body weight and anakinra 200 mg/die for 1 month. Due to the onset of refractory migraine, she was switched from anakinra to tocilizumab (162 mg/7 days). Three weeks later, the patient presented high fever, arthralgias, skin rash, pancytopenia (Hb 8 g/dL, WBC 1120/mmc, N 670/mmc, L 330/mmc, PLT 41000/mmc), increased transaminases, decreased fibrinogen, hypertriglyceridemia and increased level of ferritin (4814 ug/L). The patient developed multiorgan failure needing non-invasive ventilation, continuous renal replacement therapy, red blood cells and platelets transfusions and fibrinogen and albumin supplementation. Clinical MAS diagnosis was supported by the bone marrow biopsy, showing the presence of hemophagocytosis. Treatment with anakinra 600 mg/die, dexamethasone (16 mg/die) and etoposide (100 mg) was initiated. MAS clinical remission was achieved for 1 month (fig. 1 and 3). Systemic steroid was tapered, and etoposide withdrawn. Of note, evidence of positive Beta-D-Glucan was still detectable. The patient experienced a MAS relapse in concomitance with SARS-CoV-2 (fig.2 and 4) infection and disseminated lung candidiasis. Daily steroid dose was maximally increased, antimycotic treatment was administered and etoposide was started again. Nevertheless unresponsive multiorgan failure leaded to patient's exitus.
CONCLUSION: SARS-CoV-2 infection as a trigger of a cytokines storm leading to AOSD and MAS new onset or relapse has been reported. IL-1 seems to act as major driver and anakinra has been identified as an effective treatment for such cases. Regarding SARS-CoV-2 vaccination, very few cases of AOSD and MAS following its administration have been described and the cause-effect relationship is still controversial. In our case report AOSD and MAS onset occurred four months after the second SARS-CoV-2 vaccination and MAS relapsed in concomitance with SARS-CoV-2 positivity and disseminated lung candidiasis. Taking into consideration the persistence of Beta-D-Glucan positivity during the MAS clinical remission, it can be speculated that the virus has driven MAS relapse, despite the initial good response to the treatment. Under this perspective the immunosuppression condition exacerbated by MAS relapse may have been responsible for the dissemination of mycotic infection. Despite the causal role of COVID-19 infection or SARS-CoV-2 vaccination cannot be proven, physicians should be aware of this potential evolution in order to promptly initiate the most appropriate therapeutic approach.

7. THE EFFECT OF EXPOSURE TO SARS-COV-2 VACCINATION AND INFECTION ON HUMORAL AND CELLULAR IMMUNITY IN A COHORT OF PATIENTS WITH IMMUNE-MEDIATED INFLAMMATORY DISEASES

Costanzo G.[1], Deiana C.M.[1], Miglianti M.[1], Sanna G.[2], Ennas M.[1], Perra A.[3], Campagna M.[4], Littera R.[5], Sambugaro G.[1], Fenu G.[6], Palmas V.[7], Cappai R.[8], Dessi M.[8], Ledda A.G.[1], Coghe F.[9], Manzin A.[10], Del Giacco S.[1], Chessa L.[1], Firinu D.[1]

[1]Department of Medical Sciences and Public Health, University of Cagliari, 09100 Cagliari, Italy; [2]Università degli Studi di Cagliari, Cagliari, Italy; [3]Oncology and Molecular Pathology Unit, Department of Biomedical Sciences, University of Cagliari; [4]Dipartimento di Scienze Mediche e Sanità Pubblica; [5]Medical Genetics, Department of Medical Sciences and Public Health, University of Cagliari, 09100 Cagliari, Italy; [6]Department of Neuroscience, ARNAS Brotzu, 09100, Cagliari, Italy; [7] Microbiology and Virology Unit, Department of Biomedical Sciences, University of Cagliari, 09042, Monserrato, Italy; [8]Laboratory Clinical Chemical Analysis and Microbiology, University Hospital of Cagliari, 09042 Monserrato, Italy; [9]Laboratory Clinical Chemical Analysis and Microbiology, University Hospital of Cagliari, 09042 Monserrato, Italy;Laboratory Clinical Chemical Analysis and Microbiology, University Hospital of Cagliari, 09042 Monserrato, Italy;; [10]Microbiology and Virology Unit, Department of Biomedical Sciences, University of Cagliari, 09042, Monserrato, Italy

Background: For patients with immune-mediated inflammatory diseases (IMIDs), immunization against COVID-19 is highly needed, but data on the long-term kinetics of immunity are scant. We aimed to compare the humoral and cellular response to SARS-Cov-2 induced by vaccination and/or infection in a prospective cohort of IMID patients.
Method: We first evaluated humoral and cellular immunity using quantitative IgG anti-SARS- CoV-2 Spike antibody (anti-S-IgG) and neutralization assay and specific interferon-gamma (IFN-g) release assay (IGRA) before and after the third or fourth dose of BNT162b2 and/or after COVID-19. The responses were compared with healthy controls (HC).
Results: The two groups had similar median age, total exposures (vaccine shots and/or infection, median 4 events), and mostly had the infection after the third dose. Duration of symptoms and swab positivity was similar (<5 and 10 days, respectively); 1/10 infected in the IMID group required hospitalization for COVID- 19. IMID and HC were sampled respectively after a median of 140 and 301 days after the vaccine/or infection in early 2023:
At this point, 90% of HC and 36.4% of IMID were simultaneously positive for neutralizing antibodies (with a titer >1:10 PRNT90) and IGRA.
54,5% of IMID and 10% of HC had isolated antibody positivity.
0% HC and 6,3% were simultaneously positive for neutralizing antibodies and IGRA.
The magnitude of residual IGRA response to both original and variant S protein in early 2023 significantly differed between IMID and HC (0.16 vs. 1.08 IU/ml, p<0.001).
We didn't find a significant difference between neutralization titers to BA.1 in IMID and HC (median IMID 1:40 IQR 0, HC 1:40 IQR 150).
However, among IMID, there was a statistically significant correlation between the number of events (vax and/or inf) and the magnitude of IGRA response to original and variant S protein and neutralizing antibody titers (p=0.034, 0.039 and <0.001, Spearman's test).
Conclusion: Our results express the bold immune response of IMID patients to vaccination against COVID-19 regarding both vaccination and infection

8. GENDER DIMORPHISM IN IGA SUBCLASSES IN ASTHMA

Poto R., Di Salvatore A., Covelli B., Di Spigna G., Galdiero M.R., Marone G., Postiglione L., Spadaro G., Varricchi G.
Dipartimento di Scienze Mediche Traslazionali, Università di Napoli Federico II

Background: Immunoglobulin A (IgA) (1), the second most abundant immunoglobulin class in serum, plays a significant role in the homeostasis of mucosal barriers. The two IgA subclasses, IgA1 and IgA2, are transcribed from two distinct constant region genes of heavy chains, with IgA1 being predominantly present in serum and tissues, while IgA2 is primarily found in mucosal secretions (2).
Methods: In this observational study, we evaluated serum concentrations of total IgA and its subclasses (IgA1 and IgA2), total IgG and its subclasses (IgG1, IgG2, IgG3, and IgG4), as well as total IgE in patients with T2-high asthma (43 patients, mean age 46 ± 15 years) and healthy individuals (55 patients, mean age 44 ± 10 years) appropriately matched for age, sex, and body mass index (BMI). Additionally, we assessed gender differences in serum concentrations of different classes and subclasses of immunoglobulins. Total IgE, IgG subclasses, and total IgA were measured using nephelometry, while IgA1 and IgA2 were measured using turbidimetry.
Results: Total IgA levels were increased in asthmatics compared to controls. The increase in total IgA levels was more pronounced in male asthmatics compared to age- and gender-matched healthy controls. IgA1 levels were elevated only in male asthmatics, but not in females, compared to healthy controls. Serum concentrations of IgG2, but not IgG1, IgG3, and IgG4, were reduced in asthmatic patients compared to controls. Serum levels of IgG4 were lower in females compared to male asthmatics. In female asthmatics, IgA and IgA1 levels were higher in postmenopausal individuals compared to premenopausal individuals. IgA concentrations were elevated in patients with mild asthma but not in those with severe asthma. Positive correlations were observed between IgA levels and patients' age and an inverse correlation between IgA2 and IgE in asthmatics. We also found a positive correlation between total IgA or IgA2 and IgG2 levels in asthmatic patients.
Conclusions: These findings highlight for the first time gender dimorphism in IgA subclasses in both male and female T2-high asthma patients. Gender-specific immunological differences may provide new opportunities for the diagnosis and treatment of different phenotypes of asthma in the context of personalized medicine.

9. THYMIC STROMAL LYMPHOIPOIETIN (TSLP) IN ASTHMA AND BEYOND

Poto R.[1], Canè L.[2], Palestra F.[1], Marone G.[1], Iacobucci I.[2], Pucci P.[2], Loffredo S.[1], Monti M.[2], Varricchi G.[1]
[1]Dipartimento di Scienze Mediche Traslazionali, Università di Napoli Federico II; [2]CEINGE Biotecnologie avanzate, Napoli

Background: Thymic stromal lymphopoietin (TSLP) is a pleiotropic cytokine expressed by epithelial cells and various cells of the innate and adaptive immune system (1). The TSLP/TSLP receptor axis plays a central role in several chronic inflammatory diseases (e.g., asthma) and tumors. In humans, two TSLP isoforms have been characterized: a 159-amino acid isoform (lfTSLP), upregulated under inflammatory conditions, and a shorter isoform (sfTSLP) comprising the last 96 amino acids of the C-terminal domain of lfTSLP. Recently, we demonstrated constitutive mRNA expression of sfTSLP and lfTSLP in human lung macrophages (HLM). Lipopolysaccharide (LPS) selectively induced the expression of lfTSLP mRNA and the release of TSLP (2). Macrophages and mast cells are the major effector immune cells in the lungs of patients with asthma (3).
Methods: We analyzed the immunological release of two proteolytic enzymes (tryptase and chymase) from purified human lung mast cells (HLMC). Moreover, we evaluated the effects of recombinant tryptase and chymase on lfTSLP through limited proteolysis and mass spectrometry (MALDI-MS).
Results: Immunologically activated HLMCs (anti-IgE, 1 μg/ml) rapidly released tryptase and chymase in their supernatants (1 hour, 37°C). To determine if TSLP is a substrate for the tryptase and chymase secreted by activated HLMCs, recombinant TSLP was incubated with the two proteases (tryptase and chymase) under different proteolytic conditions. The experiments were conducted for 30 minutes at 37°C using an enzyme:substrate ratio of 1:1000 (w/w) for tryptase and 1:100 (w/w) for chymase. MALDI-MS spectrum of TSLP treated with tryptase showed two signals corresponding to the molecular weight of 98-132 fragments, indicating a tryptase cleavage site located at Met97. Mass spectrometry analysis of chymase cleavage sites in TSLP identified two main peaks corresponding to peptides 1-36 and 37-132.
Conclusions: These results indicate that immunologically activated HLMCs rapidly release tryptase and chymase. Our experiments demonstrate that TSLP is a substrate for tryptase and chymase released from immunologically activated human lung mast cells. The anatomical proximity between macrophages and mast cells in the human lung (4) suggests a possible bidirectional interaction between these immune cells activated at sites of allergic and tumor inflammation. In a series of ongoing experiments, we will evaluate whether TSLP cleavage by mast cell proteases induces the formation of biologically active peptides. Collectively, these findings identify a novel network between mast cells and lung macrophages mediated by TSLP, which is likely to be relevant in the pathobiology of asthma and beyond.
References:
1.Gilda Varricchi, Antonio Pecoraro, Giancarlo Marone, Gjada Criscuolo,

Giuseppe Spadaro, Arturo Genovese, Gianni Marone. Thymic Stromal Lymphopoietin Isoforms, Inflammatory Disorders, and Cancer. Front. Immunol. 9:1595, 2018.
2.Mariantonia Braile, Alfonso Fiorelli, Daniela Sorriento, Rosa Maria Di Crescenzo, Maria Rosaria Galdiero, Gianni Marone, Mario Santini, Gilda Varricchi, Stefania Loffredo. Human Lung-Resident Macrophages Express and Are Targets of Thymic Stromal Lymphopoietin in the Tumor Microenvironment. Cells 10:2012, 2021.
3. Felipe A. Vieira Braga, Gozde Kar, Marijn Berg, Orestes A. Carpaij, Krzysztof Polanski, Lukas M. Simon, Sharon Brouwer, Tomás Gomes, Laura Hesse, Jian Jiang, Eirini S. Fasouli, Mirjana Efremova, Roser Vento-Tormo, Carlos Talavera-López, Marnix R. Jonker, Karen Affleck, Subarna Palit, Paulina M. Strzelecka, Helen V. Firth, Krishnaa T. Mahbubani, Ana Cvejic, Kerstin B. Meyer, Kourosh Saeb-Parsy, Marjan Luinge, Corry-Anke Brandsma, Wim Timens, Ilias Angelidis, Maximilian Strunz, Gerard H. Koppelman, Antoon J. van Oosterhout , Herbert B. Schiller, Fabian J. Theis, Maarten van den Berge, Martijn C. Nawijn, Sarah A. Teichmann. A cellular census of human lungs identifies novel cell states in health and in asthma. Nat. Med. 25:1153, 2019.

10. THYMIC STROMAL LYMPHOPOIETIN (TSLP) IN MASTOCYTOSIS

Marcella M.[1], Poto R.[2], Petraroli A.[2], Canè L.[3], Ferrara A.L.[2], Parente R.[4], Palestra F.[2], Monti M.[3], Marone G.[2], Triggiani M.[4], Loffredo S.[2], Varricchi G.[2]
[1]Istituto di Diagnostica Nucleare (SDN-Synlab), Napoli; [2]Dipartimento di Scienze Mediche Traslazionali, Università di Napoli Federico II; [3]CEINGE Advanced Biotechnologies, Napoli; [4]Division of Allergy and Clinical Immunology, Università di Salerno

Background: Mastocytosis is a heterogeneous disorder associated with uncontrolled proliferation and increased density of mast cells in different organs. This clonal disease is related to activating mutations of the c-kit gene that encodes for KIT (CD117) expressed on mast cell membrane. Thymic stromal lymphopoietin (TSLP) is a pleiotropic cytokine playing a key role in allergic disorders and cancers (1,2). TSLP is a survival and activating factor for human mast cells through the engagement of the TSLP receptor (3). Activated human mast cells release several preformed mediators, including tryptase, which is a diagnostic biomarker of mastocytosis.
Methods: In this study, we enrolled 64 mastocytosis subjects recruited at the University of Naples Federico II and the University of Salerno, and 64 healthy controls (HC), matched for age, sex, gender, and body mass index (BMI). The diagnosis and classification of mastocytosis were made according to the World Health Organization (WHO) criteria based on the histological examination of a skin biopsy for cutaneous mastocytosis and of bone marrow biopsy for systemic mastocytosis. Patients were subdivided according to cutaneous and/or systemic involvement and the severity and frequency of symptoms.
Results: Serum concentrations of TSLP in mastocytosis subjects were lower than in HC. There was an inverse correlation between TSLP and tryptase concentrations in mastocytosis. Moreover, the incubation of serum from subjects with mastocytosis containing tryptase with TSLP concentration-dependently reduced the immunoreactive concentrations of TSLP. Similarly, recombinant β-tryptase reduced the immunoreactivity of recombinant TSLP, inducing the formation of a ~10 kDa cleavage product.
Conclusions: This study demonstrates for the first time that serum concentrations of TSLP in mastocytosis subjects were decreased compared to HC and tryptase derived from mast cells can cleave TSLP *in vivo* and *in vitro*. TSLP is a cytokine that plays a key role in the pathobiology of several allergic disorders. Reduced levels of TSLP in subjects with mastocytosis could contribute to explaining the rarity of allergic diseases (e.g., asthma) in these patients. The interaction between mast cell-derived tryptase and TSLP highlights a novel autocrine loop in patients with mastocytosis that should be further elucidated.

11. PREVALENCE OF ATOPIC MULTIMORBIDITY AND FOOD ALLERGY IN ADULT PATIENTS WITH EOSINOPHILIC COLITIS: A CASE SERIES.

Ribaldone D.G.[1], Marabotto E.[2], Savarino E.[3], Klersy C.[4]
[1]Department of Medical Sciences, University of Turin, Turin, Italy; [2]Gastrointestinal Unit, Department of Internal Medicine, University of Genoa, Genoa, Italy; [3]Gastroenterology Unit, Azienda Ospedale Università di Padova (AOUP), Padua, Italy. Department of Surgery, Oncology and Gastroenterology (DiSCOG), University of Padua, Padua, Italy; [4]Clinical Epidemiology & Biometry, IRCCS San Matteo Hospital Foundation, Pavia, Italy

Background: Atopy is a striking feature of primary eosinophilic disorder of the gastrointestinal tract (EGID). As opposed to eosinophilic esophagitis (EoE), few data are available regarding eosinophilic colitis (EC), the rarest among EGID, and particularly about its triggers and pathogenesis. The prevalence of allergic disorders in EC is also probably underestimated due to the main gastroenterological referral of patients with EC.
AIM: The main aim of this study was to evaluate the prevalence of atopic comorbidities and, among them, food allergy and sensitization profile in a cohort of adult patients with EC evaluated in a third-level allergology centre.
Methods: This was a monocentric, retrospective, and observational study. All consecutively admitted patients, n=20, (median age 38 years, IQR 25-59, 13 males) between March 2021 and December 2022 to the Internal Medicine Department of Fondazione IRCCS Policlinico San Matteo in Pavia, were included in the study. As control groups, we included adult patients with eosinophilic esophagitis (EoE), n=12, and with irritable bowel syndrome (IBS), n=21.
A diagnosis of EC was made according to current guidelines. We included socio-demographic data (age, sex), data about main allergologic comorbidities including eczema, allergic rhinitis and asthma, food allergy, allergy to drugs and to Hymenoptera venom. Data about skin prick tests (positive if > 3mm) and allergen specific IgE by FEIA for extracts and recombinant proteins to the main respiratory and food allergens, including PR-10, profilin and LTP) and were collected, cut-off level for positivity 0.1 kUa/L.
Results: No significant difference was found between EC and EoE in terms of the prevalence of atopic multimorbidity**.** Asthma was significantly more frequent in patients with EC than IBS (p= 0.022). Rhinitis was more frequent in patients with IBS (p=0001), Table 1.
By prick tests, EC and EoE patients displayed no significantly different allergen sensitization. Despite comparable total IgE levels among group (p=0.38), patients with EC and EoE showed more frequently a IgE positivity compared to IBS patients (p=0.00). Of note, sensitization to PR-10 and profilin was more frequent among EC patients than other groups (p=0.001 and p=0.021 respectively). Interestingly, Sensitization to LTP was present only in patients with EC and EoE, Table 2.
Conclusions: In our series, EC patients frequently present with allergic comorbidities, particularly asthma. Sensitization to cross-reactive allergens such as PR-10 and profilin is more frequently among EC patients than controls. Moreover, EC patients are sensitized to LTP. Sensitization to heat-labile allergens (PR-10, profilin) may be a marker of coexistent respiratory allergy while that to heat-resistant protein may a have a direct pathogenic role.

Table 1. Comparison of symptom frequency in patients with eosinophilic colitis (EC) versus patients with eosinophilic esophagitis (EoE) and irritable bowel symptoms (IBS).

Clinical manifestation	Total symptomatic patients	EC	EoE	IBS	P-value
Rhinitis, n (%)	39 (53.4)	14 (36)	8 (20.5)	17 (43.6)	0,002
Asthma, n (%)	16 (21.2)	13 (81.2)	2 (12.5)	1 (6.25)	0,035
Eczema, n (%)	12 (16.4)	6 (50)	4 (33.3)	2 (16.7)	0,245
Food allergy, n (%)	16 (21.9)	9 (56.2)	4 (25)	3 (18.8)	0,435
Drug allergy, n (%)	12 (16.4)	8 (66.7)	1 (8.3)	3 (25)	0,755
Hymenoptera allergy, n (%)	2 (2.7)	1 (50)	0 (0)	1 (50)	1,000
Anaphylaxis, n (%)	2 (2.8)	1 (50)	0 (0)	1 (50)	1,000
Atopy, n (%)	56 (76.7)	31 (55.4)	8 (14.3)	17 (30.4)	0,644

Table 2. Comparison of sensitization profile by means of specific allergen specific-immunoglobulin E (IgE) determination by FEIA between patients with EC, EoE and IBS

	Patients with a positive test	EC	EoE	EIS	
IgE for total extract IgE (n,%)					P-value
At least 1 Food	13 (23.2)	7 (53.85)	6 (46.15)	0 (0)	0,000
Wheat, Gluten or Gliadin	3 (5.4)	1 (33.3)	2 (66.7)	0 (0)	0,100
Malt,	7 (12)	0 (0)	1 (14.3)	6 (85.7)	0,883
Rice,	5 (13.9)	0 (0)	1 (20)	4 (80)	0,005
Milk, A-LA, -Big or Casein,	5 (12.8)	1 (20)	1 (20)	3 (60)	0,110
Egg, Yolk or Albumen	3 (7.3)	0 (0)	1 (33.3)	2 (66.7)	0,122
Walnut or Hazelnut,	8 (18.6)	4 (50)	4 (50)	0 (0)	0,618
Crustaceans (Shrimp, Crab)	2 (5)	0 (0)	1 (50)	1 (50)	0,218
Fish (Cod, Tuna, Salmon)	3 (7.7)	0 (0)	1 (33.3)	2 (66.7)	0,074
Soy	5 (12.8)	0 (0)	3 (60)	2 (40)	0,000
IgE for recombinant proteins					
PR-10 (Bet v 1) (n,%)	9 (18.75)	5 (55.6)	4 (44.4)	0 (0)	0,001
Profilin (Phlp 12 or Bet v 2), (n,%)	7 (14.6)	5 (71.4)	2 (28.6)	0 (0)	0,021
LTP peach (Pru p 3), (n,%)	9 (22.5)	4 (44.4)	5 (55.6)	0 (0)	0,024
LTP peanut (Ara h 9), (n,%)	7 (29.1)	2 (28.6)	3 (42.8)	2 (28.6)	0,032
LTP wheat (Tri a 14), (n,%)	2 (7.4)	1 (50)	1 (50)	0 (0)	0,214
LTP hazelnut (Cor a 8), (n,%)	3 (12.5)	0 (0)	3 (100)	0 (0)	0,062
LTP peach (BIAA), median (IQR)	-	2,87 (0,48-7,40)	4,34 (0,0-10,0)	0 (0)	0,057
LTP peanut (BIAA), median (IQR)	-	4,18 (0,2-8,16)	1,0 (0,0-1,0)	0 (0)	0,126
LTP walnut, (BIAA), median (IQR)	-	0,74 (0,14-1,34)	0,22 (0,0-0,8)	0 (0)	0,270

12. A CASE OF SYSTEMIC LUPUS ERYTHEMATOSUS AFTER BONE MARROW TRANSPLANT

Tarantini P., Maira D., Motta I., Scaramellini N., Lombardi R., Colavolpe L., Fracanzani A. L.
Unit of Internal Medicine. Fondazione Ca' Granda IRCCS Ospedale Maggiore Policlinico, Milan, Italy

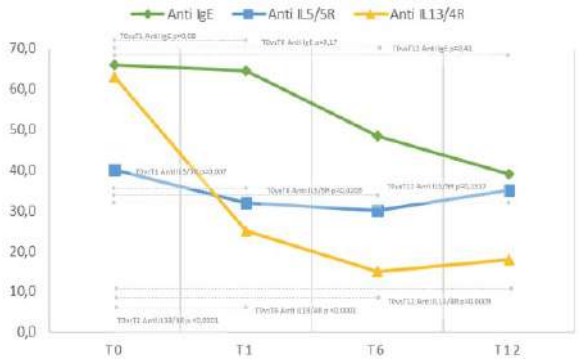
Introduction: We herein present a rare neurological complication after allogenic hematopoietic stem cell transplantation.
Case Report: In September 2022, a 62-year-old man developed fever and cognitive and language impairment. His previous medical history was significant for an allogeneic bone marrow transplant from a matched unrelated donor (in December 2020) for primary myelofibrosis. One year after the transplant, right after suspending immunosuppressive therapy with cyclosporine, he developed a low-grade fever, cough, and dyspnea with evidence of pericardial and pleural effusion. He underwent microbiological tests, which were negative for viruses, BK, and aerobic and anaerobic bacteria. This symptomatology was attributed to graft versus host disease (GVHD), and the patient was treated with steroids with symptom resolution. After the suspension of steroid therapy, low-grade fever reappeared, together with arthro-myalgia. Then, he developed an acute episode of aphasia with behavioral disturbances, for which he presented to the Emergency Department of our Institution. He underwent a brain computed tomography scan without evidence of brain bleeding and was admitted to our Internal Medicine ward. At blood tests, we found normal blood count, slightly increased inflammatory biomarkers and normal hepatic and renal function. Brain magnetic resonance imaging, lumbar puncture, and microbiological tests (on cerebrospinal fluid and blood) were all negative. He underwent an electroencephalogram that showed diffuse encephalic suffering without anomalies attributable to specific pathologies. During the hospitalization, the patient alternated phases of expressive aphasia and agitation with phases of fluent speech with progressive improvement until complete and spontaneous resolution of neurological symptoms. Given the history of low-grade fever, arthralgias, and serositis, autoimmune screening was performed with findings of reduced complement C4 and positivity of ANA (with titer 1/640), anti-dsDNA, anti-nucleosome, and anticentromere antibody. Clinical and laboratory findings were consistent with systemic lupus erythematosus (SLE) diagnosis. In the absence of ischemic or infectious events, the neurological manifestations may be attributable to the autoimmune disease (neuro-lupus). Low-dose steroid therapy and hydroxychloroquine were introduced to control the autoimmune disease.
Conclusion: SLE is a chronic autoimmune disorder characterized by autoantibodies against nuclear and cytoplasmic antigens, which may affect several organs. SLE usually affects adult women (9:1 female to male ratio). Our patient had no personal or family history of autoimmunity but had received a bone marrow transplant. Hematopoietic stem cell transplantation (HSCT) interferes with the immune system, and several types of autoimmune diseases, including SLE, are described after HSCT. The exact mechanism underlying this interference is unclear. However, it is thought that autoantibodies (antinuclear, anti-DNA, anticardiolipin antibodies, or antibodies directed against various blood cell components) may be produced by bone marrow long-lived plasma cells and may be present at low titers before HSCT, without associated pathogenicity. Plasma cells can survive vigorous lymphodepletion by HSCT; if regulatory cells controlling these autoreactive plasma cells are suppressed by conditioning therapy, clinically significant manifestations of autoimmunity may develop. De novo emergence of autoreactive B or T cells after HSCT may also contribute to autoimmunity in these patients. In our patient, the timing of sign and symptom onset was related to the discontinuation of immunosuppressive therapy after the bone marrow transplant; thus, HSCT may have uncovered autoimmunity that later manifested as SLE. From a clinical standpoint, SLE is characterized by alternating periods of remission and exacerbation and by a wide variety of clinical manifestations that may affect any organ, including the central nervous system (CNS). In neuro-lupus neurological injury is mediated by antibodies against neuronal, astroglial, or endothelial cells. Changes could also be induced in the cerebral vasculature, either through immune complex deposition or effects on the coagulation system leading to infarction. After starting the steroid therapy, we observed a resolution of the remaining symptoms (fever and arthromyalgia). Our patient was discharged with mild immunosuppressive therapy characterized by hydroxychloroquine and oral prednisone that was slowly tapered off without recurrence of symptoms.

13. A PROSPECTIVE STUDY OF THE SNOT22 COURSE IN CRSWNP RECEIVING BIOLOGICAL DRUGS: ANALYSIS AT 12 MONTHS

Ledda A.G., Sambugaro G., Canalis S., Costanzo G., Firinu D., Del Giacco S.
Università degli studi di Cagliari

Background: Severe eosinophilic asthma and Chronic Rhinosinusitis with Polyposis (CRSwNP) are disorders linked by a predominantly Th2-type response and therefore often coexisting. In a real-life scenario, biologicals are used in two main clinical pictures:
a) Patients with severe asthma with CRSwNP as comorbidity receiving mAb for severe asthma (omalizumab, mepolizumab, benralizumab, dupilumab).
b) CRSwNP patients with mild/moderate asthma or non-asthmatics that receive mAbs for the treatment of CRSwNP (omalizumab and dupilumab).
The SNOT22 (22-item Sinonasal Outcome Test) aims to evaluate the impact of CRSwNP on patients' quality of life. It consists of 22 Items which are assigned a score from 0 to 5 based on the increasing severity of the symptoms and which can be aggregated into 4 different domains: NASAL, OTOLOGYC, SLEEP, EMOTIONAL. The aim of this prospective study was to evaluate the modification of the SNOT22 score in a real life cohort of patients affected by CRSwNP receiving mAb for CRSwNP and/or eosinophilic asthma at one month (T1), six months (T6) and twelve months (T12), compared to the baseline.
Method: We enrolled 51 patients and we did a follow up visit after one, six and twelve months.We administered SNOT22 at baseline and at each follow up visit. The Wilcoxon test was used for statistical analysis.
Results: In patients treated with anti-IgE, a non-significant (p=0,08) reduction in the SNOT22 total score was observed between T0 and T1, as there was a non-significant reduction between T0 and T6 (p=0,17), and between T0 and T12 (p=0,41). Considering those on anti-IL5, we observed that the reduction in the SNOT22 total score between T0 and T1 was significant (p=0,007) as well as the reduction between T0 and T6 (p=0,0209), while between T1 and T12 was not significant (p=0,13). In those treated with anti-IL13/4R the difference in the SNOT22 score between T0 and T1 was significant (p=<0.0001), similarly comparing T0 and T6 (p=<0.0001) and also between T0 and T12 (p=0,0009). The difference between T1 and T6 was not significant (p=0,073), but there was a further significant score reduction between T1 and T12 (p=0,0500) and also the between T6 and T12 (p=0,0067). Analyzing individual domains, there was no significant difference between each T compared to the baseline in patients treated with anti-IgE. There was a significant difference for the anti-IL-5 for the NASAL domain between T0 and T1 (p=0,008), T0 and T6(p=0,0196), but not between T0 and T12(p=0,16). For the OTOLOGYC domain there was a significant difference only between T0 and T1(p=0,02), and for the EMOTIONAL domain only between T0 and T12 (p=0,0488). No significant difference was found for the SLEEP domain. About IL13-4R, there was a significant reduction in the score of each domain at each T compared to the baseline. In particular, for the NASAL domain there was a significant reduction in score between T0 and T1 (p=<0.0001), between T0 and T6 (p <0,0001) and between T0 and T12 (p=0,0016).
Conclusions: Our study limitations were the small number of patient, the brief time of follow up and the non-randomized study design.In this real-life study, no significant score reduction was found for anti- gE in each time compared with the baseline.The use of anti-IL5 and anti-IL13/4R leads to a statistically significant reduction of SNOT22 score already after 4 weeks of therapy which is maintained after 6 months of treatment, while at 12 months the significance was retained only for the anti-IL13/4R group. It can also be concluded that the greatest reduction in the score occurs within the first 4 weeks and then slowly further improves. SNOT22 assessment could be of help in order to promptly identify fast responders from low- or non- re-

sponders. In our series, only the anti-IL13/4R guaranteed a significant reduction of each domain of SNOT22 already at T1 and the significance is maintained at T6 and T12.



14. IMPACT OF TRANSCUTANEOUS AURICULAR VAGAL NERVE STIMULATION ON INFLAMMATION AND PAIN PERCEPTION: ENCOURAGING RESULTS IN SYSTEMIC SCLEROSIS

Della Torre A.[1], Carandina A.[2], Bellocchi C.[1], Scatà C.[3], Beretta L.[3], Tobaldini E.[1], Montano N.[1]
[1]1Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy; [2]1 Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy ; [3]2 Department of Internal Medicine, Fondazione IRCSS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy

Background: Systemic sclerosis (SSc) is an autoimmune disease featuring systemic inflammation, microvascular dysfunction, and widespread fibrosis of skin and internal organs. These alterations bring SSc patients to experience chronic pain, deeply affecting quality of life. Furthermore, analysis of heart rate variability (HRV) demonstrated a deregulation of autonomic nervous system (ANS) in SSc, which is known to correlate to severe fibrosis, longer disease duration, and augmented mortality. Vagal nerve branch mediates the "cholinergic anti-inflammatory pathway", since its interaction with acetylcholine receptors on macrophages and T cells promotes immunosuppressive and regulatory effects that preserve homeostasis of inflammation and immune response. Transauricular vagal nerve stimulation (tVNS) could therefore represent an innovative therapeutical approach in autoimmune diseases characterized by inflammation and chronic pain.
Objectives: The aim of our study was to evaluate the effect of tVNS on inflammation in SSc patients, as well as assessing its impact on pain and autonomic control.
Methods: A randomized interventional cross-over trial was performed on 21 adult SSc patients (Scleroderma Unit, Policlinico Hospital in Milan) who complained of chronic moderate-to-severe pain, suggesting ongoing inflammatory state. Subjects were randomly assigned to interventional group (tVNS) or to control group (sham stimulation) for one month, later moving to the opposite arm after a 4-weeks wash-out period. Before and after each intervention, blood samples were collected for major inflammatory cytokines measurement, pain was rated by Numeric Rating Scale (NRS), and 10-minute resting EKG was recorded to perform HRV analysis. Student's Paired T-test evaluated cytokines, HRV and NRS changes after tVNS and after sham stimulation.
Results: Results showed a reduction of IL-6 levels after tVNS which was not present after sham stimulation (-17% from baseline, p=0.029), as well as a significant improvement of NRS score after tVNS (p=0.002) with mean reduction of 2 NRS points. Significant variation of HRV parameters was not observed after tVNS nor sham stimulation.
Conclusions: TVNS treatment determined a significant reduction of systemic inflammatory biomarkers and pain in SSc patients. This non-invasive neurostimulation technique could represent a valuable tool for ameliorating quality of life in subjects with chronic diseases characterized by inflammatory and autonomic dysfunctions.

15. LUNG INVOLVEMENT IN SYSTEMIC LUPUS ERYTHEMATOSUS

Sottolano A.[1], Vitale P.[1], Carrieri I.[1], Agrelli L.[1], Mazzarelli U.[1], Parente R.[1], Cardamone C[1], Guida A.[2], Triggiani M.[1]
[1]Division of Allergy and Clinical Immunology, Department of Medicine, University of Salerno, Italy; [2]Internal Medicine, AOU San Giovanni di Dio e Ruggi d'Aragona, Salerno, Italy

Background: A growing body of evidence indicates lung involvement as significative cause of morbidity and mortality in systemic autoimmune diseases. The purpose of this study was to evaluate the prevalence, also, subclinical of lung involvement in patients with systemic lupus erythematosus (SLE). Furthermore we have investigated the relation, if present, between pulmonary alterations and demographics parameters, and clinical and laboratory findings.
Method: This study has been conducted among 24 patients (23 females, 46,5 mean age years) with SLE diagnosed according to the EULAR criteria. For each patient medical interview, physical examination, laboratory tests and pulmonary function test (PFT) like Spirometry and Diffusion of the lungs for carbon monoxide (DLCO), have been performed.
Results: Only 5 patients had respiratory symptoms. Spirometry resulted abnormal in 9 patients (37%) with these following patterns: 4 obstructive and 5 restrictive. DLCO displayed decreased in 19 patients (80%): 11 subjects showed a low grade reduction (80% < DLCO >60% of predicted value) and 8 a moderate grade reduction of gas diffusion (DLCO < 60% of predicted value). Mean patients age at diagnosis was 46 *ys* and two subgroups of patients were identified: one consisting of patients ≤ 46 *ys* (13) and the other with patients > 46 *ys* (11). DLCO alterations occurred almost equally in both subgroups, but in the younger patients tended to be more severely decreased (54% *vs* 25%: prevalence of DLCO moderate reduction in the two subgroups). Mean disease duration was 13 *ys* and there was no association between the disease duration and the prevalence of PFT abnormalities. Arthritis, present in 58% of patients, was associated more frequently with DLCO decrease (92% *vs* 60%, p: 0.05) and also with a more severe reduction (43% *vs* 20% moderate reduction in the subgroups with and without arthritis). Among biochemical findings, antinuclear antibodies (ANA) titer and levels of C3 and C4 did not seem to be related to the prevalence and severity of DLCO abnormalities.
Conclusion: Lung involvement in systemic lupus erythematosus is quite frequent and could be subclinical. DLCO seems to be more sensitive than spirometry to assess the lung involvement. Lung involvement, if present, does not appear to be related to disease duration, therefore PFT should be performed in all patients and also in the early phases of the autoimmune disease. Presence of arthritis potentially identifies a more severe phenotype of patients, associated with lung involvement and requiring a closer monitoring.

16. ANTI-PHOSPHATIDYLSERINE/PROTHROMBIN ANTIBODIES IN SYSTEMIC LUPUS ERYTHEMATOSUS: A FOLLOW UP STUDY FOR MORE THAN FIVE YEARS

Cavallo L.[1], Calabrese C.[1], Bozzolo E.P.[2], Moroni L.[1], Canti V.[3], Rovere-Querini P.[4], Ramirez G.A.[1], Dagna L.[1]
[1]Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS Ospedale San Raffaele, Milan, Italy and Università Vita-Salute San Raffaele, Milan, Italy; [2]Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS Ospedale San Raffaele, Milan, Italy; [3]Unit of Medical Specialties and Healthcare Continuity IRCCS Ospedale San Raffaele, Milan, Italy ; [4]Unit of Medical Specialties and Healthcare Continuity IRCCS Ospedale San Raffaele, Milan, Italy and Università Vita-Salute San Raffaele, Milan, Italy

Introduction: Systemic lupus erythematosus (SLE) is a chronic multi-organ disease characterised by increased risk of chronic disability. Systemic inflammation along with macro- and microvascular ischaemic events play a major role in SLE morbidity but little is known about potential predictors of chronic damage. Anti-phospholipid antibodies (aPL) are frequent in patients with SLE, constitute a major driver of cardiovascular morbidity and associate with haematological and neuropsychiatric (NPSLE) manifestations. Routine assays for aPL identification include isolation of anticardiolipin or anti-beta2-glycoprotein I antibodies or detection of lupus anticoagulant (1). Besides these validated tests, "non-criteria" antibodies with additional specificities are growingly being discovered and clinically tested, including anti-phosphatidylserine/prothrombin antibodies (aPSPT). We previously acquired data supporting a non-redundant additive diagnostic role of aPSPT towards

NPSLE and thrombocytopenia in patients with SLE, besides aPSPT association with thrombotic events (2). Here, we report on the prolonged diagnostic value of aPSPT profiling towards SLE-related complications more than five years after their baseline assessment.
Objectives: To assess the potential prognostic value of aPSPT with regard to thrombosis, NPSLE and/or thrombocytopenia. We also tested aPSPT potential association with SLE-related damage accrual in the medium-term.
Methods: We prospectively followed up 131 patients previously enrolled cross-sectionally and tested for aPSPT through ELISA by recording any arterial or venous thrombosis, new neuropsychiatric manifestation or thrombocytopenia. Neuropsychiatric events were recorded when they met the American College of Rheumatology (ACR) nomenclature and the Italian Society for Rheumatology criteria for NPSLE. Thrombocytopenia was defined as any confirmed SLE-related new detection of platelet values below the laboratory reference range. We also recorded whether patients had any progression in SLE International Collaborating Clinics/ACR Damage Index (SDI) from baseline. Data are expressed as percentages or median (interquartile range) unless otherwise specified.
Results: One patient died soon after baseline assessment and two were lost to follow up. 128/131 patients with SLE had available follow up data spanning over 76 (70-82) months. Of them, 50 (39%) had aPSPT. More specifically, 15/128 had aPSPT only, 55/128 had one or more "criteria" aPL with or without aPSPT and 58/128 had no aPSPT nor "criteria" aPL (4xneg). Fifty patients were already taking anti-platelet drugs and/or anticoagulants at baseline (31/50 with aPSPT). We recorded eight new thrombotic events, nine new neuropsychiatric events, 13 new events of thrombocytopenia and 69 progressions in SDI. There was no significant association between aPSPT and thrombosis, regardless of treatment. SDI progression was numerically higher in aPSPT-positive (69%) than -negative patients (47%), but no difference was found when comparing aPSPT only vs 4xneg. Conversely, new onset thrombocytopenia was proportionally higher in patients with aPSPT only (20%) than in 4xneg (9%), regardless of treatment. New NPSLE manifestations were twice higher in aPSPT-positive (10%) than -negative patients (5%). Among patients without antiplatelet/anticoagulant therapy, patients with aPSPT only had higher rates of NPSLE (18%) than 4xneg patients (4%) with a trend towards statistical significance (p=0.067 by Cox regression).
Conclusion: Notwithstanding the limitations of a relatively small sample size and short observation timeframe (preventing the achievement of statistical significance), these data apparently support the non-redundant association of aPSPT with NPSLE, thrombocytopenia and possibly global damage accrual. Furthermore, indirect inferences from treatment data are consistent with a role of vascular pathology in the pathogenesis of NPSLE, while alternative mechanisms might sustain aPL-associated thrombocytopenia. Relatively high thrombosis rates in 4xneg patients are consistent with the multifactorial pathophysiology of vascular morbidity in SLE and highlight the need to further extend the panel of biomarkers to estimate SLE-related cardiovascular risk (3).
References
1) Cohen H et al. Lupus, 2020
2) Ramirez GA et al., Autoimmunity, 2019
3) Ramirez GA et al., Rheumatology, 2019

17. USE OF MEPOLIZUMAB IN ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (ABPA): TWO CASE REPORTS

Taurisano G., Costanzo G., Ledda A., Firinu D., Del Giacco S.
AOU di Cagliari - Unità di Medicina Interna, Allergologia ed Immunologia Clinica – Policlinico Universitario "Duilio Casula"

Background: Allergic bronchopulmonary aspergillosis (ABPA) is an inflammatory disease caused by an hypersensitivity reaction against Aspergillus fumigatus. Its spores colonize the airways of patients with asthma and cystic fibrosis and results in pulmonary infiltrates, mucus plugs, elevations of total serum immunoglobulin E concentration (>1000 KU/L), positive skin test and/or Aspergillus fumigatus specific IgE and peripheral blood eosinophilia (>0.5 × 109/L). Bronchiectasis is an irreversible complication of ABPA. It is believed that globally there are about five million cases of ABPA.Patients may be asintomatic or have an uncontrolled asthma, wet cough, slight fever and sick feeling.Diagnosis of ABPA is based on a combination of clinical manifestations as well as laboratory and radiological evaluations.Systemic corticosteroids and antifungal triazoles are standard treatments, but a lot of patients do not respond to these treatments or have frequent relapses and require long-term treatment despite side effects. For these reasons we need steroids-sparing treatments. Mepolizumab is a monoclonal antibody against IL-5, a decisive key in eosinophils differentiation, activation, migration and survival. **Methods**: We describe two ABPA cases treated with mepolizumab.Case 1. A 58-year-old man, with severe eosinophilic asthma developed at 28 years old, chronic rhinosinusitis with nasal polyps (CRSwNP), ABPA with bronchiectasis, total IgE count was 6295 KU/L, Aspergillus fumigatus specific IgE was 12,7 KU/l and many positivies to sputum cultural examination for gram negative bacteria and fungi. He have a clinical hystory characterized by frequent asthmatic crises with massive use of systemic corticosteroids. He was treated with omalizumab for five years without benefits. Since february 2020 is in therapy with mepolizumab (100 mg s.c. every four weeks).Case 2. A 52-year-old-man, with allergic asthma developed at 46 years old, CRSwNP, ABPA with total IgE count to 4011 KU/L, Aspergillus fumigatus specific IgE 1.61 KU/I and absolute eosinophil count of 1200 cells/cumm. Asthma was uncontrolled despite maximum therapy and he needed systemic steroids for too long. From june 2022 to october 2022 he was in therapy with dupilumab without benefits. He started therapy with mepolizumab in february 2023.**Results:** In case 1 pre-biological exams are: ACT was 11, absolute eosinophil count of 500 cells/cumm, FEV1 was 30% - 1,03 L. After 18 months from use of mepolizumab ACT was 22, absolute eosinophil count of 100 cells/cumm, FEV1 of 38% - 1,27 L. Patient reports a clear improvement about symptoms and a complete interrumption of systemic steroids. In case 2 pre-biological exams are: ACT was 7, absolute eosinophil count of 800 cells/cumm, FEV1 was 38%. After one month from first mepolizumab administration ACT was 22, absolute eosinophil count of 100 cells/cumm, FEV1 41%. Patient reports a good asthma control without requirement to emergency drug and absence of nocturnal awakenings.**Conclusions**: Use of mepolizumab allowed improvement about clinical condition and drastic decrease about asthmatic flare-up, with total interruption with steroids. Mepolizumab may be considered whether a steroid sparing or a disease modifyng therapy in ABPA patients.

18. MACHINE LEARNING ANALYSIS: A NEW TOOL TO PREDICT THE RESPONSE TO INTRAVENOUS AND SUBCUTANEOUS IMMUNOGLOBULIN IN INFLAMMATORY IDIOPATHIC MYOPATHIES

Paladini A.[1], Antonelli E.[1], Longhi E.[2], Moroncini G.[3], Gangemi S.[4], Danieli M.G.[5]
[1]Postgraduate School in Internal Medicine, Università Politecnica delle Marche, Ancona, Italy; [2]Scuola di Medicina e Chirurgia, Alma Mater Studiorum, Università degli Studi di Bologna, Bologna, Italy; [3]Clinica Medica, Dipartimento di Medicina Interna, AOU delle Marche, Università Politecnica delle Marche, Ancona, Italy; [4]School and Operative Unit of Allergy and Clinical Immunology, Department of Clinical and Experimental Medicine, Università di Messina, Messina, Italy; [5]SOS Immunologia delle Malattie Rare e dei Trapianti, AOU delle Marche, Università Politecnica delle Marche, Ancona, Italy

Objective: To identify these scores that better predict the response to immunoglobulin both intravenous (IVIg) and subcutaneous (20%SCIg) in our cohort of patients with Inflammatory idiopathic myopathies (IIM) through the help of Artificial Intelligence (AI).
Background: IIM are uncommon disorders primarily affecting the skeletal muscle and exhibiting distinctive clinical, laboratory, and radiological features. Artificial intelligence (AI) refers to computer-based systems capable of executing intricate calculations and analyzing data with minimal human involvement. In the realm of medicine, AI has gained substantial prominence, particularly through the employment of machine learning (ML) techniques that can process vast amounts of information and make informed decisions, as well as deep learning (DL) methodologies that employ artificial neural networks to automatically learn and analyze data.
Methods: In this study, we evaluated the response to IVIg or 20%SCIg in patients with IIM through the help of AI techniques. All patients met the 2017 EULAR/ACR criteria for definite or probable IIM. The included parameters to estimate the response to therapy were: serum creatine kinase (CK) levels, muscle strength (assessed by MMT8 score), disease activity (measured by MITAX score), and disability (evaluated using HAQ-DI score). To determine the most significant predictors for a favorable response to IVIg or 20% SCIg treatment, we employed various supervised ML algorithms, such as Least Absolute Shrinkage and Selection Operator, Ridge, Elastic Net, Classification and Regression Trees, and Random Forest. These algorithms were implemented using the R statistical software.
Results and conclusion: Through the application of AI, we have successfully

identified the key indicators that can reliably predict a positive response to treatment with IVIg or 20%SCIg. Based on our findings, we noticed that the Elastic Net algorithm and similar approaches emerged as the most viable, efficient, and effective ML methods for predicting clinical outcomes, particularly related to MMT8 and MITAX, in the context of myositis.
Our analysis revealed that muscle strength, assessed by the MMT8 score during follow-up, is influenced by the presence of dysphagia and skin disorders, as well as by the initial myositis activity index (MITAX) before treatment. The correlation between MMT8 and MITAX suggests that IVIg therapy tends to be more effective in patients with more active systemic disease. The CART model was the best to predict the MITAX score at the follow-up, which was influenced by the latency between the disease onset and the start of IVIg treatment. The same model outperformed the others in prediction of a combined model of CK and MMT8 at the follow-up. The two most important foretellers for this outcome were the serum CK levels and the type of disease progression (monocyclic, polycyclic, continuous).

19. AN UNUSUAL CASE OF THROMBOCYTOPENIA

Bettini G., Casiraghi C., Serafini S., Savojardo V., Re T., Corsico F., Casarin F., Canetta C.
High Care Internal Medicine Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano

An 85-year-old woman referred to the Emergency Department due to worsening fatigue in the last few days. Her medical history was relevant for past breast cancer treated with breast-conserving surgery almost one year before; moreover, she was under anticoagulant treatment with LMWH because of an iliofemoral deep vein thrombosis dating back to two months earlier.
Upon admission, physical examination was unremarkable except for scattered petechiae and mild proctorrhagia with hemorrhoidal congestion. Blood tests revealed severe thrombocytopenia (platelet count 6000/mmc) and anemia (hemoglobin 5.2 g/dL) with a normal coagulation profile, so the patient got promptly supported with blood and platelet transfusions. Head CT was performed and excluded intracranial complications. In the meantime, the woman developed rapidly worsening respiratory failure requiring oxygen supplementation; lung ultrasonography and chest X-ray showed signs of pulmonary congestion and multiple consolidations, so diuretic and empirical antibiotic therapies were implemented. She was then transferred to our ward for further diagnostic studies. Blood count revealed refractoriness to platelet transfusions. Timing was not suggestive for heparin-induced thrombocytopenia and, in fact, specific antibodies resulted negative. Lab tests excluded broad differential, including thrombotic microangiopathies, autoimmune hemolytic anemia, antiphospholipid antibody syndrome and hemophagocytic lymphohistiocytosis. A mild and transient rise in serum creatinine was accompanied by non-pathologic urine sediment and normal electrophoresis. In the suspicion of bleeding diathesis secondary to idiopathic thrombocytopenic purpura (anti-platelet antibodies couldn't be reliable because of recent transfusions), high-dose corticosteroids (1 mg/kg) and ex juvantibus therapy with IGEV were administered, but no great response was obtained. Given the persistence of deep vein thrombosis, the patient underwent inferior vena cava filter placement since anticoagulant therapy could not be continued. All the microbiological analyses (blood and urine coltures, pneumonia screening, Parvovirus and Herpes Virus DNA, Strongyloides serology) tested negative. CT scans excluded intra-abdominal bleeding or neoplastic recurrence, showing pulmonary ground glass opacities plus septal thickening that created a crazy paving pattern really suggestive for alveolar hemorrhage [*Figure 1*]. Neither bone marrow aspiration nor bronchoalveolar lavage were carried out considering patient's fragile clinical conditions. An autoimmune panel was so performed, revealing positivity of both ANA (1:320 with an homogenous pattern) and atypical ANCA (C-ANCA and P-ANCA negative); anti-Pm/Scl 100 were detectable too, but myositis and scleroderma blot resulted negative. ENA, anti-dsDNA, ASMA, AMA, anti-glomerular basement membrane, C3/C4 and liver-related autoantibodies were also negative. As autoimmune vasculitis with pulmonary involvement appeared to be the most likely diagnosis, a steroid pulse therapy was initiated; within a few days we documented an incremental trend of both platelet count and hemoglobin level, marked clinical improvement and almost complete radiological resolution [*Figure 2*]. Steroid therapy was progressively reduced and the patient got dismissed from hospital with scheduled follow-up visits; three weeks after discharge she was in good shape with stable blood count parameters. We report this case to raise clinical awareness about Diffuse Alveolar Hemorrhage (DAH), a rare but potentially life-threatening condition. It refers to a subset of pulmonary hemorrhage that takes origin from the pulmonary microcirculation (alveolar arterioles, venules or capillaries) and represents the manifestation of several immune and non-immune diseases; ANCA-Associated Vasculitis (AAV) are reported to be the most common cause of pulmonary vasculitis and immune-mediated DAH. The association of DAH with Idiopathic Thrombocytopenic Purpura (ITP) is possible, even though very rare: less than 10 cases are reported in literature. The presence of thrombocytopenia, anemia and bilateral alveolar infiltrates should always raise suspicions for the presence of DAH; on the other hand, the absence of hemoptysis should not rule out the diagnosis, as it is lacking in up to one-third of cases, irrespective of the severity of bleeding.

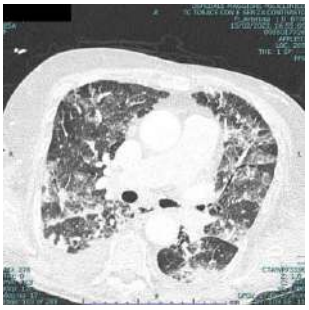


Figure 1. Chest CT performed at admission showing bilateral ground-glass opacities with septal thickening

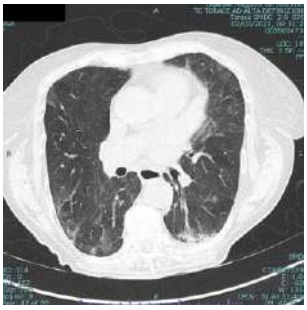


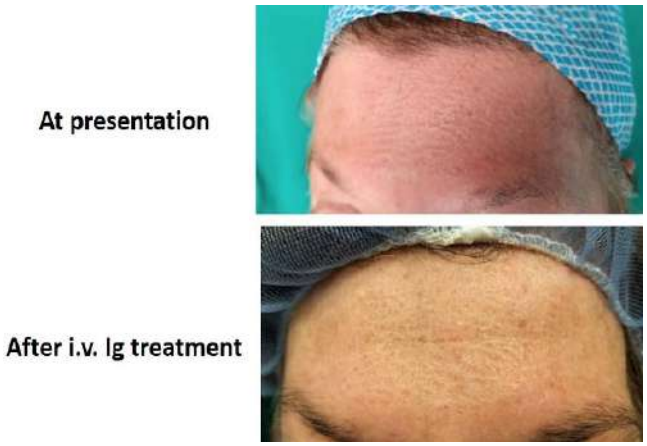
Figure 2. Marked improvement of chest CT findings after steroid pulse therapy

20. SCLEROMYXEDEMA: A CASE REPORT

Tommasoni I.[1], Galli P.[2], Landini F.[2], Di Comite V.[2], Ghidini C.[2], Rocci A.[2], Regolisti G.[2]
[1]Scuola di Specializzazione in Nefrologia, Università degli Studi di Parma; [2]Clinica e Immunologia Medica, Azienda Ospedaliero-Universitaria di Parma e Università degli Studi di Parma

Background and aim: Scleromyxedema is a rare disease involving multiple organs. It can have a severe impact on patient quality of life, and it is not easily diagnosed. We report a case of scleromyxedema in an elderly woman, highlighting the intricated process of differential diagnosis. We also report on the patient's response to treatment with of intravenous immunoglobulin treatment (IVIG) after six months, which supports the effectiveness of appropriate therapy.
Description of the case: A 77-year-old woman was brought to the emergency department for dyspnea and fever. Previously, she had been admitted to hospital on two separate occasions for the same symptoms. On arrival, her blood pressure was 125/85 mmHg, pulse rate was 108 bpm, the oxygen saturation by pulse oximetry was 87%. Laboratory exams showed normal WBC count with relative neutrophilia (WBC 7280/mL, N 92%); normal kidney (serum creatinine 0,9 mg/dL) and liver function. D-dimer was 798 ng/mL and troponin 13,8 ng/L. An arterial blood gas analysis while the patient was breeding room air revealed: pH 7,48; pCO2 38 mmHg; pO2 51,3 mmHg; HCO3- 27,9 mmol/L; P/F 244 mmHg. A chest CT scan with contrast administration highlighted interstitial involvement and excluded pulmonary embolism. On physical examination and work-up, multiple organ involvement was evident, with scleroderma, leonine face, retro-auricular waxy papules, sclerodactyly, "Shar-Pei sign" and microcheilia with 36/51 modified Rodnan score. Besides interstitial pneumonia, the patient also presented with dysphagia, cognitive impairment with a MMSE of 24,7/30 and sensory polyneuropathy of the lower limbs, collagenosic colitis, and smoldering IgG lambda myeloma without osteolytic lesions. A skin biopsy confirmed the diagnosis of scleromyxedema, in line with the clinical presentation, medical history, and absence of thyroid disorders. Histologic features included mucin and collagen deposit with fibrotic expansion. After a multidisciplinary evaluation involving internists, dermatologists and haematologists, the patient was started on intravenous immunoglobulin administration and low-dose corticosteroids treatment (prednisone 5 mg once daily). The immunoglobulin treatment was given over five consecutive days with a total dose of 2g/kg and was continued subsequently on a monthly basis. After six months, the clinical picture and the patient's quality of life were remarkably improved, with symptom remission, and improvement in skin involvement (**Figure**). Lung interstitial involvement was unchanged.
Discussion: Scleromyxedema is a rare disease which can involve many different organs. The etiology is still unknown. It can have a severe impact on daily activities and quality of life. Skin involvement is the most common clinical

feature, but multiorgan disease can develop quite unpredictably. Extracutaneous features include neurological and rheumatologic manifestations, cardiovascular abnormalities, gastrointestinal and respiratory involvement, renal impairment, and ocular disorders. Our patient was brought to the emergency department for respiratory distress. Based on her medical history, skin appearance, and extracutaneous clinical features, scleromyxedema was suspected. According to European dermatology guidelines, we also excluded thyroid impairment and acute respiratory infection (both bacterial and viral pneumonia). The skin biopsy confirmed the final diagnosis of scleromyxedema with a multiorgan involvement. The patient was started on medical treatment with the administration of IVIG every four weeks and low-dose oral corticosteroids. After six months, the patient showed an improvement of the clinical picture and quality of life. The use of IVIG has been reported as an effective treatment for scleromyxedema. Our case supports the benefit of IVIG therapy in reducing the burden of skin and organ involvement.



21. IMMUNOGLOBULIN REPLACEMENT THERAPY IN SECONDARY IMMUNODEFICIENCY, A SINGLE CENTER EXPERIENCE

Verza A., Discardi C., Bez P. , Rattazzi M., Cinetto F., Scarpa R., Agostini C.
Università degli studi di Padova, Dipartimento di medicina ospedale Ca' Foncello di Treviso

Background: The term "Secondary immunodeficiency (SID)" refers to a deficit of the immune system caused by an exogenous insult such as chemotherapy (usually for hematological diseases), drugs, protein losses, viruses, malnutrition, etc. In most cases the deficit mainly interests IgG, which may be severely reduced (<400 mg/dL) while the other components of the immune system still maintain a certain degree of activity. Patients who experience this condition are subject to recurrent infection and need a frequent and prolonged antibiotic therapy, sometimes requiring hospitalization.
Evidence regarding treatment indication of SID is still relatively limited. The mainstay of treatment is represented by immunoglobulin replacement therapy (IgRT), administrated either by intravenous or by subcutaneous injection with variable frequency, based on individualized parameters including the achieved serum IgG level. This value is called "IgG trough level" and is measured immediately before the next dose of immunoglobulins. The purpose is primarily to obtain a clinical response by reducing the number of infections and the need of antibiotics. Of note, normalizing the serum IgG levels is not always necessary to reach clinical control.
In this study we searched for differences between the intravenous and subcutaneous IgRT in terms of clinical outcomes and IgG trough levels achieved.
Methods: We used our database containing data from 136 patients who are followed at our Immunology outpatient clinic for secondary immunodeficiencies. We enrolled only patients with full available data, with well documented increased infectious diathesis and who had an adequate follow up time (at least 1 year before and 6 months after IgRT initiation for treated patients) and a recent available IgG trough level. We compared the infectious state pre- and post-therapy and the pre- and post-therapy IgG through level.
Results: Of 50 enrolled SID patients fulfilling inclusion criteria, 42 were in active IgRT. 48 were haematological with 27 patients who received a diagnosis of LNH, 6 of multiple myeloma, 6 of B-CLL, 1 of ALL. Two patients instead presented SID linked to previous prolonged steroid therapies.
Considering all the 50 patients, the mean pre-therapy infectious events were 3.1 event/year, with an average antibiotic use of 2.1 cycles/year. The mean infection-related hospitalization rate was 0.5/year. The mean IgG value was 360.7 mg/dL (range 66.0-454.0 mg/dl; local reference value 700-1600 mg/dL).
Regarding the group of 42 patients who received IgRT, 31 were treated at least once with intravenous immunoglobulins (IVIg) and 28 with subcutaneous immunoglobulins (SCIg). 17 patients were treated with both the therapies and for different reasons were switched from IVIg to SCIg.
In this subgroup the mean pre-therapy infectious events were 3.4 event/year, with an average antibiotic use of 2.2 cycles/year. The mean infection-related hospitalization rate was 0.46/year. The mean IgG value was 300.0 mg/dL (range 83-512 mg/dl). The mean dosage of IgRT was 363.2 mg/kg of body weight (range 210.5-519.5 mg/kg); no significant difference was detected between IVIg (371 mg/kg) and SCIg (356 mg/kg) (p= 0.3678).
After IgRT initiation, the infectious events dropped down to 0.32 event/year; the average registered antibiotic usage was 0.27 cycles/year and the hospitalization rate was 0.00/year. IgG trough level instead raised to a mean value of 781 mg/dL (range 518-1119 mg/dl). All differences were statistically significant (p< or =0.0001 when compared to pre-IgRT). After the introduction of IVIg treatment, the infectious events dropped down to 0.5 event/year; the average registered antibiotic usage was 0.5 cycles/year and the hospitalization rate 0.00/year. IgG trough level instead raised to a mean value of 726.9 mg/dL (range 506-1119 mg/dl).
In the SCIg subgroup we registered, on average, 0.2 infectious events/year; the average antibiotic use was 0.18 cycles/year and none was hospitalized. IgG trough level raised to a mean value of 815.0 mg/dL (range 518-1100 mg/dl). No statistically significant difference was detected between IVIg and SCIg treatment in terms of infection, hospitalization rate and need for antibiotic treatment. IgG trough level was higher in SCIg than in IVIg-treated patients, despite the difference not reaching a complete statistical significance (IVIg 727 mg/dl (range 506-1119 mg/dl) vs SCIg 810 mg/dl (range 518-1100 mg/dl) (p= 0.05).
DISCUSSION
We showed that both IVIg and SCIg replacement therapy were effective in reducing infection rate, antibiotics use and infection-related hospitalization in a cohort of SID patients. However, SCIg therapy allowed to achieve a higher IgG through level, even if without reaching complete statistical significance. Yet this result could be partly inaccurate because IVIg patients might not always receive the same amount of immunoglobulin pro kg per month since the frequency of administration may also vary due to the need for intra-hospital administration. Therefore, further studies on larger cohort will be needed to attempt to normalize these data for these variables, as well as for each single SID subtype.

22. AGOSTAR PROTOCOL: EFFECTS OF A STANDARDIZED ACUPUNCTURE PROTOCOL ON PAIN, INFLAMMATION AND AUTONOMIC CONTROL IN SYSTEMIC AUTOIMMUNE DISEASES

Tobaldini E.[1], Peta J.[2], Aronica C.[2], Carandina A.[3], Dias Rodrigues G.[4], Scatà C.[5], Arosio B. [4], Vigone B.[6], Montano N.[2]
[1]Department of Clinical Sciences and Community Health, University of Milan, 20122 Milan, Italy & Department of Internal Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, 20122 Milan, Italy; [2]Department of Clinical Sciences and Community Health, University of Milan, 20122 Milan, Italy & Department of Internal Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, 20122 Milan, Italy; [3]Department of Clinical Sciences and Community Health, University of Milan, 20122 Milan, Italy & Department of Internal Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, 20122 Milan, Italy; [4]Department of Clinical Sciences and Community Health, University of Milan, 20122 Milan, Italy; [5]Department of Internal Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, 20122 Milan, Italy; [6]Department of Internal Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, 20122 Milan, Italy & Scleroderma Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, 20122 Milan, Italy

Background: Chronic pain represents one of the main features of autoimmune diseases. Drug therapy can be not adequate to control pain and it is associated with a significant burden of side effects and adverse events. Acupuncture appears to have an important role in mediating pain and inflammation and is recommended as an adjuvant in pain treatment in many different clinical conditions. There is also preliminary evidence about an effect of acupuncture on cardiovascular autonomic control, evaluated through heart rate variability (HRV).

Objectives: In this study, we aim to evaluate the efficacy of a standardized acupuncture protocol in a cohort of patients with autoimmune diseases on chronic pain, autonomic parameters and on quality of life.
Materials and Methods. We conducted a single centre, prospective, interventional study, with a pre-post intervention analysis. We enrolled female patients from the Immunology Clinic of Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico, with an established diagnosis of Systemic Lupus Erythematous (SLE), Rheumatoid Arthritis (RA) or Systemic Sclerosis (SSc), chronic pain with Visual Analogue Scale (VAS) ≥ 3, an age comprised between 18 and 65 years old, a stable clinical disease and therapy. All patients signed an informed consent to the study.
Patients were treated with a total of 12 acupuncture sessions, during a period of seven months, with a prespecified 6 point-12 needle procedure. The first four acupuncture sessions were on weekly basis, the next four acupuncture sessions occurred every two weeks and the last four acupuncture sessions were once a month.
We evaluated patients at baseline (T0), after four acupuncture sessions (T1) and at the end of the seven months of treatment (T2). We collected the self-reported pain experienced in the last month through VAS. We performed a 10-minute ECG and breath registration with an active standing test for the evaluation of cardiovascular autonomic profile through the HRV analysis, three questionnaires on quality of life (depressive symptoms through PHQ-9 questionnaire, sleep quality through PSQI questionnaire, physical and mental functionality through SF-36 questionnaire) and we collected also blood samples for evaluation of inflammatory profile.
Our primary endpoint was the efficacy of the acupuncture protocol on chronic pain evaluated through VAS, with a clinically significance threshold of at least two points or 30% reduction. The secondary endpoint was the evaluation of the intervention effects on cardiovascular autonomic control, inflammatory profile and quality of life. We used a repeated measures ANOVA to test the effects of acupuncture on variables.
Results. A total of 12 patients were included in the study (9 SSc, 1 AR, 2 SLE), with a disease duration of 20 (±10) years and a prevalent articular and musculoskeletal pain (95% and 52% respectively). All patients were women. Even if there was not a significant reduction of pain after the first month of treatment (VAS 6.0 ± 1.4 vs 5.4 ± 1.9, p 0.135), after 7 months, there was a significant effect on chronic pain (VAS 6.8 ± 1.4 vs 3.5 ± 1.8, p 0.001).
The effects of acupuncture on quality of life appeared to be significant just after the first month of treatment as indicated by PHQ-9 on depressive symptoms (8.4 ± 4.9 vs 5.7 ± 4.6, p 0.001), by PSQI on quality of sleep (8.4 ± 4.1 vs 6.2 ± 3.3, p 0.004) and mental health domain of SF-36 on (43.7±11.7 vs 48.8±10.3, p 0.008), while there was a non-significant effect on physical health domain of SF-36 on (28.7 ± 8.9 vs 30.0 ± 8.5, p 0.174). All these effects persisted after 7 months of treatment.
The HRV analysis demonstrated a significant effect only on heart rate (74.5 ± 10.2 vs 70.9 ± 9.0 vs 66.3 ± 7.0, p 0.004), while there was no effect on all the other variables.
The analysis of inflammatory profile showed a significant reduction of the pro-inflammatory biomarkers TNF-α (9.13 ± 3.53 pg/mL vs 7.48 ± 3.27 pg/mL, p 0.037) and of TREM-1 (587±299 pg/mL vs 473±237 pg/mL, p 0.001) at the end of treatment (T2).
Conclusions: This preliminary analysis indicates that a standardized acupuncture protocol significantly decreased pain, systemic inflammation and heart rate after 7 months but not after the first month of treatment. Furthermore, a significant improvement in quality of life was observed after the first month and then maintained after 7 months.

23. FRAILTY INDEX IN SYSTEMIC SCLEROSIS AND ITS RELATIONSHIP WITH INFLAMMATION AND AUTONOMIC NERVOUS SYSTEM

Tobaldini E.[1], Asnaghi R.[2], Carandina A.[1], Mehalla A.[1], Dias Rodrigues G.[3], Scatà C.[4], Montinaro B.[1], Arosio B.[3], Bellocchi C.[1], Montano N.[1]
[1]Department of Clinical Sciences and Community Health, University of Milan, 20122 Milan, Italy & Department of Internal Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, 20122 Milan, Italy; [2]Department of Clinical Sciences and Community Health, University of Milan, 20122 Milan, Department of Internal Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, 20122 Milan, Italy & Politecnico di Milano, Department of Electronics, Information, and Bioengineering (DEIB), 20122 Milano, Italy; [3]Department of Clinical Sciences and Community Health, University of Milan, 20122 Milan, Italy; [4]Department of Internal Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, 20122 Milan, Italy

Background: Systemic Sclerosis (SSc) is a rare autoimmune disease characterized by fibrosis that affects not only the skin but also the internal organs and vessels. Due to the multifaceted nature of the pathology, clinicians lack a method for assessment of the patient's risk. For this reason, the Frailty Index (FI), a tool originally developed for geriatric patients for the evaluation of their vulnerability to stressful situations, seems to be promising.
For this purpose, we aim to investigate FI in patients affected by SSc and its relationship with Heart Rate Variability (HRV), an estimator of the Autonomic Nervous System (ANS) functioning, and inflammatory biomarkers for reliable stratification of frailty.
Methods: We enrolled a cohort of 40 patients affected by SSc, enrolled at the Internal Medicine – Immunology and Allergology Unit, Ospedale Maggiore Policlinico, Milan (age 60±10 years; Sex 10% M, 90% F; Subtype 85% limited, 15% diffuse). A 10-minute electrocardiogram (ECG) and respiration signals were recorded at rest in a clinostatic position. Additionally, demographic and clinical data, blood samples, and questionnaires, such as Health Assessment Questionnaire (HAQ), Pittsburgh Sleep Quality Index (PSQI), and Patient Health Questionnaire-9 (PHQ-9), were collected from each patient to evaluate physical and mental health and sleep quality. In particular, biomarkers evaluation from blood samples allows an evaluation of patients' inflammatory profiles.
An adaptation of FI for SSc was calculated, according to the scheme developed by the Canadian Scleroderma Research Group, that combines 44 items regarding the most critical aspect involved in the pathology and returns a frailty score between 0 and 1.
HRV and respiration variability were evaluated in the frequency and non-linear domain, through spectral and symbolic analysis, for sympathetic and parasympathetic activities assessment. Spectral analysis identifies two main oscillatory components, the Low Frequency (LFnu, 0.04-0.15) band, marker of sympathetic activation and the High Frequency (HFnu, 0.15-0.4 Hz) band, marker of vagal modulation and synchronous with respiration. Similarly, in the symbolic analysis, the percentage of pattern 2LV and 2UV represent parasympathetic modulation, while the percentage of patterns 0V represents sympathetic modulation.
Results: The data showed that our population's FI is homogeneous and ranges between 0.2 and 0.6, hence no one is classified as extremely frail (FI < 0.7). The correlation of FI with indexes of autonomic regulation and inflammatory profile reveals a relationship between frailty and increased heart rate (Pearson's r= 0.38 p= 0.03) and levels of Triggering Receptor Expressed on Myeloid cells 2 (TREM2) (Spearman's r= 0.35 p= 0.026). The former finding may suggest a cardiac involvement in patients affected by SSc and an altered sympathovagal activity. On the other hand, we may speculate that a high value of TREM2, a neuronal anti-inflammatory biomarker, may be related to a compensatory mechanism to inflammation, even if its role in scleroderma is still under investigation. Once used Principal Component Analysis (PCA) to reduce dimensionality, the first three components (45% explained variance ratio) were used to investigate the presence of subgroups. Despite no frailty-based groups were found, K-Means clustering enhanced the presence of three clusters. Retrospective statistical analysis of them revealed the following characteristics: (i) patients belonging to the first cluster show low levels of inflammation and high vagal modulation, hence good autonomic regulation; (ii) the second cluster is characterized by low levels of inflammation state and lower level of parasympathetic modulation, indicating a possible initial autonomic dysfunction; (iii) patients in the third cluster presents a higher inflammatory state and an intermediate autonomic regulation. These groups could reflect a different clinical vulnerability, even if no difference were observed in terms of frailty among groups. In fact, the severity of autonomic dysfunction seems to correlate with the disease severity.
Conclusions: Our findings highlight the importance of HRV and inflammatory state in profiling the frailty state of patients affected by scleroderma, suggesting a revision of FI for SSc that considers inflammation and autonomic dysfunction.

24. ANAKINRA FOR THE TREATMENT MACROPHAGE ACTIVATION SYNDROME IN ADULT PATIENTS: A CASE REPORT

Puccetti E.[1], Ambrosecchia M.[1], Montano N.[1], Furlan L.[1], Milani O.[2]
[1]Department of Internal Medicine, Fondazione IRCC.S. Ca' Granda, Ospedale Maggiore Policlinico, 20122 Milan, Italy 2 Department of Clinical Sciences and Community Health, University of Milan, 20122 Milan, Italy; [2]Department of Internal Medicine, Fondazione IRCC.S. Ca' Granda, Ospedale Maggiore Policlinico, 20122 Milan, Italy; Department of Clinical Sciences and Community Health, University of Milan, 20122 Milan, Italy

Case presentation: A 48 old woman with a history of Systemic Lupus Erythematosus (SLE) and moderate-severe Autoimmune Hepatitis (AIH) was admitted in our unit for fever, fatigue, hyporexia, vomit, jaundice and bilateral purpuric petechiae at the wrists. Blood exams showed pancytopenia (Hb 8,6 gr/dl, PLT 11000/cc and WBC 770/cc) with absolute neutropenia (Neutrophils 50/cc), hyperferritinemia (26000 ng/dl), elevation of c-reactive protein, LDH, direct bilirubin, cholestasis indices, GOT (five time over the normal range), hypertriglyceridemia (300 mg/dl, not previously known) and hypofibrinogenemia with normal coagulation indices without hypocomplementemia.
Diagnostic Work-Up and patients management: We initially suspected a possible infective etiology. Radiologic evaluation of the chest resulted negative, as blood cultures, beta-D-glucan, Quantiferon and serology and polymeras-chain-reaction (PCR) for the detection of CMV, EBV, HHV8, HHV6, HSV, Parvovirus B19, VZV, Histoplasmosis, Leishmaniosis. A possible autoimmune hepatitis flair was considered and dexamethasone IV at 1 mg/kg/day started with, nevertheless, no significant clinical or lab improvement.
The persistence of pancytopenia, hyperferritinemia and hypertriglyceridemia and the limited response to corticosteroid therapy led to the suspect of a Macrophage Activation Syndrome (MAS) so that a bone marrow biopsy was performed. Due to the high suspect for MAS, while waiting the histologic results on the biopsy, immunosuppressive treatment was extended to Methylprednisolone 100 mg/day and Anakinra 100 mg IV every 6 hours.
In the following days there was a significant improvement on lab exams of CRP, ferritinemia and hypertriglyceridemia. Yet, hepatic enzymes and cytopenia did not ameliorate.
In the suspect of potential contribution on liver enzymes increase and neutropenia, Anakinra dose was tapered down and Cyclosporine (50 mg twice daily) introduced as third line immunosuppressant. This therapy modification provided consistent improvement on pancytopenia and liver damage as well as patient's symptoms so that the patient was discharged after 24 days of hospitalization in good clinical status.
At two weeks the bone marrow biopsy showed the presence of haemophagocytosis, days after signs of amelioration.
Discussion: Macrophage Activation Syndrome (MAS) is a form of secondary Haemophagocytic Lymphohistiocytosis (HLH). It is a rare and life-threatening syndrome, caused by a hyperinflammatory systemic status that can be secondary to oncological, infective (mostly viruses) and autoimmune diseases.
The incidence among onco-haematologic patients is reported to be 0.36/100000 individuals/year, while mortality rates in adults can reach 40% (Griffin, G. et al. Best Pract. Res. Clin. Rheumatol. 2020). HLH 2004 Diagnostic criteria for HLH and HScore have a good overall diagnostic accuracy compared to two MAS experts diagnosis according to ICD-10 codes for HLH with reported sensitivity of 97.5% and 100% and specificity 96.1%, and 94.1% for the cutoff of 4 criteria and a score of 168, respectively, in intensive care settings (Knaak, C. et al. *Crit. Care* 2020). Hystologic findings alone do not provide adequate diagnostic accuracy, particularly in terms of specificity (Minoia, F. et al. *Arthritis Rheumatol.* 2014). Thus, considering the rapid evolution with high rate of lethality, when the clinical picture is highly suggestive of MAS, immunosuppressive treatment should be started straightforward.
Historically, the treatment of MAS has been based on Methylprednisolone, Cyclosporin A and Etoposide. Recent evidence on the role of cytokines storm in the development of this condition has led the use of recombinant anticytokine therapies, including Anakinra which specifically inhibits the interleukine-1 mediated pathway. Most of the evidence on the beneficial role of Anakinra is translated from studies on Jouvenile Idiopathic Arthritis, and several studies have proved a potential benefit of such treatments in pediatric patients (Boom, V. *et al. Pediatr. Rheumatol.* 2015). Fewer data are available for adult patients and the drug is still not specifically approved for the treatment of MAS in adults. Nevertheless, a recent guideline position paper from the Group on HLH Subtypes of the Histiocyte Society has underlined how Anakinra should be considered even as first line treatment in moderately to critically ill MAS patients nonresponsive to corticosteroids (Hines, M. R. *et al. Crit. Care Med.* 2022).
Conclusions: Macrophage Activation Syndrome is a sever and frequently lethal rare complication of autoimmune diseases. A high suspect for this condition is needed to provide prompt treatment with immunosuppressive treatment even before histological confirmation. Even if not specifically approved for MAS, several evidence from the pediatric setting and a recent position paper from experts in the field suggest to consider IL-1 inhibitor Anakinra as one of the first line treatments in moderate-severe MAS non responsive to corticosteroids.

25. RARE OR NOT RARE: THE NEED FOR AN HOLISTIC APPROACH

Miglio M.[1], Montanelli GA.[1], Rossi FG.[2], Maggioni M.[3], Croci GA.[3], Fiori S.[4], Iannotti N. [5], Furlan L.[1], Fracanzani A.L.[1], Montano N. [6], Fiorelli E.M.[1]
[1]Department of Internal Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, 20122 Milan, Italy; [2]Haematology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [3]Department of Pathology, Ca' Granda IRCCS Foundation, Milan, Italy; [4]Division of Diagnostic Hematopathology, European Institute of Oncology, IRCCS, Milan, Italy; [5]Infectious Diseases Unit, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, 20122 Milan, Italy; [6]Fondazione IRCSS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy; Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy

We present the case of a 72-year-old male, admitted to our ward to complete diagnostic work-up in diffuse lymphoadenopathies and persistent altered liver function.
Two years before he had an history of obstructive jaundice caused by increased common bile duct's wall thickness, requiring the placement of a metallic prosthesis. A biopsy of the bile duct's wall was performed at that time showing aggregates of epithelial cells of the bile ducts, some with reactive alterations. There was no evidence of malignancy.
A couple of months before admission, a follow-up CT scan showed diffuse lymphadenopathies, later confirmed with a positron emitted tomography (PET), and kidneys' hypertrophy with a poor cortico-medullary differentiation. Considering the imaging results and the complained symptoms of asthenia, itching, night sweats and weight loss of 10 Kg in the last year, the patient was referred to an oncohematological evaluation. An axillary lymphnode biopsy was performed, showing a reactive lymphadenitis with plasmacytosis. The biopsy was complicated by an abscess formation needing multiple antibiotic therapies and VAC- therapy. Laboratory testing at that time showed increased cholestasis and transaminases, initially interpreted as iatrogenic considering the high dose of antibiotic and an essentially normal follow-up cholangio-MRI, with only a slightly dilated biliary tract. Indeed, liver autoimmune serologic markers came back negative. Further laboratory testing revealed the following: positive ANA (1/2560 with a homogeneous pattern), negative HHV8 DNA, complement consumption and high serum total levels of IgG and IgG4 (8180 mg/dl and 1348 mg/dl).
Considering the clinical picture, the laboratory data and the lypmhnode hystology, a differential diagnosis between Castleman disease and IgG4 related disease (RD) was performed. The patient was then admitted to our ward to complete the diagnostic work-up.
Since the PET hypertrophic appearance of both kidneys, we decided to initially perform a kidney biopsy, not suggestive for Castleman disease, revealing some IgG4+ plasma cells (IgG4/IgG <40%) and a slight mesangial expansion with chronic lympho-plasmacellular interstitial nephritis.
A second level urine sediment came back normal, although complement consumption was confirmed. Considering the persistent altered liver function we decided to perform a liver biopsy. The latter showed destructive lesions of the biliary tract and focal periductal fibrosis with an inflammatory and plasmacellular component markedly above the norm, creating a picture highly compatible with a sclerosing cholangitis IgG4-related, coherent with the increased plasmacellular IgG4 component, despite a ratio IgG/IgG4 below the diagnostic threshold. Considering the complained xerostomia, a salivary gland ultrasound was performed showing a suspected involvement of the glands.
For worsening of the cholestasis, a cholangio-MRI was repeated, showing a swollen liver with hypertrophic caudate and left lobes. The common bile duct was dilated until the pancreas where it abruptly shrank until the papilla. The intrahepatic bile ducts were moderately dilated (hepatic duct 6 mm). No gallstones were detected. An endoscopic retrograde cholangiopancreatography (ERCP) balloon dilatation of the stenosis was then performed.
According to the 2019 classification criteria of the American College of Rheumatology/European League Against Rheumatism, considering the typical biliary tract and salivary gland involvement our patient met the entry criteria. He had no exclusion criteria. He had a dense bioptical lymphocytic infiltrate, with 60-70 IgG4 positive plasma cells/high power field (HPF) at liver biopsy, even though the IgG4+/IgG+ ratio was <40%. Furthermore, serum IgG4 were more than 5 times the upper limit, the patient had two set of glands involved (parotids and submandibular) and he presented with hypocomplementemia, therefore we made the diagnosis of IgG4 related disease with SSC and started steroid therapy with a good response.
In a single month, the jaundice disappeared together with itching and xerostomia, the complement returned to normal values and the total IgG dropped

to 1000 mg/dl. Furthermore, the hepatic function progressively improved and the kidney function went back to normal values.
IgG4-Related Disease (IgG4-RD) is an immune-mediated fibroinflammatory disease, presenting with mass forming lesions potentially affecting any organ and leading to permanent organ injury if left untreated. When the disease affects the liver, it involves primarily bile ducts, being therefore considered a cause of secondary sclerosing cholangitis (SSC).
This case shows the intrinsically deceptive nature of many immunological diseases, whose picture can be clearly interpreted only by looking at it in a holistically way. IgG4-RD is a complex condition, manifesting in many ways and therefore requiring a multidisciplinary team to be handled. Luckily, IgG4 RD with pancreato-biliary involvement is generally responsive to glucocorticoids. The patient has been referred to the center of reference for his pathology where a maintenance therapy will be evaluated.

26. DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS) PRESENTING WITH THYROID DYSFUNCTION: A CASE REPORT

Sacco S.[1], Bongiovanni A.[2], Di Lucca G. [3], Scotti R. [3], Di Terlizzi G.[3], Marinosci A. [3], Ramirez G.A.[4], Damanti S.[5], Tresoldi M. [3]
[1]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy. Università Vita-Salute San Raffaele.; [2]Unit of General Medicine and Advanced Care, Vita e Salute University, Milan; [3]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy.; [4]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy. Università Vita-Salute San Raffaele. Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS Ospedale San Raffaele, Milan, Italy.; [5]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy. Università Vita-Salute San Raffaele. Unit of Medical Specialties and Healthcare Continuity IRCCS Ospedale San Raffaele, Milan, Italy
Introduction: Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe and heterogeneous drug-induced syndrome which is mediated by T-lymphocytes (type IV hypersensitivity). DRESS diagnosis is becoming more and more common due to the increasing exposure to various drugs both in home and hospital settings. This syndrome may lead to severe and life-threatening organ involvement, with consequent intensive care unit admission or even death. DRESS also presents a complex diagnosis due to its heterogeneous and often subtle clinical manifestations and the difficult identification of liable drug(s). DRESS pathogenesis is not fully understood, but latent virus reactivation (especially Herpesviridae) may be crucial to prompt abnormal activation of T-cells and eosinophils. DRESS may be associated with long-term complications several years apart, in particular with autoimmune diseases.
Objectives: The aim is to describe a usual case of DRESS and emphasize the importance of autoimmune sequelae in DRESS survivors.
Case report: A 64-year-old man was admitted to the High-Intensity medical care in Internal Medicine Unit of San Raffaele Hospital because of weight loss and fever. These symptoms appeared one month before admission and were unresponsive to non-steroidal anti-inflammatory drugs (NSAIDs) and amoxicillin/clavulanic acid prescribed by his practitioner. During this month, blood tests were normal, except for a low TSH level and positive anti-thyroid peroxidase antibodies. At admission, blood tests showed neutrophilic leukocytosis and elevated acute phase reactants. Infection was ruled out due to negative serological tests, blood and urine cultures and imaging. His clinical course was marked by progressive liver and kidney failure up to anuria. He was started on hemodialysis. During hospitalization, a mild rash appeared all over the body, together with an increase in the peripheral blood eosinophil count up to the hypereosinophilia threshold (> 1.5 × 109/L). Liver biopsy findings were consistent drug damage on metabolic liver disease. Therefore, after excluding other diagnoses, the patient was diagnosed with DRESS, using the *Registry of Severe Cutaneous Adverse Reactions* (RegiSCAR) algorithm. The patient obtained a total score of 6, consistent with definitive diagnosis of DRESS. NSAIDs and amoxicillin/clavulanate were identified as the most likely causing drugs. The patient was treated with oral methylprednisolone resulting a rapid renal and thyroid function improvement, but not in liver function, which required intravenous immunoglobulins (2 g/kg). The patient was discharged with oral methylprednisolone and followed up to monitor liver and thyroid function. A month after discharge, blood test revealed elevated TSH and low fT4 levels. A home therapy with levothyroxine sodium was set up.
Discussion: Unlike liver and kidney involvement, thyroid dysfunction is rarely reported in DRESS patients. A literature review identified 51 DRESS cases associated with thyroid dysfunction, including 12 children and 39 adults. Adult patients were clinically divided into Hashimoto's thyroiditis, possible Hashimoto's thyroiditis (without documented anti-thyroid antibodies) and Graves' disease. Hashimoto's thyroiditis is the most common thyroid manifestation in adult patients affected by DRESS, in line with our patient presentation. Unlike our case, the median onset of Hashimoto's thyroiditis after DRESS diagnosis was six months. The pathophysiological mechanism of thyroid dysfunction in DRESS has not yet been defined, but an involvement of thyroid peroxidase has been proposed. This enzyme is involved in drugs metabolism into reactive metabolites which interact with the protein itself leading to an autoantibody mediated immune response. This case report provides further clues to investigate drug exposure history in thyroid disease patients in which DRESS is suspected and to follow them for any autoimmune complications.
Conclusion: This case report and the literature review add to the current knowledge on organ involvement in the DRESS diagnosis and treatment. The importance of clinical and laboratory follow-up in patients affected by this syndrome is therefore heightened.

CASI CLINICI

27. NEVER SAY NEVER! AN UNRECOGNIZED CASE OF OBSCURE GASTROINTESTINAL BLEEDING CAUSED BY MECKEL'S DIVERTICULUM IN PATIENT IN TREATMENT WITH NOVEL ORAL ANTICOAGULATION

Masoni G.[1], Luppi D.[2], Cavina M.[3], Leone M.C. [1], Dyrmo L.[1], Casali A.[4], Bonilauri S.[5], Sassatelli R.[6]
[1]Medicina Interna ad Indirizzo Metabolico ed Emocoagulativo, ASMN IRCCS Reggio Emilia; [2]U.O.C. Chirurgia Generale e d'Urgenza, ASMN IRCCS Reggio Emilia; [3]Endoscopia Digestiva, ASMN IRCCS Reggio Emilia; [4]Responsabile Medicina Interna ad Indirizzo Metabolico ed Emocoagulativo, ASMN IRCCS Reggio Emilia; [5]Direttore U.O.C. Chirurgia Generale e d'Urgenza, ASMN IRCCS Reggio Emilia; [6]Direttore Endoscopia Digestiva, ASMN IRCCS Reggio Emilia

Obscure gastrointestinal bleeding (OGIB) is defined as gastrointestinal bleeding from a source that remains uncertain after upper and lower gastrointestinal endoscopy. OGIB accounts for 5–10% of all cases of GI bleeding and it is divided into two types: occult and overt-OGIB. The etiology of mid-GIB is various: vascular disorders such as angiodysplasia, Dieulafoy's lesion, arteriovenous malformation (AVM), varices, phlebectasia. Inflammatory disorders include Crohn's disease, intestinal tuberculosis, Behçet's disease/simple ulcer syndrome. Iatrogenic disorders include injuries induced by drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), anticancer agents, and radiation therapy. Bleeding tumors include gastrointestinal stromal tumor, adenocarcinoma, metastatic tumor, malignant lymphoma, Peutz-Jeghers polyp, inflammatory fibroid polyp, aberrant pancreas, and lipoma. Diverticula include Meckel's diverticulum and others retracted by adhesion or gastrointestinal stromal tumor.
A 73 year-old man, with history of ischemic heart disease, mild thrombocytopenia, in therapy with Dabigatran for atrial fibrillation, access to emergency department for melena. In the 70' hospitalized for peritonitis due to perforated appendicitis; Mc Burney laparatomy was performed; Meckel diverticulum was found but not removed during that operation.
Blood exams at ER showed anemia (haemoglobin 7 g/dl); admitted to our ward, Dabigatran was stopped and he needed blood transfusions. During a 30 days long hospitalization, the patient underwent several times endoscopy (gastroscopy, colonscopy, capsule endoscopy and double balloon enteroscopy), never showing real active bleeding. Technetium-99m pertechnetate scanning and scintigrafy for ectopic gastric mucosa were performed, suspecting bleeding from Meckel diverticulum; both resulted negative. Coagulation disorders except for his known trombocytopenia were excluded (PT, aPTT, factors VII, VIII, IX and XI, Von Willebrand and platelet aggregation test resulted normal). CT angiography once showed ileum iperdensity without blushing, sign of recent bleeding. For that reason, patient was moved to Azienda Ospedaliero-Universitaria di Parma where interventional radiology is available to try angioembolization; bleeding was not confirmed so angioembolization was not performed. Persisting anemia and melena needed endoscopy, founding again no active signs of bleeding; small bowel was ink marked to limit bowel portion explored. Collegial discussion (physicians, endoscopists and surgeons) decided for surgery.

The patient underwent laparoscopy: Meckel's diverticulum was removed, no other pathological findings were found; ileostomy between the two marked places (one about 1,5 m from the Treitz, one about 80 cm from the ileocecal valve) was performed and intraoperatory enteroscopy from ileostomy excluded active bleeding. After 2 weeks ileostomy was closed, haemoglobin levels rised and bleeding never occured. Anticoagulation restored, initially with a reduce dose (Apixaban 2,5 mg BID) and after 1 month with full dose (Apixaban 5 mg BID). During the one-year follow up there was an increase haemoglobin levels (the last Hb 16,3 g/dl) and no evidence of bleeding recurrence.
Meckel's diverticulum is the most widespread congenital abnormality of the gastrointestinal system (incidence 0.6-4%). Bleeding is related to ulceration of the ileal mucosa adjacent to acid-secreting ectopic gastric mucosa in nearly all cases. Obstruction is the presenting syndrome in 14-40% of symptomatic diverticula in the adult; gastrointestinal bleeding is more common under age 40 years. In adults over 40 it remains a potential cause of bleeding that should not be underestimated.

28. HEPATO-PULMONARY SYNDROME: WHEN THE INDICATION FOR LIVER TRANSPLANTATION IS CHALLENGING

Caroleo B. [1], Perticone M. [2], Potenza G.[2], Monaco V.[2], Pascale A.[3], Cancelliere M.[1], Caruso M.[1], Fiorino G. [1], Salatino N.[1], Sciacqua A.[2]
[1]PO Basso Ionio, Soverato; [2]Dipartimento di Scienze Mediche e Chirurgiche, Università Magna Graecia di Catanzaro; [3]AO Pugliese-Ciaccio, Catanzaro

Introduction: In hepato-pulmonary syndrome (EPS), a complication of liver cirrhosis with a rapidly unfavorable prognosis, worsening hypoxemia occurs due to pulmonary vasodilatation. It dramatically benefits from liver transplantation (OLT); very often the diagnosis is difficult as respiratory comorbidities coexist, making it difficult to decide whether the patient is a candidate for a pre-OLT assessment. We describe below a complex case of concomitant pulmonary fibrosis and liver cirrhosis, characterized by progressive and severe hypoxemia arising in a short period of time.
Description: 60-year-old man, smoker, affected by alcohol- and HBV-related liver cirrhosis in alcohol abstention for 10 years and on therapy with entecavir, furosemide, spironolactone, carvedilol and rifaximin; had portal hypertension (F2 oesophageal varices. Congestive gastropathy and moderate ascites). Pulmonary fibrosis was concomitant with the following usual EGA (pH 7.413; SO2 93%; pO2 61.9 mmHg; pCO2 33.2 mmHg) and nocturnal pulse oximetry (TC 90 5.3%, SpO2 91%) pattern. Followed up for about 15 years at the internal medicine clinic of the AOU of Catanzaro first and in the hepatology clinic of the Soverato hospital then, during the clinical check-up in March 2022, he reported in the previous days marked arterial hypotension, appearance of unusual dyspnea, first with light exertion and then also at rest, with platipnea and orthodeoxia; at rest he had a saturation of 92%, but during the walking test it was reduced to 85% with the appearance of intense dyspnea and also passing from supine to upright position. The diagnostic investigation confirmed a picture of smoke-related pulmonary fibrosis on the high-resolution computed tomography; the spirometric examination was also compatible with a mild restrictive disventilatory syndrome with severe reduction of the A-C diffusion capacity of CO according to the SB method. **Echocardiography** showed an increase in estimated pulmonary pressure (PAPs: 50 mmHg) due to pulmonary fibrosis, and a small caliber (12 mm) vena cava collapsing with respiratory acts. The rapid pattern of onset of dyspnea suggested a EPS rather than an aggravation of pulmonary fibrosis. For this reason, the patient underwent **echocardiography with bubble test** which demonstrated, during the Valsalva maneuver, a marked late shunt in the left ventricle which confirmed the vascular dilatation of the pulmonary circulation, characteristic of EPS. The instrumental confirmation of the clinical hypothesis, despite a MELD score of 12, led to sending it to the Transplantation Center. Once the diagnosis was confirmed, he underwent OLT. Respiratory improvement was progressively rapid; he required oxygen therapy immediately afterwards and permanently (4 L/minute), with ever-reduced need until complete suspension for resolution of arterial hypoxemia. Furthermore, the spider nevi covering the entire body surface of the patient disappeared in the month following the transplantation.
Discussion: Liver transplantation is confirmed as a resolutive option in EPS, also in the case described; timely diagnosis is essential to activate the appropriate path quickly. The differential diagnosis is also important if there are primary respiratory comorbidities; the latter could contraindicate liver transplantation if they play a predominant role in respiratory failure. In SEP, however, the deterioration of respiratory function accelerates the transplantation process. As always happens, the clinic and the reasoning on symptoms and signs constitute the foundation of the most appropriate decision.

29. HYPERAMMONAEMIC ENCEPHALOPATHY WITHOUT LIVER CHIRROSIS: A CLINICAL CASE

Caroleo B.[1], Perticone M.[2], Marchese S.[3], Suraci E.[3], Cimellaro A.[3], Rullo R.E.[2], Volpentesta M.[2], Mitra M.[1], Pedace E.[1], Salatino N.[1], Sciacqua A.[2]
[1]PO Basso Ionio, Soverato; [2]Dipartimento di Scienze Mediche e Chirurgiche, Università Magna Graecia di Catanzaro; [3]AO Pugliese-Ciaccio di Catanzaro

Introduction: Hepatic encephalopathy in non-cirrhotic patients can only be suspected in the presence of hyperammonaemia, therefore the absence of cirrhosis is not sufficient to rule out the diagnosis of hepatic encephalopathy. In noncongenital cases, the cause of large portosystemic shunt formation in non-cirrhotic patients without portal hypertension is unclear. Overall, these are rare cases, although today the evolution of imaging examinations has made their diagnosis easier. Before the correct diagnostic classification, unfortunately many of these cases are treated as psychiatric diseases or even forms of dementia, for which hospitalizations in psychiatry, internal medicine/geriatrics or even paediatrics follow one another. One case is described below.
Description: Male, 61-year-old construction worker, diabetic, hypertensive, with known gallbladder stones; comes to our observation on 30 September 2022 sent by the General Practitioner for previous hospitalizations in an internal medicine environment caused by episodes of mental confusion and hyperammonemia. During the visit, an ideational and motor slowdown and awkward speech were evident; there was concomitant tremor in the upper limbs with large jolts. The anamnesis was negative for ethyl abuse. His wife and daughter asserted that he had always shown himself to be slow both in his conception and in his movements; such aspects were not found in his brothers. He exhibited abundant clinical documentation relating to numerous hospitalizations suffered for episodes of mental confusion and tremor; the only alteration noted on all occasions was hyperammonaemia; in all cases he had been treated with lactulose, rifaximin, branched chain amino acids and medicated enemas, with transient benefit. Laboratory tests showed a constant picture of normality of liver function parameters; in particular, cytolysis and cholestasis enzymes, INR, albumin, PCHE and also creatinine were always within the normal range; indirect bilirubinemia was always elevated. Plasma copper, ceruloplasmin, ferritin, alpha1-antitrypsin were also normal; negative viral and autoimmune markers. EEG, brain MRI and brain CT also showed a normal picture. Oncological markers were normal. Abdominal CT excluded morphology characteristic of liver cirrhosis, signs of portal hypertension, or focal arterialized lesions; an ectasia of the splenic vessels and left portal branches was reported. On the occasion of a hospitalization in 2021, he was also subjected to a liver biopsy which excluded inflammation and necrosis and highlighted a modest fibrotic expansion of the portal spaces. Esophagogastric endoscopy revealed a normal picture. Liver MRI showed an organ with normal morphology and dimensions and with a regular right lobe/caudate lobe ratio. On echocardiography: interventricular septal hypertrophy. During the visit to our clinic, all tests were within the normal range, except for the ammonium (377 mcg/dl). Assuming the presence of malformative portosystemic shunts, a thoraco-abdominal CT scan was requested, specifying the question to the radiologist specialist. The contrastographic examination revealed "intrahepatic portosystemic shunts involving S2, S3, S4a and S4b and marginally S8 with discharge in the median and left VSE. Enlarged portal vein with caliber at the hilus of 18 mm x 16 mm (estimated area 248 sq mm), at its bifurcation asymmetry can be recognized due to a clear left prevalence (left branch 17 x 14 mm with estimated area of 203 sq mm; right branch 9 x 8 mm with an estimated area of 78 sq mm), the relief suggests a prevalent inflow of portal blood towards the left liver. Left hepatic vein ectasic (13 mm) and patent. The picture points to intrahepatic portosystemic shunt type 4 according to Park. Further portosystemic shunts are appreciated in the pericholecystic site, in the gastric mucosa (body, fundus, antrum), adjacent to the stomach and in the left splenorenal site. A small arteriovenous shunt is also evident in S8. He also showed hypoplasia of the pancreatic isthmus/body and tail. Bilateral non-obstructive renal microlithiasis". The patient was referred to a transplantation center.
Discussion: In the presence of confusional states without apparent cause, it is suggested to request ammonia; in case of its alteration, evaluate whether advanced liver disease coexists with portal hypertension. Excluding these causes of hyperammonaemia, direct the diagnostics towards vascular malformation pathologies with portosystemic shunt which can be intrahepatic as in the case described, but also extrahepatic. In these cases, endovascular closure is the first treatment option when possible and above all if the dia-

gnosis is made early. In cases such as the one described, the intra-hepatic malformation involvement is extensive and has evolved over time so as to aggravate the extent of the shunts and therefore involve the patient's inclusion in a pre-transplant balance path.

30. CO-INFECTION IN ASPERGILLUS COLONIZATION?

Maggipinto R.[1], Romano D. E.[1], Barile G.[2], Lillo F.[2]
[1]U.O.C. Medicina Interna "C. Frugoni" Azienda Ospedaliera Policlinico di Bari; [2]U.O.C. Medicina Interna P.O. Monopoli ASL Bari

Introduction: Inhalation of Aspergillus spp. conidia is a common occurrence. Airway and lung disease and its clinical presentation depend on the relationship between the host's immune status and the amount of conidia exposure. Different clinical entities can sometimes coexist or have overlapping clinical and radiological signs. Correct diagnosis is often challenging. Pulmonary aspergillosis represents a diagnostic and therapeutic challenge due to the modest sensitivity and specificity of the diagnostic tests, resulting in frequent diagnostic and therapeutic delays. Clinical case: a 32-year-old woman, current smoker, with inhalant allergy and asthma undergoing chronic therapy with budesonide/formoterol. She had contracted SARS-CoV2 infection six months before. The woman experimented worsening fever and dry cough in the last week, then accessed to the emergency department for bronchospasm and dyspnoea. Pulmonary examination showed diffuse expiratory wheezes, bilateral basal crackles and reduced vesicular murmur. SARS-CoV2 antigenic swab was negative. Blood gas analysis showed hypoxemic respiratory failure, so Venturi mask at FiO2 40% was introduced. Laboratory tests showed mild neutrophilia and lymphocytopenia with negative inflammation indices. Chest radiograph showed "inhomogeneous parenchymal consolidation of the right middle lobe as for pneumonia". The patient was admitted to our Unit of Internal Medicine. High Resolution chest Computerized Tomography scan was performed and showed "right lobar parenchymal consolidation with signs of associated interstitial pneumonia". Empiric therapy with piperacillin/tazobactam and oseltamivir was introduced. Search for atypical bacteria (Legionella pneumophila serotype 1 urinary test, Mycoplasma antibodies) and SARS-CoV 2 molecular swab were negative and inflammation indices remained negative. On the third day, nasopharyngeal swab for influenza resulted positive for H3N2 subtype. In the following days, the patient went through a clinical and laboratory worsening with elevation of inflammation indices (PCR 134 mg/L – normal value <2,9 mg/L – Procalcitonin negative) and bronchospasm with significant hypoxemia so High Flow Nasal Cannula (FiO2 85%, 50 L/min) and pronation were introduced. On the fifth day, sputum culture sent on admission was positive for Aspergillus spp. so Voriconazole was introduced. On laboratory tests total IgE was moderately positive (969 kUA/L, normal value 0 - 110) but specific IgE, IgM and IgG for Aspergillus fumigatus were negative. The patient gradually improved till a complete clinical and laboratory remission and referred to pulmonological follow-up. Conclusions: Recent SARS-CoV2 infection may have favoured Aspergillus colonization (e.g. due to direct damage to the respiratory epithelium and immune dysregulation) in an asthmatic patient receiving corticosteroids. The current H3N2 infection could instead explain the rapid respiratory evolution. We are inclined to believe that the case described above reflects a co-infection (influenza associated aspergillosis) rather than an allergic bronchopulmonary aspergillosis. With the recent H1N1 influenza and COVID-19 pandemics, the incidence and clinical spectrum of pulmonary aspergillosis has increased significantly. The heterogeneity of clinical and radiological patterns and the limited sensitivity and specificity of microbiological tests represent a diagnostic challenge. However, pulmonary aspergillosis should be search among these new or atypical categories of patients in which it is often not even suspected. This clinical case shows that detection of Aspergillus can be decisive for the clinical course and lung involvement.

31. "THAT'S NOT THE PERSON I KNOW": A CASE OF ALTERED MENTAL STATUS IN AN OLD WOMAN

De Caro M., Restelli S., Rossio R., Peyvandi F.
S.C. Medicina - Emostasi e Trombosi, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Ca' Granda Ospedale Maggiore Policlinico, Milan

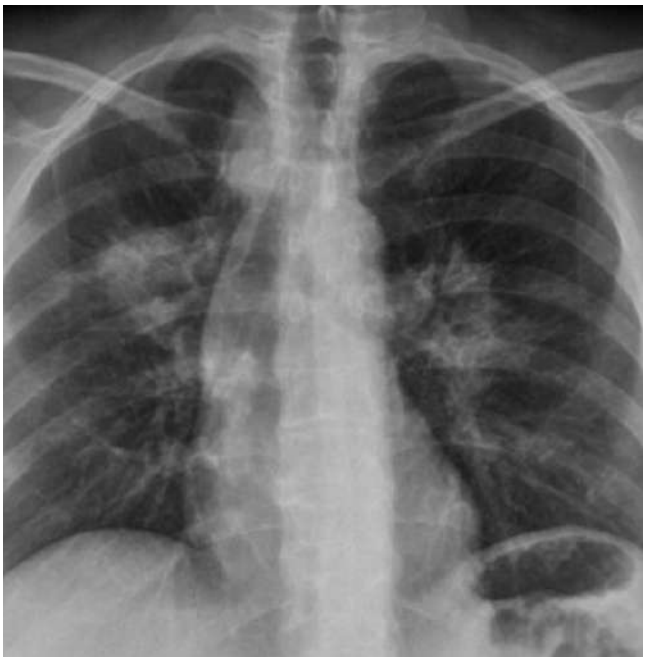
Case report: An 85 years old woman was admitted to our ED with confusion and non fluent aphasia. The patient was asymptomatic until the previous evening. She was on treatment with zolpidem since few days ago for insomnia. The patient's medical history consisted of arterial hypertension ad hypotiroidism. In the ED the body temperature was 36.5°C, the blood pressure was 200/80 mmHg, the heart rate was 60 beats per minute and the oxygen saturation on room air was 100%. Biochemical analysis showed hyponatraemia (Na 126 mEq/L) and hypokaliemia (K 2.6 mEq/L), CRP <0.4 mg/L (n.v. <10 mg/L), WBC 6950/mmc, Hb 10.7 g/dL, MCV 68 fl, PLTs 360000/mmc. The head CT scan without contrast agent excluded intracranial bleeding and acute ischemic stroke. Despite hydroelectrolytic disturbances and arterial blood pressure corrections with intravenous therapies, we observed the persistance of neurological presenting symptoms. Subsequent electroencephalogram analysis was normal. Two days after the admission, the patient was discharged with diagnosis of delirium secondary to hyponatriemia, hypokaliemia and hypnotic drug use. Next day the patient was newly admitted to our hospital due to aggressive behaviour with her daughter. On physical examination only the persistance of elevated arterial blood pressure levels (ABP 190/75 mmHg) were observed. Biochemical tests were repeated, sodium and potassium were in range. We consulted the neurologist and lumbar puncture and cerebrospinal fluid (CSF) analysis were performed (white blood cells were < 0.002; on chemical tests, glucose was 59 mg/dl and proteins were 33 mg/dl; bacterioscopy and polymerase chain reaction assays for HSV, VZV, CMV, EBV and enterovirus were negative) and a central nervous system infection was excluded. The patient subsequently developed partial seizures that evolved into status epilepticus. She was admitted to the Neurology department and antiepileptic therapy with levetiracetam, lacosamide and phenobarbital was started. Two days later a head MRI with intravenous contrast medium was obtained and T2-weighted image showed hyperintensity in the subcortical white matter of the left occipital lobe. These findings were confirmed by MR repeated five days later. In the clinical scenario described, characterized by non-fluent aphasia, seizures, hypertensive emergency, hyponaterima and hypokaliemia, the head MR images made the diagnosis of posterior reversible encephalopathy syndrome (PRES) possible. During the hospitalization the patient received three antiepileptic drugs and adequate treatment for arterial hypertension with clonidine and irbesartan. Patient's clinical status improved progressively and she was discharged after eigthteen days of hospitalization, with neurological follow-up to evaluate antiepileptic therapy decalage.
Posterior reversible encephalopathy: PRES is a clinical-radiological syndrome characterized by headache (holocranic, with moderate-severe intensity, non-responsive to analgesic therapy), confusion (with possible altered mental status or coma), visual disturbances, seizures (these are often the presenting manifestation of the syndrome) and specific findings on neuroimaging (posterior white matter edema). Risk factors are rapid ABP increase, acute kidney injury or chronic kidney disease, vasculitis, hydroelectrolytes imbalance. These situations can cause cerebral autoregulation failure and endothelial dysfunction, leading to cerebral edema. Even if no specific treatment exists, PRES is usually reversible in days to weeks with early risk factors management. At the clinical and radiological resolution, antiepileptic therapy is usually no longer required, for such a low risk of seizures recurrence and epilepsy development.
Take home message: In ED, the differential diagnosis between delirium and other CNS disorder in elderly patients is often challenging despite physical examination, blood tests and neuroimaging. Diagnosis of PRES should be suspected in presence of neurological symptoms, elevated ABP levels, hydroelectrolytes disturbances and/or kidney damage. In this case the manage of risk factors should be prompty undertaken.

32. GRANULOMATOSIS WITH POLYANGIITIS (FORMERLY KNOWN AS WEGNER'S GRANULOMATOSIS): A RARE CASE OF VASCULITIS ONSET WITH INTESTINAL HAEMORRHAGE

Errico M.[1], Parente F.[2]
[1]Medicina Interna Universitaria "C. Frugoni" Bari; [2]Medicina Interna Ospedale "Vito Fazzi" Lecce

Wegener's granulomatosis is a vasculitis, that is, an inflammation that involves the wall of medium and small caliber arteries, capillaries and venules causing necrosis and granulomas (typical lesions from chronic inflammation). After a recent hospitalization in ENT for rhinosinusitis and nosebleeds with evidence of neoformation of the right nasal fossa and involvement of the maxillary sinus, the patient accessed the U. O of Internal Medicine of the PO "Vito Fazzi" for diagnostic framing of a series of clinical manifestations present such as fever, polyarthralgia, asthenia and weight loss with the presence of suspicious lung lesions for LOS. The clinical picture in the following days changed drastically with the onset of complicated enterorrhagia in hemorrhagic shock. Therefore, in an emergency regime, the patient performed

EGDS with evidence of large ulcerated lesion of the distal third of the esophagus (not bleeding) whereas the fourth portion of the duodenum showed the presence of blood material coming from below; This was followed by treatment with mechanical hemostasis through the application of metal clips and local infiltration with adrenaline. Blood chemistry tests showed, in parallel with a worsening of renal function (urea 119 mg / dl, creatinine 4.23 mg / dl and proteinuria 24 / h 1.92 g / dl), a positivity to C-ANCA autoantibodies with Anti PR3 (Proteinase 3) for which the diagnostic suspicion of Wegner's granulomatosis was posed. In the following days, due to the onset of behavioral alterations with the appearance of temporo-spatial disorientation and ideomotor slowdown, skull CT scan was requested with the finding of "oval hypodense area in the left paratrigonal region with perilesional edema halo, suggestive for focality with inflammatory genesis".The echocardiogram performed shortly after, in order to search for any endocardial foci, documented the presence of hypoechoic formation adhered to the ventricular side of the anterior mitral flap, of non-univocal interpretation (vegetation?) for which transesophageal echocardiogram was required, however not performed due to important abdominal symptoms. The patient therefore performed CT abdomen without m.d.c. which showed, in the right iliac fossa, coarse and poorly defined formation (blind with thickened walls rather than collected), supra and submesocolic effusion, on the right, right peri and pararenal edema with locoregional lymphoadenopathies. Subsequently, after improvement of the inflammation indices, a CT scan with m.d.c. was repeated: "cecum walls altered in several extremely thin points and difficult to delimit, especially along the anti-mesenteric side and in basal conditions linear endoluminal stratification with densitometric values of blood type". For the continuation of the diagnostic-therapeutic process, the patient was transferred to the Department of Internal Medicine "Baccelli" of the Policlinico di Bari with a diagnosis of "Wegner's vasculitis with multiple localization with hemorrhagic shock due to intestinal hemorrhage and severe secondary anemia. Acute renal failure. Suspected endocarditis with suspected abscess brain lesions. Secondary lung lesions of ndd and neoformation of the right nasal fossa with involvement of the maxillary sinus (presence of granulation tissue with giant cell cells").Therefore, the antibody routine (anti-proteinase 3 (PR3) autoantibodies equal to 280.7 CU/mL (v.n. <20)) was repeated with confirmation of the diagnosis of Wegner's granulomatosis and setting up of therapy with methylprednisolone and cyclophosphamide.



33. PYODERMA GANGRENOSUM REVEALING TAKAYASU ARTERITIS IN A 65-YEAR-OLD CAUCASIAN WOMAN: A CASE REPORT

Senini E.[1], Bagnati C.[2], Donatoni M. [2], Ciocca L.[2], Di Lucca G.[3], Tresoldi M.[3], Bozzolo E.[3], Damanti S.[4], Ramirez G.A.[5]
[1]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy -Università Vita-Salute San Raffaele ; [2]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy- Università Vita-Salute San Raffaele ; [3]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy ; [4]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy- Università Vita-Salute San Raffaele- Unit of Medical Specialties and Healthcare Continuity IRCCS Ospedale San Raffaele, Milan, Italy; [5]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy- Università Vita-Salute San Raffaele- Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS Ospedale San Raffaele, Milan, Italy

Background: Takayasu arteritis (TAK) is a chronic granulomatous large-vessel vasculitis which primarily affects the aorta and its main branches. Although the disease usually presents with constitutional symptoms in the early phase and with vascular stenosis and occlusions in later stages, it can also uncommonly manifest in association with cutaneous findings such as pyoderma gangrenosum (PG).
Objective: To demonstrate the need to consider TAK when diagnosing a PG of unknown etiology.
Case report: We report on a 65-year-old Caucasian woman with simultaneous onset of PG and TAK. She presented to the Emergency Room with persistent fever and a progressive large skin ulceration on her right pretibial area causing severe pain. On admission, her complete blood count showed leukocytosis of 20.0 × 109/L (3.5-9.5 × 109/L) with 91% neutrophils, C-reactive protein (CRP) of 303.3 mg/L (0-8 mg/L) progressively increasing and erythrocyte sedimentation rate (ESR) of 120 mm/1st hour (< 20 mm/1st hour) without renal or liver impairment. Because of the lack of clinical response to empirical antibiotic therapy and persistently negative bacterial cultures (obtained from blood and from the cutaneous lesion), an infectious ulcer was ruled out. A skin biopsy of the ulcer revealed marked neutrophil infiltration of the upper and lower layers of the dermis, which led to the diagnosis of PG. Subsequently the patient was treated with oral colchicine (1 mg/d) with rapid improvement of her constitutional symptoms and inflammatory markers. Shortly later an oral corticosteroid (prednisone 37.5 mg/d) was introduced. We excluded underlying hematological disease or inflammatory bowel diseases. A total body CT (performed to investigate concomitant systemic disease) revealed uniform wall thickening of the supra-aortic trunks, of the medial trait of ascending aorta and of the aortic arch, which led to suspect a large vessel vasculitis. Physical examination did not show reduced arterial peripheral pulses or vascular bruits. According to the classification criteria of the *American College of Rheumatology*, in view of the presence of PG, asymmetric involvement of supra-aortic trunks, history of arterial hypertension, absence of signs consistent with vasculitis of the temporal arteries, absence of sudden visual loss, new temporal headache or morning stiffness in shoulders/neck, we classified the patient with TAK despite her age. Two months after discharge, at outpatient evaluation, the inflammatory markers were improved (CRP 0.8 mg/L, ESR 26 mm/1st hour) and the skin ulcer was healed. In the light of the control of both TAK and PG, prednisone was gradually tapered and methotrexate was introduced as maintenance.
Discussion: A review of the literature identified 18 similar cases of PG associated with TAK. Differently than in Asian populations, the association of TAK and PG is rare in Caucasian patients with only three reported cases. PG can occur at any stage of the disease process of TAK. As in our clinical case, PG and TAK were diagnosed simultaneously in other three cases. Our case is unique since our patient presented with PG without any other clinical symptom or sign of TAK, despite consistent imaging. This evidence supports the notion of TAK as a difficult-to-diagnose, insidiously presenting disorder requiring a high index of suspicion.
Conclusion: The remarkable clinical association between TAK and PG should encourage physicians to take into consideration TAK when diagnosing PG. Early diagnosis and prompt treatment can improve the prognosis of TAK by preventing vascular complications.

34. A RARE CASE OF PULMONARY-RENAL SYNDROME

Colavolpe L.[1], Lombardi R.[1], Tiraboschi S.[2], Serafino S.[2], Spreafico S.[2], Fracanzani A.L.[1]
[1]SC Medicina Interna-Indirizzo Metabolico; Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy; [2]Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Milan, Italy; [2]1. SC Medicina Interna-Indirizzo Metabolico; Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy

Case-report: A 61-year-old Caucasian man has been complaining for two

months serotine fever with shivering, shoulder and pelvic girdles arthro-myalgia, weight loss of about 10kg, headache and asthenia. He denied travels abroad, contact with animals and drugs abuse. His vital signs were normal and physical examination revealed only proximal muscle weakness in the four limbs, cough and bilateral basal pulmonary crackles. He was hospitalized in another centre two months before because of the same symptoms and he was diagnosed only with Sars-Cov2 infection. During the stay the patients was also diagnosed with a new onset renal insufficiency (serum creatinine 2 mg/dL), not further investigated. However, due to the persistence of his clinical conditions, he was currently readmitted to the emergency department and hospitalized in our ward.
In his past medical history, he had coronary artery disease, thalassaemic trait, hypertension and psoriasis in topical therapy.
Because of the fever, in the suspicion of an infectious disease, urine, blood and cough coltures, Borrelia, Brucella, Leishmania, Toxoplasma, HIV, CMV, EBV and hepatitis serology, anti-streptolysin titre, Legionella and pneumococcal urinary antigens, PCR Multiplex for lung viruses and bacteria and Quantiferon test were requested, but revealed only low-burden active hepatitis B. The diagnosis of endocarditis was excluded by a transoesophageal echocardiogram. Blood tests showed mild leucocytosis and elevated CRP (35 mg/dl) and worsening of renal function (creatinine 4 mg/dl), along with a polyclonal hypergammaglobulinemia without monoclonal component nor Bence-Jones proteinuria. In addition, a multifactorial normocytic anaemia was also found (Hb 7.9 g/dl), possibly consequent to the renal failure, the inflammatory state and the thalassaemic trait. Any blood loss was excluded by gastroscopy and colonoscopy. A chest and abdomen CT scan with contrast ruled out a neoplastic disease, showing only bilateral fibrosing interstitial disease, honey-combing like and thromboembolism of the segmental branches of the middle lobar artery, so that the patient was started to calcium heparin.
Given the presence of fever, headache, girdles arthro-myalgia and worsening of renal function, the suspect of an autoimmune disease arose. The electromyography ruled out a myopathy and described a chronic neurogenic distress. A doppler US of the temporal arteries ruled out a Horton arteritis and an autoimmune screening revealed only positivity for ANA (title 1:320) and p-ANCA (MPO). A total-body PET detected an uptake at the level of bilateral renal cortices, without interest of medium and large vessels. Urinalysis with second level sediment showed proteinuria (1g/l in 24h), microhaematuria and hyaline-granular casts. Finally, the patient underwent a renal biopsy which showed a necrotizing extra capillary proliferative pauci-immune glomerulonephritis.
At this point, due to the presence of p-ANCA, pauci-immune glomerulonephritis and fibrosing interstitial pulmonary disease, according to the most recent diagnostic criteria, microscopic polyangiitis was diagnosed and high-dose steroid treatment was started with methylprednisolone 750 mg for three days followed by prednisone 1 mg/kg, along with rituximab (1g the first day and 15 days apart). Therapy with entecavir, to suppress HBV viraemia, and prophylaxis for pneumocystis pneumonia with aerosol Pentamidine was added. To complete the vessels study, in the presence of systemic vasculitis, and to exclude an overlap with Polyarteritis nodosa, a brain angio-MRI and Doppler US of abdominal vessels were performed and resulted negative. Progressively a gradual improvement of symptoms and a decrease in inflammatory indexes were observed (CRP was 0.9 mg/dl and WBC 11000/ul at the discharge). However, unfortunately the patient developed end-stage-renal-disease at grade IIIB requiring nephrological follow-up. He also started pneumological follow-up for pulmonary fibrosis. Four months later, he also developed a life-threatening Pneumocystis jirovecii pneumonia, as a consequence of immunosuppressive therapy, despite prophylaxis and his renal failure worsened at pre-dialytic stage.
Discussion: Our case illustrates a microscopic polyangiitis, that is a rare, systemic, necrotizing, pauci-immune, ANCA associated small vessels vasculitis, without a granulomatous inflammation. Diagnosing microscopic polyangiitis is often difficult because of its presentation characterized by a number of non-specific symptoms, and sometimes the new onset of unexplainable renal impairment could arise the suspect. Despite the presence of diagnostic and treatment guidelines, identification remains still a challenge because of the small number of cases. As a consequence, providing a prompt and adequate therapy to these patients, able to prevent complications, sometimes could be difficult, as in our case. Furthermore, immunosuppressive therapies have many side effects, first of all the infectious risk, which is still today the leading cause of death in patients suffering from immuno-rheumatological diseases.

35. A NOVEL LIKELY PATHOGENETIC VARIANT OF THE MEN1 GENE ASSOCIATED WITH GLUCAGONOMA: A CASE REPORT

Smirne C.[1], Giacomini G.M.[1], Berton A.M.[2], Pasini B.[3], Crobu M.G.[4], Prodam F.[5], Caputo M.[5], Aimaretti G.[6], Ghigo E.[2], Pirisi M.[1]
[1]Internal Medicine Unit, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy; [2]Department of Medical Science, Division of Endocrinology, Diabetes and Metabolism, University of Turin, Turin, Italy; [3]Department of Medical Science, Medical Genetics Unit, University of Turin, Turin, Italy; [4]Laboratory of Molecular Virology, Maggiore della Carità Hospital, Novara, Italy; [5]Endocrinology, Department of Health Sciences, University of Piemonte Orientale, Novara, Italy; [6]Endocrinology, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy

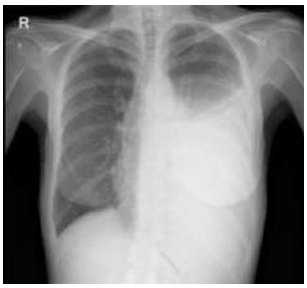
Background: Multiple endocrine neoplasia type 1 (MEN1) is a rare inherited condition caused by mutations in MEN1 tumor suppressor gene and characterized by a predisposition to the development of endocrine tumors. Most of these are usually benign, but can create striking clinical effects because of the secretion of endocrine peptides. In this respect, multiple parathyroid tumors causing primary hyperparathyroidism are the most common manifestation. Much more rarely, as in this case, glucagonomas may be present (with a reported annual incidence of 0.05-0.1/5,000,000).
Aim: The objective of the present study was to report on a family affected by MEN1, with particular concern on the possible predisposing genetic defects.
Methods: A 35-year-old Pakistani female -which had been previously diagnosed with primary hyperparathyroidism and treated with bilateral parathyroidectomy- was hospitalized for relapsing moderate hypercalcemia and new-onset diabetes. A thorough medical work-up (including laboratory, imaging and histological examinations) was conducted which resulted in a final diagnosis of MEN1: the most notable finding was the presence of multiple pancreatic glucagonomas. More in detail, technetium T-99 sestamibi parathyroid scintigraphy detected two lesions were compatible with residual adenomas. Following the detection of hyperglycemia, glucagon dosage was also required, which resulted slightly elevated (252 ng/L).
On suspicion of pancreatic glucagonoma, the patient underwent a nuclear magnetic resonance of the abdomen, which disclosed multiple pancreatic masses with maximum diameter of 16 mm and a left adrenal mass of 22 mm. Pancreas exocrine function and gastrin levels were normal. To better characterize the newly identified lesions, a positron emission tomography (PET)/computed tomography with 68Ga-DOTATOC was performed, which confirmed multiple intense 68Ga-avid areas in the pancreas head, body and tail, confirming the presence of pancreatic neuroendocrine tumors. To exclude secreting adrenal adenomas, a dosage of testosterone, dehydroepiandrosterone sulfate, urinary cortisol and urinary metanephrines was performed, all resulting within normal limits. Following high clinical suspicion for MEN1, pituitary gland was evaluated with a laboratory workup and a targeted imaging that excluded pituitary adenomas. Physical examination revealed multiple smooth skin-colored papules of 0.5 cm diameter all over the abdomen, which at biopsy were compatible with skin collagenomas, a typical non-endocrine manifestation of MEN1.
The patient finally performed a total pancreatectomy, splenectomy and left adrenalectomy. Pancreas histological examination confirmed multiple neuroendocrine well-differentiated tumors; immunohistochemistry showed strong positive staining of the neoplastic cells with anti-glucagon antibody. Left adrenal gland was confirmed as a benign well-differentiated adenoma.
Currently -about two years after the second surgery- the patient has been followed-up until recently at our endocrinology outpatient clinic: no new tumor masses have since appeared, but her diabetes shows persistent poor control. Moreover, a skin rash appeared at the left leg, which was diagnosed as necrolytic migratory erythema. Finally, for what concerns her relapsed hyperparathyroidism, she is still awaiting a second parathyroidectomy, because the surgical intervention was delayed because of SARS-COV-2 pandemic and then the patient moved abroad.
During the clinical workup a patient's blood sample was sent to genetics laboratory searching for mutations related to MEN1 to confirm the clinical diagnosis. Search for point mutations was performed through next generation sequencing (NGS) applied to the analysis of the coding regions of a selected panel of 24 endocrine tumor genes. No mutations were found in the tested regions. However, a new variant in exon 4 of MEN1 gene [c.703T>C (p.Cys235Arg)] with a possible pathogenetic effect was found. Following a genetic consult, the same variation was searched and found in the 11-year-old daughter: she was offered a screening test for MEN1-related diseases, but her mother refused because the family was in the meantime moving abroad.

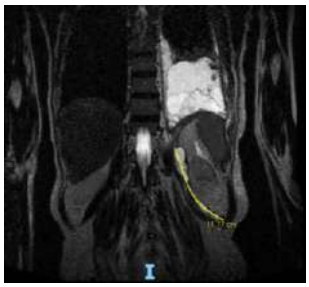
We additionally explored the functional and structural consequences of the identified variant using *in silico* analyses. The rational resides in the fact that this substitution is of non-conservative type, being between a hydrophobic and a basic amino acid. Moreover, it involves a residue that is almost invariant in evolution, inside the interaction domain with the FANCD2 protein. In particular, the cysteine 235 residue is located at the border between the beta-sheet region 6 and the alpha helix 9. The crystallographic structure of the protein indicates for this residue an "internal" (burried) position and a high score of intolerability towards any amino acid substitution. Indeed, all main bio-informatics prediction models reported intolerability of substitution in arginine.
Conclusions: Our findings establish a likely pathogenic role for this new variant, at least in the rare subset of MEN1 associated with glucagonomas.

36. WIRSUNG ATRAUMATIC RUPTURE COMPLICATED BY REFRACTORY PLEURAL EFFUSION DUE TO PANCREATIC FISTULA, TEN DAYS AFTER COLONOSCOPY: A CASE REPORT

Rigoldi C., Scarpellini F., Maestroni S., Di Cara M., Fanin A., Benetti A.
Dipartimento di Medicina Interna, Ospedale Papa Giovanni XXIII Bergamo

Background: Generally, Wirsung rupture is a consequence of major trauma, rupture of pancreatic pseudocysts or pancreatic cancer. In this clinical case, reviewing patient's history, it was hypothesised a role of the colonoscopy performed ten days before symptom's presentation.
Case presentation: A 57-year-old woman with a three-year history of diarrhea and an uncertain diagnosis of inflammatory bowel disease ('nonspecific diffuse inflammation' at a colonoscopy performed 10 days before) presented in Emergency Department with pain in the upper abdominal quadrants and dyspnoea. The chest X-ray revealed a left massive pleural effusion with lung disventilative consolidation and initial mediastinal shift (Fig. 1), whereas abdominal ultrasound was negative for acute findings. Because of respiratory acute failure, supplemental oxygen therapy was administrated and a diagnostic and therapeutic thoracentesis was performed with drainage of 2300 ml of greenish-brown pleural fluid, positive for amylase and lipase enzymes, which were high also in blood tests. The patient was transferred to the Internal Medicine department. Chest and abdominal Computer Tomography scan showed a suspected colo-pleural fistula with a retroperitoneal fluid collection; however opaque enema resulted negative. Because of pleural fluid production persistence, a Magnetic Resonance of the upper abdomen was executed, revealing Wirsung rupture with a pancreatic leak extending to the retroperitoneal collection (Fig. 2). The patient undergone endoscopic retrograde cholangiopancreatography with stent placement and subsequent full recovery.
Conclusions: Reviewing literature, there is no association between Wirsung rupture and colonoscopy, whereas rare colonoscopy complications reported are spleen rupture, bleedings, acute appendicitis and diverticulitis. In this clinical case main causes of Wirsung rupture was ruled out. Maybe the anatomical shape and/or the inflammatory gastrointestinal status of this patient played a role.
Key words: Case report, Wirsung rupture, pancreatic leak, pleural effusion, colonoscopy.





37. ATRIAL FIBRILLATION IN PATIENT WITH IMMUNE THROMBOCYTOPENIA: A COMPLEX DIAGNOSTIC AND THERAPEUTIC CHALLENGE

Chiara E.[1], Mazzetti M. [2], Silvestri E.[3], Littera M.[2], Tamburini C.[2], Prisco D.[3]
[1]Università degli Studi di Firenze; [2]SOD Medicina Interna Interdisciplinare, AOU Careggi; [3]SOD Medicina Interna Interdisciplinare, AOU Careggi; Università degli Studi di Firenze

Introduction: Immune thrombocytopenia (ITP) is a rare acquired autoimmune disorder characterized by a low platelet count resulting from platelet destruction and impaired platelet production (incidence 2-5 per 100.000 persons in the general population). ITP can be an isolated primary condition, or it may be secondary to other conditions such as autoimmune disorders, infections and malignancies. We described a 74-year-old female patient with a severe and corticosteroid-resistant ITP with concomitant diagnosis of atrial fibrillation.
Case report: A 74-year-old female was transferred to our department to further investigate the causes of ITP and to establish the consequent second line therapy. The diagnosis of ITP was made 1 years ago after the onset of spontaneous hematomas and she was treated with corticosteroids. Despite this therapy, the patient presented a relapse of ITP together with a symptomatic new onset of AF (anamnesis of hypertension). During the previous hospitalization the most frequent causes of ITP were investigated: the results were remarkable only for low-title positivity of antiB2GPI and anti-cardiolipin antibodies, ANA 1:320 pattern homogeneous; a bone marrow biopsy (BMB) was also negative. She poorly responded to first line therapy with high dose of intravenous corticosteroid and IVIG. At the admission to our department the platelet count was 5.000/mm3 under therapy with 75 mg of oral prednisone. At the physical examination we noticed an atypical hyperpigmented lesion on the left gluteus appeared in the last 2 months. The ECG confirmed AF (CHA2DS2-VASc =3). Firstly, we re-started the diagnostic workout for ITP, including serology for viruses, H. pylori stool antigen test, peripheral blood immunophenotype, autoantibodies and a total-body PET/CT scan. Simultaneously, we tried a new loading-dose of iv corticosteroid associated with short-course IVIG taking into consideration the persistence of severe thrombocytopenia. We confirmed the presence of low-title antiB2GPI and anti-cardiolipin antibodies with negative 7-Anti-B2GP1-Domain1 and ANA 1:160, that we considered not significant in the absence of other diagnostic criteria of APS. The total-body imaging was negative for malignancy. The only new finding was the positive stool antigen test for H. pylori, so we started the eradication therapy with association of amoxicillin + clarithromycin + PPI for 14 days. The hyperpigmented lesion was evaluated by dermatologist and plastic surgeon with indication to surgical asportation to exclude melanoma. We planned the surgical procedure increasing the platelet count by using platelets concentrates with a target of 30.000/mm3 PLT. Despite the therapies described and after removal of the lesion, the patient experienced continuous relapses with platelet count <10.000/mm3 over 1 month and purpuric cutaneous lesions appeared in the absence of major bleedings. After a multidisciplinary discussion with haematologist, oncologist and immunologist, we decided to start subcutaneous romiplostim, that showed a safer thrombotic profile than eltrombopag considering the contemporary presence of AF; we excluded rituximab due to the suspicion of melanoma with the ongoing histologic exam. During the first two weeks we observed a poor response. The histologic exam confirmed the presence of superficial-spreading melanoma (AJCC stage VIII, pT1a) with indication to margins extension that was also performed. However, after increasing the dose of romiplostim (6 mcg/kg/week) and 1 months after the first surgery, the platelet count started to grow up to 70.000/mm3 at the discharge. We planned an oncologic and hematologic follow-up and a specialistic outpatient visit to introduce oral anticoagulant for AF after the eventual demonstration of a stable platelet count over 50.000/mm3. We also suggested an EGDS to evaluate H. pylori eradication. After 1 months of therapy the patient stopped romiplostim with the resolution of thrombocytopenia and started apixaban 5 mg BID. The melanoma was only set in follow-up.
Discussion: We observed a corticosteroid-resistant case of ITP with a therapeutic conflict for the contemporary presence of AF. The turning point of this complex clinical picture was to find the aetiology of ITP in order to establish the correct treatment, choosing between thrombopoietino-mimetic and immunosuppressants. Although the presence of low titre of antiphospholipidic antibodies, the patient did not fulfil the criteria for APS; furthermore, although H. pylori is mentioned as a cause of ITP, the efficacy of eradication therapy in raising platelets is still controversial. Therefore, we believe that the underlying cause of ITP was melanoma. We did not find cases of association between these two conditions in literature, but a moderate number of patients with melanoma treated with immunocheckpoint inhibitors developed thrombocytopenia, suggesting that the immune system could produce antibodies directed against both platelets and cancerous cells. In conclusion, this case underline that only an accurate diagnosis can lead to correct therapeutic approaches, also when the clinical scenario seems too difficult.

38. ANCA NEGATIVE PAUCI-IMMUNE RENAL VASCULITIS

Mauceri F.[1], Bosco V.[1], Nicotra V.[1], Piro S.[2], Urso S.[3]
[1]Department of Clinical and Experimental Medicine, Internal Medicine, Garibaldi Nesima Hospital, University of Catania; [2]Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy; [3]U.O.C. Nefrologia, Garibaldi-Nesima Hospital

Introduction: Pauci-immune crescentic glomerulonephritis (PICGN) is the most common rapidprogression glomerulonephritis cause that could take to renal deficiency into some days or weeks.The disease immunological classification is based on the presence or absence of ANCA directedtowards proteinase 3 (PR3-ANCA) or myeloperoxidase (MPO-ANCA). We describe a clinical case ofpatient with negative ANCA PCGN.CLINCAL CASE. A man of 47 years with acute renal failure (creatinine 6.54 mg/gl, urea 196 mg/dl)and valid and present diuresis. During hospitalization he has undergoing Abdominal Echography,Abdominal- Thoracic TC and Superior Abdominal RM, these investigations have shown nothingrelevant, just two hepatic angiomas. Patient was subjected to Renal Biopsy, for a bettertherapeutical-diagnostic process, with ''paucimmune necrotizing crescentic glomerulonephritis"diagnosis. Cell crescents, focal fibrinoid necrosis, and basement membrane rupture have been foundto a histological and glomerular level. These findings, according to laboratory clinical value (acuterenal failure in uremic phase), allowed us to underging the patient to a peritoneal dialysis treatment,prior peritoneal catheter's placement. Well, given the histological outcome and the diseaseprogression, patient started intravenous methylprednisolone therapy for three days, thenprednisone orally and intravenous monoclonal antibodies therapy (Rituximab) with good clinical-patient response.DISCUSSION. Pauci-immune glomerulonephritis without antineutrophil cytoplasmic antibodies(ANCA) is about 10% of pauci-immune glomerulonephritis. Compared to ANCA-positive PICGN,patients with negative ANCA have an earlier onset of disease and the prevalence of extrarenalinvolvement is significantly lower in ANCA-negative patients against of more severe renal damage,as demonstrated by our clinical case. The literature data also suggest that patients without ANCAhave fewer systemic signs and/or symptoms (myalgia, fever, weight loss). Our case report thereforeconfirms that the presence of antineutrophil cytoplasmic antibodies can be interpreted as a markerof generalized vasculitis in patients with PICGN. A specific treatment protocol for ANCA negativePICGNs has not yet been codified and the therapy is based on the protocol used for ANCA-positivevasculitis. Specifically, the therapy includes: a first phase with the aim to rapidly slow down theinflammatory process by limiting tissue damage and a second phase with the aim to reduce thedisease recurrence. In the induction phase, current protocols recommend the combination ofglucocorticoids with cyclophosphamide or rituximab. Glucocorticoids play a key role in the vasculitismanagement and current guidelines suggest starting therapy with intravenous methylprednisolone(ranging from 500 to 1,000 mg, per day) for 3 days and then continuing therapy with oral prednisone1 mg/kg per day (maximum 60-80 mg/day) for 2-4 weeks with subsequent tapering. In addition tosteroid treatment, the use of rituximab (375 mg/m2) once a week for one month is increasinglyconsolidated. Rituximab, a chimeric anti-CD20 monoclonal antibody, has been shown the diseaseremission induction and is indicated in patients with relapsing disease and/or contraindication tocyclophosphamide use. The cyclophosphamide management, although highly efficiency, ischaracterized by considerable toxicity whether it is administered orally (2 mg/kg) or intravenously(15 mg/kg). Finally, in the management of the patient with vasculitis, a new therapeutic approachuseful to favoring disease remission is represented by plasmapheresis. The rationale to using thismethod is the removing possibility of all those inflammatory mediators that are involved in thepathogenesis of vasculitis, reducing tissue damage and disease progression.CONCLUSION. Patients with ANCA-negative pauci-immune crescentic glomerulonephritis representa non-negligible number. The presence or absence of anti-neutrophil cytoplasmic antibodies, as wellas having a key role in pathogenesis, also plays a key role in the clinical disease variability. Thetreatment, as for that of patients with positive ANCA, involves the immunosuppressant drugs use ascorticosteroids, cyclophosphamide, and rituximab as well as the plasmapheresis use in selectedcases.REFERENCES.- Sampathkumar K et al. ANCA negative pauci-immune glomerulonephritis with systemicinvolvement. Indian J Nephrol. 2010 Jan;20(1):43-7.- Chen et al. ANCA-negative pauci-immune crescentic glomerulonephritis. Nat Rev Nephrol 5,313–318 (2009).

39. A CASE OF RENAL PLASMACYTOMA IN A PATIENT COVID-19 POSITIVE

Bosco V.[1], Mauceri F.[1], Nicotra V.[1], Piro S.[2], Urso S.[3]
[1]Department of Clinical and Experimental Medicine, Internal Medicine, Garibaldi-Nesima Hospital, University of Catania, 95122 Catania, Italy; [2]Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy; [3]U.O.C. Nephrology, Garibaldi-Nesima Hospital, 95122 Catania, Italy

Introduction: Renal plasmacytoma (RP) is a rare clinical condition due to a single clone's neoplastic proliferation of plasma cells inside the kidney. Extramedullary plasmacytoma can represent primary symptom of multiple myeloma (MM), develop during the malignant hematologic disease or occasionally occur as solitary tumors. We describe a case report of a patient in whom the diagnosis of multiple myeloma and renal plasmacytoma was made simultaneously, starting from renal failure.
Case Report: 53-year-old man with acute renal failure (creatinine 9.30 mg/dl and urea 283 mg/dl) and a recent episode of acute anemia due to gastric ulcers. The clinical evolution was characterized by the positive finding of the swab for the search for COVID19 on the first day of hospitalization. Due to the degree of renal impairment, the patient was started on emergency hemodialysis treatment by means of femoral CVC. Furthermore, during routine examinations, it was documented a clinical-laboratory pattern compliant with micro-molecular multiple myeloma. Bone marrow biopsy documented a histological and immunophenotypic pattern mature B-cell plasmacell neoplasia compliant by multiple myeloma. Given the severity of onco-haematological pathology and the commonly accepted patient management (patient affected by multiple myeloma positive but asymptomatic for Covid-19) decision was made about anti-myeloma treatment: VD therapeutic scheme. The evolution was also characterized by positivity for high titer of CMV-DNA (28.500 copies) for which it was started targeted antiviral therapy with Ganciclovir and supportive therapy with IV immunoglobulins. The patient also underwent a renal biopsy with a diagnosis of cast-associated extramedullary plasmacytoma nephropathy and positivity for immunoglobulin kappa light chains at the level of the intratubular cylinders and of the interstitial and intravascular plasmacytoid neoplastic elements.
Discussion: Extramedullary plasmacytoma may coexist with multiple myeloma and may present as the main symptom of malignant hematologic disease. The presence of an extramedullary plasmacytoma indicates an aggressive form of the disease because there is the ability of a clone or subclone to thrive and grow independently of the marrow microenvironment. There are few cases of renal plasmacytoma documented in the literature because the main extramodular locations of plasmacytoma are head and neck. However, the cases of renal plasmacytomas are certainly underestimated especially in the secondary forms to MM and in fact the few cases of renal plasmacytomas documented in the literature are primitive forms in which the presence of MM has been excluded. Renal insufficiency is frequent in patients with MM and together with anemia, osteolytic lesions and hypercalcaemia define the "CRAB" score. Renal impairment in patient with MM by far exacts the worse prognosis. For this reason, acute renal failure in patients with new onset multiple myeloma is often not investigated histologically. However, more frequent use of renal biopsy in patients with hematologic malignant disease could certainly increase the incidence of renal plasmacytomas. The decision to perform renal biopsy in a patient with MM and AKI obviously needs to be guided by the added risks and benefits to the patient.
Conclusions: Renal biopsy plays a vital role in the study of myeloma multiple patients with acute kidney injury because it can identify causes of secondary nephropathies or identify uncontrolled proliferation of plasma cells and their infiltration into the kidney.
References: Renal plasmacytoma: Report of a rare case and review of the literature.
Refractory primary extramedullary plasmacytoma in kidney: a case report.

40. MALNUTRITION AND DECREASED SWALLOWING FUNCTION IN SARCOPENIC DYSPHAGIA: A CHICKEN AND EGG SITUATION

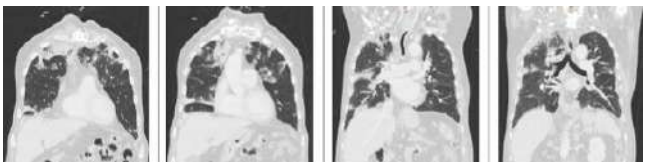
Fuda D.[1], Ferrari C.[1], Palmese F.[2], Domenicali M.[2]
[1]Department of Medical and Surgical Sciences, Alma Mater Studiorum-University of Bologna, Bologna, Italy; [2]Department of Medical and Surgical Sciences, Alma Mater Studiorum-University of Bologna, Bologna, Italy. Department of Primary Health Care, Internal Medicine Unit addressed to Frailty and Aging AUSL Romagna, Ravenna, Italy

Introduction: In an increasingly elderly population like the Italian one, particular attention must always be paid, both during hospitalization and after discharge, to the nutritional status and physical constitution of our patients, as they could conceal dangerous and potentially lethal outcomes.
Case Report: The case reported is about an 80-years old woman who used to live alone at home, autonomous in her daily chores and without cognitive symptoms (ADL 6/6; IADL 8/8) but with her family members available for help. About her medical history, she was obese (BMI 38) and hypercholesterolemic (treated with statin), diabetic in oral treatment [1], osteoporotic with multiple vertebral collapse and affected by right hip's osteoarthritis.
In April 2020 she was hospitalized for severe respiratory failure due to sars-cov2 infection. During hospitalization she was treated with corticosteroids and ventilatory support. She also lost 10 kg with a concomitant reduction of her BMI [2] [3].
After discharge she presented inappetence and further weight loss. In addition, her autonomy worsened (ADL 5/6; IADL 6/8), with functional impotence of the right hip and initial bed rest. Therefore, she decided to embark on a low-calorie diet on the advice of an acquaintance, without the supervision of a professional, thinking it would improve her functional recovery. However there was a clinical worsening, with postprandial gastroesophageal reflux and cough [4] [5].
In addition, in May 2021 she underwent right hip replacement surgery. The postoperative was complicated by nosocomial pneumonia with severe respiratory failure and necessity of intensive care with further weight loss. These complications resulted in a delay in rehabilitation program, which began after 40 days, associated with the need of walking aids.
At geriatric evaluation, the patient appeared cognitively intact but with reactive depression, not self-sufficient (ADL 3/6; IADL 4/8) and malnourished. In fact, the daily protein intake was 1/3 of the recommended one.
In conclusion, in July 2021 a high calorie density diet and protein supplementation was prescribed by the dietician. Additionally, she underwent a gradual but progressive motor reconditioning, with an improvement of autonomy (ADL 5/6; IADL 7/8) and gait with walking stick.
Discussion: Sarcopenic dysphagia is a pathological condition that very often goes unnoticed by clinical observation because of its non-specific and vague symptoms [4]. For example, a depressed swallowing strength may cause silent aspiration with blunted cough reflex and pneumonia; this leads to eating disorder, poor oral protein intake and malnutrition. The subsequent sarcopenia determines a reduction in swallowing muscles' mass and a worsening of dysphagia [5].
For this reason, it should be suspected in patients with malnutrition and gastroesophageal reflux with associated cough, as they may be both the cause and the result of each other in a continuous vicious circle in which is almost impossible to determine the true origin [4] [5].
Conclusion: When recognized, correct nutrition and motor rehabilitation must be started in order to obtain an increase in muscle mass and a reduction of other health issues related to dependence [6].
[1] Izzo A, Massimino E, Riccardi G, Della Pepa G. A Narrative Review on Sarcopenia in Type 2 Diabetes Mellitus: Prevalence and Associated Factors. Nutrients. 2021 Jan 9;13(1):183. doi: 10.3390/nu13010183. PMID: 33435310; PMCID: PMC7826709
[2] Piotrowicz K, Gąsowski J, Michel JP, Veronese N. Post-COVID-19 acute sarcopenia: physiopathology and management. Aging Clin Exp Res. 2021 Oct;33(10):2887-2898. doi: 10.1007/s40520-021-01942-8. Epub 2021 Jul 30. PMID: 34328636; PMCID: PMC8323089
[3] Klein GL. THE EFFECT OF GLUCOCORTICOIDS ON BONE AND MUSCLE. Osteoporos Sarcopenia. 2015 Sep 1;1(1):39-45. doi: 10.1016/j.afos.2015.07.008. PMID: 26557727; PMCID: PMC4635469
[4] Dellis S, Papadopoulou S, Krikonis K, Zigras F. Sarcopenic Dysphagia. A Narrative Review. J Frailty Sarcopenia Falls. 2018 Mar 1;3(1):1-7. doi: 10.22540/JFSF-03-001. PMID: 32300688; PMCID: PMC7155347
[5] Ebihara T. Comprehensive Approaches to Aspiration Pneumonia and Dysphagia in the Elderly on the Disease Time-Axis. J Clin Med. 2022 Sep 10;11(18):5323. doi: 10.3390/jcm11185323. PMID: 36142971; PMCID: PMC9504394
[6] Chen KC, Jeng Y, Wu WT, Wang TG, Han DS, Özçakar L, Chang KV. Sarcopenic Dysphagia: A Narrative Review from Diagnosis to Intervention. Nutrients. 2021 Nov 12;13(11):4043. doi: 10.3390/nu13114043. PMID: 34836299; PMCID: PMC8621579

41. DAPTOMYCIN-INDUCED EOSINOPHILIC PNEUMONIA: A CASE OF ACUTE RESPIRATORY FAILURE

Cagnin S.[1], Torres S.[1], Cola M.[2], Angeli P.[1], Di Pascoli M. [1]
[1]Unit of Internal Medicine and Hepatology (UIMH), Department of Medicine (DIMED), University-Teaching Hospital of Padova, Padua, Italy; [2]Infectious Diseases Division, Department of Medical Sciences, University-Teaching Hospital of Padova, Padua, Italy

Background: Acute eosinophilic pneumonia is a rare lung condition which can be idiopathic or secondary. Drug-induced eosinophilic pneumonia is most frequently caused by daptomycin and mesalamine, but its prevalence is not known due to lack of consistent pharmacovigilance reports. It can be a rapidly progressive and severe lung condition, leading to an increase in morbidity and mortality. Temporal association between drug initiation and the development of symptoms is a key factor for diagnosis that needs to be confirmed by invasive tests.
Case: A 83 year-old male was hospitalized because of a left psoas muscle abscess and prosthetic aortic valve endocarditis caused by *Streptococcus gallolyticus*. The patient was treated with ceftriaxone 2g ev od, daptomycin 8 mg/kg/die and radiological drainage of the abscess was necessary. Following an initial improvement, after 2.5 weeks of therapy the patient developed acute dyspnea with hypoxemic respiratory failure and fever, needing oxygen supplementation. Medical tests ruled out heart failure and myocardial infarction, pulmonary thromboembolism and active pulmonary infection; CT scan revealed areas of parenchymal consolidation in both lungs, with perilar and mantle distribution, more extensive at the apices where thickening of the contextual interstitium with areas of ground-glass in adjacent regions were noted. No signs of septic emboli were found. Laboratory findings included an increased C-Reactive Protein and an increase in eosinophils (up to 1.51 x10^9/L). Broad microbiological tests were all negative and daptomycin-induced pneumonia was suspected. The case was evaluated by Pneumologist and Infectious Disease specialist, and we decided to discontinue daptomycin. A fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) was inconclusive, showing contaminants from the upper air-digestive tract that didn't allow a reliable eosinophil count. As the diagnosis of daptomycin-induced eosinophilic pneumonia was still probable according to the diagnostic criteria, metilprednisolone 40 mg od was started, with rapid improvement of respiratory failure and resolution of radiological findings. The BAL was not repeated due to improvement with therapy and refusal of the patient to undergo another invasive procedure.
Discussion: Drug-induced eosinophilic pneumonia is a rare condition that can complicate the clinical course of patients, and is associated with increased morbidity and mortality. It should be suspected in patients treated with a potential candidate drug, who develop fever and dyspnea with increased oxygen requirement, new infiltrates on chest X-Ray or CT and peripheral eosinophilia not explained by any other cause. The drug should be promptly discontinued and BAL should be performed, as the finding of >25% eosinophils is a key element for a conclusive diagnosis. Steroids appear to be beneficial at improving clinical manifestations of acute eosinophilic pneumonia, especially in cases where respiratory failure has developed.
Conclusion: Assessment of eosinofilic pneumonia should be considered in patients with acute respiratory failure treated with daptomycin, in the absence of other possible causes. Notification of cases to pharmacovigilance authorities is mandatory when diagnosed, as drug-induced eosinophilic pneumonia is a complication we still know little about.



42. IS IT OR IS IT NOT THE "USUAL" DYSPNEA? THAT IS THE QUESTION

Furnari M.E.[1], Leggio S.[1], Mangiafico M.[2], Impellizzieri D.[2], Stancanelli B.[2]
[1]Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy; [2]UOC Medicina Generale AOU Policlinico "G. Rodolico" - "San Marco" Catania, Italy

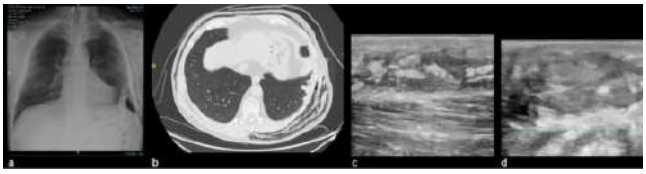
Background: *Amyloidosis* is a group of progressive infiltrative diseases characterized by extracellular deposition of amyloid fibrils: the most common

type is associated with light chain immunoglobulin (AL). Several studies demonstrated that about 75% of patients with AL amyloidosis show proteinuria, often accompanied by edema, and about two-thirds develop nephrotic syndrome. This condition, can often be misunderstood with a classic pathological pattern of heart failure with declivous edema and dyspnea.
Case report: Fifty-eight-year-old man was admitted to the emergency department of our hospital, due to the presence of anasarcatic state, with asthenia and dyspnea for approximately 20 days. His remote pathological history included hypertension, papilliferous thyroid carcinoma (surgically treated about 5 years before), Obstructive Sleep Apnea Syndrome (OSAS) on treatment with Continuous Positive Airway Pressure (CPAP), Chronic obstructive pulmonary disease (COPD). After performing a Chest X-ray (negative for bilateral multifocal alveolar opacities), swab excluding Sars-CoV2 infection and routine laboratory data, including cardiac enzymes excluding Acute Coronary Syndrome, he was admitted to our Unit of General Medicine. On examination, the patient was awake and well oriented, declivous edema was present in the lower extremities, anasarcatic state with periorbital edema was also observed. A chest Computer Tomography (CT) was performed, showing bilateral fluid-dense pleural effusion and minimal pericardial effusion, so diuretic therapy was started. On routine laboratory tests, NT-proBNP values of 507 pg/mL and troponins I HS 268 ng/L were found, in absence of troponin delta change. Transthoracic echocardiography identified an unexplained asymmetric left ventricular hypertrophy (LVH), with granular and sparkling myocardial appearance, raising the suspect of cardiac amyloidosis. Furthermore, Magnetic Resonance Imaging (MRI) and bisphosphonate scintigraphy for detecting transthyretin cardiac amyloidosis were performed. Simultaneously, data resulting from the routine urine examination on admission, where proteinuria was detected, were taken into account. So, 24-hour diuresis collection was performed, showing severe proteinuria (9847 mg). Serum immunofixation (IFE) found a very modest monoclonal component lambda, while urine immunofixation was negative. In presence of a nephrotic syndrome, it was decided to perform a transcutaneous renal needle biopsy. Renal ultrasound scan was also performed, that resulted unspecific. At renal biopsy, deposition of weakly PAS-positive amorphous substance was observed that assumed positive coloration by Congo red. The combined optical, histochemical, and immunohistochemical microscopic findings were suggestive of renal amyloidosis type AL with moderate vascular involvement, mild to moderate glomerular damage, and minimal tubulo-interstitial involvement.
Conclusions: We report this case because the patient presented with edema and dyspnea, so mimicking a "usual" presentation of decompensated heart failure. The multi-organ involvement in a relatively young patient made the diagnosis more complex. Specifically, the causes of nephrotic syndrome in adults are numerous, and renal biopsy is mandatory. Despite his relatively young age, the patient was not eligible for autologous hematopoietic cell transplantation (HCT) because he did not meet all criteria (e.g., troponin I HS ≤75 ng/mL, ECOG (Eastern Cooperative Oncology Group) performance status ≤2). Treatment with Bortezomib in combination with Daratumumab, Cyclophosphamide, and Dexamethasone (dara-CyBorD) was therefore started. Dara-CyBorD led to a faster response, delaying major organ deterioration.

43. RHEUMATOID ARTHRITIS WITH CUTANEOUS AND PLEURAL INVOLVEMENT TREATED WITH RITUXIMAB: A CASE REPORT

Andreoni S.[1], Bitca V.[1], Buongarzone C.[1], Leo M.[1], Paolucci F.[1], Principi M.[1], Benfaremo D.[2], Moroncini G.[2]
[1]Scuola di Specializzazione in Medicina Interna, Università Politecnica delle Marche, Ancona, Italy ; [2]Clinica Medica, Dipartimento di Medicina Interna, AOUM, Ancona, Italy

Background: Rheumatoid arthritis (RA) is a systemic autoimmune disease that can involve not only joints, but also other tissues and organs. Although the main cause of death in patients with RA is cardiovascular disease, lung involvement plays a relevant role in RA-related morbidity, not only in terms of interstitial lung disease, but also with the development of pleural inflammation and rheumatoid nodules. Spontaneous pneumothorax could be the initial manifestation of rheumatoid nodules, which however remain mostly asymptomatic. They could be also associated with subcutaneous nodules that represents the most common extra-articular manifestation in RA, especially in Caucasian males.
Case report: We report a case of a 56-year-old Italian male, active smoker, with a six-year history of seropositive (high titre positive rheumatoid factor-RF) and erosive RA who had developed multiple skin and pleural nodules during low dose steroid therapy. The patient presented to the emergency department with chest pain and dyspnoea. Chest X-ray showed signs of left basal pneumothorax and a pleural drainage was placed. Then a chest CT-scan was performed, showing multiple diffuse pleural nodules and residual subcutaneous emphysema. The physical examination was relevant for polyarthritis (hands, wrists, knees, ankles and feet) and subcutaneous soft painless nodules on the extensor surfaces of both the forearms; the ultrasound exam revealed subcutaneous hypoechogenic nodules with undefined edges and hyperechogenic areas without doppler signal (Figure 1). Laboratory data showed a white blood count of 6550/mL with 78% neutrophils and 14% lymphocytes, haemoglobin of 12.5 g/dL, platelets of 364000/ml, while creatinine and transaminases were within normal limits. C-reactive protein was 73 mg/L, Erythrocyte sedimentation rate 62 mm/h, RF 2410 U/ml, Anti-citrullinated protein antibodies-ACPAs 20.7 U/ml, anti-neutrophil cytoplasmic antibodies-ANCAs were negative, C3 and C4 within normal ranges. Mycobacterium Tuberculosis culture was performed on bronchoalveolar lavage (BAL) and pleural effusion but resulted negative. An excisional biopsy from a pleural nodule was performed and the histopathological examination was consistent with pleural necrotizing granulomas.
Discussion: The evidence of pleural involvement associated with typical distribution of skin nodules on major pressure areas and high titre of RF allowed the diagnosis of RA with articular and systemic involvement. The patient's prior medications for RA included methotrexate and tofacitinib (both discontinued for loss of efficacy), so we decided to treat the patient with rituximab 1 g iv (at baseline and after two weeks). The pneumothorax was resistant to multiple invasive treatments (pleural drainage, endobronchial valves and plugs) and finally was surgically treated with an endothoracic transposition of latissimus dorsi muscle's flap. After three months from rituximab, the patient noted a substantial improvement of the articular and respiratory symptoms, with a progressive reduction of the subcutaneous soft nodules, without new pleural nodules, relevant morning stiffness or arthritis flares.



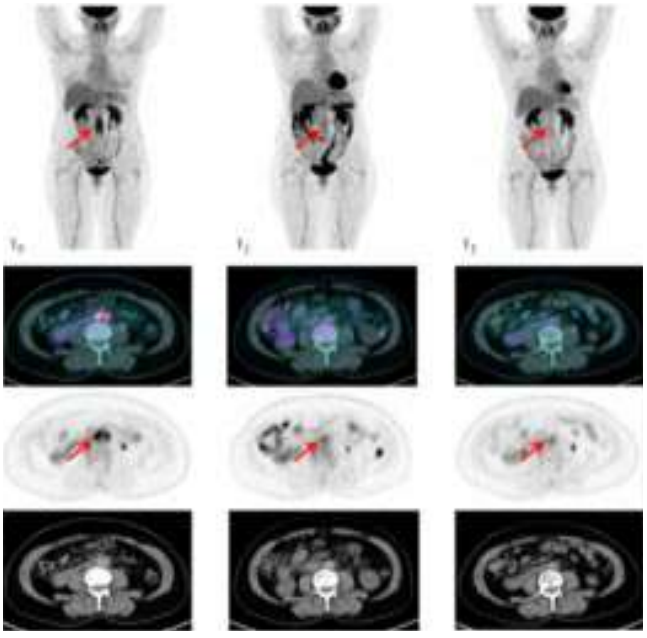
References:
Esposito AJ, Chu SG, Madan R, Doyle TJ, Dellaripa PF. Thoracic Manifestations of Rheumatoid Arthritis. Clin Chest Med. 2019 Sep;40(3):545-560. doi: 10.1016/j.ccm.2019.05.003. Epub 2019 Jul 6. PMID: 31376890; PMCID: PMC6994971.
Figus FA, Piga M, Azzolin I, McConnell R, Iagnocco A. Rheumatoid arthritis: Extra-articular manifestations and comorbidities. Autoimmun Rev. 2021 Apr;20(4):102776. doi: 10.1016/j.autrev.2021.102776. Epub 2021 Feb 17. PMID: 33609792.
Lora V, Cerroni L, Cota C. Skin manifestations of rheumatoid arthritis. G Ital Dermatol Venereol 2018;153:243-55. DOI:10.23736/S0392-0488.18.05872-8
Kim SH, Yoo WH. Recurrent pneumothorax associated with pulmonary nodules after leflunomide therapy in rheumatoid arthritis: a case report and review of the literature. Rheumatol Int. 2011 Jul;31(7):919-22. doi: 10.1007/s00296-009-1240-9. Epub 2009 Oct 28. PMID: 19862529

44. RETROPERITONEAL FIBROSIS AND HELICOBACTER PYLORI INFECTION: REPORT OF AN UNUSUAL ASSOCIATION

Agnitelli M.C.[1], Pellegrino S.[1], Ibba F.[1], Rognoni F.[1], Verrecchia E.[1], Sicignano L.[1], Gerardino L.[1], Calcagni M.L.[2], Gallo A.[1], Montalto M.[1]
[1]Medicina Interna Geriatrica, Università Cattolica del Sacro Cuore, Fondazione Policlinico Gemelli IRCCS, Roma; [2]Medicina Nucleare, Università Cattolica del Sacro Cuore, Fondazione Policlinico Gemelli IRCCS, Roma

Introduction: Retroperitoneal fibrosis (RPF), a rare disease characterized by fibro-inflammatory tissue around the infra-renal portion of the abdominal aorta and iliac arteries, is classified into primary (or idiopathic) and secondary forms. The first one is considered an immune-mediated disease that can occur in association with other autoimmune conditions, the secondary one can be associated with neoplasms, drugs, infections, surgery, radiotherapy. Since now, data about RPF secondary to infections derive from isolated case reports and the mechanisms involved are different and not clearly understood.
Case report: A 54-year-old woman referred to our Clinic complaining of

continuous back-lumbar pain irradiated in the left inguinal area, increasing in standing position. She reported no fever. She only underwent appendectomy about twenty years before. Physical examination was normal.
A lumbosacral spine magnetic resonance showed a periaortic tissue at L3 level of uncertain significance; a computerized tomography (CT) also showed hypodense tissue surrounding sub-renal aorta for 8 cm. To rule out a malignant etiology, endoscopic evaluation was performed. A colonoscopy was normal; an esophagogastroduodenoscopy with biopsies revealed *H.pylori* gastritis.
Urine, blood tests, autoimmunity serum markers and IgG4 were normal, quantiferon test negative.
A positron emission tomography (PET)-CT scan with 18F-fluorodeoxyglucose (FDG) confirmed increased uptake of the retroperitoneal tissue, with a longitudinal diameter of 73 mm (Fig. 1, T0).
The histological examination of tissue after a CT-guided needle biopsy revealed fibrosis with foci of subacute-chronic inflammation, without atypia. IgG4 immunohistochemistry reaction was negative. So, a diagnosis of an apparently idiopathic RPF was made.
Before any suppressant therapy, a first-line treatment for *H.pylori* was started, without success. Second-line treatment led to eradication of the infection. She referred complete resolution of the above mentioned symptomatology.
In absence of any other medication, three months later, a 18F-FDG PET-CT showed a marked reduction of the uptake of metabolic tracer at retroperitoneal level (Fig 1, T1).
After another three months, a second PET-CT was repeated to get updated scans; it showed metabolic inactivity of the metabolic tracer (Fig 1, T2).
Discussion: This is the first case of possible remission of RPF after eradication of *H.pylori* infection.
Primary RPF is the most common form, often immune-mediated. Secondary RPF can be associated with neoplasms, drugs, infections, surgery.
Data about infectious RPF derived from isolated case reports. Infective agents may act as trigger of a fibro-inflammatory process, like *Schistosoma spp* and *Histoplasma capsulatum*. Another mechanism consists in involvement of immune reactions, such as *M.tuberculosis*, that can induce inflammatory and autoimmune diseases. Association between *H.pylori* and RPF has never been described. *H.pylori* may cause an extragastric chronic inflammation by immune dysregulation, vascular alterations, cell injury. Our patient failed first line therapy; it is likely that infection was supported by a multi-resistant strain, may be able to cause more severe inflammation. A microbiological assessment of tissue specimen was not possible, so our relationship between *H.pylori* infection and retroperitoneal fibrosis can only be supposed. Moreover, we cannot exclude anti-inflammatory properties of antibiotics used. The excellent response to a specific antimicrobial agent represents the key element in favor of a direct link between the two conditions. Moreover, the course of disease and its rapid resolution resulted quite unusual for a primary RPF. In conclusion, RPF always requires a diagnostic effort. Since the impact of different treatment strategies according to etiology, also in the apparently idiopathic forms, search for secondary infectious causes should be encouraged.



45. POLYCYSTIC KIDNEY AND LIVER DISEASE: WHEN COMBINED TRANSPLANTATION IS UNAVOIDABLE

Perticone M.[1], Caroleo B.[2], Vallone G.[3], Cufone S.[3], Marra F.[2], Silipo M.[2], Iacopino R.[2], Dimasi C.[2], Scozzafava A.[1], Toscani A.F.[1], Salatino N.[2], Sciacqua A.[1]
[1]Dipartimento di Scienze Mediche e Chirurgiche - Università Magna Graecia di Catanzaro; [2]UO di Medicina Interna - PO "Basso Ionio" di Soverato - ASP di Catanzaro; [3]UOSD di Medicina Interna - PO "Annunziata" di Cosenza

Introduction: Polycystic kidney disease is a condition that can cause bloating syndrome; hepatic involvement is common and sometimes, it can cause a further mass effect, compressing structures such as the great venous vessels, mainly the inferior cava and the abdominal viscera and causing anorexia and weight loss; these symptoms can become so severe as to justify percutaneous surgical drainage of the cysts with temporary benefit for which, although rarely, and even if in the absence of hepatic insufficiency or portal hypertension, combined liver/kidney transplantation remains the definitively effective therapy.
Clinical case: 51-year-old hypertensive female with polycystic kidney disease with normal renal function; she was discontinued on tolvaptan due to hepatotoxicity. Two pregnancies completed at 32 and 36 years old. At the age of 47 she underwent robotic laparoscopic hysteroannexectomy for endometrial cancer; there was no indication for further chemotherapy or radiotherapy. Imaging over the years had shown the presence of some centimeter cysts in the liver. In the last 4 years the patient noticed a progressive increase in the volume of the abdomen not attributable only to the increase in the size of the polycystic kidneys but to the progressive increase in the number and volume of the liver cysts, some of which reached a diameter of about 9 cm. Having come to our observation, the objective examination revealed a globular and tense abdomen with the appreciability of numerous swellings spread throughout the abdomen; there were evident edemas of the lower limbs and also a slight dyspnoea during the dialogue and above all in the transition from the supine position to the orthostatism. She was undereating due to a sense of precocious fullness and noticed a progressively constipated bowel. The most recent blood tests revealed blood urea nitrogen/creatinine levels of 40/1.0 mg/dl; normal transaminases; gammaGT of 57 U/L, normal bilirubin, prothrombin time and albumin. The latest magnetic resonance allowed to detect a liver greatly increased in volume and unstructured due to the presence of numerous cystic formations with a maximum diameter of 8.5 cm. The inferior vena cava in his cranial tract was compressed and small in calibre. The gallbladder and extrahepatic bile ducts cannot be identified. Even the kidneys had considerably increased in volume, subverted by the presence of very numerous cysts with a maximum size of about 9 cm. Compression of the inferior cava, dyspnoea due to slight efforts, physical decay, despite normal organ function, led to sending the patient to a reference transplant centre.
Conclusions: It is difficult to hypothesize a combined replacement approach for a patient with normal liver and kidney function. On the other hand, the resolution of the encumbrance syndrome could only be obtained with a reduction in intra-abdominal pressure which had reached levels such as to undermine the quality of life and the patient's life itself; the data submitted to the literature, albeit referring to very small series, demonstrate that patients treated for abdominal obstruction syndrome with joint liver and kidney transplantation or with liver transplantation followed by kidney transplantation have a very favorable prognosis.

46. A SEVERE AND ISOLATED HYPOMAGNESEMIA REFRACTORY TO ORAL REPLACEMENT IN A PATIENT WITH LONG-TERM USE OF PPIS: CASE REPORT

Manzitto L.[1], Catania F.[1], Russo M. J.[1], Lenzo O.[1], Maiuzzo R.[1], Campanelli L.[1], Frazzetto E.[1], Privitera G.[1], Campagna C.[1], Judica A.[2], Incognito C.[1], Signorelli S.[1]
[1]Dipartimento di Medicina Generale - Azienda Universitaria Policlinico G. Rodolico; [2]UO Gastroenterologia Policlinico Gaspare Rodolico Catania

Background: Magnesium (Mg2+), one of the most important intracellular cations, is involved in numerous biochemical functions. Mg2+ intestinal absorption occurs predominantly in the small intestine, primarily in the distal jejunum and ileum *via* paracellular pathway. Furthermore Mg2+ uptake occurs in the caecum and colon through the transcellular pathway mediated by membrane channel proteins TRPM6/7. Intestinal absorption, excretion and renal re-absorption ensure Mg2+ homeostasis. We describe a case of se-

vere hypomagnesemia treated in our Internal Medicine Unit.
Case Report: A 61-year-old man was admitted at Emergency Room (ER) for visuo-spatial hallucinations, dizziness, tremors, abdominal pain, vomit and diarrhoea. Patient anamnesis: episode of myocardial infarction (with PTCA) in 2019 and cerebral ictus in 2021. Domiciliary therapy: pantoprazole, ASA, clopidogrel, rosuvastatin, bisoprolol, spironolactone, perindopril, indapamide and amlodipine. Severe hypomagnesemia (HyMg) (0.49mg/dL), neutrophilic leucocytosis (17.64 mmc3 N: 75%), and C reactive protein (PCR) (200.41mg/L) have been detected in blood tests. Neurological examination showed postural instability, nystagmus, upper limbs intention tremor without sensitivity deficit. Imaging exams (brain CT and MR) evidenced chronic cerebral vasculopathy signs. Baseline and sleep-deprived EEG were negative for epilepsy. Vestibular function tests reported posterior canal benign paroxysmal positional vertigo (PC-BPPV). Normal sodium, potassium and calcium level were found in two 24h urine collections. Plasmatic renin and aldosterone levels were normal when measured after diuretics and antihypertensives drug washout (orthostatic P-renin 14.07 microUI/mL – clinostat P-renin 6.75 microUI/mL – orthostatic P- aldosterone 4.26 ng/dL – clinostat P- aldosterone 2.87 ng/dL). Gitelman's and Bartter's syndrome were excluded by the absence of hypocalciuria, hypokalemia and normal aldosterone and renin levels in 24 h urine collection. Due to patient bowel symptoms, a stool specimen was evaluated using BioFire Film Array Gastrointestinal Panel which was then found to be positive for Klebsiella pneumoniae. Intravenous Mg2+ replacement (16mEq of Mg sulphate in 500 ml of Sodium chloride 0.9% solutions once a day) and oral antibiotic therapy (metronidazole 500 mg 3 times a day for 7 days) were administered. After replacement, Mg2+ plasma levels reached 1.7mg/dL. The patient was diagnosed with severe hypomagnesemia related to Klebsiella Pneumoniae intestinal infection and posterior canal benign paroxysmal positional vertigo and oral Mg2+replacement domiciliary therapy was prescribed. Two weeks later the patient was admitted again to ER for abdominal pain, dizziness, and widespread shivers. Laboratory finding severe hypomagnesaemia (0.3mg/dL) anew, treated with intravenous Mg replacement. Based on this data, intestinal malabsorption syndrome was suspected. Colonoscopy and EGDS were performed: diverticulosis of sigma and multiple erosions of the body and gastric fundus mucosa (Histological findings: Helicobacter pylori negative and intestinal metaplasia). Abdominal CT with contrast evidenced duodenum second part and ampullary region widespread concentric thickening with reactive lymphadenopathy. Chromogranin A (40 ng/ml) and gastrin (42 pmo/ml) excluded Zollinger-Ellison Syndrome or other NETs. Gallium-68-dotate PET/CT showed no anomalies. Considering EGDS evidences and the consequent malabsorption syndrome, IPP therapy (pantoprazole 40mg/die) has been replaced by H2 antagonist (famotidine 40mg/die). Blood Mg2+ levels were progressively restored (1.83mg/dl) and maintained also without intravenous Mg2+ replacement. The patient was discharged with the diagnosis of severe hypomagnesemia related to malabsorption in duodenitis aggravated by concomitant IPPs therapy.
Conclusions: Among electrolyte imbalances, hypomagnesemia is not the most common (occurs up to 15-20% in hospitalized patients and rises to 60-65% in critical patients). Moreover, electrolyte imbalances are frequently multiple and rarely isolated. The onset of symptomatology could focus the diagnosis on encephalic pathology, especially in a patient with history of stroke and chronic cerebral vasculopathy. Rare kidney diseases as Gitelman's or Bartter's syndrome were excluded, so we focused on possible intestinal malabsorption and PPIs role. PPIs, widely used in clinical practice, often for long periods, appear to induce HyMg through inhibition of gastrointestinal Mg2+ absorption by altering TRPM 6/7 channels. This case highlights a potentially fatal effect of long-term PPIs treatment. Our experience is reported to underline serious consequences of HyMg, especially in elderly multimorbid patients admitted in Internal Medicine Units.

47. PERIPHERAL EMBOLIZATION IN ESCHERICHIA COLI INFECTIVE ENDOCARDITIS: AN EMBLEMATIC CASE

Re M.[1], Serafino S.[1], Tiraboschi S.[1], Bustamante M.[1], Currà J.[1], Ungaro R.[2], Motta I.[3], Fracanzani A.L.[4]
[1]Medicina Interna ad Indirizzo Metabolico, Fondazione Cà Granda IRCCS Ospedale Maggiore Policlinico; [2]Malattie Infettive, Fondazione Cà Granda IRCCS Ospedale Maggiore Policlinico; [3]Dipartimento di Scienze Cliniche e di Comunità, Università degli Studi di Milano; [4]Dipartimento di Fisiopatologia Medica e dei Trapianti, Università degli Studi di Milano

Introduction: Infective endocarditis is a multisystem disease that results from infection, generally of bacterial origin, of the endocardial surface of the heart. Peripheral embolization is a major complication of infective endocarditis: septic emboli can involve almost every organ with a wide spectrum of clinical manifestations. We herein report the case of *Escherichia coli* infective endocarditis, a rare causative agent of endocarditis.
Case presentation: A 77-year-old man was admitted to our internal medicine ward for disabling low back pain in the past month; he did not report fever. The general practitioner prescribed him nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, and opioids; however, this treatment failed to resolve the symptoms. He also prescribed a magnetic resonance imaging of the spine without contrast, which showed a dural sac lesion of L3-L5. After this diagnostic test, the patient was admitted to our ward. As far as the patient's past medical history is concerned, he was diagnosed with hilar cholangiocarcinoma undergoing right hepatectomy in 2016, with negative follow-up to date, hypertension, benign prostatic hypertrophy and colonic diverticulosi. On admission, the physical examination showed the presence of jaundice, anasarca, and dehydration. Vital signs were normal, except for mild tachycardia (heart rate 96 beats/minute) and tachypnoea (respiratory rate 26 acts/minute). The 12-lead ECG showed sinus rhythm and a right bundle branch block. Laboratory tests showed increased inflammatory markers (WBC 18310uL, CRP 14.36mg/dl), microcytic anemia (Hb 7.5g/dl, MCV 77.5fl), an elevation in liver function test with hypoalbuminemia (albumin 1.9g/dl) and acute renal failure (creatinine 2.19mg/dl). The latter was presumably multifactorial due to the excessive use of NSAIDs and dehydration related to the septic state. Lactates at arterial blood gas analysis were normal. Therefore, intravenous hydration, albumin supplementation, and diuretic were started, with laboratory and clinical improvement. The patient also received blood transfusions (in total 21 units of red blood cells), plasma transfusions and supplementation with ferric carboxymaltose to correct the anemia. During the hospitalization, the patient developed fever, and a multisensitive *E. coli* was detected in the blood and urine cultures. Given the positive blood cultures, antibiotic therapy with ceftriaxone 2g/day was started. Moreover, a bone biopsy of L3-L4 was performed, which did not show any malignancy localization. The culture of bone biopsy revealed the presence of *E. coli*.
Because of the onset of vomiting of coffee ground-like material and melena, along with anemia not responsive to blood transfusions, he underwent an esophagogastroscopy that showed erosive esophagitis and duodenal ulcers. Abdominal CT scan with contrast showed suspected findings for ischemic colitis of the right colon and an enlarged spleen with multiple infarcts. Therefore, therapy with omeprazole was enhanced, and antibiotic therapy was changed, by starting treatment with cefotaxime 2g x3/day and metronidazole. Given the multiple ischemic sites, endocarditis was suspected, and transthoracic echocardiography was performed, which did not show valve vegetations. In the following days, total body CT scan was carried out, showing new possible outbreaks of spondylodiscitis of D6-D7 and D10-D11 and the presence of abscess collections in the iliopsoas and gluteal muscles and the right glen humeral joint. Abscess drainage of the gluteal collection was performed; nonetheless, the abscess culture came out negative. Due to the persistence of the fever, blood cultures were repeated and came out negative. Antibiotic therapy was therefore enhanced: cefotaxime was increased to 2g x4/day, while tigecycline and fluconazole were added. After a few days, fluconazole was interrupted, given the negativity of beta-D-glucan in two successive determinations. Because of the high suspicion of septic embolization, transesophageal echocardiography was performed, showing mobile vegetation in the noncoronary cusp of the aortic valve, which caused moderate-severe valvular insufficiency. Due to the patient's clinical frailty and the high risk of bleeding that contraindicated anticoagulant therapy, the cardiac surgeon did not suggest any surgical treatment. Consequently, antibiotic therapy was again enhanced, increasing cefotaxime to 12 g/day by continuous intravenous infusion; tigecycline was continued. In the following days, laboratory tests progressively improved and the following blood cultures came out all negative.
Conclusion: *E. coli* is the causative microorganism in approximately 0.51% of endocarditis, with a lethality of 21%, higher than those due to Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, or Kingella (the HACEK-group gram-negative bacteria). It should be suspected in the presence of previous *E. coli* genitourinary infection. Transesophageal echocardiogram should be performed when transthoracic echocardiography is negative; thus, early diagnosis and treatment are essential to avoid diagnostic delay and promptly start antimicrobial therapy.

48. MACROPHAGE ACTIVATION SYNDROME, A POTENTIALLY FATAL COMPLICATION

Natale R., Morena A., Nasti C., Bertolini N., Pasanisi F., Santarpia L. Dipartimento di Medicina Clinica e Chirurgia, Università degli Studi di Napoli "Federico II"

Macrophage Activation Syndrome (MAS) is a potentially fatal complication of rheumatological diseases, such as Systemic Lupus Erythematosus (SLE); its etiopathogenesis is related to the hyper-activation of macrophages and T lymphocytes, secondary to a cytokine storm.
B.M., 44 years old was hospitalized due to the appearance of left latero-cervical swelling, fever and widespread skin rash.
In the medical history, thrombocytopenia that arose about ten years earlier and resolved at the same time with corticosteroid therapy, Sars-Cov-2 infection in April 2022 which progressed in a paucisymptomatic way.
Upon admission, mild anemia and elevated C-reactive protein, D-dimer, and β-2-microglobulin values were evident, on the 12th day of hospitalization, the patient presented with fever and worsening of anemia with a slight reduction in platelets; the blood cultures were negative.
Antibody measurements ruled out infectious causes; fine-needle aspiration of the laterocervical lymph node did not show cellular atypia and a biopsy of the skin lesions showed a non-specific inflammatory infiltrate; a PET-CT performed for suspected lymphoproliferative disease showed increased metabolic activity (SUV max 4.7) of the spleen and several lymph node stations.
On the 16th day of hospitalization, the fever reached 40.5°C and did not respond to paracetamol or medium-dose corticosteroids. Pancytopenia was evident, and microscopic examination of the peripheral blood specimen showed anisocytosis of platelets and red blood cells.
The study of the immune system showed a slight increase in IgG, a slight decrease in C3 and C4, a positive direct Coombs test, a positive antinuclear antibodies (ANA) and a high titer positivity of anti-SSa and anti-SSb antibodies.
About the diagnostic hypotheses, Sjogren's Syndrome and hyper-IgG4 syndrome did not meet the clinical and laboratory classification criteria.
The patient's clinical situation did not improve and the body temperature continued to reach 40°C in the absence of response to antipyretics. In the following days, proteinuria appeared and the diagnosis of Systemic Lupus Erythematosus (SLE) was made, considered the presence of the other classification criteria of the disease.
On the 19th day, haemolytic anemia with even more marked pancytopenia appeared, there was an increase of ferritin LDH, D-dimer, triglycerides, AST, ALT, GGT, ALP; fibrinogen values were decreased; a diagnosis of SAM was then made in a patient with SLE according to Ravelli's criteria: fever, bilinear cytopenia, hyperferritinemia, hypertransaminasemia, hypertriglyceridemia, hypofibrinogenemia.
The patient was treated with methylprednisolone at immunosuppressive dosage with the addition of cyclosporine.
In the following days, the fever disappeared with a gradual normalization of the blood chemistry parameters; corticosteroid therapy was gradually tapered to complete discontinuation while cyclosporine therapy was continued.

49. HEMATOGENOUS PNEUMONIA CAUSED BY KOCURIA KRISTINAE IN A PATIENT WITH A CENTRAL VENOUS CATHETER

Natale R., Morena A., Nasti C., Della Pelle C., Pasanisi F., Santarpia L.
Dipartimento di Medicina Clinica e Chirurgia, Università degli Studi di Napoli Federico II

Kocuria kristinae is a gram positive commensal bacterium which is part of the normal flora of the skin and of the oral cavity. Cases of bacteraemia in immunocompromised patients have been described in the literature.
C. D., 29 years old, was hospitalized for fever with shivering during infusion of nutritional mixture through tunneled central venous catheter (CVC) with entrance into vein right jugular.
In history, colectomy with ileorectal anastomosis in perinatal age due to pseudo-obstruction secondary to intestinal agangliosis; chronic intestinal insufficiency requiring daily parenteral nutrition/fluid therapy.
On admission, physical examination was insignificant; blood chemistry tests show: normal leukocyte formula, high C-reactive protein values, procalcitonin values not significant.
Central vein and peripheral vein blood cultures and echocardiogram were performed to exclude the presence of vegetations affecting the right heart sections. It was performed a chest X-ray which shows the distal end of the CVC projecting to the cavo-atrial confluence, diffuse thickening of the pulmonary weft with bilateral peri-hilar congestion.
A chest ANGIO-CT examination, already planned to re-evaluate a previous thrombosis of the left brachiocephalic venous trunk, shows on the right, in the lower lobe, a consolidative focus partially cavitated from inflammatory involvement and small nodular formation of similar significance in the upper lingular area close to the pleural plane.
In the suspicion of fungal infection, dosage of 1-3-Beta-d-Glucan and Galactomannan were performed but they were normal.
CVC and peripheral vein cultures were positive for Kocuria kristinae infection. The patient was treated with local and systemic intravenous Meropenem for a total of two weeks.
At the end of the antibiotic therapy, the blood cultures taken from the CVC and peripheral vein were negative, therefore the use of the CVC is restored.
On Rx control, no evidence of parenchymal lesions; there was also the negativization of inflammation indices.
On the chest CT scan performed after two months, a centimeter-sized fibrotic-dysventilatory area with a contextual aerial nucleus and a fibrotic branch of the pleural junction was evident on the right, in correspondence with the previous partially cavitated consolidative focus.
Conclusions: In our clinical case, the infection affected an immunocompetent patient, with a central venous catheter; it spared the heart valves, causing pulmonary involvement with excavated nodules, the radiological aspect of which is placed in differential diagnosis with mycotic infections.
In case of CVC infection, in addition to the risk of right endocarditis, hematogenous pneumonia must also be excluded.

50. DIABETIC KETOACIDOSIS AND INSULIN DEPENDENCE IN A PATIENT WITH UNRECOGNIZED TYPE 2 DIABETES MELLITUS, RARE AND REVERSIBLE OCCURRENCES

Natale R., Nasti C., Morena A., Santarpia L., Pasanisi F.
Dipartimento di Medicina Clinica e Chirurgia, Università degli Studi di Napoli Federico II

Diabetic ketoacidosis is an acute metabolic complication characterized by hyperglycemia, hyperketonemia and metabolic acidosis that occurs more frequently in patients with type 1 diabetes mellitus.
M. P., 51 years old, was hospitalized in September 2022 in the Internal Medicine department of the A.O.U. Federico II of Naples for cardiorespiratory insufficiency secondary to severe obesity (BMI > 60 kg/m2).
History: untreated arterial hypertension and dyslipidemia, bilateral coxarthrosis, chronic obstructive pulmonary disease with occasional need for low-flow oxygen therapy, previous myocardial infarction treated with angioplasty and thyroid goiter causing compression and right lateral deviation of the trachea. No history of diabetes mellitus.
On admission, the patient was slightly drowsy, with signs of dehydration and tachycardia, and had been reporting frequent urination with strangulation for a few days. Fasting blood sugar was 962 mg/dl at the blood chemistry tests performed on admission, confirmed by a "HI" result on the reflectometer. Arterial blood gas analyzes were therefore performed which showed pH 6.9, HCO3 20.3 mmol/l, anion gap 24.7 mmol/l, ketonemia dosage on capillary blood sample 5.8 mmol.
A diagnosis of glycometabolic decompensation with ketoacidosis was therefore made in a patient with unknown diabetes and intravenous therapy was carried out with insulin in continuous infusion 8 IU/h using an infusion pump, potassium, bicarbonates and hydration with physiological solution until electrolytes and pH were normalized and until acceptable glycemic values are reached.
The dosage of the anti-GAD, anti-insulin, anti-IA2, anti-ZNT8 antibodies was negative and the insulinemia and C-peptide values indicated for the diagnosis of type 2 diabetes mellitus.
After about a month of hospitalization, the patient showed moderate glycemic control with subcutaneous insulin treatment (basal-bolus pattern with about 50 IU/day) in addition to metformin 500 mg twice a day; he also practiced therapy for arterial hypertension (perindopril 10 mg + amlodipine 10 mg) and for dyslipidemia (atorvastatin 40 mg).
Upon discharge, the patient was sent to a cardiorespiratory and cardio-metabolic rehabilitation clinic; after two months of nutritional therapy and physical activity, she achieved weight loss of about 20 kg with a reduction in blood pressure values, the need for oxygen therapy and above all weaning from insulin therapy and adequate glycemic control only with oral hypoglycaemic drugs (metformin 1000 mg x 2/ die).

51. A RARE CASE OF MULTIPLE MYELOMA WITH MULTIPLE ATYPICAL FEATURES

Nasti C., Natale R., Morena A., Della Pepa R., Pasanisi F., Santarpia L.
Dipartimento di Medicina Clinica e Chirurgia, Università degli Studi di Napoli Federico II

An old woman came to our observation for asthenia, haematochezia, acute anemia (Hb 8.2 g/dl) and progressive weight loss. The patient had been hospitalized two months earlier in another hospital for rectal bleeding with severe anemia;
In Medical History ischemic heart disease, biological aortic valve prosthesis, arterial hypertension, hepatic steatosis, colonic diverticulosis, previous breast cancer (about 7 years ago).
On admission physical examination and vital signs were normal. Blood chemistry tests revealed anemia, increased inflammation indices, monoclonal peak IgG lambda, slight increase in faecal calprotectin, without Bence-Jones proteinuria.
Due to the presence of the monoclonal peak, a dosage of the free chains on serum and urine and a myelobiopsy were performed, which diagnosed of Multiple Myeloma (MM).
Due to the persistent drop in hemoglobin, the need for blood transfusions and recurrent episodes of hematochezia, colonoscopy and video capsule examination were performed which showed the presence of clots and partially oxidized blood in the ascending colon, with no evidence of active sources of bleeding. During hospitalization, on the 10th day, the patient presented pain with intermittent cyanosis in the right hallux with characteristics similar to Raynaud's phenomenon, poorly responsive to painkillers and vasodilators. Over the days, this phenomenon became more and more accentuated until it led to ischemic necrosis of the hallux.
To search for any osteolytic lesions, a PET-CT scan was performed which showed an increase in the uptake of the tracer throughout the bone marrow compartment and a nodular thickening in the midfield of the right lung associated with a thickened appearance of the neighboring parenchyma (SUV max 5.1). Rare cases of ascending colon bleeding from amyloidosis in a patient with multiple myeloma, rare cases of hypoperfusion with toe ischemia due to myeloma hyperviscosity, and one case of pulmonary plasmacytoma in a patient with MM have been described in the literature.
Once the diagnosis of MM and the probable correlation of the rare secondary manifestations were confirmed, the patient started therapy with Daratumumab - Lenalidomide - Dexamethasone.
Since the first administrations, the patient has no longer presented intestinal bleeding; 6 months after the start of haematological therapy, the patient obtained a good partial response of the disease (according to the IMWG criteria) and the peripheral vascular symptoms partially regressed.
The documentation present in the literature and the response to haematological therapy have allowed us to confirm the relationship between MM and the different atypical manifestations which initially seemed to be comorbidities in their own right.

52. REFRACTORY TAKAYASU ARTERITIS SUCCESSFULLY TREATED WITH INFLIXIMAB: CASE REPORT AND REVIEW OF LITERATURE

Dipaola V.[1], Susca N.[2], Leone P.[3], Vacca A.[4], Racanelli V.[5], Prete M.[3]
[1]Department of Interdisciplinary Medicine, Postgraduate School in Hygiene and Preventive Medicine, School of Medicine, 'Aldo Moro' University of Bari.; [2]Department of Interdisciplinary Medicine, Emergency Department Unit, School of Medicine, 'Aldo Moro' University of Bari.; [3]Department of Interdisciplinary Medicine, Section of Internal Medicine, School of Medicine, 'Aldo Moro' University of Bari.; [4]Department of Precision and Regenerative Medicine and Ionian Area, Section of Internal Medicine, School of Medicine, 'Aldo Moro' University of Bari.; [5]Department of Cellular, Computational and Integrative Biology - CIBIO, University of Trento, Trento, Italy

Takayasu arteritis (TA) is a rare, chronic inflammatory disease of large arteries which progressively develop stenosis, occlusion or aneurismal degeneration. The pathogenesis of disease is unknown but several studies have demonstrated an association with human leucocyte antigens, suggesting a genetic predisposition for the immune-mediated process. Conventional therapy with glucocorticosteroid (GC) often fails to determine clinical remission. Treatment with Infliximab, an anti-TNF-α monoclonal antibody that specifically binds to and neutralizes soluble TNF-α, has been proposed for the treatment of TA in patients refractory to conventional therapy. No RCTs have been done evaluating TNF inhibitors in TAK; however, data across studies showed that ~70% of patients were able to achieve remission with anti-TNF therapy (including infliximab, etanercept, and adalimumab) in patients who had previously failed non-GC non biologic medications.
Here, we report the case of a young patient affected by TA unresponsive to conventional therapy who was then successfully treated with infliximab and obtained a clinical remission of the disease.
In 2020, a 35-year-old caucasian patient presented with chest pain and poor exercise tolerance. Cardiological examinations excluded cardiac problems. In the following months, she complained of scotomas, neck pain and paresthesias in all four limbs and occasionally to the scalp. Laboratory data revealed high inflammation parameters (ESR 93 and CRP 31) and negative autoimmune autoantibodies (ANA, ENA screening, antidsDNA, p and cANCA). In November 2021, for episodes of self-limiting pain in the cervico-dorsal spine and associated intermittent claudication with a maximum range of 800 meters, pain in the lower limbs and left radial wrist anisohyposphygmia, she performed ultrasonography of supra-aortic trunks vessels and of the lower limbs with finding of concentric stenosis at the origin of the common carotids with a "*macaron sign*" type, appearance and ipsilateral subclavian stenosis. Total body CT showed "*circumferential and regular thickening of the vascular wall of the rachiocephalic trunk, right carotid artery, left common carotid artery and left subclavian artery, thickening extended to the ascending carotid artery and aortic arch*". A PET scan confirmed vascular involvement and showed increased metabolism along the parietal profile of the ascending aorta, aortic arch, left subclavian artery, and bilateral common carotid artery.
The diagnosis of TA type IIa was formulated. Treatment with corticosteroids 0.8 mg/kg and methotrexate 15 mg/week was set which was subsequently increased to 20 mg/week due to the onset of left ear hypoacusia and episodes of phosphenia scotomas with persistent headache. On May 2022, she performed an imaging revaluation due to an increase in inflammation indices (ESR 44, CPR 14) in the absence of new relevant clinical manifestations. PET showed persistence of diffuse uptake (SUV max 4.2) in the disease sites and MR angiography revealed thickening and reduction in the caliber of the descending thoracic aorta, left subclavian and abdominal aorta. MRI of the pelvis showed aseptic necrosis of the femoral head without treatment with clodronate acid. Therapy with infliximab 5 mg/kg (300 mg) was started according to the 0, 2, 6 week schedule which made it possible to reduce the corticosteroid dosage over four months to 7.5 mg/day. On October 2022 the patient is asymptomatic and the laboratory parameters showed (ESR 10 and CRP 0.7). The last outpatient checkup on February 2023 confirmed the state of disease remission.

53. GASTRIC MASS AS AN ATHYPICAL PRESENTING SIGN OF GRANULOMATOSIS WITH POLIANGIITIS (GPA)

Carmen P.[1], Prencipe A.[2], Leone P.[3], Susca N.[4], Guastadisegno C.M.[2], Vacca A.[2], Racanelli V.[5], Prete M.[3]
[1]Department of Emergency and Organ Transplantation, Nephrology, Dialysis and Transplantation Unit, School of Medicine, 'Aldo Moro' University of Bari.; [2]Department of Precision and Regenerative Medicine and Ionian Area, Section of Internal Medicine, School of Medicine, 'Aldo Moro' University of Bari.; [3]Department of Interdisciplinary Medicine, Section of Internal Medicine, School of Medicine, 'Aldo Moro' University of Bari.; [4]Department of Interdisciplinary Medicine, Emergency Department Unit, School of Medicine, 'Aldo Moro' University of Bari.; [5]Department of Cellular, Computational and Integrative Biology - CIBIO, University of Trento, Trento, Italy

Background: Granulomatosis with polyangiitis (GPA) is an atypical, multisystem disease with unknown etiology characterized by necrotizing granulomatous inflammation and belongs to the family of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides. It is an uncommon disease that primarily affects the upper and lower respiratory tracts and the kidneys. Early diagnosis of GPA can be difficult, especially in patients with atypical symptoms and is established by a clinical examination along with laboratory tests for anti-neutrophil cytoplasmic antibodies (ANCA) and specimen observation.
Findings: We describe the case of a 58 year-old Caucasian female with an unusual presentation of gastric involvement in GPA, developing perforation of the bowel after one year from onset of the abdominal symptoms.
In May 2021, she presented with complaints of abdominal distention and cramps, fever, anorexia and anemia for 2 months. Gastroscopy was carried out two times, and stomach cancer was suspected. However, histopathology of gastric biopsy revealed a chronic inflammation with mucosal ulceration, infiltration of neutrophils, eosinophils and lymphocytes, glandular distortion and local granulomatous formation, whereas no sign of stomach carcinoma was observed. PET (positron emission tomography) examination confirmed gastric uptake with SUV of 8.5. A diagnosis of granulomatosis intestinal disease, like Crohn's disease was suspected. The patient was successfully treated with corticosteroids and azathioprine replaced with methotrexate due to progressive anemia for fifteen months. In August 2022, the patient pre-

sented to Emergency department for trigeminal headache, fever and episodes of epistaxis. She was admitted to Internal Medicine Unit where the hypothesis of systemic vasculitis was considered and specific clinical investigations were performed. Routine serological tests showed alteration of indices of inflammation with VES 131 mm/h, PCR 44 mg/dl and ferritin 8408 ng/ml; ANA were positive (1/320) as well as c-ANCA with anti-PR3 >500 Q/mL. Facial MRI revealed spheno-ethmoid-maxillary sinus inflammatory disease. Chest CT showed multiple lung nodules, larger on the right (2 cm), some with air bronchogram in the context. Total body PET-CT displayed hyper accumulation in the right nasal cavity of the ipsilateral ethmoidal and maxillary bone (SUV 19.1), to the posterior basal segment of LLR (SUV 7.4), to the upper apical segment of LLL (SUV 4.7) and to the walls of sigma-rectum (SUV 5.8). BAL test was unremarkable. During hospitalization, she presented sudden abdominal pain symptoms with signs of paralytic ileus. An emergency CT scan of the abdomen was performed and showed ischemia at the mesentery level of some jejunal loops. After one month from surgery, anti-CD20 rituximab therapy was started at a dose of 300 mg once a week for four weeks (total dose 1,200 mg). Follow-up to six months showed a remission was achieved.
Conclusions: Patients who present only with gastrointestinal manifestations represent challenges to diagnosis. ANCA testing can serve as a decisive diagnostic tool. Although uncommon, GI involvement may be a major feature in GPA, sometimes presenting as gastric tumor-like lesions. Diagnosis of GPA should be considered in patients presenting with GI symptoms accompanied by evidence of systemic vasculitis, and ANCA test should be used as a diagnostic measurement to clarify differential diagnosis.
The course of disease of this GPA patient suggests that very early initiation of intensified immunosuppressive treatment, preferentially with B cell depletion strategies, needs to be considered to avoid life-threatening complications of GI involvement.

54. SAPHO (SYNOVITIS, ACNE, PUSTULOSIS, HYPEROSTOSIS, OSTEITIS) SYNDROME: A RARE DIAGNOSIS IN THE EMERGENCY DEPARTMENT

Susca N.[1], Leone P.[2], Vella F. S.[2], Amati V.[2], Sabbà C.[2], Racanelli V.[3], Prete M.[2]
[1]Department of Interdisciplinary Medicine, Emergency Department Unit, School of Medicine, 'Aldo Moro' University of Bari.; [2]Department of Interdisciplinary Medicine, Section of Internal Medicine, School of Medicine, 'Aldo Moro' University of Bari; [3]Department of Cellular, Computational and Integrative Biology - CIBIO, University of Trento, Trento, Italy.

A 52 years old woman came to the emergency department (ED) with a one month ago history of fever (with a maximum body temperature of about 38°C), polyarthralgia and pustules on trunk, scalp, genital area, hand palms and foot. Antibiotics and corticosteroids were administered, without improvement.
Strong tenderness of the chest wall was documented upon physical examination; these symptoms had forced the patient to have several accesses to the ED in the past and cardiac causes were always excluded.
Moreover, the patient reported back pain. In the suspicion of SAPHO syndrome, the patient was admitted to the Internal Medicine Unit.
A routine blood test panel showed a high value for the ESR (109 mm/1 hour). Firstly, investigations of infectious diseases were performed. Serologic tests for the major herpetic viruses were carried out. Anti-VCA IgM and IgG, and anti-EBNA IgG were positive. But the clinical scenario was not considered typical for infectious mononucleosis, and the avidity test for ant-VCA IgG was high, so this diagnosis was excluded. Then, IGRA (interferon gamma release assay) test was performed obtaining an indeterminate value. Mantoux test was negative. *Veneral Disease Research Laboratory* (VDRL) and *Haemoagglutination Assay* (TPHA) were both negative, as well as blood cultures. Autoimmune serology showed a low ANA positive value (1/80 titer) with a nuclear homogeneous pattern which was not considered significant.
Finally, an MRI scan of the chest wall and pelvis showed bone edema of the medial portion of both clavicles and sternum (near the sterno-clavicular joint), and of the D4 and from D6 to D9 vertebral bodies. These findings suggested bone inflammation due to sterile ostheomyelitis.
A clinical diagnosis of SAPHO syndrome was made based on polyarthralgia expression of suspected synovitis, diffused skin pustulosis, osteitis with a typical distribution (chest wall at the level of the sterno-clavicular joint and vertebrae) and fever.
Since three month, she has been given therapy with NSAIDS and the follow-up for the disease has just begun.

55. A RARE CASE OF CUTANEOUS POLYARTERITIS NODOSA: A CHALLENGING DIAGNOSIS

Berardi E.[1], Antonica G.[1], Prete M.[1], Procaccio A.[1], Martiradonna M.R.[1], Magnifico A.[1], De Toma F. M.[1], Sgura G. F.[1], Costanza F.[1], Sisto A.[1], Manfredi T.[1], Marziliano D.[1], Sabbà C.[1], Racanelli V.[2]
[1]Department of Interdisciplinary Medicine, Section of Internal Medicine, School of Medicine, 'Aldo Moro' University of Bari; [2]Department of Cellular, Computational and Integrative Biology - CIBIO, University of Trento, Trento, Italy

First described by Adolph Kussmaul and Rudolph Maier, Polyarteritis nodosa is an uncommon necrotizing vasculitis with systemic involvement. Its rarer skin-limited variant (Pagnoux et al., 2010), namely cutaneous pan (cPAN) is characterized by dermis and subcutaneous tissue involvement. Its commonest findings include digital gangrene, livedo reticularis, tender subcutaneous nodules. Even in its skin-limited form, cPAN poses significant morbidity and mortality due to skin ischemia and necrosis which can undergo superinfection. We describe a rare case of cutaneous PAN in a 78-years old female presenting with digital ischemia and leg ulcers associated with pulmonary hypertension. This is the first time these two conditions have been associated as pulmonary hypertension has never been related to cPAN or PAN (Adams et al., 2018) in all the known literature. Skin biopsy reported a necrotizing fibrinoid necrosis of small and mid-sized vessels of the dermis. She was treated with glucocorticoids, vasodilators and cyclophosphamide.

56. HEMOPHAGOCYTIC SYNDROME SECONDARY TO CHRONIC NOROVIRUS COMMON VARIABLE IMMUNO-DEFICIENCY (CVID)-RELATED ENTEROPATHY

Bruno C.[1], Tomasello G.[2], Parisi F.[2], Caff A.[2], Impellizzieri D.[2], Di Prima P.[2], Stancanelli B.[2]
[1]UOC Medicina Generale, Policlinico-S. Marco Catania, Italy, Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy; [2]UOC Medicina Generale, Policlinico-S. Marco Catania, Italy, Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy

Background:
Hypogammaglobulinemia and susceptibility to recurrent infections characterize the common variable immunodeficiency (CVID). It is the most frequent symptomatic antibody deficiency, affecting 1/25.000 Caucasians . The most common clinical manifestations are infections, mainly involving respiratory and gastrointestinal systems. Several upper and lower respiratory tract infections often result in bronchitis, bronchiectasis and interstitial lung disease. Gastrointestinal tract infections manifest with chronic or acute diarrhea. Immunocompromised patients may develop a chronic Norovirus infection, that is the most common cause of acute non-bacterial gastroenteritis. This condition could lead to the development of a severe CVID-related enteropathy, characterized by diarrhea, malabsorption, and histological aspects similar to celiac disease, including duodenal villous atrophy and lymphocytic infiltration of mucosa.
Case Report: A 52-year-old woman was admitted to the emergency department for serotine fever and cachectic status (BMI = 14.67 kg/m2). Past medical history: ulcerative rectocolitis with extra-intestinal clinical manifestations (arthralgias), unresponsive to mesalazine and beclomethasone dipropionate therapy; pneumonia and bilateral bronchiectasis; previous Bartolini's gland abscess. Chest X-ray showed left lung basal parenchymal thickening. She was admitted to the Department of Internal Medicine where empiric antibiotic therapy with piperacillin/tazobactam was quickly started, followed by mild and transient clinical and laboratory improvement. Laboratory data showed severe hypogammaglobulinemia (gamma globulin: 1%), with depletion of all Ig classes. Given this last laboratory finding, the following tests were performed: serology for toxoplasma, HBV, HCV, HIV, EBV, HHV6, Mycoplasma, Brucella, Salmonella, Paratyphi. They were all negative, as did evaluation of tyroid function. Chest and abdomen CT scan with dye injection was also performed: neoplastic lesions were excluded. Due to the persistence of diarrhea, BioFire FilmArray Gastrointestinal Panel (FGP) was carried out and Norovirus-, Campylobacter-, and Cryptosporidium-positive results were isolated. Despite the administration of antibiotic therapy and replacement therapy with IGIV (400 mg/Kg/day for 5 days), a progressive clinical-laboratory deterioration was detected during the hospitalization, characterized by persistent fever and diarrhea, severe anemia and pancytopenia, hypertriglyceridemia and hyperferritinemia (haemoglobin = 7 g/dl; platelets = 47 10^3/ µL; leukocytes = 1.

46 10^3/ μL; triglycerides = 322 mg/dl; ferritin > 15000 ng/ml). The suspicion that the patient may have developed hemophagocytic histiocytosis has been raised; therefore hematologic evaluation was performed: HScore for reactive hemofagocytic syndrome resulted > 99.27%. Subsequently, the bone marrow biopsy confirmed the diagnosis of macrophage activation syndrome.
Conclusions: Hemophagocytic histiocytosis is a severe, albeit rare, immune dysfunction leading to macrophage and T-cell cytotoxic hyperactivation. The acquired form of this disorder is more common in adults and is related to infections, malignant neoplasms, immunologic and autoimmune diseases. In our case, it was hypothesized that the hemophagocytic syndrome was secondary to the systemic inflammatory state induced by chronic norovirus enteropathy.

57. HEMATEMESIS: A RARE AND DRAMATIC SIGN OF SUPERIOR VENA CAVA SYNDROME

Zarrella A.F.[1], Bologna C. [2], Cozzolino A. [3], De Luca C.[2], Fierarossa C. [1], Tartaglia B.[1], Gammaldi V. [1], Petrosino C P.[1], De Sena A. [2], Tirelli P.[2], Madonna P. [2]
[1]Dipartimento di Medicina Clinica e Chirurgia. Università degli Studi di Napoli "Federico II"; [2]UOC Medicina Generale. P.O. "Ospedale del Mare", ASL Na1 Centro; [3]UOC Gastroenterologia. P.O. "Ospedale del Mare", ASL Na1 Centro

Superior Vena Cava Syndrome (SVCS) is a combination of signs and symptoms caused by a reduction of the caliber of Superior Vena Cava (SVC) by an occlusion or an obstruction. The most common cause of SVCS is malignancy, mainly lung cancer or lymphoma, which creates an obstruction *ab estrinseco*. Devices, such as defibrillator or pacemaker leads and central venous catheters (CVC), can cause another benign form of SVCS on the rise in recent years. CVC, especially those used for hemodialysis, produce both intralumial obstruction and vascular wall stress, by direct and respiration trauma and by high flow during hemodialysis, leading to a progressive occlusion of the lumen. A 67-years-old Polish male patient, in hemodialysis for 3 years due to a terminal stage chronic kidney disease of obscure etiology, referred to our Department of Emergency Medicine complaining episodes of hematemesis and an accidental fall. Other anamnestic datas were Arterial Hypertension, active smoking of about 15 cigarettes a day and a reported right kidney surgery for unclear reasons. At the time, the vascular access used for hemodialysis was an artero-venous fistula and it had been used for one year. Previously a tunnelled Tesio catheter was employed for two years and was removed after packing the A-V fistula. The first blood tests showed a normochromic and normocytic anemia, with a Hemoglobin of 7.2 g/dL. Liver function, cholestatic and cytolisis enzymes were normal. Two units of packed red blood cells were immediately trasfused. The patient, then, underwent an esophago-gastro-duodenoscopy which highlighted the presence of four esophageal varicose cords occupying more than one third of the lumen with signs of bleeding, which were promptly subjected to ligation. Subsequently, the patient was transferred to our General Medicine Ward. A complete physical examination draw the attention to the presence of multiple chest and abdomen venous circles and of large, symmetrical, swelling of the head, upper extremities and neck (Collar of Stokes), with a marked morning worsening and an evening improvement. Chest and cardiac examination were almost normal. We performed an abdomen ultrasound and a more in-depth evaluation of the blood tests to rule out a chronic epatopathy. The liver structure was coarse, the Portal Vein presented a normal caliber (Antero-Posterior caliber: 9 mm) and a hepatopetal flow, the spleen was small in size (Bipolar diameter: 70 mm) and no ascites was reported. Futhermore, platelets count, coagulation test, hepatotropic viruses serology and cholesterol were all normal. Consequently, the suspicion of a SVCS was strengthened. A contrast-enhanced chest and abdomen Computed Axial Tomography (CT) endorsed the diagnostic suspicion highlighting a complete occlusion of the SVC close to the right atrium outlet. This occlusion produced an upstream vein ectasia and the formation of numerous collateral circles, all tributaries of the Inferior Vena Cava with azygos an hemiazygos vein distension. No significant epatic alteration was found. Given the instrumental evidence, we could diagnose a SVCS. The patient was then referred to our vascular interventional radiology unit, where he was subjected to a Cavography. The inferior Cavography confirmed a complete occlusion immediately after the opening into the right atrium. After the use of a hydrophilic guide and a 5 French catheter to overcome the occlusion, a superior Cavography was performed. The procedure showed collateral circles to the Inferior Vena Cava via a flow reversal in the Azygos vein. Afterwards, a dilatation of the stenosis was obtained trough 8, 10 and 12 mm balloons. No stents were placed due to the proximity of right atrium. The following day, the upper extremities swelling resulted reduced, the evidence of venous circles of chest and abdomen had faded. No more macroscopic bleeding events were reported. The blood count, carried out on a daily basis, was consistently stable. Subsequently, 1000 mg of Ferric Carboxymaltose was administered to the patient, to replenish the Iron stores. After seven days of observation, during which the patient had regular hemodialysis sessions, a new contrast-enhanced chest CT was performed to assess possible new Superior Cava size reduction. The caliber remained stable and the patient could, therefore, be discharged. The benign SVCS incidence is increasing in recent years due to a rising use of devices. Recent studies on SVCS in hemodialysis patients with a tunneled catheter reported a remarkably high occurrence. Although often asymptomatic, SVCS should be recognized during clinical practice and the presence of a device should be considered as a red flag. Moreover, this case report shows that, even if in rare cases, SVCS may present with a life-threatening medical emergency.

58. ASCITES AND DIPLOPIA IN A SEPTIC PATIENT: A CASE REPORT

Rainone C.[1], Bologna C.[2], Lugarà M.[2], De Sena A.[2], Coppola M.G.[2], Madonna P.[2]
[1]Department of Translational Medical Sciences, Federico II University of Naples, 80131 Naples, Italy; [2]Internal Medicine Unit, Ospedale del Mare, ASL Napoli 1 Centro, Naples ,Italy

Background: Staphylococcal toxic shock syndrome (TSS) is a syndrome associated with infection by toxins produced by Staphylococcus Aureus beta-hemolytic group A. It is a clinical illness characterized by rapid onset of fever, rash, hypotension, and multiorgan system involvement. The particularity of our case is related to diplopia caused by paralysis of abducentes nerve associated to general symptoms of TSS.
Description: A 42-year old woman went to the Emergency department because of acute abdominal pain, fever and hypotension associated with nausea and diarrhea from three days. There was a negative medical history except for allergy to rovamycin, trimetopim-sulfimethoxazole and NSAID. Physical examination on admission revealed tense abdomen and diffuse pain on palpation. Biochemical exams showed neutrophilic leukocytosis (GB 19.56), microcytic anemia (Hb 10.3 g/dl), increase in inflammation indices (CRP 48.51 mg/dl), neutrophilic leukocytosis, mild pancreatitis, acute renal failure. Blood cultures and both infective and autoimmune exams were negative. Abdominal imaging (CAT) showed: peritoneal fluid in the perihepatic and peri splenic areas, along the colic edge, in the Douglas and between the intestinal loops. Moderate distention with entero-fecaloid content. For this reason fast was indicated and also nasogastric tube. Patient started empiric antibiotic therapy with ceftriaxone 2 g once a day and metronidazole 500 mg three times a day. During the hospitalization the patient manifested diplopia. A neurological evaluation made a diagnosis of paralysis of abducentes nerve. Brain MRI revealed a phlogistic process in some areas. The patient started corticosteroid therapy and changed antibiotic with piperacillin-tazobactam 4,5 g three times a day. The etiology was still unknow, until the patient referred an incorrect use of an intravaginal tampon during period that left inside for over 36 hours. Symptoms appeared after its removal. Diagnostic and evacuative paracentesis revealed a bacterial peritonitis so the diagnosis was of staphylococcal toxic shock syndrome. After antibiotic and steroid therapy the patient recovered and also the diplopia resolved.
Conclusions: Among the diagnostic criteria of Staphylococcal toxic shock syndrome (TSS) there are no focal neurological signs but simply disorientation and confusion. In our case however, the paralysis appeared at the same time as the syndrome and completely regressed after 4 weeks. Comparison with other published case reports would be useful for a possible revision of the diagnostic criteria of the TTS syndrome.

59. PERNICIOUS ANEMIA MIMICKING THROMBOTIC THROMBOCYTOPENIC PURPURA (WHAT A GREAT HAEMATOLOGICAL IMITATOR IS THE VITAMIN B12 DEFICIENCY!)

Malfer G.[1], Panepinto L.[1], Moruzzi S.[1], Trevisan M. T.[2], Bonisoli G.L.[1], Ceolan J.[1], Sales C.[1], Sabbion N.[1], Machado de Oliveira P.[1], Pezzato S.[1], Pizzolo F.[1], Suardi S.[1], Cantini M.[3], Dima F.[4], Poli G.[4], Vassanelli A.[3], Pavone D.[3], Gandini G.[3], Lippi G.[4], Friso S.[1], Martinelli N.[1]
[1]Department of Medicine, University of Verona, Verona, Italy; [2]Clinical and Microbiological Chemical Analysis Laboratory, Hospital of San Bonifacio, Verona, Italy; [3]Department of Trasfusional Medicine, AOUI Verona, Verona, Italy; [4]Section of Clinical Biochemistry, University of Verona, Verona, Italy

Background: The classic clinical presentation of vitamin B12 deficiency is historically exemplified by macrocytic anemia, with or without neurologic symptoms. However, the clinical features of B12 deficiency may be variable and atypical, even mimicking other different haematological conditions from myelodysplastic syndromes to thrombotic microangiopathies (TMAs). Here we present a case of vitamin B12 deficiency-related pernicious anemia with clinical onset mimicking thrombotic thrombocytopenic purpura (TTP).
Case Report: A 79-year-old man went to the Emergency Department complaining of asthenia and dyspnoea. Laboratory investigations showed a marked macrocytic anemia (haemoglobin 4.9 g/dL, red blood cells 1,911,000/mcL with MCV 131.6 fL) associated with relative mild reticulocytosis (3.37% with absolute count 64,400/mcL), rise of total bilirubin (2.0 mg/dL) and LDH (2,125 U/L) levels, as well as with significant thrombocytopenia (24.000/mcL). Haptoglobin levels were low (<0.08 g/L) and the direct Coombs test was negative. The peripheral blood smear showed significant schistocytosis (2% - Figure 1, panel A), thus defining a condition of microangiopathic haemolytic anemia (MAHA). Renal function was normal and no signs and/or symptoms of specific organ damage were observed. The patient was transfused with 5 units of concentrated red blood cells (RBCU) and 2 doses of pooled platelets (PPD). On the basis of the co-presence of MAHA and thrombocytopenia the clinical suspicion of TTP was posed and the patient was transferred to our Internal Medicine Department. A blood drawn to test the activity of the plasma protease ADAMTS13 was immediately performed, but unfortunately the patient arrived on Friday evening and at our laboratory the analysis of this blood sample would have been possible only for the following Monday – anyway within 72 hours. The PLASMIC score, a validated tool to estimate the probability of ADAMTS13 activity <10 percent, was then calculated with a result of 6 on 7 points thus defining a high probability of TTP. The only feature not satisfied for the PLASMIC score was that defined by MCV <90 fL. On the basis of the high probability of TTP by PLASMIC score and the availability of ADAMTS13 activity dosage within 72 hours, according with the guidelines of Italian Society of Haematology, a comprehensive therapeutic approach for immune-mediated TTP was initiated with plasma exchange, full-dose glucocorticoids (prednisone 1 mg/kg), and caplacizumab. Meanwhile, a severe vitamin B12 deficiency was also detected, for which a parenteral supplementation with cyanocobalamin was started. After the first 3 days of treatment, no substantial improvement was observed from a laboratory point of view, although the patient remained clinically stable. The dosage of ADAMTS13 (24%) was not critically low, therefore not confirming the diagnostic hypothesis of TTP. The therapy with caplacizumab was suspended, while plasmapheresis continued for 2 days for a total of 5 plasma exchange sessions in the light of the persistent haemolysis. Glucocorticoids were also rapidly reduced and stopped. Taking into account the possibility of other types of TMA, although no recent bloody diarrheal illness was reported and no renal involvement was present, diagnostic assessment for Shiga toxin-mediated haemolytic uremic syndrome was performed, but both stool cultures and Shiga toxin protein assays were negative. Among further laboratory analyses, plasma levels of the complement fractions C3 and C4 were low, while the traditional blood tests for autoimmune diseases were negative. Flow cytometry showed a clonal population of paroxysmal nocturnal haemoglobinuria (PNH) in red blood cells, but not in other cell lineages. In the meantime, the patient continued the parenteral supplementation with cyanocobalamin leading to a progressive improvement of both general clinical conditions and laboratory parameters with a marked absolute reticulocytosis (519,600/mcL).
Haemoglobin level and platelet count substantially returned to normal ranges and schistocytosis disappeared (Figure 1, Panel B). Notably, C3 and C4 plasma levels also rose progressively within the normal ranges and the PNH clone on the erythrocyte population was no longer detectable. Figure 2 summarizes the trend of the main laboratory parameters during hospital stay and early after discharge. As regards diagnostic work-up for vitamin B12 deficiency, antiparietal cell antibodies were negative while intrinsic factor-blocking antibodies were positive. Finally, a gastroscopy with biopsy showed a condition of autoimmune metaplastic atrophic gastritis justifying the severe deficiency of vitamin B12 and defining a diagnosis of pernicious anemia. The patient had a complete recovery. At discharge lifelong parenteral cobalamin replacement and endoscopic surveillance were recommended.
Conclusions: Severe vitamin B12 deficiency may mimic TTP. In the clinical setting of suspected thrombotic microangiopathy, high MCV and low increase in reticulocyte count should suggest a vitamin B12 deficiency for which a high clinical suspicion should be maintained.

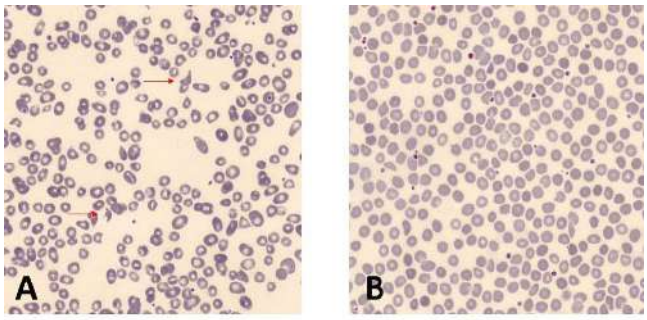


Fig. 1 The peripheral blood smears at the time of hospital admission showing significant schistocytosis (2% - Panel A) and after 60 showing a complete disappearance of schistocytes (<0.1% - Panel B)

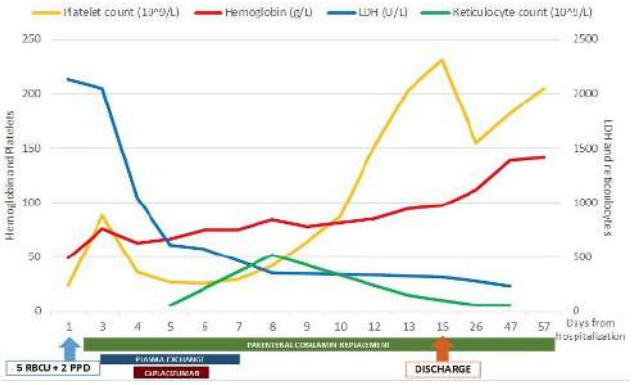


Fig. 2 The trend of the main laboratory parameters during hospital stay and early after discharge.

60. IGG4-RELATED HYPERTROPHIC PACHYMENINGITIS: AN INTERNISTIC APPROACH TO A COMPLEX CASE

De Marco A.[1], Fanin A.[2], Betelli M.[2], Benetti A.[2]
[1]Dipartimento di Medicina e Chirurgia, Università degli studi di Milano;
[2]Dipartimento di Medicina Interna, ASST Papa Giovanni XXIII

Background: IgG4-related disease was first described as a form of autoimmune pancreatitis. Nowadays it is mainly known as a systemic disease and the most frequently involved organs are the pancreas, the biliary tree and the salivary glands. CNS (*Central Nervous System*) involvement is less common and meningeal involvement with a subsequent thickening of the dura mater is even rarer and described only in case reports and series.
Discussion: Our patient is a 52-year-old Caucasian female with a history of paraplegia due to a polytrauma spinal cord injury (D7-D8), a previous episode of iliofemoral deep vein thrombosis under DOAC (*Direct Oral Anticoagulant*) anticoagulation and hypothyroidism. She suffered from gluteal abscess and pressure sores (bilateral ischial and median sacral) and was scheduled for surgical toilette and fasciocutaneous flaps reconstruction preceded by a protection colostomy. During the hospitalization the ulcer swab resulted positive to CRAB (*Carbapenem-Resistant Acinetobacter baumannii*) and *Proteus mirabilis*, so an antibiotic therapy with ampicillin/sulbactam and tigecycline was started. She was transferred to the Internal Medicine department due to an episode of severe bradycardia (average heart rate 30-35 bpm), hypotension (mean arterial pressure 90/50 mmHg) and sensory numbness. This episode was first identified as vasovagal, and it partially regressed after atropine administration. However, although the numbness resolved, bradycardia and hypotension persisted. The patient underwent an EEG (*Electroencephalogram*) and a transthoracic echocardiogram, both negative. A Holter monitor was placed, which confirmed a marked sinus bradycardia with no further anomalies. A brain CT scan was performed, which showed an unusual posterior temporal and bilateral parietal cerebral sulci obliteration of uncertain interpretation (**Figure 1**).

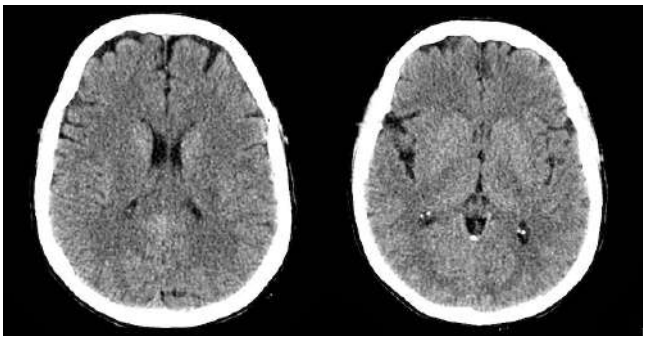


Figure 1.
Given the suspicion of possible beta-lactam antibiotic toxicity, the therapy with ampicillin/sulbactam was first suspended without benefit; subsequently also tigecycline was interrupted and a therapy with cefiderocol was started. The clinical picture rapidly solved after that, so the episode was identified as a consequence of tigecycline toxicity. To better investigate the report of the CT scan, a brain MRI was performed, with images compatible with pachymeningitis, extended to the distal spine (**Figure 2**).

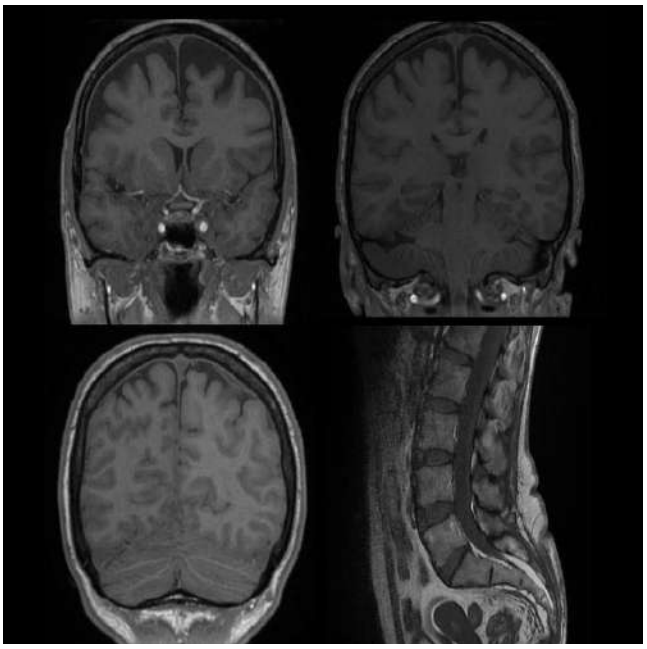


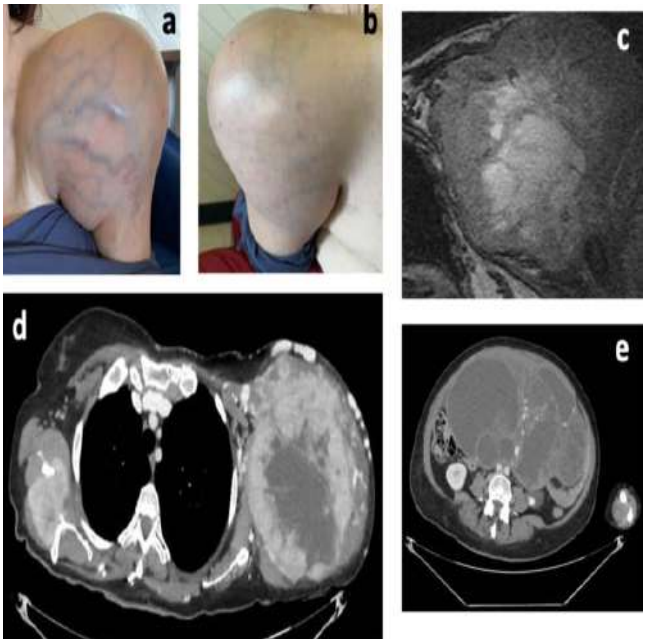
Figure 2.
To define the aetiology of the disease, a lumbar puncture was performed: the cerebrospinal fluid appeared clear and transparent, with mild hypoglycorrhachia and high protein level. Autoimmune panel was negative. Microbiological and cytological exams came out negative, except for QuantiFERON-TB Gold. A second lumbar puncture was performed, to exclude sarcoidosis and tubercular meningitis, that showed a negative ACE (*Angiotensin Converting Enzyme*) titolation (confirmed even on the serum examination), and negative PCR (*Polymerase Chain Reaction*) and microbiological exam for Mycobacteria. Finally, considering a possible IgG4-related disease, the serum IgG4 levels were tested and resulted increased (4314 mg/dl; Reference range 39,2-864,0 mg/dl). To determine if the IgG4-related disease was systemic or localized to the CNS, a total-body CT scan was performed, showing no other sites of IgG4 disease: an IgG4-related pachymeningitis was finally diagnosed. Given the positivity to the QFT exam, a glucocorticoid therapy, which is the first-line therapy in IgG4-related disease, was contraindicated. Since the patient was asymptomatic, a therapy with isoniazid was first started. The therapeutic program was to treat the patient with isoniazid for a total of 6 months and to start the steroid therapy after the first month of isoniazid therapy.
The patient was finally discharged, after 63 days of hospitalization, and transferred to a rehabilitation department.
Conclusion: The literature precisely describes the hallmark histopathological features of IgG4-related pachymeningitis: a lymphoplasmacytic infiltration of IgG4-positive plasma cells, storiform fibrosis and obliterative phlebitis. Therefore, to make a definitive diagnosis a meningeal biopsy is necessary. In this case report, after ruling out all the possible aetiologies of pachymeningitis, since the biopsy was excluded given that the patient was asymptomatic, and considering the increased plasma levels of IgG4, we made a diagnosis of exclusion.

61. AN UNUSUAL PRESENTATION OF SEX CORD-STROMAL TUMORS

Lipari A.[1], Pero E.[1], Camilli S.[1], Macerola N.[1], Murace C.A.[1], Fusco D.[1], Brandi V.[1], Gallo A.[1], Landi F.[2], Montalto M.[2]
[1]Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy;
[2]Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy; Catholic University, Rome, Italy

A 50-year-old woman was admitted to our Internal Medicine Department for a large mass on her left shoulder, rapidly growing in six months, painful at palpation and causing a significant functional limitation.
Past medical history was unremarkable. Physical examination showed a non-pulsating, warm on palpation, large mass with visible superficial venous reticula (Figure 1a,b) at level of left shoulder. No other palpable masses, nor hepatosplenomegaly or superficial lymphadenopathies were revealed. She denied fever, night sweats, pruritus, weight loss, respiratory symptoms, or abdominal discomfort. Laboratory analyses were unremarkable, with mild elevation of serum alpha-fetoprotein, CA 125, CYFRA 21-1 and enolase. CEA, CA 19-9 and CA 15-3 values resulted within the normal range, as well as plasma levels of estradiol, progesterone, testosterone and dehydroepiandrosterone sulfate.
A contrast-enhanced magnetic resonance imaging (MRI) of the left shoulder was performed, showing a large mass (diameter of 22x18 cm) disrupting normal shoulder anatomy, with an area of non-homogeneous enhancement indicating the presence of a large necrotic core (Figure 1c). A biopsy of the mass was performed, showing macroscopic findings compatible with an epithelial-like tumor, with a trabecular growth pattern and adipose and cystic components. Immunohistochemical analysis resulted positive for AE1/AE3, SF1 WT1, CD99 and inhibin; vimentin, TTF1, desmin, SMA, caldesmone, CDX2, ERG, SOX10, CD45, CD20, TLE1 and p63 resulted negative, while synaptophysin, CK7, GATA3, PAX8, calretinin, FOXL2 resulted not expressed. In conclusion, the histological picture resulted compatible with a stromal sex-cord tumor metastasis.
A total-body contrast-enhanced computer tomography (CT) was therefore performed, confirming the large mass with central necrosis in the left shoulder (figure 1d), and showing a voluminous hypodense mass in the abdominal cavity (diameter of 30x16x23 cm), most likely originating from left ovary, with a tortuous and well depicted vascular pedicle (Figure 1e). Another hypodense mass of 46x21 mm was found in the right pterygopalatine fossa extending up to the right nasal cavity.
A sub-segmental pulmonary embolism was incidentally detected, therefore anticoagulant therapy was started.
Given the high surgical risk and the absence of abdominal symptoms or constipation, chemotherapy with carboplatin and taxol was started.
After three cycles of therapy, the patient underwent a total-body contrast-enhanced CT with contrast medium, showing a severe progression of disease.Given the conditions of treatment resistance and limited therapeutic options, the patient was referred to best supportive care and active control of symptoms, with no further chemotherapy. About two months later, the patient died. Ovarian sex cord-stromal tumors (SCSTs) are a rare clinical entity, often misdiagnosed and hardly distinguishable from other non-epithelial ovarian tumors. SCSTs are perhaps thought to stem from ovarian non-epithelial tumors, together with pure stromal tumors and pure sex cord tumors. Among SCSTs it is possible to distinguish adult and juvenile granulosa cell tumors, Sertoli-Leydig cell tumors, and steroid cell tumors. From a gynecological perspective, SCSTs affecting women are thought to originate from embryonic gonadal sex cords and often show an indolent course.
Their most common initial manifestation is virilization (41%); sometimes they can show estrogenic manifestations or hypercortisolemia, mimicking Cushing's syndrome. Although most of these tumors are associated with an indolent behavior and slow growing, some of them are malignant and aggressive. The malignant forms usually are greater than 8 cm of diameter, have signs of macroscopic necrosis and hemorrhage. Vascular and nodal invasion is observed very rarely. Our case represents one of the largest forms described since now, both regarding the primary site and the metastatic lesion of the shoulder. Lymph node metastases are rare, and clinical and therapeutic management of these patients is not well defined. Some studies discourage routinely lymphadenectomy while performing surgery. Likewise, hematogenous

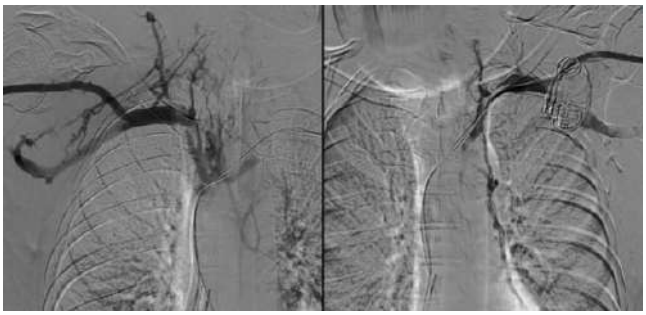
metastases seem to be very uncommon, most of them involving peritoneal cavity, and less frequently distant sites, such as liver. Bone metastasis from steroid cell tumors is a quite singular case, with just few cases in literature reported since now. In addition, the large volume of this unusual localization, the absence of any alteration of hormonal values nor the presence of any hormonal symptoms, make our case almost unique. Even though in our patient the biopsy of the primary pelvic tumor has not been performed, the finding of multinucleated cells with a large necrotic core, together with the immunohistochemistry profile of the metastasis, allowed the diagnosis of steroid cell tumor. This case shows how these types of tumors can be malignant and very aggressive, with an unusual metastatic pattern and early diagnosis is fundamental to give an appropriate treatment chance to our patients.



62. "STILL NOT CONVINCED": A COMPLEX, TRAP-FILLED WORK UP OF A CASE OF UPPER BODY EDEMA.

Tirelli R.[1], Di Francesco P.[2], Milani O.[2], Peta J.[2], Montano N.[2]
[1]Dipartimento di Medicina Interna, IRCCS Ca' Granda Ospedale Maggiorne Policlinico, Milano, Italy.; [2]Dipartimento di Medicina Interna, IRCCS Ca' Granda Ospedale Maggiorne Policlinico, Milano, Italy

Introduction and case presentation: Upper body edema is a relatively frequent condition that can hide underlying benign or malignant causes. Very much emphasis is placed on diagnostic imaging to arrive to a definite diagnosis. A 58-year-old man presented for recurrent episodes of dyspnoea associated with oedema of neck, face, and upper limbs. Physical examination demonstrated telangiectasias on chest's surface. He had a history of allergic asthma, oral allergy syndrome and had a cardiac pacemaker for advanced AV block. Symptoms started 11 months before our evaluation. For a suspected angioedema antihistaminic and steroid therapy was started with no benefit; omalizumab was then administered, without changes. In the ER he was dyspnoeic and dysphonic, vitals were always stable. Initial lab tests, EKG and chest X-ray were normal. A fibro laryngoscopy excluded glottis edema. Initially was performed a contrast-chest CT, that showed right anonymous vein thrombosis without evident thoracic lesions. After 4 days of anticoagulation a control chest CT was performed to evaluate thrombosis extension and resulted completely negative.
Clinical hypothesis: Even if we had two negative radiologic tests our clinical suspicion was high for superior vena cava syndrome (sVCS).
Diagnostic pathways: Deep vein thoracic venography was performed showing an occlusion of left subclavian vein and stenosis of superior vena cava in correspondence with pacemaker's wires. Surgical removal of PM was excluded, due to high procedural risk, as well as stent placement. Therefore we continued with only anticoagulation therapy. After two months resolution of edema and symptoms' reduction were observed.
Discussion and learning points: A long-lasting diagnostic process might be a confounding factor in a suspected diagnosis. We attributed a high pre-test probability to a specific diagnosis, thus our clinical suspicion was not undermined by a negative test. We chose the most appropriate test based on our diagnostic suspicion solving this diagnostic challenge. sVCS is a potentially fatal complex syndrome. In most cases it has a malignant origin. Although PM-related superior vena cava syndrome is a rare cause of sVCS, is becoming more frequent due to increasing use of intravascular devices.



63. A MAN WITH DYSPNEA, WEIGHT LOSS AND NAUSEA WITH MEALS

Rando M.M.[1], Biscetti F.[1], Nardella E.[1], Cecchini A L.[2], Rossini E.[1], Nicolazzi M.A.[1], Pecorini G.[1], Scarpati R.[2], Massetti M.[3], Gasbarrini A.[4], Flex A.[1]
[1]Cardiovascular Internal Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy; [2]Università Cattolica del Sacro Cuore, Largo Francesco Vito 1, 00168 Roma, Italy; [3]Department of Cardiovascular Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy; [4]Department of Medical and Surgical sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy

An 87-year-old male patient was admitted to the ward because of dyspnea, weight loss and nausea with meals. The patient had a history of coronary artery disease with percutaneous coronary intervention six months before hospitalization, atrioventricular block requiring a pacemaker implantation in 2015, pulmonary emphysema, dyslipidemia, moderate chronic kidney disease, impaired fasting glucose, nonalcoholic fatty liver disease and biliary sludge. He reported receiving aspirin 100 mg qd, clopidogrel 75 mg qd, pantoprazole 40 mg qd, furosemide 25 mg tid, spironolactone 25 mg qd, rosuvastatine 5 mg qd, ursodiol 450 mg qd. Clinical examination revealed crackles at the base of the lungs. An electrocardiogram showed pacemaker rhythm. Blood tests revealed renal insufficiency (serum creatinine 1.46 mg/dl), higher level of NT-proBNP (8830 pg/ml), and higher level of total bilirubin (1.3 mg/dl). Other laboratory tests results included normal levels of albumin, ferritin, folic acid, vitamin B12, LDH, TSH, ALT, AST, GGT, alkaline phosphatase, amylase, total cholesterol, and total triglyceride. Urinalysis was normal. 24-hour urine collection for proteinuria was negative. Protein electrophoresis showed a slight increase in gamma-globulin level (21.7%). A chest X-ray was normal. An abdominal ultrasound showed a bright liver. Esophagogastroduodenoscopy showed nonspecific mild gastropathy and duodenitis. Colonoscopy was normal. To assess for the presence of heart failure, echocardiography revealed concentric hypertrophy of the left ventricle with significant dysfunction (ejection fraction of 34%); severe diastolic dysfunction such as restrictive cardiomyopathy and severe tricuspid regurgitation. Cardiac MRI was performed to exclude infiltrating cardiomyopathy. The exam revealed the presence of transmural myocardial late gadolinium enhancement, suggestive of cardiac amyloidosis. Serum protein immunofixation showed oligoclonal bands, and urine protein immunofixation showed the presence of albumin and gamma-globulins. Urinalysis for Bence Jones proteinuria was negative. Serum free light chain analysis showed a slight increase in kappa (61.4 mg/L) and lamba chains (28.4 mg/L), with an increase of their ratio (2.16). Bone tracer cardiac scintigraphy with 99mTc-labeled hydroxymethylene diphosphonate showed a grade 3 positive bone tracer cardiac scintigraphy. So, a diagnosis of transthyretin amyloidosis (ATTR) cardiomyopathy (CM) was made.
ATTR-CM refers to the deposition of misfolded transthyretin (TTR) proteins as amyloid fibrils in the myocardium and elsewhere. It is mainly a disease of the elderly. ATTR-CM is subdivided into two types: hereditary (ATTRh), caused by mutations in the TTR gene, and wild-type ATTR (ATTRwt), his-

torically known as age-related or senile amyloidosis, which occurs in the absence of a TTR gene mutation. The main clinical feature of ATTR-CM is heart failure. Other cardiovascular manifestations are arrhythmias and aortic stenosis. Some patients also have multiple age-related comorbidities, some of which may be exacerbated by ATTR, including neurologic, musculoskeletal, and gastrointestinal problems. Alternative diagnosis includes AL amyloidosis. However, it is important to note that an unrelated monoclonal gammopathy of undetermined significance may be associated with ATTR-CM even if identification of the monoclonal protein suggests AL amyloidosis. In particular, identifying the specific etiology of cardiac amyloidosis has important implications for optimal medical management and introduction of disease-modifying therapies. Furthermore, genetic testing for patients with confirmed ATTR-CM, even older patients who are more likely to have ATTRwt, is critical to determine eligibility for novel ATTR disease modifying therapies, risk for extracardiac involvement, prognosis, and to determine the need to screen family members.

64. AN UNEXPLAINED CASE OF LOWER EXTREMITY GANGRENE

Scarpati R.[1], Cecchini A. L.[1], Biscetti F. [2], Rando M. M.[2], Nardella E.[2], Rossini E.[2], Nicolazzi M. A.[2], Pecorini G.[2], Massetti M.[3], Gasbarrini A.[4], Flex A.[2]
[1]Università Cattolica del Sacro Cuore, Largo Francesco Vito 1, 00168 Roma, Italy; [2]Cardiovascular Internal Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy; [3]Department of Cardiovascular Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy; [4]Department of Medical and Surgical sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy

A 73-year-old woman was admitted to the hospital with non-traumatic painful left toes and heel gangrene, developed over two months. History of ischemic heart disease treated with angioplasty and stent placement, abdominal aneurysm, paroxysmal atrial fibrillation on DOACs, hypertension and smoking habit. Physical examination revealed swelling in the left leg and foot, normal limb skin temperature and peripheral arterial pulses, without neurological deficits. Laboratory exams showed Hb 10.2 g/dL, WBC 10.630 mm3, creatinine 0.97 mg/dL, CK 104 IU/L, aPTT 45.5 seconds, CRP 73 mg/l, NTproBNP 2185 pg/ml. Antibiotic therapy and adequate analgesia were prescribed. Considering comorbidities and patient risk factors, atherosclerotic macrovascular involvement initially appeared to be the most plausible cause of lower limb ischemia. A Doppler-ultrasound of lower extremities was then performed documenting only distal obstruction of the left posterior tibial artery. Collaterally, bilateral distal deep vein thrombosis was found. In view of the minimal arterial atherosclerotic burden which did not explain the severity of ischemia, other underlying causes of the patient's ischemic ulcers were investigated. Considering the unusual site of arterial occlusion, the long history of AF with no reported embolic complications, and optimal anticoagulant therapy, cardioembolism seemed less likely. In addition, echocardiogram excluded macroscopic thrombi and regional wall akinesia. Furthermore, dilated heart with mean left ventricular dysfunction (EF 47%), moderate functional mitral regurgitation, grade II diastolic dysfunction and pulmonary hypertension were documented. Among other macrovascular causes of ischemia, atheroembolism was investigated with chest and abdomen CT scan, which confirmed the presence of abdominal aortic aneurysm (49 mm x 38 mm x 42 mm) stable in size, with thrombotic apposition. The case was discussed in a multidisciplinary team giving the indication for conservative treatment with ongoing triple antithrombotic therapy and regular follow-up. However, in view of the need for elective vascular surgery in the event of aneurysm enlargement, the patient underwent diagnostic coronary angiography which documented RCA in-stent restenosis, and a new stenosis of the proximal-mid LAD. An angioplasty of the stenoses was performed and dual antiplatelet therapy prescribed. As the most common thrombotic causes of lower limb ischemia were reasonably excluded and given the multifocal thrombosis within the venous and arterial vasculature despite optimal antithrombotic therapy, the suspicion of a rarer underlying thrombotic disease arose. Therefore, the patient's history was further investigated for possible clues to support a thrombophilic condition and multiple abortion history, and an episode of left retinal vein occlusion was discovered. Furthermore, during hospitalization, the aPTT values were persistently prolonged. A systemic disease underlying the patient's thrombotic diathesis was evaluated with immunological tests and a triple positive antiphospholipid syndrome (APS) was found (presence of ANA 1/160 with coarse speckle pattern, Anti-cardiolipin IgM 46.3/ < 20.0 U/mL, Anti -beta2-glycoprotein1 62/< 20.0 U/mL and Lupus Anticoagulant positive in two determinations three weeks apart). The remaining exams were negative, and a rheumatologic evaluation ruled out the possibility of superimposed vasculitis or connective tissue disease. The final diagnosis of gangrene for microvascular involvement in triple positive APS was made and anticoagulant therapy was switched to warfarin (target INR 2.5-3.5). Finally, an MRI of the left foot was ordered, and local osteomyelitis was documented, then the patient underwent a Chopart amputation, heel escharotomy, and dermal-epidermal graft surgery was performed.
The global prevalence of peripheral artery disease (PAD) is steadily increasing with the expanding atherosclerotic burden and an aging population. However, there is a broad spectrum of disorders in the context of nonatherosclerotic PAD (NAPAD), which remains underdiagnosed or misdiagnosed in the emergency department. Clinical suspicion of NAPAD should arise in the presence of ulcers in an unusual site, absence or minimal atherosclerotic risk factors, and clinical signs/symptoms for which the cutaneous manifestation is only an epiphenomenon of the underlying systemic disease. APS represents one of the major causes of NAPAD and although dermatological manifestations are not included in the classification criteria, skin involvement may be the leading cause of ED admissions for this syndrome and plays a key role in achieving the diagnosis.
However, the dermatologic presentation of APS is extremely heterogeneous and lacks a pathognomonic pattern. Thus, ulcers involving uncommon sites in patients with multifocal venous and arterial thrombotic involvement should raise suspicion of this rare condition. Early diagnosis is essential to prevent further disabling complications. This report highlights the need for greater awareness of rare diseases, such as NAPAD, which collectively account for nearly 8-10% of global diseases.

65. LOCKED-IN SYNDROME: A CORPSE WITH LIVING EYES

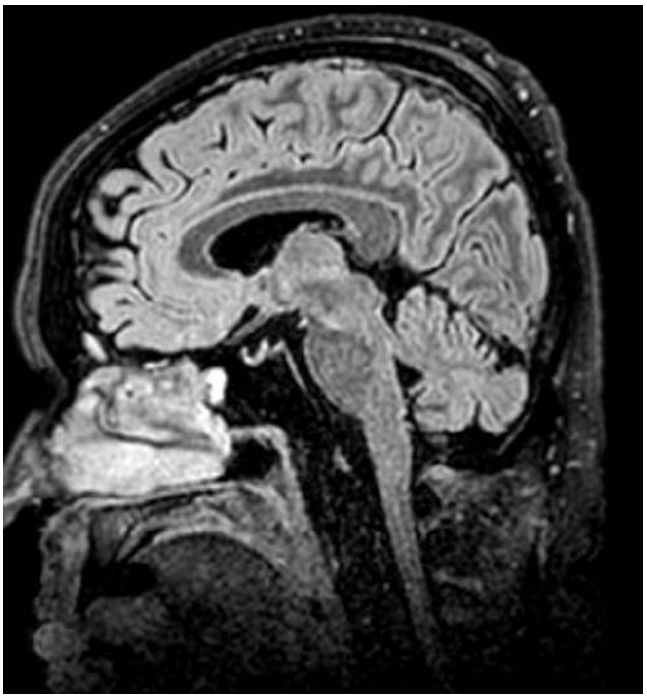
Gravina F.[1], Del Toro R.[2], Fulco E.[3], Domenicali M.[2]
[1]Santa Maria delle Croci, Ravenna, Università degli studi di Bologna; [2]Santa Maria delle Croci, Ravenna; [3]Santa Maria delle Croci, Ravenna, Università degli studi di Bologna

We present a case of a self-sufficient 58-years-old man with panhypopituitarism in primary empty sella and previous total thyroidectomy for carcinoma, under replacement treatment with cortisone acetate and levothyroxine.
He was admitted to our hospital for severe hyponatremia (Na 109 mmoli/L) secondary to inadequate cortone supplementation adjustment during a recent SARS-CoV2 infection and to SSRI intake for new onset depressive syndrome. The patient was treated with intravenous hydrocortisone and hypertonic solution observing an increase in sodium values (Na 149 mmol/L at 72 hours). SSRI was also suspended. Returning home, he presented a rapid and progressive cognitive and motor decline with lethargy, mutism, dysphagia and loss of autonomy. Once back in the emergency room he showed a clear ideomotor slowdown, with poor functional and motor capacity and episodes of absence with open eyes. Laboratory tests showed mild hyponatremia (126 mmol/L), whereas brain CT and rachicentesis resulted negative for acute events and infections. The suspicion of pontine myelinolysis was raised, therefore a brain MRI was performed confirming this hypothesis. Our patient, after losing swallowing function, developed aspiration pneumonia and respiratory failure requiring ventilatory assistance with IOT and eventually resuscitation, followed by a long period of rehabilitation. Pursuing a radiological and neurological reevaluation, a picture of locked-in syndrome was described. The patient presented open eyes with pupils reacting to light stimulus and to threat, but he was unresponsive to pain and unable to speak, move or even lock the examiner's gaze. Radiological damage to the structures of the brainstem was noted, with involvement of the ascending reticular formation and disconnection between brainstem and cortical areas, in association with injury of the descending motor pathways. Pontine myelinolysis is a rare and very severe complication that can arise after overly rapid correction of hyponatremia. Chronic hyponatremia (for more than two to three days) is associated with loss of osmotically active osmolytes (myoinositol, glutamate, and glutamine) from astrocytes, resulting in brain cell swelling. Following a rapid correction, organic osmolytes cannot be quickly replaced, while the loss of cell water combined with movement of sodium back into these cells determine injury to astrocytes and oligodendrocytes, reduction of brain volume and demyelination. (1;2) With this case report we want to emphasize the importance of adequate supplementation of cortone in patients with adrenal insufficiency in conditions of stress, trauma or infection

and a careful evaluation of concomitant drug therapy such as use of antidepressants. As regards the episode of depression that the patient presented, this could also be a manifestation of latent adrenal insufficiency that was ongoing. It is also underlined the importance of careful attention in the replenishment of sodium, which should not exceed 6 to 8 mmol/L in any 24 h period, even in acute conditions of severe hyponatremia.

References:

(1) Lien YH, Shapiro JI, Chan L. Study of brain electrolytes and organic osmolytes during correction of chronic hyponatremia. Implications for the pathogenesis of central pontine myelinolysis. J Clin Invest. 1991 Jul.
(2) Sterns RH, Silver SM. Brain volume regulation in response to hypo-osmolality and its correction. Am J Med. 2006 Jul.
(3) Sterns RH. Treatment of Severe Hyponatremia. Clin J Am Soc Nephrol. 2018 Apr 6.



66. THE USUAL CASE OF COUGH AND DIFFICULTY BREATHING?

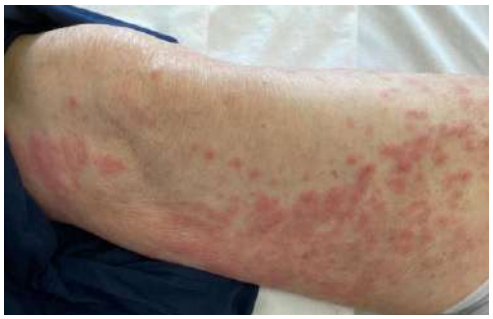
Santoro M.[1], Cecchini A. L.[1], Biscetti F.[2], Rando M. M.[2], Nardella E.[2], Rossini E.[2], Nicolazzi M. A.[2], Pecorini G.[2], Massetti M.[3], Gasbarrini A.[4], Flex A.[2]
[1]Università Cattolica del Sacro Cuore, Largo Francesco Vito 1, 00168 Roma, Italy; [2]Cardiovascular Internal Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy; [3]Department of Cardiovascular Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy; [4]Department of Medical and Surgical sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy

AT is a 73-year-old male patient presenting to the emergency department for chest pain, reporting also fever, dyspnea and cough with purulent sputum 3 days prior. No other comorbidity besides a suspected diagnosis of chronic obstructive pulmonary disease was reported. Until then, the patient had led a very active life with regular physical activity despite being a former smoker with a cumulative pack-year score of 45. Upon admission to the hospital arterial blood pressure was 185/111 mmHg, and EKG showed lengthened QRS and nonspecific repolarization abnormalities.
No significant laboratory abnormalities were found.
The cardiologist was consulted in the ER and bedside echocardiogram revealed severe aortic stenosis with left ventricular hypertrophy and post-stenotic aortic aneurysm.
Blood pressure-lowering therapy was increased and the patient was then admitted to our department to continue the diagnostic workup.
A thorough investigation of the patient's past medical history confirmed the absence of other relevant diseases, except the presence of a known history of heart murmur since youth. An official echocardiogram confirmed a severe aortic stenosis with moderate regurgitation, anular calcification, post-stenotic aortic aneurysm and documented a marked left ventricular ventricle remodeling with eccentric hypertrophy (IVSd 24mm, LPWTd 13mm). Furthermore, moderate mitral regurgitation, moderately reduced ejection fraction and II-degree diastolic dysfunction with associated atrial dilation were also reported. Subsequently, Angio CT scan was performed to evaluate the ascending aorta aneurysm and the coronarography initially excluded significant coronary artery disease. The case was then discussed in the Hearth Team giving an indication for elective aortic valve surgery and ascending aorta replacement. In addition, a cardiac MRI was ordered to further investigate the highly suspicious cardiac hypertrophy pattern. The MRI documented the presence of late contrast enhancement in the interventricular septum with increased extracellular volume adt T1 mapping. The findings were mostly significant for infiltrative hypertrophic cardiomyopathy with suspected transthyretin amyloidosis. Therefore, bone-tracer cardiac scintigraphy was requested for confirmation but resulted negative. Other causes of amyloidosis have been studied. Preliminary blood test screening for hematological malignancies was negative and the patient's periumbilical fat biopsy and blood samples were collected to test for rarer genetic causes of amyloidosis. One month after discharge, the patient underwent surgical replacement of the aortic valve and ascending aorta with a biological prosthesis implantation. Cardiac myomectomy and biopsy could also be performed intraoperatively. Echocardiographic evaluation after implantation was performed and procedural success was confirmed, the exams also reported persistence of mild systolic dysfunction and mild pericardial effusion. The postoperative period was complicated with atrial fibrillation episodes, successfully cardioverted with intravenous amiodarone, and platelet deficiency (65*10^9/l). The patient was transferred to a cardiac rehabilitation center. Finally, the results of the biopsy of the fat sample arrived, but they were negative while histopathological analysis of the surgical heart sample confirmed cardiac amyloidosis.During the stay in rehabilitation, a follow-up echocardiogram documented significant fluid formation around the heart and the patient was immediately transferred back to our emergency department for evaluation. In the ER echocardiography and subsequent chest CT-scan confirmed the presence of hemopericardium with collapse of both atria with clinical signs of tamponade. The patient was admitted to our cardiac surgery unit. Blood tests upon admission showed worsening platelet counts (47*10^9/l) and hematologic consultation was requested to perform a bone marrow biopsy. Given the need for evacuation of the hemopericardium, a new cardiac and coronary CT for preoperative planning was requested showing significant previously undetected stenosis of the anterior descending artery and circumflex artery. Progressive spontaneous rise of platelet count allowed the execution of surgical revision of the pericardium with complete hematoma evacuation confirmed by follow-up echocardiograms. In the absence of immediate complication the patient was transferred to an in-hospital intensive cardiac rehabilitation unit. Several days after surgery, bone marrow biopsy documented a pathological expansion of plasmacellular component (6-8% with lambda clonal restriction) and reduced erythroid and megakaryocytic line. Therefore, the patient is undergoing regular hematological visits to monitor the evolution of the clonal plasma cell disease and we are waiting for the genetic analysis to identify the mutation of the likely genetic amylodosis.

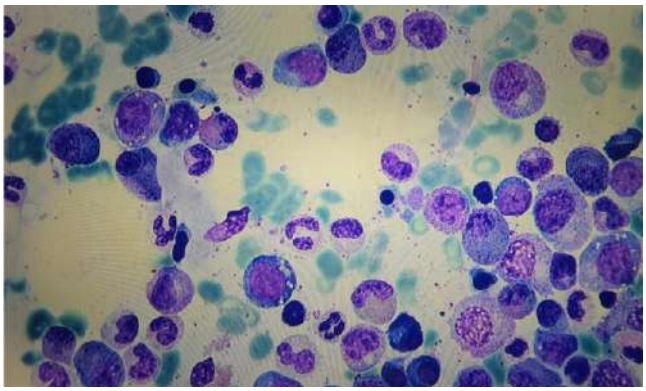
67. THE TRUTH OF THE SKIN

Soldini D.[1], Bontempelli E.[2], Betelli M.[2], Benetti A.[2]
[1]Dipartimento di medicina e chirurgia, Università degli studi di Milano; [2]Dipartimento di medicina interna, ASST Papa Giovanni XXIII Bergamo

An 83 years-old man with a history of hypertension, dyslipidaemia, benign prostatic hypertrophy showed at our emergency department complaining of fever, night sweats, weight loss and cutaneous rash (*figure 1*).



His clinical history showed the onset of skin rash on the face and limbs for about six months. Soon after the onset a skin biopsy was performed, which showed a lympho-histiocytic infiltrate, with no signs related to cutaneous vasculitis. A blood count was also performed, showing macrocytic anaemia for which folic acid and vitamin B complex were prescribed. For the skin rash oral corticosteroid was prescribed, with tapering over one month. At the end of the steroid therapy, the rash reappeared along with fever.
He was then admitted into a Medicine ward of another Hospital. He underwent numerous exams, including a blood panel, serologies for various antibodies, celiac disease, blood-cultures and a total-body CT-scan. Except for positive markers of inflammatory response, no significant findings were found. He was evaluated by a dermatologist which concluded for a possible diagnosis of chronic eczematous dermatitis. He was discharged without steroid or antibiotic therapy. From the day of discharge the patient complained the persistence of the cutaneous rash, continuous fever, night sweats. He was given several courses of various antibiotic therapy by his primary care physician, without success.
At the arrival in our ward, on clinical examination the fever had no clear organ-related origin. He underwent a complete blood-panel, showing signs of inflammatory activation (ESR 114 mm/h, CRP 5.1 mg/dl). Blood count showed a macrocytic anaemia. Other significant tests included a raised B2-microglobulin levels and an electrophoretic tracing compatible with inflammatory phase. Screening blood tests for human immunodeficiency virus (HIV) type 1 and 2, Lyme disease, Cat scratch disease (CSD), Brucellosis, Q-fever, hepatotropic viruses, Mycoplasma were negative. Interferon-γ release assay for Tuberculosis was negative. Serologies for EBV, CMV, Toxoplasma showed previous infection by these agents but no current infection. Blood cultures sets for both aerobic and anaerobic microorganisms were negative. Procalcitonin levels were low and no antibiotic therapy was given during the hospitalization.
Radiologist tests included a negative chest X-ray and a transoesophageal echocardiogram showing no signs of endocarditis.
It was therefore decided to perform a PET-total body with 18F-fluorodeoxyglucose: the examination highlighted lymphnode-hyperfixation in the mediastinum, findings suggestive for an inflammatory/infectious disease as well as a lymphoproliferative/granulomatous disorder.
Suspecting an autoinflammatory syndrome he underwent a bone-marrow biopsy.The examination of the bone marrow smare showed cytoplasmic vacuolation of granular and erythroid progenitor cells (*figure 2*) and mild eosinophilia. The cytofluorometric analysis found a B lymphocyte clone SIG-Lambda, for a total of 5% of bone marrow cellularity. There was no evidence of peripheral bool lymphocytosis. The findings were consistent with monoclonal B lymphocytosis chronic lymphocytic leukaemia-like (MBL CLL-like). Bone marrow biopsy findings did not fill the criteria for myelodysplastic syndrome. He was therefore discharged with oral steroid after a high-dose load and with a short-term revaluation.
The diagnosis of VEXAS syndrome (acronym for vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) was made by the sequencing and finding of a mutated UBA1 gene (p. Met41).
VEXAS is a syndrome first reported in 2020 in 25 men with adult-onset inflammatory disease and myeloid dysplasia. It's a monogenic disease caused by somatic mutation of the UBA1 gene in hematopoietic progenitor cells. The gene is essential for the regulation of protein turnover involved in cell cycle, cell death. The pathophysiological mechanism of this disease is still fully to be understood, but these patients show an increased level of serum inflammatory markers and aberrant activation of the immune signalling pathways. Examination of the bone marrow smears typically show the presence of vacuoles in the cytoplasm of myeloid medullary progenitor cells, especially in erythroid and granular precursors. However this finding is not pathognomonic. The symptoms are typically inflammatory, including fever, arthritis, skin involvement and lung involvement and haematologic symptoms resulting from cytopenia. In approximately 50% of cases VEXAS is associated with MDS (myelodysplastic syndrome).
It is a disease with poor prognosis and requiring the use of high-dose glucocorticoids. There are various therapeutic approaches,such as azacitidine or the inhibitors of the Janus kinase pathways (Ruloxitinib).
Our patient, discharged with an oral glucocorticoid therapy, underwent an improvement of the anaemia and remission of fever in the first period of time. However after three months he was readmitted with a new erythema of the left leg, fever and a pulmonary infiltrates suggestive of opportunist pathogens infection.



68. HEPATITIS C VIRUS-ASSOCIATED MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS WITHOUT DETECTABLE CRYOGLOBULINEMIA: A RARE CASE PRESENTATION

Cavallaro C.[1], Biscetti F.[2], Rando M. M.[2], Nardella E.[2], Rossini E.[2], Cecchini A. L.[1], Nicolazzi M. A.[2], Pecorini G.[2], Scarpati R.[1], Massetti M.[3], Gasbarrini A.[4], Flex A.[2]
[1]Università Cattolica del Sacro Cuore, Largo Francesco Vito 1, 00168 Roma, Italy; [2]Cardiovascular Internal Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy ; [3]Department of Cardiovascular Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy; [4]Department of Medical and Surgical sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy

Background: Hepatitis C virus (HCV) infection has been shown to affect the kidneys with various histopathological patterns on renal biopsy. These commonly include a membranoproliferative glomerulonephritis (MPGN) pattern with mixed cryoglobulinemia (CG), thrombotic microangiopathy, membranous nephropathy, or vasculitis involving the medium and small vessels of the kidneys causing polyarteritis nodosa. However, HCV infection without CG is rarely associated with MPGN . We present the case of a 51-year-old male who presented to us with HCV-associated MPGN without detectable cryoglobulinemia.
Case presentation: A 51-year-old man with a history of intravenous drug abuse, alcohol use disorder, hypertension and chronic kidney disease (CKD) diagnosed 1 year ago, presented to our attention for high blood pressure, poorly responsive to home medical therapy. His blood pressure was persistently above 180/90 mmHg despite the maximum allowable doses of ACE-inhibitor, beta-blocker, calcium channel blocker and alpha-lytic. He had never had relevant pitting oedema. Initial laboratory tests revealed a normal WBC count, mild anemia (hemoglobin 12.9 g/dL) and thrombocytopenia (platelet count 67x10^9/L). His creatinine at admission was 1.07 mg/L. His liver enzymes were normal and serum albumin was 19 g/L. His initial urinalysis showed albuminuria (2 g/L) without presence of red blood cells/hpf. His C-reactive protein was persistently normal. Renal ultrasonography revealed normal sized kidneys with diffuse hyperechoic echostructure, slightly reduced cortico-medullary differentiation, and a thin fluid layer in the right perirenal site, indicative of acute nephropathy. His 24 h urinalysis showed severe proteinuria with an excretion of 7.8 g per day. The search of anti-nuclear antibodies (ANA), HBsAg and HIV antibodies was negative. Complement C3 was low at 81,5 mg/dL (normal range 90-180). Anti-HCV antibodies were positive with an HCV-RNA viral load of 1209392 IU/ml, genotype 1a. Cryoglobulins and circulating immune complexes were undetectable in two determinations. An ultrasound-guided kidney biopsy was performed and a diagnosis of advanced-stage immune complex-mediated MPGN pattern was made. Direct-acting antiviral (DAA) treatment was promptly started observing a progressive resolution of the proteinuria and the lowering of blood pressure to normal values.
Conclusion: HCV infection can cause several distinct patterns of renal disease . The most frequent kidney lesion associated with chronic HCV is MPGN mainly due to cryoglobulinemia-induced vasculitis. HCV-related MPGN is due to the precipitation of cryoglobulins in the glomerular endothelial layer cells, which is distinguished by fingerprint pattern and subendothelial IgM and IgG deposition in the glomerulus capillary wall. Very rarely HCV-associated MPGN may occur as a consequence of an immune complex-mediated mechanism without detectable CG . The treatment of

HCV-related nephropathy primarily includes treatment of the HCV infection, although in some cases, it may be necessary to initiate immunosuppressive therapy to achieve remission of the nephropathy . Interestingly, although infrequent, even rarer forms of glomerulonephritis (such as membranoproliferative type 1 without cryoglobulinemia) could be found in association with HCV infection and benefit from DAA treatment.

Johnson RJ, Willson R, Yamabe H, Couser W, Alpers CE, Wener MH, et al. Renal manifestations of hepatitis C virus infection. Kidney Int. 1994; 46:1255–63

Sumida K, Ubara Y, Hoshino J, Suwabe T, Nakanishi S, Hiramatsu R, et al. Hepatitis C virus-related kidney disease: Various histological patterns. Clin Nephrol. 2010;74:446–56

Markowitz GS, Cheng JT, Colvin RB, Trebbin WM, D'Agati VD. Hepatitis C viral infection is associated with fibrillary glomerulonephritis and immunotactoid glomerulopathy. J Am Soc Nephrol. 1998;9:2244–52

Hepatitis C virus associated glomerulopathies. Ozkok A, Yildiz A. World J Gastroenterol. 2014;20:7544–7554

Membranoproliferative glomerulonephritis—a new look at an old entity. Sethi S, Fervenza FC. N Engl J Med. 2012;366:1119–1131

Dammacco F, Sansonno D (2013) Therapy for hepatitis C virus–related cryoglobulinemic vasculitis. N Engl J Med 369:1035–1045. https://doi.org/10.1056/NEJMra1208642

69. SUPERIOR MESENTERIC ARTERY STENOSIS IN PATIENT WITH MULTIVESSEL CORONARY ARTERY DISEASE: A MULTIDISCIPLINARY TEAM MANAGEMENT CASE REPORT

Barberio A.[1], Biscetti F.[2], Rando M. M.[2], Nardella E.[2], Cecchini A.L.[1], Rossini E.[2], Nicolazzi M. A.[2], Pecorini G.[2], Massetti M.[3], Gasbarrini A.[4], Flex A.[2]

[1]Università Cattolica del Sacro Cuore, Largo Francesco Vito 1, 00168 Roma, Italy; [2]Cardiovascular Internal Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy ; [3]Department of Cardiovascular Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy; [4]Department of Medical and Surgical sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy

A Caucasian 66-year-old woman came to our Hospital with symptoms suggesting abdominal angina, progressively increasing in frequency and severity since 5 months. She complained of abdominal pain increasing after meals, progressive reduction of food intake with a weight loss of more than 15kg in 5 months. After several medical consultations, including an ultrasound that ruled out alterations in organs and systems, a computed tomography (CT) angiography revealed thrombotic occlusion of the superior mesenteric artery immediately after the origin, with stenosis of the celiac axis and hypogastric arteries. Her past medical history included: aortic stenosis, previous Hodgkin lymphoma treated with radiotherapy and splenectomy, previous subarachnoid hemorrhage, previous retinal ischaemia, glaucoma, arterial hypertension, carotid artery stenosis, nodular thyroid disease in euthyroidism, chronic HBV infection. Non-smoker, exposed to passive smoke for more than 40 years, familiarity with cardiovascular disease. Recent SARS-CoV2 infection (10-15 days before the appearance of gastrointestinal symptoms). At the hospital admission the physical examination did not show any relevant alteration. The patient underwent total body CT to rule out the paraneoplastic etiology of the thrombosis, and the consulted hematologist excluded recurrence of lymphoma. The CT provided evidence of likely post-radiation paramediastinal fibrosis findings, calcifications of the thoracic aorta and coronary arteries. Thrombophilic screening was negative. Cardiovascular risk evaluation was executed by supra-aortic vessels doppler-ultrasound that revealed 35% stenosis of external right carotid artery and low-limb ultrasound that ruled out hemodynamically relevant stenosis. The echocardiogram described absence of segmental kinetic alterations, aortic valve of tricuspid morphology with low to medium grade transvalvular gradients and low flow (described as "paradoxical" low-flow low-gradient) associated with mild regurgitation. The patient also complained of several pre-syncopal episodes, mainly after physical efforts or after meals; cerebral TC excluded acute alterations, Holter electrocardiogram of the 24 hours excluded relevant arrhythmias, lower limb venous doppler ultrasound ruled out deep vein thrombosis in the suspicion of pulmonary embolism. Considering the cardiovascular risk profile, the patient underwent a coronarography that described a multivessel disease with 80%+70% middle anterior-interventricular stenosis, 95% proximal circumflex-artery stenosis, 80% middle circumflex-artery stenosis, 80% ostial-left-coronary stenosis, 60% of middle and distal left-coronary stenosis. The clinical case was thus discussed in the multidisciplinary Heart Team and it was concluded that the high risk of embolization of the mesenteric artery lesion made a surgical approach preferable to the endovascular treatment. Anyway, multi-vessel coronaropathy made prohibitive the surgical risk of open vascular treatment of the mesenteric artery, and at the same time, mesenteric ischemia and fibrotic mediastinal alterations due to the previous radiotherapy treatment contraindicated the open surgical coronary treatment. Because of the complexity of the percutaneous endovascular treatment of the coronaropathy, the team decided to treat superior mesenteric artery with percutaneous revascularization, evaluating at the resolution of the mesenteric issue the treatment of the coronaropathy and the aortic valvulopathy, sharing with the patient the intra-operatory risk of the treatment. The patient underwent the percutaneous revascularization and a superior mesenteric artery percutaneous transluminal angioplasty (PTA) was executed, requiring a deep sedation with anesthesiologic support, with the positioning of a bare-metal stent into the superior mesenteric artery and a covered stent in the inferior mesenteric artery. The patient began a dual antiplatelets therapy (DAPT) with ASA 100 mg/die and clopidrogrel 75mg/die for 30 days, then discontinued clopidogrel. Statins were also administered. At one-month checkup, the patient reported relief from digestive symptoms and a general well-being, with a weight gain of 1,5 kg. A doppler ultrasound excluded a stent-restenosis. She also denied symptoms referring to her coronaropathy. After the suspension of DAPT, the patient underwent cardiac surgery with an "off-pump" bypass of the anterior interventricular artery and the diagonal branch. An endovascular treatment of the circumflex coronary artery was afterwards performed. Often, patients with chronic mesenteric ischaemia have an increased risk of all cardiovascular events related to the systemic presence of atherosclerotic disease. In this case, the patient was diagnosed with a multivessel coronary artery disease besides a moderate aortic insufficiency (possibly symptomatic) and this, together with the history of mediastinal irradiation with sequent fibrosis, made the case notably challenging, underlining the importance of a multidisciplinary discussion for a tailored medicine. A step-by-step planning is in fact mandatory to reduce the intraoperative risk of such a complex treatment.

70. A CASE OF A YOUNG MAN WITH TAKAYASU AND UNUSUAL RECURRENT BLEEDING: NEVER JUDGING BY APPEARANCES

Metsovitis T.[1], Cecchini A. L.[1], Biscetti F.[2], Rando M. M.[2], Nardella E.[2], Rossini E.[2], Nicolazzi M. A.[2], Pecorini G.[2], Massetti M.[3], Gasbarrini A.[4]

[1]Università Cattolica del Sacro Cuore, Largo Francesco Vito 1, 00168 Roma, Italy; [2]Cardiovascular Internal Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy; [3]Department of Cardiovascular Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy; [4]Department of Medical and Surgical sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy

We report the case of a 42-year-old male whitewasher, affected by Takayasu, quiescent since 2003 on steroids and methotrexate, admitted to the Emergency Department for pain, swelling, and functional limitation in the left thigh. No traumatic events were reported. The patient had a history of aortic regurgitation treated with aortic valve replacement but native aortic root sparing. Warfarin was prescribed for the mechanical prosthesis. On admission, vital signs were in the normal range. Laboratory tests were performed showing INR on target (2.37), prolonged aPTT (67.7 seconds), normal hemoglobin (14 g/dL), and CRP mildly elevated (18.5 mg/L). An ultrasonography exam documented an extensive hematoma in the anterior-lateral region of the left thigh (7x5x15 cm). Over the next few days, despite only mild tachycardia and fatigue, hemoglobin levels dropped rapidly (down to 9.7 g/dL) so a CT scan with contrast was performed showing local bleeding with active arterial blush. The patient underwent arterial embolization of a branch of the first perforating artery originating from the deep femoral artery and was transfused with one unit of packed red blood cells. Anticoagulation was continued by substituting warfarin for cautiously escalating doses of low molecular weight heparin (LMWH) to preserve the mechanical valve. During the stay in our Internal Medicine Department, the hematoma significantly reduced and the left limb mobility gradually improved after several sessions of physiotherapy. Hemoglobin and CRP levels gradually returned to normal, while aPTT remained slightly elongated.

The patient's history was further investigated and interestingly, four similar episodes of spontaneous muscle hematoma had occurred in the previous years, since oral anticoagulation with Warfarin was started despite an optimal

control of INR and immunosuppression for Takayasu. In those cases a conservative approach was preferred without the need for transfusions, Warfarin was always temporarily replaced with LMWH. Bleedings were considered as "expected" complication of anticoagulation in a manual worker.
Concerning the recurrence of non-traumatic-muscle hematomas without CT-detected local predisposing factors (muscle pseudotumor), other causes were investigated. Therefore, the patient underwent rheumatologic evaluation, after a PET-CT negative for active arteritis, and his ongoing immunosuppressive therapy was confirmed. Among the patient's previously available laboratory tests, only aPTT values were always above the normal limits. Finally, other patient's family members were examined for possible clues of bleeding diathesis, and a higher incidence of mucosal bleeds and soft tissue hematomas was discovered in the patient's uncle.
Therefore, in view of the possible presence of underlying bleeding disorders, coagulation factors levels were tested and factor IX was found to be slightly decreased (34.4%), which was consistent with mild B hemophilia. Genetic testing was performed and confirmed the presence of the c.275T>C variant of the F9 gene in hemizygosity. This identified variant was not reported in the main reference databases or present in the frequency databases of the general population and was not reported in scientific literature. A prophylactic administration of recombinant factor IX was initiated together with anticoagulation due to the thrombotic risk associated with the mechanical valve prosthesis. Furthermore, transthoracic echocardiography was performed, which excluded any thrombotic complications on the mechanical valve, and showed increased diameters of the aortic bulb (49 mm), ascending aorta (56 mm), and aortic arch (42 mm). A CT with contrast confirmed the aortic aneurysmatic dilatation and documented also the presence of a pseudoaneurysm of the aortic bulb postero-lateral wall, further confirmed by trans-oesophageal echocardiography. After a multidisciplinary discussion, the patient underwent a procedure of aortic valve and ascending aorta replacement, tailoring immunosuppressive therapy and recombinant factor IX infusion to the intervention. Takayasu arteritis is a systemic vasculitis often involving the aorta and its major branches. Aortic dissection is a common complication of Takayasu frequently extending to the aortic valve that requires surgical repair, preferably including the combined aortic valve and root replacement procedure due to less late complications (including pseudoaneurysms). The decision between bioprosthetic or mechanical valves should be personalized on the patient's life expectancy, occupation at risk, and, in particular, anticoagulation-related bleeding risk. However, the recurrence of hematoma in an unusual site (non-traumatic muscle hematoma) in relation to the patient's age, the absence of systemic or local predisposing factors (history of bleeding diathesis, unexplained discrepancies in coagulation tests) should lead to more precisely exploring additional underlying causes of bleeding such as hemophilia, which in mild presentation is often not diagnosed until adulthood. Bleeding risk can be managed with the prophylactic administration of recombinant factors also together with anticoagulation.

71. IBRUTINIB-RELATED HEMORRHAGIC PERICARDIAL DISEASES

Valenti A., Maestroni S., Betelli M., Assolari A., Scarpellini F., Soldini D., Cumetti D., Benetti A.
Dipartimento di Medicina, Ospedale Papa Giovanni XXIII, Bergamo

Introduction: Ibrutinib is a inhibitor of B cell proliferation. It is approved for the treatment of several B-cell malignancies and as a first-line therapy of Chronic Lymphocytic Leukemia (CLL). It is generally well tolerated, however in the last years cardiac side effects and major bleedings emerged. We collected trhee cases of haemorrhagic pericardial effusions. To the best of our knowledge, only few cases of this rare complication have been reported.
Case series: Case 1 : A 75-years-old man affected by LLC on treatment with Ibrutinib from two months, who presented pericarditic chest pain and shortness of breath . At the emergent evaluation a cardiac tamponade was discovered and concomitant atrial fibrillation. The pericardiocentesis drained 770 ml of bloody pericardial fluid.
Case 2: A 67-years-old man with a history of LLC on treatment with Ibrutinib from ten months, who had chest discomfort, acute dyspnea and instrumental evidence of cardiac tamponade and concomitant atrial fibrillation. The patient underwent an emergent pericardiocentesis with the removal of 700 ml of serous-hemorrhagic fluid.
Case 3: A 74-years-old man affected by LLC and chronic atrial fibrillation. The home medications were ibrutinib from three years and warfarin. He complained acute dyspnea and the emergent echocardiogram revealed severe pericardial effusion without hemodynamic instability. The INR was whithin the target range. The pericardiocentesis, performed the day after hospital admission, collected 1600 ml of bloody fluid.
In all patiens the clinical presentation was acute and in case 1 and 2 it was associated with new onset of atrial fibrillation, typical pericarditis symptoms and significant elevation of inflammation markers. These two patients did not assume antiplatelet nor anticoagulant treatment. All the pericardial fluid samples were negative for infections and malignancies. Blood tests for autoimmunity were also negative. In all patients ibrutinib was promptely interrupted. In case 1 metilprednisolone was started (20 mg twice a day). In case 2 the patient was treated with ibuprofene (600 mg every 8 hours), colchicine (1 mg once a day) and prednisone (5 mg once a day). In case 3 only colchicine (1 mg once a day) was started. In case 2 ibrutinib was restarted after 4 months from cessation. In none patient pericardial effusion reoccured at the echocardiographic follow-ups.
Discussion and conclusions:
Ibrutinib is an irreversible inhibitor of Bruton's tyrosine kinase (Btk). BTK signaling pathway is critical for B-cell development and interfears with platelet function. The bleeding tendency associated with ibrutinib and eventually increased by concurrent antiplatelet or anticoagulant therapy can determine a challenging clinical scenario mainly if others cardiac adverse effects are present. Moreover in these cases the best therapy is not well established, except for the interruption of ibrutinib.

72. AN UNUSUAL ABDOMINAL OCCLUSION.

Kalaja D.
Dipartimento di Medicina, Università di Genova

Background: thalassemia is an inherited hematological disorder categorized by a decrease or absence of one or more of the globin chains synthesis. Beta-thalassemia is caused by one or more mutations in the beta-globin gene. The absence or reduced amount of beta-globin chains causes ineffective erythropoiesis which leads to anemia. Extramedullary hematopoiesis often occurs in hemoglobinopathies, hemolytic anemias, leukemias, lymphomas, and myeloproliferative disorders. Extramedullary hematopoietic masses are often microscopic and asymptomatic, but sometimes they lead to tumor-like masses. We describe massive intrathoracic and abdominal extramedullary hematopoiesis in a 57-year-old man with previously undiagnosed major beta-thalassemia.
Case report: A 57-year-old man presented in emergency medicine room with abdominal pain, nausea, vomit and progressive weakness in the last three weeks. Laboratory blood tests showed severe microcytic and hypochromic anemia (Hb 5.6 g/dl – MCV 59.6 fl, MCH 17.5 pg) without sign of gastrointestinal bleeding in physical examination. Chest-X-ray showed a polylobate right paramediastinic mass. Total CT body scan was then performed with the evidence of splenomegaly (17 cm) and multiple masses with not homogenous contrast enhancement in the extrapleural paravertebral space along the entire thoracic spine (max at right 6x5 cm) and in the pelvis - a large presacral mass with bony spiculations in the context – with the diameter of 13x12 cm. Liver increased in size and gallbladder containing lithiasis formations. No dilatation of intra and extrahepatic biliary tract. No ascites.
On physical examination the patient presented awake and oriented. Presence of jaundice, 2/VI systolic murmur at the aortic focus, flat and treatable abdomen with evident venous reticulum, not sore or painful, peristalsis present. Perimalleolar ulcer at left lower extremity. On rectal examination presence of pasty, normocolic stools without blood traces.
After transfusion of two units of blood, further investigations were performed: increased ferritin values (923 mcg/l – only partly related to the transfusions), severe folate deficiency with preserved B12 levels were found. Markers of haemolysis were also investigated: total bilirubin 2.5 mg/dl (direct 0.5 mg/dl), haptoglobin consumed 0.100 g/l, slightly increased LDH (191 U/l), negative Direct Coombs test. Reticulocyte index 1.4 indicative of hypoproliferative anaemia.
The **peripheral blood smear** showed marked anisopoikilocytosis with hypochromia of the red blood cells, reticulocytes characterised by dimensional and morphological abnormalities, numerous schistocytes and sparse erythroblasts; white series without morphological abnormalities, platelets with some dimensionally increased forms.
Hemoglobin electrophoresis - sample partly contaminated by previously blood transfusion - showed an adult haemoglobin (HbA) proportion of 85.2%, HbA2 4.5% and foetal haemoglobin (HbF) of 10.3%. Sickle-cell haemoglobin variant (HbS) is absent.
With the suspicion of haemoglobinopathy, we sent samples for genetic anal-

ysis to the Regional Microcythaemia Centre. Molecular characterisation (Next Generation Sequencing - NGS) revealed a homozygously mutation in the gene for beta-thalassaemia (the Portuguese type beta+) with a phenotype called **thalassaemia intermedia**, in which the classic complications of thalassaemia major (Cooley's disease) frequently appear in adulthood, as the mutation in the beta globin gene does not completely block the synthesis of the protein, but leads to a reduction in its synthesis and stability, guaranteeing the patient a minimum quota of effective erythropoiesis useful for reducing transfusion requirements. MRI for iron balance was then performed, showing severe liver iron overload, while cardiac still in normal ranges. The patient was then referred to our regional centre for hemoglobinopathies for transfusion support and iron chelation therapy.
Conclusion: These observations provide further support to include extramedullary hematopoiesis among the differential diagnosis of tumor-like masses. Masses distribution and tomography features can help Internist to rule out of other causes of expansive lesions. A strict dialogue with radiologists should be encouraged. A careful evaluation of blood cells count and morphology should be always considered in the diagnostic process in patients with suspected hematologic diseases.

73. A FATAL DRUGS INTERACTION BETWEEN CAPECITABINE AND BRIVUDINE

Benedetto C., Setti P., Thneibat A., Kalaja D., Ceccardi A., Bellodi A., Ballestrero A.
Dipartimento di Medicina Interna, Università degli studi di Genova

Background: Brivudine, a Thymidine analogue, it's an antiviral drug used in the treatment of the reactivation of varicella zoster virus (VZV). It is well known as a cause of irreversible inhibition of Dihydropyrimidine dehydrogenase (DPD). This enzyme is the initial and rate-limiting factor in the pathway of uracil and thymidine catabolism. Gene mutations of this enzyme or its inhibition result in increased risk of toxicity in patients receiving 5-Fluorouracil chemotherapy. Brivudine is then strictly contraindicated in patients undergoing 5-FU chemotherapy.
Case Report: We report the case of a 78 years old male with colo-rectal cancer in adjuvant therapy with Capecitabine (reduced dose 30% for age and comorbidities). The patient went to the Emergency Room (ER) because of the onset of mucositis associated with intense fatigue. In the ER departement the patient told Physicians that in the past 5 days He assumed Brivudine after the onset of signs and symptoms suggestive for VZV reactivation.
Laboratory test showed mild anemia (Hb 7.9 g/dl), mild thrombocytopenia (Platelets 104000/mm3), whilst White blood cells count was initially in normal range.
The patient was then transferred in the Internal Medicine ward where the diagnostic suspect of the drug interaction between Brivudine and Capecitabine was promptly made.
The Poison Control Centre of Pavia was called and the possibility of the utilization of an antidote to the overdose of Capecitabine (Uridine Triacetate) was discussed, even if we were out of the recommended timing for administration (no further than four days after the last dose of capecitabine).The administration of Uridine Triacetate started as soon as the antidote was available since it had to be bought from United Kingdom (seven days after admission in the ER and eleven days after the last dose of capecitabine). The administration was complicated by the need of nasogastric tube due to severe mucositis and progressive impaired state of consciousness.
In the next few days, despite the antidote and the massive supportive therapy (daily blood and platelets transfusions, Granulocyte colony stimulating factors (GCSF) administration) the lab test showed a worsening severe pancytopenia and, after about a week from first medical contact, the patient presented a WBC count ranging from 350 to 170, with 20 to 0 Neutrophils, Hb 9 to 7.3 and platelets 20.000 to 4.000.
According to the lab tests the patient's clinical conditions showed a deterioration with the worsening of the mucositis (oral, eye, anal) and the onset of fever and severe sepsis.
Several blood cultures were performed and showed the presence of *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Enterobacter cloacae complex*.
Appropriate antimicrobial drugs were administered (ceftolozane/tazobactam, daptomycin, caspofungin) without a real clinical improvement despite of the resolution of the fever.
Unfortunately, in spite of the efforts, after 13 days from first medical contact the patient had a cardiac arrest and died regardless of prolonged cardio-pulmonary resuscitation.
We highlight the case for the importance of drug to drug interactions, which can be sometime serious and even fatal; internists, as clinicians of complexity, must be aware of these events and must be prepared to make proper and timed interventions.

74. AN UNUSUAL CASE OF CHRONIC HEPATOPATHY

Iorio M.[1], Biscetti F.[2], Rossini E.[2], Rando M. M.[2], Nardella E.[2], Cecchini A.L.[1], Nicolazzi M. A.[2], Pecorini G.[2], Massetti M.[3], Gasbarrini A.[4], Flex A.[2]
[1]Università Cattolica del Sacro Cuore, Largo Francesco Vito 1, 00168 Roma, Italy; [2]Cardiovascular Internal Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy ; [3]Department of Cardiovascular Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy; [4]Department of Medical and Surgical sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy

A 75 years old man was admitted to our ward for disorientation started one week prior, acute respiratory failure in massive left pleural effusion, acute on chronic renal failure, hypokalemia and cholestasis. In the Emergency Department a cerebral Computerized tomography (CT) scan proved negative for acute ischemic or hemorrhagic events, an abdominal ultrasound showed no major abnormality, and a left thoracostomy catheter was placed, with clinical benefit.
The patient experienced polyserositis after receiving the initial dose of the COVID-19 vaccine, which led to the sudden development of pericardial effusion, pleural effusions, and ascites. High-dose steroid therapy was initiated, and autoimmune and rheumatological conditions were ruled out. The patient was referred to a hepatologist for persistent ascites and elevated liver enzymes. Extensive diagnostic investigations were performed, suggesting cardiogenic congestive hepatopathy. A diagnosis of fibro-adhesive pericarditis with a constrictive pattern was made based on echocardiogram and cardiac MRI findings. The patient underwent cardiac catheterization, revealing mild post-capillary pulmonary hypertension and diffuse arteriosclerosis. Steroid therapy was gradually tapered and discontinued, and a trial with Anakinra was initiated instead of surgical intervention. During this period, the patient developed bilateral lower limb edema, leading to an increase in oral diuretic therapy.
The patient's clinical history also included atrial fibrillation successfully cardioverted (in direct oral anticoagulants), chronic renal disease, recently diagnosed type 2 diabetes, mild multifactorial anemia and arterial hypertension.
At our evaluation the patient appeared alert, disoriented, apyretic, with normal vitals. No signs of meningitis were present, and an encephalogram and cerebral MRI turned out negative. Considering the patient's history of congestive hepatopathy, we suspected an hepatic encephalopathy, and serum ammonium was dosed, resulting above range even after evacuation (82 gamma/dl, n.v. 19-54). With the introduction of oral lactulose, we witnessed a prompt improvement of the patient's cognitive status, alongside an improvement of the general clinical conditions and a decrease of ammonium.
The echocardiogram performed on admission showed normal biventricular contractility with preserved ejection fraction (EF 68%) and improvement of only 2 over 7 parameters of constrictive pericarditis after one month (absence of annulus reverse and reduced suprahepatic veins caliber); as such, the patient was considered substantially non-responder to Anakinra. The pleural fluid resulted to be transudate rather than exudate, suggesting that the patient's clinical manifestations were mainly due to heart failure with preserved EF, ascribed to his cardiological condition.
Because of a single fever episode alongside a consensual increase of C-Reactive Protein (137.3 mg/L versus 29.9 mg/L at the admission), a SARS-CoV2 swab was performed, resulting positive, and a thoracic CT showed signs of COVID-19 pneumonia; a one shot therapy with Sotrovimab was prescribed.
All other microbiological investigations turned out negative, including Quantiferon; pleural fluid, sputum, urine and several blood cultures for bacteria, mycobacteria and mycetes; serology for EBV, CMV, HSV and atypical pneumonia bacteria. These findings corroborated the hypothesis that the majority of the patient's clinical manifestations on presentation were due to the underlying CP.
The case was discussed with a multidisciplinary team, and the indication to pericardiectomy was confirmed. The cardiac surgery was scheduled as soon as the patient turned out negative for SARS-CoV2, but two days prior the planned surgery the clinical course was complicated by a massive iliopsoas and retroperitoneal hematoma (a known feature in anticoagulated patients with COVID-19 pneumonia), which lead to hemorrhagic shock and brief cardiocirculatory arrest. The patient was transferred to the Intensive Care

Unit, and after an initial quick improvement he is now in critical condition because of multiorgan failure due to Klebsiella pneumonia sepsis.
Discussion: Constrictive pericarditis (CP) is a condition characterized by a thickened, rigid pericardium that restricts the expansion of the ventricles during diastole, leading to severe diastolic heart failure. Patients typically present with right-sided symptoms of heart failure. The exact prevalence of CP is uncertain, but it is commonly seen in patients who have undergone cardiac surgery, experienced pericardial trauma or inflammation (including radiation therapy), or have idiopathic causes. Transthoracic echocardiography is often the initial diagnostic tool, while CT and MRI provide additional information. Cardiac catheterization has been the gold standard for diagnosis, but non-invasive tests can be sufficient in certain cases. CP is a progressive and potentially life-limiting condition, but it can be cured through surgical pericardiectomy, especially when performed in specialized centers. Anti-inflammatory therapy may be effective, particularly in patients with subacute symptoms and evidence of ongoing inflammation.

75. MULTIPLE CAUSES, ONE CHOLESTASIS TO EXPLAIN: IDIOPATHIC CHOLESTASIS IN HODGKIN'S LYMPHOMA

Mantovani A., Dalbeni A., Giusino G., Natola L.A., Filice A., Paon V., Sacerdoti D.
Liver Unit, General Medicine C, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata Verona

A 69-year-old woman with a recent diagnosis of Hodgkin's lymphoma from an axillary lymph node biopsy (stage IIIB), was admitted to our ward after a referral from the haematologist. Before starting chemotherapy, the haematologist found increased levels of cholestasis (total bilirubin 26 mg/dl, direct 24 mg/dl, alkaline phosphatase 229 U/L and GGT 90 U/L) and transaminases (ALT 978 U/L, AST 404 U/L).
Past medical history of the patient reported rheumatic polymyalgia, autoimmune thyroiditis, and episodic migraine. During the outpatients visit, she was started on steroids and continued her ongoing therapy with allopurinol (started several months before the admission); she denied any alcohol intake or illegal substance assumption. The abdomen ultrasound and computer tomography (CT) scan showed a slightly enlarged but homogeneous liver, steatosis, no dilatation of the biliary tract, normal spleen size and patent portal vein. Viral and autoimmune screening resulted negative, although a progressive increase in the cytomegalovirus (CMV) viral load was observed at two weeks after admission.
Liver biopsy showed focal aspects of canalicular and hepatocytic cholestasis, marked inflammatory infiltrate at the level of portal spaces (with infiltration of bile duct wall and in some areas of the ductal lumen), minor inflammatory infiltrate in lobular site. Hepatocyte damage with feathery degeneration and foci of hepatic necrosis were present, while no evidence of significant fibrosis or localization of lymphoproliferative process was found. No signs of CMV inclusions or positive CMV-specific immunohistochemistry were found on biopsy.
During her hospitalization we observed a progressive worsening of liver and renal function, the patient developed ascites and was started on antibiotics for sepsis. Steroids were therefore tapered down, while ganciclovir was started due to the increased CMV viral load (that reached 20.700 UI/ml). General conditions worsened and the patient was transferred to ICU for renal filtration.
A multidisciplinary discussion between hepatologists, haematologists and infectious disease specialists first led to the hypothesis of idiopathic cholestasis related to Hodgkin's lymphoma. Decreased lymphoma-related immune competence and steroid therapy may have played a role in the reactivation of CMV, which probably contributed to further deterioration of liver function. Drug-induced liver injury (DILI) related to the ongoing allopurinol therapy, even without improvement with steroids, was a less considered option. The patient was then started on brentuximab, an anti-CD20 chimeric monoclonal antibody, achieving a progressive improvement in liver function, a decrease in cholestasis indices (bilirubin 3.8 mg/dl), and a slight progressive improvement in general condition. Subsequent positron emission tomography/CT scan showed an overall improvement.

76. CATCH ME IF YOU CAN. A CASE-REPORT OF RECURRENT FEVER OF UNKNOWN ORIGIN.

Celano R.[1], Donadoni M.[1], Tonelli F.[2], Leone M.[3], Radovanovic D.[4], Ceriani E.[5]

[1]Dipartimento di Medicina Interna, Ospedale L. Sacco, Università degli Studi di Milano; [2]Dipartimento di Medicina del Lavoro, Ospedale L. Sacco, Milano; [3]Dipartimento di Medicina del Lavoro, Ospedale L. Sacco. Milano; [4]Dipartimento di Pneumologia, Ospedale L. Sacco, Milano; [5]Dipartimento di Medicina Interna, Ospedale L. Sacco, Milano

A 61-years-old woman, employed as a school secretary and with history of undifferentiated connective tissue disease, presented to the emergency department (ED) due to fever and dry cough. Two similar episodes occurred the month before, shortly after a SARS-CoV-2 infection and were successfully treated at home with an antibiotic therapy.
At the ED presentation blood exams revealed increased inflammatory markers (WBC 15450/mm3 with 12760/mm3 neutrophils, CPR 65 mg/L). Given the negative result of chest radiography, she was discharged from the ED with one-week oral antibiotic and rest prescription. After 10 days of well-being, she experienced the same symptoms with high fever and dry cough short after workplace return. At this point she was admitted to the internal medicine ward where the fever was investigated with blood culture, serology for viral infection (CMV, HSV, HBV, HCV, HIV), procalcitonin, immunological assay (ANCA, ANA, ENA) all with negative response. A total body CT exam revealed no septic or neoplastic sources, and the transthoracic echocardiogram was negative for endocarditis. This time no antibiotic therapy was started, and the patient spontaneously began to improve her clinical condition so that she was discharged after 8 days of hospitalization. Unfortunately, after two weeks from discharge and resumption of work, she experienced fever and cough. This time blood exams revealed a severe inflammation (WBC 28000/mm3, CPR 38 mg/L) and the chest CT performed during symptoms showed bilateral infiltrates suggestive for hypersensitivity pneumonitis (HP). The subsequent bronchoalveolar lavage (BAL) showed a prevalence of alveolar macrophages and few lymphocytes, meanwhile microbiologic investigation were negative (bacterial cultural exams, Bacillus Koch cultural exam and PCR for Bacillus Koch). Functional respiratory tests showed mild impair of diffusing capacity. Because no elevated eosinophils were detected in the complete blood count analysis and the total IgE values were within the normal range, specific IgG antibodies against the major antigens commonly implicated in HP were measured in serum. The results showed multisensitization to various environmental antigens, commonly found anywhere (Figure 1). The patient presented again a spontaneous recovery during hospitalization. In consideration of the multiform sensitization, the therapeutical approach was the suggestion of the use of disposable mask outdoor and to perform smart-working. The patient did not experiment any respiratory discomfort in the further period and subsequent assessments were negative. The workplace investigation showed moulds on walls and was sanitized. In the following month the patient gradually abandoned mask and returned in her workplace without any recurrence.
The extrinsic allergical alveolitis (EAA), better known as Hyersensitivity Pneumonitis (HP), is an immune-mediated respiratory syndrome to inhaled environmental antigens in susceptible individuals[1]. Immunological reaction, mediated by both cellular and humoral mechanisms, involves both the alveoli and the interstitium, and it is a secondary response to prolonged and repeated exposition to substances to which the patient is sensitized and hyper responsive. The common antigens that can cause this condition are organic (from bacterial, fungal, animal source) or inorganic (chemical material). The symptoms often described are cough and dyspnea that become more evident after the exposition to the allergen, meanwhile radiological and clinical findings are compatible with the interstitial pneumonia[2].
The diagnostic evaluation involves different steps, including an exposure history and clinical signs and symptoms, high-resolution computed tomography (HRCT) interstitial involvement (bronchiolocentric inflammation, ground glass opacities), lymphocytosis (>30%) highlighted in the bronchoalveolar lavage (BAL). Additional assessments are the research of Precipitins, specific serum IgG antibodies against suspected triggers[3]. A precox diagnosis is necessary to prevent the progression to fibrosis[4] as these findings are not specific. Thus, accurate differential diagnosis of HP necessitates to multidisciplinary approach[5].
References
J Med Cases
J Investig Allergol Clin Immunol
Diagnostics
European Respiratory Review
Front Med (Lausanne)

Specific serum IgG antibodies	Values
ALTERNARIA ALTERNATA SPECIFIC S- IgG	6.14 mg/L
CANDIDA ALBICANS SPECIFIC S- IgG	25.30 mg/L
LEATHERS AND PIGEON STOOL SERUM PROTEINS SPECIFIC S- IgG	50.10 mg/L
ASPERGILLUS NIGER SPECIFIC S- IgG	22.20 mg/L
ASPERGILLUS FUMIGATUS SPECIFIC S- IgG	26.80 mg/L
CURVULARIA LUNATA SPECIFIC S- IgG	32.40 mg/L
SETOMELANOMMA ROSTRATA SPECIFIC S- IgG	19.90 mg/L
PENICILLIUM CHRYSOGENUM SPECIFIC S- IgG	19.00 mg/L
MICROPOLYSPORA FAENI SPECIFIC S- IgG	22.40 mg/L

Figure 1. Specific serum IgG antibodies against suspected triggers for HP. Method: EIA.

77. BEHEADED MENINGITIS: A CASE REPORT

Menchi S.[1], Santoro S.[1], Di Terlizzi G.A.[2], Damanti S.[3], Ramirez G.A.[4], Tresoldi M.[2]
[1]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy Università Vita-Salute San Raffaele; [2]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy; [3]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy, Università Vita-Salute San Raffaele; [4]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy Università Vita-Salute San Raffaele, Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS Ospedale San Raffaele, Milan, Italy

Background: Acute meningitis is a medical emergency, associated with a high potential risk of permanent brain morbidity and of mortality if not treated promptly. Nonetheless, meningitis can present insidiously, preventing timely diagnosis and treatment and increasing the risk of complications. Here, we the describe the case of a patient with acute meningitis, where atypical presentation delayed diagnosis and initiation of adequate treatment complicated the resolution.
Case Report: A 55-year-old male presented to an emergency department with headache and fever for two days. He had a history of smoke and bronchial asthma on inhaled corticosteroids. He denied any recent travel or exposure to sick contacts. His neurological examination was normal. Chest X-Ray showed hilar pneumonia. Therefore, the patient was started on ceftriaxone and levofloxacin and discharged home. Over the next four days, his clinical condition worsened prompting readmission to our Hospital. Fever associated with agitation and neck stiffness along with positive Kernig's sign were found on physical examination. A lumbar puncture was performed, and cerebrospinal fluid (CSF) analysis revealed clear CSF. The CSF cell count was 800/μL, with elevated protein and low glucose levels. Polymerase chain reaction for viruses and bacteria was negative. Based on these findings, the patient was started on empirical intravenous antibiotics (ceftriaxone and ampicillin) and acyclovir. Diffuse myoclonus set in, and vigilance worsened, prompting intubation and transfer to Intensive Care Unit. A new lumbar puncture was performed, which showed cloudy CSF, cell count =1200/μL. Magnetic resonance showed meningeal enhancement. CSF cultures were negative for Listeria and herpesviruses. Therefore, only ceftriaxone was continued. Follow up CSF analysis showed a significant decrease in CSF cell count (61/μL), normalization of glucose levels, and declining protein levels (141 mg/dL) along with evidence of small lymphocytes and monocytes. The patient also tested negative for autoimmunity, West Nile Virus, and antibodies for Brucella, Borrelia, and tuberculosis. The patient's clinical condition and electroencephalographic tracings improved with the treatment, enabling progressive respiratory weaning and tracheostomy removal. The patient completed a course of antibiotics and was discharged to the rehabilitation department with a good clinical outcome. He was advised to follow up with a neurologist for further management and monitoring of any long-term complications of meningitis.
In this case, meningitis presented without neck stiffness that is with the most typical sign in the characteristic triad of fever, headache and neck stiffness. Delayed diagnosis resulted in rapid deterioration of the patient's condition, while inappropriate antibiotic treatment at presentation prompted failure of microbiological identification when meningitis symptoms became overt. On the other hand, early antibiotic treatment has priority over completion of the diagnostic work-up due to the risk of irreversible clinical deterioration. Indeed, while no definite etiological agent could be identified for this patient (although S. pneumoniae might be preferentially hypothesized due to its tropism for the respiratory tract), appropriate antimicrobial therapy based on CSF findings was sufficient to prompt remission.
Conclusion: Acute meningitis is a medical emergency that requires prompt diagnosis and treatment. Early recognition and appropriate management are essential to prevent serious complications and improve the outcome. This case emphasizes the fact that meningitis can present with atypical clinical phenotypes and its diagnosis be confounded by non-targeted antibiotic treatments, highlighting that CSF analysis plays a critical role in the diagnosis, and empirical antibiotics should be administered as soon as meningitis is suspected even without microbiological isolates.

78. MUCINOUS ASCITES IN AN OTHERWISE HEALTHY PATIENT: A CLINICAL CHALLENGE

Morelli R., Baccaro S., Brunelli V., Lanna R., Giordano M., Paolisso G.
Università degli Studi della Campania Luigi Vanvitelli

A 68-year old Caucasian woman was admitted to the Emergency Department complaining of malaise, generalized abdominal pain, exertion dyspnea, and progressive enlargement of abdominal circumference during the course of the previous 3 months. She denied additional symptoms. Her past medical history showed allergic rhinitis (dust mites), for which she occasionally took anti-histamines and corticosteroid medication. The patient had no other relevant past medical history. Diuretic therapy with Furosemide and oxygen therapy with nasal cannulae (2 L/min) was initiated.
She was admitted to the Internal Medicine Department for complementary study. Here, on examination, she had bloated and distended abdomen, not tender to palpation. The cardiopulmonary examination was normal. The woman presented with peripheral edema (3+) of the inferior limbs bilaterally.At admission, blood pressure was 120/70 mmHg, peripheral O2 saturation was 93%, HR was 75 bpm. Weight at admission was 94 kg. Initial blood tests revealed increased levels of CRP (6.85 mg/dL), decreased serum albumin (3.23 g/dL), the remaining findings were normal. Diuretic therapy with Furosemide and Canrenone was initiated. Bedside ultrasound examination showed diffuse presence of abundant corpusculated fluid. Paracentesis was performed, with limited drainage of dense gelatinous ascitic fluid (about 20 ml), which was sent to cytologic analysis and revealed amorphous acellular material. Thus, MRI of abdomen and pelvis was requested, but it was not performed due to the poor compliance of the patient. CT scan of abdomen was then performed, which documented conspicuous ascitic fluid in all supra- and sub-mesocolic recesses; splenomegaly (140 mm); liver was not enlarged, with regular homogeneous parenchyma, without evidence of focal lesions. Due to the persistence of the respiratory distress, Chest CT scan was performed, which showed thromboembolism of segmental and sub-segmental branches of inferior pulmonary lobes; no evidence of pleural effusion. The patient thus started anticoagulant therapy with LMWH and oxygen-therapy with nasal cannulae at need. Gradual improvement of the patient's respiratory functions was observed, and contextually oxygen administration was reduced. At 15 days from admission, the patient's weight had decreased to 89 kg, with contextual reduction of peripheral edema, echocardiography was performed, showing marked compression of right atrium due to the abdominal ascitic fluid, with the patient being at risk for cardiac tamponade, therefore diuretic therapy was discontinued. Surgical consultation was performed, which excluded necessity for surgical intervention.Further examination were performed for diagnostic characterization: ANA, ENA, AMA, anti-LKM1, C3, C4, thrombophilia screening, peripheral blood smear, tumor markers (CEA, CA19-9, CA-125, CA15-3, HE4, AFP), viral markers for HIV, HBV, HCV, fecal immunochemical tests, all with negative result. PET-CT scan showed hyper-uptake at the level of the thyroid gland (SUV max 8.6) and hyper-accumulation of the right gluteus maximus muscle (SUV max 5.4). Due the abdomen being persistently severely bloated, although the corpusculated nature of the fluid rendered the procedure extremely challenging, the paracentesis was repeated, with about 600 cl of fluid being drained, and the cytologic examination showed amorphous material with mesothelial cells, diagnostically inconclusive.Finally, after about 3 weeks from admission, the patient performed MRI of pelvis and abdomen with contrast, which documented voluminous right ovarian segmented mass measuring about 25 x 20 cm, determining hepatic compression with its superior pole, and bladder compression with its inferior pole. The mass caused dislocation of small intestine and colon. The patient, hemodynamically stable, was then transferred to a onco-gynecologic facility where she underwent surgical intervention for removal of the ovarian mass. Histology revealed a mucinous cystadenoma of the ovary. Conclusions: Differential diagnosis of non-liver-related ascites must necessarily comprehend the study of female genital tract pathology, in order to identify ovarian neoplasms as early as possible. More specifically,

the use of MRI can be decisive when every other imaging method fails. In this particular case, although we performed every instrumental, laboratory and cytologic examination, we would not have been able to reach a definite diagnosis had it not been for the use of magnetic resonance imaging. In a patient with a mucinous cystic neoplasm, MRI demonstrates a large, unilateral, multiloculated cystic mass of varying complexity. Surgical intervention was decisive and necessary for the histopathologic study of the mass and for the conclusion of the diagnostic-therapeutic iter.

79. PULMONARY HISTIOCYTOSIS - CASE REPORT

Crescenti R.[1], Crescenti F.[2], Ando' F.[3], Nicolosi F.[4], Garufi L.[5], Crescenti A.[2]
[1]Internal Medicine AO Papardo Messina; [2]General Medicine - ASP Messina; [3]Pulmonology - Univ. Messina; [4]Radiology - ASP Messina; [5]Oncology - "S. Camillo de Lellis" Hospital Rieti

Pulmonary Langerhans cell histiocytosis is a disease in which monoclonal CD1a-positive Langerhans cells (a type of histiocyte), accompanied by lymphocytes, plasma cells, neutrophils, and eosinophils, infiltrate the bronchioles and alveolar interstitium. The etiology of pulmonary Langerhans cell histiocytosis is unknown, but the disease occurs almost exclusively in smokers 20 to 40 years of age. Men and women are equally affected, it is a rare disease with a prevalence of 1-2/100,000. Typical symptoms and signs of pulmonary histiocytosis are dyspnea, nonproductive cough, fatigue, fever, weight loss, and pleuritic chest pain, sometimes spontaneous pneumothorax. There may be extrapulmonary involvement with bone cysts, rash, polyuria due to central diabetes insipidus. The physical examination is usually normal. The disease is suspected on the basis of the history and chest x-ray and is confirmed by high-resolution CT and bronchoscopy with biopsy and bronchoalveolar lavage. Chest x-ray classically shows bilateral symmetrical nodular opacities in the middle and upper lung fields, with cystic changes and normal or increased lung volumes. Often the lung bases are spared. Confirmation of middle and upper lobe cysts and/or nodules with interstitial thickening on high-resolution CT is considered diagnostic for pulmonary Langerhans cell histiocytosis. Pulmonary function test results are normal, restrictive, obstructive, or mixed depending on when the test is done in the course of the disease. Most commonly, diffusing capacity for carbon monoxide (DLCO) is decreased and endurance is impaired. Bronchoscopy and biopsy are indicated when imaging and pulmonary function tests are inconclusive.; 5-year survival is about 75%, and median survival is 12 years. The main treatment of pulmonary Langerhans cell histiocytosis is smoking cessation, which leads to resolution of symptoms in up to a third of patients. The empirical use of corticosteroids and cytotoxic drugs is widespread even if their efficacy is not demonstrated. Lung transplantation is an option in otherwise healthy patients with accelerated respiratory failure, but the disorder may return to the transplanted lung if the patient continues or returns to smoking.
Case Report: 72-year-old man, BMI 31, smoker with pack years 75. Comorbidities: diabetes mellitus, atherosclerosis with PAD in lower limbs, previous peptic ulcer. He comes to our observation for asthenia, mild dyspnoea on exertion. Physical examination Chest: hypoexpandable hemithoraxes, hypomobile bases, reduced MV over the entire lung area, no pathological sounds added. SO2 in AA and at rest 97%. The chest X-ray showed accentuation of the interstitial texture and enlargements of the vascular type ili. For the anamnestic data, he performed a chest CT scan: ".. cystic lesions with a diameter of less than a centimeter surrounded by a thin wall, some of which are conglobated or arranged aligned in the subpleural site, the cysts are typically located in the upper lobes, and to a minimal extent in the apical segment of the right upper lobe. This finding leads to a pulmonary histiocytosis X in a non-precocious phase of fibrotic organization ..". Spirometric parameters were within normal limits (FEV1/FVC 74%; FEV1 lt 2.72; FVC lt 3.30). Diffusion test (DLCO) documented mild diffusion deficit (64%). The patient was referred to an anti-smoking center for smoking cessation but the subject refused any path to quit smoking and still smokes 20 cigarettes a day. After about six months, the pulmonary evaluation showed stable respiratory functional tests with the onset of "hypoxemia that does not require oxygen therapy and hypercapnia with compensated respiratory acidosis". Cigarette smoking cessation counseling is underway.
Discussion and conclusions: the clinical case describes a rare pathology such as pulmonary histiocytosis of Langerhans and outlines how the authors followed a step-by-step diagnostic procedure. After the radiological examination of the chest, which highlighted an accentuation of the interstitial plot, the diagnostic procedure was continued due to the anamnestic data of cigarette smoking, despite the chest radiography showing no significant alterations. Chest CT then documented lesions consistent with pulmonary histiocytosis. The study was deepened with a DLCO exam which highlighted a slight diffusion deficit and blood gas analysis with hypoxemia, hypercapnia and compensated respiratory acidosis. This clinical case can be paradigmatic of how a multidisciplinary team (general practitioners, internists, radiologists, pulmonologists) following a methodology based on articulated clinical reasoning and the rational use of diagnostic methods can allow the discovery of a rare pathology .

80. HIV, AIDS AND NEOPLASIA: CLINICAL CASE AFTER SELF-SUSPENSION OF CART THERAPY

Fiori P., Taras M.S., Maninchedda P., Pittalis M.
Patologia Medica, AOU Sassari

Male patient, 50years old, with a medical history of HIV infection diagnosed approximately 8 years ago, who suspended the therapy after only 1 year. He was admitted to another medical ward one month prior due to right hypochondrium pain, and a CT scan revealed liver structure alteration with multiple nodular lesions, likely repetitive lesions, thickening of the sigmoid wall with apparent substenosis, and lymphadenopathy in the pelvic and inguinal regions. After selfdismissal, he presented again to the emergency department of our hospital with the same symptoms. During the observation blood tests were performed showing abnormal liver function with increased AST (102 U/L), ALT (143 U/L), gammaglutamyl transferase (907 U/L), alkaline phosphatase (682 U/L), inflammation markers (PCR 5.7) and a normal complete blood count. Therefore, he was admitted to our internal medicine department. At the time of evaluation, he appeared in poor general condition, cachectic, symptomatic with exacerbated right hypochondrium pain upon superficial and deep palpation, exhibiting defensive contraction. The physical examination revealed mild peripheral edema, oral, palmo plantar, and nail mycosis. Empirical intravenous antibiotic and antifungal therapy, mild intravenous hydration, oral diuretics, and the continuation of the remaining home therapy was initiated. Blood tests showed high HIV viral replication with 653.000 copies/mL, low CD4+ count, and a CD4+:CD8+ ratio of <1, elevated Beta 2 microglobulin, and active replication of EBV and CMV with a modest number of copies/mL. Due to altered liver function and pharmacological interactions (current and future chemotherapy in suspicion of neoplasia), treatment with Descovy (Emtricitabine/tenofovir disoproxil) in combination with Ralteg ravir was initiated. A colonoscopy was performed, which revealed an initial peridiverticular colopathy of the sigmoid colon. An abdominal ultrasound revealed a floating thrombus in the inferior vena cava and confirmed the CT scan findings of altered liver structure due to the presence of multiple nodular lesions, some of which were partially confluent. An ultrasoundguided biopsy was performed on these lesions, and the pathological analysis showed histological findings compatible with large cell lymphoma. However, it was not possible to initiate any oncoh-ematological therapy due to the patient's death.
Conclusion: By discontinuing the antiretroviral therapy, which was started early, the patient facilitated the occurrence of AIDS defining events that ultimat ely predisposed him to the development of his neoplasia.

81. A CASE OF PAINFUL BLACK TOE

Terrannova R.[1], Rando M.M.[2], Biscetti F. [2], Nardella E.[2], Cecchini A.L.[1], Rossini E.[2], Nicolazzi M.A.[2], Pecorini G.[2], Ercolano V.[1], Massetti M.[3], Gasbarrini A.[4]
[1]Università Cattolica del Sacro Cuore, Largo Francesco Vito 1, 00168 Roma, Italy; [2]Cardiovascular Internal Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy ; [3]Department of Cardiovascular Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy; [4]Department of Medical and Surgical sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy

A 57-year-old female patient was admitted to the hospital with pain and cyanosis of the first toe of the right foot. The patient had a history of anxiety-depressive syndrome and a smoking habit. She denied a history of miscarriages and known cardiovascular disease. She reported a similar first toe cyanotic episode a year earlier that resolved spontaneously, but no diagnostic studies were available. Clinical examination revealed cyanosis of the first toe of the right foot. An electrocardiogram showed sinus rhythm. An ecocolor-Doppler arterial ultrasound of the right lower extremity showed occlusion of the distal posterior tibial artery, proximal to the ankle, and distal

anterior tibial artery by intraluminal hypoechoic material. A CT scan of the lower extremities confirmed occlusion of the posterior tibial and anterior tibial arteries of the right lower extremity.
Blood tests showed mild kidney disease (1.3 mg/dl), higher white blood cell levels (10.97 x 10^9/l), higher LDL cholesterol levels (140 mg/dl), higher Lp(a) levels (86), a higher c-reactive protein content of 43.7 mg/L. INR and PT were in range. A urine test was negative. Serum electrophoresis showed no abnormality.
Echocardiography showed ventricular hypertrophy and grade I diastolic dysfunction without atrial dilation.
A CT scan of the thoracic aorta ruled out an embryonic origin and revealed nephritis involving the kidneys. An ecocolor-Doppler of the superior trunks of the aorta documented the presence of a hypoechoic atherosclerotic component extending from the left carotid bifurcation to the origin of the internal carotid artery and revealed a stenosis of approximately 40%.
To assess the presence of systemic disease, immunological testing was performed, taking into account the presence of first toe ischemia associated with higher C-reactive protein levels, mild renal insufficiency, and renal nephritis involvement detected on CT scan. Tests for ANA, ENA, ANCA autoantibodies, and cryoglobulins were negative. C3 and C4 were within normal range. To rule out thrombophilia, we performed blood tests for homocysteine, protein S, and protein C, all within range. Leiden factor V mutation was absent. Lupus anticoagulant functional coagulation test was negative. Autoantibodies against beta2-glycoprotein I (IgM 22.1 U/ml) and anticardiolipin (IgM 56.5 U/ml) were present. Given the acute ischemia of the first toe, infusions of therapeutic doses of anticoagulants and prostacyclin analogs were initiated, delineating cyanosis of the right first toe. Given the lack of a source of embolism, high LDL-cholesterol levels in blood tests, and positive results for anti-β2-glycoprotein I and anticardiolipin (which required confirmatory testing at least 12 weeks later), we discharged the patient and recommended treatment with high-dose statins, 100 mg aspirin and 2.5 mg rivaroxaban twice daily. After one month of follow-up, ecocolor-Doppler examination of the lower extremity arteries was performed again, which showed that the occlusion of the posterior tibial artery and anterior tibial artery of the right lower extremity completely disappeared. About two months later, due to complete necrosis of the first toe of the right foot, the patient entered our department for amputation of the first toe of the right foot. Blood tests were repeated during hospitalization and were negative for lupus anticoagulant, while they showed positive titles of anticardiolipin, and IgM anti-β2-glycoprotein I autoantibodies. So, a diagnosis of antiphospholipid antibody syndrome was made. Antiphospholipid antibody syndrome is a clinical autoimmune syndrome characterized by episodes of venous and/or arterial thrombosis and pregnancy abnormalities associated with persistent antiphospholipid antibody positivity. This suspicion is raised clinically by detection of unexplained thrombotic events, especially in younger patients, and by adverse pregnancy outcomes such as fetal death after 10 weeks of gestation, severe preeclampsia, or placental insufficiency leading to premature birth, or loss of multiple embryos before 10 weeks of gestation. The final diagnosis is based on confirmation of positive antiphospholipid antibodies repeated at least 12 weeks apart. Treatment can include preventive strategies (aspirin, hydroxychloroquine) and anticoagulation for thrombosis.

82. DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLIA: USEFULLNESS OF VENOUS THROMBOEMBOLISM PROPHYLAXIS IN A PATIENT WITH HISTORY OF LYMPHOMA AND MYASTHENIA GRAVIS

Pardeo R.[1], Lorello G.[2], Calabrò F.[3], Mandraffino G.[3], Morace C.[3], Bellone F.[3], Orlando L.[3], Gigliotti De Fazio M.[3], Imbalzano E.[3], Squadrito G.[3]
[1]Department of Cardiology, Polyclinic "Madonna della Consolazione", Reggio Calabria, Italy; [2]Department of Medical Sciences, Internal Medicine Unit, University Hospital "G. Martino", Messina, Italy; [3]Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

Introduction: Venous thromboembolism (VTE) is a common and potentially life-threatening condition with a multifactorial pathogenesis. Obesity, prolonged immobilization or bed rest, use of estrogen-progestin medications and tumors are recognized like some of the more common acquired risk factors for VTE. The relatively high incidence of this condition sparkly contrasts with high rates of underdiagnosis or misdiagnosis. Several studies warned about the increased risk of deep vein thrombosis (DVT) in individuals undergoing surgical interventions and subsequent immobilization of the entire lower limb. Based on this evidence, last ACCP guidelines recommend antithrombotic therapy in such patients. Conversely, evidence about thromboprophylaxis in patients with immobilization of the lower limb below the knee is scarce, because the risk of VTE in these patients has not been sufficiently studied. For this reason, to date, guidelines do not recommend antithrombotic therapy in this patients setting. Here we present the case of a forty-one years-old man with type B1 thymoma who underwent cast immobilization of the right ankle after a fracture of the malleolus due to an accidental fall.
Case Report: Past medical history of the patient was characterized by a diagnosis of diffuse large B-cell nasopharingeal lymphoma in 2012 treated with both radiotherapy and R-CHOP chemotherapy. In 2015 type B1 thymoma was diagnosed and excised the year after; a relapse occurred in 2019 (parietal pleural recurrence) requiring a left radical pleurectomy. In 2020 myastenia gravis was diagnosed and treated with several cycles of plasmapheresis and non-invasive mechanical nocturnal ventilation because of subsequent respiratory disturbances. In April 2021, he accidentally fell and reported a fracture of the right malleolus, that was treated with cast immobilization of the right ankle and no thromboprophylaxis. In September 2021, during a follow-up contrast CT scan of the chest performed to monitor the course of thymoma, an incidental diagnosis of pulmonary embolism was made. At the admission to our department the patient was watchful, lucid, eupnoic with normal oxygen saturation, blood pressure and heart rate were regular; a significant swelling was detected at the right leg, which was painful on palpation. INR was 1.01 and D-dimer 2.76 mcg/mL; there were no significant change in other blood test. The prognostic risk was considered low with a pulmonary embolism severity index (PESI) of class I. On day one of hospitalization, venous doppler ultrasound of the lower limbs showed the presence of extensive venous thrombosis within the right femoral-popliteus axis; the superficial femoral vein and the popliteal vein were fully replenished of thrombotic material, with instrumental features of recent onset, while the common femoral vein was partially recanalized (about 20%) with internal patent saphenous vein. On the other hand, the ultrasound of the left lower limb did not show any abnormal finding. Color-Doppler echocardiogram revealed was normal. Since the findings were consistent with VTE, the patient was treated with fondaparinux 7.5 mg, and after 5 days the treatment was switched to a direct oral anti-coagulant (DOAC) edoxaban 60 mg for the following 3 months. At the end of the third month, the patient was re-evaluated: he did not experienced episodes of blending, and the venous doppler ultrasound showed a partial recanalization of the common femoral vein (with thrombus occupying about 30% of the lumen) and with partial thrombosis of the superficial femoral vein and popliteal vein; therefore DOAC treatment was continued. The resolution of VTE was found at the six-month follow-up eco-color-Doppler.
Conclusions: This is a peculiar case that highlights the need of appropriate balance between risks and benefits of individual patients at risk of thrombosis and underlines the usefulness of pharmacological thromboprophylaxis. According to updated ACCP guidelines, the role of pharmacological prophylaxis in patients with lower leg immobilization is not clear. Fair-quality evidence showed that low molecular weight heparin (LMWH) compared to placebo reduce the risk of VTE in such patients. More recent studies, also, demonstrated that DOACs were non-inferior to LMWH in terms of treatment and prevention of recurrence risk of DVT of the lower leg; moreover DOACs were characterized by a good safety profile (risk of bleeding) and greater ease of use. Information regarding environmental risk factors, evidence of tumors, genetic determinants and blood chemistry parameters (such as coagulation factors), should be always collected in clinical practice in order to predict with major accuracy the risk of VTE in patients with below-knee lower limb immobilization, but further studies are needed to better understand the role played by these factor. Non-pharmacological prophylaxis, instead, does not involve the bleeding risk; for this reason recently it is receiving particular attention, with several studies recommending adequate physiotherapy during the period of limb immobilization.

83. A CASE OF BLEEDING FROM VARICES OF THE GASTRIC FUNDUS (GOV2) IN A PATIENT WITH MINOR THROMBOPHILIA

Russo M.J[1], Catania F.[1], Lenzo O.[1], Manzitto L.[1], Privitera G.[1], Judica A.[2], Giuffrida E. [2], Vacirca F.[3], Frazzetto E.[1], Incognito C.[1], Signorelli S.S.[1]
[1]Medicina Generale Azienda Ospedaliero-Universitaria Policlinico" G. Rodolico-San Marco" - Presidio G.Rodolico; [2]Dipartimento di Gastroenterologia Azienda Ospedaliero-Universitaria Policlinico"G. Rodolico-San Marco" - Presidio G.Rodolico; [3]Dipartimento di Radiologia Interventistica Azienda Ospedaliero-Universitaria Policlinico"G. Rodolico-San Marco" - Presidio G.Rodolico

Introduction: We present a case in which minor thrombophilia (due to co-

agulative protein C deficiency) led to a very relevant thromboembolic clinical manifestation (thrombosis of the vena cava).
Presentation Clinical Case: A 41-year-old male patient was admitted to the Emergency Room (ER) of our hospital for syncope haematemesis and melena. In the ER he underwent oesophago-gastroduodenoscopy in which bluish-coloured varicose cords with a tortuous course were found with red marks but without bleeding. Haemostasis with cyanoacrylate at the level of the fundus of the stomach was necessary; roundish ulcers with fibrinous fundus at the level of the antrum were also present. The remote pathological history indicated previous portal thrombosis. Once hospitalized, he was placed on an absolute fast, while proton pump inhibitors (80 mg/day EV) and Terlipressin (2 mg slow bolus) were prescribed. Laboratory exams showed anaemia (Hb 9 g/dl), iron deficiency (sideremia 37 mcg/dl, ferritin 139.1 ng/ml, transferrin 204 mg/dl, with transferrin saturation of 12%), which required support therapy, and also thrombocytopenia (81000/mm3) and lymphocytopenia (0.57 x 103/uL). The diagnostic procedure required for varices of the oesophago-gastric tract demonstrated: reduction of coagulative protein C (36 %) and Factor XII (51 %); in addition, no variant of the factors in the genetic thrombophilia panel was mutated. A Computed Tomography examination of the abdomen showed spleno-portal vascular tortuosity and multiple perigastric, spleno-renal and Retzius system porto-caval anastomoses, as collateral compensation circles; varices of the distal tract of the oesophagus in intraparietal location and a greatly enlarged spleen (max. diameter 18 cm), with hypodense formation, in first hypothesis granuloma and/or parasitic cyst, were found. The walls of the transverse and ascending colon were thickened, with apparently stenotic lumen and walls with post contrastographic enhancement. The colonoscopy examination was negative. A liver biopsy was necessary, which was compatible with liver stasis disease.
Conclusion: Among the markers of thrombophilia (congenital/acquired), the quantitative deficiency of coagulative protein C alone appears to be modestly frequent. In the case we present, portal vein thrombosis was the main element of suspicion, since the patient's history in this regard was silent. Although the onset in the emergency room was macroscopic because of the presence of varices at different levels (portocaval, splenorenal and Retzius) and therefore the portal hypertension was clear, the diagnosed thrombophilic defect was minor. In conclusion, we present the above case to invite us internists to consider that small defects (coagulative C protein) can be associated with severe clinical conditions.

84. A PECULIAR CASE OF EDEMA RELATED TO AN ALTERED VASCULAR PERMEABILITY: THE POLYNEUROPATHY, ORGANOMEGALY, ENDOCRINOPATHY, MONOCLONAL PLASMA CELL DISORDER, SKIN CHANGES SYNDROME

Gaimarri I.[1], Bissolotti I. [1], Palladini B.[1], Accardi G.[1], Bellissimo G.[1], Piccinini M.[1], Carsillo M.[1], Arcuri M.L.[1], Bottaro L.[1], Younes A.[1], Pera C.[1], Ferrari M.[1], Galli P.[2], Landini F.[2], Dalla Palma A.B.[3], Chierici E.[4], Passeri G.[1], Regolisti G.[2], Cabassi A.[1]
[1]U.O.C. di Clinica e Terapia Medica, Azienda Ospedaliera Universitaria, Università degli studi di Parma; [2]U.O.C. di Clinica e Immunologia Medica, Azienda Ospedaliera Universitaria, Università degli studi di Parma; [3]U.O.C. di Ematologia, Azienda Ospedaliera Universitaria, Università degli studi di Parma; [4]U.O.C. di Neurologia, Azienda Ospedaliera Universitaria, Università degli studi di Parma

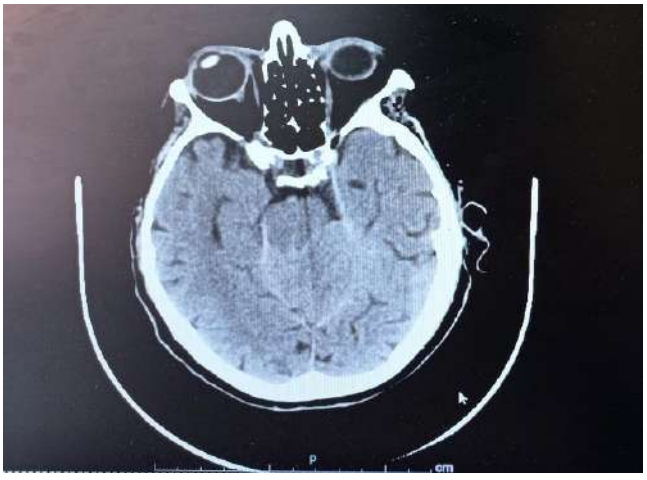
A 62 years old man was admitted to the hospital because of bilateral pitting edema a month earlier associated to arms tingling. He had a history of colon cancer, diagnosed in 2017 and underwent surgery and chemotherapy treatment, and in 2015 an inferior STEMI (treated with PTCA+DEs). At admission, arterial and venous Doppler ultrasonography were negative for thrombosis and cardiac ultrasound showed hypo-akinesia of inferior wall, normal chamber volume, preserved kinetic (ejection fraction 60%). Blood tests, including complete blood count, serum electrolytes, renal and hepatic function, glyco-lipemic profile, cholestasis indices, coagulation, inflammation and autoimmunity parameters were normal, as well as urine protein and albumin excretion. Albuminemia was 3.5 g/dl, while total proteins were 6.5 g/dl. Blood test showed a mild increased of TSH level (7,212 uU/ml) and a positive anti-thyroglobulin antibody title; autoimmune hypothyroidism was diagnosed and a hormone replacement therapy was introduced. Serum protein electrophoresis showed monoclonal protein in gamma region with detection of IgG λ in serum and urine immunofixation; negative was Bence-Jones proteinuria assay. A chest-abdomen-pelvis CT scan showed abdominal lymphadenopathy and a lytic area with polylobulated margins in the left hemi-pelvis. The bone marrow biopsy showed a bone marrow plasmocytosis at <5%. The patient referred a worsening fingers paresthesia with progressive involvement of the lower limbs and walking difficulties. A further evaluation showed lower limbs erythema when in orthostatic position. In our opinion, such a clinical pattern was not only justified by vitamin B12 and folate deficiency. Electromyography and electroneurography showed demyelinating polyneuropathy, which did not benefit from Ig-vein therapy. In addition, we found low anti-myelin antibodies, positive antibodies anti-neuron (1:120) and line BLOT; the circulating anti-gangliosides IgG and IgM were negative. POEMS syndrome was then suspected due to the concomitant presence of polyneuropathy, monoclonal plasma cell disorder, skin changes, and lymphadenopathy. A low-dose total body CT scan was performed with detection of a large lytic bone lesion with sclerotic "bubble-like" polycyclic margins, at the left acetabular roof with involvement of the ipsilateral ileum and ischium. This lesion had 18-FDG positive uptake during PET scan. The patient underwent limited field radiation therapy on the bone lesion and systemic chemotherapy (6 cycles of Lenalidomide-Dexamethasone). Physiokinesitherapy was also initiated to improve basic motor abilities. After 6 months, we reported partial improvements of the clinical conditions and neuropathy, with the disappearance of the pitting edemas.
The above-described case refers to POEMS diagnosis, which is a syndrome characterized by polyneuropathy, organomegaly, endocrinopathy (thyroid disease, diabetes mellitus), monoclonal plasma cell disorder, skin changes. There are other important clinical features not included in the POEMS acronym, including papilledema, edema, sclerotic bone lesions, thrombocytosis/erythrocytosis, and increased vascular endothelial growth factor (VEGF) levels. The pathogenesis is unknown, although the chronic overproduction of proinflammatory cytokines (IL 1β, TNF-α, IL 6[1]) seems to have an important role, potentially manifesting with microangiopathy, vascular endothelial edema (due to overproduction of VEGF) and polyneuropathy. POEMS is a rare disorder; the actual incidence is not clearly defined. It occurs more frequently in the 5th-6th decade in males (2/3)[2]. The diagnosis is based on clinical and laboratory criteria. It is confirmed by the presence of both major criteria (typically demyelinating polyneuropathy and monoclonal proliferative disease, typically λ), of at least 1 of 3 other major criteria (Castelmann disease, sclerotic bone lesion, increased of VEGF) and at least 1 of 6 of the minor criteria (organomegaly, peripheral edema, pleural effusion or ascites, endocrinopathy, skin changes, papilledema, Thrombocytosis/erythrocytosis). Other signs and symptoms include clubbing, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diathesis, decreased vitamin B12 levels.[3]
An isolated bone lesion without bone marrow involvement may characterize POEMS: in this case a limited field radiation therapy program on the bone lesion can provide definitive disease control[4]. On the other hand, in case of bone marrow involvement, the treatment consists in autologous stem cell transplantation after induction with chemotherapy[5] or only in systemic chemotherapy with anti-VEGF and anti-TNF-a and corticosteroids. The syndrome presents chronic features, leading to severe impairment of motor skills until bedridden.
1) Kanai K et al., Neurology.2012;79(6):575-82; 2) Dispenzieri A et al., Blood.2003;101(7):2496; 3) Rajkumar SV et al., Lancet Oncol.2014;15 (12):e538; 4) Humeniuk MS, et al.Blood. 2013;122(1):66-73; 5) Zhao H. et al., Leukemia.2019;33(4):1023-9.

85. MULTIFACTORIAL ANEMIA IN CHRONIC RENAL FAILURE IN DIALYSIS TREATMENT: WHAT YOU REALLY DON'T EXPECT

Pietrantonio F., Lordi M., Rella S., Grappasonni G., Di Lorenzo J., Ceci G., Vinci F., Pascucci M., Rosiello F., Di Rienzo F., Delli Castelli M., Ciamei A., Cipriano E.
UOC Medicina Interna Ospedale dei Castelli, ASL Roma 6, Roma, Italy

Patient F 80 years arrives in the ward transferred from the Emergency Room where she was admitted due to the finding of severe anemia (Hb 3.9 g/dl). Medical history: bleeding gastric ulcer treated endoscopically 3 months earlier, CRF under dialysis treatment since the previous month, recent spontaneous hematoma of the left leg subjected to evacuation and bandaging. He denies allergies and known family history of familial or congenital coagulopathies. At admission Hb 8.1 g/dL, PLT 240000, MCV 89, reticulocytes 3.6%, folic acid <2.2 ng/ml, serum iron 56 mcg/dl, ferritin 2950 ng/ml, vit B12 362 pg/ml, PCR 60.21 mg/L, WBC 13500, PCT 0.89 ng/ml, HCV antibody negative, blood and urine cultures negative. At the EO ed except multiple cutaneous ecchymoses; moreover, the left calf is enlarged, sore and painful on palpation, tibial pulses present and valid at the ankle, normothermic limb with sensitivity and motility preserved. Videat

of Vascular Surgery is performed with ultrasound examination and finding of a non-recent subfascial hematoma extended to the gastrocnemius muscle of the left leg and indication for CT Angio of the lower limbs with contrast medium showing hematomas supplied to the right lower pararenal space, right iliac muscles and left soleus. The Videat of Interventional Radiology indicates angiography with embolization, but the procedure does not show any active bleeding. Normocytic anemia persists with Hb around 7 g/dL, remaining blood count and baseline coagulation values in order, inconclusive martial status and continuous need for blood transfusions. Are performed: blood smear (anaemia, anisocytosis and hypochromia); SOF negative; LDH 517 U/L; EGDS normal and Gastroenterological Videat recommending CT angiography of the abdomen and control left leg with stability of the known hematomas and absence of free fluid layers in the abdomen. Not indications to treatment of Vascular Surgery. Therapy with retacrit, folin and tranexanic acid iv was set up with apparent stabilization of Hb values around 8 g/dL. The Hematology Videat recommends: ferinject iv; Hb>8 g/dl via blood transfusion; INR assay, aPTT, fibrinogen, AT3, Ddimer and study of LAC, coagulative protein C, protein S, activated protein C resistance and factor II, factor VII, factor VIII, factor IX, factor X, von Willebrand factor, cryoglobilins, protein electrophoresis , rheumatoid factor, AMA, ASMA, ANA, ENA, antiphospholipid Ab, HCV antibodies, haptoglobin, transferrin, iron, ferritin, cobalamin, folate, oncomarkers; reevaluation of therapy with tranex if no new bleeding or rapid drops in Hb and if abnormal findings contact regional reference center for coagulopathies. A further CT scan of the abdomen and lower limbs with contrast medium shows the absence of direct or indirect signs of bleeding in progress, the known less hyperdense hematomas unchanged and at the level of the right common femoral artery, site of the recent arterial access, a small supplied pseudoaneurysm which is successfully embolized. The patient resumed walking with stable Hb 8.5 g/dL values, no further signs of blood loss, hypochromic microcytic anemia, PLT 150,000 and WBC 5700. Hemostasis study shows: PT/INR=101%/0.99, aPTT=41 sec, ratio 1.24, Fbg=313 mg%, AT III= 83%, FVIII 247.7%, F von Willebrand antigen 315.5%, ristocetin cofactor 370.5 %, FXIII 104%, F II 85%, FIX 122.7%, FX 103.2%, anti-PL antibodies within limits, LAC present ICA=10.95, TTI=1.9, dRVV ratio=1.33, platelet aggregation markedly reduced at low and intermediate doses of ADP and collagen, severe reduction of TRAP6 aggregation even at high doses (50 uM) and presence of platelet aggregates in the sample with reduced platelet-rich plasma count. Suddenly the patient complains of objective dizziness, nausea, vomiting and headache. The following are performed: brain CT (large left hemispheric cerebellar parenchymal hematoma with perilesional edema and discrete mass effect); Neurological Videat (tp with mannitol and brain CT Angio at 8 hours or if variations) and NCH Videat which excludes possible surgical manoeuvres. This haemorrhage worsened with an increase in the left cerebellar hematoma and edema and extension to the contralateral cerebellar hemisphere, greater mass effect, complete obliteration of the IV ventricle and prepontine cistern and herniation of the left cerebellar tonsil, GCS 3; for which the patient died. The regional reference center for coagulopathies concludes by stating that the clinical history suggests a pathology of acquired hemostasis. Hemostasis screening tests excluded acquired hemophilia, acquired von Willebrand, or acquired FXIII deficiency and were not consistent with DIC. On the basis of the outcome of the platelet aggregation, in the first hypothesis the bleeding diathesis can be attributed to an acquired deficit of the platelet function, a condition which can be associated with end-stage CRF requiring dialysis treatment or also to the presence of antibodies interfering with the platelet function (Acquired Glanzmann's thrombasthenia, acquired delta storage pool disease) associated or not with autoimmune diseases.



86. A RARE CAUSE OF HYPERCALCEMIA

Tosti F.[1], Armenes S.[2], Moh'd Jadallah S.[2], Ambrosecchia M.[2], Furlan L.[2], Montano N.[2], Tobaldini E.[2]
[1]1 Department of Internal Medicine, Fondazione IRCC.S. Ca' Granda, Ospedale Maggiore, Policlinico, 20122 Milan, Italy. 2 Department of Clinical Sciences and Community Health, University of Milan, 20122 Milan, Italy; [2]1 Department of Internal Medicine, Fondazione IRCC.S. Ca' Granda, Ospedale Maggiore Policlinico, 20122 Milan, Italy. 2 Department of Clinical Sciences and Community Health, University of Milan, 20122 Milan, Italy

Case presentation: A 80-year-old man was admitted to our unit because of diffuse abdominal pain, vomiting and severe exertional dyspnea and dysphonia. He reported involuntary weight loss of about 10 kg and deep asthenia in the last six months. His past medical history included multiple relapses of low grade non-invasive urothelial carcinoma treated with transurethral resection of bladder tumor (TURB) and Bacillus Calmette-Guerin (BCG) instillations, nephroureterectomy for urothelial carcinoma, stage 4 chronic kidney disease (CKD) and paroxysmal atrial fibrillation with a previous episode of ischemic stroke. At admission blood tests showed hypercalcaemia (albumin-corrected calcium 13.2 mg/dl, ionized calcium 1.57 mmol/L) with low PTH and normal 1-25-dihydroxyvitamin D and 25-hydroxivitamin D. All other screening blood tests, incuding thyroid tests, were normal with the exemption of slightly increase in c-reactive protein (PCR 6.63 mg/dl) and cholestatic markers (gamma-GT 159 U/L, alkaline phosphatase 139 U/L)
Patient management and diagnostic workup: The patient did not take any medication possible related to hypercalcaemia and was initially treated with saline solution with slight improvement of calcium levels but no significant clinical benefit. Paraneoplastic hypercalcaemia was initially suspected. Serum protein electrophoresis, Bence Jones proteinuria, lambda/kappa light chain ratio, total body contrast medium CT scan, PET/CT scan, colonoscopy and gastroscopy were all negative for suspected neoplastic or infectious diseases. Due to dysphonia video-laryngoscopy, otolaryngological examination and thyroid and neck ultrasound were performed but all resulted negative. Given the presence of a bladder lesion TURB with radical resection was performed. The histological examination showed a low-grade papillary urothelial carcinoma. Paraneoplastic hypercalcaemia was thus ruled out with good probability. Possible granulomatous diseases were then considered even though extensive radiologic tests did not show any suggestive findings. We then focused our attention to the persistence of increased cholestasis indices and evidence of hepatomegaly at abdomen ultrasound. We thus decided to perform a liver biopsy. The histological examination concluded for granulomatous hepatitis. Considering the patient's history of intravesical instillation of BCG, disseminated BCG infection vs. idiopathic systemic granulomatous reaction was suspected. Quantiferon tuberculosis (TB) and DNA extraction and microscopic analysis for M. tuberculosis and nontuberculous mycobacteria (NTM) on liver sample resulted negative. Culture exams are still underway. Mycobacterial tests on urine gave positive microscopic and PCR results on three different samples while mycobacterial microscopic and PCR search in stool was negative. Given the rapid worsening of clinical condition, steroid therapy (metilprednisolone 40 mg/die) was started after biopsy with partial laboratory benefit (albumin-corrected calcium 11.8 mg/dl, ionised calcium 1.45 mmol/L) but great clinical benefit so that the patient was discharged with close followup. Two months later the patient developed fever and increased inflammatory indices in the absence of clear organ recall. Suspecting possible disseminated BCG infection, therapy was therefore started with isoniazid, rifampicin and ethambutol. Koch bacillus (BK) detection on sputum gave positive results.
Discussion: Although BCG instillation is generally safe, disseminated M. bovis disease is a rare and serious adverse reaction that can occur following intravesical BCG therapy. Prevalence of such complication is reported to be lower than 5% so that a high index of suspicion is required (Lamm DL et al. J Urol. 1992). Moreover, much of our knowledge comes from individual case reports, thus hampering a comprehensive understanding of this entity. The pathogenic mechanisms underlying the development of complications following BCG instillation remain not fully understood, and considerable debate exists about whether it represents a form of hypersensitivity reaction or an active mycobacterial infection (Pérez-Jacoiste Asín MA et al. Medicine (Baltimore). 2014). However, the detection of M. tuberculosis complex DNA in locations distant from the genitourinary tract reinforces the hypothesis that the direct invasion and hematogenous spread of BCG underlie the development of the complication, rather than a mere hypersensitivity reaction. Definitive diagnosis of BCG infection may be established via positive M. bovis BCG culture (of bodily fluids and/or tissue from involved sites, when obtainable). M. bovis only grows in selected culture media under special la-

boratory conditions and at a very slow rate so that its' detection can be challenging. Thus, in clinical practice, the decision whether to pursue biopsy or initiate empiric anti-M. bovis BCG treatment involves careful risks/benefits analysis. Furthermore, steroids may have a role in the treatment as many of the symptoms are immunomodulated.

87. A CASE OF MULTISYSTEM INFLAMMATORY SYNDROME (MIS-A) IN AN ADULT WOMAN AFTER COVID-19 INFECTION

Ferrazza G.[1], Grisolia D.[1], Cassandra F.[1], Gervasi R.[1], Nucera A[1], Piciucchi G.[1], Ballanti M.[1], Davato F.[1], Proietti G.[2], Anemona L.[2], Rizza S.[1], Cardellini M.[1], Federici M.[1]
[1]Dipartimento di Scienze Mediche, Policlinico Tor Vergata; [2]Dipartimento di Scienze Sperimentali, Policlinico Tor Vergata

Multisystem inflammatory syndrome (MIS) is a rare but severe condition initially recognized in children and adolescents (MIS-C) infected with SARS-CoV-2. Adults prior infected with SARS-CoV-2 might also develop MIS (MIS-A) days to weeks after the infection. In MIS-A inflammation involves the whole body.
A 33 years old woman presented to our emergency department for fever, dyspnea and myalgias. Symptoms had been on for 10 days. One month earlier, she entered the emergency room for headache and asthenia and diagnosis of Covid-19 infection was made with RT-qPCR amplification from nasopharyngeal swab sample. She was discharged with the prescription of antipyretic drugs. The patient had no history of recent travel, no sick contacts, no animal exposure and no consumption of raw dairy products. She orihìgined from Romania but lived in Italy for the past 20 years. Her medical history was negative for both assumption of chronic medications and allergies. In the emergency department, the patient had fever, hypotension and tachycardia. Her physical examination was negative with exception of erythematous maculopapular rash over arms and legs and congested throat. Blood gas analysis showed respiratory alkalosis and blood tests showed neutrophilic leucocytosis, increased inflammatory markers (VES 93 mm/h, PCR 177.50 mg/L, ferritin 6231 ng/ml and fibrinogen 1063 mg/dl), increased d-dimer (12622 ng/ml), and LDH (399 U/L). We also found mildly elevated hepatic enzymes (GOT 67 U/L, GPT 63 U/L, Gamma GT 195 UI/L) and heart failure marker (BNP 377 pg/mL). A Chest-abdomen CT scan with contrast agent was done and was negative for infection or pulmonary embolism but showed mediastinal and left axillary lymphadenomegaly and hepatomegaly. Blood cultures from peripheral veins and dosage of IFN Tubercolosis were also negative. In emergency department empirical antibiotic therapy with Ceftriaxone was administered.
The patient was transferred in Internal Medicine division 3 days later: she had fever (39°C) and tachycardia, pharyngodynia with pharyngeal and tonsillar mucosa hyperemia. Due to persistent fever, multiple diagnostic investigations were performed to identify autoimmune or infective etiology. Rheumatologic, microbiological and virological laboratory tests were all negative. We repeated a contrast-enhanced chest-abdomen CT, which showed new multiple increased lymph nodal formations. The patient underwent a total body PET scan which showed a significant increased uptake of FDG in many lymph node stations (latero cervical site bilaterally, left supra and subclavian, upper and lower para tracheal, axyllary and left retro pectoral, pulmonary hilar bilaterally). Moreover, the subdiaphragmatic area showed increased metabolism in para-aortic lymph nodes and along the left iliac chain (Fig. 1). Considering the increased lymph node uptake shown at PET-CT, we decided to perform an excisional biopsy of axillary lymph nodes to carry out histological studies. Six lymph nodes were analysed macroscopically, the largest of 2.5x1.7 cm with a "fish meat" appearance; the smaller lymph nodes instead showed focal haemorrhagic areas and were partially replacing by adipose tissue. The diagnosis made taking into consideration the microscopic picture, the reported clinical data and the molecular biology data, concluded for a reactive lymphadenopathy with mixed features, with a prevailing paracortical zone reactivity (T dependent). In light of the clinical, laboratory and histological data the diagnosis was MIS-A. The CDC case definition of MIS-A aligned with our patient's findings, with all alternative diagnoses excluded. The patient had fever for more than three consecutive days, mucocutaneous and neurologic manifestations (rash, headache and weakness), laboratory evidence of inflammation (elevated CRP and procalcitonin, hyperferritinemia); measures of disease activity (elevated BNP and neutrophilia) and laboratory confirmed SARS-COV 2 infection in four prior weeks. The patient's condition improved during the course of the hospitalization: we observed progressive improvement of dyspnea and myalgias after 7 days, regression of fever after 14 days, and normalization of laboratory tests (inflammatory markers came down to normal levels) despite no treatment was applied. When seen in the outpatient clinic 1 month following discharge from the hospital, the patient's symptoms resolved although some general weakness. Her repeat chest Tc scan was completely normal. MIS-A manifests in a broad range of organ involvement, which is easily confused with infectious or autoimmune etiology. The CDC's inclusion criteria are easily available for MIS-A diagnosis, but most of the criteria are nonspecific, with the warning to rule out alternative diagnoses first. This diagnostic approach needs a prompt but wide exclusion of pathological, which can be challenging.

88. KODAMAEA OHMERI LEG SKIN ULCERS INFECTION IN AN IMMUNOCOMPETENT PATIENT: A CASE REPORT.

Aita.A[1], Lelli.D[2], Gherardi.G[3], Pedone.C[4], Antonelli.R[4]
[1]Unità Operativa di Ricerca di Medicina Interna, Fondazione Policlinico Universitario Campus Bio-Medico, Roma, Italia; [2]Unità Operativa di Ricerca di Geriatria, Fondazione Policlinico Universitario Campus Bio-Medico, Roma 00128, Italia; [3]Unità di Laboratorio Clinico, Fondazione Policlinico Universitario Campus Bio-Medico, Roma, Italia Unità di Scienze Batteriologiche Applicate, Dipartimento di Medicina e Chirurgia, Università Campus Bio-Medico, Roma, Italia; [4]Unità Operativa di Ricerca di Geriatria, Fondazione Policlinico Universitario Campus Bio-Medico, Roma, Italia

Case report: A 69-year-old male, was admitted to our Internal Medicine acute care ward in December 2022 for multiple secreting, foul-smelling, bloody and painful (Numerical Rating Scale -NRS- 9) ulcers of the legs, with a patchy pattern (Fig.1A). These ulcerative lesions occurred in April 2022, probably due to an accidental sulfur dioxide chemical burn released by the explosion of the gas system in the camper's kitchen where the patient lived. He did not seek for professional medical treatment and the lesions were automedicated only with chlorhexidine, that was ineffective. In December the patient eventually went to the Emergency Department of our hospital due to worsening of the ulcers. At hospital admission the patient was in poor hygienic conditions at inspection, apyretic; blood examination showed white blood cells 5.26 x 103/ul, neutrophils 4.2x103/ul, red blood cells 2.9 x106/u, hemoglobin 9.4 g/dl, mean corpuscular volume 99 fl, mean corpuscular hemoglobin concentration 32,80 g/dl, C-reactive protein 10.99 mg/dl (normal values < 0.5 mg/dl). **Diagnostic hypothesis**: Given the absence of comorbidities (with the exception of COPD), the uncertain association with the chemical burn, and the arrangement of symmetrical ulcers, we decided to exclude, besides venous or arterial insufficiency and ulcer infection, also an autoimmune disease. **Diagnostic work up**: Blood autoimmune panel (cryoglobulins, extractable nuclear antigens (ENA), C-ANCA, P-ANCA, rheumatoid factor, immunoglobulins IgA,IgG,IgM) was negative, with the exception of ANA (positive 1:160). The fragment of skin biopsy showed ulcerated epidermis with pseudoepithelial hyperplasia. In the dermis was appreciated granulation tissue, fibrosis and abundant infiltrate of lymphoplasmic cells and granulocytes with perivascular eosinophils. Direct immunofluorescence for IgG, IgM, IgA and C3 on the fresh skin sample was negative. Blood screening for hepatitis B and C, and HIV were negative, arterial and venous lower limbs ultrasound was negative for thrombosis and for venous or arterial insufficiency. A CT scan of the lower limbs documented bilateral osteomyelitis of the distal third of the femurs, the proximal third of the tibias, and the distal third of the tibiofibular bone, that was not contiguous to the skin ulcers. A culture of the swab of the most secreting skin ulcer was performed. **Diagnosis**:The swab culture was positive for Kodamea ohmeri. 1 mm white cells were isolated on sheep blood agar medium. Subsequently on Sabouraud dextrose selective medium containing chloramphenicol (Becton Dickinson) creamy-white, smooth, paste-like columns were isolated (Fig 2). The colonies were identified by matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS). Given the aspecific histopathological picture of the skin biopsy, compatible with the diagnosis of ulcerative process of reactive and reparative nature, the worsening of ulcers and the osteomyelitis were attributed to Kodamea ohmeri infection.
Treatmeant: After 5-day, the empiric antibiotic therapy with piperacillin/tazobactam 4.5 g tid was interrupted on the basis of the culture examination and of the antimycogram, and intravenous voriconazole 200 mg once a day was administered intravenously at the hospital for 9 days and, then, at home for 25 days. After 60 days from discharge, the skin wounds were improved, and a new swab culture was performed, which demonstrated the eradication of K. ohmeri (Fig.1B). It was not possible to follow the evolution of osteomyelitis due to the poor compliance of the patient with subsequent checks.
Discussion: Kodamaea ohmeri is a new emerging fungal pathogen, which

belongs to Saccharomycetes family. It is the telomorphic form of Candida Guilliermondii var. membranaefaciens. It has been isolated from different environmental sources, such as sand, pools, sea water and fruits. In the last decades K. ohmeri has been recognised as a rare pathogen that causes life-threatening infections associated with high mortality in immunosuppressed patients. To the best of our knowledge, this is the first case of Kodamea ohmeri infection of skin ulcers in an immunocompetent patient.

Fig. 1A. Ulcers leg - day 0

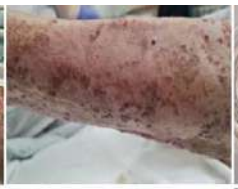


Fig. 1B. Ulcers leg - day 60

Fig.2 Kodamaea Ohmeri colonies.

89. URTICARIA: ONSET OF DIFFERENT AUTOINFLAMMATORY DISEASES, TWO CLINICAL CASES COMPARED

Claudi I.[1], Buti E.[1], Apricena A.[2], Auria S.[1], Bilò M.B.[3], Moroncini G.[4], Danieli M.G.[5]
[1]Postgraduate School of Allergy and Clinical Immunology, Università Politecnica delle Marche; Ancona, Italy; [2]Postgraduate School of Allergy and Clinical Immunology, University of Turin; Turin, Italy; [3]Allergy Unit, Department of Internal Medicine, AOU delle Marche, Università Politecnica delle Marche; Ancona, Italy; [4]Clinica Medica, Department of Internal Medicine, AOU delle Marche, Università Politecnica delle Marche; Ancona, Italy; [5]SOS Immunologia delle Malattie Rare e dei Trapianti, AOU delle Marche, Università Politecnica delle Marche; Ancona, Italy

Background: We present two clinical cases of autoinflammatory diseases, characterized by urticaria as the only onset manifestation: a clinical case of Still's disease and one of Sweet 's syndrome.
Adult-onset Still's disease (AOSD) is an inflammatory disorder characterized by fever, arthritis, and an evanescent rash. A serious complication may be macrophage activation syndrome (MAS). The Yamaguchi's classification criteria are currently the most sensible for diagnosis.
Sweet 's syndrome (acute febrile neutrophilic dermatosis) is characterized by painful, oedematous, erythematous skin papules, plaques, or nodules associated with fever and may also involve other organs and systems (eye joints, muscles, internal organs). Sweet 's syndrome is distinct in a classic form (frequently caused by a respiratory or gastrointestinal infection, or by inflammatory bowel disease or pregnancy), a form associated with cancer and a drug-induced form.
Case Reports: A 21-year-old girl and a 56-year-old woman come to our Center due to the appearance of urticarial lesions that have been present for several months and are partially responsive to antihistamine and steroid therapy. Three months after the onset of the urticaria, the 21-year-old girl presented with systemic symptoms (high fever, night sweats, migrating arthralgia and palpable lymphadenopathy). Blood tests found an increase in inflammation indices, transaminases, triglycerides, and ferritin (> 5,000). During hospitalization in our Center, a further increase in ferritin levels was found (up to 20,000 ng/ml) which led to the diagnosis of Still's disease complicated by macrophage activation syndrome. She was treated with high-dose glucocorticoids until resolution of the acute phase. She was subsequently treated with canakinumab (monthly dosage of 4mg/kg s.c.).
The steroids were slowly tapered down to discontinuation. The clinical case of the 56-year-old woman began in 2016 after a mourning with urticaria, then in 2018 nocturnal fever episodes appeared (5 episodes per month) associated with oral aphthosis, arthromyalgia and night sweats treated with cycles of steroid therapy, with exacerbation on steroid withdrawal. In blood tests there were: high inflammation indices, GB 16000 cells /mmc (N 88.8%, L 7.6%), increased levels of IL-6, ferritin, fibrinogen, and serum amyloid A. Skin biopsy found neutrophilic dermatitis. Other causes of urticaria were excluded including infectious, neoplastic, and autoimmune diseases. The patient was treated with steroid therapy and colchicine, subsequently in 2010 she started therapy with anakinra (100 mg/ day s.c.) associated with oral colchicine 1 mg/day.
Conclusions: Idiopathic urticaria, especially when not completely responsive to conventional therapy (antihistamines and corticosteroids), can be indicator of other systemic diseases, such as autoinflammatory syndromes, for which a multidisciplinary and internal medicine approach is important to exclude underlying pathologies. In the case of urticaria associated with autoinflammatory diseases, management with anti-IL1 biologics therapy (canakinumab and anakinra) is essential.

90. A CASE REPORT OF ASSOCIATION BETWEEN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) AND NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMOSD)

Antonelli E.[1], Paladini A.[1], Auria S.[2], Moroncini G.[3], Danieli M.G.[4]
[1]Postgraduate School of Internal Medicine, Università Politecnica delle Marche, Ancona, Italy; [2]Postgraduate School of Allergy and Clinical Immunology, Università Politecnica delle Marche, Ancona, Italy; [3]Clinica Medica, Dipartimento di Medicina Interna, AOU delle Marche, Università Politecnica delle Marche, Ancona, Italy; [4]SOS Immunologia delle Malattie Rare e dei Trapianti, AOU delle Marche, Università Politecnica delle Marche, Ancona, Italy

Background: Neuromyelitis optica spectrum disorder (NMOSD, previously known as Devic's disease) is a rare antibody-mediated disease of the nervous system that mostly affects the optic nerve and spinal cord. Highly specific serum autoantibodies against aquaporin-4, a water channel protein expressed on astrocytes, are present in 75% of patients and they are useful to differentiate neuromyelitis optica from other diseases with preferential nervous system involvement. Frequent relapses could lead to disability.
Objective: To describe our experience in a complex case of NMOSD refractory to several drug lines and treated with eculizumab.
Case report: In 2014 a 39-year-old Caucasian woman was admitted to our hospital because of a well-defined truncal sensory level under the navel, which hypoesthesia and paresthesia associated with sensation of urinary retention. She had been diagnosed with SLE in 1999 when she presented with cutaneous rash, arthralgias, renal involvement (Class III glomerulonephritis) and positive ANA and anti-dsDNA. First episode of myelitis transverse was in 2001, associated with optic neuritis in 2005. Moreover, in 2005 Graves' disease was diagnosed. In the following years, she experienced multiple relapses treated with plasmapheresis (2001 and 2002), azathioprine, cyclophosphamide, mycophenolate mofetil and steroid boluses. In 2014, during hospitalization, autoantibodies against aquaporin-4 were identified and the diagnosis of NMOSD was done. She underwent intravenous methylprednisolone boluses (1 g i.v. for 5 consecutive days) and, from day 4, with oral prednisone (50mg/die) with slow tapering. From 2014 symptoms were managed with low dose steroids and mycophenolate mofetil. In June 2022 after the occurrence of new neurological symptoms, Rituximab (two 1 g i.v. infusions, separated by two weeks) was added. However, a complete resolution was not observed. In 2023 she reported symptoms suggestive for relapses (gait disturbance, hypoesthesia, bladder retention). Nevertheless, the MRI did not report any new lesions of the spinal cord. Thus, we decided to start eculizumab (Soliris®, Alexion) (900 mg/once a week for the first month followed by 1200 mg/two weeks). The treatment was well tolerated.
Conclusion: NMOSD is a severe disease with frequent relapses. An aggressive treatment is necessary to prevent disability, without increasing the infective risk, due to high immunosuppressive therapy. Even if in our case it is too early to draw a definite conclusion, eculizumab, a monoclonal antibody directed against the complement protein C5, blocking formation of the terminal complement complex, can represent a valid therapeutic option.

91. THE RISKS OF LONG-TERM USE OF PROTON PUMP INHIBITORS (PPIS): A CHALLENGING DIAGNOSIS OF SEVERE HYPOMAGNESEMIA AND ASSOCIATED HYPOCALCEMIA IN MICROSCOPIC COLITIS WITHOUT DIARRHEA. A CASE REPORT

Cassone FD., Gino M., Morra di Cella S., Porta M.
Internal Medicine 1U; Città della Salute e della Scienza di Torino, Presidio Molinette; Department of Medical Sciences, University of Turin, Italy

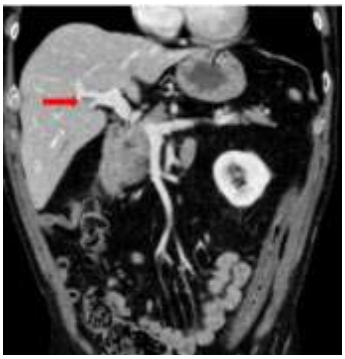
Background: Since first reported in 2006, hypomagnesemia and associated hypocalcemia are increasingly recognised as rare long-term side-effects of PPIs (PPI-induced Hypomagnesemia-PPHI). PPIs can inhibit the gastrointestinal absorption of magnesium (Mg) through pH-interference on both active channels and passive diffusion. The most classic sign of severe hypomagnesemia is hypocalcemia related to PTH-resistance (inappropriately low PTH) and reduced conversion of 25-hydroxy-Vitamin D (25OHD), leading to reduced bone and intestinal calcium (Ca) resorption. Refractory hy-

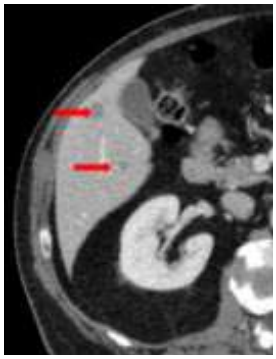
pokalemia is also a possible associated occurrence (40 to 60%), due to renal potassium (K) wasting, via interference on ROMK channels. Thus, PPHI can cause neuromuscular hyperexcitability (spasms and cramps, tetany, positive Trousseau and Chvostek signs) and cardiovascular manifestations (ECG changes like QT prolongation and arrhythmias such as Torsades de pointes). Intravenous (IV) Mg replacement provides only short-term relief if PPIs are continued. Hence, the only effective way to reverse PPIH is discontinuation of PPIs supported by Mg supplementation, which usually leads to rapid (about 4 days) normalization of electrolytes.
Microscopic Colitis (MC) is an umbrella term for Collagenous Colitis (CC) and Lymphocytic Colitis (LC), included in the wider Inflammatory Bowel Disease (IBD) spectrum. The pathogenesis is complex and multifactorial (luminal and immune factors, genetic predisposition). Smoking, chronic use of PPIs (at least 1 year) and non-steroidal anti-inflammatory drugs (NSAIDs), more so when combined, are associated with increased risk and have been suggested to induce MC. Altered microbiota and decreased Mg absorption are potential inductive mechanisms of PPI-related MC through immune dysregulation and intestinal inflammation. MC mainly affects the elderly and is characterized by the combination of non-bloody watery diarrhea (84 to 100%), macroscopically normal ileocolonoscopy and typical histologic findings. MC should be managed by avoiding smoking and offending drugs. Debilitating symptoms may be relieved by oral budesonide.
CASE REPORT: On March 2023, a 76-year-old male was admitted to our Internal Medicine Unit for cramps, nausea and vomiting persisting for 1 month, with severe hypocalcemia (Ca++ 0.62 mmol/L, NV: 1.12-1.32 mmol/L) without tetany and diarrhea. His medical history included smoking (60 pack-years), hypertension, dyslipidemia, ischemic heart disease with LVEF (40%) that required a combined implantable Cardiac Resynchronization Therapy-Defibrillator (CRT-D) in 2010. In 2020 he was investigated for vomiting, diarrhea and weight loss; a colonoscopy showed uncomplicated sigmoid diverticulosis, and he underwent a polypectomy on a sigmoid tubular adenoma with low-grade dysplasia. Upper endoscopy revealed chronic atrophic gastritis and ruled out celiac disease. The patient remained asymptomatic since. Medication included ramipril, aspirin, ezetimibe and omeprazole 10 mg daily (for at least 13 years). At admission an ECG showed a paced rhythm. Baseline blood tests showed extremely severe hypomagnesemia (Mg 0.14 mmol/L, NV: 0.76-1.06 mmol/L), normokalemia (K 3.6 mmol/L, NV: 3.5-5.1 mmol/L), inappropriately low PTH (9.9 ng/L, NV: 6.5-36.8 ng/L) and low vitamin D (25OHD 17.4 µg/L, NV: > 30.0 µg/L) with normal kidney function (serum creatinine 0.87 mg/dl, eGFR 89 ml/min/1.73 m2 CDK-EPI). Both urinary Mg and Ca excretion were very low (0.2 and 0.3 mmol/d respectively, NV: uMg 0.7-7.4 mmol/d, uCa 2.5-7.5 mmol/d), suggesting preserved renal tubular reabsorption. Omeprazole was discontinued from the beginning, and the patient initially received IV Mg and Ca replacement and oral Vitamin D. Because of the severely low basal levels of Mg and slow response to treatment, we suspected intestinal malabsorption, in particular CC, as contributory mechanism despite the absence of diarrhea and negative fecal calprotectin (21 mg/Kg, NV: < 50 mg/kg). The patient underwent a colonoscopy with random biopsies and was started on oral budesonide *ex juvantibus*, with rapid improvement (Mg 0.74 mol/l, Ca++ 0.98 mmol/L, PTH 17.7 ng/L). One week later, histology confirmed the hypothesis of CC by demonstrating a thickened colonic collagenous band (30 µ). In addition, bone mineral densitometry showed generalized osteopenia (T score -1.8). It was decided to stop PPI and aspirin and start clopidogrel.
CONCLUSION: This case report suggests a causal relationship between hypomagnesemia/hypocalcemia, CC and long-term PPI administration, as supported by the normalization of electrolyte abnormalities after discontinuing PPIs and beginning oral budesonide. Moreover, it highlights the potential complications of continuous PPI use, including severe electrolyte disturbances (in this case the presence of a CRT-D may have prevented fatal arrhythmias), that should be considered in clinical practice.

92. CASE REPORT: DIAGNOSTIC EVALUATION OF NON CIRROTHIC PORTAL VEIN THROMBOSIS

Ruscitti C.
Dipartimento di Medicina Interna ad indirizzo fisiopatologico, Ospedale Sacco, Università degli Studi di Milano

Background: Portal vein thrombosis (PVT) is an infrequent clinical condition associated with multiple etiological factors and diseases. PVT typically occurs in patients with hepatic cirrhosis and/or prothrombotic conditions.
Introduction: A 65-years old man referred to the Emergency Room for acute abdominal pain and hematochezia. He reported a history of gastroesophageal reflux disease and moderate alcohol intake (4 alcohol units daily). Abdomen contrast-enhanced CT scan performed with urgency showed thrombosis of the right portal vein branch and small hypodense non-univocal areas in the hepatic parenchyma. He was admitted to our Internal Medicine Department.





Diagnostic Work Up: The diagnostic work up excluded hepatic diseases (platelets, transaminases, albumin were normal; abdomen ultrasound did not show signs of hepatopathy; fibroscan was normal; screening for viral hepatitis was negative; screening for autoimmune hepatic diseases was negative). The diagnostic investigation ruled out both hereditary (factor V, protein C, protein S, antithrombin 3) and acquired prothrombotic conditions (antiphospholipid antibodies, anti-cardiolipin antibodies, anti- beta2glycoprotein antibodies in the suspicion of antiphospholipid syndrome; PNH mutation for paroxysmal nocturnal hemoglobinuria; CD34 and erythropoietin mutation for polycythemia vera; V617F JAK2 mutation in suspected myeloproliferative diseases). In order to rule out local tumors, an abdomen CT scan with triphasic enhancement evaluation was repeated, showing no evidence of malignant masses; it was, therefore, concluded that such hypodense hepatic areas were compatible with parenchyma alterations owing to the thrombotic event. Microbiological tests excluded abdominal infections and inflammatory markers were negative throughout the hospitalization. The patient had a benign clinical course on anticoagulation therapy, with the radiological imaging showing a partial regression of the thrombosis. On discharge, he has been addressed to hematologic follow up. The genome sequence has been performed to exclude other gene mutations less commonly associated with myeloproliferative diseases, such as calreticulin and MPL [1]. In conclusion, the final diagnosis was idiopathic portal vein thrombosis.
Conclusion: Portal vein thrombosis is a clinical condition usually related to cirrhosis [2]. Even though in some cases the etiology remains unknown, in non-cirrhotic patients PVT is frequently caused by local factors (abdominal tumors, infections, trauma) and prothrombotic conditions, often myeloproliferative diseases [3]. These last should be actively tested and ruled out through specialistic diagnostic evaluation.
Bibliography: [1] T. Klampfl *et al.*, "Somatic Mutations of Calreticulin in Myeloproliferative Neoplasms," *N. Engl. J. Med.*, vol. 369, no. 25, pp. 2379–2390, 2013, doi: 10.1056/nejmoa1311347.
[2] N. M. Intagliata, S. H. Caldwell, and A. Tripodi, "Diagnosis, Development, and Treatment of Portal Vein Thrombosis in Patients With and Without Cirrhosis," *Gastroenterology*, vol. 156, no. 6, pp. 1582-1599.e1, May 2019, doi: 10.1053/J.GASTRO.2019.01.265.
[3] A. Plessier *et al.*, "Acute portal vein thrombosis unrelated to cirrhosis: A prospective multicenter follow-up study," *Hepatology*, vol. 51, no. 1, pp. 210–218, 2010, doi: 10.1002/hep.23259.

93. WHEN WEAKNESS BECOMES THE STRENGTH

Puoti M., Galiero G., Schettini F., Franzese A., Giordano M.
Università degli Studi della Campania L. Vanvitelli

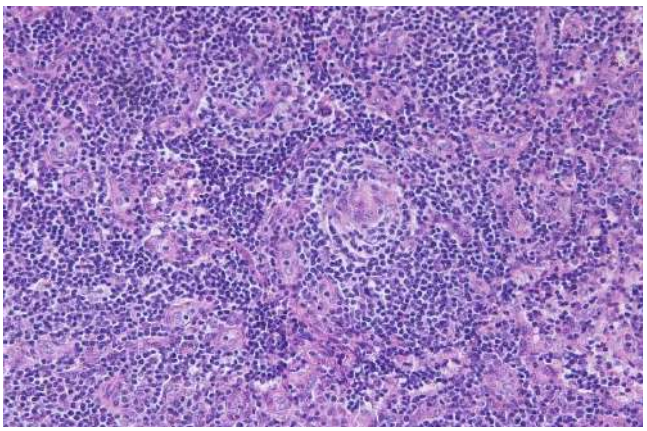
We discuss the clinical case of a 83 years old man who came to the hospital for fever and lower limb hyposthenia with severe walking impairment. When arrived, he presented in discrete clinical conditions: on neurological examination he had paraplegia and hyporeflexia in the lower limbs with preserved sensitivity to tactile and nociceptive stimuli. Additionally, a large herpetic rash on the lips was observed. His blood pressure was 150/80 mmHg, his pulse was 80 beats per minute rhythmic, peripheral saturation of oxygen was 95% on air, finally he was apyretic. He reported his walking

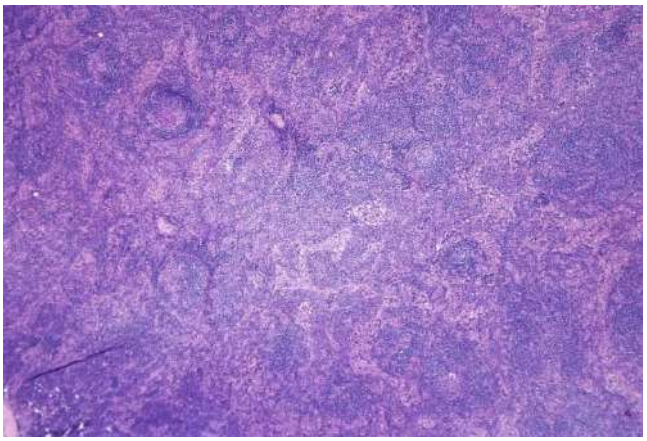
impairment had started about 10 days before hospitalisation. He had a complex medical history: he suffered from arterial hypertension, previous HCV infection that resolved with spontaneous seroconversion, previous bladder carcinoma treated with radical cystectomy and packaging of ileal neobladder and ureterocutaneostomy on the right side of the abdomen, chronic renal failure with hydronephrosis grade IV to the left kidney, venous insufficiency, finally a Tarlov cyst at the sacral site of the vertebral canal. Due to his bladder urological disease he suffered from frequent urinary tract infection, actually he reported the last one about a month before that was successfully treated with antibiotics. Blood tests showed high inflammatory markers (WBC 18.000, PCR 7 mg/dL) and a slight impairment of renal function (eGRF with CKD-EPI: 43 ml/min/1.73m2). Additionally, urinalysis was suggestive of inflammation of the urinary tract. An RX chest was done, it did not describe any sign of ongoing parenchymal inflammatory process. Considering the clinical history of recurrent urinary tract infection, an empiric antibiotic therapy was immediately started. Meanwhile a proper physiotherapy program with a adequate neurological follow-up was done, in the suspicion that Tarlov cyst was the cause of his peripheral neurological condition. Unfortunately, after approximately 3 days of hospitalisation his clinical conditions worsened: hyposthenia had arisen to both his arms as well. Consequently, the suspicion of Guillain Barrè syndrome became very strong. An urgent cranial CT scan was performed with a view to excluding stroke or other acute pathological disease interesting the central nervous system. Following this, a rachicentesis with cerebrospinal CSF sampling was performed: a filmarray panel meningitis-encephalitis was done, which excluded any bacterial infection while confirming the presence of HSV1 infection; in addition the chemical-physical analysis showed a low total white cell count (6 leukocytes and zero polymorphonuclear leukocyte), elevated protein levels and albumin-cytologic dissociation (albumin was 1729 mg/dL compared to the usual upper limit of 15 mg/dL). That's the typical pattern required for Guillain-Barrè syndrome diagnosis. It's a rare autoimmune acute polyradiculoneuropathy with potentially severe symptoms, usually presenting with bilateral weakness starting in the distal lower limbs and spreading proximally and to include the upper limbs. Onset usually follows infection or another immune-stimulating event, with an interval of about 1-4 weeks. Reported mortality 3%-7%, usually due to respiratory failure, infection, or autonomic dysfunction while symptoms are progressing (usually within 2-4 weeks of symptom onset). Therefore, a strict cardiopulmonary monitoring was started, no corticosteroids were administered and he was immediately transferred to the Neurology department in order to provide the best assistance to the patient without wasting any time. Here he was receiving first-line therapy, the most commonly used treatment for Guillain-Barré syndrome is intravenous immunoglobulin (IVIG) - they provide some benefits if started within 1 month of the onset of the disease - with a gradual improvement in the neurological symptomatological picture, with slow resumption of mobilisation of the lower limbs. He is currently under continuous neurological follow-up in order to obtain as good a restitutio ad integrum as possible.

94. A CHALLENGING ANASARCA: A TAFRO SYNDROME CASE REPORT

Paladini A.[1], Gamba L.[1], Sordillo R.[1], Cocco C.[1], Cozzi M.F.[1], Manfredi L.[2], Filosa A.[3], Goteri G.[3], Moroncini G.[2]
[1]Scuola di Specializzazione in Medicina Interna, Università Politecnica delle Marche, Ancona, Italia; [2]Clinica Medica, Dipartimento di Medicina Interna, AOU delle Marche, Università Politecnica delle Marche, Ancona, Italia; [3]Anatomia Patologica, AOU delle Marche, Università Politecnica delle Marche, Ancona, Italia

Background: Castleman's disease (CD) is a rare systemic inflammatory disease, that describes a group of diseases with similar hystopatological features. Several clinical characteristics and etiology allow to identify different pictures. CD includes unicentric CD (UCD) or multicentric CD (MCD). The MCD could be divided in HHV-8 related MCD, idiopathic MCD (iMCD), POEMS associated MCD, TAFRO syndrome and not otherwise specified (NOS-iMCD). TAFRO syndrome was described in Japan in 2010 and is characterized by severe hyperinflammatory syndrome with thrombocytopenia, anasarca, renal dysfunction, organomegaly and often aggressive clinical course. As for other Castleman's disease subtypes, hystological analysis could present hyaline hypervascular, plasmocytic or mixed features (1,2).
Case presentation: A 63-years-old Caucasian man was admitted to our hospital in December 2022 with generalized oedema for 5 months, weight gain of about 30 kg, dyspnoea worsened in the last month with mild desaturation. He reported a history of cutaneous psoriasis in treatment with anti-IL-23 (last administration July 2022), class 1 obesity.
In September 2022, he was admitted to another hospital where he performed a chest-abdomen CT scan with detection of bilateral pleural, perihepatic and pelvic effusion and enlarged mediastinal lymph nodes (maximum diameter of 1.5 cm), abdominopelvic and inguinal lymph nodes with a diameter of 4 x 2.5 cm. The blood tests showed an increase of inflammatory markers (C-reactive protein 5 mg/dl, ESR 120 mm/h), polyclonal gammopathy, no hepatic and renal dysfunction. Infectious disease screening (Toxoplasmosis, Borreliosis, Rickettsiae, Leishmaniasis, hepatotropic viruses, CMV, HIV, blood cultures) and immunological screening were performed with negative results. Heart failure and portal hypertension were excluded. Pleural effusion analysis reported reactive features without neoplastic cells. PET/CT examination detected intense focal FDG uptake in the abdominal, mediastinal, pelvic and inguinal lymph nodes. The biopsy of the left inguinal lymph node found a nonspecific and nondiagnostic histological picture with follicular reactive lymphoid hyperplasia. In the meantime, the patient was treated with oral furosemide and canrenone, with mild improvement of oedema and dyspnoea, loss of about 18 kg and he was discharged.
In December, the patient presented with moderate global respiratory insufficiency requiring low-flow oxygen therapy. On physical examination, he presented widespread subcutaneous oedema partially marked, mostly in the abdominal area and lower limbs, with associated skin discolouration. He gained weight (135 kg) and the inguinal biopsy site had a dehiscence with lymphorrhea. The blood tests confirmed the increase of inflammatory indices (ESR 112 mm/h, CRP 3 mg/dl), polyclonal gammopathy (2.5 g/dl), and moderate thrombocytopenia (between 100,000 and 50,000/mmc). We repeated a CT scan, which showed moderate bilateral pleural, pericardial, abdominal effusion with significant soft tissues imbibition, multiple lymphadenopathies, mild hepatomegaly, no focal lesions. The search for infectious disease was completed with quantiferon tests, HCV, HIV, HBV, CMV, EBV, VZV, HHV-6 and HHV-8, all negative. Autoimmune serology was negative. The serum levels of IL-6 (11.2 pg/ml) and IL-2R (1098 U/ml) were increased. Since a second biopsy approach was difficult and the clinical suspicion of HHV8 negative multicentric Castleman's disease or IgG4 disease (serum IgG4 increase) remained high, a review of the previous lymph node biopsies was required. The anatomopathological report described overlapping features with regressed germinal centers bordered by mantellar lymphocytes and peripheral plasma cells with polyclonal secretion, hypervascularization (high endothelium with hyalinized wall). No increase in IgG4, negative immunohistochemistry detection of HHV8. In view of the histological report and the clinical picture, after a bone marrow biopsy, the diagnosis of Castleman's disease mixed type, plasma cell and hyaline-vascular HHV8 negative with TAFRO syndrome was performed (1,2). During hospitalization, medium-dose steroid therapy was started (methylprednisolone 20 mg/day) with progressive dyspnoea improvement, weaning from oxygen therapy and weight reduction (107 kg at discharge). Therapy with Siltuximab (anti-IL-6) 11 mg/kg every 21 days was started, with improvement of the clinical picture and reduction of inflammatory indices. The CT scan after four Siltuximab infusions, showed absent pleural effusion, reduction of mediastinal and abdominal lymphadenopathy.

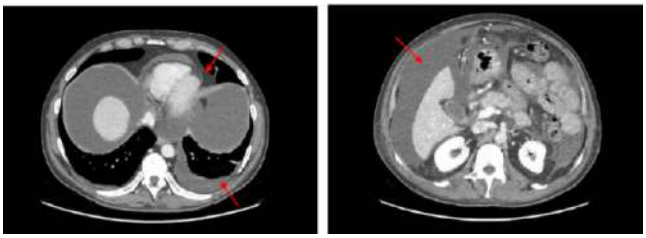


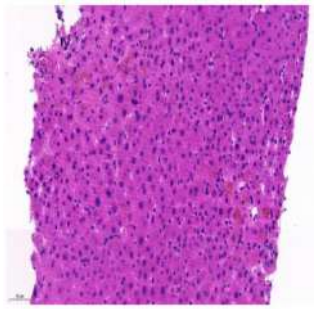


95. A CASE OF POLYSEROSITIS, CHYLOUS ASCITES AND HEPATITIS INDUCED BY IMMUNE CHECKPOINT-INHIBITORS

Castelli M.[1], Betelli M.[1], Merelli B.[2], Loglio A.[3], Benetti A.[1]
[1]Internal Medicine Unit, ASST Papa Giovanni XXIII, Bergamo, Italy;
[2]Oncology Unit, ASST Papa Giovanni XIII, Bergamo, Italy;
[3]Gastroenterology, Hepatology and Transplantation Unit, ASST Papa Giovanni XXIII, Bergamo, Italy

Background: Immune checkpoint inhibitors (ICPI) enhance immune system identification and destruction of tumoral cells. Thus, ICPI are used in several tumor types like melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma, hepatocellular carcinoma, and Hodgkin lymphoma. Among them, nivolumab is a fully human immunoglobulin G4 that selectively blocks the interaction of the Programmed Death – 1 (PD-1) receptor with its ligands, disrupting signals that downmodulate T-cell activation and proliferation.This action is often related with immune – mediated adverse drug reactions (ADR) involving different organs, expecially gastrointestinal, cutaneous, and hepatic sites; serositis with pericardial, pleural and/or peritoneal effusions are also described in case reports and series. This kind of ADR is usually responsive to drug suspension and immunosuppression with glucocorticoids; alternatively, immune modulating agents including infliximab, anti-interleukin-6 agents, or intravenous immunoglobulin (IVIG) have been used but prospective studies on their safety and efficacy are still lacking.
Case description: In 2016, at the age of 39, a man was diagnosed with a stage IIIC melanoma (T3aN2M0) on his right leg. He underwent partial right inguinal lymphadenectomy, then he received adjuvant therapy with pembrolizumab, achieving complete remission. Due to the relapse of disease with metastases to lymph nodes and colon, in February 2022 he was treated with encorafenib and binimetinib, then nivolumab plus ipilimumab. At the end of the induction treatment, he was in complete remission. Therefore, in October 2022 he started maintenance therapy with nivolumab 480 mg every 4 weeks.
Six weeks later he developed fever and periorbital edema, and the therapy was suspended. After two more weeks he presented at the emergency department with malaise and dyspnea: a total body CT showed pleural and pericardial effusion and ascites, with no findings suggesting melanoma relapse. He was admitted to our Internal Medicine Ward: microbiology and autoimmunity panels were negative, echocardiography was normal except for small pericardial effusion without hemodynamic impact; nephrotic syndrome was excluded; pleural, pericardial and abdominal effusions size was not permissive for invasive procedures. He was treated with furosemide and iv methylprednisolone 1 mg/kg for five days then, documenting echographic reduction of effusions, he continued with 1 mg/kg oral prednisone. He was discharged in good general conditions after 12 days.
Two weeks later, the patient was hospitalized again due to swelling of his legs, weight gain of 9 kg and fatigue. A new CT scan confirmed absence of disease relapse but showed massive ascites, pleural and pericardial effusion **(Figure 1)**. We performed a diagnostic paracentesis, draining 500 cc of chylous fluid. Laboratory tests were remarkable for a biochemical thyroiditis, hypoalbuminemia (2.8 g/dl) and elevated cytolysis and cholestasis indices (AST/ALT 144/273 U/L, ALP/γGT 209/205 U/L), with normal bilirubin.
The patient was started newly on steroid treatment with 1 mg/kg of methylprednisolone, a fat and triglycerides-free diet and received albumin along with iv furosemide with minimal effect. Therefore, we added high dose iv immunoglobulin (IVIG) at the dose of 400 mg/kg per day for five days. His condition gradually stabilized, as evidenced by decreased peripheral edema and gradual weight loss.
However, during the steroid tapering a new rise of transaminase and cholestasis indices (γGT 1000 U/L) occurred, and the patient presented again ascites.
Abdominal MRI and total body PET were negative for melanoma recurrence; a transjugular liver biopsy showed scleroatrophy of the bile duct as per immune mediated hepatitis **(Figure 2)**. Therefore, we increased methylprednisolone 2 mg/kg and started mycophenolate mofetil (MMF).
Discussion: This clinical case is peculiar because ICPI – related chylous ascites is very uncommon, and the association with polyserositis suggests a severe endothelial dysfunction, both vascular and lymphatic; moreover, these rare toxicities occurred many weeks after nivolumab discontinuation, whereas these systemic syndromes were mostly reported in early phases of anti-PD1 treatment.
Parameters to identify patients at risk of severe toxicities and prospective data about different immunomodulating therapies efficacy are still lacking. More studies on probability of response and the risk of the toxicity are needed to evaluate the benefice/risk balance of ICPI treatment.





96. THE CORRELATION BETWEEN HEART DISEASE AND LOW BACK PAIN: A CASE REPORT

Carbone E.[1], Biscetti F.[2], Rando M. M.[2], Nardella E.[2], Cecchini A.L.[1], Rossini E.[2], Nicolazzi M. A.[2], Pecorini G.[2], Scarpati R.[1], Massetti M.[3], Gasbarrini A.[4], Flex A.[2]
[1]Università Cattolica del Sacro Cuore, Largo Francesco Vito 1, 00168 Roma, Italy; [2]Cardiovascular Internal Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy ; [3]Department of Cardiovascular Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy; [4]Department of Medical and Surgical sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy

Background: Amyloidosis are a group of diseases characterized by the extracellular deposition of autologous fibrillar proteins, they can be classified into four main types according to their constitutive protein (AL, AA, AF, ATTR). [1] AA amyloidosis is the most common type of amyloidosis, it is associated with infections and chronic inflammatory disorders (rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, and others), it targets kidney, liver and spleen in an early phase, the heart is affected in a late phase. [1, 2]
Case presentation: We report the case of a 57-year-old man presenting with weakness, exertional dyspnea, and chest pain started a week before admission. The patient reported a history of systemic hypertension, chronic kidney disease, atrial fibrillation, hypertrophic cardiomyopathy with late gadolinium enhancement, diabetes, prior stroke 7 years before, cigarette smoking. He also reported a history of recurrent low back pain started some years before,

never investigated with radiological exams. Blood analysis at the time of admission showed an increased level of NT-proBNP (2700 pg/ml), an altered but stable level of cardiac troponins in two determinations (179 ng/L and 161 ng/L), an increased value of serum creatinine (1.3 mg/dL). Albuminuria was found at urinalysis (> 2g/L). An echocardiogram was performed, revealing a biventricular hypertrophic cardiomyopathy with hypokinetic evolution (ejection fraction of 38%), in absence of relevant valvulopathies. A coronarography showed no signs of stenosis of the coronary arteries. An abdomen ultrasound revealed the presence of splenomegaly, in absence of signs of hepatopathy. Serum and urine immunofixation were normal, Bence jones proteins were not detected on urine, serum free light chains ratio was normal. Technetium-labeled cardiac scintigraphy resulted negative for ATTR amyloidosis. In consideration of persisting dyspnea, reduced expansion of the thorax and hypoxemia found at arterial blood gas analysis, a chest high-resolution CT scan was performed revealing a mild thickening of the bronchial walls, diffuse degeneration of the vertebral bodies, calcification of the anterior longitudinal ligament and the interspinous ligaments. Considering the radiological features of the spine, the patient underwent a skeletal X-ray that showed marginal bone production both in the dorsal spine and the lumbar spine and confirmed the calcification of the anterior longitudinal ligament.
Conclusions: we report the case of a man affected by long-standing spondyloarthritis, newly diagnosed during an inactive phase of the disease and likely associated with AA amyloidosis. The diagnosis of spondyloarthritis associated with AA amyloidosis is crucial to ensure timely treatment, protect organs from amyloid deposition, understand prognosis, select appropriate therapies, and provide genetic counseling and family screening. Early detection and management can significantly improve outcomes and quality of life for patients with this condition.
References
1. Real de Asúa D, Costa R, Galván JM, Filigheddu MT, Trujillo D, Cadiñanos J. Systemic AA amyloidosis: epidemiology, diagnosis, and management. Clin Epidemiol. 2014 Oct 29;6:369-77. doi: 10.2147/CLEP.S39981. PMID: 25378951; PMCID: PMC4218891.
2. Obici L, Merlini G. AA amyloidosis: basic knowledge, unmet needs and future treatments. Swiss Med Wkly. 2012 May 31;142:w13580. doi: 10.4414/smw.2012.13580. PMID: 22653707.

97. THE NEVER ENDING STORY OF CHALLENGING HEPATITS DIAGNOSIS

Profili N.I.[1], Frau A.[2], Meloni P.[2], Arru L.[2], Farche T.[2], Masala S.[2], Poddighe A.[2], Manetti R. [2]
[1]Clinica Medica, Dipartimento di Medicina, AOU Sassari; [2]Clinica Medica, Dipartimento di Medicina, AOU Sassari

A case report of a 50 years old patient, with hystory of multiple Venous-thromboembolism and surgery of colecistectomy, ernioplasty and Sleeve gastrectomy (April 2021); the patient was brought to the Emergency Room with abdominal pain in epigastrial region that arose 24h earlier, and accompained by algic swating without vomit. not related with meal.
In the Emergency Room during the physical examination, performed by superficial and deep palpation, the patient presented abdominal tenderness and ache in epi-mesogastial region, in absence of other relevant findings. The patient was taken for a Computed Tomography scan with contrast agent, which was negative excepted for a known adrenal adenoma; Laboratory tests shown the increase of hepatic necrosis indexes of more than double of normality range, the other Haematic parameters were in the range of normality, so the patient had been hospitalized in our unit with a dignosis of n.d Hepatitis. The patient's history excluded a food related hepatitis, for the ingestion of mussels and/or raw food, as well as toxic hepatitis, for the consumption of alcoholic substances and/or psychotropic drugs, also a zoonosis were excluded. The pharmacological anamnesis pointed out a chronical consumption of Pradaxa, Pantoprazole and Liraglutide; the latter at gradually increased dosage week by week –at the moment in the 3rd week-, as an adjuvant of sleeve gastrectomy surgery. The patient also reported the assumption of one 1000mg Paracetamol tablet when the abdominal pain appeared. Blood tests for viral hepatitis (HAV, HBV, HCV, EBV, HS, Varicella Zooster, Toxoplasma, Rosolia, CMV) and autoimmune hepatitis (ANA, AMA, C-ANCA, P-ANCA, ENA) were done and resulted all negative except for gp210. Suspecting a pharmacological hepatitis, the Liraglutide Theraphy has been precautionary suspended and in few days the hepatic necrosis indexes subsided into normality ranges, with concomitant regression of the abdominal simptoms shown at the beginning of the hospitalization.
Conclusions: In literature few cases of Liraglutide induced hepatitis had been reported but it is important to keep it in mind because of an increasingly off-label application for the optimization of ponderal loss in patients with mild-severe obesity or non resposive/low compliance to dietary treatments-
Furthermore the systematic control of hepatic functionality has a remarkable role during the treatment with this medication. A limit in our case is due to the lack of Liraglutide assumption as a demonstration test.

98. SARS-COV2 INFECTION AS TRIGGER OF AUTOIMMUNE DISEASES: A CASE OF SLE IN A YOUNG PATIENT AFFECTED BY PAUCI-SYMPTOMATIC COVID-19

Imperatore F., Tenace V., Cavallo R., Corrado A., Tiso A., Villani R., Sangineto M., Serviddio G.
Liver Unit, University of Foggia

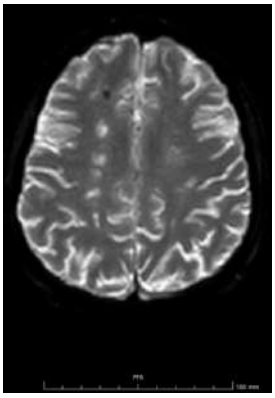
Severe acute respiratory syndrome coronavirus 2 (SARS-COv 2) is a highly transmissible and pathogenetic coronavirus that emerged in late 2019 and has caused a pandemic of acute respiratory disease which threatened human health and public safety.
This infection affects the upper and lower airways with different aspecific synthoms: fever, cough, asthenia, dyspnoea up to acute respiratory failure. In scientific literature are several cases of autoimmune diseases raised after Sars CoV2 infection have been reported. The pathogenetic hypothesis stands in the uncontrolled immune reaction leading to autoimmunity attack on self antigens (molecular mimicry).
Systemic Lupus Erythematosus (SLE) is an autoimmune disease more represented in women, especially subjects with genetic predisposition and exposed to environmental factors such as smoke, western diets, pollution, comorbidities, socioeconomical condition, bacterial and viral infections (e.g. EBV, cytomegalovirus, parvovirus B19, retroviruses, dengue fever virus). A possible relationship between SLE and Sars CoV2 infection has been identified in very few cases, with a mean interval between COVID symptoms and SLE onset of about 25 days.Here, we present the clinical history of a 31 years old young female hospitalized for petechiae localized at lower limbs, and lower extremity edema, hence signs of vasculitis. Ten days before she presented flu-like symptoms and Sars CoV2 infection was detected in the emergency room by qPCR on nasopharyngeal swab, which showed a high viral load. She was not vaccinated for SARs-CoV-2. The clinical history and biochemical assessment underlined the very recent origin of the infection. Lab tests showed pancytopenia (WBC 3.79x103/ul, RBC 3.27x 106/ul, Hb 8,3 g/dl, PLT 35.000/ul), hypocomplementemia (C3 41 mg/dl, C4 1 mg/dl) and positivity to ANA (1:1289) and anti DSDNA autoantibodies (99 U/ML), proteinuria (250 mg/24h), pericardial effusion in association with skin lesions. Overall, these data suggested a diagnosis of SLE according to EULAR/ACR criteria; therefore, a therapy with methylprednisolone and then with prednisone and hydroxychloroquine was initiated. Particularly, in contrast with previous reports, this case showed SLE onset only few days after SARS-CoV2 infection.
The several cases of autoimmune manifestations following Sars CoV2 infection are an important demonstration of a connection between viral infections and autoimmune diseases. Moreover, Type 1-interferon and autoantibodies to INFa (anti-INFa) are involved in both systemic lupus erythematosus (SLE) and COVID 19 pathogenesis.

99. NEUROPSYCHIATRIC DISORDER AS EARLY CLINICAL PRESENTATION OF MARANTIC ENDOCARDITIS IN PATIENT WITH NEWLY DIAGNOSED POORLY DIFFERENTIATED ESOPHAGO-GASTRIC JUNCTION ADENOCARCINOMA: A CASE REPORT.

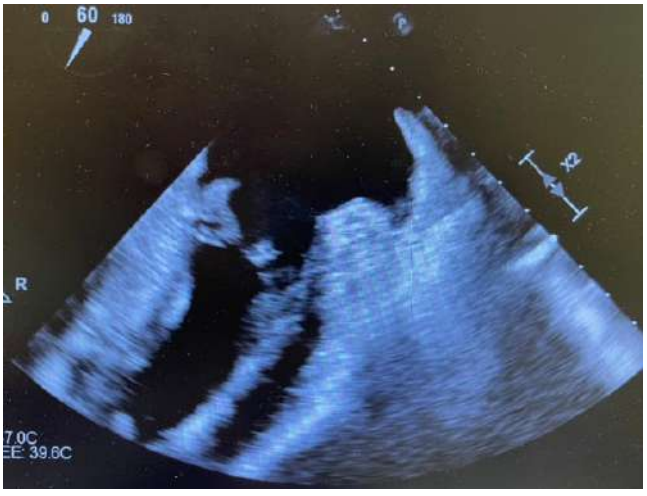
Ferrentino F., Campana S. , Torri M. , Nardi C., Guerrini S., Ascione G., Nesi I., Rostagno C.
Medicina Interna 3, Azienda Ospedaliero-Universitaria Careggi, Firenze

Background: Nonbacterial thrombotic endocarditis (marantic endocarditis) is a sterile thrombotic disease that occurs as a paraneoplastic phenomenon during hypercoagulable state like cancer or chronic inflammatory syndromes. The most common malignancies associated with NBTE include lung, pancreas and gastric adenocarcinoma. The aseptic masses are composed of platelets and fibrin on the heart valves and usually are demonstrated in autopsy. Pathogenesis of NBTE is incompletely understood. Elevated levels of circulating cytokines associated with cancers, such as TNF or IL-1 may also result in local tissue damage that instigates vegetation formation. Vege-

tations in NBTE are neither associated with bacteremia nor with destructive changes of the underlying valve. Diagnosis is based on strong clinical suspicion in the context of a disease process associated with NBTE, presence of a heart murmur, negative blood cultures, absence of response to antibiotic therapy, and evidence of multiple systemic emboli. Up to 15% of cancer patients having thrombotic phenomena and the most common presentation was stroke (54%). There are few reported cases of NBTE as a presenting manifestation of gastric cancer, and the majority occur in advanced disease.
Case report: We describe the case of 64-year-old man, presenting to the ED for general conditions impairment starting 2 months before with progressive mental confusion, asthenia and inappetence conditioning weight loss, until then attributed to work-associated stress. For intercurrent presyncopal episode and acute confusional state he performed several assessments including: cardiac echocolor-Doppler, supra-aortic trunks ultrasound, coronarography, brain CT scan, neurological and internist examination, all of which showed no pathological findings; he therefore started psychoactive therapy after psychiatric counseling. His medical history was notable for quiescent ulcerative rectocolitis, type 2 diabetes and hypertension. On emergency room examinations have been detected normocytic anemia (Hb 10,4 g/dL; hemoglobin value in the previous month was 14,8 g/dL); hypokalemia (K 3,1) and INR 1.4 (spontaneous). During hospitalization, a total body CT scan was performed and showed: several brain ischemic outcomes, the most voluminous in the left frontal site; multiple diffuse thoraco-abdominal lymphadenopathies, some colliqued and tending to confluence. For subsequent febrile spike, blood culture samples were taken (which were negative) and empiric therapy with ceftriaxone 2 g/day was undertaken. To better investigate brain lesions an EEG was performed and showed no epileptiform abnormalities; Angio-CT of the intracranial vessels showed only anatomic variants; encephalic MRI showed supra and subtentorial encephalic signal changes referable to embolic-based ischemic lesions (Fig.1).



Transesophageal cardiac echocolor-Doppler showed mitral valve endocarditic vegetations (Fig. 2) and interatrial septal aneurysm with foramen ovale patency and massive right-left interatrial shunt.



Therefore, new cold blood cultures were requested (3 + 1 for BK, which were later found to be negative) and antibiotic therapy was modified by increasing dosage of ceftriaxone to 2 g 2 times/day and adding vancomycin 1 g/day ev. Other in-depth investigations were also requested to exclude endocarditis infectious nature: serology for cysticercosis (WB), toxocara, strongyloides, trichinella, culture test for helminths, PCR for toxoplasma on blood, serologies for Lue, CMV DNA, EBV DNA, Parvovirus B19 DNA, all of which were negative. The case was also discussed with cardiac surgeons who did not consider surgery indicated due to brain involvement. A FDG PET scan confirmed the presence of multiple diffuse areas, some confluent, of intense glucose hypermetabolism of lymph node relevance; it also reported, in esophago-gastric region, a macro area of intense hypermetabolism. The excision of left lateral-cervical region lymph node package was performed. EGDS documented the presence of vegetating and sub-stenosing lesion of esophago-gastric junction. Following melena and anemia, 2 bags of UGC were transfused and anticoagulant therapy could not be started. On histologic examination on lymph nodes and endoscopic biopsy samples, a low-grade adenocarcinoma with a castellated ring cell component was diagnosed. The case was then evaluated by oncologists who, in view of severe general clinical condition, severe cognitive impairment, and poor prognosis related to poor responsiveness to anti-neoplastic treatments, did not consider active antineoplastic treatment indicated but supportive therapy only. Patient presented progressive worsening of clinical condition; he was finally transferred to hospice and died 11 days after discharge.
Discussion: In this clinical case, the absence of neurological symptoms at onset did not lead to suspicion of organic brain involvement from the start, framing the problem as a psychiatric disorder. This emphasizes that clinical presentation of marantic endocarditis can be very heterogeneous; the high percentage of distant embolization can give even totally non specific symptoms making the diagnosis even more difficult.

100. A PRECISION MEDICINE APPROACH FOR THE CLINICAL EVALUATION OF A LEAN PATIENT WITH NAFLD

Periti G., Pelusi S., Bianco C., Moretti V., Prati M., Ronzoni L., Valenti L.
Precision Medicine Lab, Biologic Resource Centre and Transfusion Medicine, Department of Transfusion Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico

Nonalcoholic fatty liver disease (NAFLD) has a global prevalence of approximately 25-35% and when associated with inflammation (nonalcoholic steatohepatitis – NASH) can lead to cirrhosis and hepatocellular carcinoma (HCC). NAFLD is associated with other metabolic features such as obesity and type 2 diabetes but in about 10-15% of the cases it manifests in normal weight individuals. Thus, clinicians are called to recognize other causes of steatosis such as alcohol consumption or rarer causes for example medications (corticosteroids, methotrexate, tamoxifen, amiodarone), and hereditary conditions as hypolipidemias or mitochondrial disorders.
We report a case of a 23-years-old man, blood donor at the Policlinico di Milano, who came to the attention due to elevated transaminases l (ALT 103 IU/l, AST 47 IU/l), promptly ameliorated by dietary restriction but recurrent and associated with dietary excesses. There was a family history of hepatic disease of unknown origin, as his grandfather died for cirrhosis and his dad, who is obese, was under medical evaluation for a hepatic nodule, emerged to be a regenerative nodule in cirrhosis. The BMI was 23.5 kg/m2, the clinical examination, abdominal circumference and blood pressure were within the normal limits. The exams were as follow: total cholesterol 83 mg/dl, triglycerides 48 mg/dl, calculated LDL 24 mg/dl, GGT 20 IU/l (n.v. 2-50), ANA, AMA, ASMA, anti-LKM e anti-transglutaminase were negative, ceruloplasmin was 0.22 mg/dl (n.v. 0.20 – 0.60), TSH was 0.35 μU/mL (n.v. 0.27 - 4.2). The most common hepatotropic virus infections were excluded. Abdominal ultrasound showed moderate to severe hepatic steatosis, confirmed also by transient elastography/Fibroscan® (CAP 347 dB/m), Liver Stiffness was 6.6 kPa. To confirm hypobetalipoproteinemia we requested ApoB measurement that was severely decreased (0.17 g/L; n.v. 0.8-1.55 g/L) and levels of vitamin A and vitamin E which were normal.
To obtain genetic characterisation, we proceeded to whole exome sequencing (WES) focusing on a virtual panel of 82 genes responsible for hepatic and metabolic diseases. As suspected, a variant of apolipoprotein B (*APOB)* gene was identified; the implicated variant, p.Ser2429Ter, leads to the transcription of a truncated form of hepatic ApoB100, resulting specifically in defective secretion of very low density lipoproteins (VLDL) from the hepatocytes. Familial hypobetalipoproteinemia (FHBL) is an autosomal codominant genetic disorder caused by loss-of-function mutations in the *APOB* gene.
Familial hypobetalipoproteinemia (FHBL) is characterized by a defective

lipid export through triglycerides-rich lipoproteins due to the loss-of-function mutations in the apolipopotein B gene (*APOB)* encoding for ApoB100 and ApoB48 necessary for the synthesis of VLDL and chylomicrons in the liver and intestine, respectively. Homozygous FHBL due to mutations affecting also ApoB48 synthesis manifest in early childhood or infancy with lipid malabsorption, growth impairment, liposoluble vitamins deficiencies that may lead to neurological disturbances and hemolysis. Heterozygous FHBL is characterized by low circulating lipid levels and hepatic steatosis. The estimated prevalence of FHBL in the general population is between 1:1,000 and 1:3,000. WES allowed us to identify also a heterozygous missense mutation in the *SERPINA1* gene, associated with alpha 1 antitrypsin deficiency (AA1TD), a recessive condition, but one that can predispose to progressive liver disease even in heterozygosity when associated with steatosis.
Finally, the genetic analysis has allowed to evaluate the inherited predisposition to NAFLD determined by common genetic variants, as captured by polygenic risk score-5 (PRS-5), resulting in an increased score of 0.733 (n.v. <0.435), determining a high risk of progression to hepatocellular carcinoma (HCC) in the presence of metabolic cofactors. The PRS-5 is based on a combination of common variants, namely polymorphisms, in genes involved in hepatic lipid metabolism and takes into account four genes whose products predispose to NAFLD, fibrosis, and HCC (*PNPLA3, TM6SF2, MBOAT7*, and *GCKR*), as well as a gene whose variant is protective against the development of advanced fibrosis and HCC (*HSD17B13*). In fact, NAFLD has a strong genetic component, and the content of liver fat is a determinant for the development of inflammation, ballooning, and liver fibrosis, the main prognostic factor in these subjects.
In this case, genetic analysis allowed us to reach the correct diagnosis and establish an individualized follow-up and familial genetic counselling. Indeed, the co-occurrence of the pathogenic *APOB* mutation with a high-risk genetic profile contributed to explain the clinical presentation in a young lean individual but at very high risk of developing liver events. Comprehensive evaluation of genetic data can represent an important integration in the stratification of clinical risk, contributing to the development of precision medicine focused on the individual patient. Personalized therapeutic approaches with vitamin E supplementation and statins are being considered for halting disease progression.

101. DRESS SYNDROME (DRUG REACTION WITH EOSYNOPHILIA AND SYSTEMIC SYMPTOMS) FROM ALLOPURINOLO

Postorino D. M., Cartenì B., Bovo M., Mereu D., Ruscitti C., Paladino A., Appolloni V., Guglielmi V., D'Adamo M., Sbraccia P.
Internal Medicine and Obesity Center Unit – Tor Vergata Hospital

Introduction: Allopurinol is a widely used drug in clinical practice for hyperuricemia treatment. Its action is based on xanthine oxidase inhibition, leading to reduced uric acid. Then, allopurinol results in a hypouricemic effect and promotes the mobilization and dissolution of urate deposits in skin, bones, joints and renal-interstitial tissue. Since allopurinol and its metabolites are eliminated through the kidneys, impaired renal function can lead to drug accumulation due to prolonged half-life.
Clinical Case: D.M., an 83-year-old woman, arrived at the Emergency Department of Tor Vergata Hospital in March 2023 with diffuse urticaria on trunk and upper limbs, which showed poor response to antihistamine therapy and persistent postprandial vomiting for a few days.
Her medical history reports the development of permanent atrial fibrillation and the subsequently initiation of DOAC (*Edoxaban*) therapy. She was also treated for exacerbated chronic heart failure with preserved ejection fraction, due to community-acquired pneumonia and had a history of bronchial asthma. About three previously weeks, she started allopurinol therapy due to recently diagnosed hyperuricemia.
Initial blood tests revealed acute kidney injury, likely of pre-renal origin due to dehydration induced by vomiting. She required urgent hemodialysis sessions, which led to a progressive improvement in clinical and laboratory parameters. Concurrently, there was an increase in pancreatic function indices and eosinophilia. An abdominal ultrasound was performed, showing no abnormalities in the abdominal parenchyma. Considering the persistent skin rash and the patient's positive history of allergic asthma, an autoimmune nature of the rash was excluded.
Due to the laboratory findings of eosinophilia, acute renal dysfunction, elevated pancreatic function indices, and the persistent skin rash, as well as the recent introduction of allopurinol in her therapy, a suspicion arose that the clinical picture was attributable to an adverse drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) caused by allopurinol intake. Upon discontinuation of the drug and initiation of high-dose systemic corticosteroid therapy (Methylprednisolone 1 mg/kg/day), a progressive improvement was observed for both renal and pancreatic function, complete blood count, normalization of eosinophilia, and cutaneous clinical improvement, leading to the complete resolution of the rash.
Conclusions: DRESS syndrome is a rare but potentially life-threatening adverse drug reaction. It is characterized by fever, papulopustular rash, eosinophilia, atypical lymphocytosis, lymphadenopathy, and systemic involvement (hepatitis, acute renal failure, interstitial pneumonitis, pleural effusion, pericarditis, and myocarditis) and usually occurs approximately 2-8 weeks after drug exposure. It most commonly occurs after the administration of antiepileptic drugs (such as carbamazepine, phenytoin, and lamotrigine), but cases of DRESS induced by allopurinol, febuxostat, dapsone, olanzapine, sulfasalazine, minocycline, vancomycin, imatinib, and sorafenib have also been reported with some frequency. Patients expressing specific HLA phenotypes are predisposed to develop this type of reaction following the intake of a particular drug. The expression of HLA-B58:01, for example, is associated with a higher susceptibility to allopurinol-induced DRESS. The identification and early discontinuation of the causative drug are essential therapies, even in cases involving the liver, lung, or kidney. While systemic steroid therapy has not shown any benefit in cases of drug-induced liver injury, it is recommended in cases of lung or kidney involvement (0.5-2 mg/kg/day of prednisone or equivalents), and it should be continued until clinical improvement is achieved and laboratory parameters normalize, then tapered over 8-12 weeks until discontinuation. Although there is limited evidence for the use of cyclosporine, it is considered a second-line treatment for patients with DRESS who do not respond to systemic steroid therapy.
Bibliografia:
- Cacoub P, et al. The DRESS syndrome: a literature review. Am J Med. 2011 Jul;124(7):588-97.
- Husain Z, Reddy BY, Schwartz RA. DRESS syndrome: Part I. Clinical perspectives. J Am Acad Dermatol. 2013 May;68(5):693.e1-14.
- Kirchhof MG, Wong A, Dutz JP. Cyclosporine Treatment of Drug-Induced Hypersensitivity Syndrome. JAMA Dermatol. 2016 Nov 1;152(11):1254-1257.

102. A RARE CASE OF GITELMAN SYNDROME WITH NORMOCALCIURIA, IRON-DEFICIENCY ANEMIA AND HYPOTHYROIDISM

Gamberini A., Sechi L.A., Cavarape A.
Clinica Medica, Department of Medicine (DAME), University of Udine, 33100 Udine, Italy

Introduction: Gitelman Syndrome (GS) is a rare hereditary renal tubulopathy transmitted as an autosomal recessive trait. In the majority of cases, mutations have been identified in the solute carrier family 12, member 3 gene, SLC12A3, which encodes the thiazide-sensitive Na-Cl cotransporter. The prevalence of heterozygotes is approximately 1% in Caucasian populations. GS is characterized by hypokalemia, metabolic alkalosis, hypomagnesemia and low urinary calcium excretion. Frequently, symptoms do not appear before the age of six and the disease is usually diagnosed during adolescence or adulthood. Unlike the Bartter syndrome, clinical manifestations are generally less severe and usually polyuria is absent. Thyroid dysfunctions are also reported. Additional symptoms are nycturia, polydipsia, salt craving and dizziness. As a result of chronic salt wasting and electrolytes urinary loss, blood pressure is often lower than in the general population and potassium and magnesium depletion can potentially lead to ventricular arrhythmias. According to the criteria developed by KDIGO consensus, clinical features for suspecting a diagnosis of GS are chronic hypokalemia below 3.5 mmol/L with inappropriate renal potassium wasting, metabolic alkalosis, hypomagnesemia with inappropriate renal magnesium wasting, hypocalciuria, high plasma renin activity or levels, fractional chloride excretion above 0.5%, low or normal-low blood pressure, normal renal ultrasound.
Case Description: A 63-year-old man presented to the Internal Medicine outpatient clinic with >5 years clinical history of general fatigue, limb weakness and referred chronic hypokaliemia. He denied diarrhea and the use of drugs (i.e. diuretics), laxatives, natural drugs, supplements or herbal preparations. He also referred salt craving and normo-hypotension (mean arterial pressure was approximately 75 mmHg). Members of the patient's family (mother, sister and brother) reported chronic hypokaliemia, none of them were affected by arterial hypertension. Biohumoral laboratory parameters revealed sideropenic anemia with low hemoglobin levels (10.4 g/dL), reduced mean cell volume (72.4 fL),

low plasma iron concentrations (32 μg/dL), low levels of circulating ferritin (11 ng/mL) and low transferrin saturation (7%). The persistence of hypokalemia was confirmed (3.12 mMol/L). We also observed hypomagnesemia (0.44 mMol/L), hypocalcemia (1.04 mMol/L) and metabolic alkalosis with bicarbonate values found slightly above normal limits (29.7 mMol/L). Liver profile and renal function parameters were normal. Furthermore, high plasma levels of renin were detected in upright position (176.9 μUI/mL) and hypothyroidism was also confimed (5.829 μUI/mL) with free triiodothyronine levels slightly above normal limits (4.29 pg/mL) and negative autoantibodies. Moreover, 24-hour urine collection was performed and it revealed increased excretion of chloride (334 mMol/24h), sodium (353 mMol/24h) and magnesium (7,3 mMol/24h), with normocalciuria (3.33 mMol/24h) and phosphaturia levels within limits. These findings were interpreted as a sign of a probable congenital renal tubulopathy. Genetic test was subsequently performed and it revealed homozygous variant of c.2687G>A in the exon 23 of the SLC12A3 gene determining amino acid replacement of arginine in position 896 by glutamine. Eventually, the diagnosis of Gitelman Syndrome was established.
Conclusions: In this case report the family history, clinical presentation and laboratory findings were interpreted as suggestive features of a congenital renal tubular disease. There are two main aspects to underline: the first one is the finding of normocalciuria and the second one is the late diagnosis of a hereditary disease. Interestingly, this case presented thyroid dysfunction, in particular non-autoimmune hypothyroidism: it has been shown that rat thyroid expresses the angiotensin II receptor subtype 1, AT1. Considering that GS patients show enhanced levels of angiotensin II, thyroid function might be affected through the angiotensin II action on AT1 receptors. Futhermore, another abnormal laboratory finding in the presented case was iron-deficiency anemia: even if iron deficiency/microcitic anemia can coexist with GS, there are no direct known correlations between these two medical conditions. General management of GS should be individualized, considering that there is no specific or target therapy for this type of disease. In this case report, the particularity lies in the fact that the diagnosis of GS has been established in a 63-year-old man with chronic hypokaliemia, hence the real prevalence of GS might also be underestimated. According to the KDIGO consensus levels of calciuria are not always diagnostic: since genetic testing becomes more accessible and available, this opportunity should be offered to all patients with a clinical suspicion of GS.

103. ARDS (ACUTE RESPIRATORY DISTRESS SYNDROME) SECONDARY TO BILATERAL INTERSTITIAL PNEUMONIA FROM METAPNUEMOVIRUS WITH ASSOCIATED BACTERIAL SUPERINFECTION TREATED WITH NON-INVASIVE MECHANICAL VENTILATION (NIV)

Postorino M., Cartenì B., Bovo M., Ruscitti C., Paladino A., Appolloni V., Guglielmi V., D'Adamo M., Sbraccia P.
Internal Medicine and Obesity Center Unit, Tor Vergata Hospital;

Introduction: ARDS (Acute Respiratory Distress Syndrome) is a heterogeneous syndrome that must meet four criteria: i) oxygenation deficit (reduced PaO2/FiO2 ratio) on arterial blood gas analysis, ii) onset of respiratory symptoms within one week, iii) Bilateral radiographic abnormalities (asymmetric multiple opacities secondary to non-cardiogenic pulmonary edema) and iv) absence of cardiac decompensation, heart failure, or volume overload that would explain the respiratory failure.The acute and diffuse inflammatory lung injury results in increased permeability of the pulmonary vascular component, loss of aerated lung volume, arteriovenous shunting, increased dead space, and reduced thoracopulmonary compliance. One of the causes of direct lung injury is pneumonia.Viral pneumonia caused by Metapneumovirus, with associated bacterial superinfection, is one of the causes of hospitalization and ARDS in patients with Chronic Obstructive Pulmonary Disease (COPD).In these patients, non-invasive support may avoid endotracheal intubation. High-flow nasal cannula (HFNC) and non-invasive ventilation (NIV) are the most effective therapeutic tools.
Clinical Case: N.N.M., a 72-year-old woman, arrived at the Emergency Department of Policlinico Tor Vergata in February 2023 with worsening dyspnea, non-pitting edema in the lower limbs, and bilateral pleural effusion, as seen on a chest X-ray performed at another facility.In her medical history, she had Chronic Obstructive Pulmonary Disease (COPD), a history of smoking, glaucoma, hypertension, dyslipidemia, and complicated type 2 diabetes.A chest CT scan was performed, confirming bilateral pleural effusion with atelectasis of the adjacent lung parenchyma. It also showed areas of altered parenchymal density known as "ground-glass opacities," consistent with an inflammatory and subedematous pulmonary condition.Initial blood tests revealed mild normochromic normocytic anemia, relative neutrophilia and lymphopenia, elevated B-type natriuretic peptide (BNP), albuminuria, and glucosuria. Urinary antigen tests for Legionella and Streptococcus pneumoniae were negative, and a SARS-CoV-2 swab test was negative.An echocardiography with color Doppler revealed moderate tricuspid regurgitation with a pulmonary artery systolic pressure (PAPs) of 35 mmHg and preserved ejection fraction.Due to the lack of clinical improvement despite antibiotic and diuretic therapy, arterial blood gas analysis showed a clear picture of hypoxic hypercapnic respiratory failure (type 2), and non-invasive mechanical ventilation (NIMV) with a mask interface was initiated.The nasopharyngeal swab for influenza viruses showed positivity for Metapneumovirus. A follow-up chest CT scan revealed a typical picture of ARDS with areas of "ground-glass opacities" and partially consolidated lung tissue evident in all lobes, along with diffuse thickening of the interlobular septa, consistent with subedematous pulmonary edema.Considering the suspected multifactorial etiology of ARDS, a fiberoptic bronchoscopy was performed, and microbiological examination of the bronchoalveolar lavage (BAL) confirmed positivity for Haemophilus influenzae.Antibiotic therapy with Tazocin (Piperacillin/ Tazobactam) and Vancomycin was initiated, leading to progressive clinical and blood gas analysis improvement, eventual weaning off NIMV, and stabilization of the respiratory condition.Due to the underlying chronic respiratory failure secondary to COPD, low-flow oxygen therapy was continued at home.
Conclusion: ARDS is characterized by acute respiratory failure with bilateral infiltrates on chest imaging, not explained by heart failure or fluid overload (non-cardiogenic pulmonary edema). Predisposing factors are diverse, including pneumonia (especially nosocomial, but also community-acquired in the presence of risk factors), sepsis, trauma, and pancreatitis.The external insult acts as a stimulus for a cascade of unregulated inflammatory responses and cytokine activation, causing damage to the alveolar-capillary barrier, edema, and respiratory exchange impairment.Regarding pneumonia, numerous viral etiological agents such as rhinovirus, parainfluenza viruses, metapneumovirus, respiratory syncytial virus, and coronaviruses can rapidly cause ARDS, especially in individuals at high risk of infections. Additionally, prognosis worsens in cases of bacterial coinfection.Non-invasive ventilation strategies include high-flow nasal cannula (HFNC), non-invasive ventilation (NIV), or positive end-expiratory pressure (CPAP) through facial masks or helmets.The use of these strategies preserves the physiological airway protective pathways (e.g., cough and secretion clearance) and is capable of directly reducing complications associated with orotracheal intubation and invasive mechanical ventilation.Bibliografia
-Mayer N., et al. Lancet, 2021; 398: 622-637.
-Garman E. et al, Lancet, 2022; 400: 1157-1170.
-Grieco L. et al, Intensive Care Medicin. 2021; 47:857-867.
-Walter J.M., Wunderick R. Infect Dis Clin North Am 2017; 31 (3): 455-474.

104. STAND UP FOR YOUR BREATHS: AN ATYPICAL PRESENTATION OF ALS.

Borrelli K., Ghigliazza G., Serafini S., Barbetta L., Rossi S., Canetta C.
High Care Internal Medicine Unit Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico Milano

A 63-years-old male patient was hospitalized for leg swelling and acute pulmonary edema on suspected cardiogenic basis, with diffuse negative T waves at EKG and elevation of troponins, with values never exceeding 200 ng/L. The patient had a history of unspecified brainstem stroke, conditioning multiple episodes of vertigo and falls, a Dupuytren's contracture in his left hand and a SARS-CoV-2 infection during the previous year, after which relatives noticed a progressive decline in performance status and pulmonary function. The patient denied any history of tobacco and alcohol use. Under clinical and biochemical suspicion of heart failure, the dosage of pro-BNP and a color-doppler echocardiography were carried out. All of this exams resulted normal and allowed us to retain the cardiogenic nature of the pulmonary edema less probable: the non-specific electrocardiographic alteration and the non-significant troponin curve were interpreted as a consequence of tissue hypoxia. Even though the leg swelling, the pleural effusion and the lung edema resolved with diuretic therapy and BiLevel ventilation, there was no improvement in lung function. In particular, without BiLevel support, especially lying supine in the bed, the patient quickly developed respiratory distress with hypoxia and hypercapnia. Under the suspicion of an underlying infection a high resolution lung CT scan was performed, which resulted negative for acute diseases, and the antibiotic therapy was quickly quitted, because of the absence of clinic and biochemical signs of inflammation. All microbiological test resulted negative, including SARS-CoV-2 test.Under the suspicion of a neurological disorder, because of the history of a brainstem stroke, even thought a first-level neurological evaluation was negative, a head

TC was performed which resulted negative as well.A EMG was performed, which was positive for a non-specific pattern, compatible with a suffering of both the upper and lower motor neuron. Under the suspicion of a multifocal motor neuropathy the research of anti-GM1 antibodies was performed, but resulted negative. Additional neurological investigation, like MEP (Motor Evoked Potentials), SSEP (Somato-Sensory evoked potentials) and head MRI were not tolerated by the patient, because of the impossibility to undergo those exams without BiLevel support.In the end, after an accurate neurological examination performed by a highly specialized neurologist, an amyotrophic lateral sclerosis (ALS) diagnosis with diaphragmatic involvement was put forward.Soon after a lumbar puncture was performed, which excluded all the different diagnosis.
This case is particularly interesting because of this atypical manifestation of ALS.To begin with, the first respiratory failure the patient presented with may actually have been of cardiogenic origin: the hypoventilation caused by ALS may have induced a state of tissue hypoxia and thus myocardial suffering. This might explain the rapidity of clinical response with moderate diuretic therapy and oxygen therapy.Hence, how did ALS induce hypoxemia? Our hypothesis is on mechanical basis: while standing, the hindered diaphragm was rescued by accessory respiratory muscles (e.g. intercostal musculature), whereas, while laying, as the geometry of ventilation changes, the accessory muscles couldn't hold up a valid breathe.What made the diagnosis more difficult, was the absence of any evident clinical sign or symptom of neurological involvement, except for the respiratory failure. We didn't think of his left hand atrophy and contracture as due to a neurological involvement, because the patient was given a Dupuytren diagnosis before.What is more, he wasn't dysarthric, although his voice was usually quiet in some circumstances he laughed loudly, nor dysphagic, and during hospitalization he walked the hallway without any episodes of fall or vertigo.Only a highly specialized neurologist was able to recognize the contracture and atrophy of the left hand as a result of ALS and to notice very subtle yet diffuse muscular atrophy and fasciculations of the upper and lower limbs.

105. NONBACTERIAL THROMBOTIC ENDOCARDITIS AND DIFFUSED INTRAVASCULAR COAGULATION IN RAPIDLY PROGRESSING PROSTATIC ADENOCARCINOMA: A CLINICAL CASE

Peracino R.[1], Di Terlizzi G.[2], Marinosci A.[2], Di Lucca G.[2], Scotti R.[2], Ramirez G. A.[3], Damanti S.[4], Tresoldi M.[2]

[1]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy. Università VIta- Salute San Raffaele, Milan, Italy; [2]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy.; [3]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy. Università VIta- Salute San Raffaele, Milan, Italy. Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS Ospedale San Raffaele, Milan, Italy; [4]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy.Università VIta- Salute San Raffaele, Milan, Italy. Unit of Medical Specialties and Healthcare Continuity IRCCS Ospedale San Raffaele, Milan, Italy

Background: Nonbacterial thrombotic endocarditis (NBTE) is a spectrum of valvular lesions ranging from small platelet aggregates to large vegetations affecting healthy valves, in the absence of systemic infection. Advanced malignancy is the most common cause, with the highest prevalence seen in adenocarcinomas (up to 19%). Other systemic inflammatory conditions are also known causes for NBTE, such as systemic lupus erythematosus (11% prevalence), and less commonly rheumatoid arthritis, burns, and sepsis. Systemic hypercoagulable state is believed to be at the basis of thrombus formation, even if the inciting event leading to the activation of the thrombotic pathway has yet to be clarified. Of note, around 18-50% of patients with NBTE show laboratory or clinical signs of disseminated intravascular coagulation (DIC), suggesting its involvement in at least some cases of NBTE. The clinical presentation is variable and related to the consequences of peripheral embolization. Vegetations tend to be more fragile and unstable than their septic counterpart, with potentially devastating organ damage. Unfortunately, many patients are misdiagnosed with infective endocarditis, or remain undiagnosed. For this reason, NBTE is most commonly diagnosed postmortem, with a reported incidence of about 1% in autopsy series.
The case: A 62-year-old man, was admitted to the General Medicine High Intensity Care Unit of San Raffaele Hospital in February 2022. He presented to our emergency department due to the sudden onset of extensive bruising of the limbs, trunk and abdomen, and confusion, gait impairment and short-term memory deficits. Diagnosed in 2020 with metastatic prostate adenocarcinoma, stage T2N2M1b, involving lymphnodes, pelvis and bone, he was treated with radiotherapy and androgen blockade, with complete biochemical response. On arrival at the emergency room, his labs showed moderate thrombocytopenia, prolonged PT and aPTT, mildly consumed fibrinogen, elevated LDH and D-dimer, and progressively increasing CRP levels. He also developed fever. Empiric therapy with ceftriaxone and acyclovir was started suspecting CNS infection. Serial blood cultures resulted negative. Urgent brain CT revealed new-onset, diffused hypodensities involving cortical and subcortical areas, consistent with ischemic events. Still febrile with progressive deterioration of neurological status, marked disorientation and uninhibited behavior, he was admitted to our High Intensity Internal Medicine Unit. Worsening of coagulation tests led to diagnosis of overt DIC, deemed to be either infectious or paraneoplastic. Progressively increasing PSA values despite suppressed testosterone indicated rapid castration-resistant cancer progression. Supportive therapy with fresh frozen plasma and heparin prophylaxis was started, and a wider empiric antimicrobial coverage with ceftriaxone, acyclovir, ampicillin and vancomycin was chosen. Contrast brain MRI confirmed evidence of disseminated ischemic micro-embolic lesions. A first transthoracic echocardiogram showed no evidence of vegetations suggestive of endocarditis, but a whole-body CT scan found a left ventricular thrombus and multiple microinfarcts of the spleen and kidneys. Subsequent transesophageal echocardiogram showed aortic endocarditis with severe valvular regurgitation. The clinical and imaging findings, in the context of repeated negative blood cultures and neoplastic progression, strongly suggested NBTE associated with severe DIC. Patient's condition was further complicated by NSTEMI due to coronary artery thrombosis followed by congestive heart failure and acute bilateral lower limb ischemia due to tibial artery embolization. The multidisciplinary meeting with oncologists and heart surgeons concluded that there was no room for active treatment of cancer and surgical valve replacement. The patient was set on supportive care and palliation until death.
Discussion Timely diagnosis of NBTE is critical, especially in advanced cancer patients who can derive benefit from active cancer treatment before they experience the devastating consequences of peripheral embolization. Management of NBTE should aim to reduce the risk of embolic events with prompt anticoagulation, address significant valvular dysfunction and treat the underlying cause. Indeed, there is evidence that unfractionated heparin therapy reduces the incidence of thromboembolic complications, particularly in patients with malignancy. Surgery may also be considered in patients with large vegetations or uncontrolled disease despite anticoagulation. The risk-benefit ratio must be carefully assessed, as surgical mortality is high. Ultimately, the key to managing NBTE is to treat the underlying disease whenever possible. Thus we suggest that clinicians should be aware of this condition in patients with known risk factors, peripheral emboli and negative blood cultures. If neglected, the hypercoagulability state associated with cancer and NBTE may rapidly evolve to overt DIC and become fatal.

106. 50 SHADES OF SHOCK: A COMPLEX DIAGNOSIS AND MANAGEMENT IN A MULTIFACTORIAL SHOCK

Poloni V.A.[1], Semproni E.[2], Rossio R.[2], Ghigliazza G.[1], Casiraghi C.[1], Vaccari M.[1], Re T.[1], Porretti S.[1], Peyvandi F.[3], Canetta C.[1]
[1]High Care Internal Medicine Unit, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy.; [2]Hemophilia and Thrombosis Center and Fondazione Luigi Villa, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.; [3]Haemophilia and Thrombosis Center, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy

A 62 years-old man was admitted to the emergency department (ED) for dyspnea. He suffered from hypertension, Gilbert syndrome, chronic renal failure, psoriasis and erythroderma of unknown origin, for which he had been treated with methotrexate and steroids. The patient had undergone several skin biopsies which were unconclusive for the two main differential diagnosis between erythrodermic psoriasis and mycosis fungoides.A diagnosis of community-acquired pneumonia with mild respiratory failure was made. After having collected urine and blood cultures, antimicrobic treatment with piperacillin/tazobactam was begun and the patient was transferred to the Hemostasis and Thrombosis Internal Medicine Unit.During the first days of hospitalization, the patient complained about left leg pain so a muscular ultrasonography scan was performed: an abscess of 5 x 16 cm of diameter was found in the soleus muscle and an upgrade of antibiotic therapy with clindamycin and vancomycin was then made. Blood cultures resulted positive for a

Methicillin-sensitive Staphylococcus aureus (MSSA) and oxacillin was started, replacing previous antibiotic therapy; in addition, urinary antigen test was positive for Legionella pneumophila and a high titer of Herpes simplex virus-1 DNA was found in blood, thus levofloxacin and acyclovir were added. Caspofungin was introduced in the next days for beta-D-glucan positivity and cutaneous intertrigo. A diagnosis of fasciitis was made and the abscess was surgically drained without immediate complications. The night after the procedure, however, the patient started to be hypothermic (body temperature decreased down to 32 °C), thus hot fluids were administered intravenously and a thermal blanket was used, without benefit. Gradually, the patient entered a state of shock with oliguria, hypotension, confusion, hyperlactatemia in addition to anaemia, severe hypernatremia and anasarca. Organ perfusion was supported with norepinephrine, albumin, fluids and blood transfusion. However, patient's conditions remained critical, thus he was transferred in the Intermediate Care Unit.In this setting the patient was stabilised with noradrenaline and cautious IV volume optimisation because of the pathophysiological complexity of the clinical scenario.On one hand, the patient was infected; in addition, the underlying dermatological pathology caused a significant increase in perspiration, which required large amounts of liquids that made fluid losses complex to estimate. Several formulas from other clinical settings, such as Parkland's for extensive burns, to evaluate the patient needs may have increased this risk by overestimating fluids amount.On the other hand, the cutaneous pathology also caused important desquamation, causing protein dispersion from the skin and subsequent third-space fluid loss in synergy with sepsis.Furthermore, episodes of advanced atrioventricular block resulted in circulation overload treated with benefit with isoprenaline. No PM implantation indication was given due to the patient's intercurrent septic state and good response to pharmacological therapy. The echocardiography after cardiological stabilisation was unremarkable.Blood cultures from both peripheral vein and PICC tested positive for Corynebacterium striatum, Enterococcus faecium and VIM-producing Enterobacter Hormaechei, found on left leg wound's purulent material swabs too.PICC was removed, a new vascular access positioned, previous antibacterial therapy stopped and cefiderocol, vancomycin and metronidazole were started.A left limb contrast-enhanced CT scan was performed as post-surgical follow-up, which showed a reduction of the known collection, that the orthopaedic still deemed passible of surgical reintervention.Since the dermatological diagnosis was still uncertain and the patient developed transient pancytopenia, when the sepsis was under control, skin and bone marrow biopsies were done, and diagnosis of mycosis fungoides without blood and bone marrow involvement was made.Following the newly diagnosed onco-haematological disease and after having obtained a stable clinical status, the patient was transferred to the Haematology department to start specialistic treatment.Unfortunately, after surgical debridement of the left leg, sepsis worsened and the patient died of septic shock.This is a particularly interesting case for different reasons.Firstly, we highlight the challenge of fluid management in such a complex patient, for whom fluid losses could only be briefly estimated. In summary, the classification and the treatment of the patient's shock was hard to be determined, with a dual septic and hypovolemic aetiology; nevertheless, fluid dispersion and bradycardia-induced heart failure implied the need for albumin and diuretic therapy as well.Moreover, formulas for skin losses except for burns still lack.Secondly, the dermatological diagnosis, for a long time sought after in out-patient care with several inconclusive biopsies, was finally made: this has to remind us the importance of always revising all the possible diagnosis even after previous negative work-up if the pre-test probability remains high.

107. PANCA-ASSOCIATED VASCULITIS COMPLICATED BY RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS AND MYOPERICARDITIS: A CASE REPORT

Mereu D., Starnino D., Mosti A. L., Nguena Mawamba P. S., Zupo F., Musumeci F., Zamparelli C., Guglielmi V., Colangeli L., D'Adamo M., Sbraccia P.
Unit of Internal Medicine and Obesity Center - Tor Vergata Hospital Rome

Introduction: ANCA-associated vasculitides (AAV) are a heterogeneous group of multifactorial diseases with an autoimmune pathogenesis. They are characterized by the infiltration of inflammatory cells within small and medium-sized blood vessels, leading to damage and weakening of the vessel walls, eventually resulting in necrosis. These vasculitides are characterized by anti-neutrophil cytoplasmic antibodies (ANCAs) that cause vascular inflammation and damage to various organs and tissues such as the kidneys, lungs, upper respiratory tract, gastrointestinal tract, skin, nervous system, eyes, and heart. There are two responsible antibodies: p-ANCA, directed against myeloperoxidase (MPO), and c-ANCA, directed against proteinase 3.
Clinical Case: G. K., a 51-year-old woman, arrived at the Emergency Department of Tor Vergata Policlinic on March 21, 2023, with fatigue, anorexia, significant weight loss (11 kg in 2 months), diffuse abdominal pain, nausea, and vomiting. In her medical history, the patient reported 10 miscarriages in the context of 3 full-term pregnancies, recent admission to the emergency department in March for pneumonia, where a uterine fibroid was detected, and a previous infection with SARS-CoV-2 for which she was not vaccinated.
Upon arrival at the Emergency Department, the patient was afebrile, in fair general condition, with vital signs within normal limits, and a normal physical examination. Initial blood tests revealed anemia (Hb 9.3 g/dL), creatinine level of 3.02 mg/dL (last creatinine in March '23 was 1.34), with a BUN/creatinine ratio of < 10, a CRP level of 316.50 mg/L with associated mild neutrophilic leukocytosis. Urine analysis showed microscopic hematuria with approximately 324 red blood cells per high-power field. A 24-hour urine protein test resulted in a value of 800 mg/24h. The clinical presentation and laboratory tests indicated a picture of acute kidney injury (AKI) in the context of a nephritic syndrome. In suspicion of post-streptococcal glomerulonephritis or infection-associated glomerulopathy, a throat swab, ASO titer, and serology for HIV, HCV, HBV were requested, all yielding negative results.
In suspicion of lupus nephritis, Goodpasture's syndrome, or ANCA-associated vasculitis, ANA, C3, C4, anti-Sm, anti-dsDNA antibodies, anti-glomerular basement membrane antibodies, and c-ANCA were requested. All of these tests were negative/normal, except for high-titer p-ANCA (230.7).
For further diagnosis, the patient underwent renal biopsy and subsequent histological and immunofluorescence examination, which revealed a picture of rapidly progressive necrotizing pauci-immune glomerulonephritis.
During hospitalization, the patient developed myopericarditis with acute heart failure, reduced ejection fraction, acute pulmonary edema, elevated troponin (TnI hs > 2000 ng/L), and sinus tachycardia (heart rate of 125 BPM). Acute respiratory failure secondary to acute pulmonary edema required respiratory support with non-invasive mechanical ventilation and continuous intravenous diuretic therapy. Renal function indices also progressively worsened. Following treatment with high-dose intravenous methylprednisolone (1000 mg for 3 days, followed by 1 mg/kg/day) and cyclophosphamide (500 mg intravenously every 15 days), a complete resolution of the cardiac inflammatory picture was observed, as documented by echocardiography with normalization of previous abnormalities, ejection fraction, and renal function (last known creatinine: 1.3 mg/dL).
Conclusions: ANCA-associated vasculitides (AAV) rarely involve the heart. When cardiac involvement is present, the prognosis is worse. The 2021 KDIGO guidelines recommend a rapid diagnosis due to the rapidly progressive nature of the disease. In cases of clinical and laboratory presentation of AAV, it is advised not to delay the initiation of therapy while waiting for renal biopsy, especially in patients with rapid clinical deterioration. Acute-phase therapy consists of a combination of high-dose glucocorticoids and cyclophosphamide or rituximab.
Bibliografia:
1) Almaani S, Fussner LA, Brodsky S, Meara AS, Jayne D. ANCA-Associated Vasculitis: An Update. J Clin Med. 2021 Apr 1;10(7):1446. doi: 10.3390/jcm10071446. PMID: 33916214; PMCID: PMC8037363.
2) Kitching AR, Anders HJ, Basu N, Brouwer E, Gordon J, Jayne DR, Kullman J, Lyons PA, Merkel PA, Savage COS, Specks U, Kain R. ANCA-associated vasculitis. Nat Rev Dis Primers. 2020 Aug 27;6(1):71. doi: 10.1038/s41572-020-0204-y. PMID: 32855422.

108. ACQUIRED NEUROGENIC FOREIGN ACCENT SYNDROME IN A RIGHT-HEMISPHERE BRAIN ABSCESS

Tadeo S.[1], Magni L. [1], Teofilo F. I. [1], Pirovano M. [1], Scopelliti F. [1], Festorazzi C.[2], Moreo G. [1]
[1]Dipartimento di Medicina Interna, Clinica Polispecialistica San Carlo, Paderno Dugnano; [2]Dipartimento di Medicina Interna, Clinica Polispecialistica San Carlo, Paderno Dugnano

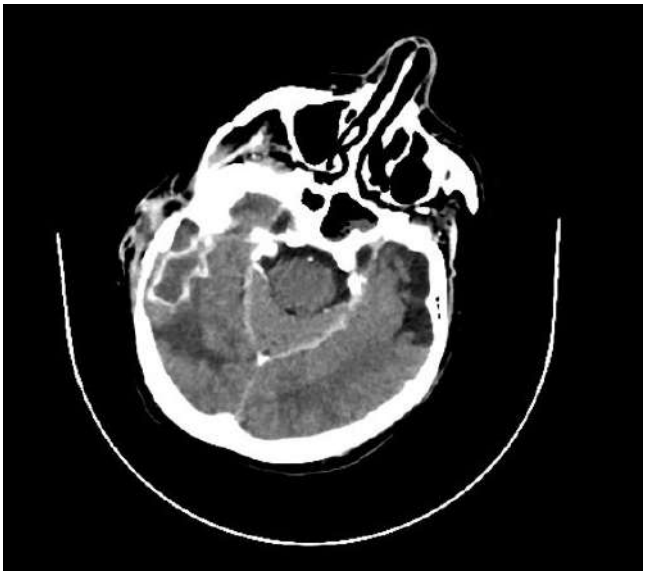
Case description: A.M. was a fully right-handed, 62-year-old Caucasian female native speaker of Italian, who suffered a brain abscess operated for evacuation. A.M.'s neurologic history before her brain abscess was psychosis and cognitive impairment, without speech problems, for a post traumatic cerebral haemorrhage operated 10 years before. A.M. came to the emergency room with fever, left hemiplegia, left hemianesthesia, left lateral homonymous hemianopsia , a brain right-hemisphere abscess was diagnosed with laboratory tests and CT of the brain. She was hospitalized in Internal Medicine , immediately started broad spectrum antibiotics able to cross the blood brain

barriers as guidelines , and she underwent neurosurgery on the fifth day. After neurosurgery intervention side neurological signs were reverse, persisted cognitive and behavioural disorders with deficit of executive functions and attention (evaluated by careful neuropsycological testing), , fatuous behavior, no speech problems. Three weeks after surgery she was re-admitted in internal medicine to complete the antibiotic treatment and to stabilize the metabolic compensation. A month after surgery she started suddenly an atypical speech disorders characterized by an alteration of prosody with a portuguese accent and production of "truncated" words, with lack of the last one or two syllables.

Discussion: Acquired neurogenic foreign accent syndrome (ANFAS) is a motor speech disorder in which, after brain damage, patients start speaking with a new accent, which sounds to the listeners as "foreign". ANFAS patients usually have suffered a neurological impairment, and the accompanying speech, language and/or cognitive deficits can be directly related to a vascular lesion (e.g. stroke), brain trauma, infectious disease (e.g. encephalitis), neuroinflammation (e.g. multiple sclerosis). The condition has been documented in at least 172 case reports. In most patients, lesions were located in the language-dominant, left hemisphere. These lesions mainly affected the primary motor cortex (BA4), the premotor cortex (BA6), the internal capsule, the corona radiata, or the basal nuclei. ANFAS following right-hemisphere damage is extremely rare. Critchley (1962, as cited in Mariën et al., 2019) first described a right-hemisphere-damaged patient who showed ANFAS and aphasia. The role of the cerebellum in ANFAS has been highlighted only recently (Keulen et al., 2017). Indeed, has been reported ANFAS in several patients after right posterior fossa lesions, causing cortical hypometabolism through cerebellocortical diaschisis.

Conclusion: Our patient had an atypical speech disorder charactyerized by anomics, alteration of prosody with portuguese accent and production of "truncated" words. We believe that this could be a rare case of foreign accent syndrome following right-hemisphere damage.Internists need to be aware of these rare complications because increasingly such patients are being managed in internal medicine departmens.

Magnetic Resonance Imaging (MRI) post intervention.



109. SUPINE RESISTANT ARTERIAL HYPERTENSION ASSOCIATED TO SEVERE ORTHOSTATIC HYPOTENSION IN A WOMAN WITH HEADACHE AND STUBBORN CONSTIPATION: MANY SYMPTOMS, ONE VILLAIN

Manzi P.[1], Vergatti A.[1], Altavilla N.[1], Forte A.[1], D'Elia L.[1], Rendina D.[1], De Martino M.[1], Venetucci P.[2], Gisonni P.[3], Barbato A.[1]
[1]Dipartimento di Medicina clinica e chirurgia, AOU Federico II;
[2]Dipartimento di Scienze biomediche avanzate, AOU Federico II;
[3]AOU Federico II

A 56-year-old patient came to our observation for severe arterial hypertension resistant to medical treatment (according to ESH guidelines), asthenia, tremor, headache, obstinate constipation and reported weight loss (about 15 kg in the last year). A history of hypothyroidism post Hashimoto's thyroiditis on hormone replacement treatment and a recent worsening of renal function (e-Gfr: 39 mL/min/1.73m2, stage IIIB according to KDIGO, on admission) was reported.

The blood pressure was elevated in the supine position (mean values: 190/110 mmHg) with a reduction in systolic and diastolic blood pressure values of approximately 60 mmHg in upright position, showing a picture of severe orthostatic hypotension.

During hospitalization, abdominal ultrasound revealed an ovoid lesion approximately 42 mm posterior to the left kidney, in the proximity of the ipsilateral renal artery, which shifted when assuming orthostatic position. Abdominal MRI confirmed the lesion and showed a central area of cystic and necrotic-colliquative degeneration suggestive of an atypical pheochromocytoma. Subsequent whole-body PET-CT scan showed tracer accumulation in the ovoid formation close to the left adrenal gland. The patient also underwent colonoscopy which revealed a stenosing inflammatory lesion adjacent to the adrenal lesion. Lastly, brain MRI was performed, showing multiple gliotic outcomes suggestive of chronic hypertension damage.

Norepinephrine (2485 ug/24h) and dopamine (808 ug/24h) levels were above normal at 24-hour urinary collection. Serum renin, aldosterone and cortisol levels, assessed for secondary hypertension screening, were also elevated. Suppression testing (short and long) with dexamethasone was then performed, which was compatible with the diagnosis of Cushing's disease.

After a multidisciplinary evaluation, surgical removal of the left adrenal gland was agreed upon, despite the patient's comorbidities. The operation resulted in the removal of an 8 cm lesion. After the surgery, there was a rapid normalization of blood pressure values with disappearance of orthostatic hypotension and immediate resumption of intestinal transit with regulation of alvus. One month after surgery, the patient's examinations showed a marked improvement in renal function (e-Gfr: > 90 mL/min/1.73m2) and at the same time the histopathological services confirmed the diagnosis of pheochromocytoma. The patient is currently undergoing instrumental follow-up without the need for chemotherapy.

In conclusion, the management of the comorbidities that emerged during hospitalization (Cushing's disease, intestinal obstruction, chronic renal failure, cerebral vasculopathy) constituted a challenge for the internist, who had to play a central role among the various specialists involved (endocrinologists, surgeons, anesthetists, oncologists) by guiding the patient through the process of diagnosis, treatment and follow-up.

110. A RARE CASE OF SYSTEMIC NOCARDIA WALLACEI INFECTION WITH CEREBRAL ABSCESSES IN COURSE OF IBRUTINIB

Maffi G., Lombardi R., Curioni M., Fracanzani A.L.
[1]SC Medicina - Indirizzo Metabolico, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy; [2]Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Milan, Italy

Case report: A 76-year-old man was admitted to our ward of Internal Medicine for new onset confusion, disorientation and ideomotor slowdown since 5 days. In his past medical history, he has Waldenstrom's Macroglobulinemia in third line treatment with Ibrutinib, arterial hypertension, previous prostatic adenocarcinoma treated with radical prostatectomy and hypothiroidism in multinodular goiter.

At the emergency department the general physical examination was unremarkable as well as the neurological examination except for the presence of confusion, disorientation and a mild impairment in the left arm at the Mingazzini I test. Blood exams, chest radiography and 12-lead-ECG were normal. A head CT scan with contrast was performed, showing 2 left frontal lesions (the bigger of 32 mm of diameter associated to a central necrotic component) and one left cerebellar lesion with contrast enhancement and peri-lesion oedema, all suspect for neoplastic metastasis. An anti-oedema therapy with mannitol and dexamethasone was started and the patient was then admitted to our ward for further investigations.

At admission the patient presented still confused but vital parameters and physical examination were unremarkable. Despite the neurological status progressively normalized over the first days, probably due to anti-oedema therapy. In the suspect of cerebral metastasis of unknown origin a total body CT scan with contrast was performed, without evidence of cancer lesions; however, it showed the presence of multiple micronodular lesions of the lungs of possible infective genesis. Moreover, the hematologist excluded a possible evolution of Waldenstrom disease and suggested to temporarily sus-

pend Ibrutinib until a definitive diagnosis was made. Finally, a dermatological evaluation excluded cutaneous or mucosal melanoma. For a better characterization of the brain lesions a cerebral magnetic resonance with contrast was performed, showing multiple cerebral and cerebellar lesions of uncertain nature (abscess versus neoplastic lesions). An empiric antimicrobial treatment was temporarily avoided because of the absence of fever, organ recall or increase in inflammatory markers. Given the negativity of all the infective tests (multiple blood cultures, quantiferon for Mycobacterium Tubercolosis, serum galattomannan antigen and beta-D-glucan, Cryptococcus antigen on blood, serology for Toxoplasma gondii, HIV, Coxiella and Brucella, EBV-DNA on blood), including a negative transesophageal echocardiography, in order to define the nature of the encephalic lesions a targeted brain biopsy of the frontal left cerebral lesion was made. Histology was negative for cancer, conversely cultures of the brain specimen were positive for Nocardia wallacei. In addition, a subsequent re-evaluation of the multiple nodular lesions previously found at the thorax CT scan, defined those lesions as compatible with Nocardia pul-monary localizations. Therefore, the diagnosis of pulmonary Nocardiosis with cerebral localizations was made and a targeted intravenous antibiotic treatment with linezolid and trimetoprim/sulfametoxazole was started. After stabilization of the patient's clinical conditions, he was discharged with indication to continue follow-up and antibiotic therapy as outpatient. The patient continued the intravenous antibiotic therapy for 6 weeks, subsequently shifted to oral trimetoprim/sulfametoxazole course, with an expected total duration of antibiotic therapy of one year. After 12 weeks, a control thorax and brain CT scans showed stabilization of cerebral lesions and improvement of the lung ones.

Conclusions: We report a case of systemic Nocardia wallacei infection complicated by cerebral abscesses in course of Ibrutinib. Nocardiosis is a rare infectious disease, usually localizing in lungs and sometimes leading to disseminated infection. It mainly affects immunocompromised hosts, as our patient who suffered from a hematologic neoplastic condition in treatment with a tyrosine kinase inhibitor. In the recent years Ibrutinib has been introduced as a possible and effective treatment for Waldestrom disease but possibly fostering the onset of opportunistic infections, as Nocardiosis. Despite the first clinical presentation of cerebral Nocardiosis was misdiagnosed with a neoplastic disease, it is important to keep in mind that also opportunistic infections involving the central nervous system may arise only with impairment in the cognitive state, without fever or positivity of microbiological tests, as in our case, making the diagnosis very tricky. When technically feasible, cerebral biopsy remains the gold standard to identify the etiology of cerebral lesions.

111. ACUTE HEPATITIS AND LABIO-GENITAL HERPES FROM CMV AND HSV-1 REACTIVATION IN A PATIENT WITH AUTOIMMUNE HAEMOLYTIC ANEMIA ON CHRONIC CORTICOSTEROID THERAPY

Postorino D.M., Marcanio S., Bovo M., Ruscitti C., Paladino A., Ferrante A., Cotrino V., De Cilla A., Appolloni V., Guglielmi V., D'Adamo M., Sbraccia P.
Internal Medicine and Obesity Center Unit – Tor Vergata Hospital

Introduction: After infection, Herpes Viruses remain in a latent form in the body and can reactivate in case of immune system weakness, for example, during HIV infection, chemotherapy, or chronic immunosuppressive therapies for autoimmune diseases or organ transplantation.
Herpes simplex virus 1 (HSV-1) causes infections in mouth and facial region, while HSV-2 is predominantly found in the genital region (genital herpes). Cytomegalovirus (CMV) infections generally proceed asymptomatically, but in immune compromised patients, it can cause severe complications such as esophagitis, pneumonia, hepatitis, retinitis, and encephalitis.
Clinical Case: C.A., a 67-year-old woman, arrived at the Emergency Department of Tor Vergata Hospital in April 2023 with jaundice and low-grade fever. She recently received an idiopathic autoimmune hemolytic anemia diagnosis and underwent high-dose corticosteroid therapy (Prednisone 100 mg/day).
Blood tests revealed a picture of mixed hyperbilirubinemia with a predominantly direct component, and normal hemoglobin levels without evidence of hemolysis. Abdominal ultrasound did not show any findings consistent with an obstructive picture. However, due to intermittent fever and suspicion of cholangitis, antibiotic therapy with Piperacillin/Tazobactam was initiated. During hospitalization, there was a progressive increase in bilirubin levels (mixed hyperbilirubinemia) and transaminases (consistent with acute hepatitis), accompanied by severe lymphopenia and thrombocytopenia without anemia. Therefore, serological testing for major and minor hepatotropic viruses (EBV, CMV, HAV, HBV, HCV, HDV, HEV) was performed, revealing positive results for IgG anti-EBV antibodies, IgM anti-EBV antibodies, and IgG anti-CMV antibodies.
Painful and bleeding vesicular-crusted lesions appeared in the oral cavity, as well as in the vulvar, perineal, and inguinal regions, consistent with herpetic skin lesions.
PCR testing for EBV DNA, Adenovirus, HHV-6, HHV-7, HHV-8, HSV-1, and HSV-2 in plasma results negative, as the measurement of ANA, ASMA, c-ANCA, and p-ANCA antibodies, which were conducted to exclude an autoimmune nature of hepatitis or cholangitis. Moreover, blood cultures from peripheral veins and influenza virus testing from a nasal swab were consistently negative. Conversely, vaginal swab testing for herpetic viruses showed positivity for HSV-1.
In suspicion that the acute hepatitis was secondary to CMV reactivation, a plasma CMV DNA PCR test was performed, which indicated active viral proliferation (55,467 IU/ml). However, CMV testing in urine and plasma yielded negative results. The examination of the fundus of the eye ruled out the presence of CMV retinitis. Following the guidelines, specific antiviral therapy was initiated with Ganciclovir at a dose of 5 mg/kg every 12 hours for 14 days, followed by Valganciclovir at a dose of 900 mg every 12 hours, with weekly monitoring of viremia and tapering of corticosteroid therapy to Prednisone 25 mg/day. The levels of hyperbilirubinemia gradually decreased with the resolution of fever. However, the herpetic lesions, especially in the genital area, persisted. Prolonged bed rest and severe immunosuppression predisposed the patient to severe nosocomial infections. A urinary tract infection caused by multidrug-resistant pathogens (Pseudomonas aeruginosa, Enterococcus faecium VRE, and Klebsiella pneumoniae) was treated with specific antibiotic therapy. However, it resulted in septic shock, disseminated intravascular coagulation (DIC), and multiple organ dysfunction syndrome, leading to the patient's demise. The shock was characterized by acute anemia that poorly responded to transfusion therapy. Initially, reactivation of hemolysis was suspected, but the absence of hemolysis indices excluded autoimmune hemolytic anemia as the cause. This suggested that the clinical picture was fully attributable to the systemic infection.
Conclusions: Intermediate half-life corticosteroids (such as Prednisone) are the first-line therapy for the treatment of autoimmune hemolytic anemia. Prolonged use of corticosteroids predisposes patients to infections caused by multidrug-resistant organisms, which are associated with high mortality and morbidity rates. The decision to use corticosteroids requires careful evaluation of the risk-benefit ratio, considering that effective preventive or therapeutic interventions are not currently available for some of the undesirable effects associated with their use.

Bibliografia:

- Bunchorntavakul C, Reddy KR. Epstein-Barr Virus and Cytomegalovirus Infections of the Liver. Gastroenterol Clin North Am. 2020 Jun;49(2):331-346. doi: 10.1016/j.gtc.2020.01.008. PMID: 32389366.
- Mares Bermúdez J, Plaja Román P, Calico Bosch I, Javier Manchón G, Ortega Aramburu JJ. Enfermedad por virus citomegálico en pacientes inmunodeprimidos [Cytomegalovirus disease in immunosuppressed patients]. An Esp Pediatr. 1988 Mar;28(3):211-6. Spanish. PMID: 2837117.
- Garland SM, Steben M. Genital herpes. Best Pract Res Clin Obstet Gynaecol. 2014 Oct;28(7):1098-110. doi: 10.1016/j.bpobgyn.2014.07.015. Epub 2014 Aug 4. PMID: 25153069.

112. WHIPPLE'S BACKLASH: IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME. A CASE REPORT

Angiulli S.[1], Marinosci A.[2], Damanti S. [3], Ramirez G.[4], Di Lucca G.[2], Di Terlizzi G.[2], Da Prat V.[2], Soddu D.[2], Scotti R.[2], Rovere Querini P.[1], Tresoldi M.[2]
[1]Università Vita-Salute San Raffaele; [2]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy; [3]Unit of Medical Specialties and Healthcare Continuity IRCCS Ospedale San Raffaele, Milan, Italy ; [4]Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS Ospedale San Raffaele, Milan, Italy

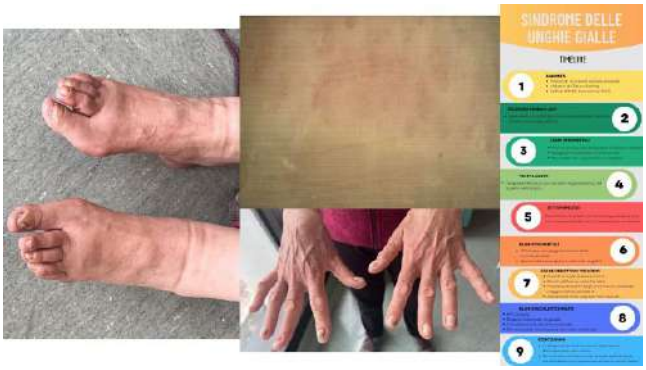
Introduction and AIM of the Case Report: Whipple's disease (WD) is a systemic, rare, chronic infectious disease caused by the Gram positive bacterium Tropheryma whipplei. It mainly affects Caucasian males, aged 50- 60 years. Involvement of the small intestine is most typical, but early non-intestinal manifestations (mainly arthritis/arthralgia, fever, asthenia, anemia, lymphadenopathies, together with involvement of eye, skin, lungs, central nervous system [CNS] and heart) can lead to misdiagnosis, incorrect treatment, and disease progression. Systemic complications constitute a major chal-

lenge in the management of WD. In particular, 10-17% of patients are estimated to develop Immune Reconstitution Inflammatory Syndrome (IRIS), a paroxysmal, potentially life-threatening flare-up of inflammatory signs and symptoms following effective antimicrobial treatment. Little is known about presentation of and risk factors for IRIS in WD due to WD rarity. Herein, we present a paradigmatic case of sequential WD and IRIS occurrence, focusing on the challenges posed by their non-specific clinical phenotype.
Case Description and Discussion: A 57-year-old man diagnosed with heart failure and native mitral valve endocarditis with negative blood cultures, who had been previously treated with several lines of empirical antimicrobial therapies with no clinical response, was admitted to our Unit. The patient complained of recent weight loss (up to 13 kg in two months). Past clinical history was significant for fever, migrating arthralgia, diffuse lymphadenopathy, and macular rash ten years earlier. Autoimmunity markers were negative. The patient had long been treated for seronegative arthritis with immunosuppressants (steroids, methotrexate, hydroxychloroquine, colchicine, leflunomide, anti-IL1, anti-IL6, anti-TNFα) with little and transient benefit on fever and arthralgia. In 2021, the patient had also been hospitalized for systolic-diastolic heart failure, and signs of myo-pericarditis had been found on magnetic resonance imaging at that time. In addition, he had more recently developed diarrhea without endoscopic signs of inflammatory bowel disease. In light of the association of abdominal symptoms, refractory arthritis and pan-carditis, we suspected WD and performed bacterial genome search on blood, saliva, urine, stools and cerebrospinal fluid (CSF). T. whipplei genetic sequences were detected in urine and CSF. CNS involvement was investigated, despite the absence of neurological signs, being it frequently asymptomatic but associated with poor prognosis as a hotspot for recurrences. Notably, PCR test and PAS staining on duodenal biopsies were negative. The patient was treated with intravenous ceftriaxone 2g daily, followed by oral hydroxychloroquine (200 mg three times daily) and doxycycline (100 mg twice daily). After two weeks of appropriate antimicrobial therapy with initial improvement, the patient worsened and developed fever along with increased inflammatory markers. After ruling out other possible infectious causes, we thought that IRIS might account for patient symptoms. Therefore, we started the patient on oral steroid therapy (prednisone 50 mg, slowly tapered), prompting persisting symptom remission and normalization of laboratory tests. An immunocompromised state induced by T. whipplei and characterized by low CD4+ cell count and IFN-γ production, increased T-regs activity, alternative macrophage activation, and elevated IL-10 production has been claimed as the core pathogenic basis of IRIS. These events might also be exacerbated by immunosuppression and eventual immunosuppressive drug withdrawal, causing defective immunization and pathogen control followed by widespread dysregulated inflammation after immune reconstitution and exposure of large amount of bacterial antigen due to antibiotic treatments. Consistently, our patient had long been exposed to immunosuppressive drugs and showed a non-septic rebound of systemic inflammation weeks after initiating his antibiotic treatment, which is compatible with a delayed-type inflammatory response.
Conclusions: This case report emphasizes the importance of recognizing an insidious disease like WD, which sometimes hides in plain sight, along with the risks of secondary IRIS after WD treatment. In particular, while adding evidence to current knowledge on the clinical phenotype and course of WD, it emphasizes the persisting risks of morbidity and mortality associated with WD even following appropriate treatment start and sheds lights on the WD-related IRIS nosography and epidemiology.

113. YELLOW NAIL SYNDROME: A RARE DISEASE WITH A MULTIDISCIPLINARY APPROACH

Petraccia L.[1], Mastrostefano A.[1], Ciarciaglini E.[2], Mastropasqua E.[3], Piperno G.[3], Cilenti V.[3], Papale M.[3]
[1]Dipartimento di Fisiologia e Farmacologia Vittorio Erspamer, Scuola di specializzazione in farmacologia e tossicologia clinica, Sapienza Università di Roma; [2]Dipartimento di Medicina Traslazionale e di Precisione, Scuola di specializzazione in medicina interna, Sapienza Università di Roma; [3]UOSD Fisiopatologia Respiratoria, IFO IRCCS Roma

Yellow Nail Syndrome (YNS) is characterized by a triad of thickened yellow nails, primary lymphedema and respiratory manifestations. It is an acquired condition of unknown etiology. YNS is associated with different conditions involving lymphatic system diseases, autoimmune diseases or cancers. Whereas Samman & White's first description of YNS included only nail discoloration, Emerson added pleural effusion to the diagnostic criteria. Although the presence of two out of the three conditions associated to YNS is sufficient for the diagnosis, it seems uncertain to define a YNS without a nail abnormality. Moreover, the three manifestations do not need to coexist but may appear individually and sequentially, thus making YNS diagnosis difficult. The complete triad is present only in 27–60% of the patients. Our case report aims to highlight the central role of the clinician in formulating complex diagnoses. In fact, in spite of several instrumental examinations during the last years, the physical examination was crucial to reach the correct diagnosis. The patient is a 69-years-old woman, smoker until 2018 (40 p/y), neither allergic nor exposed to pneumotoxic agents. She had recurrent pneumonia from youth, Gilbert's disease and MTHFR deficiency (mutation T677 in homozygosity). In January 2019 the patient was hospitalized for pneumonia with multiple outbreaks and pleural effusion associated with diffuse urticaria. During her stay: transbronchial lung biopsies and cytology for neoplastic pathology, BAL for common germs, cultured BK, HIV test, TNF for respiratory pathogens and quantiferon were all negative. She was treated with antibiotic therapy with partial improvement of the radiological imaging. During the years he performed radiological examinations which showed pulmonary thickening and recurrent pleural effusion. The patient reported a sense of chest tightness and the presence of a productive cough but pulmonary function test (global spirometry, DLCO, blood gas analysis, walking test) and cardiological investigations was substantially negative. In this period, feedback of drumsticks fingers was finally observed. In September 2021 the patient came to our attention at the IFO IRCCS Respiratory Physiopathology Clinic due to exacerbation of respiratory symptoms with productive cough and greenish sputum. All the tests were normal normal except for chest CT with worsening bronchiectasis and moderate accentuation of known areas of pulmonary consolidation. For the detection of edema of the left lower limb she also performed MRI of the ankle and foot which showed a moderate amount of fluid at the level of the tibio-talar and posterior talo-calcaneal capsulea. First diagnostic hypothesis of yellow nail syndrome. For the presence of onychodystrophy of hands and feet bilaterally, the patient was subjected to: incisional nail biopsy, nail swab, capillaroscopy wich showed nails hyperkeratosis and superficial fungal spores like Candida Glabrata susceptible findings of psoriatic onychopathy. So the patient performed topical antifungal therapy for six months. Due to the partial response to antifungal therapy and the growing suspicion of Yellow Nail Syndrome in March last, the following were performed: dermoscopy, confocal laser microscopy and optical coherence tomography of the nails. The specialist Dermatologist with experience of patients with this syndrome confirmed our diagnostic hypothesis of Yellow Nail Syndrome complicated by mycotic infection and nail Pseudomonas. Since the aetiology of the syndrome being treated is not yet known, the patient will have to undergo therapy for the individual manifestations of the latter: targeted pharmacological therapy and folic acid supplementation; the patient will be followed up over time with CT and Spirometry. As can be seen from the case report, the diagnostic process of this rare syndrome is long and investigative until the pathognomic symptom triad appears; it is also emphasized that the clinical diagnosis is strictly dependent on the experience of the clinician and on the knowledge of the syndrome.



114. MULTIPLE HEPATIC ABSCESSES AND ULCERATIVE COLITIS: A RARE BUT POSSIBLE ASSOCIATION

Perego M.[1], Taino A.[2]
[1]Università degli Studi di Milano, Scuola di Specializzazione in Medicina Interna, Ospedale Sacco; [2]Ospedale Sacco, ASST Fatebenefratelli Sacco, Milano

Hepatic abscesses are the most common cause of visceral abscess (1;2). Localization following bacterial peritonitis or hematogenous spread (e.g., endocarditis) and complicated evolution of biliary lithiasis or penetrating traumas are the most frequent causes. An association with colorectal cancer

was also demonstrated (3). Predisposing factors for the development of hepatic abscesses include diabetes mellitus, liver or pancreatic pathology and regular use of PPIs (1;2).
Case presentation: A 75-year-old man presented to the emergency department (ED) with a 3-days history of fever (up to 39°C) and abdominal pain. He reported the onset of diarrhea and a 2-3 kg weight loss over the past few months.
The patient had a known history of rheumatoid arthritis in chronic therapy with hydroxychloroquine and methylprednisolone 4 mg, methotrexate-induced interstitial lung disease, ulcerative colitis, sigmoid diverticulosis, occult hepatitis B and gastroesophageal reflux disease.
In the ED, laboratory tests showed elevated inflammatory markers (WBC 20,000/mm^3, CRP 479 mg/dL), increased liver necrosis values (AST 413 U/L, ALT 388 U/L) and a deterioration in renal function tests (creatinine 1.51 mg/dL, urea 130 mg/dL).
A contrast-enhanced CT scan of the abdomen revealed multiple focal abnormalities in both liver lobes, the largest measuring 7.5 cm in the left lobe. The lesions appeared heterogeneously hypodense with septations and showed faint peripheral contrast enhancement. The CT scan raised suspicion of superinfected metastases as the primary diagnostic hypothesis. Concurrently, it showed a thrombosis of the inferior vena cava and the middle and left hepatic branches. Antibiotic therapy was initiated with piperacillin/tazobactam at a dosage of 4.5 g three times a day, along with anticoagulation therapy. All 5 sets of blood cultures showed positive results for *Streptococcus intermedius* infection (part of the *Streptococcus milleri* group). Based on the microbiological findings, the antibiotic therapy was downgraded to ceftriaxone.
Additional investigations were performed to rule out the possibility of superinfected metastatic lesions. These included contrast-enhanced CT scans of the chest and brain, colonoscopy, esophagogastroduodenoscopy, assessment of tumor markers, dermatological evaluation of skin nevi to exclude melanocytic lesions, positron emission tomography, two liver needle aspirations, and two liver biopsies. All the tests yielded negative results for neoplastic lesions, including the liver biopsies.
Considering the multiple hepatic infectious localizations and the monomicrobial blood isolation, a transthoracic echocardiogram was performed, ruling out endocarditis. Infection by Entamoeba histolytica or other parasites was also excluded through fecal testing and serum antibody testing.
Therefore, antibiotic therapy was continued for a total of 6 weeks, resulting in an excellent clinical response and almost complete resolution of the radiological findings confirming the diagnosis of non-neoplastic liver abscesses.
Discussion: What caused the hepatic abscesses in this patient? The patient's hepatic abscesses may have been caused by several predisposing factors, including long-term use of proton pump inhibitors and methylprednisolone. However, only ulcerative colitis provided a pathogenic hypothesis consistent with the clinical presentation (4).
Liver abscesses are a rare complication of Inflammatory Bowel Diseases (IBD), with most cases reported in patients with Crohn's disease (CD). Conversely, only 11 cases of liver abscesses associated with ulcerative colitis (UC) have been published before 2013 (4).
These abscesses are typically monomicrobial, with *Streptococcus* being the most frequently identified pathogen (5).
The exact pathogenesis of liver abscesses in IBD patients remains unclear, but it is hypothesized that compromised integrity of the intestinal mucosal barrier allows intestinal organisms to disseminate via the portal venous system. Studies demonstrating a higher incidence of portal bacteremia in patients with IBD support this hypothesis (4).
Conclusions: The scarcity of reported cases of liver abscesses in UC makes this clinical case particularly intriguing. Additionally, it underscores the importance of considering and ruling out first more probable and serious causes, such as neoplastic etiology, during the differential diagnosis process, as was done in this patient.
References:
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3 Lai HC, Lin CC, Cheng KS, et al. Increased incidence of gastrointestinal cancers among patients with pyogenic liver abscess: a population-based cohort study. Gastroenterology 2014.
4 Xian-rui Wu, Bo Shen, Liver Abscess in Patients with Underlying Inflammatory Bowel Diseases, Inflammatory Bowel Diseases 2013
5 Vakil N, Hayne G, Sharma A, Hardy DJ, Slutsky A. Liver abscess in Crohn's disease. Am J Gastroenterol 1994

115. THE ANAMNESIS BIAS: A CASE REPORT OF A PATIENT WITH PULMONARY SARCOIDOSIS AFTER SARS-COV-2 INFECTION IN A BRCA2 MUTATION CARRIER

Castellani J.[1], Farina F.[1], Festorazzi C.[1], Galimberti G.[1], Tresoldi M.[2], Rovere-Querini P.[1]
[1]Unit of Medical Specialties and Healthcare Continuity IRCCS Ospedale San Raffaele, Milan, Italy; [2]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy

Background: Sarcoidosis is a multi-system disease of unknown etiology characterized by non-necrotizing granulomas infiltrating different organs. Its incidence is estimated to be between 2.3 and 11 per 100,000 individuals in one year. Typically, sarcoidosis develops in adults under 50. The disease has a variable clinical presentation that depends on organ involvement and its severity. The lungs are affected in more than 90% of patients. Pulmonary sarcoidosis can manifest clinically in a number of different ways. Patients may present with persistent nonspecific symptoms such as a cough, dyspnea on exertion, and fatigue, or they may present with asymptotic symptoms that are discovered inadvertently on a chest x-ray taken for unrelated causes. Bilateral perihilar lymphadenopathy and perilymphatic pulmonary nodules, seen in the upper lobe, are the most typical imaging findings.
Case Description: We report the case of a 48-year-old female patient, worker at a dry ice company with no contact with crystalline silica dust, whose medical history was significant for familiar BRCA2 mutation and subsequent breast cancer, in complete remission after quadrantectomy followed by chemo- and radiotherapy. The patient presented at the emergency department with persistent fever after SARS-CoV-2 infection, dyspnea and stubbing chest pain.
A chest X-ray showed a subtle consolidation in the lower right lobe; elevation in inflammation markers was noted. The patient was initially diagnosed with lobar pneumonia and started on empiric antibiotic therapy with levofloxacin. After a few days, however, no decline in CRP levels nor clinical improvement was noted, with ongoing night sweats, stabbing chest pain and persistent fever not responding to NSAIDs. Several consecutive blood cultures resulted negative for any microorganism, both during antibiotic therapy and after its interruption. Subsequently, the patient developed hypoxiemic respiratory failure, requiring additional low flow oxygen via nasal cannula.
A chest CT was performed to rule out pulmonary embolism; the exam revealed a bilateral diffuse reticulonodular interstitial pattern and multiple mediastinal adenopathies, rising suspicion for breast cancer relapse with associated neoplastic lymphangitis. After 48 hours from the beginning of low-dose steroidal therapy coupled with low dose furosemide, a marked improvement in the patient's conditions was noted: the night sweats and the stubbing chest pain waned, a quick decline of the inflammatory markers was observed and supplemental oxygen was no longer needed. Marked clinical improvement with steroidal therapy is not much consistent with the occurrence of a solid neoplasm, but it is more frequently associated with lymphoproliferative disorders. Patient's history of previous chemotherapy administration raised concern for secondary lymphoma, although pulmonary lymphangitis is not a common associated sign. Inflammatory disorders such as sarcoidosis might be associated with rapid improvement after steroid administration as well. To definitely rule out a breast cancer recurrence and to assess for lymphoproliferative or inflammatory disorder we performed a mediastinoscopy with lymph node biopsy which showed the presence of non-necrotizing small granulomas with giant epithelioid cells, consistent with sarcoidosis. Following the European respiratory society clinical practical guidelines, steroidal therapy (prednisone 0.5 mg/kg) was initiated. To complete the diagnostic work-up, ABG and respiratory functional tests were performed and resulted within normal range, as for Quantiferon test for BK; vitamin D was below normal range and ACE level was markedly elevated. Finally, a bronchoscopy was performed to definitely rule out infection and assess for CD4/CD8 ratio in bronchoalveolar lavage fluid which showed no significant alterations. A FDG-PET scan showed no extrapulmonary involvement. Soon after starting prednisone the patient was discharged for outpatient follow up.
Discussion: Although the patient presented with a sarcoidosis-like clinical phenotype, we evaluate both patient's symptoms and radiological findings considering the previous medical history, leaving behind the chance of an additional illness. Additionally, the lack of more specific or even pathognomonic signs of sarcoidosis, such as erythema nodosum or lupus pernio, contributed to our initial misdiagnosis. Along with a few other recent reports, we add other case of a possible SARS-CoV-2 induced sarcoidosis, the first one in a BRCA2 mutation carrier patient.
In conclusion, it is important while evaluating patient's symptoms to focus

on past medical history and without overlooking the whole broad spectrum of differential diagnosis.
Further studies are needed to determine a clear pathophysiology of sarcoidosis, and SARS-CoV-2 triggered forms might offer additional clues.

116. AORTIC PROSTHETIC INFECTION AND PERIPROSTHETIC ABSCESS DURING TRANSIENT BACTEREMIA AND COMMUNITY PNEUMONIA

Postorino D.M., Cartenì B., Marcanio S., Bovo M., Ruscitti C., Paladino A., Appolloni V., D'Adamo M., Guglielmi V., D'Adamo M., Sbraccia P.
Internal Medicine and Obesity Center Unit – Tor Vergata Hospital

Introduction: Prosthetic infections are a rare complication of aortic disease treatment, with an extremely high mortality rate. S. aureus is the main culprit, but other bacteria such as coagulase-negative Staphylococci, P. aeruginosa, E. coli, Enterococci, C. perfringens, and B. fragilis may also be involved. The contact of bacteria with an inert material leads to their microbial proliferation, which can be associated with a generalized infectious syndrome. In clinical practice, the role of angio-CT and PET-CT is crucial at the diagnosis, but also at follow-up and for the setup of a proper long-term antibiotic therapy.
Clinical case: A.M., a 54-year-old man, arrived at the Emergency Department of Tor Vergata Hospital in March 2023 with persistent fever, which had been treated with antibiotic therapy and high doses of paracetamol with little benefit.
In his past medical history, he had chronic ischemic cardiomyopathy following an acute myocardial infarction, an aneurysm of the descending aorta treated with endoprosthesis placement, and aortic coarctation surgically corrected in youth.
Laboratory tests showed a moderate increase in inflammatory markers and liver function without alteration in cholestatic markers. Chest X-ray revealed findings consistent with left-sided community-acquired lobar pneumonia, while a complete abdominal ultrasound showed hepatic steatosis.
Antibiotic therapy was initiated with Levofloxacin 750 mg, one vial every 24 hours. However, the patient continued to experience remittent evening fever accompanied by fatigue and dorsal chest pain, and the inflammatory markers remained elevated. A panel for the investigation of fever of unknown origin was requested, including testing for viruses, bacteria, and parasites, which yielded negative results. Serial peripheral blood cultures also returned negative results.
A contrast-enhanced chest and abdominal CT confirmed the diagnosis of left-sided lobar pneumonia without any other abnormalities. Subsequently, a PET-CT scan was performed, revealing abnormal tracer uptake in the thoracic descending aortic prosthesis (max SUV 9.7) associated with a crescent-shaped abscess collection, confirming the previously noted pneumonia. The prosthesis appeared to be functioning properly and in place.
In accordance with the infectious disease specialist, treatment was initiated with Daptomycin at a dose of 10 mg/kg/24 hours for a total of 30 days (combined with Ceftriaxone 2 g every 24 hours and Levofloxacin 750 mg every 24 hours for the first 7 days). Maintenance therapy consisted of Trimethoprim + Sulfamethoxazole at a dose of 860+160 mg every 12 hours.
After 2 days of starting the antibiotic therapy, the patient no longer had fever and chest pain, and there was a significant decrease in inflammatory markers. Considering the clinical improvement and proper functioning of the prosthetic device, surgical removal of the prosthesis was not recommended, and a conservative approach was preferred. However, it was proposed to repeat the PET-CT scan approximately 1 month after discontinuing intravenous antibiotic therapy with Daptomycin.
The follow-up PET-CT scan showed signs of persistent but reduced pathological uptake in the prosthesis, with the previously reported abscess collection resolved. However, an area of increased uptake was noted in the left subclavian artery (max SUV 5.7).
Clinically, the patient remained asymptomatic and well-tolerated the maintenance antibiotic therapy. Close clinical monitoring continued, and the inflammatory markers remained negative.
In agreement with the infectious disease colleagues, after discontinuation of Trimethoprim + Sulfamethoxazole, an off-label antibiotic therapy with Dalbavancin at a dose of 1000 mg every 14 days on alternate months was chosen, with strict radiological monitoring.
Conclusions: Although rare, transient bacteremia secondary to other infectious foci predisposes to the formation of a biofilm on prosthetic devices in anatomically susceptible patients. The clinical picture was suggestive of infection of the aortic prosthesis associated with hepatotoxicity due to paracetamol overdose.
Considering the clinical presentation, performance status, and integrity of the prosthesis, it is reasonable to attempt empirical antibiotic therapy as a conservative treatment and continue with clinical and radiological monitoring, including nuclear imaging.
However, the role of PET-CT in the clinical follow-up of prosthetic and periprosthetic infectious pathology is still under discussion in the literature
Bibliografia:
- Seeger JM. Am Surg. 2000 Feb;66(2):166-77.
- FitzGerald SF, et al. J Antimicrob Chemother. 2005 Dec;56(6):996-9.
- O'Connor S, et al. J Vasc Surg 2006;44(1):38–45
- Bergamini TM, et al. J Vasc Surg 1988;7(1):21-30
- Orton DF, et al. Radiographics 2000;20(4):977–93.
- Keidar Z, Nitecki S. Q J Nucl Med Mol Imaging. 2009 Feb;53(1):35-40
- Wassélius J, et al. J Nucl Med. 2008 Oct;49(10):1601-5.

117. SCHMIDT SYNDROME IN A PATIENT WITH SEVERE THROMBOPHILIA

Pucci M. , Paoletta D. , Esposito R., Biondi B.
Department of Clinical Medicine and Surgery, Federico II University Hospital, Naples, Italy

Background: Schmidt syndrome or autoimmune polyglandular syndrome (APS) type 2 is a rare polyendocrinopathy characterized by primary adrenal insufficiency often referred to as Addison's disease with autoimmune thyroiditis and/or diabetes mellitus type I.
Case ReportDescription: 46-year-old woman comes to our clinical observation for abdominal pain, worsening dyspnea, palpitations and asthenia.
Past medical history: Hashimoto's thyroiditis, gestational diabetes and previous deep vein thrombosis of the lower limbs during estrogen-progestogen therapy for PCOS, in presence of double heterozygosis factor V Leiden and factor II.
On physical examination: arterial hypotension (95/60 mmHg), tachycardia (105 bpm) and marked skin hyperpigmentation.
Management: Blood chemistry reveal hyponatremia and hyperkaliemia. Abdominal CT is performed to rule out thrombotic events and reveals adrenal atrophy. ECG is performed with detection of sinus rhythm and typical hyperkalemia alterations. For the reported symptoms, electrolyte disturbances found, evident melanodermia and adrenal atrophy the suspicion of adrenal insufficiency arises; hormonal investigations are carried out with the finding of ACTH values equal to 1670 pg/ml (nv 10-130) with serum cortisol values < 0.20 ug/dl (nv 4.3-22.4), high renin values of 484 pg/ml (nv 2.52-35.82) with low aldosterone values < 37 pg/ml (nv 40-310), CLU 20 (nv 21 – 292) , TSH 5.074 (nv 0.41 – 4.30). Therefore, a diagnosis of primary adrenal insufficiency was made.
Treatment: hydrocortisone therapy iv is immediately started with careful monitoring of blood pressure and glycemic values. Furthermore, is also undertaken therapy with fludrocortisone, obtaining a significant improvement in clinical conditions and normalization of electrolyte disorders. Our patient also presented a subclinical hypothyroidism with TSH values of 5.074 at the blood chemistry tests, but the therapy with Levothyroxine already in progress (Eutirox 175 mcg daily) was not modified until the adrenal function normalized.
Autoimmune screening: being described in literature the association of autoimmune polyglandular syndromes with antiphospholipid antibody syndrome, in our patient acquired thrombophilic screening was also performed: with detection of weak positive LAC but in course of anticoagulant therapy (Rivaroxaban 20 mg) that the patient is carrying out for the prevention of DVT recurrences.
Complete autoimmune screening was also performed and resulted negative: Rheumatoid Factor, Anti-CCP (cyclic citrullinated peptide) antibodies, Anti-neutrophil cytoplasmic antibodies (ANCAs), Anti-nuclear antibody (ANA), Anti-double stranded DNA (anti-dsDNA), Anti-extractable nuclear antigen (anti-ENA), anti-smooth muscle antibody (SMA) and anti-liver kidney microsomal type 1 (anti-LKM-1) antibodies.
Discussion: APS type 2 has a prevalence of 1:1000 and its diagnosis is often delayed due to non-specific symptoms and existing comorbidities. This clinical case underlines the importance of a multidisciplinary approach, early diagnosis and above all timely treatment of adrenal insufficiency, as there is an increased risk of adrenal crisis and diabetic ketoacidosis, which are life threatening.

118. CATCHING FIRE: UNMASKING THE UNCOMMON CULPRIT - BENZODIAZEPINES AS A TRIGGER FOR STEVENS-JOHNSON SYNDROME

Albanesi E.[1], Bulgheroni M.[2]
[1]Univeristà degli studi di Milano; [2]Ospedale Luigi Sacco, Milano

Stevens-Johnson syndrome (SJS) is a rare and potentially life-threatening skin disease that can progress to a severe form of skin necrosis known as Toxic Epidermal Necrolysis (TEN), which is associated with a high mortality rate due to extensive skin involvement and an increased risk of infections.
A 58-year-old patient with a previously unremarkable medical history presented to our hospital with a rash spreading across the trunk. The rash consisted of painful merging flat and raised lesions and was accompanied by fatigue and fever few days before. Reviewing the patient's medication history revealed recent initiation of antidepressant therapy with Vortioxetine and Clonazepam, as well as a single dose of ketoprofen taken on the day the rash appeared.
Physical examination showed widespread skin lesions with a sparing of the face and mucous membranes, along with a fever. No other signs were present and parameters were fine. Blood tests ruled out infectious diseases such as syphilis, HSV, hepatitis and HIV. Despite negative results in autoimmune and infective panels, elevated levels of circulating immune complexes supported the hypothesis of severe immune activation as the underlying cause. Unfortunately, the patient's condition deteriorated rapidly, with the lesions spreading to whole body including mucous membranes and evolving into large blisters. We initiated high-dose steroid therapy with methylprednisolone and discontinued other medications. While the mouth and conjunctiva lesions showed improvement, the skin lesions remained large and confluent, with the development of open sores; we observed worsening of liver and renal function. Unexpectedly, we found out that the patient self-administered a small dose of Lormetazepam to treat insomnia. Even this medication was immediately discontinued, the steroid therapy was promptly increased, and parenteral hydration was enhanced. With time the patient's clinical picture along with liver and renal function improved.
One month after discharge, the patient was examined and tested for NSAID allergy, but all resulted in negative reactions. Our allergology consultant supported the hypothesis that BDZ were responsible for the reaction.
This case highlights the potential for uncommon reactions even with commonly prescribed drugs. In the discussion of this case, it is important to note that SJS typical presentation of SJS/TEN involves bullae and erythema with extensive mucocutaneous reactions. In our case skin lesions were present, but mucosal lesions appeared later, which made harder to figure the diagnosis.
Drug-induced SJS is associated with various medications, including antibiotics, anticonvulsants, nonsteroidal anti-inflammatory agents. Symptoms of SJS/TEN typically start within eight weeks from drug intake, with an exposure period of four days to four weeks. The underlying mechanism of the disease involves a T-cell-mediated hypersensitivity response against antigens keratinocytes antigens. Prodromal signs of SJS/TEN include malaise and fever and then rash appears. Initially, the lesions are well-defined erythematous macules that coalesce and evolve into blisters and bullae, accompanied by severe pain. Systemic abnormalities in the blood precede the rapid progression from SJS to TEN. The SCORTEN score is a useful tool to identify patients with a higher likelihood of developing TEN and to determine the probability of death. In our case, SCORTEN score was 3, suggesting approximately a death rate of 35%. Benzodiazepines (BDZ) have rarely been reported as the cause of SJS, mostly in a few case reports(5,6). The mechanism of action in these cases is unknown, although most involve patients with epilepsy being treated with BDZ in addition to other antiepileptic drugs. In contrast, our patient was taking only a few medications, none of which are frequently linked to SJS. The clinical presentation and recent drug intake strongly suggest a correlation, even though BDZ class drugs are rarely associated with such severe allergic reactions. Additionally, the timely discontinuation of the implicated drug limited the progression of the skin lesions. It is recommended to initiate immunosuppressant therapy as soon as possible, such as high-dose steroids, intravenous immunoglobulins (IVIG), and immunosuppressants, to halt the progression of the disease. SJS/TEN should be distinguished from other skin diseases, such as acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. Although similar therapeutic approach, AGEP and DRESS syndrome present with different types of lesions (macular, non-bullous), sparing of mucous membranes, and high eosinophil counts, but lower death risk. These findings were not observed in our patient, in which mucosal lesions were prominent allowing us to confidently exclude these two potential diagnoses. In conclusion, we presented a case of SJS probably induced by benzodiazepines, rarely associated with SJS. This case highlights the possibility of uncommon reactions even with common drugs.

119. FROM SEVERE RECTAL BLEEDING TO HEART SURGERY: AN INCIDENTAL FINDING OF GIANT PERICARDIAL LIPOMA

Campana S., Ferrentino F., Guerrini S., Nardi C., Nesi I., Ascione G., Torri M., Rostagno C.
Medicina Interna 3, Azienda Ospedaliero-Universitaria Careggi, Firenze;

Background: Lipomas are rare primary heart tumors and may involve the endocardium, myocardium, or pericardium; are soft masses of fat tissue which are often encapsulated by a thin layer of fibrous tissue. Signs and symptoms depend on the tumor location and size, as well as extent of myocardial involvement and range from chest discomfort to syncope but they are usually asymptomatic, often the discovery is incidental on cardiac imaging. Noninvasive cardiac imaging is the diagnostic method of choice for diagnosis of cardiac lipomas, they can be recognized by their features on radiologic imaging; in particular, MR imaging depicts the typical fatty composition of the tumor comparable to subcutaneous adipose tissue, even liposarcoma can be excluded by CT imaging because, in contrast to the lipoma, it possesses a higher HU number than normal subcutaneous fat. Surgery is recommended for all patients with the diagnosis of an intrapericardial mass because the surgical histopathological examination is essential to confirm the diagnosis and rules out malignancy criteria; while making only a biopsy has high risks of execution and may not be diagnostic because analyze a portion of a large mass.
Case Report: We describe a case of a 48-years-old woman who access to the E.R for episodes of intestinal bleeding, when she arrived blood pressure was 100/50mmHg heart rate 65 beats/min, Hb 10 g/dl, no other cardiac symptoms, with bleeding episodes for which she underwent urgent colonoscopy and subsequent removal in election of intestinal polyps (histological examination shows adenoma tubule-villous intestinal with expressions of high-grade epithelial dysplasia, she is in current endoscopic follow up). Computed tomographic and ultrasound demonstrated a huge cardiac mass; the CT scans showed mediastinal mass with homogenously adipose content completely surrounding the heart to the origin of the epiaortic vessels (maximum diameters on the axial plane 17 x 11 cm), this mass shows in its interior some septa with over water density in the absence of contrastographic impregnation. The patient was completelly asintomatic for cardiac disorder, ECG sinus rhythm at 66 b/min, no pericardial effusion at onset. At the transthoracic echocardiography hypo-isodense mass with trabeculars that circumferentially contours the cardiac chambers, maximum thickness before 6 cm. Cardiac MRI wasn't performed for claustrophobia, the mass was detected by PET to rule out possible malignancies. Pericardial lipoma should be differentiated from other space-occupying diseases like pericardial mesothelioma, pericardial cyst (which appears as an anechoic region) and pericardial secondary tumor (often secondary to lymphoma, melanoma, lung cancer).

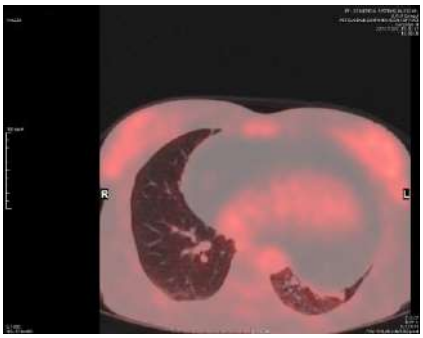


Figure 1. Giant pericardial lipoma on PET scan

The captation at PET of this mass orientates for the presence of pathological tissue with minimal/absent metabolic activity in the mediastinal for which wasn't possible to differentiate the exact nature (SUVmax 1.4, epatic SUV2.5) (Figure 1.). Because of the size, excisional thoracic surgery was quickly planned by median sternotomy. The neoformation of lipomatous appearance shows a vascularized peduncle on the anterior portions of the epicardium. Surgical resection was complicated by pericardial effusion; slowly increased , from 2 cm to 3.2 cm, until a subsequent hospitalization was necessary for circumferential pericardial effusion with initial hemodynamic commitment (kneeling of the right atrium and rotational movement of the left ventricle). Cardiosurgical assessment has no surgical indication to evacuate, it was subjected to cortisone therapy with benefit and slow reduction of the effusion for which it is in current follow up. Definitive histological examination has

evidenced the presence of mature intrapericardial lipoma, that will be submitted to periodic follow up with CT.
Conclusion: Cardiac lipoma are a rare tumor of the heart, and they are usually asymptomatic because the symptoms are related to the size and position of the tumor; the main difficulty is in radical resection, which can involve risks and complications but is essential in large lipomas to confirm the diagnosis and prevent future complications due to overgrowth and infiltration into cardiac tissue. Accurate diagnosis and comprehensive evaluation of cardiac lipoma is highly dependent on multimodality imaging methods,these are often incidental diagnosis. In this case we experience how important is early detection and how the patient's comorbidities may affect early treatment of the disease ; we had to figure out the major bleeding before the heart surgery, but also the quickness is important to avoid an unfavorable outcome due to overgrowth.

120. VERTEBROBASILAR FUSIFORM ANEURYSM TREATED WITH PARALLEL STENTS PLACEMENT: A CASE REPORT

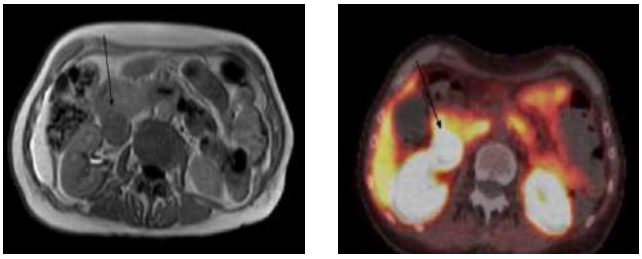
Bossi.F, Caso.V, Paciaroni M.
Università degli studi di Perugia

Background: Vertebrobasilar fusiform aneurysm (VBF) incidence ranges from 0.6 to 5.8%, while the 5-year mortality rate ranges from 23% to 35%. Endovascular treatment (EVT) is the first-line treatment of intracranial aneurysms. However, wide-necked, fusiform aneurysms remain a technical challenge for EVT.
Case presentation: A 68-year-old man was admitted to our department with dizziness, vomiting, motor deficit and paresthesia of the left upper limb. His medical history included a posterior ischemic stroke and a basilar artery aneurism (BAA) 7 years before. A cerebral MRI, completed with angiogram and 3D reconstruction, was performed where an acute ischemic lesion of the right brain steam and an increase of the known BAA size (maximum axial diameter 26 mm), with brain-stem compression from the V4 segment of the left VA up to the proximal segment of the BA was evidenced. During hospitalization his neurological conditions were unstable with medical therapy and therefore EVT approach was chosen. Two stent-flow diverters (Derivo 6 mm x 50 mm and 1 stent Derivo of 6 mm x 40 mm) were placed and overlapped one another from the BA apex to the left VA in its V4-tract, to rebuild the BA lumen inside the thrombus excluding the aneurysm (Fig.1). At discharge, the patient recovered without neurological sequelae with no changes at 3-6-12 months of clinical follow-up.
Conclusion: In our patient EVT with multiple parallel stents seems to be a feasible approach to treating giant fusiform VBA.

121. PARANEOPLASTIC CUSHING SYNDROME CAUSED BY A PANCREATIC NEUROENDOCRINE TUMOR PRODUCING ACTH: A CASE REPORT

Nardi C., Ferrentino F., Campana S., Ascione G., Guerrini S., Nesi I., Torri M., Rostagno C.
Medicina Interna 3, Azienda Ospedaliero-Universitaria Careggi, Firenze, Italy

Background: Pancreatic neuroendocrine tumors (pNETs) are rare (1-2% of all pancreatic tumors) and nonfunctioning in 70% of cases.
When functioning, they usually produce peptide hormones (e.g. insulin, glucagon). Rarely, adrenocorticotropic hormone (ACTH) can be secreted, thus leading to Cushing's syndrome.
In any case the diagnosis is challenging because tumors may be occult and difficult to find during common radiology exams due to their small size. Sometimes they need a (18) FDG-PET scan and other nuclear medicine imaging in order to be diagnosed.
Case report: A 62-year-old woman suffering from rheumatoid arthritis and sjogren syndrome, and who was discharged from our unit after being diagnosed with Sars-Cov2 pneumonia one month earlier, came back to our attention presenting mental confusion, abnormal behavior and muscular weakness with limb hyposthenia. In the last week she noticed facial hair growth. She had high blood pressure (144/82mmHg) and a metabolic alkalosis with severe hypokalemia (pH 7.634, pCO2 52, pO2 72, K 2.0, Na 135, HCO3 57) that required an aggressive infusion of KCl. Glucose blood levels were high (264 mg/dL).
Clinical findings were consistent with Cushing syndrome so serum and urinary cortisol levels have been analyzed and found to be high (1.271,0 nmol/L; 16.290,1 nmol/24h) as did the ACTH levels (579 pg/mL), suggesting ah ACTH dependent Cushing syndrome.
Cushing disease (hypophyseal adenoma) has been excluded by a negative MRI of the sella turcica.
The rapid onset of symptoms was consistent with paraneoplastic origin so a contrast enhanced CT scan has been performed and has shown a contrast uptake area of 48X45X35 mm near the first and second portion of the duodenum and the uncinate process of the pancreas but without any possible characterization. Further investigations including a contrast enhanced MRI of the abdomen (Fig 1) and a 68 Gallium-PET (Fig 2) diagnosed a neoplasia which had an elevated expression on somatostatin receptors. At fine needle aspirate the presence of atypical cells has been confirmed.
During the hospitalization she developed several Cushing syndrome complications: in particular she had several psychosis episodes that required antipsychotic therapy.
Hormonal therapy with metyrapone at low dosage (250 mg three times a day) has been started and was carried out until surgical removal of the lesion when high dose steroids (hydrocortisone 100mg) were administered.
The post surgery has been complicated by development of pseudoaneurysm of the superior mesenteric artery and the gastroduodenal artery that required embolization, of biliary fistula and lately by cholangitis that required large spectrum antibiotics and several internal-external drainage positioning and stenting. Once she gradually recovered from the complications, she has been discharged with indication to taper the long term acetate cortone therapy after the acute surgical complications to 12.5mg.
Conclusions: The clinical presentation suggested the diagnosis of Cushing syndrome despite the absence of later manifestation of the Cushing syndrome such as the lunar facies and the rubrae striae, which is typical of paraneoplastic Cushing syndrome that develops hypercorticosurrenalism in short time. This rapid onset required an aggressive therapy to correct electrolytes and hyperglycemia and also for the acute psychosis status.
It is also noteworthy that pNET discerning ACTH are rare: there are few anecdotal cases of Cushing syndrome in literature due to pancreatic NET, which usually produce physiological pancreatic hormones.
Moreover, the initial radiological exams were not consistent with pancreatic neoplasia until further investigations including nuclear medicine imaging were performed.
In some case reports published the diagnosis has been delayed by the low radiology sensibility and this led to very poor outcomes. In our case, despite the severe paraneoplastic syndrome associated and the post-surgical complications, the cancer was at first stage (G1, local) and therefore the patient had a good outcome.



122. WHEN CALCIUM GOES TO HEAD

Bortolin G.[1], Comand J.[1], Candusso G.[2], Baiano V.[2], Bulfone L.[2], Catena C.[2], Sechi L.A.[2]
[1]Clinica Medica, Department of Experimental and Clinical Medical Sciences, University of Udine, Udine, Italy ; [2]Clinica Medica, Department of Experimental and Clinical Medical Sciences, University of Udine Udine, Italy

Background: Hypercalcaemia is a common finding in the setting of primary care. Hypercalcaemia is diagnosed when the concentration of serum calcium is 2 standard deviation above the mean values. Mechanisms associated with hypercalcaemia are classically divided into parathyroid hormone and non-parathyroid hormone mediated. Parathyroid related causes of hypercalcaemia comprise primary and tertiary hyperparathyroidism. Primary hyperparathyroidism has an estimated incidence ranging from 0.41 to 2.16 cases per 100.0000 population annually in the United Kingdom and United States. Hypercalcaemia of non parathyroid origin is due to a variety of causes including malignancy, vitamin D related deaseases, endocrine disorders, drugs (thiazide diuretics, lithium,..) and many others. Malignancy associated hypercalcaemia

is estimated to affect 2.7% of people with cancer in the US. [1]
Case Presentation: A 59-year-old patient with Turner syndrome presented to the emergency department for gradually worsening low-back pain. In the anamnesis, the patient had a previous superficial spreading melanoma of the right auricle removed with disease-free resection margins and a previous diffuse large B cell non-Hodgkin lymphoma in complete response. Recently performed MRI showed multiple disc protrusions. She was discharged from the emergency department and a vertebro-medullary surgical visit was scheduled for the following day. She re-entered the emergency room the next day with slurred speech and impaired mobility, also reporting two episodes of vomiting in the evening. Blood tests showed an increase in CRP (164 mg/L), creatinine 1.39 mg/dL (baseline value: 0.57), hypokalemia (2.98 mMol/L). Head CT was performed for acute slowdown, which was negative.
Upon admission to the Medicine ward, the patient appeared to be apyretic, with stable vitals parameters, alert, slightly confused and with slurred speech. She reported cough and no fever at home. Objectively, there were no alterations, and under ultrasound, there was a thickening in the mid-basal field of the right lung, with B lines and a slight pleural effusion. Therefore, with the suspicion of community acquired pneumonia, empiric antibiotic therapy with ceftriaxone was started. Blood tests revealed severe hypercalcaemia (value: 4.63 mMol/L with serum albumine of 38 g/L) for which abundant hydration, intravenous furosemide, corticosteroids and zoledronic acid were started with improvement but always keeping the calcaemia slightly above the upper limits. PTH was normal. In suspecting myeloma, protein electrophoresis, immunofixation and Bence Jones proteinuria were evaluated, with normal results. In the following days there was a worsening of the neurological state, with the appearance of feverish peaks. It was known from a friend who had come to visit that a few weeks earlier they had gone on a trip to the mountains; in the suspicion of a possible tick bite, to exclude meningo-encephalitis, lumbar puncture was performed, and empiric therapy with ampicillin and acyclovir was started. Since there was no clinical improvement with fluctuating inflammation indices, a total body CT with contrast agent was requested without any findings of inflammatory or malignant anomalies. Brain MRI resulted negative for meningitis. Autoimmunity panel, viral serologies and onconeural antigens on blood and CSF were negative. In suspected lymphoma recurrence BOM was performed, which highlighted medullary infiltration of melanoma cells, subsequently characterized (positive for BRAF V600E mutation). PET CT was also performed with evidence of diffuse skeletal hyperuptake. For the reactivation of melanoma, therapy with dabrafenib and trametenib was started. During her hospitalization in oncology, the patient developed acute heart failure in the context of sepsis caused by E. faecium VR and Enterobacter cloacae and likely Takotsubo's SDR with consequent exitus.
Discussion: If hypercalcaemia is found, it is important to evaluate patient's serum albumin; if not possible or if it is altered, evaluate ionized calcium. In the preliminary evaluation of hypercalcaemia, serum PTH must be determined to distinguish the forms related to hyperparathyroidism from those not related to PTH. In the clinical case reported, PTH was normal, and once the possible infectious causes of neurological alterations had been excluded, the neoplastic hypothesis remained to be examined, given the patient's anamnesis.
Conclusions: It's always important to keep in mind that hypercalcemia can be related to very serious diseases such as malignancies. The first line therapy includes massive hydration, the use of corticosteroids, bisphosphonates and loop diuretics but the indication always remains to find and eliminate the triggering cause as soon as possible.
1. M*inisola S. et al., BMJ 2015; 350: h2723*

123. POTS: A MYSTERIOUS TACHYCARDIA

Mariani C.[1], Taino A.[2]
[1]UOSD Medicina ad indirizzo fisiopatologico, Ospedale L. Sacco, Università degli Studi di Milano; [2]UOSD Medicina ad indirizzo fisiopatologico, Ospedale L. Sacco, Università degli studi di Milano

Background: Postural orthostatic tachycardia syndrome (POTS) is a form of autonomic dysregulation characterized by an excessive increase in heart rate in the presence of symptoms of orthostatic intolerance. POTS primarily affects young women (ratio of 4.5-5:1 female: male), particularly in the age range of 15 to 50 years. The prevalence of this condition ranges from 0.1% to 1% of the population. The gold standard for diagnosis is the observation of an increase of at least 30 bpm in heart rate within the first 10 minutes of assuming an upright posture during a tilt test, without significant changes in blood pressure as measured by non-invasive monitoring. Typically, the heart rate is around 120 bpm or higher. Some of the main associated symptoms include fatigue, headache, palpitations, sleep disturbances, nausea, and anxiety.
A 30-year-old female patient presented to the emergency department with sporadic palpitations that had been occurring for approximately 3 years. These palpitations had significantly worsened and become disabling over the past three days, particularly upon postural changes from a supine to an upright position. The patient also reported profuse sweating and chest pain accompanying these episodes. Her medical history included three previous COVID-19 infections, Raynaud's phenomenon and autoimmune gastroduodenitis. In recent months, the patient experienced a week-long episode of systolic blood pressure values > 150 mmHg, which led to an evaluation in another hospital. She was discharged with instructions to undergo laboratory tests to exclude endocrine disorders, that showed normal thyroid-stimulating hormone (TSH) levels, elevated parathyroid hormone (PTH) likely due to vitamin D deficiency, normal orthostatic aldosterone, and a renin level of 131 pg/mL and abdominal US that showed a possible adrenal lesion.
However, during her stay in our department, blood pressure values remained within normal limits. Other blood tests were performed, which did not reveal any electrolyte imbalances or other significant abnormalities. ECG was conducted in both the supine and upright positions, demonstrating an increase in heart rate from 96 to 150 bpm, associated with episodes of intense precordial pain and profuse sweating upon positional changes, but without significant changes in blood pressure measurements that were observed at t0, t1, and t3 during orthostatic testing.
Throughout the hospitalization, the patient's overall clinical examination remained unremarkable, if not for retrosternal pyrosis, which was treated with magnesium hydroxide. Due to initial suspicion of an endocrine disorder, urinary catecholamine levels, urinary cortisol, 17-OH progesterone, dehydroepiandrosterone (DHEA), aldosterone and renin in the supine position, as well as parathyroid hormone, calcitonin, and prolactin were measured and resulted all within normal limits. Abdominal ultrasound was repeated and MRI was done for diagnostic completion, ruling out adrenal injury. Telemetry electrocardiographic monitoring was done, revealing an average heart rate of 100 bpm with preserved nocturnal fluctuation and an exaggerated heart rate response during positional changes, consistently exhibiting increases of 30 bpm or more, without other arrhythmias.
Given the absence of endocrine abnormalities and organic pathologies that could explain the patient's symptoms and persistence of rapid heart rate increments (>30 bpm) upon transitioning from a supine to an upright position without associated blood pressure changes, a diagnosis of postural orthostatic tachycardia syndrome (POTS) was established. This diagnosis was supported by the patient's clinical and symptomatic presentation, including spontaneous profuse sweating, gastrointestinal symptoms, and the absence of laboratory findings indicative of endocrine disorders. Further investigation revealed that the patient had experienced asthenia and sleep disturbances for several months, with varying sleep-wake schedules on different days.
Treatment with propranolol at a dosage of 10 mg twice daily was initiated, leading to immediate benefits for the patient, including a reduction in average heart rate and symptom improvement. This further supported the diagnosis and resulted in the patient's discharge with beta-blocker therapy, instructions for appropriate physical activity, increased fluid intake, and a plan to undergo a tilt test after discontinuing propranolol.
Etiology of POTS is not fully known, but several pathophysiological mechanisms have been recognized, including autonomic neuropathy, autoimmunity, hypovolemia, and deconditioning, all of which can ultimately contribute to orthostatic intolerance and tachycardia.
Treatment approach for this condition includes non-pharmacological strategies, such as gradually increasing physical activity, increasing fluid and salt intake, using compression stockings and the administration of medications such as beta-blockers, fludrocortisone, alpha-1 adrenergic agonists, clonidine/methyldopa, or pyridostigmine.
Prognosis for POTS appears to be favorable, as most patients experience an improvement in symptoms or complete resolution within 5 years.

124. ACQUIRED FACTOR VII DEFICIENCY IN SYSTEMIC MASTOCYTOSIS WITH AN ASSOCIATED MYELOID NEOPLASM

Camerlo S., Rosati G., Dalmazzo M., Padrini M., Busana T.T., Morotti A.
University of Turin

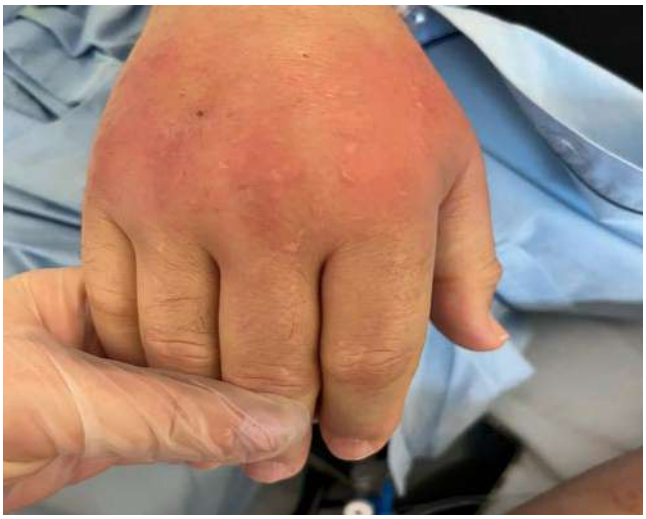
Introduction: Factor VII (FVII) deficiency is a rare bleeding disorder, classified as congenital or acquired. Most of the acquired cases are based on the vitamin K deficiency or liver disease and therefore are associated with the defects in other vitamin K dependent clot factors, with prolongation of the

aPTT ratio as well. Isolate acquired FVII has been rarely described, as reported elsewhere. In a previous study and report of the literature, few cases were associated with the presence of inhibitors or auto-antibody. In other cases, acquired FVII deficiency was reported during sepsis, as a potential consequence of proteolytic degradation, induced by the activation of monocytes or endothelial cells. In other cases, malignancies have been showed to delete circulating FVII due to direct binging to cancer cells. Interestingly, acquired FVII deficiency was not linearly correlated with bleeding, suggesting a complex physio pathological mechanism.
Systemic mastocytosis (SM) is a disease sustained by clonal proliferation of abnormal mast cells (MC). World Health Organization has classified SM accordingly to the pathological and clinical characteristics of this disease. SM can present as an indolent/smoldering SM (ISM/SSM) or advanced SM, which includes aggressive SM (ASM), form associated with hematological neoplasm (SM-AHN) and mast cell leukemia (MCL). Here, we will focus on a SM-AHN patient presenting with an acquired FVII deficiency, which benefit from the systemic treatment with midostaurin.
Case report: A 57-year-old man was followed in our division of Internal Medicine Hematology because of a Jak2-V617F mutated Polycythemia vera. During the beginning of 2023, he was referred to us because of progressive fatigue and abdominal discomfort due to splenomegaly. At the blood examination, patient presented with mild thrombocytopenia (114.000/uL), increase in GGT (175 U/ml) and alkaline phosphatase (638 U/L) with normal transaminases values. Bone alkaline phosphatase was selectively increased (115 ug/l) and was associated with the diffuse infiltration of various skeletal segment at the NMR. An abdominal NMR was performed revealing hepatosplenomegaly (spleen of 20 cm of diameter), with liver steatosis. Liver synthesis indexes were normal, while PT ratio was prolonged (1,80) with normal aPTT (1.16 ratio) and normal fibrinogen levels. In the hypothesis of an evolution of PV into myelofibrosis, patient received a bone marrow biopsy, which resulted as a dry tap. At the histology, the morphology and immunohistochemical analyses were coherent with the diagnosis of SM. Notably, tryptase was 772 mcg/l (normal value < 10). Due to the prolonged and isolated PT ratio, a marked reduction in FVII concentrations was observed. FVII concentrations were 38% of activity, 36% at 1:40 dilution and 36% at 1:80 dilution, ruling out the presence of inhibitors. No spontaneous bleeding manifestations were observed, beside a minor local bleeding during bone marrow biopsy. Due to the diagnosis, patient was treated with midostaurin. Progressively, clinical conditions of the patient were significantly improved. Strikingly, PT time was also progressively and rapidly normalized and just after one month of treatment FVII levels turned to normal values (73% at one month). Tryptase levels were also progressively, but slowly, reduced (181 mcg/l after 2 months).
Conclusion: This case report points to a potential link between SM-AHM and acquired isolated FVII deficiency. In various published works, SM has been associated with bleeding manifestations, but the mechanisms are not clear. Few reports linked bleeding manifestations to the release of heparin-like anticoagulant from pathological mastocytes. Here, we suggest that further evaluations are advisable in patients with SM to better understand the link between pathological mastocytes and clot factor concentrations.

125. ERYTHEMA INDURATUM

Bergamasco A., Salvia R., Casamassima A.M., Coppola C., Ibrahimi R., Magnifico A., Martiradonna M.R., Perrone A.S., Triggiani D.
Dipartimento Interdisciplinare di Medicina, Università degli Studi di Bari "Aldo Moro"

Background: Bazin's disease (also called "erythema induratum") is a rare inflammatory disease which is usually associated to active or latent tuberculosis. It is characterized by subcutaneous erythematous nodules, due to a panniculitis. It is a diagnosis of exclusion and its treatment depends on the underlying disease.
Case report: The patient C. G., 63 years old, is a former military who worked in Afghanistan during the Gulf War in the 90s. He reported good health until September 2022, when subcutaneous nodules had appeared on his limbs, with a relapsing-remitting trend. He had neither traveled abroad nor had contacts with wild animals in the previous weeks. In February 2023 he went to the Emergency Department for a lateral neck lump, which was diagnosed as a lateral cervical abscess, treated with antibiotic therapy. About 10 days later, he went again to the Emergency Room for fatigue and for a new flare of subcutaneous nodules on his hands, so he was admitted to our Internal Medicine ward.



He underwent a wrist CT, which showed a suspicious septical arthritis. The thorax CT showed blurred lung nodules and intrathoracic linfadenopathies, without corresponding respiratory distress.
During the days later, the limb nodules progressively disappeared, but an orbital cellulitis suddenly emerged on his left eye and it was apparently healed by antibiotical therapy. Suspecting Lofgren syndrome, serum ACE dosage was carried out and an axillar lymph node was analyzed: both exams had a negative outcome. The search for other autoimmune, neoplastic and infective disease did not carry out remarkable outcomes. The only exception was the Quantiferon TB Gold, which tested positive on two different determinations. When the nodules appeared again on the inferior limbs, one of the biggest was surgically removed and analyzed by the pathologists, who described just a modest inflammatory infiltration. After 3 weeks from the first episode, the orbital cellulitis recurred. Having already ruled out all the most likely clinical conditions and considering the positive result of the Quantiferon, Bazin's disease was suspected. So, the patient was treated with high dosage corticosteroid therapy, which made all the signs and symptoms disappear. During the cortisone tapering after the patient's discharge, there was one more flare of the orbital cellulitis on the right eye, which disappeared again with an increase of the cortisone dosage. The patient, again in good health, is now visited periodically in the tuberculosis clinic, where he will start soon the eradication therapy for the underlying disease.

Discussion: The differential diagnosis of subcutaneous nodules is a hard challenge for the Internal Medicine specialist. First of all, it is correct to assess the most common diseases, especially the neoplastic, infective and autoimmune ones. Even though it is more frequent among young women, we have to consider the Bazin's disease as a possible diagnosis in patients with positive Quantiferon test and skin manifestations which are not relatable to other clinical conditions. Excluding clinically and radiologically an active infection from Mycobacterium tuberculosis is essential: when this is possible, the corticosteroid therapy is a good solution in order to stop the inflammatory processes in a short span of time; then, the eradicating therapy for tuberculosis should be prescribed, under the guidance of the Infectious Diseases specialist. Considering the stigma related to the tuberculosis, an appropriate communication with the patient in a proper way is critical, in order to avoid inappropriate negative psychological reactions and to gain a good compliance during the treatment.

126. ACUTE PROMYELOCYTIC LEUKEMIA AND BRUGADA SYNDROME: A REPORT ON THE SAFETY OF ARSENIC TRIOXIDE/ALL-TRANS-RETINOIC ACID THERAPY

Rosati G.[1], Camerlo S.[2], Dalmazzo M.[2], Padrini M.[2], Busana T.T.[2], De Gobbi M.[2], Morotti A.[2]
[1]University of Turin; [2]Univesity of Turin

Introduction: Brugada syndrome (BrS) is an inherited disease associated with an increased risk of fatal arrhythmic events and sudden death. Currently, the diagnosis of BrS can be established either in presence of a spontaneous type 1 ECG pattern, or in case of survival to a cardiac arrest – caused by ven-

tricular fibrillation or polymorphic ventricular tachycardia – combined with an induced type 1 ECG pattern. Patients with this disease must avoid a number of drugs that favor the occurrence of arrhythmic (and possibly fatal) events. Acute promyelocytic leukemia (APL) is an aggressive form of acute myeloid leukemia (AML), characterized by the translocation t(15;17), where the retinoic acid receptor alpha (RARA) gene and the promyelocytic leukemia (PML) gene merge to form the PML-RARA fusion protein. The combination of all-trans-retinoic acid (ATRA) and arsenic trioxide (ATO) has become the frontline therapy of APL in low-risk patients, in place of cytotoxic chemotherapy. Side effects of arsenic include increased liver enzymes, neurotoxicity with peripheral neuropathy, and prolongation of the QTc interval, which can lead to arrhythmic events. Little is known about the safety of APL treatments in patients affected by BrS. Therefore, we aim to point out the diagnostic and therapeutic challenges the clinician might deal with when these two rare conditions are combined.

Case Description: A 38-year-old Caucasian male was admitted to the emergency department for the appearance of bilateral inguinal swelling fatigue. Smoking habits, former drug addiction (cocaine assumption up to 7 months earlier) and Brugada syndrome were reported in his past medical history. At the blood examination, a pancytopenia was revealed and therefore admitted to our division because of the suspect of acute leukemia. In previous years the patient had been tested for BrS due to his family history: the ECG presented a drug-induced type-1 pattern, whereas the 24-hour ECG monitoring and the ergometric test were negative. He never had syncopal or arrhythmic events. At the admission, basal ECG was found normal, as can typically happen in inducible type-1 BrS. For this reason, the patient was monitored with telemetry during the first days of hospitalization. Bone marrow biopsy was conducted while monitoring the ECG, upon intravascular midazolam 6 mg for sedation and subcutaneous mepivacaine 200 mg as a local anesthetic administration. No heart rhythm alterations or other adversities occurred during and after the procedure. Both cytofluorimetric analysis on bone marrow aspirate and histological examination confirmed the diagnosis of APL. Given the low white blood cell count, the patient was considered at low risk and therefore was started on ATO 0.15 mg/kg/day intravenously (15.3 mg/day in total) and ATRA 45 mg/m2/day per os (50 mg/day in total) divided into two doses for 28 days. The supportive therapy regimen consisted of acyclovir 400 mg twice a day, fluconazole 100 mg/day and allopurinol 300 mg/day. During the treatment, daily ECG and electrolytes tests including magnesium were performed in order to rapidly identify possible alterations in heart rhythm. No arrhythmic or syncopal events occurred during the first course of therapy.

Discussion: The safety of APL treatment in Brugada syndrome has never been investigated. Consequently, when the two conditions come together, the assessment of the arrhythmic risk for medications used in the diagnostic and treatment phase remains challenging. Thus, when evaluating the biopsy, we chose to replace lidocaine with mepivacaine as the local anesthetic. Furthermore, for sedation we decided to use the benzodiazepine midazolam, considering its short half-life. Once the diagnosis was established, the safety of supportive treatment and chemotherapy had to be assessed. In AML patients posaconazole is the preferred drug for fungal prophylaxis for its higher efficacy. Nevertheless, fluconazole was used instead, in relation to its lower risk of both cardiac events and interaction with ATRA. Based on the be "low-risk" APL, ATRA + ATO is the treatment of choice. Although QTc prolongation is a common event during the treatment with arsenic and exposes the patient to the risk of developing ventricular arrhythmia (i.e. torsade de pointes), various studies showed that significant arrhythmias are rare and can be prevented with ECG monitoring and management of electrolytes disturbances and concomitant medications. As far as we know, the safety of arsenic in Brugada syndrome was never studied. So far, neither arrhythmic events nor ECG alterations were recorded.

Conclusion: APL and BrS are two rare diseases, and no data are available in literature about the safety of APL treatment when these conditions are both present. Our experience, based on a single case, has shown no adverse heart events during the induction treatment with ATRA and ATO in a patient affected by BrS. We hope this case could be a starting point to fill a gap of the literature and it could help the clinicians in the difficult management of these two rare diseases.

127. RECURRENT STROKES, TRANSIENT ISCHEMIC ATTACKS, SEIZURES: WHAT ARE WE MISSING?

Senzacqua M. [1], Marconi F. [2], Martino G.P.[3], Angelici S.[3]
[1]UOC Medina Interna AST Fermo; [2]AST Fermo; [3]UOC Medicina Interna AST Fermo

In 2015 a 62-year-old man arrived at the emergency department after he had fallen to the ground during physical activity because of a generalized seizure. Brain MRI performed during hospitalization showed multiple focalities of altered signal with ischemic significance and in various stages of development with an acute ischemic lesion in the medial paratrigonal site on the left. To study the acute ischemic lesion, in search of an embolic source, the following exams were performed: ECG which showed a sinus rhythm; Echocardiogram with transcranial doppler with relief of patent foramen ovale (PFO); thrombophilia screening which showed a weak and non-significant anti-cardiolipin IgM antibody positivity and a borderline positivity of LAC. Anticonvulsant and antiplatelet therapy was started. A loop-recorder was positioned to exclude any atrial fibrillation and the patient was sent for cardiological evaluation for PFO.

In 2016 while the patient was awaiting PFO repair surgery, he went to the emergency department again for dysarthria and aphasia with spontaneous resolution after few minutes. Also in 2016 he performed percutaneous surgery to close the PFO.

In 2017 the loop-recorder logged six hours of atrial fibrillation. Antiplatelet therapy was suspended and NOAC therapy was started with apixaban (CHA2DS2-VASc: 3).

In 2022 the patient went to emergency department again due to recurrence of seizures with diagnosis of cerebral acute ischemia affecting the posterior portion of the left corona radiata in multi-infarct encefalopathy. The medical team decided to replace NOAC (dabigatran).

In 2023 the patient repeated thrombophilia screening which results unchanged. A genetic analysis was performed in the suspicion of CADASIL syndrome (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) and the patient was found to be heterozygous for the pathogenic mutation p.R1006C in exon 19 of the NOTCH3 gene.

CADASIL is a rare monogenic hereditary small vassel disease characterized by the onset of subcortical lacunar infarcts and leukoencephalopathy in mid-adulthood. It can frequently hide behind more common symptoms such as recurrent strokes of ischemic nature, transient ischemic attacks, seizures, multiple psychiatric symptoms, migraines and cognitive impairment therefore represents a diagnostic challenge. Moreover the lack of awareness about the disease in the general clinical community make the path to diagnosis for most CADASIL patients complex and often lengthy.

128. INTERNIST LOOKS AT WHAT OTHERS SEE: A HARD CASE OF FUO

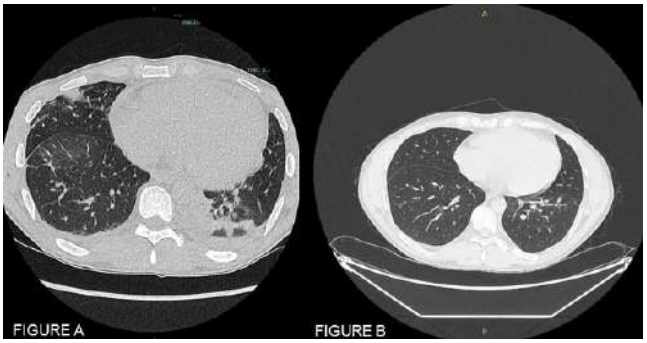
Vitale P., Di Giacomo I., Agrelli L., Sottolano A., Mazzarelli U., Carrieri I., Cardamone C., Parente R., Triggiani M.
Dipartimento di Medicina Interna, Università degli Studi di Salerno, Italy

Fever of unknown origin (FUO) is defined by a body temperature ≥ 38.3°C for at least 3 weeks in an immunocompetent patient, without the identification of an etiological cause, despite proper investigation during at least one week of hospitalization. The differential diagnoses include infectious, autoimmune, autoinflammatory and neoplastic diseases.

A young man, with no medical history, presented to the ED with intermittent fever for 10 days (T max 40°C) and a recent onset of stabbing chest pain, worsening with deep inspiration. The fever did not respond to domiciliary antibiotic treatment with macrolides. Blood tests showed leukocytosis (white blood cells 17,000/mm3) with neutrophilia (14,900/mm3), normochromic normocytic anemia, elevation of D-dimer (5000 ng/mL), inflammatory markers (CRP 80 x ULN, ESR 120 mm) and troponin (700 ng/L). The instrumental examinations revealed the presence of pulmonary infiltrates associated with pleural and pericardial effusion, while the ECG, myocardial necrosis enzymes and CT angiography excluded an acute coronary syndrome or pulmonary embolism. During hospitalization at the Internal Medicine Department, despite several lines of antibiotic therapy, fever and elevation of the inflammation markers persisted and the neutrophilic leukocytosis worsened (white blood cells 36,000/mm3, neutrophils 33,000/mm3) associated with onset of hypertransaminasemia. Bronchoscopy with bronchoalveolar lavage analysis was performed to investigate the pulmonary infiltrates, along with blood cultures, polymerase chain reaction and serology for the main viruses, bacteria and fungi, but all tested negative.

The only data that emerged was the presence of 300 copies/mL of EBV DNA in blood samples, combined with IgG antibodies against EBV. Furthermore, follow-up transthoracic echocardiography confirmed pericardial effusion and ruled out endocarditis. The persisting fever for more than 3 weeks was classified as FUO. Whole body contrast-enhanced CT scan, tumor markers and the absence of autoantibodies excluded both neoplastic and autoimmune

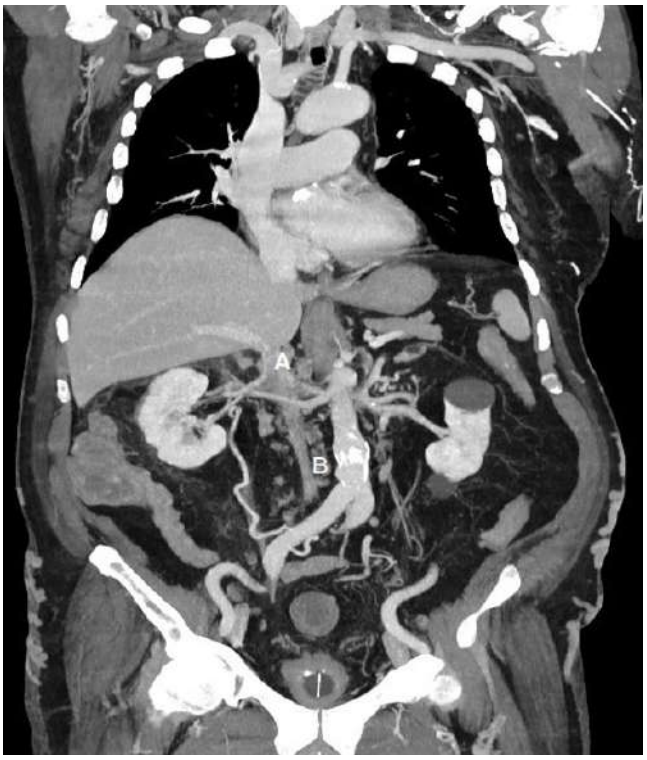
diseases. Ferritin levels, on the other hand, were markedly increased (13,000 ng/L, with normal values below 282).
Therefore, a peripheral blood smear and lymphocyte subpopulations dosage were executed with normal results, while a bone marrow biopsy revealed a trilinear hypercellular bone marrow and images of erythrophagocytosis; this is typical but not pathognomonic of a Macrophage Activation Syndrome (MAS), which was excluded due to the absence of cytopenia, hypertriglyceridemia and hypofibrinogenemia.
The fever pattern, non responsive pulmonary infiltrates to antibiotic treatment, the pleuropericarditis, the neutrophilic leukocytosis, the absence of autoimmunity, the elevation of ferritin and the hypertransaminasemia shifted the diagnosis towards an autoinflammatory disease. Specifically, the negativity of the molecular analysis of the genes associated with autoimmune and autoinflammatory disorders of the immune system excluded the monogenic forms and directed the diagnosis towards an adult-onset Still's disease (AOSD), with probable reactivation of EBV, typical of immunologic and rheumatological diseases. According to the guidelines, the steroid dose was increased (methylprednisolone 40 mg twice a day) and therapy with colchicine and ibuprofen was introduced, with consequent improvement of the clinical condition (apirexia), laboratory values (reduction of inflammation indices and normalization of the blood count) and radiological pictures (reabsorption of the effusions).
The patient was then discharged with indication for specialist outpatient follow-up. After a few days he presented at our immunorheumatology clinic for hyperpyrexia reappearance, arthralgia and pulmonary CT scan worsening; for this reason, treatment with anakinra (IL-1 receptor antagonist) was started, obtaining, over the weeks, clinical and laboratory remission, improvement in pulmonary findings, the tapering of steroid dose and the reduction of possible complications (evolution into MAS). At the end of 3 months of therapy, the patient presented at follow-up visit in good clinical conditions and asymptomatic, maintaining normal laboratory and radiological findings, with indication to continue drug administration and control examinations.
AOSD is a rare and difficult to treat disease and above all to diagnose. The variability of the clinical pictures requires the exclusion of other more common pathologies. The patients often find themselves into a long course, often full of diagnostic mistakes and delays that expose them to dangerous complications, such as MAS. Given the absence of specific markers for AOSD, the clinical history and objective findings are fundamental in the diagnosis of this pathology.
This case report is particular for the atypical onset of the AOSD and for the pronounced pulmonary involvement. In this scenario, the role of the internist is to raise suspicion for a timely and accurate diagnosis in order to initiate a prompt and optimal treatment.

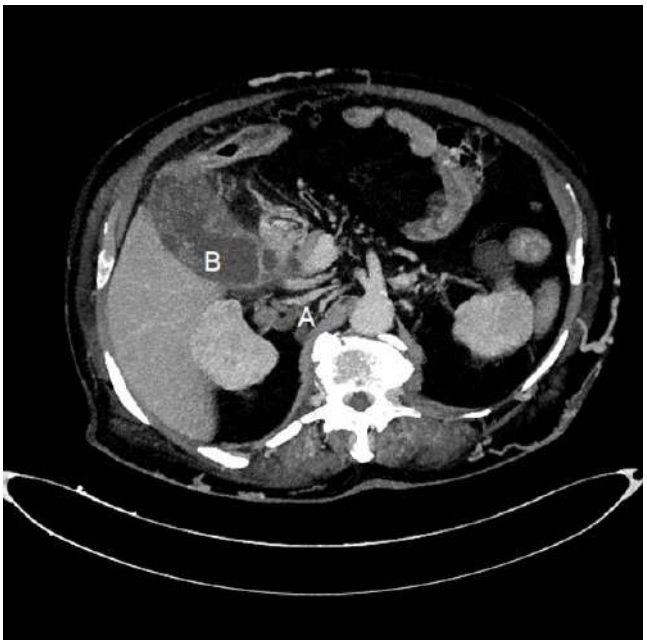


129. PAY ATTENTION TO DEHYDRATION AND EMPHASIZE COLLABORATION: A PARTICULAR CASE OF AKI

Vitale P.[1], Marotta P.[2], Restivo A.[2], Farre G.[2], Meccia D.V.[3], De Siero M.[3], Guida A.[4], Triggiani M.[1], Iacuzzo C.[2]
[1]Dipartimento di Medicina Interna, Università degli Studi di Salerno, Italy; [2]UOC Nefrologia, Dialisi e Trapianti Rene, AOU San Giovanni di Dio e Ruggi d'Aragona, Italy; [3]UOC Radiologia Vascolare ed Interventistica, AOU San Giovanni di Dio e Ruggi d'Aragona, Italy; [4]Centro per le Malattie Emorragiche e Malattie Trombotiche, AOU San Giovanni di Dio e Ruggi d'Aragona, Italy

Acute kidney injury (AKI) is a heterogeneous clinical syndrome that has multiple and variable aetiologies, pathogenesis and outcomes. Dehydration may be one of these, especially in patients with hereditary thrombophilic condition and congenital abnormalities.
A 72-year-old man was referred to the emergency department for loss of consciousness with severe fatigue, dyspnea and confusion, preceded by abdominal pain. At arrival, vital signs were normal except for tachycardia and a body temperature of 38°C, abdominal pain persisted associated with an episode of fecaloid vomiting and oligoanuria, without any neurological signs or symptoms. At physical examination only venous ectasia in lower limbs and abdominal wall and severe dehydration with hot and sweaty skin. At ECG ventricular bigeminism and compensated metabolic acidosis on ABG. Blood tests showed leukocytosis with neutrophilia, hypochromic microcytic anaemia, acute renal failure (serum creatinine 4,43 mg/dl, eGFR, 12 mL/min/1,73 m2) and elevation of D-dimer (4000 ng/mL) and C-reactive Protein (CPR) with rhabdomyolysis. Other coagulation tests (PT, PTT,) and platelets were normal. An abdominal CT angiography revealed intestinal obstruction, overdistension of sigma with endoluminal disomogenity and hydropic gallbladder, while a chest CT angiography ruled out pulmonary embolism. According to the diagnosis of intestinal subocclusion, he began antibiotic and rehydration therapy and diuretic stimulation. Intense rehydration therapy resolved the subocclusion but for the persisting anuria and the worsening of renal failure (AKI 3) the patient was referred to the nephrolgy ward, requiring hemodialysis treatment. What happened? According to the discrepancy between the normal morphology of the kidneys and the persistence of elevated creatinine levels after rehydration, a review of the CT angiography of the abdomen was performed. This second look revealed a thrombosis of a collateral branch of the inferior vena cava (IVC) associated with hypoplasia of IVC and ectasia of superior vena cava. This finding was discussed with the interventional radiologists, vascular surgeons and haemostasiologist with an indication for anticoagulant therapy with low-molecular-weight heparin at antithrombotic dosage (enoxaparin at a dose of 1 mg/kg/24, because of AKI). The patient had no history of recent surgery or immobilization, but he reported an episode of deep vein thrombosis approximately 10 years before. Thrombophilia study was performed and it revealed only heterozygousity of prothrombin G20210A gene mutation and mildly elevated homocysteine levels. Subsequent slow progressive improvement in renal function begun, with recovery of valid diuresis and dialysis discontinuation. The patient was discharged normohydrated, normotensive, apyretic, with stable renal function indices (serum creatinine 1,15 mg/dl, eGFR 60 mL/min/1,73 m2) and electrolytes in the normal range, with a rehabilitation program in an accredited facility. Once the renal function and the septic state had normalized, an indication was given for oral anticoagulant therapy following follow-up at our hemostasis and thrombosis centre.
This case highlights how the triple association between dehydration due to the fever, hypoplasia of IVC and heterozygousity of prothrombin G20210A gene mutation, also with hyperhomocysteinaemia, triggered the thrombosis of the collateral branch of the hypoplasic IVC with consequent venous insufficiency, reduced cardiac return and cardiac output with finally mesenteric ischemia and sub-occlusion. So hypoperfusion in association with rhabdomyolysis and septic state were responsible for functional AKI evolved into organic with organ failure and need of dialysis therapy. The prothrombin G20210A gene mutation is the second most commonly inherited thrombophilia after Factor V Leiden. Estimates of the prevalence of prothrombin G20210A gene mutation heterozygousity range between 1% and 6%, with an overall prevalence estimate of 2% of the general population. Congenital IVC abnormalities also are uncommon and may be unnoticed for a long time due to the development of a system of collateral venous drainage. Their prevalence is roughly 0.6% in the general population. Many writers believe that IVC hypoplasia is caused by intrauterine or perinatal thrombosis, which is caused by a condition of hypercoagulability caused by protein C, protein S and antithrombin III deficiency or mutation of the prothrombin and factor V Leiden genes. These conditions cause venous stasis and tends to lead to venous thrombosis. The peculiarity of this clinical case is linked to its rarity and to the clinicians' ability to establish the right sequence of events leading to loss of renal function. In order to obtain management and resolution of the case, it was invaluable the close collaboration between specialists: nephrologist, interventional radiologist and internist expert in thrombosis.

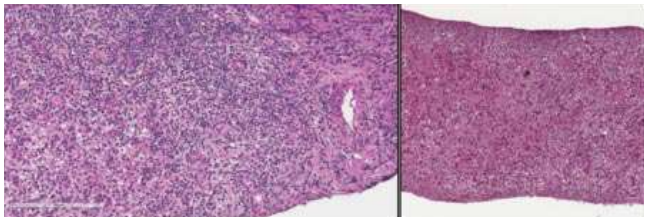


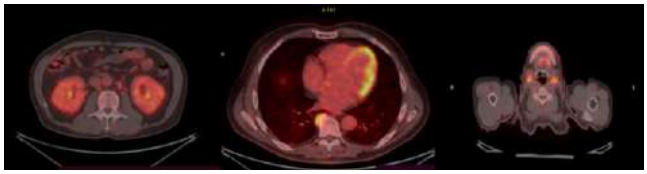


130. A CASE OF SNEAKY AKI

A. Sottolano[1], P. Vitale[1], I. Carrieri[1], L. Agrelli[1], U. Mazzarelli[1], A. Guida[2], R. Parente[1], C. Cardamone[1], M. Triggiani[1]
[1]Division of Allergy and Clinical Immunology, Department of Medicine, University of Salerno, Italy ; [2]UOC Medicina Interna, AOU San Giovanni di Dio e Ruggi d'Aragona, Salerno, Italy

Introduction: Acute kidney injury (AKI) is defined as the sudden decrease of kidney function resulting in the inability to maintain electrolyte, acid-base, and water balance. This condition is one of the most challenging situation in internal medicine department and is associated with an increased risk of mortality, cardiovascular events, and progression to chronic kidney disease. Phenotypes of AKI could be similar, but the etiology may differ greatly. A prompt detection of the underlying cause of AKI is essential to begin the appropriate treatment, which directly influences the prognosis. This report describes a case of AKI as presentation of a rare disease.
Case Report: A 60-yrs-old male, without other comorbidities, was referred as outpatient to our internal medicine department for progressive increase of creatinine serum levels (creatinine 2.3 mg/dl EGFR 36.2 ml/min at the moment of the visit, creatinine 1.63 mg/dl EGFR 51.1 ml/min 4 months before), asthenia and microcytic anaemia. Urinalysis displayed a reduced specific gravity and urinary sedimentation examination revealed a large amount of white blood cell casts, and no dysmorphic erythrocytes. The physical examination was normal except for bilateral swelling of the salivary glands. We performed an ultrasound examination, showing increased size in both kidneys and poor corticomedullary differentiation, without hydronephrosis or alterations of renal perfusion. Other blood tests were done resulting in significant increase of inflammatory parameters (VES 103mm, PCR 2xULN), eosinophilia (1600/mm3), hypergammaglobulinemia (2.7 g/dl) with IgG 2760 mg/dl, presence of rheumatoid factor 10xULN, reduced level of C3 (77.50 mg/dl) and a low grade of proteinuria (500 mg/24 h). These findings suggested an intrinsic renal parenchymal disease due to an acute tubular necrosis. The most common causes of acute tubular necrosis are: i) renal hypoperfusion due to hypotension or sepsis, major surgical interventions, nephrotoxicity (i.e. NSAIDs, radiological contrast, myoglobin), ii) autoimmune diseases (i.e. Sjogren's syndrome). Due to the persistence of the impaired renal function, in absence of other clear causes associated to AKI, renal biopsy was performed, according to the current guidelines. The histological examination revealed a severe lympho-monocytic infiltration, a high-grade of tubulo-interstitial nephritis and storiform fibrosis with normal basal glomerular membrane. Staining with Congo-red was negative for amyloids and the immunofluorescence confirmed an increased number of IgG4-positive plasma cells suggestive of IgG4-related disease. This diagnosis was further supported by the significant serum increase of IgG4 (9xULN). Considering clinical, radiological, serological and pathological data, according to the ACR/EULAR 2019 criteria, a diagnosis of IgG4-related disease(IgG4-RD) was done. In our clinical practice, after making this kind of diagnosis, we usually request a PET/TC scan, both to rule out a paraneoplastic nature of IgG4-RD and to find out the type and degree of organ-involvement. The PET-CT scan showed augmented size of submandibular glands with an increased SUV of 5.4, a hypodense nodular mass of 25mm at D7-D8 level at right anterior paravertebral side (SUV max 3.9) and increased kidneys size with thickened perirenal adipose tissue. The nodular lesion was more accurately investigated by MRI and it resulted compatible with an inflammatory lesion. According to the ACR/EULAR guideline, the patient started immunosuppressive therapy with prednisone (0.7 mg/kg/day). After thirty days an improvement in renal function (serum creatinine 1.75 mg/dl, EGFR 41 ml/min) and parameters of inflammation was observed. After 3 months this positive response was confirmed through laboratory parameters (serum creatinine 1.3 mg/dl, EGFR 60 ml/min), ultrasonography findings with a reduction in renal size and submandibular gland size and MRI, which revealed a reduction in the size of the paravertebral lesion, confirming the inflammatory nature in the context of an IgG4-related disease.
Currently the patient is tapering his corticosteroids dose and the renal function indexes are still improving.
Conclusions: IgG4-RD is a rare disease with heterogeneous clinical features. The spectrum of disease is continuously expanding and several new phenotypes have been recently included as components of the IgG4-related disease. In this particular case report there was the presence of three different part involved: kidneys, submandibular glands and paravertebral soft tissues. IgG4-RD as leading cause of AKI should be considered in our clinical practice. In this clinical case, the early identification and treatment of the underlying cause of acute kidney injury has allowed us to achieve a successful outcome.

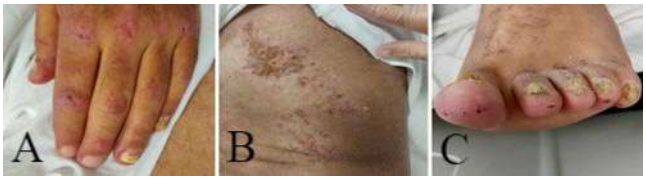




131. AMYOPATHIC DERMATOMYOSITIS: A CASE OF LOCALLY ADVANCED GASTRO-ESOPHAGEAL JUNCTION CANCER ASSOCIATED WITH A PARANEOPLASTIC FORM

Nesi I.[1], Guerrini S.[1], Campana S.[1], Nardi C.[1], Ferrentino F.[1], Ascione G.[1], Tozzetti C.[2], Rostagno C.[1], Torri M.[2]
[1]Division of Internal Medicine 3, University of Florence; [2]Division of Internal Medicine 3, AOU Careggi (Florence)

Background: Amyopathic dermatomyositis (CADM), previously known as "dermatomyositis without myositis", is currently considered a distinct form of dermatomyositis (DM) characterized by the presence of suggestive skin lesions and mild instrumental and/or laboratory findings of myositis. CADM shows a close association with malignancies, so cancer screening is required at the time of diagnosis.
Case report: A 52-year-old man arrived at the emergency department in September 2022 for a presyncopal episode associated with nausea and vomiting. In his medical history epilepsy treated with carbamazepine. From about 5 months, he reported the appearance of diffuse erythematous-desquamative eruption, associated with weight loss (-10kg), joint pain and muscle weakness, not responsive to steroid therapy.On physical examination, he presented widespread scaly hyperpigmented areas alternating with hypopigmented areas; face edema with heliotrope rash; Gottron papules (picture A); ulcerative and scratching lesions with signs of superinfection on the trunk (picture B); rat bite lesions of the toes (picture C). He also showed poor trunk control and important weakness of the lower limbs with bilaterally absent osteo-tendon reflexes; less evident weakness of the neck and upper limbs. He had inexhaustible nystagmus in lateral gaze bilaterally, dysarthria and rhinolalia. Finally, dysphagia and cough with mild respiratory insufficiency were assessed.Blood tests showed macrocytic anemia (Hb. 8.5g/dL) without signs of haemolysis (negative direct and indirect Coombs test), thrombocytopenia (PLT 100x10^9/L), lymphopenia (immunophenotype not significant), CPK in the range and high aldolase levels (10U/L).Considering neurological symptoms, his skin lesions and the dark color of urine to exclude Cutanea Tarda Porphyria levels of total urinary porphyrins were measured, which resulted elevated (612microg/24h). This value was not confirmed in the second urine sample. It has been interpretated as porphinuria secondary to carbamazepine intake.The EMG of the lower limbs showed compatible findings for non-active myopathic damage.Autoimmune diseases workup showed positive anti Jo-1, anti Ro-52 and, above all,positive anti TIFy.In the suspicion of amyopathic dermatomyositis, a high dose of steroid therapy was started (methylprednisolone 125mg for 6 days).Subsequently the patient showed rapid deterioration of neurological condition with worsening of dysarthria and dysphagia and new onset of diplopia in all directions of gaze, therefore we excluded other neurological causes with brain MRI with contrast medium and EEG, which resulted negative. Anti-ganglioside, anti-sulfatide, anti-onconeural, anti-neuronal surface and anti-muscular plaque antibodies were all negative. It was interpreted as a rare manifestation of DM involving the extrinsic muscles of the eye and immunoglobulin therapy (0.4g/kg for 5 days) was started with improvement of the neurological symptoms.In the strong suspicion of a paraneoplastic syndrome, considering the recent weight loss and anemia, abdominal ultrasound and 18F-FDG PET were performed; the latter showed uptake at the level of the distal esophagus, cardia and precarinal lymph nodes and lower paraesophageal.EGDS revealed the presence of an ulcerated lesion of cardia which underwent biopsy, suggestive for adenocarcinoma of the gastroesophageal junction.Chest-abdomen CT highlighted a locally advanced disease with loco-regional lymph node involvement; at the thoracic level, bilateral ground-glass areas compatible with interstitial disease associated with DM were described.The patient underwent neoadjuvant radiotherapy, after packaging a protective jejunostomy and setting up a personalized nutritional plan to prevent protein-calorie malnutrition before the surgical procedure. At the same time, maintenance infusions of immunoglobulins and oral corticosteroids continued (deltacortene 1mg/kg with slow tapering). Four months later, he underwent robotic partial esophagectomy.At the pre-surgical outpatient check-ups, a substantial dermatological improvement was recorded, without, however, a consensual improvement in the muscular framework, with persistence of weakness and need for assistive devices for mobilization.
Conclusion: It has been demonstrated that dermatomyositis, even in its amyopathic variant, can be associated with different types of tumors such as tumors of the genitourinary tract, breast, nasopharyngeal district, gastro-intestinal tract (especially the colorectal cancer and metastatic gastric cancer), prostate and lung. Despite the limited data in the literature, an association between amyopathic dermatomyositis and locally advanced gastroesophageal junction cancer has been demonstrated in our experience.



132. AORTA FLOATING THROMBUS IN A PATIENT WITH HIGH LEVELS OF FACTOR VIII. A CASE REPORT

Montalbano G., Parisi F., Patane F., Abbate M., Di Paola D., Stancanelli B. Dipartimento di Medicina Sperimenatale e Clinica, Università degli studi di Catania

Background: The aorta floating thrombus is a rare pathological condition with potentially fatal embolic complications. Main risk factors could be aorta atherosclerosis and clotting disorders. Coronavirus infection (SARS-CoV-2) could represent a potential causal factor, by inducing hypercoagulable state. We report a case of floating thrombus in the aortic arch and proximal tract of descending aorta in a patient with recent SARS-CoV-2 infection with acute embolic complications and high level of factorVIII.
Case report: A 60-year-old female was admitted to the hospital due to multiple fractures. In pathological history was reported a colon neoplasia surgically treated in august 2021 and pulmonary embolism in September 2021, treated with DOAC. Moreover, patient presented several obesity (BMI > 35). Initially was treated conservatively for SARS CoV2 infection and after resolution she was planned to undergo surgical treatment of fractures. During hospitalization the patient begins to complain intense abdominal pain. AngioCT that showed presence of floating thrombus in aortic arch and proximal tract of descending aorta, pulmonary embolism, spleen thrombosis, left renal artery partial thrombosis and left common femoral vein thrombosis, extending to the ipsilateral common iliac vein. A laboratory workup for autoimmune and clotting disorders (antiphospholipid antibodies, homocystinemia, protein C, protein S and antithrombin III deficiency, Factor V) did not detect significant alterations, except for factor VIII, that doubled the normal value. A genetic test for thrombophilia-related genes was carried out and the patient was found to be heterozygous for polymorphism for 5,10-methylentetrahydrofolate reductase (MTHFR) C677T, A1298C. Due to the high risk of complications anticoagulant therapy was performed initially by intravenous unfractionated heparin 25000UI iv (aPTT 80-100) for 7 days, followed by 10000 UI of fractioned heparin twice daily. After three weeks a chest abdominal CT scan was performed, showing the thrombus disappearance.
Conclusions: Floating thrombus in aorta is a condition associated with a high risk of embolization and mortality. Prognosis of this event can be predicted on the basis of clinical characteristics. In fact, floating thrombi in the ascending aorta and in the aortic arch most frequently embolizes at the level of central nervous system, while thrombi in descending tract embolizes more frequently in the peripheric arterial tree. Another important feature is whether the thrombus is sessile or pedunculated. The pedunculated thrombus has a higher risk of peripheral embolism. In the literature a strong association between SARS CoV2 infection and thromboembolism was reported, and some studies demonstrated a close link between SARS CoV2 infection and high levels of factor VIII, the mechanism whereby arterial thrombosis occurs. In the diagnostic work-up, CT angiography is the method of choice because it allows the correct visualization of the thrombus and its characteristics, such as dimension and morphology (sessile or pedunculated), with high sensitivity and specificity. In our case, we performed a first angioCT at the time of symptoms onset, and after 3 weeks, to monitor the response to anticoagulant therapy. Differential diagnostics should include laboratory work-up for antithrombin III deficiency, protein C, protein S, factor V Leiden, factor VIII, homocysteine levels, autoimmunity and genetic test for thrombophilia-related genes. Currently, there are no guidelines regarding therapy. On the basis of literature, there are two possible approaches, surgical or with anticoagulant therapy. Which of the two approaches is more correct depends on the characteristics of the thrombus, such as localization, size, morphology (sessile or pedunculated). We report a successful outcome successfully with anticoagulant therapy.

133. MANAGEMENT OF A PLURIPATHOLOGICAL PATIENT

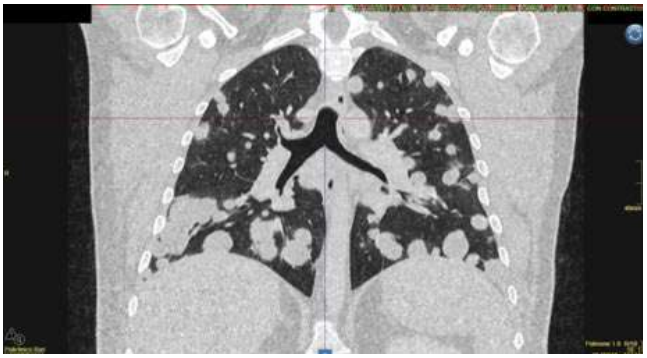
Ricciardi R.M., Cipollone A., D'Ardes D., Cipollone F., Guagnano M.T.
Institute of Clinica Medica, Department of Medicine and Science of Aging, "G. d'Annunzio" University of Chieti-Pescara

Keywords: subarachnoid hemorrhage, pulmonary embolism, rectal bleeding, mediastinitis, osteomyelitis
Abstract: a pluripathological patient goes to the ED for traumatic brain injury (TBI) with subarachnoid hemorrhage (SAH). During hospitalization he develops pulmonary embolism with respiratory failure, rectal bleeding with anemia, infection of the wound (recent cardiac surgery), causing sepsis and death
It is difficult to define a causal link and a timeline of the events
Introduction: 71 yo male with recent myocardial revascularization + left carotid TEA, malnutrition, bed rest syndrome, T2DM, PAD, carotid vasculopathy, total dependence on ADL
Case report: Accesses ED due to confusion following a fall
Brain CT: hygroma in the bilateral fronto-temporo-parietal area; SAH in the right parieto-temporal, left parietal and temporo-occipital sites; tentorial blood level (absence of neurosurgical indications). TBI is the most common cause of SAH. Traumatic SAH (tSAH) is a common finding in moderate and severe TBI (33–60% of patients) [1]. According to Bullock *et al*., management of tSAH should be targeted at avoiding secondary injury, [2] maintainance of cerebral perfusion pressure and oxygenation [3] The management in a specialized neurosurgical center is bladder catheterization, early enteral nutrition, analgesia, antiemetic and antiepileptic medication [4].
According to neurologist, EEG was performed (negative for epileptiform graphelements) and re-evaluation with brain CT at 24, 48 and 72h (superimposable).
There is severe acute respiratory failure: on blood tests GB 17580, PCT 5.92, D-dimer 15.47.
He performs CT angio-thorax: right lower lobe subsegmental embolism; ground glass areas with phlogistic alterations. VMK (FiO2 31%) and Piperacillin+Tazobactam are set up.
In order to study the etiology of pulmonary embolism (PE), he performs venous Echocolor Doppler: absence of thrombi.
Anticoagulation is fundamental for PE theraphy. Massive PE may warrant thrombolytic therapy. One controversy is the benefit or otherwise of treating subsegmental PE [5]. Due to the clinical compromission, the introduction of anticoagulant is postponed.
A clinical deterioration follows due to rectal bleeding with anemia. The patient performes blood transfusions, abdominal CT (negative) and rectosigmoidoscopy: rectal ulcer, treated with metal hemoclips and adrenaline infiltration.
In thoracic scans of abdominal CT, an abscess in the retrosternal site is noted
Cardiac surgeons and vulnologists perform debridement and stitch removal and infectivologists added Vancomycin
Chest CT is performed: the abscess extends into the anterior mediastinum in the retrosternal area (hyperdense material and air bubbles)
Sternal diastasis and retrosternal abscess with a fistula cornfirm severe mediastinitis, osteomyelitic lesions and retrosternal purulent abscess
Treatment of post-operative mediastinitis include targeted antibiotic, early wound exploration, debridement, sternal reconstruction/closure. Vac therapy can be a single line therapy or a bridge to sternal reconstruction/closure [5]
Given the clinical severity, sternal reconstruction is not an option, so the vulnologist recommends only Vac therapy.
Post-sternotomy mediastinitis is associated with high mortality and morbidity. Despite improvements in surgeons and perioperative care, mediastinitis remains a devastating post-operative complication [5]
The patient undergoes a clinical deterioration up to the exitus
Discussion: The patient's scenario is complex with the continuous appearance of new acute events
Despite the involvement of specialists (neurologists, infectivologist, cardiac surgeons, vulnologists) the patient is died
Conclusion: Severe mediastinitis with sternal osteomyelitis was the most serious and irreversible event
It is difficult to reconstruct the exact timeline of events and causal relationships. Despite the intervention of specialists and the optimized therapies, we were unable to avoid the death of the patient.
It is still difficult to treat patients suffering from multiple acute events that lead to an exponential worsening of the clinical scenario.
References:
1. Griswold DP, Fernandez L, Rubiano AM Traumatic Subarachnoid Hemorrhage: A Scoping Review. J Neurotrauma 2022 Jan;39(1-2):35-48. doi: 10.1089/neu.2021.0007 Epub 2021 Apr 22 PMID: 33637023 PMCID: PMC8785754
2. Bullock MR, Hovda DA Introduction to traumatic brain injury Chapter 322. In: Richard Winn H, editor. Textbook: Youmans Neurological Surgery. 6 th ed. Saunders p3267
3. Dinsmore J. Traumatic brain injury: An evidence-based review of management. Oxford Journals BJA. Contin Educ Anaesth Crit Care Pain - 2013;13(issue 6) p. 189-95
4. Chung P, Khan F. Traumatic brain injury (TBI): Overview of diagnosis and treatment. J Neurol Neurophysiol 2013;5:182
5. Doherty S. Pulmonary embolism An update. Aust Fam Physician 2017 Nov;46(11):816-820 PMID: 29101916
6. Goh SSC Post-sternotomy mediastinitis in the modern era. J Card Surg. 2017 Sep;32(9):556-566 doi: 10.1111/jocs.13189 Epub 2017 Aug 22 PMID: 28833518

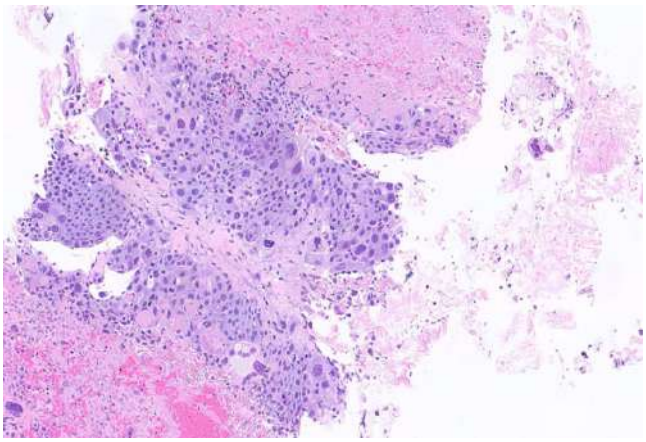
134. AN ADULT-ONSET CASE OF AGGRESSIVE EXTRAGONADAL CHORIOCARCINOMA IN A BARIATRIC PATIENT

Giuliano AFM., Luglio C., De Luca A., Giampetruzzi A., Belfiore A., Di Ciaula A., Portincasa P.
Clinica Medica "A. Murri", University of Bari "Aldo Moro" Medical School, Bari, Italy

Extra-gonadal germ cell tumours (EGGCTs) are rare neoplasms defined by unclear pathogenesis, challenges in differential diagnosis and a highly aggressive behaviour with poor life expectancy. Among them is choriocarcinoma, a non-seminomatous cancer commonly developing in the testes, but often found in other midline locations such as the anterior mediastinum and retroperitoneum, as well as solid organs such as the brain, thymus, bladder, kidneys, and prostate. A 40-year-old male was admitted to the emergency room for fatigue and dyspnoea. Symptoms had started two weeks previous as mild neck pain and tension, unaffected by kinesiotherapy. Medical history was unremarkable, save for asymptomatic COVID-19 and a sleeve gastrectomy intervention in 2022 for class III obesity. The patient had undergone a chest X-ray four months prior and a full abdominal ultrasound two weeks prior, with no notable findings. Initial radiological assessment showed diffuse nodulations in both lungs; a subsequent full body CT scan revealed enlarged regional lymph nodes, as well as a large (8,5 x 7 cm), irregular mass of the upper anterior mediastinum, partially colliquated, with bone loss of the sternum, involvement of right pectoral muscles and ab extrinsic compression of the superior vena cava. Metastatic lesions were detected in the liver and spleen as well. Laboratory tests revealed elevated serum levels of β-human chorionic gonadotropin (180.486 mUI/ml – range < 2 mUI/ml) and β2-microglobulin (2.06 mg/L – range 0.9-2 mg/L), liver transferases, bilirubin, and C-reactive protein. Thyroid hormones and α-fetoprotein concentrations were within normal ranges. A testes ultrasound yielded no abnormal results.



A biopsy was performed on the lesion, with histologic characteristics identifying it as a highly aggressive choriocarcinoma (CKCAM 5.2+, CK7+, Ki-67+ proliferating fraction: 85%). The patient died two weeks later due to thromboembolic complications.



Extragonadal choriocarcinoma in males is a rare occurrence, representing less than 5% of all germ cell neoplasms. Its aetiology is still unclear, either from abnormal migration of germ cells during embryogenesis, secondary locations of spontaneously regressed gonadal tumours or ex-novo differentiation of a stem cell in malignant epithelium. It is often diagnosed in children and adolescents, with age and brain metastases being independent prognostic factor. In this case, the neoplasm was diagnosed in an adult subject, and was characterized by an unclear primary site (lungs or thymus), no involvement of the gonads or thyroid as well as a remarkably accelerated development, rapidly leading to patient exitus. Furthermore, the patient's history of bariatric surgery might be relevant, as cancer risk is reported to be lowered in post-op subjects: a persistent, low-grade activation of inflammation pathways and immune functions might have played a role in disease progression.

135. A PARTICULAR CASE OF ITP: A PARANEOPLASTIC SYNDROME

Farina A., Scialabba E., Marcacci M., Sirotti V., Pietrangelo A.
Internal Medicine and Centre for Hemochromatosis, University Hospital of Modena, University of Modena and Reggio Emilia (Italy)

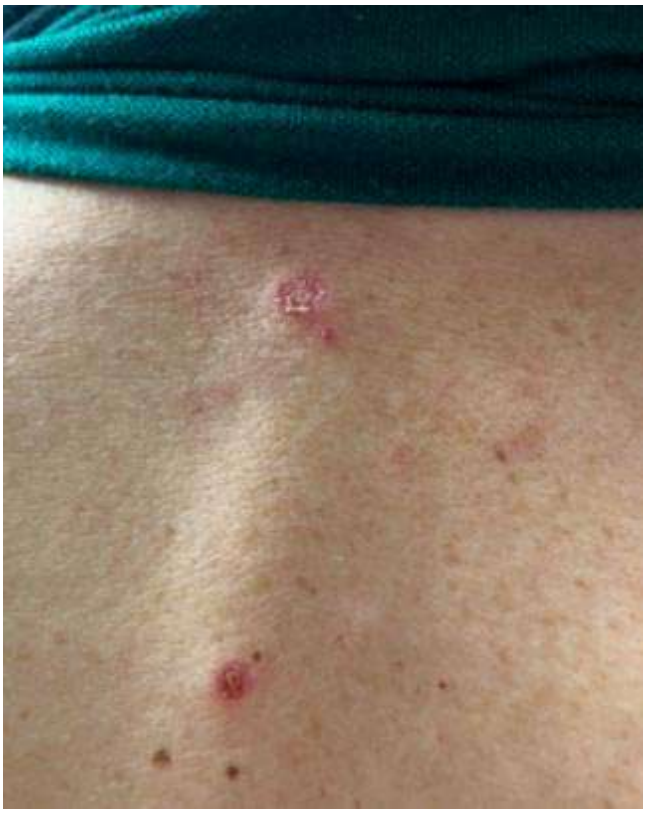
A 72-years old man was admitted to our Internal Medicine Unit for severe anemia and low platelets count at the biochemical examinations (Hb 6,3 g/dl, MCV 98.4 fl, PLTs 18.000/mmc), associated with cough and fever.
Medical history included: multiple clipped brain aneurysms, minor stroke and previous SARS-COV2 infection, active smoker. Apart from PPI-Therapy and antibiotics for suspected bronchitis, he didn't take medications.
The physical examination was completely normal without petechiae or cardiopulmonary findings.
Because of melena, blood transfusion and an urgent gastroscopy were performed, showing a Dieulafoy ulcer, treated with clipping and adrenalin injection.
Considering the severe thrombocytopenia (<20.000/mmc), associated with hemorrhagic complication, a platelet transfusion was carried out.
Since prior to the hospitalization the platelets count was normal (to the lower limit), an acute or sub-acute cause was more likely, while genetic or a chronic low-production conditions were excluded.
An abdominal ultrasound examination was performed, which ruled out the presence of portal hypertension and of splenomegaly.
The absence of other cell lines abnormalities and of hemolysis markers made a diagnosis of leukaemia, lymphoma, PNH or deficiency disorders unlikely.
To identify the etiology of thrombocytopenia, screening for viral (HIV, HBV, HCV) and bacterial agents (QUANTIFERON and Helicobacter pylori fecal antigen) was performed, with negative results. Furthermore no chemicals or drugs exposition was identified.
By new diagnosed pneumonia, an antibiotic therapy with levofloxacin was begun, the state of thrombocytopenia remained constant after the recovery.
The result of the peripheral blood smear showed no anisopoikilocytosis, high reticulocytes values, preserved WBC and no sign of dysplasia or microangiopathy. The antiplatelets antibodies were negative, while the autoimmunity screening reported a mild positivity for anti-SSA, considered as non-specific.
A DIC-score of 2 ruled out a disseminated intravascular coagulation state.
Under the assumption of immune thrombocytopenia (ITP), the patient was treated with an intravenous immune globulin (IVIG), with benefit.
However, a few days later, the patient was re-hospitalized in our unit because of a relapse of thrombocytopenia during a Lancefieldella parvula-induced sepsis.
Because of the finding of anterior segments of the left lung opacification, a CT-scan was performed, showing a complete obstructive atelectasis by a rounded solid formation.
The final diagnosis was invasive poorly differentiated squamous cell lung carcinoma (T3, N2 LV1, R0).
During the sepsis, the patient underwent an urgent pneumectomy. The collegial discussion opted for an adjuvant chemotherapy with carboplatin/vinorelbine, followed by a maintenance therapy with atezolizumab. During the postoperative course, multiple radiological scans and a final histological exam excluded a tumour recurrence.
The ITP may be an expression of paraneoplastic syndrome, associated with hematological malignancies1. This condition is rarer in solid tumors, and among them, more often in patients with lung and breast cancer2. Half of the cases of thrombocytopenia are synchronous with tumoral disease2.
Actually specific antibodies are not available for the identification of this condition1, therefore ITP is usually a diagnosis of exclusion.
The recommended therapy for ITP is corticosteroids, which in most cases are effective2. IVIG and platelet transfusion also represent a first line treatment.
Monitoring the platelet count and the risk of bleeding is always mandatory3.
The second-line therapy consists of Rituximab, TPO-RA and splenectomy3.
Specifically, in paraneoplastic ITP, after tumor removal, platelets count rarely reaches cut-off values for normality and in very rare cases these values are maintained over time2.
In our patient hemoglobin levels were steadily in range, apart from a single episode of epistaxis during therapy with DOAC (introduced for atrial fibrillation arisen after pneumectomy). In this case three cycles of immunoglobulin were started, but corticosteroids were not administered because of concomitant sepsis.
At first, we registered a good response to the above-mentioned therapy, but after a few days a relapse of low platelet count occurred. On the other hand, after surgery and during the oncological follow-up (at present lasting 5 months), platelets have always been within the cut-off and stably over 200*109/l. During the last medical examination, the patient was in a good performance status. Since the fact that thrombocytopenia occurred simultaneously with the first symptoms of cancer and that we are recognising a prolonged remission of ITP after cancer healing, we could conclude that it was a case of paraneoplastic autoimmune thrombocytopenia.
References: 1Maverakis E. The Etiology of Paraneoplastic Autoimmunity. Clinic Rev Allerg Immunol, 2012, 42:135–144.2Krauth MT. Paraneoplastic autoimmune thrombocytopenia in solid tumors. Critical Reviews in Oncology/Hematology, 2012, 81.1: 75-81.3Neunert C. American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Advances, 2019, 3.23: 3829-3866.

136. CONSTITUTIONAL SYMPTOMS AND DIFFUSE LYMPHADENOPATHY: A CASE OF A SYSTEMIC LUPUS ERYTHEMATOSUS WITH HEMATOLOGICAL MANIFESTATIONS AT ONSET

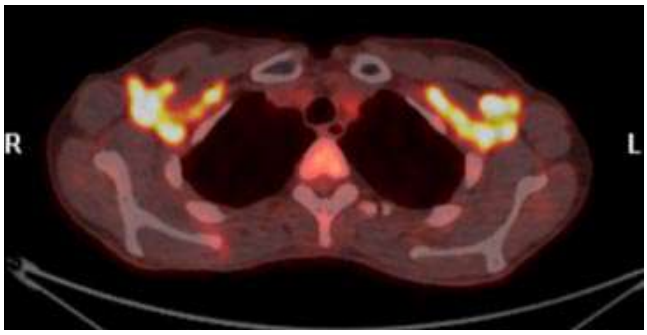
Guerrini S.[1], Nesi I.[1], Campana S.[1], Nardi C.[1], Ferrentino F.[1], Ascione G.[1], Tozzetti C.[2], Torri M[2], Rostagno C.[1]
[1]Divisions of Internal Medicine 3, Azienda Ospedaliero-Universitaria Careggi, University of Florence, Italy.; [2]Divisions of Internal Medicine 3, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy.

Background: Systemic lupus erythematosus (SLE) is a chronic autoimmune multisystemic disease with an unknown etiology. Though lymphadenopathy is not considered a clinical criterion in the 2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria, some reports have suggested that it can be the first manifestation of SLE.
Case report: In April 2023 a 39-year-old woman arrives in DEA after 3 weeks of fever, asthenia and cough; already completed antibiotic cycle at home. Previous antibiotic cycle in December 2022 for left basal pneumonia. In her medical history organ autoimmunity with thyroiditis (elevated anti-TG levels), DM type 1 and alopecia; about a year earlier she had developed arthralgia which led to the diagnosis of undifferentiated connective tissue disease with positivity of ANA 1/1280 and anti-ENA (antiSmD, U1RNP and weak positivity for RN70); also positivity of anti-dsDNA FEIA but negativity in CLIFT. She had neither proteinuria nor complement consumption. Patient was treated with intermediate dose steroids with partial benefit, so she started hydroxychloroquine. On physical examination, she had multiple oral aphthae

affecting hard and soft palate; laterocervical, axillary and inguinal bilateral lymphadenopathies (LAP) (>2cm) of rubbery consistency, painful to palpation; some red, disk shaped, raised and desquamated skin lesions (Picture 1: nummular eczema). She also referred mild arthralgia of small joints. No other clinical manifestations of systemic autoimmunity (not Raynaud's sign, dry mouth/eyes or photosensitivity).



Blood tests revealed lymphopenia (CD4+ <200/mmc) and hyporegenerative microcytic anemia (Hb 7g/dL, reticulocytes 0.3%) in the absence of iron/vitamin deficiency or hemolysis. Elevated levels of ERS (120mm/h) and Beta2 microglobulin (6.6pg/mL). In the protein electrophoresis there were not monoclonal components and serum immunoglobulins were normal. Urinalysis revealed subnephrotic proteinuria (1.57g/24h). Autoimmune diseases workup confirmed anti-dsDNA positivity and showed new evidence of complement consumption (C3 0.33g/L, C4 0.02g/L).
During hospitalization the patient presented with persistent fever and evening pruritus poorly responsive to antihistamine therapy.
We started broad-spectrum empirical antibiotic therapy and, considering lymphopenia, prophylaxis with Bactrim.
In consideration of constitutional conditions associated with multiple LAP, the differential diagnosis were infectious, neoplastic and autoimmune diseases although the suspected diagnosis was lymphoma.
Infectious causes were ruled out (blood and urine culture were sterile; serologies for HIV, HBV, HCV, EBV, CMV, HSV, VZV, treponema, toxoplasma, HHV6, HHV8, parvovirus B19, leishmania, Coxsackievirus were negative).
The patient underwent a neck and abdominopelvic CT which revealed bilateral, supra- and subdiaphragmatic lymphadenopathy, moderate splenomegaly (14.8cm), minimal pericardial effusion and a thin layer of fluid in the pelvic region; in the end, it was found left upper lobe pneumonia. The 18F-FDG PET investigation confirmed the suspicion of lymphoproliferative disease (picture 2). Hematologists considered the case suggestive of lymphoproliferative neoplasia (Hodgkin's lymphoma?) or Castelman disease.

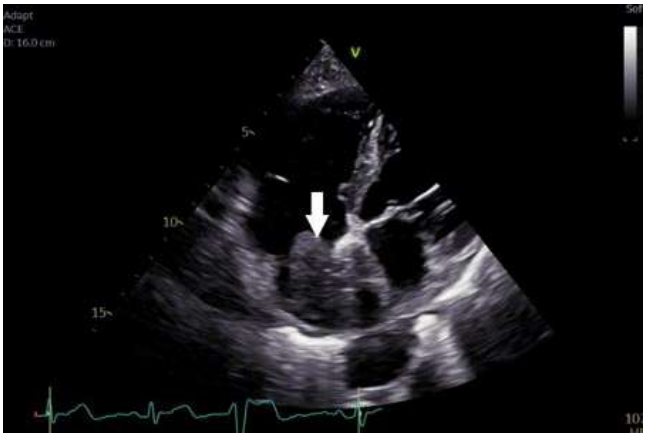


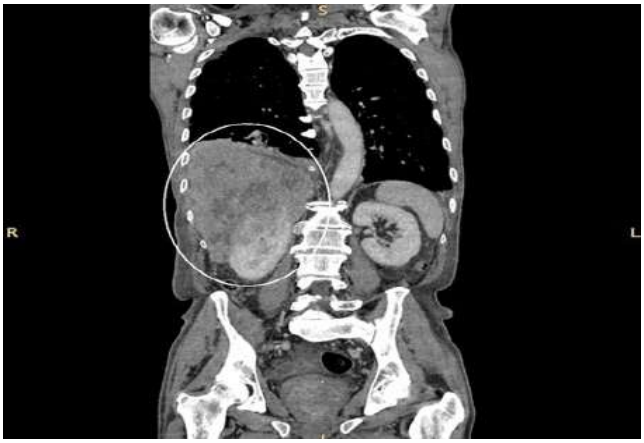
Finally bone marrow biopsy with marrow blood immunophenotype were performed, which showed depression of B lymphoid hematopoietic progenitors and normal myeloid hematopoietic progenitors; no abnormal cells.
The left laterocervical lymph node excisional biopsy showed histopathological features that were suggestive of SLE or Kikuchi disease (necrotizing lymphadenitis without neoplastic cells). A hematologic malignancy was excluded. Haematological manifestations in SLE are frequently observed; the most described in the literature are hemolytic anemia, immune thrombocytopenia and leukopenia; also lymphadenopathy is described. The lupus lymph nodes are usually soft, painless and located mainly in the cervical, axillary, and inguinal regions. The lymph node enlargement can be due to a flare phase of the SLE (lupus lymphadenitis). Insteas, manifestation with constitutional symptoms and diffuse lymphadenopathy is rare. There are no specific laboratory tests to distinguish between a lymphoid malignancy and reactive LAP due to infection or SLE disease flare and, sometimes, biopsy is required for differential diagnosis. However, lupus lymphadenitis responds quickly to glucocorticoids, decreasing in size. It was started therapy with high dose steroids (methylprednisolone 1mg/kg/day), with improvement of symptoms and disappearance of fever. Topical cortisone applied to skin lesions had benefit. Symptoms did not reappear during steroid decalage.
Conclusion: Lymphadenopathy is a common but non specific feature of many diseases, representing a large spectrum of etiologies such as infectious, inflammatory diseases or malignancies. This case shows that SLE can present as generalized LAP with constitutional symptoms, and hence it should be considered in the differential diagnosis.

137. NEW-ONSET ATRIAL FIBRILLATION DUE TO AN INTRA-ATRIAL METASTATIC MASS IN B CELL LYMPHOMA: A CASE REPORT AND LITERATURE REVIEW

Purificati C.[1], Di Vincenzo A.[1], Pavone S.[1], Portinari C.[1], Chinello E.[2], Landa G.[2], Maisano D.[3], Rossato M.[1], Vettor R.[1]
[1]Dipartimento di Medicina Interna 3, Azienda Ospedale-Università di Padova; [2]Azienda Ospedale-Università di Padova; [3]Università di Padova
Abstract
The diagnosis of an intracardiac mass is mainly incidental during an imaging study. Intracardiac masses visualized by echocardiography are commonly clots, vegetations, and calcifications. Cardiac tumors represent a rare cause of intracardiac masses and can be distinguished into primary and secondary tumors. Primary cardiac tumors are mainly benign (84.6%), and the most frequent type is represented by myxoma (68.7% of the benign primary cardiac tumors); 9.7% of the primary cardiac tumors are malignant and cardiac sarcoma represents about 90% of them. Clinical manifestations depend on the nature of the mass, the size, the localization, and the infiltration degree of the cardiac tissue, but most cases are asymptomatic or with nonspecific symptoms. Rhythm disturbances may be observed, but the occurrence of atrial fibrillation secondary to intra-cardiac neoplastic masses is not well defined. Here, we report a case of a 79-year-old man hospitalized for palpitations and chest pain. A diagnosis of new-onset atrial fibrillation was rapidly made and, during instrumental evaluations, an intra-cardiac mass in the right atrial was detected in transthoracic echocardiography. A subsequent contrast-enhanced transesophageal echocardiography confirmed the presence of the lesion also suggesting its neoplastic nature (Fig. 1). Then the patient underwent a thoracoabdominal CT scan revealing a mass in the upper right abdominal quadrant, involving the liver but extending to the adrenal and the inferior cava (Fig. 2, 3). The biopsy of the abdominal mass concluded for a diffuse large B-cell lymphoma.
Metastatic cardiac tumors usually arise from lung, breast, renal cancer, and lymphoma. Tumor spread can occur to the pericardium, myocardium, and endocardium, and less frequently to the intracavitary regions. Dissemination

can take place by blood, lymphatic system, transvenous, or by contiguity with adjacent tissues. The cardiac manifestations are usually represented by dyspnea, chest pain, and heart failure. Arrhythmias and electrical disturbance can also occur in the case of the cardiac conduction system, invasion despite the precise prevalence is not defined. In the literature are reported few cases of new-onset atrial fibrillation due to intracardiac masses, mostly arising from peripheral tumors such as colon and thyroid cancer. Atrial fibrillation in the context of metastatic intracardiac hematological malignancies is rarely described. Recently has been described a case of a man with non-Hodgkin lymphoma invading the right atrium but in which the atrial fibrillation was asymptomatic and the diagnosis incidental on the EKG. In our case, the atrial fibrillation represented the first manifestation of the lymphoma, leading to rapid detection of the neoplasm. Non-Hodgkin lymphomas are characterized by a poor prognosis due to the absence of symptoms leading to a diagnostic delay. The occurrence of the arrhythmia helped to an early diagnosis of the disease and a prompt treatment of the patient.





138. ACUTE HEPATITIS AND LYMPHADENOPATHIES: WHAT'S UNDERNEATH?

Leoni S.[1], Motta I.[2], Tiraboschi S.[3], Cassinerio E.[4], Scaramellini N.[2], Fracanzani AL.[5]
[1]S.C. Medicina ad Indirizzo Metabolico, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; Università degli Studi di Milano, Milan, Italy; [2]S.S. Centro emoglobinopatie e disordini ereditari del metabolismo e del sistema immunitario, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; Dipartimento di Scienze Cliniche e di Comunità, Università degli Studi di Milano, Milan, Italy; [3]S.C. Medicina ad Indirizzo Metabolico, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [4]S.S. Centro emoglobinopatie e disordini ereditari del metabolismo e del sistema immunitario, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [5]S.C. Medicina ad Indirizzo Metabolico, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Milan, Italy

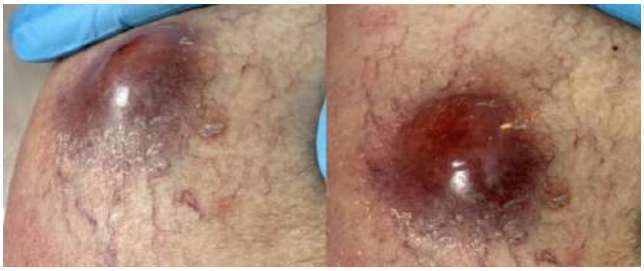
In April 2023, a 28y.o. man with transfusion-dependent thalassemia (TDT), originally from Egypt but settled in Milan and regularly followed at "Centro emoglobinopatie e disordini ereditari del metabolismo e del sistema immunitario" of Fondazione IRCCS Ca' Granda Ospedale Policlinico, presented to a local Emergency Department (ED) complaining of fever, dysuria, and mild hematuria for two days and acute, intense abdominal pain in left side radiating to the homolateral groin. In his past medical history, he had splenectomy and arterial hypertension.
In the suspect of left renal colic, an abdominal Computed Tomography (CT) with contrast medium was performed, showing normal kidneys with a small ureteral stone (later spontaneously expelled), hepatomegaly with mild congestion of the walls of the gall bladder, and **multiple abdominal lymphadenopathies** of unknown significance. In addition, lab tests showed acute hepatitis (AST 829 IU/L, ALT 642 IU/L). Considering the possible urinary tract infection and the susceptibility of thalassemic patients to Yersinia enterocolitica (a siderophage microorganism) infections, iv ciprofloxacin was initiated. The following day the patient was referred to our ED, where lab tests were repeated, showing a worsening of the values. Therefore, he was admitted to our Internal Medicine ward with the diagnosis of acute hepatitis.
At admission, antibiotic therapy was continued, and abundant iv hydration and fitomenadione (vitamin K) were introduced. A detailed history was collected: he reported only the above-mentioned symptoms the days before the admission and denied diarrhea, nausea, or vomiting. He also denied unusual food or medication but reported a recent 10-day travel to Egypt.
To rule out the main causes of acute hepatitis, the following tests were performed: **both IgM and IgG for HAV were positive with high titer.**
A rapid progression to acute liver failure was noticed that required an urgent evaluation by the liver transplant team. Meanwhile, a peritonitic abdomen was observed, and acute cholecystitis was diagnosed through an abdominal ultrasound (US). Antibiotic therapy was then upgraded to piperacillin/tazobactam, with a slight improvement in the clinical picture.
Following the onset of mild respiratory failure and to study better the hepatic and cholecystic inflammation and the described lymphadenopathies, a CT scan of the abdomen and thorax was requested, showing edema of the cholecystic walls with ascites, dimensional stability of the abdominal lymphadenopathies, bilateral basal pleural effusion with calcific micronodulations in both lungs and reactive bilateral axillary lymph nodes.
Supposing such a diffuse lymph node involvement to be unlikely related to acute hepatitis, differential diagnosis of lymphadenopathies included:
Subsequently, a slow and gradual improvement of this complex and severe clinical condition, probably due to the concomitant presence of two infectious agents was observed. Laboratory tests (LDH, indices of inflammation and liver tests) returned to normal, beta-2-microglobulin levels (4.1 mg/L) and the ultrasound gallbladder picture also improved.
Despite the negative culture, however, the patient had started ciprofloxacin therapy early and before the culture examination, abdominal adenitis due to Yersinia enterocolitica seems a likely diagnosis that will be confirmed by resolution of the adenopathic picture with CT scan and PET already scheduled.

139. LOOKS CAN BE DECEIVING: WHAT WE HAVE LEARNED FROM NEUROLOGICAL AND CUTANEOUS SIGNS

Profili N.I., Meloni P., Boschi M., Frau A., Farche T., Manetti M.
Clinica Medica, Dipartimento di Medicina, AOU Sassari

A case report of a 75 years old woman with history of chronic cerebral vasculopathy, hypereosinophilic syndrome (2010) with consequent Churg-Strauss syndrome diagnosis, complicated by neuropathy, in treatment with Methotrexate, Sars-Cov-2 infection (April 2022), complicated by Tachymyopathy with cardiac insufficiency, Atrial fibrillation in therapy with New Oral Anticoagulants, osteoporosis with multiple vertebral collapses, right lung pneumonia (December 2022). The patient showed a deterioration of her general conditions accompanied by gait disease, apathy and drowsiness, which changed during different phases of Methotrexate treatment, increasing immediately after the consumption of the drug end decreasing the days before the consumption of the next dose. For these symptoms the patient was brought to the Emergency Room where she underwent to Laboratory tests, showing neutrophilic leukocitosis and a light increase of flogosis indexes, and a Magnetic Resonance with contrast agent study, which showed a multifocal leukoencephalopathy of likely viral or toxic etiology. In light of this report she had been hospitalized in our unit for diagnostic testings and treatments, with a suspected viral leukoencephalopathy diagnosis. Neurological examination was substantially negative excepted for the presence of postural and action tremor in the superior limbs, and ideational apraxia. During the physical examination a cutaneous red-violet nodular lesion,

with clear vascularization, associated to a subcutaneous plaque on the left hip emerged. The remaining physical examination was in range of normality. Suspecting a pharmacological adverse reaction Methotrexate's treatment was precautionary suspended. Neurological and infetivological evaluations were requested, which, in suspect of a progressive multifocal infectious leukoencephalopathy, gave indication to the execution of rachicentesis and specific exams on liquor: Cytochemical (showed an increase of glucose and proteins values); cultural test for common germs and Koch's Bacillus; research of neurotropic agents (EBV- DNA, JCV- DNA, HHV8-DNA); meningitidis- encefalitis bacterial panel (Escherichia Coli K1, haemophilus influenzae, listeria monocytogenes, neisseria meningitidis, streptococcus agalactiae, streptococcus pneumoniae), viral panel (CMV- HSV1- HSV2- HHV6- Human parechovirus- VZV- Adenovirus-DNA), yeast panel (cryptococcus neoformans/gattii). Also aerobic and anaerobic hemocultures as well as Leishmania and zoonosis PCR analysis were done. All of the liquoral and haematological tests were negative, so the infectious leukoencephalopathy diagnosis was excluded. Since the patient underwent a clinical-neurological improvement after the suspension of Methotrexate, she was diagnosed with a drug-induced Leukoencephalopaty. In spite of the neurological symptoms improvement, the clinical development was complicated by the appearance of other two cutaneous hypervascularized lesions in the left knee and thigh, similar to the one seen in the left hip during the first physical examination. The first suspect was of infectious etiology, but on the other side, the ultrasound showed an hypervascolarized lesion with high vascular resistance index, typical of neoplastic lesions. For this a punch biopsy was done in the hip left lesion, while an ultrasound-guided biopsy was done in the bigger and most vascularized lesion of the left knee and thigh. Bioptic samples were sent to microbiology for cultural common germs, fungi, tuberculous mycobacteria and non tuberculous mycobacteria tests, all of these resulted negative. Both samples were sent also to anatomical pathology unit for histopathological and cytopathological studies, which showed, in all the specimens, a diffuse large B cell Non-Hodgkin lymphoma appearance. After this diagnosis the Hematology unit was entrusted with the care of the patient. In conclusion it is important to underline the relevance of drugs-adverse reactions which can appear during the assumption of the therapy, in this case of Methotrexate, and so the need of clinical conditions supervision at short time intervals, even though the drug did not cause adverse reaction in the first period of treatment. Nonetheless it is to highlight the importance of knowing and studying even the most rare and atypical disease's manifestations, since these do not always contextually appear with the most common signs, resulting in difficult diagnosis. Through all of these, even if the infectious pathologies are the first to be suspected, it is important to not underestimate the neoplastic risk in patients which undergo immunosuppressive treatments as a long-term therapy.



COVID-19

140. RADIOLOGICAL MONITORING OF INTERSTITIAL PNEUMONIA FROM COVID-19. THE "SCOVID-19" STUDY

Landi R., Ciammaichella M.M., Di Castri C. , Marzano M.A., Ulissi A., Pignata D. , De Paola G., Fanfarillo F.
UOC Medicina Interna ad Alta Intensità di Cure, Dipartimento di Medicina Interna, A.O. S. Giovanni-Addolorata, Roma

Introduction: The authors present their experimental CXR scoring system applied to 15 hospitalized patients with COVID-19 pneumonia to quantify and monitor the severity and progression of this new infectious disease. Therefore, the Authors present the study "SCOVID-19", an acrostic deriving from "SCore radiOgraphic in pneumocoVID-19". A retrospective analysis was performed on 15 patients aged between 64 and 82 years enrolled with COVID-19 interstitial pneumonia, hospitalized in the period January 2022-December 2022. A comparative analysis was performed for continuous variables with test parametric "t" of Student to verify if there is a significant relationship between the values of the Radiological Score at T0 and at T15. Purpose of the work: The "SCOVID-19" study has the following objectives: 1) verify any existing relationships between the Radiological Score values at T0 and at T15 in the 15 patients enrolled during the period January 2022 - December 2022; 2) verify the statistical significance found by applying the parametric test "t" of Student as a comparative analysis test for continuous variables to establish whether the relationships of the variables considered are due to chance. Material and method: The test then calculates the relative value (VR) of the index t to be associated with the difference found according to the following formula: t = (M1-M2) / √DS12 /N1 + DS22 /N2. Therefore, the value of "t" obtained with Degrees of Freedom (GL)=14 is 7.23. Being the Critical Value (VC) of "t" 4.073 with GL=14 for p=0.001, the Relative Value (VR) of "t" equal to 7.23 expresses an absolute positive agreement of the covariation between the values of the two variables considered (Radiological Score T0 and T15) which is highly significant with p<0.001. Analysis of results: Student's "t" test applied to 15 patients shows a highly significant correlation (p<0.001) of the two variables examined (Radiological Score values at T0 and T15) and, therefore, cannot be attributed to chance. In fact, the value of "t" obtained is 7.23 and the VC (critical value) of "t" for p=0.001 is 4.073 with GL=15 Discussion: The "SCOVID-19" study demonstrated a statistically significant correlation between the CRX score values obtained at T0 and those obtained at T15. Conclusions: The "SCOVID-19" study demonstrated how the radiological score obtained at T0 and T15 in patients with interstitial pneumonia from COVID-19 due to its high statistical significance can be an excellent tool in the clinical-radiological monitoring of patients with pneumonia interstitial from COVID-19

141. PREVALENCE OF PULMONARY EMBOLISM IN 40 PATIENTS WITH SARS-COV-2 INTERSTITIAL PNEUMONIA. THE "PREMOVID" STUDY

Pignata D., Ciammaichella M.M., Fanfarillo F., Di Castri C., Ulissi A., Marzano M.A., De Paola G.
UOC Medicina Interna ad Asta Intensità di Cure, Dipartimento di Medicina Interna, A.O S. Giovanni-Addolorata, Roma

Background and Purpose of the Work: The authors evaluated the prevalence of pulmonary embolism in 40 patients with SARS-CoV2 related interstitial pneumonia,of which 20 with areas of "ground glass" and 20 with areas of "crazy paving".The "PREMOVID" study,acrostic deriving from "PREvalence of pulmonary embolism in cOVID-19",carried out a retrospective analysis on 40 patients enrolled with COVID-19 pneumonia.The diagnosis was confirmed by the radiological picture (CT-CXR),by the positivity of the molecular swab for SARS-CoV-2.The "PREMOVID" study has the following objectives:1) verify any relationships existing between the cases of pulmonary embolism in patients with areas of "ground glass" and areas of "crazy paving"; 2) verify the statistical significance found by applying the Chi-square.
Material and Methods: The Chi-square test was used to compare the frequency of PE in the two groups of 20 patients with "ground glass" and "crazy paving" areas.
Analysis of Results: In total there are 8 (20%) cases of PE. In the Crazy group the percentage of patients with PE is significantly higher than in the Ground Glass group.
Discussion: The "PREMOVID" study demonstrated a statistically significant correlation between the number of cases of pulmonary embolism detected and the "crazy paving" tomographic variant. It is hypothesized that the "crazy paving" variant may be the trigger of pulmonary embolism.
Conclusions: In conclusion, the "PREMOVID" study demonstrated that the prevalence of pulmonary embolism is significantly associated with the "crazy paving" variant of SARS-CoV2 pneumonia.

142. ROLE OF BIOMARKERS IN 15 PATIENTS WITH SARS-COV2 INTERSTITIAL PNEUMONIA. "BIOCOV" STUDY

De Angelis M., Ciammaichella M.M., De Paola G., Fanfarillo F., Pignata D., Ulissi A., Marzano M.A., Di Castri C.
UOC Medicina Interna ad Alta Intensità di Cura, Dipartimento di Medicina Interna, A.O. S. Giovanni-Addolorata, Roma

Introduction: The Authors examined 15 patients with interstitial pneumonia

from SARS-CoV2 in the "BIOCOVID" study, an acrostic deriving from COVid BIOmarkers". This is a retrospective analysis on 15 patients aged between 64 and 82 years enrolled in the period January 2022-December 2022. All patients underwent, among other tests, Lymphocyte Count, PCR, LDH, Dimer, Procalcitonin at day 0 (T0, time of admission) and at day 15 (T15, control during hospitalization), whose values are shown in Table 0. Therefore, a database with Microsoft Access© called "BIOCOVID" was created. The database contained the following fields: 1) patient number, 2) T0-T15 lymphocyte count, 3) T0-T15 Dimer values, 4) T0-T15 LDH values, 5) T0-T15 Procalcitonin values, 6) T0 PCR values -T15. SCOPE OF WORK: 1) Analyze the values of Lymphocytes, CRP, LDH, Procalcitonin, Dimer at T0 and T15 2) Verify if there is a statistically significant correlation between the 5 variables considered
Material and Methods: Parameters were reported as median value and interquartile range (Q1-Q3). The Wilcoxon test for paired data was used to evaluate the variation of parameters over time. The median change (q1-q3) was reported for each parameter. Pearson's linear correlation between parameter change was calculated. All analyzes were done with Stata 16.1, a p value <0.05 was considered statistically significant.
Results Analysis: Data from 15 subjects at T0 and after 15 days were analysed. There was a significant variation between the two times for all parameters. The median variation (ie at least 50% had this variation or greater) is 3 for Lymphocytes, 3.4 for Dimer. 16.7 for PCR, 12 for Procalcitonin and 4997 for LDH. The variation is positive (the values increase) for Lymphocytes and negative for all the other parameters
Discussion: The BIOCOV study shows that there is a statistically significant correlation between the variations at T0 (day of hospitalization) and at T15 (15th day of hospitalization) of the lymphocyte count, Dimer values, LDH values, Procalcitonin values, PCR values, expression of the bioclinical improvement of the patients.
Conclusions: The Authors presented the "BIOCOV" study which highlighted the statistically significant variations at T0 and T15 of the values of CRP, LDH, Procalcitonin, Lymphocytes, Dimer, expression of the bioclinical improvement of patients enrolled with COVID-19

143. BIOCHEMICAL-RADIOLOGICAL CORRELATION IN 15 COVID-19 PATIENTS: THE "MISCOVID" STUDY

Ciannamea C., Ciammaichella M.M., Di Castri C., De Paola G., Fanfarillo F. , Pignata D. , Ulissi A., Marzano M.A.
UOC Medicina Interna ad Alta Intensità di Cure, Dipartimento di Medicina Interna, A.O. S Giovanni-Addolorata, Roma

Introduction: The authors present their experimental CXR scoring system applied to 15 hospitalized patients with COVID-19 pneumonia to quantify and monitor the severity and progression of this new infectious disease. Therefore, the Authors present the study "MISCOVID", an acrostic deriving from "correlation between biochemical parameters and radiographic SCore in pneumocoVID-19". A retrospective analysis was performed on 15 patients aged between 64 and 82 years enrolled with COVID-19 interstitial pneumonia, hospitalized between September 2022 and December 2022. All patients underwent, among other tests, CRX on day 0 (T0, time of hospitalization) and on day 15 (T15, control during hospitalization), whose values are shown in Table 0, by sampling for Dimer, Lymphocytes, PCR, Procalcitonin, LDH on day 0 (T0, time of admission) and on day 15 (T15, control during hospitalization).
Material and Methods: Parameters were reported as median value and interquartile range (Q1-Q3). The Wilcoxon test for paired data was used to evaluate the variation of the score and of the bioclinical parameters between T0 and T15. The median change (q1-q3) was reported. The Pearson linear correlation between the parameter variation and the radiographic score variation and the score value at T0 was calculated. All analyzes were done with Stata 16.1, a p value <0.05 was considered statistically significant.
Analysis of the Results: The radiographic values at T0 vary between 6 and 14 with a median value (q1-q3) of 11 (9-13). At 15 days the values vary between 2 and 8 with a median value (q1-q3) of 4 (3-5) (p<0.001). The median change (q1-q3) is -6 (-8; -5) all subjects have a reduction in score.
Discussion: The "MISCOVID" study demonstrated a statistically significant correlation between the CRX score values obtained at T0 and those obtained at T15 and between the CRX score values at T0 with the Dimer and Lymphocyte values at T0. There is no statistically significant correlation between the values of the bioclinical parameters at T0 and T15. This scoring system is designed solely for a semi-quantitative assessment of the severity and progression of lung involvement in hospitalized patients with COVID-19. It is quite simple and can be easily replicated in other clinical settings. It is obvious that this method requires a continuous comparison with the clinical data of the patients and that its validity depends mainly on the quality of the CXR images and on the experience of the observers. The "MISCOVID" study documents how an improvement in the Radiographic Score obtained in the first 15 days of illness corresponds to a statistically significant reduction in Lymphocytes and a statistically significant increase in Dimer at T0. On the contrary, at T15 the improvement obtained with the Radiographic Score does not correspond to a significant variation of the biochemical parameters considered.
Conclusions: In conclusion, the "MISCOVID" study demonstrated how the radiological score obtained at T0 and T15 in patients with interstitial pneumonia from COVID-19 due to its high statistical significance can be an excellent tool in the clinical-radiological monitoring of patients with COVID-19 interstitial pneumonia. This score correlates in a statistically significant way with the values of Dimer and Lymphocytes at T0 but does not correlate with the values of the biochemical parameters at T15.

144. EPICARDIAL ADIPOSE TISSUE IN COVID PATIENTS: "EATID" STUDY

Cozzolino D., Ciammaichella M.M., Marzano M.A., Ulissi A., Pignata D., Fanfarillo F., De Paola G., Di Castri C.
UOC Medicina Interna ad Alta Intensità di Cure, Dipartimento di Medicina Interna, A.O. S. Giovanni-Addolorata, Roma

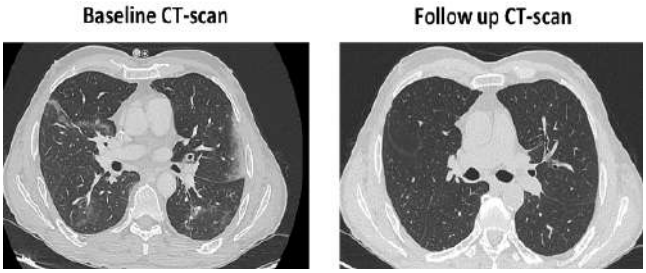
Introduction: The Authors presented the study "EATID", an acrostic deriving from "Epicardial Adipose Tissue in patients with covID-19". This is a retrospective analysis that enrolled 41 patients with Sars-CoV2 interstitial pneumonia hospitalized at the Unit of Internal Medicine in Urgency and Sub-Intensive Care in the period September 2022 - December 2022. All patients underwent HR CT Chest for the iconographic diagnosis confirmed by the positivity of the nasopharyngeal swab. HR chest CT scans were compared with those of 36 patients hospitalized in the same period with a diagnosis of no-COVID pneumonia based on iconographic findings, nasopharyngeal swabs, serology. In comparison, the Authors qualitatively evaluated the volumetric increase of epicardial adipose tissue possibly present in patients with COVID pneumonia and no-COVID at the time of hospitalization.
PURPOSE OF THE WORK: The "EATID" study has the following objectives: 1) verify any relationships between the qualitative volumetric increase of EAT in patients with COVID interstitial pneumonia and no COVID in patients enrolled during the quarter September 2022 - December 2022; 2) verify the statistical significance found by applying the ODDS RATIO to establish whether the relationships of the variables considered are due to chance.
Material and Methods: The odds ratio is 8.73. The Chi-Square is 3.86. The CI (95%) was 1.4-54.4. The p-value is 0.0494 with p<0.05.
Analysis of Results: The "EATID" study shows that the qualitative analysis of the volumetric increase in EAT has a statistically significant correlation in patients with COVID-related interstitial pneumonia compared to patients with no-COVID pneumonia (p<0.05) as demonstrated in Table 1 of 2x2 contingency with Odds ratio of 8.73, Chi-Square 3.86, p-value of 0.0494. In the 8 patients with qualitative volumetric increase in EAT, a check with CT Chest HR was performed which showed a volumetric normalization of EAT at 30 days in relation to the inflammatory regression of the clinical picture.
Discussion: With coronavirus disease 2019 (COVID-19), cardiac injury has attracted attention owing to the risk of mortality and morbidity. The incidence of cardiac injury associated with COVID-19 reaches 7–31%, depending on the patient population and definitions. Possible mechanisms of the cardiac injury are angiotensin-converting enzyme 2- (ACE2) mediated direct myocardial injury, hypoxia-induced injury, microvascular damage, and systemic inflammatory response syndrome. There are cases of acute myocarditis as a cardiac manifestation in COVID-19. Among the possible mechanisms of cardiac injury, ACE2-mediated direct myocardial injury and inflammation are specifically suggested as significant contributors to myocarditis associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. Epicardial adipose tissue (EAT) , located between the myocardium and visceral pericardium, is a unique fat depot with multifaceted features such as local and systemic physiological effects. This tissue has the highest rates of lipogenesis and fatty acid metabolism among the visceral fat depots and displays metabolic, thermogenic, and mechanical properties. Malavazos et al. raised an interesting issue regarding EAT and the incidence of myocardial injury in COVID-19. Since they share similar risk factors and mechanisms related to cardiac inflammation, it can be assumed that patients with cardiac injury would have a higher level of EAT. The SARS-CoV-2 infection is triggered by binding of the spike protein of the virus to

ACE2, which is highly expressed in the heart and lungs. From a previous experiment, ACE2 and the inflammatory cytokines tumor necrosis factor-(TNF) a and interleukin-6 (IL-6) have been demonstrated to be expressed at higher levels in EAT in heart explants removed from obese patients. The cascade of inflammatory factors such as TNF-a and IL-6 has been linked to a diminished inotropic effect and decreased cardiac function, resulting in aggravation of hypoxia and a systemic myocardial inflammatory response. The higher prevalence of cardiac injury associated with COVID-19 in these specific populations may be linked to EAT acting as a 'fuel for cardiac inflammation'. We need to speculate on the role of EAT in the cardiac manifestations related to COVID-19 with utilization of big data from the accumulating global experience.
Conclusions: The Authors presented the "EATID" study which enrolled 41 patients with interstitial pneumonia from COVID-19. In 8 of these, a qualitative increase in EAT was found, an expression of the inflammatory involvement of the EAT itself during COVID-19 infection.

145. RELAPSING COVID-19 IN IMMUNOCOMPROMISED PATIENT

Mattei M., Rosellini V., Ciurleo G., Iozzia M., Martini L., Giovagnini E., Coppola A., Puma A., Abatangelo S., Simonetti V., Rossi Ferrini G., Hennig M.C., Morettini A.
Medicina Interna 2- AOU Careggi

Introduction: We present the case of B.M., a 63-year-old male patient, who admitted to the emergency department on 28/04/2022 for the onset of serotin fever during last 10 days (peaks over 38°C) in absence of signs or symptoms referable to organ localisation. In the E.R. he carried out routine blood tests, with normocytic and normochromic anaemia (Hb 10.6 g/dL with MCV 86.9 fL), slight PCR movement (68 mg/L) and lymphocytopenia. SARS-COV2 PCR test was performed and negative. On chest X-ray there was mantle thickening in the left middle and basal field and shaded thickening also in the right middle field. Background: In 2014 diagnosis of follicular non-Hodgkin's lymphoma initially underwent followup only. In 2019, due to disease progression, he underwent 6-month chemotherapy cycle, with complete remission, confirmed at PET and CT scan in 2020. At the time of hospital admission, the patient was on maintenance therapy with Obinutuzumab, administered every 2 months. The last administration was the previous month. Patient also has a history of a pauci-symptomatic Sars Cov 2 infection in December 2021, at that time he underwent monoclonal antibody administration. Differential diagnosis: During hospitalisation in our division, first-level infectivological investigations showed no microbial cause that could explain the fever: blood cultures taken before starting antibiotic therapy from both PORTH and peripheral vein were negative, as were urinalysis and urine culture. Beta D-glucan, PCR and viral serologies were also all negative (CMV, EBV, HBV, HCV, HIV, Parvovirus19), as were serologies for Brucella, Toxoplasma, Rickettsiae, Borrelia, Bartonella, Coxiella, Legionella, Mycoplasma pn, Clamydia pn. The occult infectious focus was sought by performing contrast-enhanced CT scan of chest and abdomen, revealing a predominantly mantle lung interstitiopathy. We therefore performed a bronchoscopy with bronchoalveolar lavage and sample collection for microbiological (extended immunocompromised panel) and immunophenotypic investigations. From this investigation we did not identify a microbial agent or a picture suggestive of recurrence of lymphomatous disease in lungs. The BAL, however, detected the persistence of the SARS-COV2 genome. In the meantime, due to the persistence of fever peaks above 38°C despite broad-spectrum antibiotic therapy, we decided to discontinue this therapy to perform an antibiotic wash-out and perform other microbial examinations, which were however negative. We also decided to remove his PORTH, as a possible infectious source, without cessation of daily fever. We also investigated the possibility of endocarditis, even with negative blood cultures, although serology for atypical bacteria was negative, by performing both thoracic and transesophageal echocolordoppler, which showed no suspicious valve vegetations. In order to rule out the hypothesis of a recurrence of haematological disease despite monoclonal therapy, we finally decided to perform a PET-FDG scan, which showed signs of strong uptake only in lung parenchyma. Immunophenotype on peripheral blood and BAL was normal, as were LDH and Beta 2 microglobulin.
Conclusions: Giving the inconclusive FUO work up and pulmonary findings typical of covid-related pneumonia, with persistence of the SARS-COV2 genome at alveolar level, we hypothesised a 'COVID-19 relaying' disease, explaining persistent fever. Therefore the patient started therapy with the antiviral drug Nirmatrelvir/Ritonavir (monoclonal antibodies not indicated as they had already been administered during the primary infection and IgG spike was detectable as protective). Within 24 hours after the first administration, fever completely ended, allowing hospital discharge. The patient underwent a follow-up chest CT scan one month later, which showed complete resolution of the pulmonary findings (Figure 1)



146. POST COVID-19 TRASVERSE MIELITIS

Mattei M., Rosellini V., Ciurleo G., Iozzia M., Martini L., Giovagnini E., Coppola A., Puma A., Abatangelo S., Simonetti V., Rossi Ferrini G., Hennig M.C., Morettini M.
Medicina Interna 2- AOU Careggi

Introduction: We present the case of Mrs. G.F., a 75 year old female that presented to the ER in February 2022 with sudden onset of muscle weakness first in the left leg and subsequently in the right leg. The patient had been experiencing lower back pain for a week. SarS-CoV2 test resulted positive. At first medical contact in the ER the patient presented muscle weakness in the left leg and could not lift it up while lying in bed, reflexes were normal and the upper extremities resulted within normal range of motion. Blood exams showed neutrophilic leukocytosis, negative PCR. A head CT and an angiogram of the aorta were performed, both resulted negative. The patient was admitted and progressively developed paraparesis with complete anesthesia of the left leg with positive Babinski, hypoestesia of the right leg, total absence of reflexes on both lower extremities, acute urinary retention and faecal incontinence. The threshold of sensitivity was localized at the intermammary line. Upper extremities and cranial nerves always remained intact and free of any kind of neurological deficit. Background: hypertension, type II diabetes mellitus, 2016 right hemicolectomy due to colorectal cancer with negative follow up; at the time of presentation the patient was not vaccinated for SarS-CoV2. Differential diagnosis: an MRI showed a hyperintensive signal in the anterior medullary cone from D2-D5 and D9-D11, without contrast enhancement. The findings resulted compatible with myelitic lesions and were less likely to be of ischemic nature. Ten days later another MRI was performed and it showed worsening of the lesions with a total extension from C7 to D11. Brain MRI showed no encephalic involvement. A lumbar puncture was performed, showing clear liquor with mild protein count (0,52g/dL) and no other identifiable cells, no germs were identified (including SarS-CoV2, borrelia, treponema p., mycoplasma pneumoniae), antibodies like anti-AQP4 and anti-MOG and tumor markers all resulted negative. The hypothesis of paraneoplastic myelitis was ruled out by total body CT-scan, colonoscopy, mammography and pap-smear. We ruled out vitamin deficiency, autoimmune disease and markers for sarcoidosis resulted negative.
Conclusions: considering the fact that all radiological, endoscopic, histological and biochemical exams resulted negative, we believe that this patient is affected by post-infective transverse myelitis caused by SarS-CoV2. The patient was then treated with high-dose steroid therapy without clinical benefit. She was also evaluated by Neurologists who recommended treatment with plasmapheresis, which was also carried out without benefit. The patient subsequently underwent neuromotor rehabilitation without recovery of function but also without further progression.

147. PREVALENCE AND CLINICAL - ELECTROCARDIOGRAPHIC CHARACTERISTICS OF SYNCOPAL EPISODES IN A POPULATION OF HOSPITALISED PATIENTS WITH COVID-19

Guerrieri E.[1], Santini S.[1], Giuliani L.[1], DiBlasi I.[1], Pierdomenico G.[1], Venanzi F.[1], Zaccone V.[2], Nitti C.[2], Falsetti L.[2], Moroncini G.[3]
[1]Emergency Medicine Residency Program, Università Politecnica delle Marche, Ancona; [2]Internal and Subintensive Medicine Department, Azienda Ospedaliero-Universitaria delle Marche, Ancona; [3]Clinica Medica, Università Politecnica delle Marche, Ancona

Introduction: Syncope is not a characteristic feature of COVID-19 representing an infrequent cause of the admission of these patients. We evaluated the prevalence and clinical and electrocardiographic characteristics of patients with syncope and COVID-19 in a population of patients admitted to the sub-intensive care medical area.
Methods: During the period 04/01/2020-04/01/2023 we assessed, in COVID-19 patients: (i) prevalence of syncope; (ii) clinical manifestations (iii) ECG characteristics; (iv) discharge diagnosis.
Results: 296 patients with COVID-19 were considered, 11 admitted for syncope (age:74.8 +/- 10.6 years, male gender:54%). On ECG, 9 presented sinus rhythm, 2 atrial fibrillation; none showed alterations in PR, QRS or ST-T. Considering the relationship with infection, 8 subjects were admitted for syncope with subsequent diagnosis of COVID-19 in the P.H. (group I), 3 were admitted from the P.H. for syncope after discharge for COVID-19 (group II). In group I we observed: 1 tachyarrhythmic syncope, 3 bradyarrhythmic and 4 reflex syncope. Of these, 6 presented with interstitial pneumonia with respiratory failure, 2 with asymptomatic positivity. The patients in group II all presented with reflex syncope: in this group we observed two cases of lobar pulmonary embolism.
Conclusion: Syncope has a low prevalence in patients with COVID-19. Arrhythmic syncopes occurred in patients with active COVID-19, probably due to the known myocardial involvement of SARS-CoV-2 in the acute phase. In syncopes occurring after negativity, the cause was reflex with associated findings of pulmonary embolism, suggesting a different nature of syncopal episodes in relation to COVID-19 disease status.

148. GLOBAL CARDIOVASCULAR RISK, COVID-19 SEVERITY AND POST-COVID-19 SYMPTOMS: A CLINICAL STUDY

Santini S.[1], Guerrieri E.[1], Giuliani L.[1], Venanzi F.[1], Nesci A.[2], Giupponi B.[3], Tosato M.[4], Landi F. [5], Gasbarrini A.[6], Santoro L.[2], Santoliquido A.[2], Falsetti L.[7], Nobili L.[7], Zaccone V.[7], Moroncini G.[8]
[1]Emergency Medicine Residency Program, Università Politecnica delle Marche, Ancona; [2]Department of Cardiovascular and Thoracic Sciences, Gemelli IRCCS; [3]Department of Emergency Medicine, Gemelli IRCCS; [4]Geriatrics Department, Gemelli IRCCS; ; [5]Geriatrics Department, Gemelli IRCCS; [6]Department of Medical and Surgical Sciences, Gemelli IRCCS; [7]Internal and Subintensive Medicine Department, Azienda Ospedaliero-Universitaria delle Marche, Ancona; [8]Clinica Medica, Università Politecnica delle Marche, Ancona

Introduction: Post-COVID-19 is defined by signs and symptoms that develop after COVID-19, last for more than 12 weeks and are not explained by an alternative diagnosis. The present study aimed to assess whether the cardiovascular risk (CVR) of patients with COVID-19 correlates with symptoms and changes in respiratory function parameters in post-COVID-19. The association between CVR and severity of acute disease was also considered.
Methods: During the period 21/04/21-01/09/21 we enrolled 1782 consecutive patients with COVID-19. These subjects were divided into (i) 4 levels based on severity of COVID-19 (home care; hospitalised/no oxygen therapy; hospitalised/oxygen therapy; hospitalised/NIV-ICU), (ii) 3 levels based on CVR calculated according to ESC-SCORE tables. All subjects underwent a 3-month follow-up considering: arterial blood gas analysis, post-COVID-19 symptoms and spirometric data (P/F and DLCO).
Results: In post-COVID-19 patients, high CVR was associated with (i) increased risk of hospitalisation for COVID-19 ($p < 0.0001$), (ii) higher prevalence of severe clinical manifestations and ICU admission ($p<0.0001$), (iii) development of post-COVID-19: fever ($p=0.002$), exhaustion/asthenia/fatigue ($p=0.002$), diarrhoea ($p=0.0001$), headache ($p=0.0001$), anosmia ($p=0.0001$), dysgeusia ($p=0.002$), red eyes ($p=0, 007$), decreased vision ($p=0.017$), dizziness ($p=0.035$), arthralgia/arthritis ($p=0.025$), chest pain ($p=0.003$) and persistent dyspnoea ($p=0.049$). We observed a significant correlation between a decrease in P/F and DLCO and an elevated CVR ($p<0.001$).
Conclusions: we found a statistically significant association between CVR, severity of COVID-19 and post-COVID-19 symptoms and signs at 3 months after the end of acute disease.

149. MARKERS OF LIVER FUNCTION AS POTENTIAL PROGNOSTIC INDICATORS OF SARS-COV-2 INFECTION: A RETROSPECTIVE ANALYSIS DURING THE FIRST AND SECOND WAVES OF COVID-19 PANDEMIC

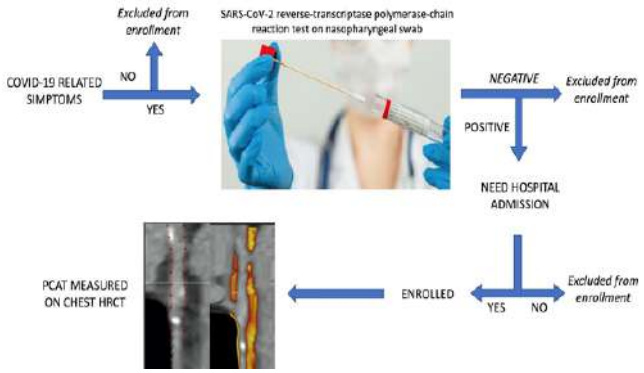
Esposito L.[1], Guarino M.[1], Perna B.[1], Ciccarone A.[1], Cesaro A. E.[1], Manza F.[1], Pretula A.[1], Costanzini A.[1], Maritati M.[2], Forini E.[3], Spampinato M.D.[1], De Giorgio R.[1], Contini C.[2]
[1]Dipartimento di Medicina Traslazionale, Università di Ferrara; [2]Dipartimento di Infettivologia, Università di Ferrara; [3]Dipartimento di Statistica, Azienda Ospedaliero-Universitaria S. Anna di Cona

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic is known to cause a predominant respiratory disease, although extrapulmonary manifestations can also occur. One of the targets of Coronavirus disease 2019 (COVID-19) is the hepatobiliary system. The present study aims to describe the correlation between the increase of liver damage markers (i.e. alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin [TB]) and COVID-19 outcomes (i.e., in-hospital mortality [IHM] and intensive care unit [ICU] transfer).
Methods: All patients with confirmed SARS-CoV-2 infection admitted to the Infectious Disease Unit of the St. Anna University-Hospital of Ferrara from March 2020 to October 2021 were retrospectively included in this single-centre study. ALT, AST and TB levels were tested in all patients and IHM or ICU transfer were considered as main outcomes. Comorbidities were assessed using Charlson Comorbidity Index.
Results: A total of 106 patients were retrieved. No hepatic marker was able to predict IHM, whereas all of them negatively predicted ICU transfer (ALT: OR 1.005, 95%CI 1.001-1.009, p= 0.011; AST: OR 1.018, 95%CI 1.006-1.030, p= 0.003; TB: OR 1.329, 95%CI 1.025-1.724, p= 0.032). Age was the only parameter significantly related to mortality.
Conclusions: The present study, by correlating liver damage markers with COVID-19 outcome, showed that an increase of ALT, AST and TB predicted patients' severity, although not mortality.

150. CORONARY INFLAMMATION ON CHEST COMPUTED TOMOGRAPHY AND COVID-19 MORTALITY

Tuttolomondo D., Gaibazzi N.
Cardiology Unit, Azienda Ospedaliero-Universitaria di Parma, Via Antonio Gramsci 14, 43126 Parma, Italy.

Background: The main factors associated with coronavirus disease-19 (COVID-19) mortality are age, comorbidities, pattern of inflammatory response and SARS-CoV-2 lineage involved in infection. However, the clinical course of the disease is extremely heterogeneous, and reliable biomarkers predicting adverse prognosis are lacking.
Purpose: Our aim was to elucidate the prognostic role of a novel marker of coronary artery disease inflammation, peri-coronary adipose tissue attenuation (PCAT), available from high-resolution chest computed tomography (HRCT), in COVID-19 patients with severe disease requiring hospitalization.
Materials and Methods: Two distinct groups of patients, admitted to Parma University Hospital in Italy with COVID-19 in March 2020 and March 2021 (first and third wave peaks of COVID-19 pandemic in Italy, with prevalence of wild-type and B.1.1.7 SARS-CoV-2 lineage, respectively) were retrospectively enrolled. The primary endpoint was in-hospital mortality. Demographic, clinical, laboratory, HRCT data and coronary artery HRCT features (coronary calcium score and PCAT attenuation) were collected to establish which variables were associated with mortality.
Results: Among the 769 patients enrolled, 555 (72%) were discharged alive and 214 (28%) died. In multivariable logistic regression analysis age ($p<0.001$), number of chronic illnesses ($p<0.001$), smoking habit ($p=0.006$), P/F ratio ($p=0.001$), platelet count ($p=0.002$), blood creatinine ($p<0.001$), non-invasive mechanical ventilation ($p<0.001$), HRCT visual score ($p<0.001$) and PCAT ($p<0.001$), but not the calcium score, were independently associated with in-hospital mortality.
Conclusion: Coronary inflammation, measured with PCAT on HRCT, was independently associated with higher mortality in patients with severe COVID-19, while the pre-existent coronary atherosclerotic burden was not associated with adverse outcomes after adjustment for covariates.



151. CLINICAL SIGNIFICANCE OF SERUM AUTOANTIBODIES IN HOSPITALIZED PATIENTS WITH COVID-19

Tonutti A.[1], Ceribelli A.[1], Motta F.[1], Isailovic N.[2], Guidelli G.M.[2], Lanza E.[3], Lleo A.[4], Selmi C.[1], De Santis M.[1]
[1]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy; Rheumatology and Clinical Immunology, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy; [2]Rheumatology and Clinical Immunology, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy; [3]Department of Radiology, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy; [4]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy; Hepatology and Internal Medicine, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy

Background. A high prevalence of antinuclear antibodies (ANA; 57%) was previously reported by our group in a cohort of hospitalized patients with non-severe COVID-19 pneumonia (i.e. not requiring intensive care support) and no past medical history of autoimmune diseases. We also described a high prevalence of antibodies directed towards specific antigens (SAA – i.e. NXP2, RIG-1, MDA5, and Scl70; 20%), which are classically associated to connective tissue diseases, such as inflammatory myositis and systemic sclerosis. We first described the presence of antibodies against RIG-1, a cytoplasmic protein with antiviral function closely related to MDA5, involved in mitochondrial activation and type I interferon signature. The clinical significance of such findings has not been elucidated yet.
Objective. We aimed at assessing the correlation of serum autoantibodies (ANA, SAA, and antimitochondrial antibodies (AMA) to E2/E3 pyruvate dehydrogenase complex) with clinical, radiological, and laboratory features in hospitalized patients with COVID-19.
Methods. A retrospective analysis was performed. Sera from 35 patients with COVID-19 and no history of autoimmune diseases were tested for autoantibodies (indirect immunofluorescence on HEp-2 cells, immunoprecipitation, and ELISA), as previously described. Clinical data were collected from electronic clinical records. Lung involvement at admission was evaluated with quantitative CT scan: ground-glass, consolidative, hyperinflated, and normal areas were quantified; *extensive lung involvement* was defined if the sum of ground-glass and consolidation areas was > 20% of the lung.
Results:

	ANA+ (20)	ANA– (15)	p
P/F at admission [median (IQR)]	300 (244-324)	309 (276-380)	.17
Need for O2-therapy (%)	18 (90)	10 (67)	.09
Max FiO2 [median (IQR)]	35 (28-35)	28 (21-31)	.02
Need for CPAP (%)	2 (10)	0 (0)	.21
CPK (IU/L) [median (IQR)]	81 (38-170)	134 (92-203)	.07
TnI (pg/mL) [median (IQR)]	8.3 (5.0-10.3)	12.1 (6.3-34.4)	.03
BNP (ng/L) [median (IQR)]	41 (22-59)	148 (77-456)	.00
D-dimer [median (IQR)]	292 (209-699)	312 (282-1330)	.27
Pulmonary embolism (%)	1 (5)	4 (27)	.07

Figure 1. Respiratory failure tended to be more prevalent among ANA-positive subjects (90% vs. 67%, *p*=0.09), and ANA positivity was significantly associated to more oxygen requirement (median FiO2 35% vs. 28%; *p*=0.02) compared to seronegative patients. Two patients required CPAP support, and both were ANA positive. Cardiovascular events and other comorbidities were similar in the ANA-positive and ANA-negative groups, but ANA positivity was associated to lower levels of serum myocardial enzymes (BNP, troponin I) at admission, and to a lower frequency of pulmonary embolism.

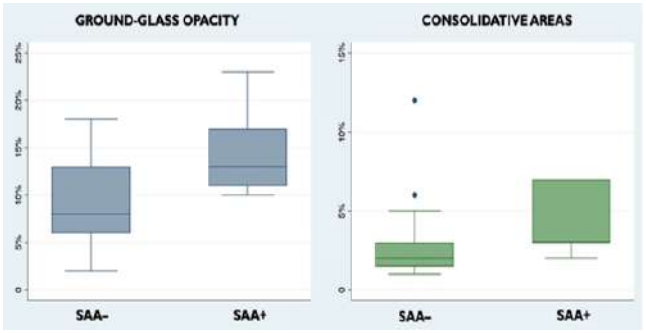


Figure 2. Patients testing positive for SAA were more frequently women (71% vs 40%, *p*=0.04) and had a larger extension of ground-glass opacities (13% vs 8%, *p*=0.02) and consolidative areas (3% vs 2%, *p*=0.02) (**Figure 2**); *extensive lung involvement* was more frequent in patients with SAA positivity (43% *vs* 12%, *p*=0.04).
AMA were positive in 31% of the patients and tended to be associated to a shorter duration of hospitalization (median 9 (IQR 7-19) vs. 17 (IQR 9-25) days in AMA-negative patients, *p*=0.088), lower levels of C-reactive protein (4.8 vs 8.0 mg/dL, *p*=0.07) and procalcitonin (0.07 vs 0.14 ng/mL, *p*=0.06). No patient ever manifested clinical symptoms or signs attributable to connective tissue diseases or other autoimmune conditions.
Conclusions. Serum autoantibodies are common in patients with non-severe COVID-19 pneumonia requiring hospitalization and no history of autoimmune diseases. ANA positivity is associated to more severe respiratory insufficiency but could be protective from the occurrence of thromboembolic events. The presence of SAA is associated to extensive pneumonia at CT scan, with more ground-glass and consolidative areas compared to seronegative subjects. AMA positivity seems to be associated to a less severe inflammation in COVID-19 and, thus, briefer length of hospitalization. The mechanistic and clinical significance of these observations, along with the interplay between mitochondrial function and type I IFN signature, remains to be investigated.

152. IS THERE A RELATIONSHIP BETWEEN FATIGUE AND SERUM 25-HYDROXY-VITAMIN D IN SARS-COV-2 PATIENTS? A MATCHED CASE-CONTROL STUDY

Fulco E.[1], Delvecchio A.[1], Del Toro R.[2], Palmese F.[1], Domenicali M.[1]
[1]Department of Medical and Surgical Sciences, Alma Mater Studiorum – University of Bologna; [2]Department of Primary Health Care, Internal Medicine Unit Addressed to Frailty and Aging, Santa Maria delle Croci Hospital, AUSL Romagna, 48121 Ravenna

Background: Fatigue can be defined as severe exhaustion that is not alleviated by rest. Fatigue is a common symptom among patients with COVID-19, and vitamin D may play a role in its pathogenesis, due to the inhibition of the activity of some atrophy-related transcription factors as well as the expression of myostatin, a factor that is associated with muscle weakening. We performed a matched case-control study to test the association of fatigue with serum 25-hydroxy-vitamin D (25-OH-D) in hospitalized patients with COVID-19. We also evaluated the association of fatigue with handgrip strength (HGS).
Methods: We enrolled 65 patients; the "cases" were 35 hospitalized patients with COVID-19 and "controls" were 30 hospitalized patients without COVID-19. Coarsened exact matching was performed by sex (same) and age (1 year) and was considered by all descriptive and inferential analyses. Fatigue was assessed using the fatigue assessment scale (FAS), which is a 10-item questionnaire that evaluates symptoms of chronic fatigue and handgrip strength (HGS) using an electronic dynamometer. Median regression was used to evaluate all associations of interest.
Results: Fatigue was inversely associated with serum 25-OH-D and HGS expressed as both kg and SDS, independently of SARS-CoV-2 status. Importantly, we found no evidence that COVID-19 modifies or independently contributes to the relationship between fatigue, serum 25-OH-D and handgrip strength expressed both in kg and SDS.
Conclusions: in this matched case-control study of hospitalized patients with

and without COVID-19, we detected an inverse association between fatigue, vitamin D, and muscle strength which was independent of SARS-CoV-2 status. Matched cross-sectional and cohort studies are needed to confirm such an association and better investigate whether it is causal in nature.

153. REAL-WORLD ANALYSIS OF IMPACT OF THERAPY WITH CORTICOSTEROIDS AND ANTIBIOTICS OF COVID-19 OUTPATIENTS IN SARDINIA

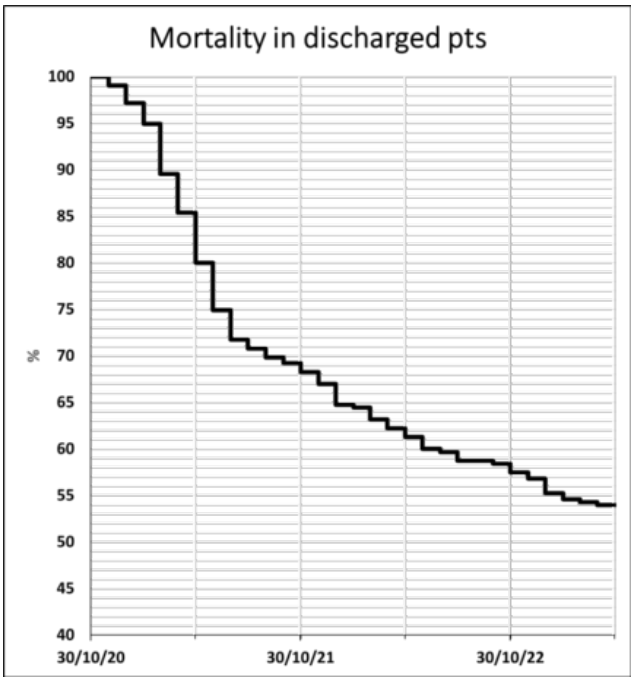
Cabras F.[1], Rapallo G. [2], Ntoukas D.M.[3], Flore E.[4], Piu F.[5], Garau M.[6]
[1]Unit of Infectious Diseases, Dep. of Medicine, Surgery and Pharmacy, University of Sassari, Sassari, Italy; [2]Dep. of Biomedical Sciences, Division of Neuroscience and Clinical Pharmacology, University of Cagliari. ; [3]Internal Medicine Unit, Dep. of Medical Sciences and Public Health, University of Cagliari; [4]USCA - Cagliari (Italy); [5]Dep. of Biomedical Sciences, Section Neuroscience and Clinical Pharmacology, University of Cagliari.; [6]Infectious Diseases Unit, SS Trinità Hospital, 09121 Cagliari, Italy

Study design This retrospective, observational cohort study identified non-hospitalized COVID-19 outpatients (19/05/2020-31/12-2021) using the USCA of Cagliari digital database and the digital database of Asl Cagliari to analyze the impact of early treatment with systemic corticosteroids and Azythromycin
Methods Of 7191 patients with COVID-19 diagnosis registered in the USCA of Cagliari digital database, we included 2875 patients: mean (standard deviation [SD]) age was 55 (19.2) and 46,2% are males. Comorbidity burden was low (mean [SD] Charlson comorbidity index score of 1 (2,3)). However, the 39,1% have at least one comorbidity, among which the most frequent were: hypertension (21%), cardiopathies, including arrhythmias (10%) and diabetes mellitus (9,3%). 557 (19,3%) patients were hospitalized for severe COVID-19 disease and 19 (0,7%) patients were hospitalized for not related COVID-19 disease. there were 101 (3.5%) deaths (All-cause death within 90 days to the onset of disease). 2047 (73,5%) patients were under 65 years: old mean (standard deviation [SD]) age was 46 (13.9) and 45,7% are males. Comorbidity burden was low (mean [SD] Charlson comorbidity index score of 0 (1,01)) The 26 % have at least one comorbidity: hypertension (7,3%), asthma (6%), obesity (4,4%). 253 (12%) patients were hospitalized for severe COVID-19 disease and 14 (0,7%) patients were hospitalized for not related COVID-19 disease. there were 10 (0,49%) deaths (All-cause death within 90 days to the onset of disease). 828 patients were over 65 years: old mean (standard deviation [SD]) age was 76 (8) and 47,1% are males. Comorbidity burden was medium (mean [SD] Charlson comorbidity index score of 4 (2,2)) The 78 % have a least a at least one comorbidity: hypertension (53%), cardiopathies, including arrhythmias (28%), diabetes mellitus (23%). 304 (37%) patients were hospitalized for severe COVID-19 disease and 5 (0,6%) patients were hospitalized for not related COVID-19 disease. there were 91 (10,9%) deaths (All-cause death within 90 days). The primary outcomes were: progression to a Covid19 severe disease such as to require hospitalization or home oxygen therapy; and 60-day mortality. Secondary outcome was to evaluate other factors, such as comorbidities, increased the risk of progression to a Covid19 severe disease and 60-day mortality. For the statistic analysis we used the single logistic regression and the Kaplan-Meier survival test. We used MedCalc® version 20.121.
Results: 916 patients (32%) received systemic corticosteroids, (methylprednisolone, dexamethasone, prednisone) among these: 660 (23%) received it within 10 days of the onset of symptoms for a mild-to moderate COVID19 disease, 134 (4,7%) received it during and after hospitalization for related COVID19 disease, 179 (6,2%) received this treatment for a severe COVID 19 disease or after 10 days of the onset of symptoms, 302 (11%) received inhaled corticosteroids (budesonide, beclomethasone). 1318 patients received at least one antibiotic, 999 (35%) received Azithromycin, 274 (9,5%) received B lactam antibiotics and 43 (1,5%) received a fluoroquinolone. The patients with a mild-to moderate COVID19 disease that received an early treatment with systemic corticosteroids had a higher risk of being hospitalized than those who did not received (ODDS RATIO 1,7462 p< 0,0001 95% CI 1,4267 to 2,1372). In the cohort under 65 years the patients that received this treatment had even higher risk of being hospitalized (ODDS RATIO 2,5054, p< 0,0001, 95% CI 1,9064 to 3,2927). In the cohort over 65 years there wasn't a statistic significant difference (ODDS RATIO 1,0658, p=0,6981, 95% CI 0,7727 to 1,4700). The patients that received Azithromycin also had a higher risk of being hospitalized than those who did not received (ODDS RATIO 1,2878 p=0,0097, 95% CI 1,0646 to 1,5578), as in the cohort under 65 years old (ODDS RATIO 2,1045 p< 0,0001 95% CI 1,6213 to 2,7317). In the cohort over 65 years old there wasn't a statistic significant difference (ODDS RATIO 0,6313, p=0,0650, 95% CI 0,3816 to 1,0445). To the 60-day mortality: there wasn't a statistic significant difference between the patients that received an early treatment with systemic corticosteroids and who did not received (ODDS RATIO 0,8647, p=0,5546, 95% CI 0,5305 to 1,4095), as the cohort over 65 years old, (ODDS RATIO 0,3381 p 0,0586 to 1,0444) .There wasn't a statistic significant difference between the patients that received Azithromycin and who did not received it ODDS RATIO 0,7032, (p= 0,1182, CI 95% 0,4470 to 1,1061), similarly in the cohort over 65 years old (ODDS RATIO 0,6313, p=0,0650, CI 95% 0,3816 to 1,0445). In the cohort under 65 years old the mortality was too low (0,43%) to make the statistic analysis.
Conclusions In outpatients with COVID-19 with a mild to moderate disease, an early treatment with systemic corticosteroids and/or Azithromycin did not demonstrated efficacy to treat the disease. Indeed, the early intake of systemic corticosteroids seems to determine an increased risk of progression to a Covid19 severe disease.

154. COVID IN ELDERLY: TWO YEARS LATER

Guerci M.[1], Biancucci M.[2], Tavecchia L.[1], Abenante A.[2], Tripodi P.M.[2], Larroux B.[2], Castelletti F.[2], Molteni M.[1]
[1]Department of Internal Medicine, Galmarini Hospital, ASST Sette Laghi, Tradate, Italy; [2]School of Specialization in Internal Medicine, University of Insubria, Varese, Italy

Background and Aim: Studies involving very elderly patients (>80 years) affected by COVID19 (C19) have shown increased mortality in these subjects.This study represents a long-term follow-up of our previous study (mortality in C19 patients: one-year later) and aims to determine the two-year mortality rate in patients aged >80 years, hospitalized for C19 during the Second Wave (SW) in a Spoke Hospital of Varese province (Galmarini Hospital, Tradate, Italy).
Methods: Data was collected from 26th October 2020 to 22nd May 2021. The C19 ward's capacity was of 76 patients. All the data was anonymized; age, sex, discharge modality, length of hospitalization (LOH), main diagnoses etc. were gathered and coded. The patients admitted were mostly elderly and not eligible for invasive treatment. Standard Therapy was composed of intravenous steroids, deep vein thrombosis prophylaxis, O2 therapy and i.v. antibiotics if indicated. Differences between the Discharged and the Not-Survived population group were discussed in the previous studies; in the present study we focussed on the follow-up period and more specifically the differences observed between the One-Year-Follow-up (OYF) and the Two-Year-Follow-up (TYF). Follow-up was carried out through telephone calls which aimed to find out patients' vital status and overall health status. If patients had died, we defined the date of death through their relatives. The Patients' survival status in patients lost at follow-up was assessed through the Regional Health Database.
Results: The total number of patients admitted to our ward was 1,116 (mean age 76.9 yrs, range 18-99), 835 pts (74.8%) were discharged, 281 pts (25.2%) died during hospitalization. 525 patients were aged over 80 (mean age 87.4, range 80-101). Amongst them, 210 patients died (40%, males 94, mean age 89.7, range 82-101) whilst 315 patients were discharged (60%, males 128, mean age at discharge 85.9 yrs, range 80-98). The mean age was significantly (p< 0.0001) lower in the Discharged group compared to that of the deceased patients. At OYF, 126 patients (40%, males 45) were lost at follow-up; 74 of 189 searched out pts (23.5%, males 33) had died, the remaining 115 pts were alive (36.5%, males 50. At TYF, we obtained a noticeable reduction of patients lost at follow-up (17 patients, 5.4%, males 11). Of the initial 315 discharged patients, 145 had died (46%, males 61) and 153 were alive (48.6%, males 56). The mean age was significantly higher in the patients who had died compared to the ones alive at follow-up (87.1 vs 84.8 years, respectively; p<0.0001). Surprisingly, the mean age was significantly increased also in females versus males who had survived (85.3 vs 84 yrs, respectively; p<0.0366). No differences were found in the TYF-LOH (TYF-Length of Hospitalization) between the not-survived and the survived groups (14.4 versus 12.6 days, respectively). The not-survived group's mean survival at TYF was 179.9 days (min 1, max 772), no significant difference in survival was found between males and females (177.7 vs 182.9 days, respectively).
Conclusions: Most of the elderly patients (38.7%) discharged alive after C-19 hospitalization had already died at OYF. At TYF mortality rate had increased to 46% (+7.3%). Our study has many limitations. Firstly, the elderly patients admitted to our ward were patients who had no indications to invasive therapy, therefore, our study population could not reflect the real-life elderly population as a whole. Second, data on comorbidities was not analyzed during this study.



155. STILL POSITIVE IN A SPOKE HOSPITAL

Guerci M.[1], Biancucci M.[2], Abenante A.[2], Tavecchia L.[1], Turato S.[1], Tripodi P.M.[2], Castelletti F.[2], Giannò D.[2], Ibrahim M.M.M.[2], Molteni M.[1]
[1]Department of Internal Medicine, Galmarini Hospital, ASST Sette Laghi, Tradate, Italy; [2]School of Specialization in Internal Medicine, University of Insubria, Varese, Italy

Background and Aim: After three years, COVID19 (C19) remains the cause of death for many. The increased risk of hospitalization and higher mortality rate are still challenging the Public Health Organization. This study, conducted in a Spoke Hospital (Varese province, Italy), will focus on the C19 patients' length of hospitalization (LOH) and aims to highlight the factors by which it is influenced.
Methods: Data was collected from 23rd August 2022 to 13th March 2023. All the data was anonymized; age, sex, length of stay, vaccination status, main diagnoses, laboratory data, etc. were gathered and coded. Therapy administered for C19 was in line with the indications in effect at that time. If the patients were eligible for intensive care, they were transferred to a Hub hospital.
Results: The total number of patients admitted was 121. Of these, 21 pts were excluded due to a lack of data. Of the remaining 100 pts (mean age 82.4 yrs, min 61, max 97), 84 were discharged (39 males) and 16 died during hospitalization (ten males). The mean age in the discharged group was of 82.1 years, and of 84.1 years in the deceased patients; no difference was found between the two groups. A lack of statistical difference was found between the LOH in discharged and the deceased patients (mean days 18 vs 24, respectively) as also between LOH and age in the discharged group. Six patients had had no vaccination for C19 (no-vC19), nine were vaccinated with one or 2 doses (2-vC19), 50 with 3 doses (3-vC19) and 35 with 4-doses (4-vC19). Amongst the patients who had died (n=16) the vaccination status (VaxS) was the following: one with no-vC19 (6.3%), four with 2-vC19 (25%), five with 3-vC19 (31.3%) and six with 4-vC19 (37.5%). The Discharged patients' (n=84) VaxS was comprised of five with no-vC19 (6%), five with 2-vC19 (6%), 45 with 3-vC19 (53.6%) and 29 with 4-vC19 (34.5%). In discharged group, the mean number of days with a C19's antigenic swab positivity (MdSP) was of 11.3 days. We found a positive correlation between age and MdSP (p=0.0327, R=0.2332). If compared through VaxS, no-vC19 had 9.6 MdSP, 2-vC19 had 10.4 MdSP, 3-vC19 had 11.3 MdSP and 4-vC19 11.8 MdSP. No difference was found between the four groups. The LOH compared through VaxS, was 16 days for no-vC19, 13.6 days for 2-vC19, 19.2 days for 3-vC19 and 16.5 days for 4-vC19. No difference was found between the four groups. The average of the days elapsed between the last vaccination and the swab positivity (VaxToSP) was 267.1 days. When compared through VaxS, 2-vC19 had 393.8 VaxToSP days, 3-vC19 had 333.7 VaxToSP days and 4-vC19 had 141.8 VaxToSP days. No correlation was found between overall VaxToSP and MdSP. MdSP was not correlated with creatinine, Interleukine-6, CKD-EPI, 25OH-Vitamin D, C-reactive protein, haemoglobin, white blood cell count, albumin levels and Lactate dehydrogenase levels.
Conclusions: There are many limitations to our study: firstly, the total number of patients is smaller than that of other studies which have been published. Patients admitted to our ward had no indication to invasive forms of therapy; this pre-selection doesn't reflect the real-life population as a whole. Multivariate analysis was not performed particularly regarding comorbidities. Finally, there was no follow-up for discharged patients and no data is available on the quality of life of these patients after the hospitalization.

156. COVID-19 VACCINATION DURING DELTA AND OMICRON WAVES: EFFECTS ON THE PROGNOSIS OF PATIENTS ADMITTED TO AN ITALIAN THIRD-LEVEL ACADEMIC MEDICAL CENTER

Rio P.[1], Caldarelli M.[1], Cianci R.[1], Franza L.[2], Pignataro G.[2], Massaro M.G.[1], Tota A.[1], Ocarino F.[1], Sacco Fernandez M.[2], Franceschi F.[2], Gasbarrini A.[1], Gambassi G.[1], Candelli M.[2]
[1]Department of Translational Medicine and Surgery, Fondazione Policlinico Universitario A. Gemelli, IRCCS, 00168 Rome, Italy; [2]Emergency Medicine Unit, Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario A. Gemelli, IRCCS, 00168 Rome, Italy

The SARS-CoV-2 pandemic has a high impact on hospitals worldwide. Viral variants arise from mutations in the virus's spike protein to evade protection from vaccines. The Omicron variant with its higher infectiousness has overtaken the Delta variant. Vaccination prevents the spread of the virus and limits the severity of the disease. However, such protection declines with time from vaccination, and it depends on patient characteristics, vaccine types and immunization regimens.
Our study evaluates the impact of mRNA vaccination on the in-hospital prognosis of patients with SARS-CoV-2 infection who were admitted to an academic medical center during the Delta and Omicron waves.
This is a retrospective monocentric observational study that was conducted in an Italian third-level academic medical center in Rome (Fondazione Policlinico Agostino Gemelli—IRCCS). The analysis includes patients who presented to the Emergency Room between 1 July and 30 September 2021 during the SARS-CoV-2 Delta variant wave, and in January 2022, during the SARS-CoV-2 Omicron variant wave. We collected data concerning vaccination status, comorbidities and clinical parameters, lung involvement, laboratory parameters and pharmacological treatment. The selected outcomes were intensive care unit (ICU) admission and 30-day all-cause mortality.
The analysis includes 821 patients (mean age 62 ± 18 years; range 18-100), of whom 59% were men. 545 patients (66%) resulted positive during the Delta wave and 276 (34%) during the Omicron wave. The proportion of patients vaccinated was higher during the Omicron variant wave than during the Delta variant wave (57% vs. 37%, respectively). Vaccinated patients were significantly older (68 vs. 57 years, $p < 0.001$). The proportion of patients with comorbid conditions was higher among vaccinated ones. At presentation, PaO2/FiO2 ratio was significantly lower in unvaccinated patients, compared to vaccinated ones. Monoclonal antibodies were used mostly in vaccinated patients, while Tocilizumab use was considerably higher among unvaccinated patients.
Overall, 20% of the patients were admitted to ICU and the all-cause mortality rate at 30 days was 14%. There was no difference in 30-day all-cause mortality in the two waves (OR 0.6, 95% CI 0.3–1.0). Conversely, the need for intensive care unit admission was significantly associated with Delta variant (OR 1.9, 95% CI 1.2–3.1). Unvaccinated patients were more frequently admitted to the ICU than vaccinated patients (OR 2.0, 95% CI 1.3–3.1). This protection was mostly observed among patients with more than one dose of vaccine. Unvaccinated subjects had a higher mortality rate at 30 days than those who received two doses (OR 1.9, 95% CI 1.5-2.9) or one dose (OR 1.7, 95% CI 1.3-2.7).
During the Omicron wave, patients were significantly older and had a greater number of medical comorbidities, and the vaccination rate was much higher than during the Delta variant wave. The higher vaccination adherence among older individuals is the probable explanation. The age difference between vaccinated and unvaccinated patients explains the higher prevalence of chronic comorbid conditions, as well as medication use, among those who were vaccinated. Non-vaccinated patients had a lower mean age and, at initial presentation, were in worse clinical condition with a more severe pulmonary involvement.

Patients with two or three doses of vaccine were less likely to be admitted to the intensive care unit compared to unvaccinated patients. Furthermore, patients who had been vaccinated once or twice presented a lower 30-day mortality, while the same was not true for those who had received a booster dose. This can be explained by a higher overall non-viral-related mortality among patients indicated to receive a booster dose.
In a small subset of patients for whom information was available, influenza vaccination resulted in a reduced mortality rate. Influenza vaccination likely elicits antiviral protection not limited to its target, thus boosting immune protection even in elderly persons. Also, individuals adhering to both COVID-19 and influenza vaccination campaigns are more compliant. They likely refer to the hospital earlier and in less severe conditions, than those who do not.
In patients hospitalized for COVID-19, vaccination against SARS-CoV-2 provides significant protection. The protective effect on ICU admission is seen only after two doses of the mRNA vaccine, independently of the viral variant, while mortality appears to be reduced by one or two vaccine doses but not by a booster dose. Further research is needed to demonstrate protection against other viral variants and to test new vaccines, different vaccination schedules and regimens.

157. ADULT-ONSET STILL'S DISEASE DEVELOPING AFTER SARS-COV-2 VACCINATION

Del Vecchio M.[1], Martellucci O.[1], Farroni S.[1], Palladino M.[1], Gigante A.[1], Alessandri C.[2], Muscaritoli M.[1]
[1]Department of Translational and Precision Medicine, Sapienza University of Rome; [2]Department of Clinical, Internal Medicine, Anesthesiological and Cardiovascular Sciences Department, Sapienza University of Rome

Case presentation: In September 2021, a 56-year-old man was hospitalized at Policlinico Tor Vergata for fever (body temperature-BT >39 °C), and dyspnea since two weeks and bilateral swellings of the legs. In May 2021, he received the first dose of SARS-CoV-2 vaccination (Johnson & Johnson/Janssen); in anamnesis referred recurrent pharyngitis and tonsillitis and successive tonsillectomy. Blood tests showed: thrombocytosis (platelets 544000/mm3), increased inflammatory indices (C-reactive-protein-CRP 21.5 mg/dl, ferritin 622 ng/ml). High-resolution computed tomography (HRCT) scan of the chest and transthoracic echocardiogram showed abundant bilateral pleural effusion, focal thickening-atelectasis of the basal lung segments and a small circumferential hypoechoic space (maximum 14 mm), non-hemodynamically significant. Serological testing for infectious and autoimmune diseases were negative. Therefore, broad-spectrum intravenous antibiotics (cefditoren pivoxil 200 mg twice a day and levofloxacin 500 mg daily) and steroid therapy with oral prednisone (25 mg once daily) were administered with partial clinical remission. The patient was discharged with diagnosis of "pneumonia, bilateral pleural effusion and pericardial effusion". At discharge, follow-up with blood tests, echocardiography, computed tomography (CT) scan of the chest and rheumatological consultation were recommended. Moreover, the positron emission tomography (PET) CT scan performed on October 2021 was negative for cancer but showed reduction in the pleural effusion, and a small area of parenchymal thickening with air bronchogram sign in the basal segment of left lung.Between November 2021 and May 2022, the patient experienced widespread arthralgia, mainly at the level of the proximal interphalangeal joints of the hands. Rheumatologist recommended Salazopyrin 2 g/day, but the patient interrupted therapy after the first administration because of hyperthermia (BT 37-37.5°C). In January 2022, the patient received the booster dose of Covid-19 Vaccine (Pfizer/BioNTech). In June 2022, he was admitted to our ED for dyspnea at rest and on mild exertion accompanied by oppressive chest pain from one week. Blood pressure was 130/80 mmHg, peripheral oxygen saturation 97% in ambient air, heart rate 105 bpm (regular), BT 37.3 °C. Bilateral basal cracklings were observed. Blood chemistry tests showed leukocytosis with neutrophilia, thrombocytosis, and increased acute phase reactants; chest X-ray and transthoracic echocardiogram showed pleural and pericardial effusion. The patient was then admitted to our Unit of Internal Medicine presenting fever up to 39 °C, arthralgias, lymphadenopathies and polyserositis. Bacterial blood cultures were negative and autoimmunity testing for antinuclear antibody and rheumatoid factor were negative, while serological tests for specific IgG to Epstein-Barr virus and Herpes Simplex virus antigens were positive. Cancer was further excluded by ultrasound of the abdomen and CT scan of the chest. The symptoms were consistent with Yamaguchi's classification criteria for Adult-Onset Still's Disease (AOSD). A combined treatment with intravenous methylprednisolone 20 mg twice a day and colchicine 0,5 mg/day was started, with a slight improvement of patients symptoms after few days. In July 2022, the patient was then discharged and followed up to the outpatient clinic. In September 2022, because of the worsening of symptoms, a second line therapy with the recombinant IL-1 receptor antagonist (Anakinra) was started at the dosage of 100 mg once daily subcutaneously. After about a month of therapy, echocardiography showed reduction of pericardial effusion (5 mm) and the blood chemistry tests highlighted a reduction of inflammation indices (CRP 0.07 mg/dL, ferritin 438.2 ng/mL, erythrocyte sedimentation rate-ESR-2 mm/h) and a normalization of white blood cells (WBC) and platelets (WBC 9.1*103/mmc, platelets 273*103/mmc). Also, the patient has referred to a significant improvement of symptoms and quality of life.
Conclusions: Recent studies reported clinical and laboratory similarities between Covid-19 infection and AOSD. The cytokines storm is the central pivot of the AOSDs' pathogenesis; IL-1, IL-6, IL-15 and IL-18 are all highly expressed in the AOSD and likewise in COVID-19. Given the temporal relationship between vaccine administrations and onset of symptoms, excluded malignancies or other infections, we hypothesized that Covid-19 vaccination may have facilitated the clinical development of AOSD. Moreover, treatments with IL-6 inhibitor Tocilizumab or IL-1 inhibitor Anakinra are highly effective in both clinical conditions. Anti-IL-1 treatment was also effective in our patient. In conclusion, further data are needed to establish the safety of the Covid-19 vaccines; even if benefits of being vaccinated outweigh the risks, serious vaccine side effects should be carefully evaluated and monitored.

158. MILLER-FISHER SYNDROME PRESENTING WITH FACIAL DIPLEGIA WITH COVID-19 CO-INFECTION SUCCESSFULLY TREATED WITH PLASMAPHERESIS

Miano N.[1], Urso S.[2], Di Marco M.[1], Scilletta S. [1], Musmeci M.[1], Leggio S.[1], Scicali R.[1], Piro S.[1], Purrello F.[1], Di Pino A.[1]
[1]Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy; [2]Department of Nephrology and Dialysis, Garibaldi-Nesima Hospital, Catania, Italy

Background: Coronavirus disease 2019 (COVID-19) pandemic has rapidly spread around the world from Jan-2020, with more than 755,000,000 cases confirmed so far. SARS-CoV-2 mainly affects the respiratory system, although, central and peripheral neurological manifestations associated with SARS-CoV-2 infection have been increasingly reported. More recently, some case reports showed an association between the spectrum of Guillain–Barré syndrome (GBS) and severe acute respiratory syndrome coronavirus-2 (SARS- CoV-2). Miller Fisher Syndrome (MFS) is a rare variant of Guillain-Barré syndrome, an autoimmune disease of the peripheral nervous system, characterized by ophthalmoplegia, ataxia, areflexia and elevated cerebrospinal fluid (CSF) protein concentration. We report a case of Miller Fisher syndrome associated with SARS-CoV-2 infection. Plasmapheresis was performed with a significant clinical improvement.
Case Presentation: A 75-year-old male presented at our emergency room with 1-week history of jaw pain followed by blurred vision, bilateral ptosis, drowsiness, headache with vertigo, fever and marked truncal and appendicular ataxia. The admission examination showed bilateral ptosis, complete extrinsic ophthalmoplegia and left facial diplegia. He was afebrile (temperature 36°C) with a pulse rate of 72/minute, blood pressure of 170/80 mm Hg, and oxygen saturation of 95%. On neurological examination, higher mental functions were intact. Muscle tone was normal, tactile and proprioceptive sensitivity were not impaired. Deep tendon reflexes were absent in all four limbs. Hematologic baseline examination revealed neutrophilic leukocytosis and increased C-reactive protein values. Chest X-ray, non-contrast head CT and MRI on admission were normal. CSF examination revealed 18 cells, protein-98 mg/ dl and glucose-111 mg/dl with sterile blood and urine cultures. Therefore, samples were sent for the dosage of antiganglioside antibodies (negative) and after neurological advice, a five-day course of daily Intra Venous Immunoglobulin IVIG (0.4 g/kg/day) was commenced without benefit but with a progressive clinical deterioration. Afterwards for the onset of dysphonia, dysphagia and visual impairment we repeated a chest X-Ray and a CT chest showing bilateral patches of consolidation. Based on clinical and radiological findings we performed a qualitative real-time reverse transcriptase polymerase chain reaction assay for SARS-CoV-2 on the patient's oropharyngeal swab testing positive. C-reactive protein (47.4 mg/dl) and WCB (53.2 x 103/mL) were raised, while the blood culture was sterile. In view of a neurological syndrome of ophthalmoplegia and areflexia with albumin-cytological dissociation on the CSF examination, diagnosis of Miller Fisher syndrome concurrent with SARS-CoV-2 infection was made and he was moved to a semi-intensive care COVID ward. Given the clinical worsening,

a CVC was urgently placed in the right femoral vein with ultrasound guided method and subsequent treatment with plasmapheresis was started. Under heparinization, N 5 sessions of plasmapheresis were performed on alternate days. The plasma volume for each session was 3 L and 100 ml. After plasmapheresis, the patient showed a gradual resolution of neurological deficit.
Discussion: Fever and respiratory symptoms are well recognized features of COVID 19 illness, even though, recently many publications have described neurological findings affecting nervous system of patients with COVID-19 infection. Only 12 patients with COVID-19 associated MFS have been reported to date. In the majority of cases, MFS followed COVID-19 after a mean time of 14.75 days after the diagnosis of COVID-19. In our case, the patient presented with neurological symptoms, followed by COVID-19 illness with an evident worsening of his clinical condition. Additionally, our patient presented headache, which is not a common symptom in MFS.
The majority of patients affected with MFS with concurrent COVID-19 illness were treated with IVIG, showing a marked improvement. However, Yeh et al [1] reported that plasmapheresis is indicated for the treatment of complicated MFS. Based on the current evidence and on the present case we propose that patients with severe MFS should be evaluated for plasmapheresis.
Conclusion: New neurological symptoms and presentations of COVID-19 are emerging, as well as innovative therapies such as plasmapheresis. Thus, the importance of a neurological assessment in order to recognize and treat syndromes like MFS early in COVID 19 pandemic.

159. A PULMONARY-RENAL SYNDROME SUSPECT FOR IGA-MEDIATED ANTI GLOMERULAR BASEMENT MEMBRANE DISEASE AFTER COVID-19 VACCINATION/INFECTION: A CASE REPORT

Carbone E.[1], Funaro B.[1], Paradisi A.[2], Manna R.[3], Ria F. [4], Gasbarrini A.[1]
[1]Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Department of Translational Medicine and Surgery, Roma, Italy; [2]Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Dermatology, Department of Translational Medicine and Surgery, Roma, Italy; [3]Periodic Fevers and Rare Diseases Center, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Department of Internal Medicine, Rome, Italy; [4]Dept of Laboratory Medicine, Department of transational Medicine and Surgery, section of General Pathology, Università Cattolica del Sacro Cuore, Rome, Italy

Background: Anti-glomerular basement membrane disease is a rare small vessel vasculitis affecting kidneys and lungs, mediated by IgG autoantibodies (rarely IgA [1]), directed against type IV collagen. An association with COVID-19 has been recently speculated [2].
Case presentation: We report the case of a 58-year-old man presenting with anuria who had received vaccine for COVID-19 two weeks before, tested positive for COVID-19 the day of admission but negative two days later. The patient reported a history of systemic hypertension, smoking history, and professional exposure to chemicals. Past blood analysis didn't show any signs of kidney failure. In consideration of a significant increase of serum creatinine value (35 mg/dL) hemodialysis was immediately started. He also needed several blood transfusions because of severe anemia, without hemoptysis. The patient developed a serious respiratory failure requiring high flow nasal cannula oxygen therapy, with chest CT scan revealing pulmonary emphysema, ground glass opacity and small consolidation areas. The patient also had non confluent, palpable, papulovesicular skin lesions in number < 30 on the hands, legs and to a lesser extent on the back. Serologic tests for autoimmunity (ANA, ENA, ANCA) were negative, while immunoglobulin dosage showed an IgA increased value. Western blot for anti-glomerular basement membrane tested negative, as regularly occurs in IgA mediated disease [1]. Immunofluorescence performed on monkey esophagus however revealed a strong positivity for IgA directed against the epithelium basal layer. Kidney biopsy could not be performed because of high bleeding risk, preventing a definitive diagnosis. A skin biopsy was performed, revealing histological features of cutaneous vasculitis. The patient was also tested for anti-BP 180/230 and anti-desmoglein 1/3 to rule out a bullous disorder which resulted negative. As the clinical condition worsened, high dosage steroid therapy was started with an impressive improvement of the respiratory failure, allowing oxygen therapy discontinuation. A control chest high resolution CT scan revealed a notable reduction of the consolidation areas. On the other hand, renal function didn't improve at all.
Conclusion: In conclusion we reported the case of a patient affected by a systemic vasculitis. Even if a renal biopsy could not be performed, considering the result of immunofluorescence we can hypothesize he was affected by IgA mediated anti-glomerular basal membrane disease. This rare form of anti-glomerular basement membrane disease is characterized by heterogeneous autoantigens, different from the ones involved in IgG anti-glomerular basement membrane disease. The presence of cutaneous vasculitis allows it can be included in a microscopic polyangiitis variant. The etiopathogenesis can be discussed but the onset after Covid-19 arises the suspicion of an immune/infectious trigger.
References
1. Wen YK, An unusual case of IgA-mediated anti-glomerular basement membrane disease. Int Urol Nephrol. 2013
2. Prendecki M, Anti-glomerular basement membrane disease during the COVID-19 pandemic. Kidney Int. 2020

160. POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME IN YOUNG WOMAN AFFECTED BY SARS-COV2 DISEASE

Angelici S., Verzicco I., Ferrari M., Gaimarri I., Quarantelli D., Accardi G., Bottaro L., Qako E., Morelli A., Adler F., Rotelli L., Massera C., Palladini B., Brusasco I., Tedeschi S., Cabassi A.
DIpartimento di Medicina Generale e Specialistica, UOC di Clinica e Terapia Medica

We report the case of a 48-years old woman, with history of type 2 diabetes mellitus in diet therapy and hypothyroidism in hormone replacement therapy, admitted to the Emergency Room because of rapid onset of nausea and vomiting associated with headache, photophobia, diplopia and disequilibrium, occurred few days earlier. A brain CT scan showed edematous hypodensity of the anterior-inferior convexity of the right cerebellar hemisphere, exerting mass effect on the lateral recess of the fourth ventricle, associated with hydrocefalic dilatation of the lateral ventricles horns and initial surfacing of cerebral tonsils on magnum foramen. A further Neurological evaluation confirmed diplopia also revealing convergent strabismus, ataxia and dysmetria; conversely no hypostenia was detected at limbs. A Neurosurgeon consult, in order to manage the cerebral edema, indicated intravenous therapy with hyperosmolar agents (Mannitol) associated with high dosage of corticosteroids (Dexamethasone). As the Patient resulted positive for SARS-CoV-2-RNA, she was then admitted to our Covid Unit.
During a detailed examination, Patient referred mild fever and weakness occurred about ten days prior. Given the timing and the absence of common symptoms of COVID-19 such as fever, dyspnea or acute respiratory distress, the infectivologist did not indicate starting specific antiviral therapy.
Thus, Patient underwent a Brain MRI highlighting hyperintense T2 FLAIR signal alteration without enhancement signs, affecting the internal capsules, the cerebral peduncles, mesencephalon, brainstem and cerebellar regions with mass effect on the subtentorial region.
In order to rule out rare neurologic diseases as Bickerstaff encephalitis or autoimmune Rhomboencephalitis, we performed several microbiological tests including L. Monocytogenes, T. Gondii, B. Burgdorferi, T. Pallidum and serum screening for HIV, CMV, VZV, EBV, HSV-1 and HSV-2; we tested general autoimmunity and specific autoantibodies for synaptic intracellular antigens GAD65, as well as antiganglioside antibodies, resulted negative.
Blood pressure was in normal range, as well as renal function, electrolytes levels, and serum TSH concentration. While clinical conditions slowly improved and once SARS-CoV2 swab resulted negative, the Patient was admitted to Neurologic Unit. A second Brain MRI showed partial resolution of the alterations previously described; the imaging was diagnostic for posterior reversible encephalopathy syndrome (PRES), in resolution. Thus, steroid tapering was started and the Patient was then discharged. A month later, a further brain MRI showed complete resolution.
We consider this case of interest as PRES is a neurological syndrome, more common in women, characterized by headache, confusion, visual changes and seizures, associated with neuroimaging findings as posterior cerebral white matter edema and may also represent a life threatening conditions. PRES can occur in several clinical conditions, such as autoimmune disease, eclampsia, hypertensive emergencies, red cell blood transfusions or associated with electrolyte disorders as hypomagnesemia1. Interestingly, the association of PRES and COVID-19 has been well described in a recent systematic review which included patients with mean age (56.6 ± 15.3 years) presenting typical neurological findings; intriguingly, hypertension and diabetes mellitus were common comorbidities. The most likely underlying mechanism may involve the inflammatory response secondary to cytokine storm leading to endothelial damage and increased permeability of the ce-

rebral vessels causing the vasogenic edema of brain. In addition, given the detection of SARS-CoV-2 in cerebrospinal fluid and the evidence of a high neuronal and glial cell expression of Angiotensin Converting Enzyme-2 receptors as a potential virus target, direct viral damage should be considered. Hence, virion may directly disrupt endothelial integrity of the blood-brain barrier2. Considering the reversibility condition of PRES, a prompt diagnosis especially if the infection develops in patient with hypertension and diabetes, should be performed in order to prevent severe neurological complications. Moreover, high dosage of steroid therapy in our hypothesis may have improved both the brain edema and the inflammatory cytokine storm. Hence, in relation to the rising cases of neurological manifestation in patients affected by COVID -19, clinicians and radiologists should be aware, as these findings may occur more frequently among the wide broad spectrum of clinical manifestations of COVID-19.

Zappia et al.
Posterior reversible encephalopathy syndrome in an oncological normotensive patient: evidence for a pathogenic role of concomitant low magnesium serum levels and chemotherapy treatment.
Acta Biomed. 2020; 91(2): 365–372.
Iftikhar et al
The association of posterior reversible encephalopathy syndrome with COVID-19: A systematic review
Annals of Medicine and Surgery 72 (2021) 103080.

161. MICROVASCULAR MORPHOLOGICAL ALTERATIONS IN PATIENTS WITH PREVIOUS SARS-COV2 INFECTION

Bevacqua C.[1], Bressa S.[1], Agabiti Rosei C.[1], Rossini C.[1], Malerba P.[1], Nardin M.[2], Chiarini G.[1], Boari GEM[3], Petelca A.[1], Lemoli M.[1], Baresi M.[1], Salvotti F.[1], Cattaneo C.[1], Porteri E.[1], Rizzoni D.[4], Muiesan M.L.[1], De Ciuceis C.[1]
[1]Internal Medicine, Department of Clinical and Experimental Sciences, University of Brescia; [2]General Medicine 3, ASST Spedali Civili of Brescia; [3]General Medicine of Montichiari, ASST Spedali Civili of Brescia; [4]Internal Medicine, Department of Clinical and Experimental Sciences, University of Brescia; General Medicine of Montichiari, ASST Spedali Civili of Brescia

Background: SARS-CoV2 infection is associated with inflammation and coagulation alterations that induce endothelial dysfunction and vascular damage. It has been shown that patients with acute SARS-CoV2 infection present hemorrhages, thrombosis and neoangiogenesis at the level of the skin capillaries (J Hypertens. 2022;40(12):2385-2393.).
Purpose: The aim of this study was to evaluate possible morphological alterations of the skin capillaries after 3 and 12 months from acute SARS-CoV2 infection.
Methods: Fifty-nine patients (mean age 57.6±10.8 years) were included in the study, admitted between February and April 2020 at the ASST Spedali Civili Brescia / University of Brescia for SarsCov2 infection. All patients underwent capillaroscopy in order to measure basal and total capillary density (expressed in number x unit of area) in the dorsum of the 4th finger and to evaluate capillary morphological alterations in the nailfold after 3 months (baseline) and after 12 months (follow up) from acute infection. The morphological characteristics (morphology, architecture, tortuosity, presence of ectasias, microhaemorrhage/microthrombosis, neoangiogenesis, arterial and venous loop diameter) were assessed by semi-quantitative score (score 0-5).
Results: The results are shown in the table (* $p < 0.05$; ** $p < 0.05$, ***$p < 0.001$). An improvement of the nailfold capillary morphology was demonstrated with complete and statistically significant reduction of both neoangiogenesis phenomena and venous loop diameter at follow-up, compared to baseline. These results were associated to a reduction in basal and total capillary density in the dorsum. A direct correlation between the presence of inhomogeneous architecture ($r=0.315$, $p<0.05$), tortuosity ($r=0.287$, $p<0.05$) or capillary ectasias ($r=0.326$, $p<0.05$) and systolic blood pressure values was observed. A positive correlation between venous loop diameter and baseline values of systolic and diastolic blood pressure was shown (respectively $r=0.345$ and $r=0.257$, $p<0.05$).
Conclusions: Patients with recent SARS-CoV2 infection present a significant capillary loss and an improvement in the morphological alterations of the nailfold microcirculation after 12 months from the acute phase. Further studies are needed to clarify the mechanisms underlying long-term microvascular damage.

	Basal	Follow up
Basal capillary density (nailfold)	9,4 ± 1,6	9,1 ± 1,7
Total capillary density (nailfold)	9,5 ± 1,6	9,7 ± 1,9
Basal capillary density (dorsum)	85,8 ± 15,0	80,0 ± 15,8*
Total capillary density (dorsum)	99,2 ± 16,0	88,1 ± 18,2***
Morphology	1,29 ± 0,77	1,07 ± 0,67*
Architecture	0,86 ± 0,66	0,780 ± 0,59
Tortuosity	1,29 ± 0,70	1,14 ± 0,63
Ectasias	0,390 ± 0,67	0,37 ± 0,55
Microhaemorrhages/microthrombosis	0,07 ± 0,25	0,14 ± 0,43
Neoangiogenesis	0,34 ± 0,48	0,14 ± 0,35**
Arterial loop diameter µm	10,19 ± 1,90	10,47 ± 1,88
Venous loop diameter µm	12,73 ± 1,90	13,46 ± 1,89**

162. THE WORLDWIDE IMPACT OF COVID-19 ON CANCER CARE: A META-ANALYSIS OF SURVEYS PUBLISHED AFTER THE FIRST WAVE OF THE PANDEMIC

Susca N.[1], Di Cosimo S.[2], Apolone G.[3], Silvestris N.[4], Prete M.[5], Leone P.[5], Racanelli V.[6]
[1]Department of Interdisciplinary Medicine, Emergency Department Unit, School of Medicine, 'Aldo Moro' University of Bari; [2]Platform of Integrated Biology Unit, Department of Applied Research and Technological Development, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [3]Scientific Directorate, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; [4]Medical Oncology Unit, Department of Human Pathology "G. Barresi", University of Messina, Messina, Italy; [5]Department of Interdisciplinary Medicine, Section of Internal Medicine, School of Medicine, 'Aldo Moro' University of Bari; [6]Department of Cellular, Computational and Integrative Biology - CIBIO, University of Trento, Trento, Italy

Background: The rapid and global spread of COVID-19 posed a massive challenge to healthcare systems, which came across the need to provide high-intensity assistance to thousands of patients suffering from SARS-CoV-2 infection while assuring continuous care for all other diseases. This has been of particular importance in the oncology field. This study explores how oncology centers responded to the pandemic at a single center level by assessing surveys addressing different aspects of cancer care after the pandemic outbreak.
Methods: We performed a systematic review and meta-analysis of the cancer care surveys published until December 11th, 2020. PubMed, Scopus and Web of Science were used as the research sources. Data were analyzed according to three main areas of interest, namely health care organization, including cancellation/delay and/or modification of scheduled treatments, cancellation/delay of outpatient visits, and reduction of overall cancer care activities; routine use of preventive measures, such as personal protective equipment (PPE) by both patients and health care workers, and systematic SARS-CoV-2 screening by nasopharyngeal swabs; and implementation of telemedicine through remote consultations.
Findings: The literature search yielded 6026 after duplicates removal. Of these, 56 articles were found eligible for the systematic review, and 50 were included in the meta-analysis. These fifty surveys reported data on 9150 providers from 121 countries on 5 continents were included. Cancellation/delay of treatment occurred in 58% of centers. Meta-regression considering the geographical area in which the survey was conducted and the week of survey beginning (n=17) seemed to explain a small amount of heterogeneity (R2 15.9%, I2 95.7%), with the test of moderators in the meta-regression not being statistically significant (p=0.43); delay of outpatient visits was reported in 75% of the studies. The analysis of geographical area with the study sample size explains all the heterogeneity, with no residual heterogeneity (n=9, R2 100%, I2 0%, p-value for the test of moderators <0.0001, p-value for the Q-test for heterogeneity=0.4); changes in treatment plans occurred in 65% of the surveys. A model including geographical area and week of survey end and specialty yielded an R2 of 100%, with no residual heterogeneity (n=9, the p-value for the test of moderators<0.0001, p-value for the Q statistic of residual heterogeneity=0.59); a general reduction in clinical activity was observed in 58% of the cases. A meta-regression model considering specialty and geographical area accounted for some of this heterogeneity (n=12, R2 40.5%, I2 88.3%, p-value for the test of moderators=0.2, Q-test for residual heterogeneity<0.0001). Routine use of PPE by patients was reported by 81% of the centers. GRSI (Government Response Stringency Index) alone explained a great part of the observed heterogeneity (n=5, R2 74.2%, I2 79.6%, p-value for the test of moderators=0.03, p- value for the Q-test of residual heterogeneity=0.002). Adding sample size to GRSI in the model further im-

proved heterogeneity explanation (n=5, R2 92.9%, I2 43.8%, p-value for the test of moderators<0.0001, p-value for the Q-test of residual heterogeneity=0.17); 80% of centers reported routine use of PPE by the healthcare personnel. A meta-regression model including geographical area, week of survey end and sample size accounted for a substantial part of this heterogeneity (n=10, R2 78.9%, I2 80.7%, p-value for test of moderators <0.0001, p-value for the Q-test for residual heterogeneity=0.006). Adding GRSI resulted in a better explanation of heterogeneity (n=8, R2 98.7%, I2 17.1%, p- value for test of moderators <0.0001, p-value for the Q-test for residual heterogeneity=0.27); systematic SARS-CoV-2 screening by nasopharyngeal swabs was reported by only 41% of centers. A meta-regression model including geographical area, specialty, sample size and the center/operator categorization seemed to explain a part of the true heterogeneity, but without statistical significance (n=20, R2 29.7%, I2 92.3%, p-value for the test of moderators=0.39, p-value for the Q-test for residual heterogeneity<0.0001); Virtual visits were implemented by the majority (72%) of centers. A meta- regression model including specialty, sample size and center/operator categorization explained part of the heterogeneity (n=17, R2 24.6%, I2 95.6%, p-value for the test of moderators=0.13, p-value for the Q-test for residual heterogeneity <0.0001).
Publication bias was detected only for the modification of treatments outcome (Egger test p-value=0.03).
Interpretation: These results describe the negative impact of COVID-19 on cancer care, the rapid response of cancer centers in terms of preventive measures and alternative treatment approaches such as telemedicine, and confirm that surveys can provide the valuable, low-cost and immediate information that critical situations require.

163. REACTIVATION OF HERPESVIRUSES IN PATIENTS WITH MODERATE-SEVERE CORONAVIRUS DISEASE

Smirne C.[1], Crobu M.G.[2], Mercandino A.[2], Briasco M.[2], Macaluso P.[2], Faolotto G.[2], Riggi M.[2], Impaloni C.[2], Martello C.[2], Pirisi M.[1], Ravanini P.[2]
[1]Internal Medicine Unit, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy; [2]Laboratory of Molecular Virology, Maggiore della Carità Hospital, Novara, Italy

Background: Herpesviruses (HV) are double-stranded DNA viruses and are capable of establishing latency in their hosts with the potential for reactivation in immunocompromised patients.
During the coronavirus (COVID-19) pandemic, some studies showed a high incidence of herpesvirus reactivation in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS CoV 2). Moreover, a recent large observational study reported a herpes simplex virus 1 (HSV-1) reactivation with a low cycle threshold (CT) value in COVID-19 critically ill patients, and suggested that this may be associated with an increased mortality. In this respect, the possible reactivation of HV and their ability to change the clinical course of COVID-19 patients are concerns to be further investigated.
Aims: Our primary objective was to evaluate the prevalence of herpesvirus reactivation, comparing a population of SARS-CoV-2 infected and non-infected patients. Secondly, we aimed to investigate the prevalence of herpesvirus reactivation in the subset of COVID-19 patients admitted to the intensive care unit (ICU).
Methods: In this study we retrospectively analyzed 50 non-consecutive patients admitted for acute respiratory failure to the Novara University Hospital and recruited in a COVID-19 observational study, whose nasopharyngeal swab samples had been stored. The recruitment period was from January 2022 to July 2022; 28 of these had been admitted to the COVID-19 ICU and required invasive mechanical ventilation, while the remaining 22 required medium intensity care. All patients were monitored at that time with standard clinical and laboratory workup. In particular, the diagnosis of COVID-19 was confirmed by an automated real-time polymerase chain reaction (PCR) (Alinity m SARS-CoV-2 assay; Abbott Molecular). The patient group was compared with a group of 39 healthy controls years willing to donate a swab sample.
For the purposes of this study, all swab samples were retested using a quantitative PCR (ELITe MGB® Kit; ELITechGroup) for the following targets: HSV-1, HSV-2, varicella-zoster virus (VZV), human cytomegalovirus (HCMV), Epstein-Barr virus (EBV), human herpesvirus 6 (HHV-6), HHV-7, and HHV-8. Herpesvirus reactivation was defined as a HV-positive RT-PCR in any respiratory sample. All clinical and microbiological data were collected from medical charts and laboratory archives.
Results: In our study all 89 patients were tested for SAR-CoV-2: 39 subjects resulted negative (21 M and 18 F; median age 54 years) and 50 were positive (36 M, 14 F, median age 70 years). 69/89 (77%) of the patients tested positive for at least one HV, and 48 (54%) showed coinfection with two or more viral subtypes. These two proportions were significantly more prevalent in the subset of COVID-19 positive patients compared to COVID-19 negative ones (respectively: 45/50 (90%) vs. 24/39 (62%), p=0.002; 36/50 (72%) vs. 11/39 (28%), p<0.001). The most prevalent herpesvirus was HHV-7, both in the whole study population (56%) and when considering COVID-19 positive and negative subjects (64% and 46%, respectively). HSV-1, EBV and HHV-6 were more prevalent in the SARS CoV 2 positive subset of patients (respectively: 36% vs. 3%, p<0.001; 42% vs. 18%, p=0.02; 54% vs. 18%, p<0.001). No reactivation with HSV-2, VZV and HHV-8 was observed. When focusing on the COVID-19 positive 50 patients, no viral reactivation was associated with the 28-day mortality rate. When dividing these subjects into those admitted to medium intensity care (non-ICU) and to ICU, the 22 patients in the first group were, as expected, significantly less comorbid compared to the 28 latter ones (27% had at least a concomitant chronic disease compared to 89% in the second group), with a mean shorter hospital stay (12 vs. 31 days, respectively) and ultimately a global better prognosis (28-day mortality rates of 0% and 46%, respectively). Our data did not indicate an association between HSV-1, EBV, HHV-6 and HHV-7 reactivation and the severity of COVID-19 disease; only HCMV was more prevalent in the subpopulation of most critically ill patients (25% vs. 0%, p=0.01). Finally, when analyzing CT values of COVID-19 PCRs, lower values were not associated to an increased HV reactivation, except for HHV-6 (p=0.02).
Conclusions: The prevalence of herpesvirus reactivation in SARS-CoV-2 positive patients was significantly higher compared to negative subjects; these data may suggest that SARS-CoV-2 favors their reactivation. When focusing on the more severe COVID-19 infections, there seemed to be an increased HCMV reactivation, which could unfavorably affect the duration of hospitalization, but not the overall patient prognosis. Instead, our data did not confirm previous reports of a high HSV-1 reactivation rate in critically ill patients with low COVID-19CT values. This may probably be due to the small sample size of this pilot study. Taken together, our data suggest that, in patients symptomatic for moderate-severe COVID-19, the diagnosis of HV co-infections could have a clinical utility, in that it would help to predict a possible worsening of the clinical conditions.

164. WORSENING IN FLOW-VOLUME SPIROMETRY IN HYPERTENSIVES RECOVERED AFTER SARS-COV-2 INFECTION: A PILOT STUDY

Marozzi M.S.[1], Mancini F.[2], Corvasce F.[1], Desantis V.[3], Loponte L.[2], Solimando A.G.[2], Vacca A.[2], Cicco S.[1]
[1]Unit of Internal Medicine "Guido Baccelli" and Unit of Hypertension "A.M. Pirrelli", Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), University of Bari Aldo Moro, AUOC Policlinico di Bari, Italy; [2]Unit of Internal Medicine "Guido Baccelli", Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), University of Bari Aldo Moro, AUOC Policlinico di Bari, Italy; [3]Unit of Internal Medicine "Guido Baccelli" and Unit of Pharmacology, Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), University of Bari Aldo Moro, AUOC Policlinico di Bari, Italy

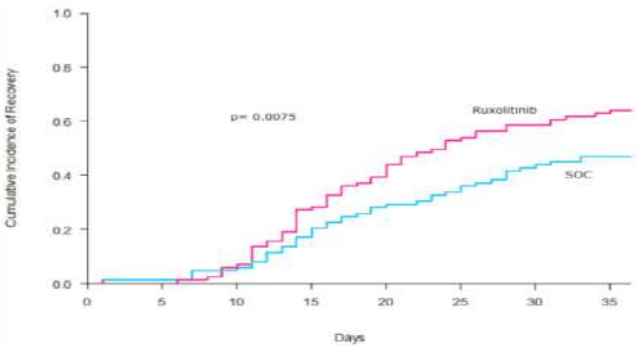
Introduction: Angiotensin Converting Enzyme 2 (ACE2) is an endothelial cell receptor used by SARS-CoV- 2 virus to enter cells. Pulmonary function tests (PFTs), mainly flow-volume spirometry, are diagnostic tools for most respiratory functions, and mandatory for assessing the response to therapy. Hypertension is a well-recognized risk factor for poor prognosis in COVID-19 patients. Due the role in hypertension, the ACE pathway inhibitors were first evaluated for the prognostic risk but few data are available in follow-up PFTs according to the hypertension and treatment.
Aim: we evaluated hypertensives after Sars-Cov-2 infection through flow-volume spirometry and the role of ACE inhibitors/angiotensin receptors blockers (ACEIs/ARBs) in their follow-up.
Methods: We evaluated 112 Caucasian COVID-19 patients 3-6 months after negative molecular or antigenic nasopharyngeal swab. Patients were divided into: Group 1 (18 females and 30 males treated hypertensives, aged 63.47±14.24), and Group 2 (32 females and 32 males, untreated normotensives aged 53.03±16.66). Distal airflow obstruction (DAO) was evaluated as forced expiratory flow (FEF) at 25%, 50% and 75% of total flow. PFTs values were related to age, sex and BMI before comparison.
Results: Group 1 presented lower peripheral oxygen saturation percentage (SpO2) vs Group 2 (p<0.05). By analysing flow volume spirometry data, Group 1 showed significant worsening in FEV1, FEF 25-75 and FEF 50 as

absolute volume. However, these results could be conditioned by the differences of the two groups in terms of hypertension and treatment. When adjusted and related to age, sex and BMI, spirometry data were confirmed showing worsened results in Group 1 as predicted percentage: Forced Expiratory Volume (FEV1, p<0.05), Forced Vital Capacity (FVC, p<0.05), and Tiffenau Index (p<0.05). Group1 showed reduced FEF 25 (p<0.05), FEF 50 (p<0.05), FEF 25-75 (p<0.05), and in FEF 75 (p<0.05). Hypertensives treated with ACE2Is/ARBs did not present differences compared to other treatments.
Conclusions: Respiratory function was shifted towards the lower limits in hypertensives, albeit within normal limits. Hypertension results associated to a subclinical worsening of PFTs although treatment with ACEIs/ARBs did not affect PFTs at follow-up after recovery. Thus, COVID-19 should be considered not only a pulmonary disease, but also a further vascular impairment when a previous cardiovascular comorbidity occurs.

165. RUXOLITINIB IN SEVERE AND CRITICAL COVID-19 REQUIRING CPAP

Festuccia M.B.[1], Evangelista A.[2]
[1]SC Medicina Interna - AUSL Valle d'Aosta; [2]Divisione di Epidemiologia Clinica - Città della Salute e della Scienza di Torino

Background: Northern Italy has been one of the first European areas which experienced a major COVID-19 outbreak in 2020. The most common complication triggered by COVID-19 is the acute respiratory distress syndrome, often seen in the presence of cytokine storm and immune system hyperactivation, leading to an extremely high mortality rate in older and frail patients. Several immune modulators have been studied in this setting, as well as steroids or interleukin 1 or 6 antagonists. Janus kinase (JAK) – STAT signaling is another critical cellular pathway involved in the inflammatory response. Thus, the JAK 1/2 inhibitor Ruxolitinib, recently approved for the treatment of steroid-refractory graft-versus-host disease, appeared as a promising agent for patients with severe or critical COVID-19.
Aims: To assess the clinical impact of Ruxolitinib on patients with severe or critical COVID-19.
Methods: We collected data of all COVID-19 patients admitted to the Aosta Valley Regional Hospital, Italy, since the beginning of the pandemic. We restricted the analysis on patients requiring continue positive airway pressure (CPAP) support. Ruxolitinib was given through a compassionate use program (CUP) approved by the Italian National Health Authorities and the Ethics Committee at Spallanzani Hospital in Rome, Italy. Written informed consent was obtained for all patients. We compared the outcome of patients admitted before April the 11th, date of Ruxolitinib availability in our Center, with all patients consequently enrolled in the Ruxolitinib CUP until its closure, on December the 15th 2020. The primary objective of the study was time to recovery, defined as the time from hospital admission to the end of oxygen requirement or discharge, or death for any cause. The 30-day cumulative incidence of recovery comparison was estimated with the Gray test. The impact of variables on outcome was estimated accordingly to the Fine&Gray model for competing risks. The study was performed before COVID-19 vaccines availability.
Results: Overall, 178 patients were considered eligible for the analysis, 89 (50%) in the standard of care (SOC) group, 89 (50%) in the Ruxolitinib group. Ruxolitinib was given at the dosage of 5mg BID for 7 days, followed by 3 days of 5mg once a day. The median age of patients in the SOC group was 70.4 (IQR 63.3 - 79.4) years, versus 76.0 (IQR 68.8 – 82.2) years of patients in the Ruxolitinib group (p= 0.005). No statistically significant differences emerged between the two groups among the other variables analyzed, such as gender, comorbidities, COVID-19 symptoms, previous treatment with anti-aggregants or anti-coagulants, chest X-ray Brixia severity score at admission. 30-day cumulative incidence of recovery were 43.8% and 58.8% in SOC group and Ruxolitinib group, respectively (p= 0.0075). When covariates were included in the Fine&Gray model, patients in the Ruxolitinib group showed significantly better time to recovery [Hazard Ratio 1.54 (95%CI 1.05 – 2.26, p= 0.028)]. The propensity score on time to recovery, estimated using multinomial logistic modelling on the same variables used in the covariates adjustment, showed an Hazard Ratio of 1.91 (95%CI 1.29 – 2.83, p= 0.001) between patients in the Ruxolitinib group compared to SOC. No severe adverse events have been reported in patients treated with Ruxolitinib.
Summary/Conclusion: Despite a significantly higher median age, patient with severe and critical COVID-19 requiring CPAP treated with Ruxolitinib showed a significantly better time to recovery and reduced mortality compared to SOC patients, in a single-Center experience. No severe drug-related toxicity has been reported. Ruxolitinib immune-modulating potential should be further explored.



166. CELL BLOOD COUNT ALTERATIONS IN THE POST-ACUTE PHASE OF SYMPTOMATIC SARS-COV-2 INFECTION

Di Terlizzi F.[1], Bergamaschi G.[2], Barteselli C.[2], Calabretta F.[2], Lenti M.V.[1], Soriano S.[1], Santacroce G.[1], Merli S.[2], Rossi C. M.[2], Sabatini U.[1], Corazza G. R.[1], Di Sabatino A.[1]
[1]Internal Medicine Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; Department of Internal Medicine & Medical Therapy, University of Pavia, Italy; [2]Internal Medicine Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Introduction: Sars-CoV-2 infection is often characterized by hematologic manifestations such as anemia, cell blood count alterations and disorders of hemostasis like venous thromboembolic events and hemorrhagic phenomena. Few data are available concerning abnormal blood cell counts or hematological parameters in the post COVID period. In our study we investigated the prevalence of abnormalities in hematological parameters during a follow-up period lasting up to one year in patients previously hospitalized for COVID-19 in an Internal Medicine Unit.
Patients and methods: We conducted a single-center, retrospective, observational study on the prevalence of abnormalities in hematological parameters after clearance of SARS-CoV-2 infection in patients who had been admitted to the internal medicine unit of San Matteo Hospital Foundation (Pavia, Italy), during the acute phase of the disease.
We investigated 83 patients, admitted to the internal medicine unit with a laboratory-confirmed diagnosis of COVID-19, for whom hematological data collected 1 to 12 months following disease onset were available. Median time to follow-up was 83 days (IQR 62-99 days), hematological parameters evaluated are: hemoglobin value, count of polymorphonuclear cells, lymphocytes, eosinophils, platelets, IgM B memory cells. Symptoms that may have affected quality of life in the post COVID period were not evaluated.
Results: During follow-up Hb concentration and number of lymphocytes and eosinophils increased, but remained below the lower limit of normal in over 30% of cases. Peripheral blood neutrophils (PMN) decreased and platelets increased during follow-up, but only a minority of patients had abnormal PMN or platelet counts. At both diagnosis and follow-up anemia was more prevalent in females, but gender-related differences were not statistically significant due to the low number of females in the study. At diagnosis the number of lymphocytes was not influenced by gender; during follow-up, in contrast, lymphocytes were lower in females and more females had lymphocytes below 1.5x10 9 /L (13 of 21 compared with 22 of 61 males; OR 2.88, 95% CI 1.04-8.02, p=0.045). The number of IgM memory B cells was assessed in a small subset of patients (N=7); IgM memory B cells increased at follow-up, but in all tested patients both baseline and follow-up values well below the lower limit of normal.
Conclusions: Follow-up was characterized by a general improvement in blood cell counts. Although Hb concentration, platelets, lymphocytes and eosinophil number increased during follow-up, a significant proportion of patients had persistent anemia and/or low lymphocyte and eosinophil counts, with over 70% of patients showing some blood cell count alteration at follow-up. Despite the low number of cases, we could show that IgM memory B cells increased significantly during follow-up, but remained below the lower limit of normal in all tested patients .

167. PERSISTENLY ELEVATED PENTRAXIN 3 IN PATIENTS THAT DEVELOP ANXIETY AND DEPRESSION AFTER COVID-19

De Lorenzo R.[1], Mazza M. G. [2], Sciorati C.[3], Palladini M.[2], Merolla A.[1], Bottazzi B.[4], Garlanda C.[4], Ciceri F. [5], Benedetti F.[2], Rovere-Querini P.[3], Manfredi A.[6]
[1]Vita-Salute San Raffaele University, Milano, Italy; [2]Psychiatry & Clinical Psychobiology, Division of Neuroscience, IRCCS Scientific Institute Ospedale San Raffaele, Milano, Italy; [3]Unit of Innate Immunity and Tissue Remodeling, Department of Internal medicine, Division of Immunology, Transplantation and Infectious Diseases, IRCCS Ospedale San Raffaele, Milan, Italy; [4]IRCCS Humanitas Research Hospital, Rozzano; [5]Hematology and Bone Marrow Transplant Unit, IRCCS Ospedale San Raffaele, Milan, Italy; [6]Unit of Autoimmunity and Vascular Inflammation, Division of Immunology, Transplantation and Infectious Diseases, IRCCS Ospedale San Raffaele, Milan, Italy

Background: Clinical manifestations of Coronavirus Disease 2019 (COVID-19) often persist after acute disease resolution. Underlying molecular mechanisms are largely unclear.
Methods: Ninety-four COVID-19 patients, prospectively followed at a single-reference hospital during the first pandemic wave, were included. Plasma levels of pentraxin 3 (PTX3), the complement components C3a and C5a, and of chitinase-3 like-protein-1 (CHI3L1) were measured at baseline, at 1 and at 6 months after hospital discharge. Associations with post-COVID-19 sequelae at 6 months were investigated.
Results: Baseline PTX3, C5a, C3a and CHI3L1 did not predict post-COVID-19 sequelae. The extent of the reduction of PTX3 over time associated with lower depressive and anxiety symptoms at 6 months (both $p < 0.05$). When entering sex, need of intensive care unit or non-invasive ventilation during hospital stay, psychiatric history, and baseline PTX3 as nuisance covariate into a Generalized Linear Model (GLZM), the difference between baseline and 6-month PTX3 levels (delta PTX3) significantly predicted depression ($\chi2=4.66$, $p=0.031$) and anxiety ($\chi2=4.67$, $p=0.031$) at 6 months. No difference in PTX3 levels or in delta PTX3 was found in patients with or without persisting or new onset physical symptoms at 6 months. Plasma levels of C3a, C5a, and CHI3L1 did not correlate with PTX3 levels at either time point and failed to associate with residual or *de novo* respiratory or systemic clinical manifestations of the disease at 6 months.
Conclusions: Persistently high levels of plasma PTX3 after acute COVID-19 associates with depressive and anxiety symptoms, suggesting a potential involvement of PTX3 in post-COVID-19 psychopathology.

168. EFFICACY AND SAFETY OF ANTI-COVID-19 MONOCLONAL ANTIBODIES AND ANTIVIRALS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

Ramirez G.A.[1], Gerosa M.[2], Arroyo-Sánchez D.[3], Asperti C.[1], Argolini L.M.[4], Gallina G.[1], Bellocchi C.[5], Cornalba M.[2], Scotti I.[4], Suardi I.[2], Beretta L.[5], Moroni L.[1], Bozzolo E.P.[6], Caporali R.F.[2], Dagna L.[1]
[1]Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS Ospedale San Raffaele, Milan, Italy and Università Vita-Salute, Milan, Italy; [2]Department of Clinical Science of Community Health and Research Center for Adult and Pediatric Rheumatic Diseases, Università degli Studi di Milano, Milan, Italy and Unit of Rheumatology, ASST Gaetano Pini, Milan, Italy.; [3]Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS Ospedale San Raffaele, Milan, Italy; Department of Immunology, Hospital Universitario 12 de Octubre, Madrid, Spain and Instituto de Investigación Biomédica Hospital 12 de Octubre, Madrid, Spain; [4]Unit of Rheumatology, ASST Gaetano Pini, Milan, Italy; [5]Department of Clinical Science of Community Health and Research Center for Adult and Pediatric Rheumatic Diseases, Università degli Studi di Milano, Milan, Italy and Referral Center for Systemic Autoimmune Diseases, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy; [6]Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS Ospedale San Raffaele, Milan, Italy

Introduction: Systemic lupus erythematosus (SLE) is a chronic multi-organ disease characterised by immune dysregulation prompting autoimmune phenomena and dysfunctional response to infections. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-related disease (COVID-19) has been a major public health challenge for the last three years, causing an unprecedented global increase in death and disability rates. Although COVID-19-related morbidity and mortality are currently declining in the general population, patients with immune-mediated disorders such as SLE might still be at increased risk of severe COVID-19 course and post-COVID-19 sequelae (1). SARS-CoV-2-specific antiviral drugs and monoclonal antibodies have been developed to facilitate COVID-19 resolution in vulnerable subjects but data on their efficacy and safety in patients with immune-mediated diseases are scarce (2).
Objectives: To assess the course of SARS-CoV-2 infection in patients with SLE treated or untreated with COVID-19-specific agents and to evaluate SLE status after COVID-19.
Methods. We enrolled patients with SLE who had COVID-19 from February 2020 to December 2022 and who were treated with antivirals and/or monoclonal antibodies among three tertiary referral centres. Each SLE patient treated with antiviral/monoclonal antibodies was matched with two untreated patients by age, sex, SLE extension and duration. We collected data on COVID-19 clinical features at presentation, time to viral clearance and post-COVID-19 sequelae. COVID-19 severity at presentation was measured through a 0-4 analogue scale as per the World Health Organization Guidelines (3). In parallel, we recorded information on SLE activity (SLE disease activity index 2000, SLEDAI-2K) and damage (SLE International Collaborating Clinics/American College of Rheumatology Damage Index, SDI) before and after COVID-19 and concomitant treatments. Data are expressed as median (interquartile range, IQR) unless otherwise specified.
Results: In the three-year observation timeframe, 39% of the whole three-Centre cohort had COVID-19 at least once. Twenty-one patients (19 women) were treated with antivirals (n=15) or monoclonal antibodies (n=6) and were compared to 42 untreated patients. Treated patients with SLE had higher levels of disease activity [SLEDAI-2K=4(1-5) vs 0 (0-2); p=0.009] and numerically higher burdens of chronic damage [SDI=1 (0-4) vs 0 (0-2); p=0.060] than control subjects. Patients who received antivirals/monoclonal antibodies were also taking higher doses of prednisone [5 (0-10)mg vs 0 (0-3)mg; p=0.002] at COVID-19 onset. While vaccination coverage did not differ between the two groups, treated patients had more severe COVID-19 than controls but did not demonstrate differences in terms of short- and long-term course (Table 1), including the development of SLE exacerbations. Two patients reported mild adverse events with monoclonal antibodies (muscle cramps, chest pain that resolved spontaneously); one patient developed an itchy skin rash and gastrointestinal symptoms with nirmatrelvir/ritonavir.
Conclusions: Patients with SLE and COVID-19 who were treated with antivirals/antibodies had a favourable COVID-19 and post-COVID-19 course, despite a more severe presentation and a higher risk of deterioration due to disease activity and therapies. Treatment with targeted drugs for COVID-19 was generally well tolerated.
References
1) Strangfeld A et al, Ann Rheum Dis, 2021
2) Talarico R et al., Clin Exp Rheum, 2023
3) World Health Organization. Clinical management of COVID-19; Interim guidance 27 May 2020.

Table 1. COVID-19 presentation and course. Treated (n=21) - Untreated (n=42)

	Untreated (n=42)
Number of vaccine doses	3 (2-3)
Time from last vaccine administration (days)	120 (41-210)
COVID-19 features	
WHO class at presentation	0 (0-1)
Symptoms at presentation: n (%)	
Dyspnoea	3 (7)
Fever	25 (60)
Upper Respiratory Symptoms	35 (83)
GI symptoms	2 (5)
Pneumonia	3 (7)
COVID-19 course	
Time to symptom resolution (days)	7 (3-7)
Time to viral clearance (days)	10 (7-14)
Any complication: n(%)	6 (14)
Hospitalisations: n(%)	0 (0)
Long COVID: n(%)	6 (14)
Deaths: n(%)	1 (3)
SLE follow up after COVID-19	
Lupus flares: n(%)	4 (10)

169. MULTI HORMONAL AND METABOLIC DEFICIENCY IN HOSPITALIZED PATIENTS WITH COVID-19 SYNDROME

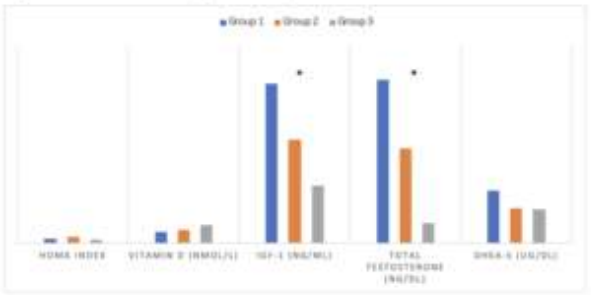
Arcopinto M., D'Assante R., Rainone C., D'Argenzio C. , Crisci G., Giardino F., Cittadini A.
Dipartimento di Scienze Mediche Traslazioni, Università Federico II di Napoli

Introduction: The novel coronavirus infection, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread worldwide over the past couple years, with than 760 million confirmed cases and over 6 million deaths globally, as reported by the World Health Organization (). The clinical presentation of SARS-CoV-2 infection is highly variable, ranging from asymptomatic infections to severe cases of Acute Respiratory Distress Syndrome (ARDS) that can be life-threatening. In accordance with such clinical variability, symptomatic patients who need hospitalization may require a wide array of respiratory support including conventional oxygen therapy, noninvasive respiratory support strategies (HFNO, helmet NIV) or intubation in refractory cases. Although several predictors of in-hospital outcomes have been proposed, little evidence exists regarding the hormone profile in such patients and their impact on in-hospital outcomes. This appears particularly relevant insofar as a multiple hormone deficiency syndrome is known to impact on the progression of several diseases. In particular, no comprehensive, multivariable hormonal/metabolic evaluation has been performed in this setting.
Methods: We enrolled ninety consecutive patients hospitalized between 2020 and 2021. All patients were blood sampled as clinically required, received standard medical care and ventilatory support as needed. All patients underwent an additional blood sample within 24 hours from the admission to evaluate the following hormonal parameters of interest: vitamin D, total testosterone, dehydroepiandrosterone-sulfate (DHEA-S), thyroid hormones, insulin-like growth factor-1 (IGF-1), vitamin D and insulin. The following clinical outcome measure were collected: maximum ventilatory support, length of stay, rate of orotracheal intubation. Baseline hormonal profile of the patients' population has been evaluated according to the disease severity indicated by the maximum ventilatory support needed during the hospital stay according to the following subdivision: no need of oxygen (group 1); oxygen therapy needed (group 2); helmet NIV or orotracheal intubation (group 3).
Results: Baseline clinical information including anthropometrics, comorbidities, maximum respiratory support used and length of stay, as well as hormonal profile at the admission are reported in Table 1. No patients at the admission were on ventilatory support. The evaluation of the individual hormone variables in the three severity subgroups (Fig. 1) showed that hormone values at study entry were decreasing as the severity of the underlying covid-related pathology increased. This observation is confirmed for total testosterone (ANOVA, p=0.048), IGF-1 (ANOVA, p=0.002) and, partially, for DHEA-S. On the other hand, insulin resistance did not show any significant difference across the severity spectrum. Finally, circulating vitamin D levels appear positively correlated with the degree of severity developed by patients; this trend is in keeping with the emerging immunomodulatory role of this hormone.
Conclusion: A multiple hormone deficiency syndrome is common in the COVID-19 disease and there is also a graded association between the number of HD and the extent of the patients' ventilatory impairment. These findings confirm the pivotal role of preserved hormone axes in COVID-19 progression.

Table 1. Demographics, clinical and hormonal profile, in-hospital outcomes of the study population.

Data are shown as mean ± standard deviation where not indicated.

Fig. 1. Trend in hormonal levels according to disease severity



170. INTERPLAY BETWEEN INFLAMMATORY AND IMMUNOLOGIC MARKERS IN THE PATHOGENETIC CHAIN OF RESPIRATORY FAILURE OF COVID-19 PATIENTS

Regolo M.[1], Sorce A.[2], Vaccaro M.[3], Stancanelli B. [4], Giangreco F. [5], Fichera D.[3], Castelletti F.[1], Lanzafame A.[1], Noto P.[3], Malatino L.[1]
[1]Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy; [2]Department of Health Promotion Sciences, Maternal and Infant Care, Internal Medicine and Medical Specialties, "G. D'Alessandro" (PROMISE), Unit of Nephrology and Hypertension, European Society of Hypertension Excellence Centre, University of Palermo, Palermo, Italy; [3]Department of Emergency Medicine, San Marco-Polyclinic Academic Hospital, Catania, Italy; [4]Unit of Internal Medicine, San Marco-Polyclinic Academic Hospital, Catania, Italy; [5]Academic Unit of Internal Medicine, Cannizzaro Hospital, Catania, Italy

Introduction and aim: The severe respiratory failure caused by COVID-19 is primarily manifested as acute respiratory distress syndrome (ARDS), which is atypical, although often falling within the Berlin definition of ARDS. As a matter of fact, inflammation plays a key role in the disease worsening, if any, of COVID-19 patients.
In the present study, we evaluated the dynamic changes of neutrophils, lymphocytes and CRP during hospitalization. Finally, we also assessed the link between CRP, neutrophils and lymphocytes with PaO2/FiO2 ratio, to better understand the individual role of mediators leading to respiratory failure.
Methods: In this retrospective, multicentre, observational study, 764 patients were selected among a total of 963 subjects who were consecutively admitted to two hospitals in Catania, Italy (San Marco Hospital and Cannizzaro Hospital), between October 2020 and September 2022. Patients with history of pharmacological treatments or clinical conditions affecting leukocyte count and/or CRP were excluded.
Total and differential leukocyte count and CRP levels were measured three times: at baseline, on the median day of hospitalization, and at discharge.
The sample was initially divided into three groups, according to outcome

(survivors, ICU admitted, deceased). We analyzed the correlations between NLR and CRP with P/F ratio in ICU-admitted and deceased patients and assessed their strength through a multiple linear regression. A Cox regression model was also built to verify the associations between biomarkers and outcome. Finally, we performed a mediation analysis, to verify if the existing relationships between inflammatory biomarkers and P/F ratio resulted mediated by an external variable. A moderation analysis was also done to estimate if the effect of such variable could influence strength and direction of these relationships.

Results: Median age of the whole sample was 74 years (IQR 72-75) and 54% were men. As regards comorbidities, no statistically differences were observed between the three subgroups.

First, we analysed the temporal trends shown by NLR and CRP during hospitalization: deceased patients showed an increase of NLR from baseline over time; at variance, CRP steeply increased at the end of hospitalization only in ICU-admitted patients.

The correlation between NLR and P/F was not statistically significant in ICU-admitted patients ($\rho = -0.03$ $p = 0.7203$), but resulted significant in deceased patients ($\rho = -0.26$ $p = 0.0025$). An opposite phenomenon was observed in the correlation between CRP and P/F ratio in the two subgroups.

In the multiple linear regression model adjusted for age, sex, and comorbidities, only CRP significantly predicted P/F in ICU-admitted patients; conversely, only NLR predicted P/F in deceased patients. In the Cox regression model, adjusted for the main confounders, NLR predicted mortality independently of CRP and other confounders (HR 1.77, using NLR z-score, $p<0.0001$). ICU admission was significantly associated with both biomarkers, although CRP showed a higher HR, a more significant p value, and a more restricted confidence interval (HR 2.4 [1.92 – 2.61], $p<0.0001$).

Based on our results, showing a different association of NLR and CRP with P/F in deceased and ICU-admitted patients, we wondered whether the relationship between CRP and P/F could be mediated by another variable that could partly explains why CRP has a greater weight than NLR in influencing P/F in ICU patients, with no significant association with P/F in deceased patients. As first step, we demonstrated by repeated measures ANOVA that the mean levels of neutrophils and lymphocytes differed significantly in the various time intervals, comparing patients grouped for outcome.

Finally, mediation analysis was made to examine the mediating effect of neutrophils, lymphocytes, and age on the relationship between CRP and P/F. Age, ANC, CRP and lymphocytes significantly and directly influenced P/F, while the influence of CRP on P/F was also mediated by ANC, with no mediating effect of lymphocytes and age.

Moreover, the direct effect of CRP on P/F in presence of neutrophils as mediator was stronger (83.7 %; b = -2.849 $p<0.001$), as compared to indirect effect mediated by neutrophils (16.3%; b-0.035; $p=0.001$). Hence, these results suggest that neutrophils partially mediated the relationship between CRP and P/F.

Conclusions: NLR and CRP show different time-courses during hospitalization in COVID-19 patients, with a characteristic pattern depending on outcome. An imbalance between innate and adaptive immunity (increase in NLR), associated with systemic inflammation (increase in CRP), are linked to deterioration of respiratory function, with a specific prediction of outcome: NLR predicted P/F in deceased patients, whereas CRP predicted P/F only in ICU-admitted patients. The mediation analysis confirmed that CRP, neutrophils, lymphocytes and age are linked with P/F in the same pathogenetic chain leading to respiratory failure.

171. AUTOINFLAMMATORY DISEASES DURING COVID-19: A SURVEYMONKEY EPIDEMIOLOGICAL INVESTIGATION

Verrecchia E.[1], Sicignano L.L.[1], Gerardino L.[1], Massaro M.G.[1], Murace C.A.[1], Barillaro C.[1], Montalto M.[1], Rigante D.[2], Sangiorgi E.[3], Manna R.[4]
[1]Department of Geriatrics, Università Cattolica del Sacro Cuore, Rome, Italy; [2]Department od Pediatrics, Università Cattolica del Sacro Cuore, Rome, Italy; [3]Department of Genetics, Università Cattolica del Sacro Cuore, Rome, Italy; [4]Periodic Fever Center, Università Cattolica del Sacro Cuore, Rome, Italy

Introduction: In case of COVID-19 infection, excessive activation of the immune system has been observed leading to a cytokine storm, which consists in activation of pro-inflammatory cytokines [1-4]. Elevated serum cytokine and chemokine levels, NLR, activation of NLRP3 inflammasome are correlated with the severity of the disease and adverse outcome, suggesting a possible role for hyper-inflammatory responses in COVID-19 pathogenesis. Monogenic autoinflammatory diseases were initially discovered among patients with periodic fevers. The identification of mutations in MEFV, coding for Pyrine, as the cause of familial Mediterranean fever (FMF), linked for the first time a coherent autoinflammatory phenotype to a monogenic determinant. To date, more than 50 diseases have been characterized that affect different components of the innate immune response e.g. mevalonate kinase (MVD) deficiency, cryopyrinopathies (CAPS), TNF receptor mutation syndrome (TRAPS syndrome) etc. These patients are usually treated with Colchicine or biologic drugs that antagonizes Interleukin-1ß, which is considered the first cytokine initiating the inflammation.

Objectives: The purpose is to detect the natural history and outcome of COVID-19 disease in patients already being treated with colchicine or anti-IL1 biological therapy for autoinflammatory diseases.

Methods: An epidemiological observational investigation about Autoinflammatory Diseases during COVID-19 diseases including 9 specific questions (sex, symptoms, drugs, colchicine dose, severity, comorbidity) was approved by Steering Committees of Periodic Fever Research Center, Catholic University, Rome (Italy) of the International Society of Systemic Auto-Inflammatory Diseases (ISSAID) and Data Protection Officer of the "A.Gemelli" Polyclinic, Rome (Italy). It is active from June of 2019 on the SurveyMonkey platform. (https://it.surveymonkey.com/r/YWLBD9D). The access by physicians or patients is free.

Results: Patients were 68% females and 32 % males, affected by Familial Mediterranean Fever (58% of cases), PFAPA (22%), TRAPS (6%), Hyper- IgD syndrome – mevalonate kinase deficiency (6%), Cryopyrin-associated Periodic Syndrome (2%), Still's disease (2%), and other autoinflammatory diseases (4%). COVID-19 symptoms reported were similar to general population: fever (80%), fatigue (70%), cough (60%), myalgia (55%), headache (50%), gastrointestinal symptoms (40%), loss of taste and smell (25%), dyspnea (15%), other (20%). No hospitalization was observed over one month; no mechanical ventilation and none death has been reported. The pharmacological treatments taken by patients were: Cochicine (68%), Canakinumab (12%), Steroids (8%), Anakinra (5%), others (5%), none (2%) as shown in Table 1. Other results (comorbidity and other) will be published in a specific report.

Conclusion: The SURVEYMONKEY search has been demonstrated easy to access and simple to get results of multiple investigations about Autoinflammatory diseases. The main autoinflammatory disease is Familial Mediterranean Fever because of high percentage of patients afferent to Periodic Fevers Research Center in Rome. The symptoms reported are those typical of COVID-19, but no bacterial complication was observed. The treatments for autoinflammatory diseases (colchicine and IL-1 biologic treatment) were continued during the COVID-19 Infection in this cohort and they appear to be protective for the evolution of the disease, since the severity of manifestations was mild/moderate in the whole study population.

Acknowledgments: Prof Marco Gattorno (Gaslini - ISSAID) for his useful suggestions.
AIFP (Italian Association of periodic fevers). SIR (Italian Society of Rheumatology), SIMI (Italian Society of Internal medicine).

References

Kharouf F, Ishay Y, Kenig A et al. Incidence and course of COVID-19 hospitalizations among patients with familial Mediterranean fever. Rheumatology 2021;60:SI85–SI89 doi:10.1093/rheumatology/keab577Güven SC, Erden A, Karakaş O et al. COVID-19 outcomes in patients with familial Mediterranean fever: a retrospective cohort study Rheumatology International 2021; 41:715–719 https://doi.org/10.1007/s00296-021-04812-8

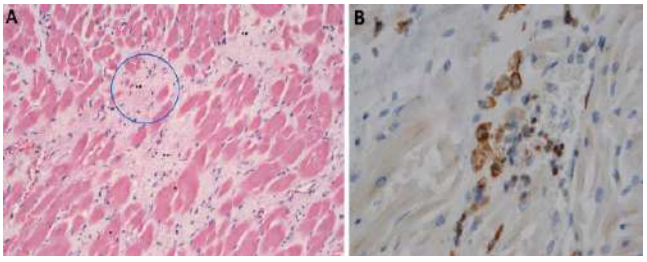
TABLE 1

TREATMENT	%
Colchicine	68,00
Canakinumab	12,00
Steroids	8,00
Anakinra	5,00
Others	5,00
None	2,00

172. CLINICAL-HISTOPATHOLOGICAL CORRELATION OF MYOCARDIAL INJURY IN SEVERE COVID-19 RELATED ACUTE RESPIRATORY DISTRESS SYNDROME.

Wu M.A.[1], Bartoli A.[1], Martini E. [1], Urso F. [1], Celano R.[1], Cogliati C.B.[1], Nebuloni M.[2], Colombo R. [3]
[1]Division of Internal Medicine, ASST Fatebenefratelli Sacco, Luigi Sacco Hospital, Department of Biomedical and Clinical Sciences, University of Milan, Milan Italy; [2]Pathology Unit, ASST Fatebenefratelli Sacco, Luigi Sacco Hospital, University of Milan, Milan, Italy; Department of Biomedical and Clinical Sciences, University of Milan, Milan Italy; [3]Division of Anesthesiology and Intensive Care, ASST Fatebenefratelli Sacco, Luigi Sacco Hospital – Polo Universitario, University of Milan, Milan, Italy

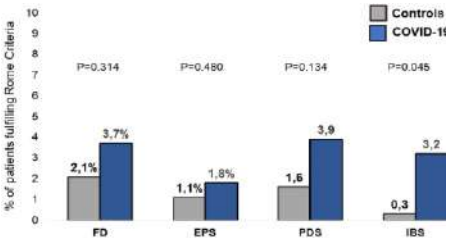
Background: COVID-19 is an illness affecting multiple organs, primarily targeting the lungs. However, the cardiovascular system is frequently involved and may be responsible for significant morbidity. It is unclear whether the myocardial injury is due to direct inflammatory involvement, strain secondary to respiratory damage, or endothelialitis. This study aimed to assess the occurrence of histologically confirmed damage to the myocardium and the correlation between clinical characteristics and pathological lung findings in individuals who died from severe COVID-19 related ARDS.
Methods: Analysis of cardiac and lung tissue samples from consecutive autopsies of patients who died in hospital from severe COVID-19 ARDS between February 2020 and March 2022. The samples were colored with hematoxylin-eosin and immunohistochemical markers (CD3, CD15, CD45, CD68, CD163) and examined by optical microscopy. The grade of inflammatory infiltrates was scored according to the Dallas criteria for myocarditis. For statistical analysis, the scores were categorized into two groups: A, no inflammatory infiltrate and B, grades 1 to 4. Furthermore, SARS-CoV-2 PCR was performed on myocardial tissue samples.
Results: 25/76 autopsies (32.9%) were in group B. Forty-one patients had complete clinical data available, 29 (70.7%) were in group A and 12 (29.3%) in group B. Major histopathological findings in the myocardium were the prevailing macrophagic infiltrate and myocardial edema, while lymphocytic infiltrate was rare. There was no difference between groups in clinical characteristics and severity at admission. However, the severity of capillary hyperpermeability reached during the hospitalization, characterized by marked hypoalbuminemia and acute fibrinous organizing pneumonia, was associated with myocardial inflammatory infiltrate. Finally, SARS-CoV-2 PCR was available in 33 patients and was positive in 10/23 (43.5%) patients in group A and 10/10 (100%) in group B (p=0.002). There were no differences in the survival curves according to the presence of myocardial inflammatory infiltrate (log-rank p=0.68) or PCR positivity (log-rank p=0.3).
Conclusions: histopathological myocardial injury occurs in one-third of severe COVID-19 patients and might worsen the clinical picture. Macrophages and myocardial strain due to lung involvement may play a role in the pathophysiology of COVID-19 myocardial injury.



173. POST-COVID-19 IRRITABLE BOWEL SYNDROME

Marasco G.[1], Cremon C.[1], Barbaro M.R.[1], Fusaroli P.[1], Ricci C.[2], Bellini M.[3], Pietrangelo A.[4], Corradini E.[4], Colecchia A.[4], Maconi G.[5], De Giorgio R.[6], Danese S.[7], Portincasa P.[8], Di Sabatino A.[9], Maggio M.G.[10], Venturi A.[1], Borghi C.[1], Zoli M.[1], Gionchetti P.[1], Viale P.[1], Stanghellini V.[1], Barbara G.[1]
[1]University of Bologna; [2]University of Brescia; [3]University of Pisa; [4]University of Modena and Reggio Emilia; [5]University of Milan; [6]University of Ferrara; [7]Humanitas University; [8]University of Bari; [9]University of Pavia; [10]University of Parma

Background: The long-term consequences of COVID-19 infection on the gastrointestinal tract remain unclear. Here we aimed to evaluate the prevalence of gastrointestinal symptoms and post-COVID-19 disorders of gut-brain interaction (DGBI) after hospitalization for SARS-CoV-2 infection.
Methods: GI-COVID19 is a prospective, multicenter, controlled study. Patients with and without COVID-19 diagnosis were evaluated upon hospital admission and after 1, 6, and 12 months post-hospitalization. Gastrointestinal symptoms, anxiety, and depression were assessed using validated questionnaires, namely theGastrointestinal Symptoms Rating Scale (GSRS), the Hospital Anxiety and Depression Scale (HADS), and the Rome IV Diagnostic Questionnaire for Functional Gastrointestinal Disorders in Adults.
Results: The study included 2183 hospitalized patients. The primary analysis included a total of 883 patients (614 COVID-19 patients and 269 controls) due to the exclusion of patients with pre-existing gastrointestinal symptoms and/or surgery. At enrollment, gastrointestinal symptoms were more frequent among COVID-19 patients than in the control group (59.3% vs. 39.7%, P<0.001). At the 12-month follow-up, constipation and hard stools were significantly more prevalent in controls than in COVID-19 patients (16% vs. 9.6%, P=0.019 and 17.7% vs. 10.9%, P=0.011, respectively). Compared to controls, COVID-19 patients reported higher rates of irritable bowel syndrome (IBS) according to Rome IV criteria: 0.5% vs. 3.2%, P=0.045. Factors significantly associated with IBS diagnosis included a history of allergies, chronic intake of proton pump inhibitors, and the presence of dyspnea. At the 6-month follow-up, the rate of COVID-19 patients fulfilling the criteria for depression was higher than among controls.
Conclusions: Compared to controls, hospitalized COVID-19 patients had fewer complaints of constipation and hard stools at 12 months after acute infection. COVID-19 patients had significantly higher rates of IBS than controls.



174. ADA-SCORE AS A PREDICTOR OF IN-HOSPITAL MORTALITY AMONG COVID-19 ELDERLY PATIENTS.

Bagnato C.[1], Alfano A.R.[1], Maggio E.[1], Taccari F.[1], Pirro M.[2], Pignatelli P.[1], Ceccarelli G.[3], Oliva A.[3], Filoni D.[1], Schipa C.[1], Caltabiano C.[1], Mereu E.[1], Usai L.[1], Bianconi V.[2], Mannarino M.R.[4], Figorilli F.[2], Cosentini E.[2], Pugliese F.[3], Ettorre E.[1], Venditti M.[5], Mastroianni C.M.[3], Violi F.[6], Loffredo L.[1]
[1]Department of Clinical Internal, Anesthesiologic and Cardiovascular Science, Sapienza University of Rome, Viale del Policlinico, 155, 00161 Rome;; [2]Unit of Internal Medicine, Department of Medicine and Surgery, University of Perugia, Perugia, Italy. ; [3]Department of Public Health and Infectious Diseases, Sapienza University of Rome, Piazzale Aldo Moro 5, 00185, Rome, Italy. ; [4]Unit of Internal Medicine, Department of Medicine and Surgery, University of Perugia, Perugia, Italy; [5]Department of Public Health and Infectious Diseases, Sapienza University of Rome, Piazzale Aldo Moro 5, 00185, Rome, Italy; [6]Mediterranea Cardiocentro-Napoli, Via Orazio, 2, 80122 Napoli, Italy

Background:COVID-19 is a pandemic associated with thrombotic events, contributing significantly to mortality and morbidity. Elderly patients hospitalized for COVID-19 have an increased risk of hospital complications and mortality. A hypercoagulation state associated with both arterial and venous thrombotic events is responsible for the most severe forms of COVID-19, probably due to the host's inflammatory response to the virus and its immune activation. Recently, ADA (Age–D-dimer–Albumin) score resulted as a useful tool to predict arterial and venous thrombosis in several settings such as COVID and acutely ill hospitalized medical patients.
Objective: Our study aims to evaluate the ADA score as a predictor of hospital mortality among elderly patients with COVID-19 severe pneumonia.
Methods: We recruited 787 hospitalized elderly (> 65 years old) patients affected by COVID-19 severe pneumonia. Anamnestic, laboratory, and clinical data were collected. The normalized ADA score was calculated according to the following formula: ADA score = -0.5 * albumin + 0.4 * D-dimer/100+ 0.3* age. Chi-square tests were run to identify risk factors associated with mortality in our sample. A logistic regression analysis was performed to iden-

tify predictors of mortality.
Results: Seven hundred and eighty-seven patients were recruited; 129 out of 787 patients died during the hospitalization. Clinical characteristics of the population and the comparisons between alive and dead patients are reported in the table. The logistic regression analysis showed that ADA Score (H.R 1,048, C.I. 95% 1,012-1,085, p=0,008), thrombotic events (H.R. 2,452, C.I. 95% 1,224-4,913, p=0,011), dementia (H.R. 4,155, C.I. 95% 2,249-7,676, p<0,0001), chronic kidney disease (H.R. 2,137, C.I. 95% 1,228-3,718, p=0,007), atrial fibrillation (H.R. 3,246, C.I. 95% 1,676-6,287, p<0,0001) and Intensive Care Unit (H.R. 3,002, C.I. 95% 1,521-5,925, p=0,002) independently predicted death in this population.
Conclusions: In this study, we provided evidence that the ADA score is an independent predictor of mortality in elderly patients with COVID-19-related pneumonia. According to the results of our study, the ADA score could help physicians to identify elderly patients at increased risk of mortality.

Table: Clinical characteristics of the population.

	Alive	Death	p
N.	658	129	-
Male	322/658 322 (48.9%)	66/129 66 (51.2%)	0,644
Obesity	41/205 41 (20%)	13/56 13 (23.2%)	0,599
Active Smoking	58/314 58 (18.5%)	22/83 22 (26.5%)	0,105
Former Smoking	11/133 11 (8.3%)	1/20 1 (5%)	0,612
Diabetes	81/433 81 (18.7%)	29/101 29 (28.7%)	**0,025**
Hypertension	313/658 313 (47.6%)	78/129 78 (60.5%)	**0,024**
Dyslipidemia	40/200 40 (20%)	8/51 8 (15.7%)	0,484
CAD	58/657 58 (8.8%)	26/128 26 (20.3%)	**<0,0001**
Heart failure	67/436 67 (15.4%)	27/100 27 (27%)	**0,006**
Peripheral arterial disease	70/657 70 (10.7%)	24/126 24 (19%)	**0,008**
Previous venous thromboembolism	9/208 9 (4.3%)	2/54 2 (3.7%)	0,839
Atrial fibrillation	49/658 49 (7.5%)	34/129 34 (26.4%)	**<0,0001**
Previous TIA/Stroke	31/658 31 (4.7%)	15/127 15 (11.8%)	**0,002**
COPD	64/655 64 (9.8%)	22/128 22 (17.2%)	**0,014**
Dementia	58/658 58 (8.8%)	48/129 48 (37.2%)	**<0,0001**
Cancer in the last 5 years	51/645 51 (7.9%)	17/117 17 (14.5%)	0,086
Thrombotic events	42/652 42 (6.4%)	31/128 31 (24.2%)	**<0,0001**
Intensive Care Unit	62/656 62 (9.5%)	37/128 37 (28.9%)	**<0,0001**
Chronic Kidney Disease	103/643 103 (16%)	55/128 55 (43%)	**<0,0001**
P/F ratio	98/658 98 (14.9%)	56/129 56 (43.4%)	**<0,0001**
IMPROVEDD	2.3±1.2	2.7±1.5	**0,003**
ADA Score	54.2±11.2	65.8±9.4	**<0,0001**
Length of Stay	19.4±18.3	18.6±13.6	0,733

175. THE ADA SCORE ACCURACY TO PREDICT MORTALITY IN SARS-COV-2 PATIENTS

Pannunzio A.[1], Palumbo I.M.[1], Loffredo L.[2], Violi F.[3], Maggio E.[4], Pignatelli P.[4], Totè C.M.[1], Magna A.[1], Pirro M.[5], Ceccarelli G.[6], Oliva A.[6], Cancelli F.[6], D'Ardes D.[7], Amitrano M.[8], Taliani G.[1], Cangemi R.[1], Lichtner M.[6], Falcone M.[9], Orlando F.[1], Pugliese F.[6], Venditti M.[6], Mastroianni C.M.[6]
[1]Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy; [2]Department of Clinical Internal, Anesthesiology and Cardiovascular Sciences, Sapienza University of Rome, Rome, Italy; [3]Sapienza University of Rome, Rome, Italy; [4]Department of Clinical Internal, Anesthesiologic and Cardiovascular Sciences, Sapienza University of Rome, Viale del Policlinico, 155, 00161, Rome, Italy; [5]Unit of Internal Medicine, Department of Medicine, University of Perugia, Perugia, Italy; [6]Department of Public Health and Infectious Diseases, Sapienza University of Rome, Piazzale Aldo Moro 5, 00185, Rome, Italy; [7]Clinica Medica, Department of Medicine and Aging, "G. D'Annunzio, University of Chieti-Pescara, Chieti, Italy; [8]Internal Medicine Unit, Moscati Hospital, Avellino, Italy; [9]Infectious Diseases Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

COVID-19 in associated with high risk of morbility and mortality due, among the other causes, to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) related pneumonia. It had been demonstrated that COVID-19 patients are at high risk of developing thrombotic events of both venous and arterial districts. In light of this evidence, the ADA score was validated to identify patients at higher risk for thrombosis in the COVID-19 setting. The ADA score is composed of: Age, D-dimer and Albumin. Nevertheless, it remains unclear whether it could be used for predicting a higher risk of mortality.
In this observational retrospective cohort multi-center study performed in non-Intensive Care Unit (ICU) medical wards and ICU, we included adult (≥18 years) patients with laboratory-confirmed COVID-19 diagnosis from March 2020 to March 2021. COVID-19 pneumonia was diagnosed by chest computed tomography. Routine analysis included D-dimer and albumin and were executed within 48 hours from the admission at the hospital. Death occurring during the hospitalization was the primary endpoint of the study. Data regarding demographic characteristics, comorbidities and concurrent therapy were collected as well as history of diabetes mellitus, hypertension, cardiovascular disease, chronic kidney disease and obesity.
Comparison between groups was performed by chi square test or Mann Whitney test. A multivariable logistic regression model was executed and the beta coefficients obtained were used to derive weighing factors of mortality. All tests were two-tailed and a value of P<0.05 was considered as statistically significant. Analyses were performed using SPSS Statistics version 25.0.
One thousand two hundred and ninety-six COVID-19 patients (48% males and 52% females) were recruited. Two hundred and fifty-three deaths (19.5%) occurred in the cohort during the hospital stay. Thrombotic events of the cohort were 145 (11,2%). Compared to survivors, patients who died during the hospitalization had a significant higher ADA Score and a higher prevalence of former smoking habit, diabetes, hypertension, CAD (Coronary Artery Disease), heart failure, peripheral arterial disease, atrial fibrillation, previous TIA/Stroke, chronic obstructive pulmonary disease, dementia, neoplasia in the last 5 years, thrombotic events, need of ICU care, chronic kidney disease and low P/F ratio. A logistic regression analysis was performed to analyze the predictors of death in COVID patients, and we found that: ADA Score (HR 1,070, C.I. 95% 1,037-1,104, p<0,0001), thrombotic events (HR 2,083, C.I. 95% 1,086-3,997, p=0,027), Intensive Care Unit (HR 2,716, C.I. 95% 1,442-5,117, p=0,002), chronic kidney disease (HR 2,029, C.I. 95% 1,196-3,442, p=0,009), atrial fibrillation (HR 3,140, C.I. 95% 1,663-5,929, p<0,0001) and previous TIA/Stroke (HR 2,732, C.I. 95% 1,277-5,845, p=0,010) independently predicted death in this population. In conclusion, this study shows that ADA score predicts mortality in patients with SARS-CoV-2 and it could be clinically useful to identify patients at greater risk of death.

176. ADA SCORE (AGE-D-DIMER-ALBUMIN) AND CT SEVERITY SCORE TO PREDICT THE IN-HOSPITAL THROMBOTIC EVENTS

Palumbo I.M.[1], Maggio E.[2], Bonito G.[3], Oliva A.[4], Pannunzio A.[1], Totè C.M.[1], Magna A.[1], Fallarino A.[1], Paraninfi A.[1], Alfano A.R.[2], Bagnato C.[2], Pugliese F.[3], Violi F.[5], Ricci P.[3], Pignatelli P.[2], Loffredo L.[2]
[1]Department of Translational and Precision Medicine, Sapienza University of Rome, Viale del Policlinico, 155, 00161 Rome; [2]Department of Clinical Internal, Anesthesiologic and Cardiovascular Science, Sapienza University of Rome, Viale del Policlinico, 155, 00161 Rome; [3]Department of Emergency Radiology and Department of Radiological Sciences, Policlinico Umberto I, Sapienza University of Rome, Viale del Policlinico 155, 00161, Rome; [4]Department of Public Health and Infectious Diseases, Sapienza University of Rome, Piazzale Aldo Moro 5, 00185, Rome; [5]Department of Clinical Internal, Anesthesiologic and Cardiovascular Science, Sapienza University of Rome, Viale del Policlinico, 155, 00161 Rome; Mediterranea Cardiocentro-Napoli, Via Orazio, 2, 80122 Napoli

Introduction: SARS-CoV2 infection has been defined an "endothelial disease", with reference to the higher risk of arterial and venous thrombotic events in affected patients. The ADA (Age-D-Dimer-Albumin) score allows to determine which COVID patients have an increased thrombotic risk; the chest CT Severity Score, on the other hand, was proposed to identify patients at high risk of severe pulmonary involvement (leading to admission to Intensive Care Units and intubation). The aim of this study was to investigate the association between the increased thrombotic risk, as estimated by the ADA Score, and the severity of disease evaluated by the chest CT Severity Score.
Materials and methods: this was a retrospective, monocentric study conducted in COVID Units of Policlinico Umberto I – Sapienza University, Rome. From March 2020 to March 2021, we included consecutively admitted patients older than 18 years with confirmed infection by SARS-CoV2 and acute severe pneumonia requiring hospitalization. Routine laboratory analyses including serum D-dimer and Albumin were performed within 48 hours from admission to the ward. Comparison between groups were made using Chi square test or Student's t test. A multivariate regression logistic analysis was performed, and the beta coefficients were used to estimate the predictive factors for mortality. Finally, we performed an analysis of variance with ANOVA and a linear correlation analysis for ADA Score and CT Severity Score.
Results: 350 patients (44% men and 56% women) were included. There were 36 deaths (10.3%) and 27 thrombotic events (7.7%). The patients who presented thrombotic events during hospitalization had higher ADA Score, CT Severity Score and length of staying than patients who didn't have thrombotic events, with higher rates of ADA Score>49 points, coronary heart disease, heart failure, peripheral vascular disease, atrial fibrillation, chronic obstructive lung disease, death, admission to intensive care units and lower P/F ratio. A logistic regression analysis was made to study the predictors of thrombotic events, and ADA Score (H.R 1,169, C.I. 95% 1,044-1,309, p=0,007), CT Severity Score (H.R 1,085, C.I. 95% 1,009-1,167, p=0,028) and chronic obstructive pulmonary disease (H.R. 3,037, C.I. 95% 1,089-8,471, p=0,034) were identified. The linear correlation analysis showed that the ADA Score correlates with the CT Severity Score ($r = 0,323$, $p < 0.0001$), P/F ratio ($r = -0,443$, $p < 0.0001$) and length of staying ($r = 0,212$, $p = 0.001$), and that the CT Severity Score correlates with the ADA Score ($r = 0,323$, $p < 0.0001$), P/F ratio ($r = -0,479$, $p < 0.0001$) and length of staying ($r = 0,126$, $p < 0.05$). Finally, the linear regression analysis confirmed the relationship between ADA Score and CT Severity Score.
Conclusions: this study showed for the first time an association between ADA Score, chest CT Severity Score and thrombotic events.

Table 1. Population characteristics

Table 1: population characteristics

	No Thrombotic events	Thrombotic events	P
N.	295	27	-
Male	44.1%	44.4%	0,970
Obesity	20.6%	0%	0,053
Active Smoking	11.6%	25.0%	0,131
Former Smoking	9.2%	14.3%	0,541
Diabetes	21.3%	14.8%	0,434
Hypertension	48.8%	51.9%	0,917
Dyslipidemia	22.7%	9%	0,312
Coronary Artery Disease	10.0%	31.3%	0,009
Heart failure	11.7%	44.4%	<0,0001
Peripheral arterial disease	15.1%	37.5%	0,019
Atrial fibrillation	7.8%	22.2%	0,012
Previous transient ischemic attack/stroke	4.8%	0%	0,372
Cronic obstructive pulmonary disease	8.8%	34.6%	<0,0001
Dementia	8.0%	20%	0,110
Cancer in the last 5 years	7.6%	13.3%	0,831
Death	8.6%	40.7%	<0,0001
Intensive Care Unit	7.2%	50.0%	<0,0001
P/F ratio<200	7.1%	29.6%	<0,0001
P/F ratio	359.6+104.0	283.2+110.6	<0,0001
ADA Score>49	41.7%	77.8%	<0,0001
ADA Score	47.5+7.9	55.4+7.6	<0,0001
Severity Score	8.8+6.0	13.0+6.9	0,001
Glomerular filtration rate (mL/min)	68.4+28.7	63.0+21.0	0,457
Length of stay (days)	20.3+21.5	32.3+15.7	0,034

177. A STUDY OF HOW CHEMOTHERAPY, ANTI-CD20, AND IMMUNE-CHECKPOINT INHIBITORS AFFECT THE IMMUNE RESPONSE TO A THIRD DOSE OF SARS-COV-2 VACCINE (THE BO0STER STUDY)

Zoppoli G.[1], Ferrando L.[2], Ravera F.[3], Dameri M.[3], Lombardo I.[2], Stabile M.[3], Fallani N.[3], Cigolini B.[3], Scarsi C.[3], Gentilcore G.[4], Bruzzone B.[2], Domnich A.[2], Orsi A.[5], Ballerini F.[2], Rinchai D.[6], Chaussabel D.[7], Bedognetti D.[3], Grivel J.C.[8], Genova C.[1], Lemoli R. [1], Ballestrero A.[1]
[1]Dipartimento di Medicina Interna e Specialità Mediche (DiMI) - Università degli Studi di Genova e IRCCS Ospedale Policlinico San Martino, Genova, IT; [2]IRCCS Ospedale Policlinico San Martino, Genova, IT; [3]Dipartimento di Medicina Interna e Specialità Mediche (DiMI) - Università degli Studi di Genova, Genova, IT; [4]Sidra Medicine, Doha, QR; [5]DISSAL - Università degli Studi di Genova e IRCCS Ospedale Policlinico San Martino, Genova, IT; [6]The Rockefeller University, New York, NY; [7]The Jackson Laboratory, Bar Harbor, ME; [8]9 Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD

Background: The immune response to two doses of mRNA-based SARS-CoV-2 vaccines (SVC) decreases after six months. This requires a booster dose to boost the immune response. Cancer drugs may affect the response to SVC differently, but a direct comparison between cancer patients and healthy controls (HC) has not been conducted. We investigated the changes in the immune system associated with the booster dose of SVC in patients treated with adjuvant chemotherapy (aCT, colorectal and breast cancer), rituximab (R, non-Hodgkin lymphoma), immune checkpoint inhibitors (ICI, solid tumors), and HC.
Methods: We performed blood transcriptome sequencing (TS), multiplex antibody titer (ABt, Spherotech), and SARS-CoV-2-specific IFN release assay (IGRA) before the third vaccine dose (TS/AT/IGRA), after 24 hours (TS), at 5 days (d - TS/IGRA), 26 days (AT/IGRA) and after six months (mo - AT/IGRA). Immune transcriptomic modules were assessed using BloodGene3.
Results: We enrolled 52 subjects: 11 R, 11 ICI, 8 aCT, and 22 HC. aCT and ICI showed similar vaccine-specific ABt compared with HC at 26 days, and the response increased at 6 months. ICI showed a significantly reduced increase of IgG2 vaccine-specific ABt at 26 days compared with HC. R showed a blunted response at 26 days. In all groups, the Env and Core ABt increased significantly at 6 months (81% of subjects), with symptomatic infection in only 31% of subjects. We observed a delayed (5 days) but efficient increase in inflammation and chemokine modules in aCT, reduced early inflamma-

tion (24 hours) and increased delayed plasma-cell response (5 days) in ICI, and reduced response to all immune modules, except for a delayed increase in IFN modules (5 days), in R compared with HC. IGRA results were consistent with IFN modules, with a 5-day increase in R.
Conclusions: Patients undergoing aCT and ICI mount a vaccine-mediated immune response that is similar to, but not identical to, HC. R patients show a blunted vaccine response, in line with the literature. A large fraction of all enrolled subjects developed antibodies against natural infection, in the absence of symptoms, at 6 months. In simpler terms, the study found that patients undergoing aCT and ICI mount a similar immune response to the booster dose of SVC as HC, while patients treated with R show a blunted response. The study also found that a large fraction of all enrolled subjects developed antibodies against natural infection, in the absence of symptoms, at 6 months.

178. BLEEDING AND THROMBOTIC EVENTS IN HOSPITALIZED COVID-19 PATIENTS DURING THE TWO PANDEMIC WAVES: A RETROSPECTIVE ANALYSIS FROM COVID-19 NETWORK

Rossio R.[1], Galbussera A.A.[2], Tettamanti M.[3], Torri A.[4], Giachi A.[5], Gualtierotti R.[6], Peyvandi F. [7]
[1]S.C. Medicina generale Emostasi e Trombosi- Fondazione IRCCS ca granda Ospedale Maggiore Policlinico Milano ; [2]Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy; [3]Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy.; [4]Fondazione IRCCS ca granda Ospedale Maggiore Policlinico, Milano; [5]S.C. Medicina generale Emostasi e Trombosi, Fondazione IRCCS Ca granda Ospedale Maggiore Policlinico Milano; [6]S.C. Medicina generale Emostasi e Trombosi, Fondazione IRCCS Ca granda Ospedale Maggiore Policlinico Milano, Università degli studi di Milano; [7]S.C. Medicina generale Emostasi e Trombosi, Fondazione IRCCS ca granda Ospedale Maggiore Policlinico Milano, Università degli studi di Milano

Background: A systemic inflammatory response is present during Sars-Cov2 infection with overproduction of cytokines that leads to endothelial perturbation and hypercoagulability. A few reports have shown a reduction in mortality for patients treated with low molecular weight heparins (LMWH), that has become part of the treatment of hospitalized COVID-19 patients.
From March 2020 in our Hospital a protocol based upon the use of different dosages of LMWH was introduced. In low-intensity care units prophylactic dosage of LMWH was used (1 mg/Kg daily), therapeutic dosage was used in intensive care units (1 mg/Kg twice daily) and subtherapeutic dosage in subintensive care units (0,7 mg/Kg twice daily).
After bleeding episodes were reported in hospitalized COVID-19 patients on heparin therapy in the absence of conclusive indications from randomized controlled trials the dosage of LMWH at the end of first wave was modified in our hospital and tailored on the severity of COVID-19. In patients using low-flow oxygen, enoxaparin 40 mg daily was introduced, in those with increased oxygen support 1 mg/kg daily was used, cases requiring non-invasive and invasive ventilation 0.7 mg/kg or 1 mg/kg were used twice daily.
Objectives: The aim of this study was to describe the incidence of major and minor bleeding events and thrombotic events in patients hospitalized with Sars-Cov2 infection and to analyze factors associated with such risk.
Methods Data were collected using the COVID-19 Network, a register promoted by Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico Milan and the Mario Negri Institute of Pharmacological Research.1 The register included all consecutive adults with positive RT-PCR for SARS-CoV-2 at hospital admission. Data were collected during the first infection wave (February 2020-June2020) and the second (July 2020-Jenuary 2021). The study was approved by the Ethics Committee.
For the aim of this study, the enoxaparin dosage of 1 mg/Kg daily was considered prophylactic regimen, whereas 1 mg/Kg or 0,7 mg/Kg twice daily were considered anticoagulant dosages. Demographic data and comorbidities at baseline were reported. The type of oxygen supplementation and the severity of respiratory failure as defined by alveolar oxygen partial pressure/fraction of inspiration O2 (PO2/FiO2 ratio) were reported. Laboratory variables were evaluated. Major and non major bleeding events were defined according to the criteria of the International Society on Thrombosis and Haemostasis (ISTH).
The results were described using medians and interquartile ranges or means and standard deviations (SDs) for continuous variables, and with frequency and percentage for categorical ones. The characteristics of patients were compared using the Pearson's chi-squared for the categorical variables and the t-test or ANOVA for the continuous ones. The stratified incidence rate was calculated as number of cases by person-days. Statistical analysis was performed using Stata v.15.1 (Stata Corp, College Station, Tx) software.
Results: Among 1143 patients enrolled in COVID-19 Network, 912 were included in the analysis. 201 were excluded due to missing data and 30 were on therapy with oral anticoagulants before hospitalization.
The mean age (± SD) was 63.4 (±16.3) years and 594 (65.1%) were males. Patients were taking 3.8 (±3.3) drugs at admission. The most frequent comorbidities were hypertension (43.3%) and diabetes (18.4%). 532 patients (74.2.%) had PaO2/FiO2 < 300, the mean value of PaO2/FiO2 being 239 (±105). 169 patients (18.5%) died during hospitalization. In 494 patients (54,2%) both markers of inflammation were elevated (ferritin >150 ng/mL and D-dimer >500). 608 patients (66.7%) were treated with heparin during hospitalization, 341 (56.1%) only with the prophylactic dosage and 66 (10.9%) only with anticoagulant dosage. The first patient group has a average length of hospital stay of 13.3 days (±21.5), the second 15.6 days (±10.5). The bleedings events were 30 (3.3%): 22 (2.4%) major and 8 (0.9%) minor. The rates of arterial and venous thrombotic events were 6 (0.7%) and 24 (2.6%). When we analyze the data according to the waves 538 patients (59%) were admitted during the first wave, 374 (41%) during the second. Markers of inflammation did not show a clear difference between the waves. The incidence of venous thrombotic events was higher in the first 0.26% (95% CI: 0.17-0.40) vs 0.05% events/day (95% CI: 0.02-0.15), while haemorragic incidence was 0.29% (95% CI: 0.19-0.43) vs 0.13% events/day (95% CI: 0.06-0.26). Patients from the first wave had a higher mortality rate of 1.45% (95% CI: 1.21-1.73) vs 0.80% deaths/day (95% CI: 0.61-1.05).
Conclusions: In the present cohort as in other retrospective studies regarding COVID-19 we found a low incidence of hemorrhagic and thrombotic events, but perhaps mild hemorragic and thrombotic events were underreported. Moreover, in our register patients hospitalized in intensive care are not included.
1Bandera A et al COVID-19 Network; the response of an Italian Reference Institute to research challenges about a new pandemia. Clin Microbiol Infect. 2020;1576-1578.

179. REAL WORLD EXPERIENCE AND CURRENT LITERATURE: HOW TO DESIGN A LONG-COVID CLINIC.

Vitali G.[1], Merolla A.[2], De Lorenzo R.[2], Critelli S.[2], Fait F.[2], Mallus M.[2], Menchi S.[2], Paolazzi G.[2], Paolelli F.[2], Ruggero M.[2], Spanò A.[2], Fumagalli A.[1], Lucini A.[1], Martinenghi S.[1], Canti V.[1], Damanti S.[2], Rovere-Querini P.[3]
[1]IRCCS San Raffaele Hospital, Milan, Italy.; [2]Vita-Salute San Raffaele University, Milan, Italy.; [3]Vita-Salute San Raffaele University Hospital, Milan, Italy

Introduction: COVID-19 public health emergency has recently been declared over. However, the four-year SARS-CoV-2 pandemic has had a remarkable impact on our society and still places a major burden in terms of post-acute sequelae. Long-COVID syndrome is now recognized as a complex systemic disease with a prevalence around 10–20%. SARS-CoV-2 infection may cause a low-grade chronic inflammation due to delayed viral clearance thus leading to a persistent catabolic state that damages vascular endothelium and induces oxidative stress. Despite considerable efforts to understand the underlying pathophysiology, no objective measures have been validated to aid diagnosis. Moreover, due to the unclear nature of the condition and the wide range of clinical presentations, long-COVID patients receive fragmented care with frequent referrals to several specialists, often leading to further delays in diagnosis and management. Therefore, this clinical entity needs to be better investigated, recognised and shared among physicians, patients, caregivers, researchers and institutions. Since the beginning of SARS-CoV-2 pandemic, San Raffaele Hospital has established a dedicated and high quality clinic for patients with COVID-19 sequelae, which still faces long-COVID challenges.
Methods: In 2020, a post-COVID-19 multidisciplinary outpatient clinic was set up at San Raffaele University Hospital, Milan, Italy. During the first two pandemic waves, hospitalized COVID-19 patients were invited for follow-up at 1-3-6 months after discharge. Subsequently, as the rate of hospitalization declined, patients requiring medical attention were referred to our clinic regardless of the time and severity of the infection. At each ambulatory visit data on demographics (age, sex, history of smoking), clinical history (arterial hypertension, coronary artery disease [CAD], diabetes mellitus [DM], chronic obstructive pulmonary disease [COPD]/asthma, chronic kidney disease [CKD], active cancer), COVID-19 course (clinical presentation, need for hospitalization, ICU admission, non-invasive ventilation [NIV] requirement) and vaccination for SARS-CoV-2 were collected. The following assessments were performed: evaluation of health status through standardized measures,

physical examination, respiratory evaluation (dyspnoea severity as assessed by the mMRC scale), nutritional assessment (anthropometrics, mini nutritional assessment [MNA] screening tool). Validated self-report questionnaires were administered to assess general health status (EQ5D, VAS), depression (ZUNG), sarcopenia (SARC-F), fatigue (FSS). All data were prospectively collected across pandemic waves.
Results: A total of 1960 patients were referred to our Clinic between April 2020 and May 2023. They had a median age of 64 years (55;75) and a higher prevalence of males (62.3%). The majority (89.5%) were Caucasian, while 5.2% were from South America, 3.6% from Asia and 1.7% from Africa. Active smoking was present in 24.5% of these patients, arterial hypertension in 44.8%, obesity in 26.5%, DM in 15.2%, CAD in 11%, COPD/asthma in 8.3%, CKD in 5% and active cancer in 4.8%. Regarding COVID-19 history, 88% were hospitalized, of whom 29.4% required NIV and 8.2% were also admitted to ICU. About 73% of these patients got vaccinated for SARS-CoV-2 at least once. A significant proportion (68%) was found to have COVID-19 sequelae. Persisting and/or new onset symptoms ranged from 1 to 12 and were: respiratory (i.e. dyspnoea, cough, rhinorrhea - 58.9%), generalized (i.e fever, myalgia, arthralgia, asthenia, fatigue - 34.5%), ear-nose-throat (loss of taste and/or smell, tinnitus, earache, sore throat, nasal congestion - 7.3%), neurological (i.e. headache, sleep disturbance, confusion, paraesthesia, tremor, amnesia - 7%), cardiac (i.e chest pain, palpitations, inappropriate sinus tachycardia - 3.7%), dermatological (i.e. rash, alopecia - 3%) gastrointestinal (nausea, vomiting, diarrhoea - 1%) symptoms. In addition, a total of 942 patients were evaluated after 6 months from the infection, of whom 7% still had clinical sequelae 1 year after infection.
Conclusion and perspectives: Our experience aligns to literature data on long-term effects of COVID-19 and suggests the utility of a dedicated post-COVID-19 clinic in order to assess clinical status, confirm the diagnosis of post-COVID syndrome and provide care for these patients. According to National Institute for Health and Care Excellence (NICE) guidelines, a multidisciplinary person-centred approach is mandatory. It should focus on comprehensive assessment and management with a strong emphasis on rehabilitation, including physical, psychological and psychiatric aspects. In addition, close collaboration with primary care professionals to ensure continuity of care could meet patients' needs, avoid fragmentation of care and therefore provide higher quality of life. A well-structured long-COVID clinic could be a valuable resource for clinicians and researchers to find better strategies to face this condition and to develop appropriate therapeutic options that still need to be defined.

180. IRON METABOLISM ALTERATIONS IN PATIENTS RECOVERED FROM COVID-19: REPORT FROM THE RESPICOVID STUDY

Randon A., Girelli D., Crisafulli E., Busti F.
Università degli Studi di Verona

Background: Following the COVID-19 outbreak, many studies have explored factors potentially implicated in developing adverse outcomes. In this context, some iron metabolism alterations (i.e., hyperferritinemia, low serum iron, and increased serum hepcidin) have elicited great interest (Girelli, 2021). Indeed, hypoferremia was associated with disease severity, more serious hypoxemic respiratory failure and lymphopenia, and increased mortality. Similarly, elevated ferritin predicted disease severity and a higher risk of death. Increased hepcidin was the major predictor of mortality in hospitalized COVID-19 patients in intensive care units, regardless of age, lung function, and degree of inflammation. The interest aroused by iron status also derives from studies indicating that iron plays a key role in inflammation and is crucial in infection defense mechanisms (Drakesmith, 2012). Finally, both iron deficiency (ID) and excess have been implicated in lung function alterations (Ali, 2017). Still, it is unknown the role of long-term iron metabolism disturbance in patients recovered from COVID-19. This study aimed to investigate the possible relationship, already verified for the acute phase of the disease, between iron status and residual lung damage in patients recovered from COVID-19.
Patients and methods: The RESPICOVID study is a prospective observational trial designed to evaluate the prevalence, clinical impact, and predictive factors of pulmonary damage in patients previously hospitalized for COVID-19 pneumonia at the University Hospital of Verona, Italy. The local Ethics Committee has approved the study protocol. All participants gave informed written consent. All consecutive patients discharged were considered. Data were collected prospectively from July 2020, four to six months after patients' discharge. We collected demographic and anthropometric variables, clinical symptoms, routine laboratory parameters, and blood gas analysis. Lung function was performed according to the international recommendations (Miller, 2005) by a flow-sensing spirometer for the measurements of forced vital capacity (FVC), forced expiratory volume in the first second9 (FEV1), total lung capacity (TLC), and pulmonary diffusing capacity for carbon monoxide (DLCO). Patients were also evaluated with a six-minute walking test (6MWT) and a chest computed tomography (CT). In addition, iron biomarkers were evaluated, including serum iron, transferrin, transferrin saturation (TSAT), ferritin, and hepcidin. Hepcidin was measured using an enzyme-linked immunoassay (ELISA) kit from International Intrinsic LifeSciences, according to the manufacturer's instructions.
Results: A total of 169 patients were included in the study. The mean age was 64.4 years (SD 12.4 years), and most participants were male (72.2%). Disease severity during hospitalization ranged from mild to severe, according to the inward medical treatment required: mild [no respiratory support, N=34 (20%)], moderate [oxygen therapy, N=114 (67.5%)], and severe [mechanical ventilation, N=21 (12.5%)]. At the study enrollment, 50.3% (N=85) of participants had at least one symptom among asthenia (34%), cough, dyspnea, or muscle fatigue, and about 40% perceived a reduction in quality of life (evaluated through the SF-26 questionnaire), both physical and mental. 35% of subjects still presented with iron metabolism alteration, including ID (absolute or functional, with or without anemia) and hyperferritinemia. Serum ferritin at follow-up was a reliable biomarker of iron stores, significantly correlated with TSAT (r=0.332; p<0.001), hepcidin (r=0.607; p<0.001), and hemoglobin (r=0.344; p<0.001), but not with CRP levels. In our cohort, persisting iron status alterations (ID, ID anemia, or hyperferritinemia) were not associated with adverse outcomes (persistence of symptoms or alteration at blood gas analysis, spirometry, 6MWT, and CT scans). On the other hand, a positive correlation of iron and TSAT with DLCO emerged (r=0.373; p<0.001 and r=0.301; p<0.001, respectively). As expected, DLCO correlated with Hb (r=0.587; p<0.001). Subjects with DLCO less than 80% predicted (N = 47, 28%) displayed lower serum iron (77.8 *vs*. 100.3 mcg/dl, p<0.001) and TSAT (23 *vs*. 28%, p=0.003), although both were in the normal range.
Discussion: alterations of iron homeostasis can persist for at least six months after the onset of COVID-19, whose biological role remains uncertain. Our study does not confirm the previously described association between persisting hyperferritinemia, severe lung damage in CT scans, and decreased performance status in patients recovered from COVID-19 (Sonnweber, 2020). On the other hand, it suggests a role of iron in the modulation of some respiratory functions, such as DLCO, in agreement with previous studies reporting a significant reduction of DLCO in ID patients affected by chronic obstructive pulmonary disease (Pizzini, 2020). Conclusively, further evaluations of the role of iron homeostasis in respiratory pathologies, including post-COVID-19 sequelae, are highly warranted.

DIABETE

181. SEX DIFFERENCES IN THE ASSOCIATION BETWEEN INSULIN RESISTANCE INDEXES AND MYOCARDIAL INFARCTION IN INDIVIDUALS WITH DIFFERENT GLYCAEMIC STATES

Riccio A.[1], Mellbin L.[2], Norhammar A.[2], Näsman P. [2], Rydén L.[2], Sesti G.[1], Ferrannini G. [2]
[1]Department of Clinical and Molecular Medicine, Sapienza University of Rome, Rome, Italy; [2]Department of Medicine Solna, Karolinska Institute Stockholm, Sweden

Background and aims: Females have a lower risk of cardiovascular disease (CVD) than males. Insulin resistance (IR) has been suggested to be a more important contributor to cardiovascular (CV) morbidity in females than in males. The purpose of this study was to investigate sex differences in the association between insulin sensitivity (IS) indexes (Quantitative insulin sensitivity check index (QUICKI), Bennett's index and McAuley index) and IR indexes (Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), visceral adiposity index (VAI) and triglycerides/high-density lipoprotein cholesterol (TG/HDL-C) index) and a first myocardial infarction (MI) independently of traditional CV risk factors.
Materials and methods: IS and IR indexes were calculated in a population (n=1403) with (n=696) and without (n=707) a first non-fatal MI, free from known diabetes. MI patients had survived at least six weeks after the event. All study participants were categorized by an oral glucose tolerance test as having normal glucose tolerance, impaired fasting glucose, impaired glucose

tolerance or newly diagnosed type 2 diabetes mellitus. Sex differences in proportions of different glycaemic states were tested by chi-square test. The associations between sex, a first MI, IS indexes, IR indexes and traditional CV risk factors were analysed by univariate and multivariate logistic regression models, where continuous variables were logarithmically transformed.
Results: Of the total population 19% were females and 81% males, out of whom 47% and 50% had a first MI respectively. Females compared with males were older, less often smokers, with lower body mass index, higher total cholesterol and C-reactive protein. No differences between the sexes were observed in the proportion of glycaemic states. In univariate analysis females were more insulin sensitive and less insulin resistant than males. In logistic regression models adjusted by major CV risk factors including sex, IS indexes were no longer associated with a first MI, whereas the associations between HOMA-IR, VAI, TG/HDL-C index and a first non-fatal MI remained significant in females, but not in males (Table 1).
Conclusions: These results support the assumption that IR is of pivotal importance as CV risk factor in females. IR indexes may contribute to CV risk stratification in females, independently of their glycaemic state.

Table 1. Multivariate analysis between non-fatal acute myocardial infarction and several risk factors for cardiovascular disease in females and males.

	Associations with non-fatal acute MI		
	IR index	OR (95% CI) in females	OR (95% CI) in males
Model 1 includes age, BMI, smoking habit, known family history of CVD, hsCRP, 2-hour post-load glucose, total cholesterol and HOMA-IR	HOMA-IR	3.5 (1.3-9.6)	1.1 (0.7-1.7)
Model 2 includes age, smoking habit, known family history of CVD, hsCRP, glucose tolerance status and VAI	VAI	1.7 (1.0-2.9)	1.2 (0.9-1.5)
Model 3 includes age, BMI, smoking habit, known family history of CVD, hsCRP, glucose tolerance status and TG/HDL-C index	TG/HDL-C index	1.9 (1.1-3.4)	1.2 (0.9-1.5)

Continuous variables were natural log transformed.
HOMA-IR was dichotomized as above or below the cut-off 3.0.
Variables incorporated into the formulas of each IR index were not computed in the single regression model of the index to avoid collinearity.

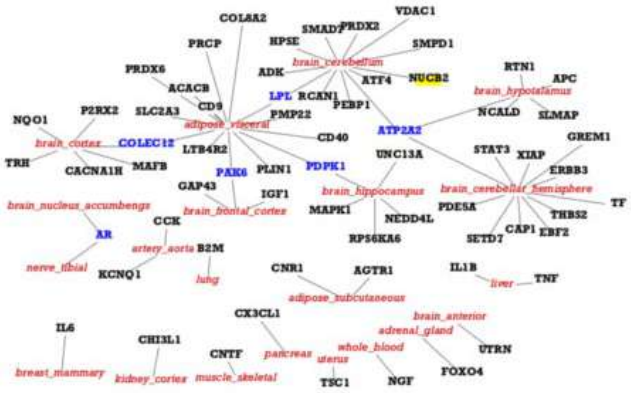
BMI: body mass index; CI: confidence interval; CVD: cardiovascular disease; HOMA-IR: homeostatic model assessment of insulin resistance; hsCRP: high sensitivity C-reactive protein; IR: insulin resistance; MI: myocardial infarction; OR: odds ratio; TG/HDL-C: triglycerides/high-density lipoprotein; VAI: visceral adiposity index.

182. TOWARDS THE ANALYSIS OF AGE-DIRECTED CHANGES IN THE EXPRESSION OF GENES RELATED TO TYPE 2 DIABETES MELLITUS COMORBIDITIES

Pedace E.[1], Mannino G. C.[2], Cortese F.[2], Succurro E.[2], Guzzi P. H. [2], Veltri P.[3], Andreozzi F.[2]
[1]ASP Catanzaro; [2]Università di Catanzaro; [3]Università della Calabria

Background: The co-occurrence of diseases, or comorbidity, may have both a genetic and environmental cause. Comorbidity, especially in chronic diseases, causes a rapid decline in the quality of life and longevity. Moreover, it contributes to an increased demand for hospital beds and higher costs for the health care system overall. Consequently, there is the need to shed light on the occurrence and progression of comorbidities by elucidating the time of their onset and their genetic relations. Finally, comorbidities can vary with age, sex, and external factors such as environmental issues related to living areas.
In this work we focused on diabetes mellitus type II (T2DM) and its comorbidities. Diabetes, with an estimated number of 415 million of adults affected, is one of the most widespread chronic diseases. The pathophysiology of T2DM is exacerbated by the aging process, which affects metabolic regulation and accelerates the progression of many comorbidities as shown by demographic and epidemiological data. For our research, we leveraged existing data and models at system level, by integrating information in a network medicine framework. We started from the hypothesis that the association with age may be explained by differences at the molecular level of genes whose basal expression is modified with age.
Materials and Methods: We selected genes correlated with comorbidities in T2DM reported in public databases such as T2DiACoD Database. We integrated such data with the expression level and age/tissue metadata as contained in the GTeX database. We implemented a computational workflow based on machine learning and network theory.
Results: We used expression data of 650 genes in 54 different tissues of patients organised into six groups of age: 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, and we obtained a list of genes whose expression level is significantly modulated with age (by means of a Kruskal Wallis Test). Such data were then integrated in a single network map as reported in Figure 1. Finally, we searched the STRING database for deriving the protein interaction networks interested by the genes whose expression resulted affected by age.
Conclusion: The results of our investigation show that the expression of some genes associated with comorbities of T2DM is modulated with age. Further studies will be necessary to unravel how these molecular changes affect the augmented risk of presenting comorbidities with T2DM.

Figure 1. Figure reports the genes which present a significant modification over time in different tissues (p value <0.05, Kruskal Wallis Test). Figure represents the association between genes (in bold) and tissue (in red italics). Blue labels evidences genes we found changed in more tissues.



183. METABOLIC MEMORY IN DIABETIC FOOT SYNDROME (DFS): EPIGENETIC CHANGES OF THE EXPRESSION OF MICRO-RNAS AND SINGLE NUCLEOTIDE POLYMORPHISMS (SNPS) FREQUENCY IN A COHORT OF DIABETIC PATIENTS WITH AND WITHOUT FOOT ULCERATION AND CORRELATION WITH INDICES OF ENDOTHELIAL AND ADIPO-INFLAMMATORY DYSFUNCTION

Del Cuore A.[1], Pipitone RM.[2], Mazzola M.[1], Puleo MG.[1], Pacinella G.[1], Riolo R.[1], Daidone M.[1], Maida C.[1], Casuccio A.[2], Di Chiara T.[1], Di Raimondo D.[1], Zito R.[3], Lupo G.[3], Agnello L.[4], Ciaccio M.[4], Grimaudo S.[1], Tuttolomondo A.[1]
[1]Department of Promoting Health, Maternal-Infant. Excellence and Internal and Specialised Medicine (PROMISE) G. D'Alessandro, University of Palermo (Italy). Internal Medicine and Stroke Care Ward, Policlinico " P. Giaccone", Palermo (Italy); [2]Department of Promoting Health, Maternal-Infant. Excellence and Internal and Specialised Medicine (PROMISE) G. D'Alessandro, University of Palermo (Italy).; [3]Department of Promoting Health, Maternal-Infant. Excellence and Internal and Specialised Medicine (PROMISE) G. D'Alessandro, University of Palermo (Italy); [4]Institute of Clinical Biochemistry, Clinical Molecular Medicine and Laboratory Medicine, Department of Biomedicine, Neurosciences, and Advanced Diagnostics, University of Palermo, Palermo, Italy

Diabetic foot is a significant cause of morbidity in diabetic patients, with a rate that is approximately twice that of patients without foot ulcers. There has been much debate in the literature about the role of genetics, particularly epigenetic modifications, in the genesis of the diabetic foot. "Metabolic memory" are all those epigenetic changes induced by chronic hyperglycaemia, despite correction of the glycaemic values themselves. Moreover, these epigenetic modifications would appear to perpetuate the damage caused by persistently elevated glucose levels even in its absence, acting at various levels, mostly affecting the molecular processes of diabetic ulcer healing. To the best of our knowledge, there are no studies in the literature that have correlated the epigenetic changes induced on miRNAs 126, 305, and 217 and on SNPs of inflammatory molecules, such as IL-6, TNF-alpha, and pro-angiogenic molecules, such as ENOS, VEGF and HIF-1alpha with endothelial dysfunction, assessed noninvasively by RHI and with serum levels of inflammatory molecules and adipokines in a population of people with diabetes with and without lower limb ulcer. Between March 2021 and June 2022, 110 patients were enrolled to the study: 50 diabetic patients with diabetic foot injuries, 40 diabetic patients without ulcerative complications and 20

non-diabetic patients, as control group.
Diabetic subjects with lower limb ulcerative lesion exhibited higher values of inflammatory cytokines, such as VEGF (191.40±200 pg/mL vs 98.27±56.92 pg/mL vs 71.01±52.96 pg/mL p=0.22), HIF-1alpha (40.18±10.80 ng/mL vs 33.50±6.16 ng/mL vs 33.85±6.84 ng/mL p=0, 10), and Gremlin-1 (1.72±0.512 ng/mL vs 1.31±0.21 ng/mL vs 1.11±0.19 ng/mL p< 0.0005). Furthermore, we observed that miR-217-5p and miR-503-5p were respectively 2.19-fold (p<0.05) and 6.21-fold (p=0.001) more expressed in diabetic foot patients than in healthy controls (Table 5, Graphic 1). Additionally, diabetic patients without lower limb ulcer complication showed a 2.41-fold (p=0) and 2.24-fold (p=0.029) higher expression of miR-217-5p and miR-503-5p, respectively, than healthy controls. Finally, diabetic patients with and without ulcerative complications of the lower limb showed a higher expression of the VEGFC2578A CC polymorphism (p=0.001) and a lower expression of the VEGFC2578A AC polymorphism (p<0.005) compared to the healthy control population. We identified a significant increase in Gremlin-1 in patients with diabetic foot and how this inflammatory adipokine is a predictive marker for the diagnosis of diabetic foot. To date, there is no study that has evaluated this inflammatory adipokine in the diabetic foot, which makes our results innovative in the literature. Our results highlighted that patients with diabetic foot show predominant expression of the VEGF C2578A CC polymorphism and reduced expression of the AC allele. These results are in line with the licterature, who showed that the reduced presence of the A allele may reduce susceptibility to diabetic ulcer. Furthermore, this polymorphism would appear to be predictive of diabetes diagnosis, thus reiterating its possible usefulness in the early diagnosis and treatment of the diabetic foot. Additionally, we found an overexpression of miR-217-5p and miR-503-5p in diabetic patients with and without diabetic foot syndrome. These results align with the licterature, who evidenced the overexpression of miR-217-5p and miR-503-5p in the context of diabetic foot. These epigenetic modifications could therefore be helpful in the early diagnosis of diabetic foot and the treatment of risk factors. However, only further studies will be able to confirm this hypothesis.

184. TREATMENT WITH 4-PHENYLBUTYRATE COUNTERACTS ER STRESS-RELATED RESPONSE IN COLONIC MUCOSA OF SUBJECTS WITH DYSGLYCEMIC CONDITIONS.

De Vito F.[1], Suraci E.[1], Marasco R.[1], Luzza F.[1], Sesti G.[2], Andreozzi F.[1], Fiorentino T.V.[1]
[1]Department of Medical and Surgical Sciences, University Magna Graecia of Catanzaro; [2]Department of Clinical and Molecular Medicine, University of Rome-Sapienza, Rome

Increasing evidence support the pathogenic role of gut barrier dysfunction in the development of Type 2 diabetes (T2DM) and its complications. Activation of endoplasmic reticulum (ER) stress is involved in glucotoxicity-mediated cellular damage, and it has been reported to affect intestinal mucosa integrity in preclinical models. Herein, we examined whether subjects with prediabetes or T2DM display an activation of ER stress in the gut along with a disruption of mucosal integrity and whether hyperglycemia directly induced these aberrations. Additionally, we investigated beneficial effects of the chemical chapenone 4-phenylbutyrate (4-PBA) on diabetes-related ER stress activation in the colonic mucosa. To this end, we studied 55 subjects who underwent a complete clinical characterization including OGTT and colonoscopy with collection of colonic mucosa biopsies. Based on their glucose tolerance, participants were classified as having NGT (n=25), prediabetes (n=14) and T2DM (n=16). Colonic levels of the ER stress markers Inositol-requiring enzyme-1 (IRE-1), C/EBP homologous protein (CHOP), phosphorylation levels of eukaryotic initiation factor 2 alpha (peIF2α) and c-Jun N-terminal kinases (p-JNK) were assessed by Western blot. As compared to NGT subjects, those having prediabetes and T2DM displayed progressively higher levels of the ER stress activation markers IRE-1 and phosphorylated eIF2α in the colonic mucosa (p<0.05). These changes were accompanied by significantly 1.5- and 2-fold increased levels of the pro-apoptotic and pro-inflammatory markers CHOP and p-JNK in subjects with prediabetes and T2DM, respectively, as compared to NGT group (P<0.05). Next, to investigate whether hyperglycemia directly induces an activation of ER stress related response in the gut, we performed organ culture experiments on colonic mucosa biopsies collected from NGT subjects cultured in absence or presence of increasingly higher glucose concentrations (HG 25mM and HG 50mM) for 8h. HG exposure significantly increased protein levels of the ER stress markers IRE-1α and p-eIF2α in human colonic specimens in a dose-dependent manner with a maximum effect at a dose of 50mM. We also found that treatment with HG 50mM resulted in an up-regulation of the pro-apoptotic and pro-inflammatory factors CHOP and p-JNK (P=0.002). Finally, in order to explore whether 4-PBA was able to counteract diabetes-related activation of ER stress in the gut, colonic mucosa explants of subjects with dysglycemic conditions were cultured in the absence or presence of 4-PBA (10mM) for 8h. Treatment with 4-PBA resulted in a down-regulation of IRE-1α and p-eIF2α levels, and exerted pro-survival effects by reducing protein levels of CHOP and p-JNK (P≤0.05). In conclusion, our results demonstrate that hyperglycemia directly induces ER stress activation in the colonic mucosa and 4-PBA treatment is able to counteracts diabetes-related cellular damage in the gut.

185. THE IMPACT OF DIABETES ON HEART RATE VARIABILITY AND ARTERIAL STIFFNESS DIFFERS IN MEN AND WOMEN

Sestu A.[1], Murru V.[1], Belfiori E.[1], Scuteri A.[2]
[1]Scuola di Specializzazione in Medicina Interna, Università di Cagliari; [2]Dipartimento Scienze Mediche e Sanità Pubblica, Università di Cagliari; Direttore SC Medicina Interna, Azienda Ospedaliero-Universitaria di Cagliari, Policlinico Universitario Monserrato

Background and aims: Diabetes is a major public health issue that significantly impacts on CV burden. Arterial stiffness – indexed as carotid-femoral Pulse Wave Velocity (PWV) – represents a good proxy of arterial aging and a predictor of CV events; additionally, it is increased in people with diabetes. Alterations in Heart Rate Variability (HRV), a marker of autonomic balance, are common in diabetes and have been associated with arterial stiffness and CV events.
In the present study we hypothesized that HRV affects arterial stiffness in a gender-specific manner and its impact differs according to the presence of diabetes.
Methods: This hypothesis was tested in 422 (55.7% male) outpatients. PWV was measured using the validated SphygmoCor device (AtCor Medical). Time-domain and frequency-domain parameters were measured to assess HRV.
Results: The 30.8% of our population had diabetes. The prevalence was slightly, but not significantly, greater in men, who also were older, more frequently hypertensive, and with greater BP and stiffer arteries than women. Multiple regression analysis showed both age and SBP to be independent determinants of PWV in each of the four groups (men and women with or without diabetes). Low-frequency activity had a significant negative correlation with PVW only in women and was greater in the absence of diabetes.
Conclusions: The impact of HRV – that reflects the balance between sympathetic and vagal activity – on PVW – a marker of arterial aging – differs in a gender-specific manner in people with or without diabetes. A better characterization of the mechanisms underlying the observed differences may improve management and treatment of diabetic patients and reduce CV burden in diabetes.

186. METEORIN-LIKE PROTEIN IS ASSOCIATED WITH IMPAIRED MYOCARDIAL GLUCOSE METABOLIC RATE IN SUBJECTS WITH DIFFERENT GLUCOSE TOLERANCE: A CARDIAC DYNAMIC 18F-FDG PET STUDY

Monea G.[1], Massimino M.[1], Rubino M.[1], Mancuso E.[1], Averta C.[1], Mannino GC.[1], Succurro E.[1], Sesti G.[2], Andreozzi F.[1]
[1]Department of Medical and Surgical Sciences, University Magna Graecia of Catanzaro, 88100 Catanzaro, Italy; [2]Department of Clinical and Molecular Medicine, University of Rome-Sapienza, Rome, Italy

Background: Meteorin-like (METRNL) is a recently identified adipomyokine that beneficially affects glucose metabolism. In vitro evidences suggest METRNL attenuates myocardial ischemia/reperfusion injury-induced cardiomyocytes apoptosis by alleviating endoplasmic reticulum stress via activation of AMPK-PAK2 signaling. In addition, METRNL increases glucose uptake via the AMPK pathway in skeletal muscle cells and increases the phosphorylation of HDAC5, a transcriptional repressor of the glucose transporter GLUT4. In humans, METRNL serum level is lower in patients with coronary artery disease and correlates negatively with inflammatory cytokines. An impaired insulin-stimulated myocardial glucose metabolic rate (MRGlu) has been shown to be a risk factor for the development of cardiovascular disease in patients with dysglycaemic conditions, especially type 2 diabetes (T2DM). The aim of our study is to examine the existence of a connection between MRGlu and METRNL levels in subjects with different grades of glucose tolerance.

Methods: We evaluated myocardial MRGlu in normoglucose tolerant individuals (NGT) (n=19), subjects with impaired glucose tolerance (IGT) (n=10), and T2DM patients (n=21). A 75 g oral glucose tolerance test (OGTT) was performed with 0, 30, 60, 90, and 120 min samplings for circulating plasma glucose and insulin measurements. Glucose tolerance was determined according to World Health Organization (WHO) criteria. Myocardial glucose metabolic rate was evaluated using dynamic cardiac 18F-FDG PET scan combined with euglycemic hyperinsulinemic clamp. The 18F-FDG PET imaging procedure started 60 minutes after the insulin infusion. The insulin-glucose infusion continued throughout the PET imaging sequence, maintaining euglycemia by continuous adjustment of the glucose βinfusion rate according to the glucose levels of the arterialized blood samples collected every 5 min. The estimation of myocardial MRGlu was performed using a Patlak compartmental modelling, provided by a graphical tool specific for cardiac images analysis (PCARD) in PMOD Software platform. Serum levels of METRNL were measured by a dedicated ELISA kit.
Results: Serum levels of METRNL were progressively reduced in individuals with IGT (87,89±23,79 pg/mL) and T2DM (76,42±15,34 pg/mL) as compared to those with NGT (102,39±24,82 pg/mL; p=0.001). MRGlu values were significantly lower in subject with IGT (16,41±6,06) and T2DM (15,15±11,59) compared with NGT (28,26±9,08; p=0.001). A partial correlation analysis corrected for age, sex and body mass index (BMI) showed that MRGlu was positively correlated with METRNL (r= 0.302, p=0.039). To evaluate the independent factors influencing MRGlu, a multivariate linear regression analysis was run in two models including age, sex and BMI as covariates. In Model 1 METRNL was included, resulting in a significant association with MRGlu (β=0,292; p=0,04). In Model 2 HOMA-IR was included as a surrogate index of insulin resistance, and the association between METRNL and MRGlu showed a mild attenuation (β= 0.249; p=0,03).
Conclusion: Our data suggest a potential role of METRNL in the regulation of myocardial glucose metabolism in subjects with dysglycaemic conditions. Further prospective studies are needed to elucidate the underlying mechanism of action and possible clinical implications.

187. A RARE COMPLICATION OF DIABETES MELLITUS: DIABETIC STRIATOPATHY

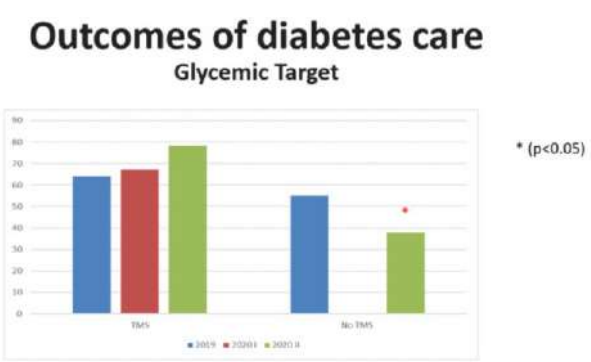
Maiorca C.[1], Tola J.[1], Belli M. [2], Di Matteo R.[2], Propato A.[2], Tricerri A.[2], Magnanti M. [2]
[1]Dip.to di Medicina Traslazionale e di Precisione, Sapienza Università di Roma and P.O. San Filippo Neri, UOC PS e Medicina d'Urgenza; [2]P.O. San Filippo Neri, UOC PS e Medicina d'Urgenza

Background: Diabetic striatopathy (DS) is a rare complication of uncontrolled diabetes mellitus (DM), mostly type 2 but also type 1, and is characterized by marked hyperglycemia, choreic movements and characteristic basal ganglia abnormalities detectable at computed tomography (CT) and/or magnetic resonance imaging (MRI), usually fully reversible. Although there are no large-scale epidemiological studies, the prevalence of SD is estimated to be < 1/100.000 and is higher in older women. The etiopathogenesis is not fully known; it is believed that, in women, the numerical reduction of estrogen receptors, characteristic of the post-menopausal age, plays a fundamental role causing an increase in the sensitivity of the dopaminergic receptors of the nigrostriatal circuit, which clinically translates into choreic movements. Abnormalities on CT and MRI are very peculiar. CT shows high attenuation in the contralateral striatum (caudate nucleus and putamen), while MRI shows T1 hyperintensity in the same areas. The prognosis is generally good; most patients present a resolution of the clinical symptoms in a short time, thanks to the restoration of normal glycemic values. Only a minority of patients require dopamine agonist drugs to relieve choreic symptoms. The clinical resolution of the symptoms is also accompanied by a reversibility of the radiological alterations but sometimes, when it is not possible to achieve adequate glycemic control, the symptoms may persist and make normal daily life difficult.
Case Report: We propose the clinical case of a 78-year-old woman who came to our observation for symptoms that arose about two weeks earlier and were characterized by involuntary movements of the left hemiface and of the left upper and lower limbs; the patient also reported dysuria. Relevant past history included: monoclonal gammopathy of undetermined significance, mixed cryoglobulinemia, arterial hypertension and mild chronic renal insufficiency. There was no known history of diabetes mellitus. The neurological objective examination, performed on admission, showed athetotic movements of the left hemiface and limbs, without further pathological elements. The hemodynamic parameters and the remaining clinical objectivity were also within the limits. The first laboratory investigations carried out in the Emergency Department showed blood sugar values > 350 mg/dl and HbA1c 12.9% with a modest increase in inflammation indices; no signs of ketoacidosis on blood gas analysis. She underwent a first brain CT which showed "presence of right nucleobasal hyperdense area compatible with intraparenchymal hemorrhage" and a second brain CT which showed "hyperdensity of the right striatum". The consultant neurologist suspected diabetic striatopathy and suggested performing a brain MRI, which highlighted "signal alteration of the right striatum" in a context of moderate cortical atrophy. Therapy with slow and rapid release insulin was undertaken and further investigations were performed in parallel to highlight any infectious etiologies underlying the newly diagnosed glycemic decompensation. Chest X-ray and full abdominal ultrasound were normal. Urinalysis with urine culture showed a S. aureus infection with significant bacterial load, which was treated with targeted antibiotic therapy. The orthopanoramic showed signs of chronic periodontal disease with periapical inflammation of 45. During hospitalization there was a progressive improvement of the glycemic profile and resolution of the neurological symptoms. The control MRI, carried out after about thirty days, showed resolution of the signal alteration at the level of the right striatum.
Conclusions: We believe that our clinical case is particularly interesting as it deals with a very rare and not well known complication of diabetes mellitus, whose singular clinical presentation can easily be interpreted incorrectly. Furthermore, in our case there was no known history of diabetes mellitus, therefore the ex-abrupto onset of choreic movements could lead to a misdiagnosis of another neurological disease. Some studies are evaluating the possibility of using scores to estimate the risk of SD onset in subjects who are already diabetic, taking into consideration various factors (gender, average fasting blood glucose values, glycated hemoglobin, etc.) but the literature is still very scarce.

188. USEFULNESS AND SAFETY OF TELEMEDICINE FOR DIABETES

Modestino M.R., De Luca M., Salzano A., Iacono O., D'Assante R., Verdoliva. R, Ferrentino L., De Fortuna U., Guardasole V., Cittadini A.
Department of Translational Medical Sciences, Federico II University, Italy

Introduction: This study aimed to evaluate the effect of a service of telemedicine on diabetic outcomes during
COVID-19 pandemic and compare it to the previous year's data
Materials and methods: A retrospective observational analysis was conducted on 77 diabetic patients who performed a telemedicine service and 69 patients who refused. The telemedicine service was offered to all patients who were scheduled for a follow-up visit to our diabetic university tertiary referral center between May and September 2020 and who were contactable by telephone during the pandemic. People who needed an urgent in-person visit were excluded from the study. The telemedicine service included two periodic tele-visits, the first of which was scheduled between May and September and the second after six months, and an e-mail address for any clinical necessity checked twice a day. Primary outcomes were considered the achievement of HbA1c target (HbA1c < 53mmol/mol without significant hypoglycemia was considered adequate), hypoglycemic episodes (defined as a measurable glucose value <70 mg/dL) and diabetes- related hospitalizations Results Among the patients who performed the telemedicine visits, 67% of patients at the first TMS visit and 78.3% at the second TMS visit were on target, with no significant difference in respect to the in-person visit experienced in 2019 before COVID-19 disease. Similarly, there was no significant difference in the numbers of hypoglycemic episodes or hospitalizations. On the contrary, among patients who refused telemedicine, there was a statistically significant reduction in the number of patients on target, from 55% to 38% (p<0.005).



No significant difference was observed in the number of hypoglycemic events nor in hospitalizations. Noteworthy tough, in the telemedicine group there were no hospitalizations nor major cardiovascular events, while in the non-telemedicine group 1 patient died, 2 patients had a major cardiovascular event (1 myocardial infarction and 1 stroke) and 2 patients were hospitalized for cardiovascular disease. These data suggest that the telemedicine service allowed offering adequate medical care to diabetic patients, with effectiveness comparable to in- person visits. Moreover, we can speculate that the persons who did not perform any kind of telemedicine service may have been prone to neglect their health status, neglecting not only diabetological follow-up but stopping any type of medical assistance during lockdown period. Regarding pharmacological treatment of patients in the telemedicine group, a positive trend was observed in the use of GLP1-Ra and DPP4i. In addition to increased guidelines adherence, this data could be explained by a more favorable safety profile of these drugs, with a negligible risk of hypoglycemia and mild side effects easily recognizable by the patients.
Conclusions: In conclusion, this study showed how telemedicine overcame difficulties for diabetic patient's care during COVID-19 emergency, with effectiveness comparable to traditional visits. Instead, patients who did not have diabetic control during lockdown had worse glycometabolic outcomes.

189. EFFICACY OF SEMAGLUTIDE ON METABOLIC PROFILE OF SUBJECTS WITH DIABETES MELLITUS TYPE 2

Bonfrate L., Di Ciaula A., Khalil M., Curci F., Mastandrea E., Noto A., Portincasa P.
Clinica Medica "A. Murri", Dipartimento di Medicina di Precisione e Rigenerativa e Area Jonica (DiMePRe-J), Università degli Studi di Bari

Background: Diabetes mellitus type 2 (T2DM) is a chronic disease, which is characterized by hyperglycemia, insulin resistance, and also relative impairment in insulin secretion. The incidence of T2DM is increasing in many countries, in parallel with increasing prevalence of obesity and severe obesity. Since obesity and excess adipose tissue are the most important risk factors for T2DM, the management of these predisposing features are mandatory in the treatment of T2DM. Several drugs have been proposed as therapeutic choices, based on the pathophysiological impaired mechanism. In the absence of contraindications, metformin is considered the initial medication of choice for hyperglycemia in type 2 diabetes, concurrent with lifestyle intervention, at the time of diabetes diagnosis. Moreover, in individuals with T2DM and overweight or obesity, semaglutide may help delay or prevent diabetes onset as well as body weight and visceral fat reduction. The present study was a double blind randomized study, and aimed to compare the efficacy of semaglutide and metformin on glycemic profile, weight and visceral fat reduction, and liver steatosis.
Results: sixty-five subjects (M:F=38:27; age 49 yrs ± 4 vs. 46 ± 6, P<0.01) were randomized to semaglutide + mediterranean diet or metformin + diet. At baseline and after 6 months the following parameters were evaluated: body mass index (BMI), abdominal girth, liver steatosis, glycemic profile, AST, ALT, GGT, adherence to the Mediterranean diet, number of daily alcoholic drinks and physical activity, and smoking habits.
After 6 months, patients randomized to treatment with metformin and diet showed a statistically significant improvement according to BMI, abdominal circumference, glycemic profile, adherence to the Mediterranean diet, but there was no improvement in liver parameters (AST , ALT, GGT, degree of liver steatosis). By contrast, patients randomized to treatment with semaglutide and diet showed a statistically significant improvement on all parameters after 6 months, including those of hepatic metabolism. Furthermore, semaglutide induced a greater decrease of all parameters, and a higher adherende to diet when compared with metformin.
Conclusion: semaglutide is effective in improving and shifting several dysmetabolic risk factors in patient with T2DM. The pleiotropic properties of semaglutide might induce a reduction in cardiovascular risk compared to classic antidiabetic treatments.

190. GLP-1RAS THERAPY IN THE ELDERLY PATIENT: FOCUS ON RENAL DISEASE ASSOCIATED WITH DIABETES

Cuttone A., Giandalia A., Muscarà A., Morace C., Quartarone C., Cucinotta D., Squadrito G., Russo G.T.
Dipartimento di Medicina Clinica e Sperimentale, Università di Messina

Diabetes mellitus type 2 (DM2) is the most frequent cause of chronic kidney disease. KDIGO estimates that at least 40 % of the diabetic population has developed or will develop diabetes-associated kidney disease (DKD), and of these, a significant number will develop kidney failure requiring dialysis or renal transplantation (1). The current Guidelines recommend glucagon-like peptide-1 receptor agonists (GLP-1 RAs) as first-line drugs in DM2 patients with atherosclerotic disease or multiple cardiovascular risk factors (CVD) and second-line drugs in DKD patients due to their proven cardio-renal beneficial effects. The AMD Annals show that outpatients with DM2 are mostly elderly (>30% of them are >75 years old) (2) and that the prevalence of DKD, assessed both as a reduction in estimated glomerular filtrate (eGFR) and as micro- or macroalbuminuria, increases with age and is associated with a worse CVD risk profile (3). Although the beneficial effects of GLP1-RAs have also been confirmed in the elderly population, the available evidence mostly comes from registrational trials, whereas data on efficacy and safety from real-world studies are insufficient to date. The aim of this study was to evaluate the effects of GLP-1RAs on DKD in a cohort of elderly patients with DM2 after a mean follow-up of 30 months.
Patients and Methods: In this retrospective study, we analyzed data from 334 DM2 patients aged ≥65 years (65-84 years), referred to the outpatient of Diabetes of the UOC of Internal Medicine of the General Hospital of Messina, who were prescribed GLP-1RAs long acting, as an add-on to the current hypoglycaemic therapy. Clinical and laboratory data were analyzed, including chronic complications, at baseline and at the end of the observation period (follow-up). Episodes of hypoglycaemia and adverse effects from GLP-1RAs were investigated. DKD was defined on the basis of the estimated eGFR value and the presence of micro- or macroalbuminuria, confirmed by at least two measurements.
Results: The results at baseline and at the end of follow-up are shown in the table. At baseline, 54.5% of study subjects had renal disease (19.2% isolated albuminuria, 66.5% isolated eGFR decline, and 14.3% both conditions). After a mean observation period of 30 months, an improvement in the main CVD risk factors examined (BMI, waist circumference, blood glucose, HbA1c, blood pressure and lipid profile) was observed. At follow-up, there was a modest reduction in the number of patients diagnosed with DKD (-5.7%), as well as in the number of patients with micro-macroalbuminuria and patients with reduced eGFR, with a significant increase in mean eGFR values (P=0.0024). In our population, the therapy with GLP-1RAs was generally well tolerated: only 21 subjects (6%) reported adverse events, not determining the interruption of the treatment. We didn't observe any episodes of severe hypoglycaemia.
Conclusions: GLP-1RAs therapy was effective and safe in this cohort of elderly DM2 patients, with favorable effects on body weight, BMI, fasting blood glucose, HbA1c, lipid profile and renal function.
Reference
Table - Metabolic and clinical parameters of study subjects, at baseline and after 30 months of treatment with GLP-1Ras
data are n, %, mean ± standard deviation.
SBP, systolic blood pressure
DBP, diastolic blood pressure
eGFR, estimated glomerular filtrate
DKD, diabetes-associated kidney disease.

191. EUGLYCEMIC KETOACIDOSIS IN PATIENTS TREATED WITH SGLT2-INHIBITORS: A COMPLICATION NOT EASY TO IDENTIFY

Lorello G.[1], Emma M.[2], Arena G.[2], Spadaro F.[1], Giandalia A.[2], Bellone F.[2], Morace C.[2], Marini H.R.[2], Quartarone C.[3], Mandraffino G.[2], Russo G.[4], Squadrito G.[2]
[1]Department of Medical Sciences, Internal Medicine Unit, University Hospital "G. Martino", Messina, Italy; [2]Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy; [3]Department of Medical Sciences, Diabetes Unit, University Hospital "G. Martino", Messina, Italy; [4]Department of Clinical and Experimental Medicine, University of Messina, Messina , Italy

Background: Diabetic ketoacidosis (DKA) is one of the most common complication of diabetes mellitus (DM), due to increase of blood ketones concentration, associated with altered blood glucose values. Some cases of DKA in patients treated with SGLT2 inhibitors (SGLT2-i) have been described. These drugs may be the cause of a particular type of DKA defined as euglycemic (EuDKA), characterized by glycemic levels below 300 mg/L. This form is particularly insidious because often has a latent onset, associated with unspecific symptomatology, until progressing to severe forms, complicated by systemic symptoms. We report two cases of EuDKA in patients treated with SGLT2-i

admitted to our department between December 2022 and March 2023.
Case report 1. Sixty-three year-old man with history of type 2 DM (T2DM) from unknown time (treated with insulin since 2013 and SGLT2-i since 2020), permanent atrial fibrillation, heart failure with reduced ejection fraction, previous heart attack. About five days before admission to our Department, occurrence of fever, asthenia and confusion; after a syncopal episode, he was referred to our Hospital's Emergency Room (ER). Routine blood tests were performed, which showed: hyperglycaemia (256 mg/d l), increased inflammation indices and altered renal function; acute brain injury was excluded by brain CT scan and neurological evaluation. On admission to our department, the patient was soporific, GSC 9 (E2 V2 M5), pyretic (CT 38.4 °C) and dehydrated; on bed-side ultrasound the inferior caval vein (ICV) measured 1 cm. Arterial blood gases showed a condition of metabolic acidosis (pH 7.082, pCO2 19 mmhg, HCO3- 9.6 mmol/L, cLac 1,1 mmol/L). Blood glucose was 312 mg/dl and ketonemia > 8 mmol/L (value out of range). For this reason, support and infusion therapy with insulin and potassium were started. Blood and urine cultures were positive for E. cloacae, therefore targeted antibiotic therapy was started. HbA1c was 83.6 mmol/mol (9.8%) and c-peptide 0.67 ng/dl (below the normal range). At the resolution of clinical status, the patient was discharged with multiple daily insulin injection (MDII) and indication to continue medical follow-up.
Case report 2. Sixty-seven years-old woman with history of T2DM for about 10 years, treated with SGLT2-i and basal insulin; hypertension and dyslipidemia. For about two months there was a gradual onset of asthenia associated with weight loss; the week before the admission to the hospital this symptomatology worsened markedly, with nausea, vomiting, inappetence, pain in the epigastrium, slowed speech and temporo-spatial disorientation. Due to further impaired consciousness, the patient was accompanied by her family to our Hospital ER, where hyperglycemia (261 mg/dl), altered renal function markers, and severe metabolic acidosis (pH 6.895, pCO2 19 mmHg, HCO3- 3.70 mmol/L) were detected. On admission to our Department, the patient was soporose, GSC 11 (E3 V3 M5) and tachypnoic (respiratory rate 30 breaths/min) with ketone breath; capillary blood glucose 241 mg/dl, ketonemia 5.3 mmol/L, slightly improving metabolic acidosis (pH 7.176, pCO2 20.1 mmHg, HCO3- 9.8 mmol/L, cLac 0,9 mmol/L). On bed-side ultrasound, ICV was small in size (1.1 cm). Therefore, volemic support already started in ER was carried on, and infusion insulin therapy and potassium supplementation were undertaken. During the hospital stay, there was a gradual clinical and laboratory improvement, until resolution of the clinical condition. HbA1c was 101.1 mmol/mol (11.4%) and c-peptide 0.81 ng/dl (below the normal range). The patient was discharged with MDII and indication for continued follow-up at our outpatient clinics.
Conclusions.: Currently, the etiopathogenetic mechanism of EuDKA in patients taking SGLT2-i is not yet known. Some of the possible causes could be increased fluid depletion induced by renal excretion of glucose and/or reduced insulin secretion. Furthermore, the SGLT2 receptor inhibition: increases the secretion of glucagon through a direct action on the α-pancreatic cells, stimulates lipolysis with a consequent increase in blood levels of free fatty acids which are substrates for ketogenesis, and determines an increased concentration of sodium ions in the renal tubular lumen leading to reduced urinary excretion of ketones. Moreover, an important role is played by precipitating factors, such as concurrent pathologies, post-operative stage, reduction in caloric and/or fluid intake, alcohol abuse, low-carbohydrate diet. However, the risk of EuDKA associated with SGLT2-i remains relatively low, deeply counterbalanced by the efficacy of these drugs for cardiovascular and renal prevention. Therefore, it appears essential that both clinicians and patients are aware of the main factors predisposing to EuDKA onset. Overall, in the context of the clinical scenario characterized by symptoms related to the increase in ketonemia and triggered by precipitating factors, it will be necessary to suspend SGLT2-I administration, to ensure adequate fluid intake and to start insulin therapy.

192. RELATIONSHIP BETWEEN CARDIOVASCULAR EVENTS AND ALTERATION OF GLUCOSE HOMEOSTASIS IN PATIENTS UNDERGOING LIVER TRANSPLANTATION

Caturano A.[1], Di Martino A.[1], Gaetana A.[1], Coppola C.[2], Galiero R.[1], Rinaldi L.[1], Monda M[3], Marfella R.[1], Sasso F.C.[1], Salvatore T.[4]
[1]Department of Advanced Medical and Surgical Sciences, University of Campania Luigi Vanvitelli, I-80138 Naples, Italy; [2]Area Stabiese Hospital, Naples, Italy; [3]Department of Experimental Medicine, University of Campania Luigi Vanvitelli, I-80138 Naples, Italy; [4]Department of Precision Medicine, University of Campania Luigi Vanvitelli, I-80138 Naples, Italy

Introduction: Death from cardiovascular disease (CVD) is described as the main cause of early mortality after orthotopic liver transplantation (OLT), followed by infection, and graft failure. The metabolic factors implicated in the increased cardiovascular risk in OLT patients have not been unequivocally elucidated. Among these, glucose homeostasis changings could play a key role that is not always easy to interpret. Therefore, we aimed at evaluating the significance of glucose homeostasis changings as predictor of cardiovascular events in OLT recipients.
Methods: We retrospectively evaluated 93 consecutive non-diabetic adult OLT recipients attending every three/six month (or more often when needed), from January 1995 to December 2020 and for at least two years after intervention. We collected anamnestic, clinical, anthropometric and laboratory parameters data.
Results: 93 eligible patients (median age 57 years [IQR: 49-62], 69.9% male) were followed for a median of 100.5 months (IQR: 51.1-205.6) after liver transplantation. During the follow-up, 29 patients (31.2%) developed a worsening glucose homeostasis (28 diabetic patients and 1 impaired fasting glucose). 14 patients developed at least one adverse CV event, 5 in the stable glycaemic group and 9 in the worsening glucose homeostasis group (7.8% *vs.* 31.0%; *P=0.004*). The Kaplan-Meier analysis showed a worse CV event-free survival in patients with worsening glucose homeostasis compared to those with stable glucose homeostasis (*log rank: 0.046*). Univariable COX regression analysis showed that worsening glucose homeostasis, BMI and waist circumference in the pre-OLT were associated with cardiovascular risk.
Conclusions: Worsening glucose homeostasis, BMI and waist circumference in the pre-OLT emerged as a predictor of cardiovascular risk in a cohort of adult OLT recipients.

193. IMPACT OF GLYCAEMIC CONTROL ON CARDIOVASCULAR OUTCOMES AND MORTALITY IN A COHORT OF PATIENTS WITH TYPE 2 DIABETES MELLITUS IN A MULTIFACTORIAL RANDOMIZED CONTROLLED

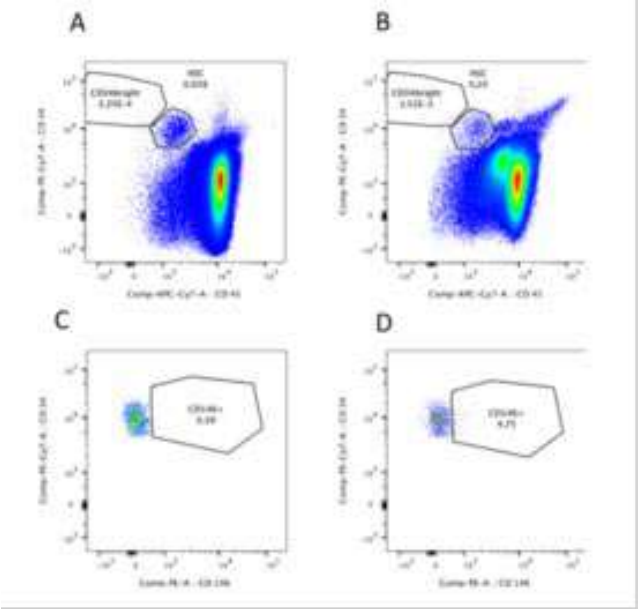
Caturano A.[1], Simeon V.[2], Galiero R.[1], Monda M.[3], Marfella R.[1], Salvatore T.[4], Sasso F.C.[1]
[1]Department of Advanced Medical and Surgical Sciences, University of Campania Luigi Vanvitelli, I-80138 Naples, Italy; [2]Medical Statistics Unit, Department of Physical and Mental Health and Preventive Medicine, University of Campania "Luigi Vanvitelli", Largo Madonna delle Grazie 1, I-80138 – Naples, Italy; [3]Department of Experimental Medicine, University of Campania Luigi Vanvitelli, I-80138 Naples, Italy.; [4]Department of Precision Medicine, University of Campania Luigi Vanvitelli, I-80138 Naples, Italy

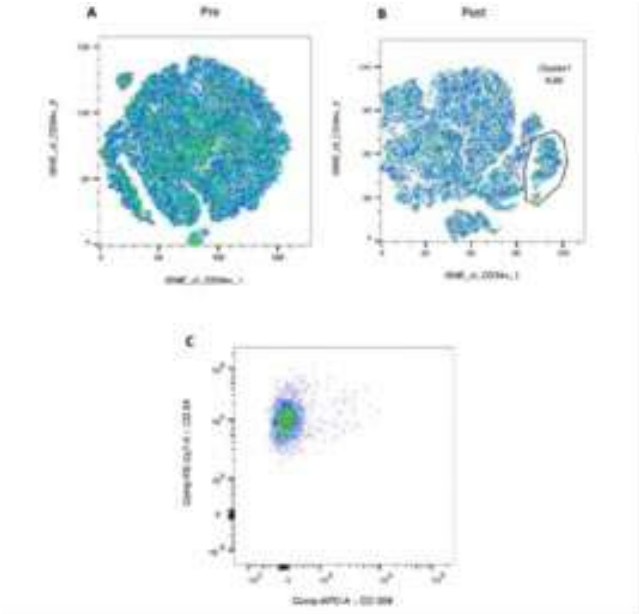
AIM: The alteration of glucose metabolism significantly influences the natural history of cardiovascular disease in diabetic patients. Several studies have evaluated the impact of glycemic control on cardiovascular risk, although its role in the context of a multifactorial intervention has not been evaluated. To evaluate the impact of glycemic control on Major Adverse Cardiovascular Events (MACE) in a multifactorial randomized controlled trial.
Methods: Nephropathy In Diabetes type 2 (NID-2) is an open randomized clinical trial conducted on a population of type 2 diabetic patients followed in 14 Italian diabetes referral centers. Patients were center randomized to intensified treatment (MT) and Standard of Care (SoC). Of the 395 randomized patients, 368 completed the intervention phase (deaths=27) and of these 321 (SoC n. 139; MT n. 182) did not suffer from MACE during the intervention and were analyzed, dividing them according to the achievement of HbA1c<7% and according to treatment (MT vs. SoC).
Results: During the post-intervention follow-up (median 7.9 years, IQR 6.6-10.4) 183 MACE occurred (56.7%), 92 in the SoC group (33 in the HbA1c <7% and 59 in the ≥7% group), and 91 in the MT group (64 HbA1c events <7% and 27 in the ≥7% group). Kaplan Meier's analysis showed a statistically significant difference between the two arms of the SoC (p=0.0256), but not in the two arms of the MT group (p=0.198). Using the TM subgroup with HbA1c<7% as a reference, by Kaplan-Meier analysis there is no statistically significant difference with the MT subgroup and HbA1c≥7% (p=0.251) and with the SoC subgroup HbA1c<7% (p =0.472), while the difference with the SoC group and HbA1c≥7% is significant (p=0.01).
Conclusions: In the context of MT, obtaining good glycemic control has little impact on MACE compared to the control of other risk factors, but it is important if it is contraindicated.

194. ROLE OF PCSK9 INHIBITORS ON THE PROFILE OF ENDOTHELIAL PROGENITOR CELLS IN PATIENTS WITH DIABETES MELLITUS: A PILOT STUDY

Simeone P.[1], Liani R.[1], De Bellis D.[1], Lanuti P.[1], Di Gregorio P.[2], Bucci M.[1], Cipollone F. [1], Santilli F.[1]
[1]Department of Medicine and Aging, and Center for Advanced Studies and Technology (CAST) "G. d'Annunzio" University of Chieti-Pescara, Chieti Italy; [2]Transfusion Medicine Department, "SS. Annunziata" Hospital, Chieti

Background: In diabetic patients being treated with statins, the levels of proprotein convertase subtilisin/kexin type 9 (PCSK9) plasma are higher and the levels of endothelial progenitor cells (EPC) are reduced compared with patients without diabetes or with diabetes not being treated with statins.
Objectives: This study has three main objectives:
a) to establish the baseline association between clinical, anthropometric and biochemical variables (e.g., glucose metabolism, lipid profile, age, gender, obesity and current therapy), endogenous plasma levels of PCSK9 and number of Hematopoietic Stem Cells (HSCs) and EPCs in naïve patients.
b) to evaluate whether the basal levels of PCSK9 are related to the vascular regenerative potential, expressed by the amount of circulating HSC and EPC.
c) to evaluate the effect of chronic treatment with PCSK9 inhibitors (PCSK9i) on the number and subpopulations of HSC and EPC in patients with and without type 2 diabetes mellitus.
Methods: Ten patients (with and without type 2 diabetes mellitus (T2DM)) who were statin intolerant and eligible for pcsk9 inhibitor treatment were enrolled in a prospective observational study. The study is still in the recruiting phase.
Patients were evaluated for clinical, biochemical and anthropometric measurements. Urine and blood sampling were performed at baseline (T0) and after 3 (T1) and 6 (T2) months of PCSK9i therapy. HSC and EPC were evaluated on whole blood by flow cytometry.
Results: Of the ten recruited subjects, six were men and four women, with age between 63 and 68 years old.
From the comparison of the number of HSC, characterized by the CD34+/CD45dim phenotype, or by the phenotype CD34+/CD45dim/CD146+, at baseline (T0, **Figure 1**, A and C), and after 3 months of treatment with PCSK9 inhibitor (**Figure 1**, B and D), there is an increase of CD34+/CD45dim (T0 vs T1; 0.058% vs 0.20%) and of CD34+/CD45dim/CD146+ (T0 vs T1; 0.39% vs 4.75%), presumably both associated with a stem cell phenotype. We also performed an unbiased cluster analysis and observed after 3 months of treatment with PCSK9 inhibitor (T1), an enrichment of the phenotype CD34+/CD45dim/CD309+ (**Figure 2**, A-B).
Conclusions: The use of PSCK9 inhibitors certainly represents a valid alternative for the treatment of hypercholesterolemia.
Patients treated with a PCSK9 inhibitor demonstrate higher levels of HSC to EPC active in the promotion of angiogenesis. This discovery could represent a novel mechanism of action of PCSK9 inhibitors with important future clinical implications in the treatment of cardiovascular diseases.
Our study is limited by the sample size, being still in phase of active recruitment, and the lack of a control group, however foreseen by the study design. However, the data presented are only preliminary and they will have to be confirmed by more consistent cases. Strengths include the originality, as there are no studies on the effects of this class of drugs on stem or progenitor cells in patients with diabetes.
Future studies should investigate the beneficial effects of PCSK9 inhibitors on other populations such as post-myocardial infarction patients and patients with ischemic cardiomyopathies, regardless of their cLDL status.





ECOGRAFIA INTERNISTICA

195. MANAGEMENT OF SPLENIC ARTERY ANEURISM AND COMPLICATIONS WITH INTERNISTIC ULTRASOUND

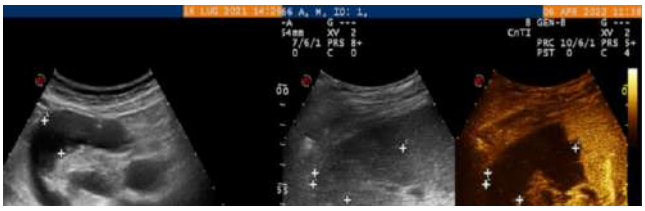
Rosica D., Sagrini E., Domenicali M.
Department of Primary Health Care, Internal Medicine Unit addressed to Frailty and Aging, AUSL Romagna, Ravenna, Italy

A 65-year-old man with history of chronic obstructive pulmonary disease (COPD), arterial hypertension not well controlled, presented to the emergency department with chest pain and shortness of breath. It was made diagnosis of COPD exacerbation which required hospitalization.
In known chronic kidney disease IV stage (CKD) (GFR 15-29) an abdominal ultrasound (US) was performed with detection of a homogeneous splenic artery ectasia with segmental aneurysm of 19 mm located in the mid-section, extended for 4-5 cm, with fusiform shape and a spleen with homogeneous echotexture (Figure 1). After diagnostic investigation first with magnetic resonance angiography (MRA) which showed a 28 mm aneurysm of the splenic

artery in its middle third and then with CT angiography (CTA), recommended by the vascular surgeon, which confirmed the caliber of the aneurysmal dilatation of the splenic artery with a coexisting parzial thrombosis not determining significant luminal stenosis, the absence of signs of rupture or covered fissure, homogeneous spleen with preserved dimensions. Then, the patient was admitted to the surgical department to perform a splenic artery embolization plus elective endovascular occlusion. After embolization he underwent contrast-enhanced ultrasound (CEUS) follow up which showed a not perfused area of the whole upper pole and part of the middle third of the spleen, corresponding to an infarcted area of 5.8x4.8 cm (about 45% of the total splenic area). Few days after he developed fever, with elevated inflammatory laboratory markers, with pain in the left upper quadrant of the abdomen with peritonism, antibiotic therapy was started. Surgeon suspected a splenic abscess and put the patient on the list for a possible splenectomy in case of clinical worsening. Due to comorbidity, and chronic kidney disease, conservative follow up with ultrasound was decided. A second CEUS reported a slight reduction in the central ischemic hilar area (5.2 cm x 3.5 cm) which appeared partially revascularized from the hilum, in the absence of "abscessual phenomena", then conservative approach was continued, and patient was discharged after clinical improvement on antibiotic therapy after few days (Figure 2). At follow up two months later patient had a good recovery, and CEUS showed complete reperfusion of the spleen through collaterals. Very often SAA are detected incidentally, as in our case, but sometimes they present acutely with rupture and/or dissection associated with high risks of morbidity and mortality. US is considered as an accessible, low-cost, radiation-free tool, with variable sensitivity for SAA depending on the patient's constitution and operator experience. CTA and MRA are accurate diagnostic tools, because they provide a three-dimensional reconstruction evaluating the size of the aneurysm, the surrounding vascular system and exclude other abdominal pathologies. The "gold standard" is arteriography which allows both diagnosis and intervention (2). The indication for surgery is related to the risk of rupture and/or dissection, location, volume increase over time. According to the literature, there is no complete consensus on follow-up times and the limiting size of the aneurysm to be treated in asyntomatic patients. US is suitable for surveillance if it can adeguately assess aneurysm growth (2). Due to comorbidities, and high anaesthesiologic risk, in our case open surgery was excluded. We therefore performed endovascular therapy, and followed patient by means of ultrasound and CEUS, technique that allowed timely bedside diagnosis of splenic infarction. Moreover, CEUS performed accurately in monitoring the size of infarcted area, excluding abscessual complications, and allowed to keep the patient on conservative therapy. In conclusion, this case report demonstrates the effectiveness of internal ultrasound with the use of contrast in both diagnostic and follow-up processes.

References:

1. Al-Habbal Y, Christophi C, Muralidharan V. Aneurysms of the splenic artery—a review. Surgeon 2010; 8(4):223–231. doi:10.1016/j.surge.2009.11.011 12.
2. Madoff DC, Denys A, Wallace MJ, et al. Splenic arterial interventions: anatomy, indications, technical considerations, and potential complications. Radiographics 2005; 25(suppl 1):S191–S211. doi:10.1148/rg.25si055504
3. Chaer RA, Abularrage CJ, Coleman DM, Eslami MH, Kashyap VS, Rockman C, et al. The Society for Vascular Surgery clinical practice guidelines on the management of visceral aneurysms. J Vasc Surg. (2020) 72:3S–39S. doi: 10.1016/j.jvs.2020.01.039



196. COMPARISON OF POINT-OF-CARE ULTRASONOGRAPHY OF THE RIGHT INTERNAL JUGULAR VEIN VS. THE INFERIOR VENA CAVA TO ESTIMATE CENTRAL VENOUS PRESSURE

Di Benedetto D.[1], Alessi C.[2], Baorda F.[1], Pedrazzoli R.[1], Pirisi M.[3]
[1]Università del Piemonte Orientale, Medicina Interna; [2]Università del Piemonte Orientale; [3]Università del Piemonte Orientale, Medicina Interna, Dipartimento di medicina traslazionale

Rationale and aim: Bedside estimation of central venous pressure (CVP) is often difficult to perform and may be aided by Point-of-Care Ultrasonography (POCUS). The POCUS method most used requires measuring the diameter of inferior vena cava in its intrahepatic tract and its collapsibility (uIVC), however its accuracy has been disputed. On the other hand, POCUS assessment of the height of the column of blood in the right internal jugular vein (uJVP) has been shown to be feasible, reproducible, and accurately predictive of an elevated CVP (Ann Intern Med 2022;175:344-51). To our knowledge, these two methods have never been formally compared. With this study, we aimed to fill this gap.

Methods: The study population included N.=27 healthy volunteers (9 males and 18 females; median age 26 years, interquartile range, IQR, 24-31; median neck circumference 32.5 cm, IQR 31-34.5). All participants were examined in a semi-supine position at 30 degrees of angulation, neck extended, and sternocleidomastoid muscles relaxed, with the examiner on the right side of the bed. The ultrasound probe (Butterfly iQ+, Butterfly Network Inc., USA) was positioned transversally at the base of the neck, above the clavicle, parallel to the floor: the right internal jugular vein was followed cranially, being careful not to artificially compress it with the probe, up to the point where it appeared smaller than the adjacent carotid artery throughout the respiratory cycle. The search for the right internal jugular vein and the evaluation of its dimensions in relation to the adjacent carotid artery were timed; furthermore, comparison with the traditional assessment of the dimensions of the vena cava in its proximity section of the liver has been documented. Time employed and results obtained by two examiners, one experienced and one unexperienced, were compared.

Results: Averaging the results of the two examiners, the median cross-sectional area of the right carotid artery was 0.27 cm2 [IQR 0.25-0.32], the median cross-sectional area of the right internal jugular vein section was 0.2 cm2 [IQR 0.17-0.23], and the median distance measured from the top of the blood column to the Louis angle was 3.1 cm [IQR 2.25-3.40]; therefore, the median estimated CVP was 8.1 cm [IQR 7.25-8.4]. The average median diameters of inferior vena cava (IVC) were 1.49 cm during expiration [IQR 1.23 - 1.63], and 0.68 cm [IQR 0.6-0.89] during inspiration. The average median IVC collapsibility index was -49.8% [IQR -57.9 - -43.8]. The average median time for uIJV measurement was 148 sec [IQR 132-182 sec], while the average median time for uIVC measurement was 234 sec [IQR 190-312 sec] (p <0.001). The interclass correlation coefficients (Table 1) showed a good agreement for all the variables between the two operators, in particular the estimate of the CVP, demonstrating the reproducibility of the examination independently of the degree ultrasonographic experience. The only discordant parameter was the examination time.

Table 1. Interobserver agreement expressed as intraclass correlation coefficients (ICC). uJVP: point-of-care evaluation of the right internal jugular vein; uIVC: point-of-care evaluation of the inferior vena cava.

Variable	ICC Independent	95% c.i.	ICC Average	95% c.i.	p
Carotid artery cross-sectional area	0.64	0.34 - 0.82	0.78	0.51 - 0.90	0.000
Internal jugular vein cross-sectional area	0.52	0.18 - 0.75	0.69	0.31 - 0.87	0.002
Distance from Louis angle	0.81	0.62 - 0.91	0.89	0.76 - 0.95	0.000
CVP estimate	0.81	0.62 - 0.91	0.89	0.76 - 0.95	0.000
IVC diameter	0.61	0.30 - 0.80	0.76	0.46 - 0.89	0.000
IVC collapsibility	0.65	0.36 - 0.83	0.79	0.53 - 0.90	0.000
Time to perform uJVP	0.21	-0.18 - 0.54	0.35	-0.43 - 0.70	0.143
Time to perform uIVC	0.31	-0.73 - 0.61	0.47	-0.16 - 0.76	0.055

At Cuzick's test, there was no association between increasing tertiles of estimated CVP by uJVP and IVC percent collapsibility (p =0.455).

Conclusion: POCUS estimate of CVP by uJVP is faster than that provided by uIVC; moreover its reproducible and easily performed even by non-expert operators. The two methods may provide complementary, rather than superimposable, information on the volume status of patients.

197. DYNAMIC CONTRAST-ENHANCED ULTRASOUND (D-CEUS) TO PREDICT BIOLOGICAL BEHAVIOR IN PANCREATIC CANCER: MONOCENTRIC STUDY PRELIMINARY RESULTS

Paratore M.
Unità di Medicina Interna e Gastroenterologia, CEMAD Digestive Disease Center, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Università Cattolica del Sacro Cuore

Introduction: Pancreatic cancer (PC) is one of the most lethal tumors worldwide, and in 2030 it will become the second leading cause of cancer related death. Computed tomography (CT) and magnetic resonance imaging (MRI) are the gold standards to stage the disease. Nevertheless, these imaging modalities are unable to provide real-time information on biological characteristics of tumors, such as vascularity, which is proportional to angiogenesis, growth rate, and necrosis. Dynamic contrast-enhanced ultrasound (D-CEUS) allows qualitative and quantitative microvascular perfusion assessment in real-time.
Aims & Methods: This study aimed to evaluate the role of D-CEUS in the characterization of PC. Thirty-eight patients with suspected PC were prospectively enrolled between October 2022 and March 2023. All patients underwent endoscopic ultrasound guided biopsy for histological diagnosis and CT or MRI for staging. According to these modalities, patients were divided into three categories: resectable PC (R-PC), locally advanced PC (LA-PC), and metastatic PC (M-PC). D-CEUS was performed the same day of lesion biopsy and time-intensity parameters were compared among tumor categories. The diagnostic performances of selected parameters was evaluated by receiver operating characteristic (ROC) analysis.
Results: PC was diagnosed in 36 (94.7%) patients and classified as R-PC, LA-PC and M-PC in 5 (13.9%), 13 (36.1%) and 18 (50%) patients, respectively. Among perfusion parameters, time to peak (TTP) showed a trend to increase in LA-PC patients (median 18.03 sec, interquartile range [IQR] 14) compared to R-PC group (median 12.9 sec, IQR 3.05) ($p = 0.05$) and it was significantly higher in LAPC group compared to M-PC group (median 12.35 sec, IQR 4.08) ($p = 0.03$). A cut-off value < 11.6 sec showed a good accuracy to distinguish LA-PC from M-PC (area under the ROC curve = 0.74) with maximal specificity (100%) but low sensitivity (50%).
Conclusion: Quantitative perfusion parameters extracted from D-CEUS seem to be useful in distinguishing the invasiveness of PC. The TTP, a parameter related to blood flow was higher in LA-PC compared to M-PC, suggesting different microvascular characteristics of the tumors. Further studies on larger population are needed to confirm these findings and to explore the biological basis for this phenomenon.

198. BED-SIDE ULTRASOUND AND ITS UTILIY IN CLINICAL PRACTICE

Lorello G.[1], Bellone F.[2], Spadaro F.[1], Andò E.[2], Fugazzotto P.[2], Di Pietro C.[1], Morace C.[2], Mandraffino G.[2], Squadrito G.[2]
[1]Department of Medical Sciences, Internal Medicine Unit, University Hospital "G. Martino" of Messina, Messina, Italy; [2]Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

Introduction. It is defined bed-side the use of ultrasound to complete a medical examination, of which it is an integral part. Depending on the instrumentation used and the operator skills, it is possible to perform a first level bed-side ultrasound, called ecoscopy, whose purpose is essentially to give dichotomous answers to simple questions (e.g. absence/presence of effusion), or a second level imaging, called point of care ultra-sound (POCUS), used to formulate definitive clinical diagnoses according to the symptom under examination or to raise diagnostic suspicions to be submitted to a second opinion, including conventional ultrasound or further second level imaging. The term FoCUS (focused cardiac ultrasound), instead, refers to a specific type of bed-side ultrasound applied to the study of the heart, aimed to provide qualitative information on the morphology and cardiac mechanics. We report the case of a patient, admitted to our Department, in which the use of bed-side ultrasound modified clinical and therapeutic approach.
Case report. Seventy-four years-old woman affected by permanent atrial fibrillation, sick sinus syndrome, for which has been implanted a bicameral pacemaker, chronic kidney disease stage III, colonic diverticulosis. About twenty years ago she underwent mitral valve replacement with a mechanical prosthesis, in cardio-embolic prophylaxis with vitamin K inhibitors drugs. In October 2022, due to onset of marked asthenia, she was admitted at our Hospital Emergency Room. Control blood chemistry tests showed iron deficiency severe anemia (Hb 7.1 g/dl) and increased inflammation indices; a chest-X-ray was performed, which showed the presence of pulmonary thickening and bilateral pleural effusion, with increased cardiac shadow probably duo to suspected pericardial effusion. She underwent a blood transfusion and then was transferred to our Internal Medicine Division, diagnosed with pneumonia and anemia. Once admitted to the ward, bed-side ultrasound was performed, to integrate the medical examination and evaluate the cardiac kinetics, the dimensions of inferior caval vein (ICV) and the presence of any abdominal and/or pleural effusions. During the evaluation in four chamber sub-costal view (Figure 1), marked dilatation of the left atrium was found, with the presence of an "isoechoic and finely not homogeneous mass, adherent to the lateral wall, about 5.1×3.3×4.5 cm in size, compatible, in the first hypothesis, with a thrombotic lesion"; the presence of this lesion was confirmed in the long axis parasternal view (Figure 2), while in the apical four-chamber view (Figure 3) it was not visible due to the presence of the rear shadow cone generated by the mitral prosthesis. The right ventricle and atrium were also increased in size; no alterations of the segmental kinetics were evident. The ICV was increased in size (2.2 cm), not modulable with breath. The finding of bilateral pleural effusion, described on chest X-ray, was confirmed, while only a minimal amount of pericardial effusion was present. Considering these findings, Cardiologists performed a transesophageal echocardiogram (Figure 4), which, however, was not clarifying in the diagnosis, because the lesion had atypical patterns. For this reason, a chest contrast agent CT-scan was performed, which confirmed the thrombotic nature of the atrial mass. Therefore, the patient was transferred to the Cardiac Surgery Division of the "Papardo" Hospital to continue diagnostic and therapeutic iter.
Conclusions. To date, the use of bed-side ultrasound is becoming increasingly evident in daily clinical practice, in order to integrate and complete the patient's assessment and to make the diagnostic process more rapid and precise. Our case shows how, through the bed-side ultrasound use, it was possible to correctly direct the diagnosis. Several studies of the most recent literature have also highlighted how this method can have a higher sensitivity and specificity than other first-level imaging, as in the case of pleural and pericardial effusions evaluation in comparison to the chest x-ray. However, its correct use requires adequate training: referring to our case, it is clear that the four-camera view alone, even if it is more immediate and easy to evaluate, it may not be enough to have an overall vision; therefore it should always be integrated with the four-chamber sub-costal and parasternal long axis view, as recommended by the most recent indications, especially in particular cases such as the presence of valve prosthesis. For this reason, to acquire the necessary skills for its use, it seems to be clear that specific training is fundamental; this should already begin during medical degree course, in order to make bed-side ultrasound an important component of medical professional background.

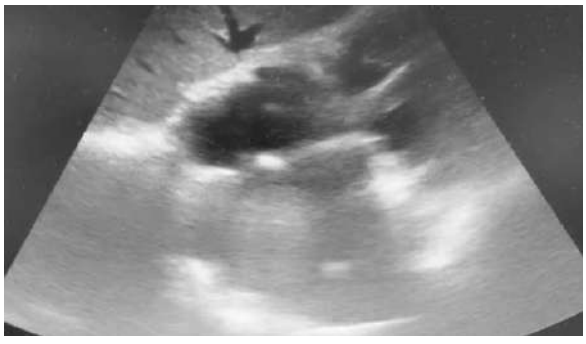


Figure 1. *Four Chamber Subcostal View (4SC).*

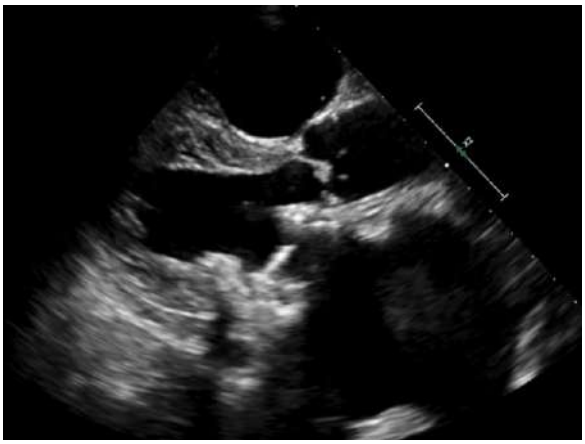


Figure 2. *Parasternal Long Axis View (PLAX).*

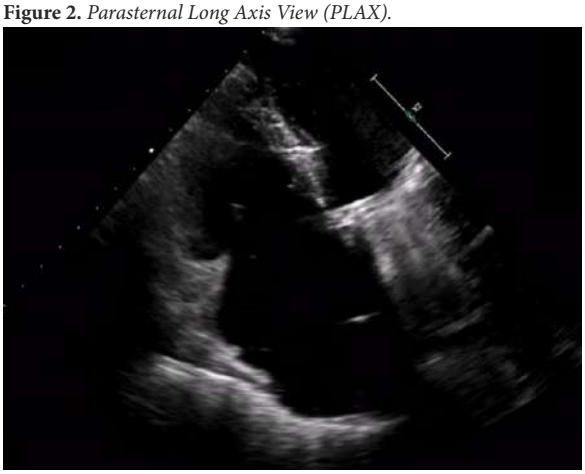


Figure 3.
Four-chamber apical view (A4C): in this view the rear shadow cone generated by mitral prosthesis does not allow to visualize the intra-atrial thrombus.

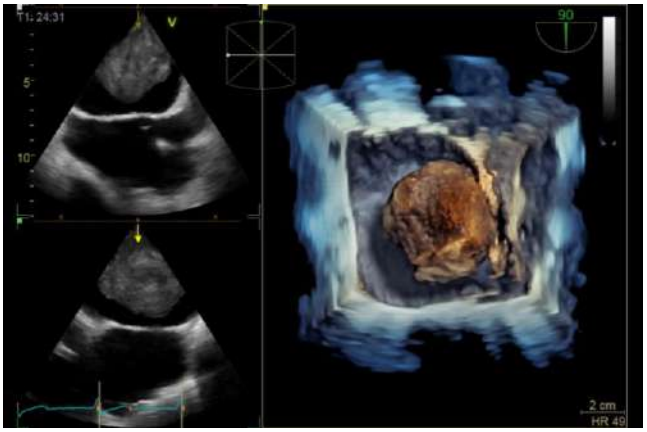


Figure 4.
Transesophageal echocardiogram and 3D-reconstruction.

199. ARTIFICIAL INTELLIGENCE SUPPORTS LUNG ULTRASOUND NON-EXPERT PHYSICIAN IN INTERSTITIAL PNEUMONIA EVALUATION. A SINGLE CENTRE STUDY

Cicco S.[1], Mancini F.[1], Marozzi M.S.[1], Corvasce F.[1], Lombardi F.A.[2], Loponte L.[1], Giliberti T.[1], Morelli C.M.[1], Longo S.[1], Lauletta G.[1], Solimando A.G.[1], Ria R.[1], Vacca A.[1]
[1]Unit of Internal Medicine "G. Baccelli", Department of Precision and Regenerative Medicine and Ionian Area, University of Bari Aldo Moro, Bari; [2]Institute of Clinical Physiology, National Research Council, Lecce, Italy

Introduction: Lung ultrasound (LUS) applies in clinical practice to identify interstitial lung diseases (ILD) and their evolution. However, high-resolution computed tomography (HRCT) remains the gold standard method to evaluate the severity of ILD. In daily clinical setting, LUS can be performed as a screening method or in follow-up after HRCT to evaluate typical pattern of interstitial lung involvement and monitor parenchyma outcomes. Minimum training is needed to better identify typical lesions. Artificial Intelligence (AI) may help in this issue.
Aim: We wondered whether AI was effective in automatic ILD recognition and scoring compared to an expert LUS sonographer. We used the 'SensUS Lung version device', an AI algorithm for the automatic recognition of the typical ILD patterns. The algorithm calculates an index that indicates a possible interstitial involvement.
Methods: We selected 33 caucasian patients (17 M and 16 F, aged 69.74±17.51 y) in follow-up for ILD from 2021 to 2023. All patients presented a typical HRCT patterns (honeycombing, groundglass, fibrosis). An expert physician evaluated all patients with LUS on twelve segments (six per side). Next, blinded to the previous evaluation, the SensUS non-trained operator performed the LUS using the same spatial evaluation. For all patients pulmonary functional test (PFT) and DLCO were available. According to the DLCO results the patients were categorized in reduced or preserved. The SensUS indicated different grades of interstitial involvement (absent, initial, intermediate, advanced) scored from 0 (absent) to 3 (advanced). To compare the SensUS results to LUS we divided the LUS total score to the number of segments evaluated. Comparison were done with Wilcoxon tests for paired values or Man-Whitney for unpaired samples; correlation were performed using Spearman Analysis; $p < 0.05$ was considered significant.
Results: SensUS was non-inferior to LUS in identifying the risk of ILD (median SensUS 1 [0-2] vs LUS 0.67 [0.25-1.54]; p=0.84). Furthermore the degree of interstitial pulmonary involvement directly related to the LUS score (r=0.607, p=0.002). SensUS values were inversely correlated to forced expiratory volume at first second (FEV1%; r=-0.40, p=0.027), forced vital capacity (FVC%; r=-0.39, p=0.03) and forced expiratory flow (FEF) at 25 percentile (FEF25%; r= -0.39, p= 0.02) while results directly correlated to FEF25-75% (r= 0.45, p= 0.04) and FEF75% (r=0.43, p=0.01). Finally, in patients with reduced DLCO the SensUS was significantly higher (reduced median 1 [1-2] vs preserved 0 [0-1], p=0.001) overlapping the LUS score (reduced median 18 [4-20] vs preserved 5.5 [2-9], p=0.035).
Conclusions: Our data suggest that AI may help non-expert physician in lung ultrasounds resulting non-inferior to expert LUS despite it tended to overestimate the ILD lesions. Therefore, AI may support physicians (in particular not expert LUS sonographer) in daily clinical practice to monitor patients with ILD. This device is simple to use and it makes a fully automatic real time analysis. However, it needs a minimum training on basic skills. Nowadays, it can support but not replace LUS and HRCT performed by expert staff in monitoring these patients.

200. THE ROLE OF RENAL ULTRASOUND IN THE EVALUATION OF SEPTIC PATIENTS ADMITTED TO MEDICAL AREA: A PROSPECTIVE STUDY OF THE RENAL RESISTIVE INDEX'S PREDICTIVE VALUE

Vannoni F.[1], Bruni D. [1], Malandrino D. [2], Boddi M. [2]
[1]Medicina Interna I, Nuovo Ospedale S. Stefano di Prato; [2]Dipartimento di Medicina Sperimentale e Clinica, AOU Careggi

Background: Sepsis-associated acute kidney injury (S-AKI) is one of the most common, early and serious complications of sepsis and causes a significant increase in mortality and in the risk of developing chronic kidney disease. Doppler renal resistive index (RRI) was recognized as an independent predictor of mortality for chronic kidney disease. Studies conducted on populations of critically ill patients admitted to intensive care units showed that the increase in RRI predicts the onset of acute kidney injury (AKI). No study investigated whether RRI could predict AKI and/or mortality in septic patients admitted to Internal Medicine departments.
Objectives: We studied whether the measurement of RRI in septic patients hospitalized in Medical Area could predict the development and severity of S-AKI and help the clinician in the early identification of the most critical cases.
Materials and methods: The study enrolled 50 patients hospitalized for sepsis from December 2021 to April 2023 in the Department of Internal Medicine 1 of "Nuovo Ospedale S. Stefano" in Prato (USL Toscana Centro). We investigated RRI measurement and the clinical and laboratory indicators of sepsis, renal function and hemodynamic status in 3 steps (T0, at admission;

T1, after 48 hours; T2, pre-discharge). Renal function was assessed by KDIGO criteria. The association between RRI and unfavorable outcome (persistent AKI/death) was studied by Logistic Regression Analysis.
Results: We found a significant difference in RRI values at admission (p=0.008) between patients who developed AKI (mean RRI 0.82 ± 0.05) and those who did not (mean RRI 0.70 ± 0.04). A significant difference was found in the RRI values (p=0.042 at T0, p=0.003 at T1) between patients who developed persistent AKI and died (mean RRI at admission 0.85 ± 0.04) and patients who developed transient AKI and survived (mean RRI at admission 0.81 ± 0.05). Multivariate Logistic Regression Analysis documented a significant association between RRI values at T1 and persistent AKI (p=0.048).
Conclusions: Elevated RRI values in septic patients admitted to Medical Area was identified as a significant predictor of worsening renal function (transient or persistent) and mortality.

EMATOLOGIA

201. A RARE BUT PROBABLY UNDERDIAGNOSED BLEEDING

Martino G.P.[1], Bitti G.[1], Girotti S.[2], Angelici S.[1]
[1]UOC Medicina Interna AST Fermo; [2]Azienda Ospedaliero Universitaria delle Marche

A 99-year-old man came to the emergency department with sleepiness, bruising of his limbs, and bruising of his arms for several days.
For about two months a rash had appeared on the back. The patient was treated by the dermatologist with antihistamine, steroid and antibiotic therapy
Type II diabetes mellitus, arterial hypertension and chronic bronchitis were reported in the medical history.
Home therapy consisted of metformin, acetylsalicylic acid, ramipril, amlodipine, simvastatin.
Blood tests showed iron deficiency anemia, prolonged aPTT and normal PT. APTT mixing study, reduced FVIII activity and presence of autoantibodies, detected by the Bethesda assay confirmed acquired hemophilia A (AHA).
The patient was treated with bypassing agents and immunosuppressive therapy with normalization of factor VIII but subsequent death from bilateral pneumonia.
AHA is characterized by neutralizing autoantibodies, called inhibitors, against factor VIII (FVIII). AHA is a rare disorder, affecting men and women of all ages. Two peaks in AHA incidence are typically observed; one associated with pregnancy, and another with older age (>60 years old).
Approximately half of patients with AHA have concomitant disorders, most often other autoimmune disorders or malignancy.
A more widespread knowledge of AHA and the relative differential diagnoses is necessary. A close collaboration with the haemophilia centers is important for optimal management.

202. EFFECT OF THE THIRD DOSE OF BNT162B2 MRNA COVID-19 VACCINE AMONG PATIENTS AFFECTED BY HEMATOLOGICAL DISEASES

Campiotti L[1], Dalla Gasperina D[2], Baj A[2], Epis E[2], Dentali F[2]
[1]Dipartimento di Medicina e Chirurgia Università dell'Insubria;
[2]Dipartimento di Medicina e Chirurgia Università dell'Insubria

Hematological diseases are characterized by immunological defects worsened by therapy and in these patients the number of vaccine doses against Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) to obtain protection is still unclear.
To evaluate the efficacy of the third dose of the BNT162b2 mRNA COVID vaccine, we performed an observational, prospective,' real life' study among patients affected by hematological diseases referred to our department. Patients were tested to evaluate antibodies against the viral spike protein (LIAISON® SARS-CoV-2 TrimericS, Diasorin) before the third dose of the vaccine (T1) and three weeks after (T2). Blood antibody levels upper 100 BAU/ml were defined as 'protective,' 'positive' in case of levels between 33.8 and 99 BAU/ml, and 'negative' for levels inferior to 33.8 BAU/ml. At 6 weeks after the third dose , patients negative were tested through measurement of T-helper cell type 1 (Th1)-associated cytokine release [interferon (IFN)-c, tumor necrosis factor (TNF)-a, interleukin (IL)-2] to evaluate T-cell response against the virus with three different procedures: Covi-FERON FIA (IFN-gamma) (SD Biosensor), QuantiFERON® SARS-CoV-2 (QIAGEN), T-Spot.COVID (Oxford Immunotec).
Between November and December 2021, 70 patients were enrolled [mean age 69 years (range 47-89), 49(70%) males ,21(30%)female] . Forty-seven patients (66%) were affected by lymphoid malignancies (LM); 17(25%) by myeloid malignancies (MM); and 6(9%) by benign hematological diseases (BD). Thirty-nine patients (55%) were in active treatment or received specific therapy during the last year (22 [56%] were affected by LM, 14 [36%] by MM, 3 [8%] by BD), and 31(45%) patients were in follow-up.
At T1, 36 patients (51.4%) had a protective serum antibody level (21 LM , 13 MM, 2 BD) ; 13 (19%) (7 LM, 3 MM, 3 BD) were positive and 21 (30%) negative (19 LM, 1 MM, 1 BD). All negative patients were in active therapy or treated during the last year [15(71%) received rituximab and chemotherapy, 5(24%) chemotherapy ,1(5%) radiotherapy]. Increased risk of negative IgG titers was linked with LM vs. no-LM ($p< 0.01$) and with rituximab therapy ($p <0.05$).
At T2, patients with a protective antibody raised from 36 (51.4%) to 57 (81%), 2 (3%) were positive and 11(16%) negative . All patients without antibody response were affected by lymphoid malignancies, and 10 (90%) received rituximab.
At six weeks after the third dose of vaccine, none of negative patients showed detectable anti-spike T-cell-mediated immune response vaccine-induced. During follow-up , 6 (54%) negative patients developed severe COVID-19 infection, and 2 died while among protected patients , we observed 4 (7%) cases of paucisintomatic SARS-COV2 infection at 7 , 10 , 11 and 12 months ($p < 0.0001$) .In our experience hematological patients with only two doses have a higher risk no protection against COVID-19 infection. The third dose of vaccine increases the seroconversion rate in hematological patients . Patients affected by LM have the highest risk of suboptimal response, increased by treatment during the last year and employment of rituximab. The absence of seroconversion was linked with the absence of a detectable T-cell vaccine-induced population .

203. A RARE CASE OF JAK2 MUTATION IN MYELODYSPLASTIC SYNDROME TREATED WITH RUXOLITINIB

Campiotti L.[1], Epis E.[2], Molteni M.[2], Orsini F.[3], Pessina C.[3], Colugnat I.[3], Pallotti F.[4]
[1]Dipartimento di Medicina e Chirurgia , università dell'Insubria;
[2]Dipartimento di Medicina e Chirurgia , Università dell'Insubria; [3]SSD SMEL Citogenetica e Genetica Medica ASST Settelaghi; [4]Dipartimento di Medicina e Chirurgia , università dell'Insubria SSD SMEL Citogenetica e Genetica Medica ASST Settelaghi

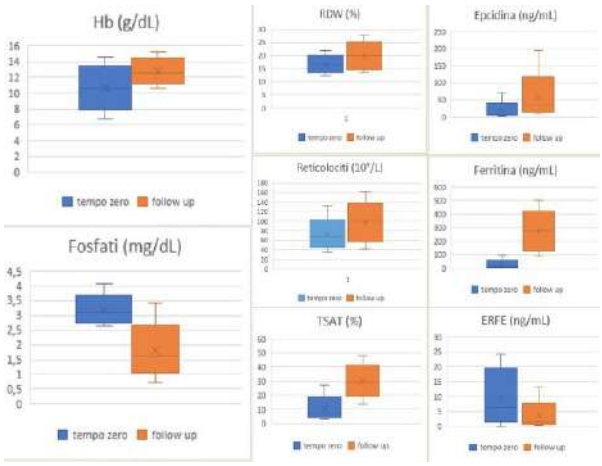
Myelodysplastic syndromes (MDS) are common condition among elderly people characterized by poor prognosis and their treatment is often difficult and unsatisfactory for patients and physicians.
In selected case elderly patients can benefit from new drugs or personalized therapy.
Next-generation sequencing (NGS) is a new test that can reveal multiple gene mutations in the genetic material of neoplastic cells .
NGS could improve not only the diagnosis of specific diseases , but also detect mutations that could be target for molecular therapy.
A 78 old-year woman was referred to our Department for a persistent pancytopenia , that need periodical blood transfusions .
Her performance status was good (ECOG 0 , IK 100%) , she did not take any therapy and her medical history was normal. She reported mild fever in the afternoon , night sweats during last four months and back pain .
Clinical examination was normal and thoracic and abdomen TC scan did not show adenopathies , or liver and spleen enlargement .
Bone marrow biopsy showed a unclassifiable myelodysplastic syndrome associated with mild fibrosis, bone marrow aspirate was impossibile (dry tap) , and conventional cytogenetic study on peripheral blood cells showed a normal female karyotype . Molecular test on peripheral blood evidenced the presence of JAK2 V617 mutation.
The symptoms referred by the patient could suggest a chronic myeloproliferative neoplasm , but were unusual in myelodysplastic syndrome .
We decided to perform a NGS analysis and genomic DNA was extracted from fresh peripheral blood samples
NGS was performed using a panel designed to detect single-nucleotide variants and small insertions and deletions within 30 genes recurrently mutated in myeloid malignancies: ASXL1, BRAF, CALR, CBL, CSF3R, DNMT3A,

ETV6, EZH2, FLT3, GATA2, IDH1, IDH2, JAK2, JAK3, KIT, KRAS, MPL, NPM1, NRAS, PHF6, PTPN11, RUNX1, SETBP1, SF3B1, SRSF2, TET2, TP53, U2AF1, WT1, and ZRSR2. The variant allele frequency limit of detection was 2% .
We observed the presence of JAK2 617F mutation associated with ASXL1 , MPL and U2AF1 mutations with an allele frequency superior to 20%.
JAK2 V617F mutation is rare in myelodysplastic syndromes and in its presence a myeloproliferative disease needs to be excluded. JAK2 V617F mutations have been reported to occur at a higher frequency in myelodyspastic syndrome with isolated 5q deletion and cases of MDS/MPN with ring sideroblasts and thrombocytosis . In addition, some cases of MDS with fibrosis have been associated with a JAK2 V617F mutation
The other mutations observed were described in unclassifiable Myelodysplastic/Myeloproliferative Neoplasms and generally are associated with a poor prognosis.
We treated our patient with erythropoietin and low dose of desametosone that resolved back pain and night sweats , because in myelodysplastic syndrome systemic symptoms are related with an expansion of cytotoxic T cells that overproduce proinflammatory cytokines (interferon γ and tumor necrosis factor α) and after the results of NGS we added low dose of ruxolitinib a selective inhibitor of JAK1/2 .
We observed an improvement of anemia and the resolution of transfusion need .
Our experience show how a specialistic test like NGS could be of support not only for clinical research or for specific diagnosis , but also could help clinicians in treatment of frail patients

204. STUDY OF RELATIONSHIPS BETWEEN IRON AND PHOSPHOCALCIC METABOLISM IN A COHORT OF PATIENTS WITH IRON DEFICIENCY TREATED WITH CARBOXYMALTOSE IRON

Mengon S.[1], Sartori G.[2], Busti F.[2], Marchi G.[2], Girelli D.[2]
[1]Dipearimento di Medicina; [2]Dipartimento di Medicina

Intravenous iron supplementation is becoming more and more popular in clinical practice in the treatment of iron deficiency due to the introduction of the so-called third generation preparations, with very favorable features in terms of safety and efficacy. Its use leads to improved outcomes in various pathological conditions associated with anemia and/or iron deficiency. Recently, it has emerged that carboxymaltose iron, one of the most widely used compounds in Italy, is commonly associated with hypophosphatemia, an effect that is often transient and asymptomatic, but it may be clinically relevant in some subjects.
Here we studied 30 patients who underwent iron carboxymaltose infusion for iron deficiency, as a model for studying the relationships between iron metabolism, erythropoiesis, and phosphocalcic metabolism. Among others, pre- and post-treatment hepcidin, erythroferrone, phosphates and C-reactive protein were analyzed.
Twenty-five patients (83.3% of the sample) showed post-infusion hypophosphatemia, often of moderate or severe grade (72 and 20% of hypophosphatemic patients, respectively). None of them presented severe adverse reactions. A higher prevalence of nonspecific symptoms (e.g., general malaise) potentially related to hypophosphatemia was observed in patients who showed this complication compared to those who did not (32 vs 20%). Subjects who developed hypophosphatemia were found to have significantly lower BMI, lower pre-infusion Hb, higher pre-infusion RDW, and lower ferritin variation (delta ferritin), suggesting possible alternative i.v. iron approach in patients with such features. The variation of pre- and post-treatment phosphorus levels (delta P) correlated significantly with reduced hepcidin delta and increased RDW delta, suggesting a close connection between hepcidin response, erythropoiesis, and hypophosphatemia. Pre-infusion hepcidin and erythroferrone levels revealed as promising predictors of iron status, much less influenced by the presence of comorbidities than ferritin, the currently used marker for the definition of iron deficiency. Their use could therefore improve the identification and treatment of iron deficient patients.
In conclusion, this study expands the knowledge about post-infusion carboxymaltose iron hypophosphatemia and lays the basis for more in-depth studies on the relationship between iron metabolism, erythropoiesis, and phosphocalcic metabolism.



205. A RARE CASE OF ADULT ACUTE LYMPHOBLASTIC LEUKEMIA

Di Paola D.[1], Montalbano G.[1], Parisi F.[2], Patanè F.[2], Vetro C.[3], Stancanelli B.[2]
[1]Departmente of Clinical and Experimental Medicine, University of Catania; [2]U.O.C. Medicina Generale Policlinico San Marco, Catania; [3]U.O.C. Ematologia Policlinico San Marco, Catania

Introduction: Acute lymphoblastic leukemia is a rare hematologic neoplasm: in Italy there are approximately 1.6 cases per 100,000 males and 1.2 cases per 100,000 females. It represents the most frequent onco-hematologic disorder in pediatric age (80% of children's leukemias), with peak incidence between 2 and 5 years of age, gradually decreasing with advancing age.
Clinical Case: Forty-four-year-old woman was hospitalized to Unit of General Medicine for intermittent fever, poorly responsive to antipyretic therapy, hyposthenia, and upper extremity pain. In remote pathological history: arterial hypertension, previous hystero-annessiectomy, Hashimoto's thyroiditis. General examination was normal (in particular, no appreciable lymphadenopathies). Nothing to report on brain CT and cervical cord MRI. Laboratory findings showed persistent increase in inflammatory parameters (CRP 152 mg/l), normochromic normocytic anemia (Hb 8g/dl, MCV 83.8 fl) and thrombocytopenia (57x 10^3/microliter).
We performed ADAMTS-13 mutation and indirect Coombs test (resulted negative), peripheral blood smear evaluation (negative for schistocytes). Autoimmunity tests (ANA, ENA, ANCA, antiplatelet antibodies, antiphospholipid antibodies, RF) were also negative.
Due to persistent intermittent fever spikes, unresponsive to empiric antibiotic therapy (negative blood cultures, TORCH Test and urine culture), ECHO scan of the abdomen was performed, showing hepatosplenomegaly. Therefore, CT-PET scan was performed showing a diffuse uptake of bone marrow pertinence, associated with tracer hyperaccumulation at the spleen level, with no focal points. A bone marrow aspirate was then performed with morphologic and immunophenotypic features consistent with Acute Lymphoblastic Leukemia B. The patient was transferred to the Hematology Unit, where, once cytogenetic and molecular biological evaluations for the BCR-ABL chimeric gene were performed, she underwent therapeutic protocol with Ponatinib and Blinatomumab. The patient still maintains clinical-laboratory remission of disease and is in satisfactory general conditions.
Conclusions: Acute Lymphoblastic Leukemia, a typical pediatric disease, can also rarely occur in adulthood, with variable and nonspecific spectrum of clinical manifestations.

206. UNRAVELING THE ROLE OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR B/Δ (PPAR B/Δ) IN ANGIOGENESIS ASSOCIATED WITH MULTIPLE MYELOMA

Leone P.[1], Prete M.[1], Solimando A.G.[2], Malerba E.[1], Susca N.[1], Racanelli V.[3]
[1]Department of Interdisciplinary Medicine, School of Medicine, 'Aldo Moro' University of Bari, Bari, 70124, Italy; [2]Department of Precision and Regenerative Medicine – Ionian Pole, School of Medicine, 'Aldo Moro' University of Bari, Bari, 70124, Italy; [3]Department of Cellular, Computational and Integrative Biology - CIBIO, University of Trento, Italy

Growing evidence suggests a role for peroxisome proliferator activated receptor β/δ (PPAR β/δ) in the angiogenesis, growth, and metastasis of solid tumors, but little is known about its role in multiple myeloma (MM). Angiogenesis in the bone marrow (BM) is a hallmark of disease progression from monoclonal gammopathy of undetermined significance (MGUS) to MM. We examined the expression and function of PPAR β/δ in endothelial cells (EC) from the BM of MGUS (MGEC) and MM (MMEC) patients and showed that PPAR β/δ is expressed at higher levels in MMEC than in MGEC and that overexpression depends on myeloma plasma cells. The interaction between myeloma plasma cells and MMEC promoted the release of the PPAR β/δ ligand, prostaglandin I2 (PGI2), by MMEC, leading to the activation and increased expression of PPAR β/δ. We also demonstrated that PPAR β/δ is a strong stimulator of angiogenesis in vitro, and that PPAR β/δ inhibition by a specific antagonist greatly impairs the angiogenic functions of MMEC. These results identify PGI2-PPAR β/δ signaling in EC as a potential target of anti-angiogenic therapy. They also support the testing of PPAR β/δ inhibitors in combination with conventional drugs as a new therapeutic strategy for MM.

207. BETA-THALASSEMIA TRAIT WITH IRON OVERLOAD: EXPLORING THE MULTI-FACTORIAL HEPCIDIN SUPPRESSION AND A NOVEL "MINI"-PHLEBOTOMIES APPROACH.

Chesini F.
UOC di Medicina Generale d'Urgenza di Verona

A certain degree of iron overload (IO) is sometimes seen in subjects with β-thalassemia trait (βTT). Previous studies observed that βTT was characterized by mild hepcidin suppression due to increased erythropoietic activity. Erythropoiesis may inhibit hepcidin synthesis via the erythroid-derived hormone erythroferrone (ERFE). Hepcidin is the master regulator of iron homeostasis which acts by inhibiting dietary iron absorption and iron release from macrophages and deposits, thus its suppression leads to an increase of iron absorption and availability in the body. In individual patients, hepcidin defect may be further aggravated by genetic (i.e. mutations in hemochromatosis genes) or acquired cofactors (e.g. alcohol abuse or non-alcoholic liver diseases). The aim of this study was to investigate conditions involved in the development of IO in βTT, through a detailed collection of clinical history, a next-generation-sequencing (NGS) analysis, hepcidin and ERFE measurement in a series of consecutive βTT-IO patients referred to our Center for Iron Metabolism Disorders in Northern Italy. A novel approach based on "mini"-phlebotomies was also studied in some patients. Blood samples were collected at enrolment and, in these selected patients, also after iron depletion.
βTT-IO patients displayed high levels of hepcidin but very low hepcidin:ferritin ratio, suggesting that hepcidin response to iron is relatively suppressed in βTT. In agreement with the presence of a mild increase of erythropoietic activity, our population showed mean ERFE concentrations higher (geometric mean 33.89 ng/ml, CI95% 21.02-54.65) than healthy individuals. Moreover, in our population we observed a significant inverse correlation between hepcidin and ERFE (R= -0.594; P=0.009) confirmed also after adjustment for age and sex (b-coeff. -0.576; P=0.019). However, hepcidin defect resulted frequently multi-factorial: a substantial alcohol consumption and the H63D mutation on HFE appeared the most common cofactors in addition to ineffective erythropoiesis. "Mini"-phlebotomies were well tolerated and effective in inducing iron depletion. After iron depletion, mean hepcidin levels and ERFE concentration significantly reduced (respectively P=0.007 and P=0.044) and Hemoglobin levels tended to increase.
IO characterization and treatment in βTT is a challenging multi-factorial condition, which prevalence is still unknown. A meticulous evaluation of the multiple factors potentially favoring hepcidin suppression and the "mini"-phlebotomies approach proposed in this study may be useful insights for clinical practice in βTT-IO patients.

208. AN UNUSUAL CASE OF PERIPHERAL ULCER: PYODERMA GANGRENOSUM AS A MANIFESTATION OF THE UNDERLYING TUMOR.

Lo Monaco G.[1], Bruno C.[1], Melita G.[1], Leone F.[1], Patanè F.[2], Lombardo E.[2], Stancanelli B.[2]
[1]Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy; [2]UO Medicina Generale AOU Policlinico "San Marco", Catania, Italy

Background: Pyoderma gangrenosum (PG) is a disorder with an estimated incidence of 3 to 10 cases per million people per year. It may occur in individuals of any age, including children. Typically, it is an ulcerative lesion characterized by neutrophil-predominant infiltrates due to an hyperactivation of innate immune response, in addition to genetic factors.
There are some rare genetic conditions like PAPA, PASH and PAPASH Syndrome, but frequently it is associated with an underlying systemic disease, such as Inflammatory bowel disease, hematologic disorders, arthritis and malignancies. Clinical, histopathologic, and laboratory findings in PG are nonspecific, so that it is a diagnosis of exclusion.
Case Report: A 80-year-old man with skin ulcer on the left leg with a history of arterial hypertension, hypercholesterolemia and lower urinary tract symptoms.
Initially, it seemed to be a venous so it was treated with medicated bandages and, after the culture isolation of Klebsiella oxytocica, E. coli and Pseudomonas aeruginosa MDR, specific antibiotic therapy was prescribed without any benefit.
Echo-Color-Doppler and several hematochemical tests were performed, such as FR, ANCA, ANA, Antiphospholipid antibodies, HIV test, liver and kidney function, serum electrophoresis immunofixation, all negative. After exclusion venous disease of the lower limbs and a possible vasculitis, a skin biopsy was performed, suggesting a diagnosis of pyoderma gangrenosum. Therefore, corticosteroid and immunosuppressive therapy was started with Cyclosporine, the latter being discontinued, due to the intolerance of the patient.
Given the hematochemical findings of increased Ca-19.9, elevated EBV IgG, EBV DNA (560 gEq/mL) and because of the evidence in literature of frequent association of pyoderma gangrenosum with neoplasms, EGDS was performed, showing erosive gastric lesions. Colonoscopy resulted inconclusive, due to insufficient intestinal toilet. Also, contrast-enhancement neck-thorax-abdomen CT scan showed minute nodular lesions with aspecific significance in the right pulmonary lobe, a large lymphnode package in the pelvi, another voluminous centrally colliquative lymphnode package (diameter of about 5 cm) on the left inguinal area and an unevenly dense prostate with calcifications. Urological evaluation, however, ruled out prostatic cancer .
After several weeks from recurrence of the ulcer, general conditions of the patient worsened, despite medical therapy, and the skin lesions started secreting greenish-yellow fluid in the distal third of the left leg, while a swollen lymphnode package in the left inguinal region developed. Due to the persistence of an increase in inflammatory indexes (CRP 128 mg/L), given the worsened clinical presentation and after Pseudomonas aeruginosa positivity on biopsy fragment culture, empirical antibiotic therapy with Cefotaxime was started, supplemented later on with Amikacin. During hospitalization MRI scan of the leg was performed, showing marked swelling and structural inhomogeneity of the cutaneous/subcutaneous soft tissues and initial excavation of the Achilles tendon. A further total body CT scan was performed, showing an increased and secondary lung lesions. Laboratory findings documented progressive anemia, further increase in CRP values, LDH and Beta-2-microglobulin. At this stage inguinal lymph node package biopsy was performed confirming the suspected diagnosis of a Lymphoproliferative disease, that is an aggressive Large B cells type lymphoma.
Conclusions: The clinical history, biopsy, and laboratory data often help distinguishing PG from other diseases. Specifically, looking for any potential primary cause could help understanding the link between primary disease and PG, so allowing to design an appropriate therapeutic approach.

209. WARBURG EFFECT: A CASE OF TYPE B LACTIC ACIDOSIS SECONDARY TO DIFFUSE LARGE B CELLS NON HODGKIN LYMPHOMA (NHL)

Lo Monaco G.[1], Melita G.[1], Abbate M.[1], Patanè F.[2], Lombardo E.[2], Stancanelli B.[2]
[1]Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy; [2]UO Medicina Generale AOU Policlinico "San Marco", Catania, Italy

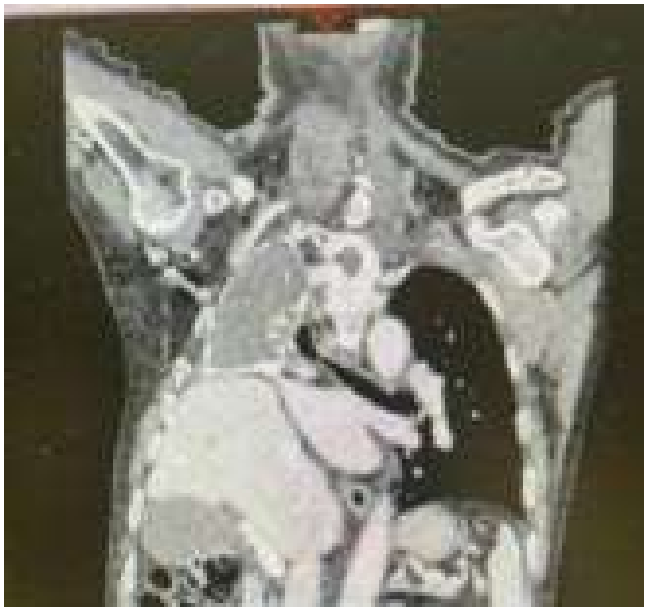
Background: Type B lactic acidosis differs from Type A by the absence of a systemic hypoperfusion. There are several causes associated with this metabolic derangement, such as diabetes, alcoholism, HIV infection, beta-adrenergic agonist abuse, other drugs and malignancies, especially of hematologic nature.
It rarely occurs in patients with leukemia, lymphoma, and solid tumors. The pathogenesis is not well understood. Anaerobic metabolism due to dense, under-perfused clusters of tumor cells and/or metastatic replacement of the liver parenchyma has been proposed. Other possible mechanisms include

increased rates of lactate production by neoplastic cells, shifting to primarily anaerobic glycolysis (the so called "Warburg" effect), also leading to hypoglycemia. This is a relevant oncological emergency related to high mortality.
Case Report: A 61-year-old man with newly diagnosed NLH and history of acute hepatitis of unidentified etiology in pediatric age. Before starting chemotherapy with Rituximab, he was found positive for HBVcAb and HBVsAb. Therefore, due to the risk of HBV reactivation, he started prophylaxis with Lamivudine. After taking the drug, the patient complained of severe abdominal pain and hyperpyrexia, associated with hyperlactacidemic metabolic acidosis, with bicarbonates loss, in absence of altered renal function (Lactate 6.4 mmol/l; pH 7.4, HCO3 16 mmol/l). On suspicion of an adverse reaction to Lamivudine, this was withdrawn, without any clinical benefit. So, a few days later the patient was admitted to the Emergency Room, where the persistence of lactic acidosis (Lac 9.7 mmol/l) was highlighted. The Pavia poison control center ruled out Lamivudine as the cause of the lactic acidosis, due to its prevalent renal excretion (70%) and its short half-life, taking into account also Lamivudine withdrawal from several days.
The patient presented apyretic, with, productive cough and subjective dyspnea without respiratory distress, stable hemodynamics, with abdominal pain and recurrent sweating. Fluid and electrolytes correction were started, followed by an initial improvement and partial decrease in lactates (down to 4.6 mmol/l). Due to the occurrence of asymptomatic hypoglycemia (46 mg/dL), 5% glucose solution was given, causing a significant and persistent increase in lactate values (from 7.2 to 12.1 mmol/l). Furthermore, since sepsis was suspected, empirical broad-spectrum antibiotic therapy was initially started with Piperacillin/Tazobactam,Cefiderocol and Fosfomycin. Blood chemistry tests detected thrombocytopenia (PLT 89 10^3/microL), hyperuricemia (10. 9 mg/dL), increase of enzymes (ALT 151 U/L, alkaline phosphatase 440 U/L, gammaGT 429 U/L, LDH 2296 mU/mL), Electrolytes and kidney function resulted satisfactory. Given the increase of inflammation CRP (182 mg/L,), we assayed serum β-D-glucan, urine and blood cultures for aerobic and anaerobic bacteria and mycetes, molecular swab for SARS-Cov2 (all negative) . CMV, EBV, Rubella and Toxoplasma antibodies were also negative. Chest and abdomen CTs with dye injection were also performed, which excluded the presence of pulmonary embolism and intestinal ischemia, while showing multiple lymphnodes and several hypodense areas at splenic. Later on the patient became oliguric, with a worsening in renal function, possibly secondary to dye injection, so that dialysis was started, with no relief of lactacedemia.
At this point, having ruled out infectious aetiology and thromboembolic hypoperfusion, our diagnostic suspicion was directed towards a form of type B lactic acidosis, somehow linked to the underlying onco-haematological disease, causing a worsening in clinical conditions, due to the increased availability of intravenous glycidic substrate. Withdrawal of glucose infusion, together Vincristine administration restored lactates within the normal range.
Conclusions: Lactic acidosis is a common, but non-specific feature that may be difficult to link with other causes. The type B lactic acidosis is rare and when is associated with hypoglycemia and concomitant neoplastic disease a *Warburg effect* should be suspected, consisting in a preferential anaerobic glycolisis in the cytosol of neoplastic cells, that are avid of glucose, as demonstrated by an increased uptake of injected radioactive glucose. It represents a true oncological emergency. Cytoreductive treatment is the cornerstone appropriate therapy with consequent correction of lactic acidosis and improvement of the patient's prognosis. Glucose infusion would be harmful because induces the *Warburg effect.*

210. JUST WHERE YOU DON'T EXPECT IT

Ferretti M.[1], Andreoni R.[1], Alfonsi A.[1], Caltabiano L.[1], Antonini C.[1], Pellone M.[1], Luzi E.[2], Bassino E.M.[2], Cicconi F.[2], Delle Monache F.[3], Ferri C.[4], Desideri G.B.[5]
[1]School of Internal Medicine, MESVA department, University of L'Aquila; [2]School of Geriatrics, MESVA department, University of L'Aquila; [3]Chief UOC Internal Medicine,"G. Mazzini" Hospital Teramo; [4]Director of the Chair of Internal Medicine, School of Internal Medicine, MeSVA Department University of L'Aquila; UOC of Internal Medicine and Nephrology Hypertension and Cardiovascular Prevention Unit - "San Salvatore" Hospital L'Aquila; [5]Director of the School of Geriatrics, MeSVA Department University of L'Aquila. Chief UOC of Geriatrics, "SS Filippo e Nicola" Hospital Avezzano

Introduction: Lymphomas are a heterogeneous group of neoplasms that originate from cells of the lymphatic and reticuloendothelial system. They are classified into: Hodgkin's Lymphomas and Non-Hodgkin's Lymphomas (NHL) which differ in several characteristics such as lymph node involvement, spread, histological classification, disease course and prognosis. Non-Hodgkin's Lymphoma represents 3% of all neoplasms in Italy and shows a higher incidence in men than in women and increases with age, being more common after the age of 65. The aetiology is unknown, but primary or acquired immunodeficiency especially after chemo- and radiotherapy and exposure to environmental toxins (herbicides or insecticides) are the main risk factors.
Clinical case: A 75-year-old retired man, a former farm labourer, was admitted for right haemithoracalgia resistant to NSAID therapy that had been present for 15 days, associated with serotinous fever in the three days preceding admission. History of pulmonary heteroplasia diagnosed 40 years previously treated with right pneumonectomy, peri-ilateral glandular emptying with main bronchus left in place and closed with chromic cutgut, adenocarcinoma of the colon in 2017 underwent left colectomy, adjuvant chemotherapy and radiotherapy, in follow-up at the time of admission, arterial hypertension, benign prostatic hypertrophy and gallbladder lithiasis. Two years earlier he performed PET-CT scan for oncological re-evaluation which excluded recurrence of disease. On physical examination on admission patient visibly in pain, no appreciable lymphomegaly in the main lymph node stations explored, minimal right eyelid ptosis. On auscultation vesicular murmur abolished in the right hemithorax. Vivid evoked pain (patient VAS 8) on acupressure of the spinous processes of the dorsal spine and all right chondro-sternal joints. Haematochemical examinations on admission showed mild neutrophilic leukocytosis and moderate increase in PCR; the remaining wards were normal. On suspicion of a compressive genesis of the algic symptoms and of the palpebral ptosis, a total body CT scan with mdc was performed, which showed the presence of solid tissue with inhomogeneous enhancement at thoracic level in the dorsal upper right area of a maximum size of 6x4.2 cm, determining structural alterations of a lytic nature in the posterior arch of the IV and V ribs and in the right transverse processes of the D4 and D5 soma. No morphovolumetrically significant lymphadenopathies bilaterally and mediastinally or abdominally. Global PET-CT with 18FDG confirmed uptake (SUV max 30.4) at the level of the known formation consistent with neoplastic pathology with high metabolic activity. It also indicated focal areas of hyperaccumulation of the tracer throughout the residual pleural cavity. For this reason, a CT-guided biopsy of the posterior arch of the IV and V ribs on the right was indicated in order to type the neoformation with histological findings of proliferation of immature lymphoid elements CD3+, CD 20-, CD 10-, CD 56-, CD 30-, ALK-, cytokeratins-, EMA- with Ki67: about 85% as for T lymphoma with a high replicative index. Antiblastic therapy was planned but never carried out due to superimposed infectious process: the patient developed gangrenous cholecystitis with subsequent septic state complicated by multi-organ failure.
Conclusions: Peripheral T-cell lymphomas are rare tumours, accounting for 5% of all lymphoproliferative disorders, with a low survival rate related to both the aggressiveness of the disease and the few treatments available. The description of this clinical case underlines how NHL is more frequent in patients with acquired immunodeficiency in relation to previous oncological treatment and how this aspect is able to condition the disease outcome with the superimposition, as in the case described, of complicated infectious processes responsible for exitus.



211. A CASE OF PRIMARY ADRENAL EBV+ EXTRANODAL NK/T-CELL LYMPHOMA

Rela E.[1], Secci M.[2], D'Angelo E.[1], Fanile M.T.[1], Bozzolo E.P.[3], Damanti S.[4], Ramirez GA.[5], Tresoldi M.[3]
[1]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy; Università Vita-Salute San Raffaele, Milan, Italy; [2]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy; University of Cagliari; [3]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy; [4]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy; Università Vita-Salute San Raffaele, Milan, Italy; Unit of Medical Specialties and Healthcare Continuity IRCCS Ospedale San Raffaele, Milan, Italy; [5]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy; Università Vita-Salute San Raffaele, Milan, Italy; Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS Ospedale San Raffaele, Milan, Italy

Introduction: Extranodal NK/T-cell lymphoma (ENKTCL) is a rare subtype of aggressive non-Hodgkin lymphoma, characterized by extranodal presentation and association with Epstein-Barr Virus (EBV) infection. We report the case of a Caucasian woman with EBV+ ENKTCL originated from the adrenal glands. There are less than 300 cases of primary adrenal lymphoma (PAL) described in the English-language literature worldwide to date (Y. Zhang, J Cancer Res Ther, 2022), and only a few cases had histopathology compatible with ENKTCL, the most frequent being diffuse large-B cell lymphoma (DLBCL).
Case Presentation: In late October 2022 a 68-year-old Caucasian woman presented to a clinic in Santo Domingo because of low back pain, fatigue and dyspnea lasting for more than one month. Lab tests showed elevated D-dimer and C-reactive protein (CRP) levels. A total body computed tomography (CT) scan excluded pulmonary embolism (PE) but detected a right adrenal gland mass (91*61*87 mm). A contrast-enhanced abdomen magnetic resonance imaging (MRI) disclosed bilateral adrenal gland masses (left mass 53*36 mm) with mild and heterogeneous contrast uptake but no adenopathies. Prednisolone 10 mg/day and ibuprofen 600 mg/day were started for pain control and she flew back to Italy.
On November 14, she was admitted to the Emergency Department of San Raffaele Hospital complaining of severe low back pain, fatigue and dyspnea, as well as visual acuity reduction in her left eye. When admitted to our Internal Medicine ward, she was febrile and tachycardic/tachypneic, with oxygen saturation 94% in room air. Erythrocyte sedimentation rate (ESR), CRP and liver enzymes were elevated; fibrinogen was normal (243 mg/dl). There were slight anemia and hyperkalemia (5.44 mmol/L). At blood gas analysis pO2 was 61 mmHg, pCO2 29 mmHg and lactate 3.93 mmol/L. Cultures and serology ruled out bacterial and fungal infections. To investigate her visual impairment a head CT scan was performed and showed thickening of pituitary gland stalk infundibulum and of the posterior side of both eyeballs. A brain MRI confirmed these findings, suggesting pituitary macroadenoma or metastasis. Lactate dehydrogenase (LDH) and 2-microglobulin were both elevated (606 U/L and 4.58 mg/L, respectively); anterior pituitary gland hormones were decreased, namely thyroid-stimulating hormone (TSH), but without need of immediate treatment. Urinary metanephrines were normal. The patient rapidly deteriorated with dyspnea and hypoxemia, cachexia, night fever and generalized edema. A total body CT showed enlarged adrenal masses, appearance of right pleural effusion and dystelectasis of the right lower lobe. No primary malignancy was detected. Positron emission tomography and computed tomography (PET-CT) showed diffuse uptake of both lungs bilaterally, especially in the upper lobes, bilateral adrenal masses, right auricle, descending colon and sigma. A biopsy of the adrenal glands was performed, which showed EBV+ ENKTCL.In the meanwhile, the clinical course was complicated by the onset of diffuse intravascular coagulation (DIC). She was them started on i.v. methylprednisolone (1 mg/kg/die) for three days, followed by a pre-phase chemotherapy with cyclophosphamide and vincristine. These drugs were chosen for both the critical clinical conditions and the risk of massive tumor lysis. Further deterioration led to acute respiratory failure and death.
Discussion and conclusion: The diagnosis of ENKTCL may be delayed or missed due to unawareness of such a rare disease (especially in non-epidemic regions), and to its tendency to present with aspecific symptoms and uncommon sites of involvement. Primary adrenal lymphoma is exceedingly rare and adrenal ENKTCL was diagnosed in very few cases. This type of lymphoma is most prevalent in Eastern Asia and Latin America where EBV infection in early childhood is the rule. Most of the affected patients are adults, with a median age of 46-60 years (age range: 9-89 years) and males, representing 55-78% of cases. Usual sites of disease are the nose, nasopharynx, oropharynx, and upper aerodigestive tract. The course can be rapidly progressive and the prognosis, though variable, is generally poor, especially in patients with high-risk features. Traditional chemotherapy regimens for aggressive lymphoma, such as CHOP, are usually ineffective, but the introduction of L-asparaginase-based regimens has improved the outcome. As showed in our case, prompt diagnosis is the key issue to start proper treatment and obtain adequate response.

212. DIAGNOSIS, THERAPY AND BLEEDING MANAGEMENT OF THROMBOCYTOPENIA IN PREGNANCY: ANALYSIS OF 63 PREGNANCIES IN 59 THROMBOCYTOPENIC WOMEN

Freddi G.[1], Vai F.[1], Quaglini S.[2], Mofaddel S.[2], Cantalupo S.[2], Bozzi V.[3], Barozzi S.[3], Noris P.[4], Beneventi F.[5], Di Maggio I. [5], Cavagnoli C.[5], Di Sabatino A.[1], Melazzini F.[1]
[1]Department of Internal Medicine, University of Pavia-IRCCS Policlinico San Matteo Foundation, Pavia, Italy; [2]Service of Biometry & Statistics, IRCCS Policlinico San Matteo Foundation, Pavia, Italy; [3]Service of Biology, IRCCS Policlinico San Matteo Foundation, Pavia, Italy; [4]Department of Geriatrics, University of Pavia-IAR Pavia, Rehabilitation Institute Santa Margherita, Pavia, Italy; [5]Department of Gynecology, IRCCS Policlinico San Matteo Foundation, Pavia, Italy

Thrombocytopenia during pregnancy can be related to severe bleeding manifestations both in the mother and the fetus. Three are the main disorders associated with this condition: gestational thrombocytopenia (GT), immune thrombocytopenia (ITP) and inherited thrombocitopenias (ITs). The diagnosis of the nature of thrombocytopenia in pregnancy is still challenging but fundamental, since it has therapeutic and outcome implications. We performed a retrospective, observational, monocentric study aimed at collecting and analyzing pregnancy outcomes. We enrolled 59 consecutive women with thrombocytopenia (63 pregnancies overall), attended to our referral Center in the last 3 years. To our knowledge, this is the first time that a significant number of patients affected with these conditions has been reported, except for inherited platelet function disorders (IPFD), with a multidisciplinary clinical characterization.
Our results show that, together with personal and family history, platelet (PLT) count trend, mean platelet volume (MPV) and PLT anisocytosis in pregnancy are helpful for the diagnosis. In GT, PLT count is the highest and the decrease during pregnancy is similar to that of ITP; in ITs PLT count is the lowest in each trimester. Regarding MPV, in GT, PLT anisocytosis is minimal and MPV is normal; in ITs and in ITP we observed significant platelet anisocytosis, associated with a higher MPV.
Of note, misdiagnosis with ITP was responsible for unnecessary and unsuccessful therapy in some GT or ITs pregnant women, determining relevant side effects. Excluding IPFD, the bleeding risk for mother with thrombocytopenia and their newborns is similar to the general population. Vaginal delivery is safer, than caesarean section, and therefore is preferable whenever obstetrical-gynaecological conditions permit, due to the lower risk of bleeding.

213. THE T-CELLS MENACE

Nocera N.[1], Pulcini E.[1], Tassara R.[1], Portesan F.[1], Thneibat, A.[1], Bellodi A.[2], Ballestrero A.[3]
[1]Dipartimento di Medicina Interna e specialità mediche DIMI, Università degli Studi di Genova; [2]Dirigente medico presso la Clinica di Medicina interna ad indirizzo oncologico, IRCCS Ospedale Policlinico San Martino; [3]Direttore di Scuola di Specializzazione in Medicina interna, Dipartimento di Medicina Interna e specialità mediche DIMI, Università degli Studi di Genova

A 75-year-old male patient, went to the emergency room for evening fever, asthenia, night sweats and the appearance of edema of the right upper limb that had occurred in the last month. He also reported swelling in the neck and face and weight loss (about 4 Kg in one month) associated with hyporexia. The patient's medical history revealed: ischemic right coronary disease treated with percutaneous transluminal coronary angioplasty and stenting in 2020, transthyretin related cardiac amyloidosis, radical prostatectomy for prostate cancer, arterial hypertension, chronic renal failure, previous single acute gouty attack, left knee and right hip prosthesis. The patient was also a former smoker. Blood tests performed in the emergency room showed: trilinear cytopenia mainly affecting platelets (50,000/mmc). Rise in lactate de-

hydrogenase to 650 U/L and C-reactive protein to 50 mg/L, rise in creatinine worsening from previously known values (1.2->1.7 mg/dL). No signs of hemolysis or vitamin deficiency. Marked hypoalbuminemia (2.3 mg/dL). Negative blood cultures. During clinical examination we observed: 39.2°C temperature, 130/70 mmHg blood pressure, heart rate of 90 beats/minute, 96% O2 saturation (room air). Swelling on the left cheek, neither sore nor painful, but fixed on palpation and characterized by wooden consistency. In the nuchal region: ecchymotic area of increased consistency. Bilateral periorbital and left upper limb edema with rubor, calor, pain and tumor but in the absence of functional limitation. On the right forearm oedematous region, erythematous, neither sore nor painful on pressure. In the right deltoid region, a 1 centimetre area of increased consistency. Ecchymosis on both upper limbs. Lymphadenopathy in the right axilla. Blood coltures were repeated and a positive finding for S. epidermidis was observed, antibiotic therapy with Piperacillin-Tazobactam was set up. Despite antibiotic coverage, hyperpyrexia persisted with feverish episodes up to 39°C mainly at night. During hospitalization, the patient remained transfusion-dependent, and trilinear cytopenia also persisted; therefore, in order to investigate the haematological condition, a bone marrow biopsy was performed with the detection of dysmyelopoietic alterations and signs of haemophagocytosis. Progressive worsening of the skin condition with increase in the diameter and consistency of the lesions was observed. Multiple punch biopsies were performed in the nuchal region, on the arm and on the forearm. We observed: atypical lymphoid infiltrate (mainly TCD3+), no areas of necrosis or granulomatous reaction. The immunomorphological finding was compatible with panniculitic T-cells lymphoma. The patient was initially treated with high-dose steroid therapy and intravenous immunoglobulins and subsequently with etoposide. Despite the chemotherapy, we reported progressive worsening of the clinical and laboratory condition. The last blood test showed leukocytes 0.46 x 10E9/L, haemoglobin 8.4 g/L, platelets 4 x 10E9/L, fibrinogen 1.65 g/L, ferritin 37186 mcg/L, findings compatible with macrophage hyperactivation syndrome. After 27 days of hospitalization, the patient died. Panniculitic T-cells lymphoma is a rare disease characterized by an aggressive clinical behaviour; this type of lymphoma is frequently associated with macrophage hyperactivation syndrome. The latter is a rare disorder of the regulation of the immune response in which hematopoietic cells are phagocytosed by monocytes and macrophages at the level of lymph nodes, bone marrow, liver, and spleen. The prognosis related to the association between these two pathologies tends to be poor.

214. PURE RED CELL APLASIA ASSOCIATED WITH AUTOIMMUNE HEMOLYTIC ANEMIA: A RISKFUL FEATURE WITH LIFE-THREATENING PERSPECTIVES

Losio A. G., Regolo M., Salmeri C., Munno G., Cassisi G., Castelletti F., Cardaci N., Lanzafame A., Fiorenza P., Torrisi E., Malatino L.
Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy

Background: Pure red cell aplasia (PRCA) is a disease characterized by severe anemia and reticulocytopenia due to reduction of erythroid progenitors in the bone marrow. It is a rare disorder, usually secondary to infections, hematological or autoimmune disease, and several drugs. The pathogenesis of acquired PRCA was not yet fully understood, except for a likely autoimmune mechanism. Association of autoimmune hemolytic anemia (AIHA) and PRCA is rare, with just a few single-case reports in the literature. In addition, there is no established treatment.
We herein report a successfully treated case of PRCA associated with AIHA throughout persistent Cytomegalovirus (CMV) infection.
Case Description: A 76-yr old man was admitted to our Department of Clinical Medicine at Cannizzaro Hospital (Catania, Italy) with severe anemia (Hb 4.6 g/dL) and elevated hemolysis markers.
The patient had a past medical history of arterial hypertension, hypercholesterolemia, benign prostatic hyperplasia and hypothyroidism on thyroxine therapy after thyroidectomy. After the occurrence of weakness, exertional dyspnea and loss of appetite, he underwent a chest Computed Tomography (CT) scan that highlighted infracentimetric mediastinal lymph nodes. Outpatient laboratory investigations showed a progressive anemia.
Direct and indirect antiglobulin (Coombs) tests were positive with mainly *warm* IgG, IgM with wide temperature range, and a strong complement activation. AIHA was also confirmed.
Autoimmune tests were performed: S-ENA, AMA and APCA were negative, S-ANA was positive with a titer of 1/320 and a cytoplasmic *fine speckled* pattern. Serum C3 was low (53 mg/dl), while C4 was within normal range; total IgG (2564 mg/dl) and IgM (614 mg/dl) were high, while total IgA were within range. Tumor markers were unremarkable. Serum viral hepatitis markers (HBsAg, HBcAb, anti-HBS, HCVAb) and anti-HIV Ab were negative.
Anti-CMV IgG (169.6 U/ml), but not IgM, resulted positive. CMV-DNA was detectable in a (3170 copies/ml). Anti-Epstein-Barr virus (EBV) antibodies were all positive: anti-VCA IgG (313.0 U/ml), anti-VCA IgM (77.5 U/ml), anti-EBNA IgG (445.0 U/ml). All other causes of infections associated with haemolytic anemia (Mycoplasma pneumoniae, Human Parvovirus B19 were excluded).
Chest and abdomen CT with dye injection showed diffuse subcentimetric and supradiaphragmatic and and subdiaphragmatic lymph nodes, with maximum size of 18X10.5 mm; bipolar diameter of spleen 12 cm.
In the suspicion of lymphoma, a bone marrow biopsy was performed, revealing a trilinear dysmyelopoiesis of moderate to severe degree, various niche and one paratrabecular lymphoid aggregates represented by B lymphocytes of small size (PAX-5+, CD79a+) and T lymphocytes (CD3+), with no diagnostic evidence; interstitial immature blasts (CD34+): 3-4%.
Immunosuppressive steroid therapy with methylprednisolone 40 mg /day was started, together with antiviral treatment with lamivudine, acyclovir and ganciclovir.
In spite of anemia worsening, no compatible packed red blood cells were available. When the minimum hemoglobin value was achieved (2.7 g/dL), transfusion after pre-medication was necessary, given the life-threatening condition with cardiovascular instability.
Due to the progression of the hemolysis, intravenous immunoglobulins (IVIG) were administered for 5 days followed by 4 cycles (one/week) of intravenous monoclonal antibodies against CD20 (Rituximab).
Hemoglobin values started to rise up the value of 13.5 g/dl within 9 weeks. Maintenance steroid therapy (initially prednisone 50 mg per day, progressively downshifted).
Eight weeks later a new hemolytic crisis occurred (Hb 10.2 g/dL, RBC 2.5*10^6/uL, reticulocytes 0.90%, haptoglobin 2 mg/dL, total bilirubin 1.9 mg/dL, LDH 651 U/I;) so he was admitted again to our Department. Serum viral tests showed a persistent CMV infection. A bone marrow aspiration was performed, with no evidence of blasts, no evident reduction of CD10 on the myeloid line cells, even if with a reduction of erythroid precursors. Coombs tests persisted strongly positive. According to the repeated hemolytic crisis without the expected reticulocytosis, concomitant diagnosis of PRCA was considered possible. The patient was switched again to a higher dose of steroid (methylprednisolone 40 mg per day) and observed therapy with cyclophosphamide (50 mg twice a day) and antiviral prophylaxis with ganciclovir. Serum hemoglobin levels started to rise and reached stable values, with the normalization of the hemolysis markers.
The patient was discharged with the prescription to undergo an esophagogastroduodenoscopy, so far not made, to exclude a MALT lymphoma.
Conclusions: This case-report underscores that a diagnosis of PRCA should be considered in patients with AIHA associated with viral infections, especially when steroid-refractory. Further investigations are needed to understand the immunological pathophysiology of acute PRCA in patients with autoimmune hemolytic anemia.

215. CHRONIC-ACTIVE-EBV INFECTION (CAEBV): AN UNDERRATED AND POTENTIALLY FATAL CAUSE OF FEVER AND LYMPHADENOPATHIES. A CASE REPORT EXPLAINING WHEN CAEBV SHOULD BE SUSPECTED AND HOW REACH THE DIAGNOSIS.

Gilardi N. [1], Scarsi C.[1], Pulcini E.[1], Thneibat A.[1], Ceccardi A.[1], Strozzi M.[1], Golgo S.[1], Cigolini B.[1], Zoppoli G.[1], Bellodi A.[2], Ballestrero A.[1]
[1]Dipartimento di Medicina Interna e Specialità Mediche, Università degli studi di Genova; [2]IRCCS Ospedale Policlinico San Martino

Background: Epstein-Barr-Virus (EBV) is a DNA virus belonging to Herpesviridae family which may induce both acute and chronic infection. EBV is classically encountered in childhood and the infection is usually pauci/asymptomatic or with mononucleosis clinical features. After acute infection, the virus hides in B-lymphocytes under T-lymphocytes control. Rarely, EBV infected patients, may develop a potentially life-threatening condition named Chronic Active EBV disease (CAEBV).
CAEBV is a rare condition whose epidemiology is not clear; it apparently affects adolescent and young man with variable median age (from 30 to 45 years according to retrospective studies) although cases of CAEBV in elderly people have also been reported. CAEBV include a broad spectrum of Lymphoprolipherative Disease (LPD) with a malignant potential but commonly

rise with mononucleosis clinical features (fever, sore throat, lymphadenopathy, splenomegaly, thrombocytopenia). CAEBV can also progress, after an indefinitely time (months or years) in to worst clinical condition like hemophagocytic syndrome (HPS) and/or malignance lymphoproliferative disease. In 2016 indeed, WHO add on CAEBV and malignant EBV-associated T/NK-cell LPD in T and NK cell Lymphoma classification. Hematopoietic stem-cell transplantation (HSCT) preceded by 3-step chemotherapy strategy is the only curative treatment strategy to date.

Case presentation: We present an 81-year-old male with recent history of macrocytic anemia, fever, splenomegaly and diffuse small lymphadenopathies (< 1cm). At laboratory tests we found positive EBV-serology and high title of EBV-DNA on blood samples (maximum value: 75'000 copies/mL). After excluding other infectious causes, we performed Positron Emission Tomography (PET) and excisional biopsy of two inguinal lymph-nodes on which histopathological and cytogenetic analyses (EBER-1 research by FISH technique) were conduct. Following the excisional procedure, by the good and stable clinical condition, the patient was discharged at home to attend the histological and cytogenetic results. EBER-1 positivity allowed to CAEBV diagnosis but, unfortunately, hospital readmission was delayed for long standing Sars-Cov-2 infection with about 50 days of swab positivity. Clinical conditions at patient readmission rapidly became critical (cachexia, high fever, hypotension, cognitive impairment) and the hospitalization was complicated by severe pneumonia initially treated with Piperacillin/Tazobactam and, after E. faecium isolation on sputum culture, with Linezolid. After clinical stabilization, CAEBV were re-staged with CT scan (showing enlargement of all lymphadenopathies) bone marrow (BM) biopsy, BM aspirate and axillary lymph-node excisional biopsy. Laboratory test showed higher systemic inflammatory state (ferritin 5236 ng/mL, C reactive protein 97 mg/L, LAD 381 U/L, Triglycerides 89 mg/dL, EBV-DNA 170'000 copies/mL). A salvage chemotherapy with modified CVP-R schedule (Cyclophosphamide, Vincristine, Prednisone and Rituximab) were performed with a significative decrease of EBV-DNA copies (last dosage: 250 copies/mL). Unfortunately, clinical conditions didn't follow EBV copies trend and worsted until patient death. Axillary lymph node biopsy, which histological result were available after patient death, showed transformation of CAEBV in aggressive bi-phenotype B and T cell Lymphoma.

Conclusion: This clinical case shows how CAEBV presents with a-specific symptoms that often leads to diagnosis delay although this LPD may have a rapid clinical course. Some chemotherapy schedule may be effective to reduce EBV copies count and to slow down disease progression if administered before a severe and critical worsening of clinical condition. Indeed, chemotherapy alone is not a curative strategy. To date, three-step chemotherapy followed by HSCT is the only curative treatment. In conclusion, EBV-LPD like CAEBV should be considered in differential diagnosis in patients with fever of unknown origin, organomegaly, lymphadenopathy or other non-specific clinical feature for at least three months and negativity for other infectivological tests. EBV serology and EBV-DNA copies are initial tests and, if positive, the diagnosis also need the presence of the virus on the involved tissue (lymph-node for example) that may be assessed with the research of EBER-1 with FISH technique.

216. THE STRANGE CASE OF MRS. L.: TREATING COMPLICATIONS WITHOUT LOOKING FOR CAUSES.

Altavilla N., Vergatti A., Abate V., Barbato A., D'Elia L., Rendina D. Department of Clinical Medicine and Surgery, University Federico II, Naples, Italy, via Sergio Pansini, 80131

D.L., a 53-year-old woman, was transferred to our Department of Internal Medicine from the Emergency Department of another hospital, where she had been admitted for difficulty in swallowing, diffuse lymphadenopathy and declivous oedemas.

At the pathological history, she reported severe mitral insufficiency in specialist follow-up, osteoporosis under treatment with alendronate and asthenia that had been progressively worsening for some years.

The ECG performed on admission showed numerous supraventricular extrasystoles and ST-segment elevation of about 2 mm, while haematochemical investigations showed anaemia (Hb 9. 7 mg/dl), hypercalcaemia (12 mEq/L), stage III renal failure (eGFR 56 ml/min) and increased n-terminal fragment of B-type natriuretic peptide (6789 pg/ml) and cardiac troponin I (124 pg/ml). The hypercalcaemia was investigated by assaying 25-OH vitamin D (14 ng/ml), phosphorus (3.9 mg/dl), magnesium (2.1 mg/dl), parathormone (PTH= 270 pg/L) and performing an electrophoretic protein panel showing the presence of a monoclonal IGg Kappa component without alteration of the albumin/globulin ratio. The subsequent assay of free light chains (FLC) in serum and urine showed their increase without, however, reversal of the formula. Severe mitral insufficiency was confirmed on echocardiographic examination, which also showed moderate tricuspid insufficiency with increased pulmonary artery pressure (PAP) and dilated and not collapsing inferior vena cava. The patient also underwent a coronarographic examination, which was negative.

Due to the finding of renal and cardiac involvement, hyperparathyroidism and increased FLCs, a periumbilical fat biopsy was performed.

Hyperparathyroidism was assessed by ultrasound of the parathyroids, scintigraphy and a Choline PET/CT, which showed no areas of pathological hyper-accumulation of the contrast medium in the parathyroids.

The patient started bisoprolol, furosemide and canrenone therapy for the treatment of heart failure at the maximum tolerated dosage. In view of the increasing levels of calcemia and PTH she started treatment with cinacalcet with normalisation of calcemia and PTH.

The biopsy was positive for Congo red and amyloid typing allowed the diagnosis of AL kappa amyloidosis. A cardiac MRI was therefore performed to assess myocardial involvement, which showed a slight reduction in global systolic function of the left ventricle (50%) due to the presence of multiple shaded areas of "late enhancement" with a confluent appearance affecting all the myocardial walls, a finding compatible with an infiltrative amyloidosis-like picture.

Finally, an osteomidullary biopsy was performed, which showed the presence of a plasma cell clone, allowing the diagnosis of multiple myeloma.

The patient was therefore discharged with the diagnosis of multiple myeloma complicated by primary amyloidosis and hyperparathyroidism.

217. WARM AUTOIMMUNE HEMOLYTIC ANEMIA: A LIFE-THREATENING PRESENTATION WITH MULTIORGAN FAILURE AND DISSEMINATED INTRAVASCULAR COAGULATION

Currà J.[1], Lombardi R.[1], Tiraboschi S.[2], Santomenna F.[1], Smith D.[1], Colavolpe L.[1], Alletto F.[1], Fracanzani A.L.[1]

[1]SC Medicina -Indirizzo Metabolico, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy. Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Milan, Italy ; [2]SC Medicina -Indirizzo Metabolico, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy

A 85-years-old man was admitted to the Emergency Department for an episode of loss of consciousness at home with no witness about the dynamic of the event since he lived alone. In his medical history he had prostate cancer lost to follow-up for at least two years. The patient presented in a comatose state, severely hypotensive (BP 70/40 mmHg) and hypothermic (BT 32.4 °C).Blood gas analysis revealed hyperlactatemia (> 17 mmol/L), while blood tests severe macrocytic anemia (Hb 3 g/dL, MCV 150 fl), erythroblastosis (24.3%), hyperbilirubinemia (total 10.16 mg/dl, indirect 5.6 mg/dl) and markedly high LDH (1251 U/L). Blood tests showed also neutrophilic leukocytosis with slight increase in CRP and procalcitonin (4.27 mg/dl and 1.39 µg/L, respectively) and multiorgan involvement with renal failure (creatinine 1.56 mg/dl, BUN 112 mg/dl), elevated transaminases (AST 448 U/L, ALT 216 U/L), severe hypoglycemia (glucose 18 mg/dl), elevated cardiac troponin (TnT 116 ng/L) and a state of disseminated intravascular coagulation (platelets 77 000/mm3, PT 2.35, aPTT 1.09, D-dimer 60715 µg/L, fibrinogen 139 mg/dl). Autoimmune hemolytic anemia was confirmed by a positive direct Coombs test. Because of the neurological state, a brain CT scan was performed and detected a slender subdural flap at the left hemispherical convexity and at the right front-parietal vertex, with only a slight compressive effect, whereas an EEG ruled out epileptiform anomalies and the toxicology test was negative. The patient was promptly treated with a heating blanket and infusion of hot crystalloids with resolution of hypothermia; euglycemia was restored with infusion of glucose solution 33%; finally steroidal therapy with methylprednisolone (1 mg/kg/die) was started and the patient was transfused with four red cell units. Given the rise in inflammatory markers, in the suspicion of an infection as a possible trigger of hemolytic anemia, broad-spectrum antibiotic therapy with piperacillin/tazobactam intravenously was started and the patient was admitted to our Internal Medicine Unit.

During the hospitalization, antibiotic therapy was continued for ten days with good laboratory response despite no microbiological findings were obtained. In particular, blood and urine culture, HBV, HCV and HIV serology, EBV-DNA, CMV-DNA, Quantiferon-TB resulted all negative.

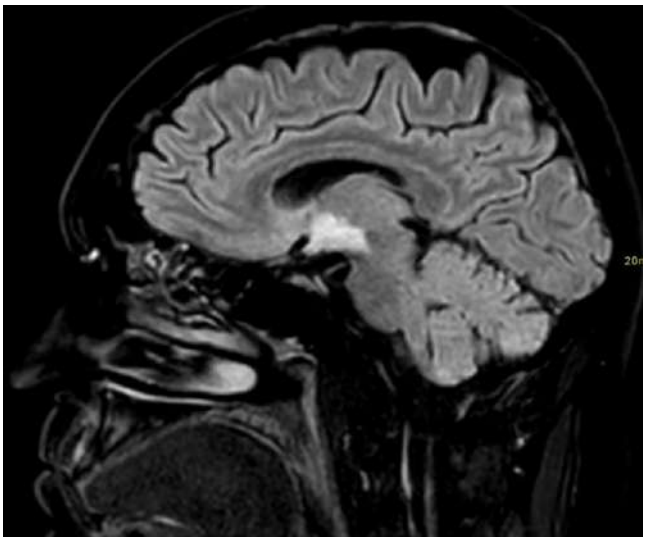
To identify any neoplastic trigger of hemolytic anemia, a total body CT scan with contrast was performed, showing only splenic infarct areas, osteolytic

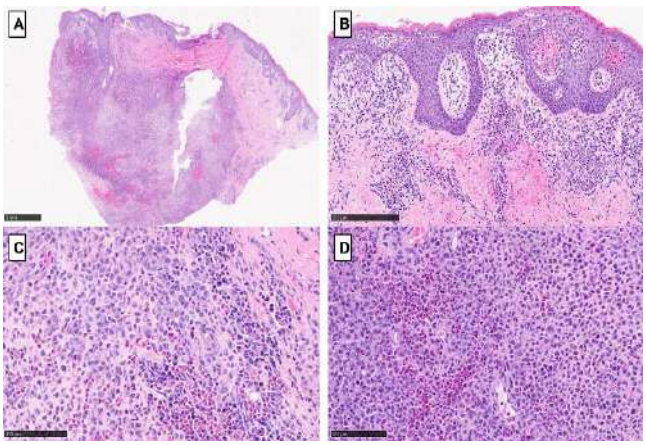
lesions in the pelvis and focal thickening of the bladder wall. However, the radiological picture remained of not univocal interpretation since both cystoscopy and urinary malignant tumoral cells research were negative and the PET-FDG scan was not diriment. Moreover, a bone marrow aspirate and biopsy did not show any alteration.
Further investigations detected pan agglutinant IgG and anti-c antibodies, suggestive for warm autoimmune hemolytic anemia, so, in order to avoid alloimmunization transfusions were administered only for Hb < 6 g/dl. In addition, high dose steroid was continued with only partial response so a cycle of five days of intravenous immunoglobulin (1 g/kg) was administered with improvement of anemia (Hb up to 7.7 g/dL at discharge) and decline in hemolysis markers (LDH 315 U/L, total bilirubin 1.47 mg/dl at discharge). Weekly erythropoietin supplementation was also introduced, as well as vitamin B12 and folate supplementation. As a consequence, multiorgan failure, as well as the disseminated intravascular coagulation and the neurological state, progressively spontaneously resolved. Finally, serial brain CT scans revealed stability of the subdural hematoma.
The patient was discharged after forty days, with stable hemoglobin values and with close hematological follow-up.
Conclusion: We report a case of warm autoimmune hemolytic anemia (AIHA) with an acute onset, probably secondary to an infectious event despite the lack of microbiological findings, characterized by multiorgan failure and disseminated intravascular coagulation, leading to subdural bleeding and a comatose state. Warm autoimmune hemolytic anemia, which is the most common type of autoimmune hemolytic anemia, is caused by IgG antibodies active at normal body temperature, contrary to the cold agglutinin disease, which is a rare disease caused typically by IgM antibodies that react at cold temperature.
Clinical presentation of autoimmune hemolytic anemia is very heterogeneous, ranging from mild to fulminant disease, as in our case, so a prompt diagnosis and rapid start of high dose steroid therapy are needed, as well as support therapy. Moreover, steroid tapering must be as slow as possible since the high risk of recurrence. Finally, approximately 50 to 60% of warm AIHA is associated with underlying conditions, like infections, lymphoproliferative disorders, immunodeficiency and pregnancy, therefore, an accurate investigation of any sustaining cause is crucial.

218. A CASE OF 20 YRS-OLD DIABETES INSIPIDUS: SORRY NO

Angela Borsellino, Angela De Luca, Chiara Valentina Luglio, Anna Belfiore, Agostino Di CIaula, Murri Internal Medicine Group, Piero Portincasa Section of internal medicine, Department of Precision and regenerative Medicine and Ionian Area (DiMePRe-J), University of Bari "Aldo Moro" Medical School, Bari, Italy;

A 55-years-old man was admitted to our Unit due to progressively worsening ideomotor slowdown and confusional episodes in the last year. The patient had a weight gain of 20kg associated with hyperphagia, arterial hypertension and type 2 diabetes mellitus. During the last 20 years, the patient has been suffering from partial central diabetes insipidus treated with Minirin/DDAVP 60mg once a day. At the time of this diagnosis a brain magnetic resonance imaging (MRI) documented the lack of cerebral lesions or areas of altered signal in the brain parenchyma. The patient did not perform further endocrinological follow up. At admission, the patient appeared oriented in time and space, with inconstant ideo-motor slowdown, absence of nystagmus or visual alterations, with adequate respiratory function and no fever. The physical exam revealed a non-secreting right inguinal lesion with regular margins, slightly painful and itchy. The blood chemistry tests showed glycemic decompensation (HbA1c 11.2% 99mmol/mol) and hormonal deficits of the hypothalamic-pituitary axis responsible for a secondary hypothyroidism (TSH 0,26mUI/l v.n.0,30-3,60, FT4 4,11pg/ml n.v. 8.10-17,10, FT3 1.10pg/ml n.v, 2,20-4,20), hypocorticosolism (plasma cortisol 1.6ug/dl n.v. 9-23), secondary hypogonadism (FSH 0.8mUI/ml n.v. 1.3-11.8, LH 0.4 n.v. 2.8-6.8, IGF-1 deficiency <4.55ng/ml n.v. 71-284). Following endocrinological consultation, the patient started therapy with hydrocortisone 20mg/die, levothyroxine 75mcg/die and insulin. An MRI of the brain-pituitary and sella turcica with contrast medium demonstrated an expansive process (11x11x17mm) at the floor of the third ventricle, involving the hypothalamus and imprinting the underlying optic chiasm; a lesion infiltrating posteriorly the mammillary bodies with initial involvement of the midbrain and, finally, an atrophy of the pituitary gland. The first hypothesis was a hypothalamic glioma. However, the neurosurgeon ruled out the possibility of performing a stereotactic biopsy due to the high risk of brain damage. A subsequent cytological examination of the cerebrospinal fluid (CSF) did not reveal neoplastic cells. At lymphocyte typing of the CSF, lymphocytes represented 90% of the leukocyte population (in particular T lymphocytes), as an expression of an ongoing neuroinflammation process. Peripheral lymphocyte typing showed nothing abnormal. Blood tests showed normal LDH, altered beta2-microglobulin (4.7mg/L, n.v. 1.01-2.53). Due to the predominant presence of T lymphocytes in the cerebrospinal fluid, an ultrasonography of the superficial lymph nodes documented highlighting rounded, hypoechoic lymph nodes with irregular margins without flow on color Doppler close to the right inguinal lesion. This finding was confirmed by a Total body CT with contrast medium. Due to the suspect of malignancy, biopsy of the right inguinal lymph nodes and adjacent skin lesion was performed. The histological examination of the lymph node concluded for chronic and non-specific lymphadenopathy, while the examination of the skin sample documented a cutaneous localization of Langherans cell histiocytosis (LCH). LCH is a rare inflammatory myeloid neoplasm characterized by infiltration of CD1a+CD207+histiocyte with immune cells (Fig 2). In adults this disease is poorly documented and the diagnosis is generally delayed(1). Any organ can be involved, individually or in combination, but bone and skin have a higher frequency of involvement. Diabetes Insipidus is the most common disease-related consequence that can predate the diagnosis or develop anytime during the course of the disease. Hypothalamic involvement can lead not only to pituitary dysfunction, but also to neuropsychiatric and behavioral disorders, autonomic and metabolic abnormalities as severe obesity and diabetes mellitus (2). In stable clinical conditions the patient was discharged with indications to hematological and endocrinological follow-up. This case underlines the importance of investigating all possible causes of a pathological manifestation such as diabetes insipidus. In the absence of data that allow to formulate a diagnosis, close monitoring over time remains essential.
References: (1) Masayuki Kobayashi et al. Langerhans cell histiocytosis in adults: Advances in pathophysiology and treatment. Cancer Science 2018 (2)Girschikofsky et al. Management of adult patients with Langerhans cell histiocytosis: recommendations from an expert panel on behalf of Euro-Histio-Net. Orphanet Journal of Rare Diseases 2013



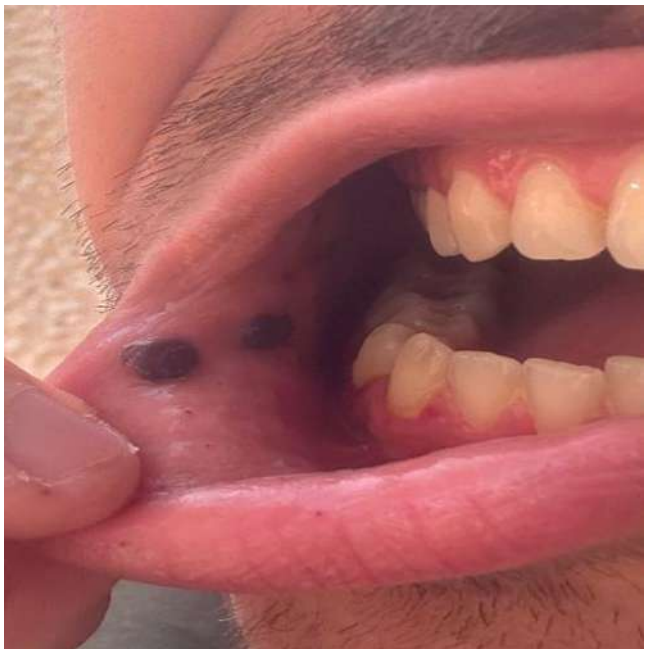


219. ACUTE, SEVERE THROMBOCYTOPENIA. THE IMPORTANCE OF COLLECTING A COMPREHENSIVE PATIENT'S HISTORY

Fattizio L., Musio V., De Luca A., Luglio C.V., Di Ciaula A., Belfiore A., Murri Internal Medicine Group, Portincasa P.
Section of internal medicine, Department of Precision and regenerative Medicine and Ionian Area (DiMePRe-J), University of Bari "Aldo Moro" Medical School, Bari, Italy

A 23 years-old man was admitted to the Emergency Room with sudden gums bleeding while brushing teeth, hemorrhagic blisters of the oral mucosa (Fig.1) and peri-malleolar purpura since the day before. Medical history included ocular hypertension since two years, frequent colds in childhood and recurrent warts on hands. The patient denied allergies, drug and alcohol use and sexual promiscuity, but reported smoking 20 cigarettes a day. He had vaccines for exanthematous diseases and Covid19, which he had contracted the year before. He also denied family history of cancer and hereditary diseases. Blood tests performed at age 7 showed slightly reduced IgG and IgA values and IgM values at lower limits of normal. However, he had never presented hemorrhagic events or major infectious diseases. The only medication taken was a citicoline supplement to treat ocular hypertension. At admission (emergency room), blood tests showed severe thrombocytopenia (1000/μL). Other findings were unremarkable. The patient underwent a platelets transfusion and he was transferred to the Internal Medicine Unit. The patient showed no further signs of bleeding, and vitals indices were stable. The abdominal ultrasound showed a mild splenomegaly (longitudinal diameter 13 cm). A complete panel of blood tests was sent to investigate major causes of thrombocytopenia, including lymphocyte typing, peripheral blood smear, autoimmunity panel, Lupus Anticoagulant study and antiphospholipid antibody search, vitamin B12, folate, LDH and B2-microglobulin assay, iron balance and coagulation indices. At admission, the main hypothesis was a post-viral autoimmune thrombocytopenia. The immunological status and serology for CMV, EBV, HSV1/2, HCV and HIV were assessed. While awaiting outcomes, in agreement with the hematologist, methylprednisolone therapy was started (1 mg/kg/day i.v.) (1). The ophthalmologist ruled out contraindications due to ocular hypertension. Results revealed no alterations, except the presence of hypogammaglobulinemia. In consideration of the medical history and previous blood tests, we assayed immunoglobulin and IgG subpopulation values, which were reduced: IgG:3.0 g/L (n.v. 7.0-16.0 g/L); IgA:0.42 g/L(n.v. 0.68-3.79 g/L); IgM:0.28 g/L(n.v. 0.40-2.30 g/L); IgG1: 2.3 g/L(n. v. 4.05-10.11 g/L); IgG2: 0.5 g/L(n.v. 1.69-7.86 g/L); IgG3: 0.3 g/L(n.v. 0.11-0.85 g/L); IgG4: 0.009 g/L(n.v. 0.03-2.01 g/L). These findings reinforced the suspect of an immunological disease and, in particular, of an immunodeficiency syndrome. Since a poor immune response to vaccines is frequent in individuals with immunodeficiency (2), we evaluated a complete serology for the viruses for which the patient had received the vaccine according to his vaccine report: varicella zoster virus (VZV), parvovirus B19, measles, mumps, hepatitis B, diphtheria, tetanus and Covid19. Results showed poor or partial coverage for Hepatitis B (anti-HBs: 1,1 mUI/ml–n.v. in vaccinated subjects: >10 mUI/ml), tetanus (0,044 UI/ml–n.v. >1.1 UI/ml), diphtheria (0,145 UI/ml–n.v. >1 UI/ml), VZV (IgG: 75,3 mUI/ml–n.v. >165 mUI/ml) and mumps (IgG: <5,00 AU/ml–n.v. > 11,0 AU/ml). Comparing these results with the patient's vaccine record, the poor response to the Hepatitis B and tetanus vaccines may be related to the vaccine booster dose that the patient reported not having performed. In contrast, the poor response to mumps and varicella vaccines further strengthened the suspect of immune-deficiency syndrome as a trigger for severe thrombocytopenia (3). In response to steroid therapy, platelets levels gradually reached a normal value (220000/μL) and the lesions of the oral mucosa disappeared. The patient was discharged from the ward in stable clinical condition, with the indication to continue oral steroid therapy with scaled-up dosing, and to continue immunological and hematological follow-up. This case highlights the importance of collecting an accurate and comprehensive patient history to identify factors that are relevant to the diagnosis, avoiding inappropriate examinations, procedures and prolonged hospital stays.

References: (1) Neunert C, et al, Blood. 2011 Apr 21;117(16):4190-207; (2) Bonilla FA. Immunol Allergy Clin North Am. 2020 Aug;40(3):421-435; (3) Mohtashami M et al, Int Rev Immunol. 2022;41(2):135-159.



220. REAL-WORLD EXPERIENCE IN THE USE OF LUSPATERCEPT IN TRANSFUSION-DEPENDENT B-THALASSEMIA: A SINGLE CENTER EXPERIENCE

Panzieri D.L.[1], Ausenda G.[2], Elli S.[1], Leoni S.[1], Ferraresi M.[1], Scaramellini N.[1], Cassinerio E.[3], Hu C.[3], Motta I.[4], A.L.[5]
[1]Università degli Studi di Milano; SC Medicina ad Indirizzo Metabolico, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy; [2]Università degli Studi di Milano; [3]SS Centro Emoglobinopatie, disturbi ereditari del metaobolismo e del sistema immmunitario. SC Medicina ad Indirizzo Metabolico; Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy; [4]Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di MIlano, Milan, Italy; SS Centro Emoglobinopatie, disturbi ereditari del metaobolismo e del sistema immmunitario. SC Medicina ad Indirizzo Metabolico; Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy; [5]Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di MIlano, Milan, Italy; SC Medicina ad Indirizzo Metabolico, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy

Introduction: Luspatercept is the first erythropoiesis-stimulating agent (ESA) recently approved by FDA, EMA and AIFA for the treatment of anemia in transfusion-dependent beta-thalassemia and in myelodysplastic syndromes associated with ring sideroblasts. Luspatercept acts as an activin receptor type IIB fusion protein ligand trap that targets the altered transforming growth factor beta (TGF-β) pathway, thus ameliorating the ineffective erythropoiesis; however, its precise mechanism of action has not been fully elucidated.
The phase 3 BELIEVE trial showed that the proportion of patients with transfusion-dependent thalassemia (TDT) who reached the primary endpoint (a reduction of the transfusional burden by at least 33% between week 13 and 24) was higher in the group treated with luspatercept compared to placebo (21.4% vs. 4.5%). Moreover, 70% of patients treated with luspatercept had at least 33% reduction in the transfusion burden in any 12-week treatment interval.
In Italy, after the availability of the drug in the early access program, luspatercept has been commercialized for β-thalassemia since December 2021.
More than 200 adult patients affected by TDT are regularly followed at our center. The aim of this study is to evaluate the safety and efficacy of luspatercept in the real life in patients with TDT regularly followed at our center.
Materials and methods: We calculated the efficacy of luspatercept therapy evaluating the number of units of blood transfused per week (unit/week) in every 12-week interval (0-12; 13-24; 25-36; 37-48) and confronting it with the number of unit/week in the 24 weeks before beginning luspatercept. Efficay was evaluated in the 23 patients who completed at least 12 weeks of treatment. We evaluated additional parameters such as pre-transfusional hemoglobin

and transfusional interval as other clinical markers of response.
To date, 35 patients have received at least one dose of luspatercept out of the clinical trials, and currently, 27 are still receiving the drug. The median age of this population is 44 (range 20 – 64), 17 are males and 18 are females. Nine out of 25 (36%) patients are splenectomized.
Results: Eight out of 35 patients interrupted the treatment. The reasons for stopping luspatercept were inefficacy (n=3; 13%), a severe adverse event (n=1; 4%), AEs (n=3; 13%), and loss of response/logistic problems (n=1; 4%). One patient developed an episode of gout which did not lead to drug discontinuation; another patient developed hypertension and is now being treated with antihypertensive therapy.
The genotype is known in 18 patients: 6 are β0/β0, 3 are β0/severe β+, 5 are β0/β+, 2 are severe-β+/severe-β+, 1 is β0/HbE and 1 is β0/triplication of α-gene, while the remaining are ongoing.
The median duration of treatment is 24 weeks (range min-max 4.4 – 120).
The mean number of units of blood transfused during the 24 weeks before luspatercept treatment was 18.1 ± 3.9, with a pre-transfusional mean hemoglobin of 9.1 ± 0.5 g/dL. The mean transfusional interval before luspatercept was 21 ± 4.4 days. The median ferritin value at baseline was 793 mcg/L (range 139-10112).
Overall, a response has been registered in 10/23 (43%) patients in any 12-week interval. The median transfusional interval in any 12 week-interval was 21 days (range 8 – 138), and the pre-transfusional mean hemoglobin was 9.05 ± 0.55 g/dL. Four patients reached a reduction ≥ 50%; among them, two became transfusion independent, but one of them interrupted the treatment for subjective intolerance. The other one is currently on treatment and, to date, is still transfusion independent (138 days without transfusions when this abstract was written).
To date, only 11 patients out of 23 reached at least 24 weeks of treatment. In the 13 – 24 week-interval, the response was reached by three patients (27%). In this span, the transfusional interval was 22.2 ± 8.6 days, and the pre-transfusional mean hemoglobin was 9.06 ± 0.58 g/dL.
Discussion: Our data confirmed the safety profile of luspatercept. In terms of efficacy, data from the real life, although limited, are consistent with those from the phase 3 clinical trial that led to the approval of the drug. In our experience, the administration of the drug was generally well tolerated, even if some AEs, comprehending 1 SAE, were recorded.
One of the factors limiting the analysis is the duration of treatment that is related to the recent approval of the drug. According to the long-term follow-up extension study, the number of responders increases over time, thus it is likely that also in the real life we will observe an increasing number of responders extending the period of treatment. Further studies to identify predictive factors for the response to luspatercept are needed, to tailor the treatment on patients' characteristics and to optimize the resources.

221. MULTI-REFRACTORY AUTOIMMUNE HEMOLYTIC ANEMIA, WHAT'S GONE WRONG? A CASE REPORT

Scarsi C., Gilardi N., Cigolini B., Thneibat A., Benedetto C., Pulcini E., Golgo S., Bellodi A., Ballestrero A.
Dipartimento di Medicina Interna Università degli Studi di Genova

Introduction: Autoimmune hemolytic anemia (AIHA) is a rare, acquired disease in which red blood cells destruction is mainly caused by autoantibodies against RBCs membrane antigens with other immunologic effectors (complement, B and T lymphocytes, macrophages) possibly taking part in the process. AIHA can be primary or secondary to lymphoproliferative diseases, solid malignancies, infections, autoimmune diseases and drugs. Direct antiglobulin test (DAT) or Coombs test is the mainstay of the diagnosis, allowing to distinguish different subtypes of AIHA, according to the autoantibody subtype and its thermal characteristic. Warm AIHA (wAIHA) is the most frequent form and usually manifests with extravascular hemolysis, positive DAT with IgG and sometimes IgG plus C, where autoantibodies bind RBCs at around 37°C. Cold agglutinin disease (CAD) is the second more frequent form, often due to IgM acting at around 4°C and activating complement, thus presenting with DAT positivity with C and high serum cold agglutinin titer. Mixed AIHA is an intermediate form where warm IgG and cold IgM are both present; lastly, PNH is a rare AIHA caused by Donath-Landsteiner antibody, a biphasic autoantibody that reacts at low temperature (4°C) and cause hemolysis at 37°C. High doses steroids represent the first-line therapy for wAIHA, but have little effect in CAD, where Rituximab alone or associated to Bendamustine can be the first choice. In case of wAIHA relapse splenectomy may be considered as 2nd line treatment in patients aging <65 years-old, with Rituximab suitable in case of ineligibility for surgery. Conventional immunosuppressive agents (Cyclophosphamide, Azathioprine, Cyclosporine) are now considered 3rd line treatments as steroid-sparing therapies. It's important to note that in front of relapse a new diagnostic work up for secondary forms of AIHA has to be done to rule out underlying diseases treatable with specific therapy. Multi-refractory AIHAs are eventually to be evaluated for enrollment in clinical trials. New therapeutic options targeting immunological effectors (B cells, complement, tyrosine kinases) are under development thanks to increasing knowledge about AIHA immunopathogenesis.
Presentation of case: We report a case of a 76-years-old Caucasian woman with known history of AIHA since 2019 and highly pre-treated, who was admitted to our department in January 2023 for hemolytic crisis. The patient was initially diagnosed with wAIHA in 2019 and treated with high doses of corticosteroids with good clinical response, but shortly after relapsed during steroidal tapering, thus making it necessary to combine a first course of cyclophosphamide. Bone marrow biopsy was carried out to rule out lymphoproliferative disease responsible for disease relapse, which was negative. Rituximab was then administered at the second disease recurrence, but with transient effect. At hospital admission the patient was markedly asthenic and had respiratory distress. Blood tests showed severe macrocytic anemia (hemoglobin (Hb) 5.6 g/dl, mean corpuscular volume 124 fL, reticulocytes 17%, haptoglobin <0.1 g/dl, lactate dehydrogenase 780 U/L, total bilirubin concentration 2.4 mg/dl, of which almost all was indirect) and positive DAT with IgG plus C and serum cold agglutinins, suggestive of mixed AIHA. The patient consistently refused blood transfusion for religious reasons. Methylprednisolone was first administered at immunosuppressive doses (1-1.5 mg/kg/die) with poor response, thus a new diagnostic workup was performed to reassess secondary causes of AIHA. A CT-scan was carried out, proving negative for neoplasms, but showing bilateral pulmonary embolism and splenomegaly; bone marrow biopsy was also repeated to exclude pathological infiltrates, which demonstrated regenerative hyperplasia of RBC, proving again negative for malignancies (fig. 1). Only minimal dysmyelopoietic features were reported. A second line therapy with Rituximab 375mg/mq/wk for 4 weeks combined with erythropoietin 40000 iu/wk was started since patient had reticulocytopenia. After the second Rituximab administration Hb levels showed an increasing trend until reaching 9 g/dl, alongside with symptom disappearance, thus allowing starting slow steroid tapering. Parenteral anticoagulation was eventually started for pulmonary embolism treatment. After fourth Rituximab administration, complete clinical and laboratory response was obtained with Hb value of 12g/dl and no signs of hemolysis. Steroid treatment was discontinued one month ago and a close monitoring is still ongoing.
Conclusions: AIHA remains a hard diagnostic challenge for the variety of underlying causes which must be re-evaluated with diagnostic workup when relapse occurs and disease becomes refractory to treatments. Current treatments are based on weak evidence and optimal therapy does not yet exist; however, increasing knowledge of immunopathological mechanisms involved in AIHA is leading to immune-target approaches, although further research and stronger evidence are needed for improvement of treatment wAIHA and CAD.

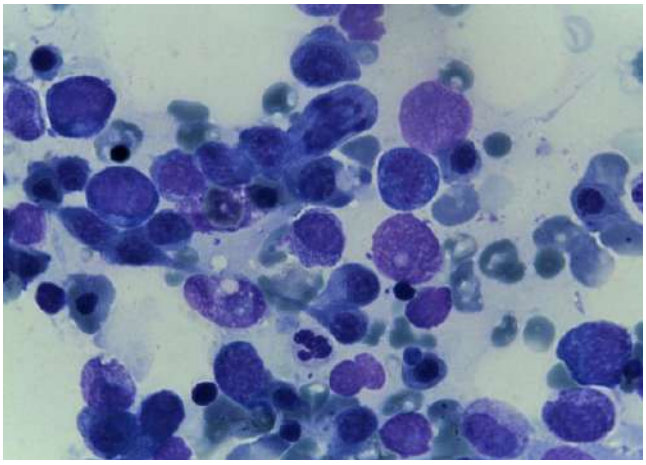


Fig. 1. Bone marrow smear: hypercellular erythroid line with different maturation stages.

222. BONE MARROW FAILURE: UNCOVERING GENETIC DRIVERS IN INBORN ERRORS OF IMMUNITY FOR PRECISION MEDICINE AND THERAPEUTIC TARGETING

Desantis V.[1], Marasco C.[2], Pappagallo F.[2], Mascolo A.[2], Marzollo A.[3], Andriano A.[2], Albanese F.[2], Ingravallo G.[4], Tabares P.[5], Montagnani M.[1], Ria R.[2], Dammacco F.[2], Vacca A.[2], Solimando Antonio G.[2]
[1]Section of Pharmacology, Department of Precision and Regenerative Medicine and Ionian Area (DiMePReJ), University of Bari "Aldo Moro" Medical School, Bari, Italy; [2]Unit of Internal Medicine "Guido Baccelli", Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe J), University of Bari "Aldo Moro" Medical School, Bari, Italy; [3]Pediatric Hematology, Oncology and Stem Cell Transplant Division, Padua University Hospital, Padua, Italy; Fondazione Citta' della Speranza, Istituto di Ricerca Pediatrica, Padua, Italy; [4]Section of Pathology, Department of Precision and Regenerative Medicine and Ionian Area (DiMePReJ), University of Bari "Aldo Moro" Medical School, Bari, Italy; [5]Department of Medicine II, University Hospital of Würzburg, Würzburg, Germany

Aplastic anemia is characterized by suppressed bone marrow function, leading to a reduction or absence of all blood cell types. It can be caused by various factors such as toxins, radiation, infections, autoimmune disorders, and genetic factors like inborn errors of immunity.
Our study was inspired by a case of a 32-year-old female patient with severe aplastic anemia who had a rare heterozygous variant of the STAT1 gene (p.Cys174Arg). STAT1 is involved in regulating the immune response. The patient presented with symptoms of anemia, along with severe oral ulcers, type 1 diabetes, and pancytopenia. Bone marrow biopsy confirmed the diagnosis of severe aplastic anemia. To investigate the association between STAT1 dysregulation and idiopathic aplastic anemia, we examined six patients with the condition. We found enhanced phospho-STAT1 levels in bone marrow immunostaining, indicating dysregulated STAT1 signaling in these patients. Further examination revealed enhanced JAK-STAT pathway signaling in pure red cell aplasia and aplastic anemia cases. Genetic variants and mutations in CD8+ T cells were associated with increased JAK-STAT pathway signaling, potentially contributing to the pathogenesis of these conditions. In addition to the STAT1 variant, we identified two other underlying genetic events in three patients with bone marrow failure.
One patient had a TNFRSF13B (TACI) gene variant involved in B-cell development and function.
The other two patients had mosaicism of trisomy 8, a chromosomal abnormality associated with bone marrow failure and other blood disorders.
Our experiments confirmed increased STAT1 phosphorylation in CD8+ T cells from aplastic anemia patients compared to healthy controls. Treatment with the JAK inhibitor ruxolitinib reduced STAT1 phosphorylation and downregulated the expression of cytotoxicity-related genes in CD8+ T cells from aplastic anemia patients. These findings suggest the potential of targeting the JAK-STAT pathway as a therapeutic approach for aplastic anemia and related disorders characterized by dysregulated STAT1 signaling, as well as those with TNFRSF13B (TACI) variants or mosaicism of trisomy 8. A comprehensive in vitro experimental validation confirmed increased STAT1 phosphorylation in CD8+ T cells from aplastic anemia patients compared to healthy controls. Treatment with the JAK inhibitor ruxolitinib reduced STAT1 phosphorylation and downregulated cytotoxicity-related gene expression in CD8+ T cells from aplastic anemia patients, supporting the potential of targeting the JAK-STAT pathway as a therapeutic approach for aplastic anemia and related disorders. Additionally, we conducted in vitro experiments to investigate the impact of TNFRSF13B (TACI) variant and mosaicism of trisomy 8.
In the case of the patient with the TNFRSF13B (TACI) variant, we observed abnormal B-cell development and function in vitro, consistent with the known role of this gene. The dysfunction of TNFRSF13B (TACI) has been implicated in various primary immunodeficiency disorders, further highlighting its significance in the context of aplastic anemia.
Regarding the patients with mosaicism of trisomy 8, our in vitro experiments revealed specific abnormalities in hematopoietic cell lines derived from these individuals. These findings suggest a potential link between mosaicism of trisomy 8 and bone marrow failure, providing further insights into the pathogenesis of aplastic anemia and related disorders. Our study highlights the importance of inborn errors of immunity in understanding the shared pathobiology of common pathological conditions. Genetic testing can identify specific mutations responsible for a patient's condition, enabling targeted treatments and better outcomes. Additionally, genetic testing can help identify individuals at risk of developing aplastic anemia, allowing for early intervention and potentially preventing disease progression.
The study's findings emphasize the potential of precision medicine in treating aplastic anemia. Identifying underlying driver genetic events, including the STAT1 variant, TNFRSF13B (TACI) variant, and mosaicism of trisomy 8, is a crucial step toward developing more effective diagnostic and treatment strategies for these complex conditions. The use of genetic testing in diagnosing and treating aplastic anemia holds promise. By identifying specific genetic mutations or abnormalities responsible for a patient's condition, targeted treatments can be developed to improve outcomes. Further, statistically powered prospective studies are needed to determine the exact role and therapeutic window for JAK/STAT targeting in aplastic anemia, especially in patients with underlying driver genetic events. Our study advances our understanding of factors contributing to bone marrow failure. Identifying underlying driver genetic events, including the STAT1 variant, TNFRSF13B (TACI) variant, and mosaicism of trisomy 8, highlights the potential of precision medicine in diagnosing and treating these complex conditions. We deepen our understanding of inborn errors of immunity pathobiology, sketching therapeutic targets, including genetic drivers of bone marrow failure.

223. HYPERHEMOLYTIC CRISIS IN SICKLE CELL DISEASE MANAGED WITH C5 INHIBITOR: A CASE REPORT

Monegatti S.[1], Menotti S.[1], Villaboni S.[1], Merlo M.[1], Vitale S.[1], Ceolan J.[1], Mazzi F.[1], Cantini M.[2], De Franceschi L.[1]
[1]Medicina Generale B, Dipartimento di Medicina, Azienda Ospedaliera Universitaria Integrata di Verona ; [2]Medicina Trasfusionale, Azienda Ospedaliera Universitaria Integrata di Verona

Sickle cell disease (SCD) is a worldwide distributed hereditary red blood cell (RBC) disorder due to a single nucleotide substitution in HBB, resulting in the sickle Hb (HbS). SCD is characterized by chronic hemolytic anemia, intermittent acute pain crises and progressive organ dysfunction as a result of recurrent vaso-occlusion events. RBC transfusion approach is still a life-saving therapeutic option for patients with SCD. Chronic inflammation and the exposition to transfused RBCs might favor the develop of antibodies against transfused red blood cells (RBCs). This might end in acute hyperhemolytic events such as the delayed hemolytic transfusion reaction (DHTR). The high rate of RBCs alloimmunization in SCD patients is due to the higher prevalence of polymorphic blood group antigens in donors (primarily European descent) than in patients of African descent and to the inflammatory plasmatic environment of SCD. Hyperhemolytic crisis (HS) represents a serious and potentially life-threatening emerging complication in SCD patients. HS refers to the sudden exacerbation of hemolysis with worsening anemia and a fall in absolute reticulocyte count after RBCs transfusion, suggesting destruction of both transfused RBCs and the patient's own RBCs. In this way it differs from the conventional DHTR. Several mechanisms have been addressed to explain HS, particularly: the interaction between sickle erythrocytes and P-selectin, which is responsible for the triggering of the hemolytic process through complement activation, amplified by free heme; the destruction of sickle RBCs and sickle reticulocytes by activated macrophages, through contact lysis and erythrophagocytosis; the bystander hemolysis phenomenon which represents a form of immune hemolysis of RBCs in the absence of RBCs alloantibodies, or when RBCs are negative for the antigen against which the relevant alloantibody is directed, suggesting the presence of other antibodies reacting with transfused foreign antigens (e.g., HLA and plasma proteins) which may lead to complement activation. The treatment of DHTR and HS is challenging. Transfusions should be avoided unless absolutely required; symptomatic patients can be treated with intravenous immunoglobulins; high doses of steroids must be avoided in order not to precipitate a sickle crisis. Since free heme and Hb can precipitate vascular damage, plasma exchange may result in an effective tool, possibly protecting the patient from hemoglobinuric and complement mediated acute kidney injury. If the patient has severity criteria additional treatment with eculizumab (monoclonal antibody against C5) as a rescue therapy has proven effective, considering the enhanced activation of complement alternative pathway in this condition. Here we report the case of a 47 year-old woman with SCD (HbS and β+ thalassemia), who presented with back pain (NRS 7/10), prostration and jaundice associated with severe normochromic normocytic anemia (Hb 5,7 g/dL) and increase of the hemolysis markers (indirect bilirubin 1,42 mg/dL, pLD 466 U/L). Considering the presence of anti-C and anti-e antibodies and a history of DHTR, she received C-e-Kell-matched RBC units and before blood transfusion she underwent plasmapheresis with S/D plasma with the aim of reducing the amount of alloantibodies. After the transfusion she also started a 5-day course of intravenous immunoglobulin therapy (IVIg) to reduce the risk of DHTR. Despite the adopted precautions 5 days

after the blood transfusion the patient's clinical conditions rapidly worsened with the emergence of fever, abdominal pain, muscle and joint pain and haemoglobinuria. The hemoglobin levels dropped from 8,9 g/dL (the day after blood transfusion) to 5,8 g/dL with the concomitant raising of pLD (466 - 1437 U/L) and the drop of HbA levels (identified by HPLC) and C3 serum levels (0,65 g/L). Considering this clinical presentation highly suggestive for HS she underwent plasma exchange and started a low-dose steroid therapy (0,5 mg/kg/die). Since the clinical conditions didn't improve, we decided to give eculizumab, as salvage therapy, in 2 fixed doses of 900 mg one week apart. Meanwhile in view of a severe splenomegaly (20 cm) and hypersplenism favored by HS, the patient was referred for splenectomy, performed without complications. During and after the surgery she was transfused with 4 RBC units without complications, either acute or delayed. With the adopted therapy we obtained a clear reduction of hemolysis indexes and a constant rise of Hb levels between 8 and 9 g/dL. The patient was dismissed from the hospital after 28 days in good clinical conditions, without the need for further blood transfusions. **Conclusions**: Only few cases of eculizumab use are reported in literature for the treatment of DHTR or HS in SCD patients. In this case the use of this agent as second line therapy resulted safe and allowed a prompt control of hemolysis avoiding further organ damage and preventing irreversible MOF. Eculizumab demonstrated a beneficial effect on hemolysis and vasculopathy and should probably be taken into consideration for the treatment of HS as soon as hyperhemolysis appears.

224. DISCORDANT DIAGNOSIS OF PULMONARY LYMPHOMATOID GRANULOMATOSIS AND EBV-NEGATIVE DIFFUSE LARGE B-CELL LYMPHOMA IN THE SAME PATIENT, A CASE REPORT

Bellino C.[1], Di Terlizzi G. [2], Marinosci A.[2], Scotti R.[2], Di Lucca G.[2], Ramirez G.A.[3], Damanti S.[4], Tresoldi M.[2]
[1]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy, Università Vita-Salute San Raffaele; [2]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy; [3]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy,Università Vita-Salute San Raffaele, Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS Ospedale San Raffaele, Milan, Italy, ; [4]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy Università Vita-Salute San Raffaele Unit of Medical Specialties and Healthcare Continuity IRCCS Ospedale San Raffaele, Milan, Italy

Background: Lymphomatoid granulomatosis (LYG) is a rare EBV-associated B-cell lymphoproliferative disorder. It especially affects men between the fourth and sixth decade of life. The most likely etiological hypothesis is the association with defective or abnormal immune response to EBV, as supported by the occurrence in individuals who present immune dysfunction even in the absence of primary immunodeficiency. Pathological findings are atypical B cells expressing EBV-encoded RNA (EBER), angiocentric T cells, and coagulative necrosis. Classification relies on the number and density of atypical EBV+ B cells and angioinvasive reactive T cells, which translates in various degrees of cell necrosis. Diffuse large B-cell lymphoma (DLBCL) is the most frequent type of non-Hodgkin's lymphoma, which is more common in old age and may arise de novo or as a progression of other more indolent lymphoproliferative diseases. In the following, we describe the atypical case of a patient with a diagnosis of both lymphomatoid granulomatosis and EBV-negative diffuse large B-cell lymphoma.
Case Description and Discussion: A 70-year-old patient was admitted to the General Medicine High Intensity Care Unit of San Raffaele Hospital in February 2022 for suspected invasive pulmonary aspergillosis. Her past clinical history was significant for marrow hypoplasia with neutropenia since 2009. Furthermore, in November 2021 she had sought clinical attention for dyspnoea and 10kg weight loss. A chest-abdomen CT scan had shown focal ground-glass opacities and areas of parenchymal thickening, some excavated, confluent at the level of the middle lobe, lingula and lower lobes, predominantly in the left lung. She had been diagnosed with pulmonary aspergillosis and started on voriconazole based on positive D-Galactomannan in blood. On admission, she underwent a repeat chest CT scan, which showed an extensive area of parenchymal thickening in the right upper lobe. The patient also had bronchoscopy twice, with evidence of a friable vegetation in the bronchus serving the right upper lobe and lavage fluid culture growth of Actinomyces graevenitzi and Candida krusei. Despite prompt antimicrobial treatment, patient conditions did not improve. Consistently, a new CT scan showed extension of the right upper pulmonary lobe thickening along with appearance of pleural effusion. Therefore, a CT-guided biopsy was made of the lung lesion, which showed grade 2 LYG (WHO). Treatment start was delayed due to paucisymptomatic but long-lasting SARS-CoV-2 infection. Patient clinical status further deteriorated. An additional CT scan showed multiple new lesions in the abdomen and peritoneum and a solid nodule in the subcutaneous tissue of the right buttock. The latter was removed with a diagnosis of EBV-negative diffuse large B cell lymphoma (DLBCL)(WHO). LYG is a rare lymphoproliferative disease most frequently located in the lung, as in the case of our patient. Generally it presents as multifocal nodular masses in the middle and lower lobes, sometimes as single nodules with frequent cavitation and central necrosis. Other sites of extranodal invovement are skin, central nervous system, liver and kidneys. Lymph node and bone marrow involvement is very rare. In grade 2 lesions, EBER expression in 5-20 cells per high-power field and focal or absent areas of coagulative necrosis are described. Classification of the disease into low (grade 1-2) or high (grade 3) histological grade is essential to define prognosis and guide therapy: although there are no established treatment guidelines, low-grade LYG generally requires immunomodulatory therapies such as interferon-gamma, while high-grade LYG is treated with chemo-immunotherapy. Though progression of LYG to aggressive EBV+ DLBCL is not a rare occurrence, coexistence of LYG with EBV-negative DLBCL is unusual. A reliable explanation of our case is that LYG skin lesions are less often positive for EBER than the lung (23%), leading to discordant EBV positivity between lung and subcutaneous sites. The patient was eventually started on R-miniCHOP chemoimmunotherapy regimen, with rapid response and clinical improvement.
Conclusions: LYG should always been taken into account in the differential diagnosis of sparse lung infiltrates without clear infectious etiology and response to antimicrobial therapy. Even if the clinical course is variable, LYG has usually an aggressive behavior with rapid widespread extranodal dissemination. Transformation to DLBCL may occur and skin/subcutaneous sites of disease may not share EBV-positivity with their lung counterpart.

225. A MULTICENTRE RETROSPECTIVE STUDY ON THE DIAGNOSIS, CLINICAL MANAGEMENT AND OUTCOME OF ACQUIRED VON WILLEBRAND SYNDROME

Ferretti A.[1], Lipari A.[2], Giovansanti F.[3], Baldacci E.[4], Chistolini A.[3], Mormile R.[4], Di Gennaro L.[1], Lancellotti S.[1], Sacco M.[2], Tardugno M.[2], Santoro C.[5], De Candia E.[6]
[1]F. Policlinico Gemelli - IRCCS, Roma; [2]F. Policlinico Gemelli - IRCCS, Università Cattolica del Sacro Cuore; [3]Ematologia, Dipartimento di Medicina Traslazionale e di Precisione, Sapienza Università di Roma; [4]Ematologia, Azienda Ospedaliero Universitaria Policlinico Umberto I, Roma; [5]Ematologia, Azienda Ospedaliero Universitaria Policlinico Umberto I, Roma; [1]These two authors equally contributed to the study; [6]F. Policlinico Gemelli - IRCCS, Università Cattolica del Sacro Cuore; [1]These two authors equally contributed to the study

Background and Aims: Acquired von Willebrand syndrome (AWVS) is a rare acquired coagulopathy, often associated to an underlying disorder (lymphoproliferative, cardiovascular, myeloproliferative, neoplastic and autoimmune disorders). The diagnosis is difficult and relies on a negative familiar and personal clinical bleeding history and a late onset in life of bleeding symptoms, associated with a laboratory pattern for Von Willebrand Disease (VWD). Aims of this study are: 1) to highlight clinical and laboratory features of this under-recognized disease and 2) to describe the experience on diagnosis and management of AVWS patients (pts) in 2 Italian centers.
Methods: Between 2004-2022 we have diagnosed and managed 20 pts [9F, 11M; median age at diagnosis 62.45 years (42.9-85.9)] affected by AVWS. The diagnosis was made based on clinical and laboratory features suggestive of AVWS (Fig.1). The increased ratio of propeptide/Ag levels was a laboratory hallmark for AVWD.
Results: Reasons for diagnosis were: recent onset of bleeding symptoms in 11 pts, mostly epistaxis (26.67%) and gum bleeding (20%), increased aPTT in 9. The median follow-up is 6.4 years (0.7-18.1). Nineteen/20 cases showed a concomitant disorder: 1 gastric B cell MALT lymphoma, 1 indolent B cell lymphoma, 13 MGUS (3 pts with concomitant or solid neoplasm history), 2 Waldenstrom Disease (WD), 1 case of Polyglandular Autoimmune Syndrome (APS-1), 1 case of prostate cancer. In 1 case AVWS was idiopathic. No cases of valvular cardiac disorders or thyroid diseases were found in our patients. The management of the underlying disorders related to AVWS is described in Table 2. Strategies to manage AVWS in pts with concomitant MGUS were: immunosuppressive therapy with prednisone (PDN) + cyclophosphamide (CTX) followed by intra venous immunoglobulins (IvIg) in 1 patient, without

response to either therapies; periodic infusion of IvIg in 3 other cases with a transient complete remission (CR) with regard to VWD plasma levels. Two patients have been treated for 2-3 years with IvIg every 6-8 weeks because of chronic anemia and recurrent gastrointestinal (GI) bleedings requiring hospitalizations, invasive procedures and blood transfusions. Periodic IvIg infusions in both patients gave good control of GI bleeding and anemia with dramatic reduction of hospitalizations and blood transfusions; no specific treatment in the other 3 MGUS cases. The idiopathic AVWS patient was treated with PDN with a CR on VWD laboratory parameters; after 3 months the patient relapsed and was treated with CTX and PDN, obtaining a second CR. Fifteen patients (75%) had bleeding recurrences during follow-up, mostly gum bleedings (36%) and haematomas (17.3%). Four patients, due to persistent and severe GI bleedings, were treated with 50 mg/die thalidomide, with a good response in 3/4 patients. Desmopressin, tranexamic acid, VWF/FVIII concentrate were used as prophylaxis or treatment of bleedings in all pts, with variable responses on clinical symptoms.

Conclusions: AVWS is a rare syndrome, underdiagnosed and unrecognized in many cases. AVWS must be suspected whenever bleeding symptoms occur later in life in a patient with no previous bleeding history and must be confirmed by typical laboratory pattern of VWD. In most cases increased pp/VWF Ag ratio and a type II VWD pattern is typically found. It is mandatory to search for concomitant diseases, especially hematologic malignant and autoimmune diseases.

Figure 1. Laboratory characteristics of the patients

	Median	Mean	Range	Normal Values
VWF:Ag	13%	19.78%	1.6-67%	BGO: 41-101%//non 0: 50-130%
VWF:RCo	13%	14.62%	3.5-33%	BGO: 41-97%//non 0: 52-124%
RCo/Ag	0.75	1.067	0.331-6.25	>0.7
FVIII:C	19.20%	23.64%	2.08-61.9%	58-130%
RIPA	1.4 mg/dl	1.55 mg/dl	0.84-3.49 mg/dl	0.7-1.2 mg/dl
VWF:pp	83%	97.45%	42.84-154.32%	70-140%
pp/Ag (PP measures with ELISA immunoassay)	6.62	11.28	2.39-51.87	<3
aPTT	1.45	1.46	1-1.87	0.82-1.16
VWF:RCo inhibitor (mixing studies)	Negative in 11 investigated patients			

Lymphoproliferative disorders related AVWS pts		
Type of disorder	**Treatment**	**Response**
Gastric B cell MALT lymphoma	Rituximab	Complete remission of lymphoma and AVWS
Waldenstrom Disease 1st pt	R-CVP Ibrutinib	After 3rd line, progression of lymphoproliferative disease and persistent AVWS
Waldenstrom Disease 2nd pt	Rituximab After two years for disease progression: Rituximab+ Bendamustine	Partial response Persistent AVWS and partial response of lymphoma
Indolent B cell lymphoma	Watch and wait strategy Rituximab	Complete remission of lymphoma and AVWS
All the other AVWS pts		
Type of disorder	**Treatment**	**Response**
MGUS 1 pt	PDN + CTX and then IvIg	No response to both therapies
MGUS 3 pts	IvIg (2 cases are under chronic treatment with IvIg every 6-8 weeks)	Transient CR as regard VWD laboratory parameters
MGUS 6 pts + 1 APS	No treatment	
Breast cancer plus MGUS 2 pts	PDN	Response to bleeding's symptoms in 1 pt The other pt underwent surgery with prophylactic therapy
Prostate cancer + MGUS 1 pt	CHT and RTX	Stable disease
Prostate cancer/splenic artery aneurysm 1 pt	No treatment	
Idiopathic AVWS 1 pt	PDN At relapse PDN + CTX	CR on VWD laboratory parameters CR on VWD laboratory parameters

226. MULTIPLE MYELOMA BEHIND REFRACTORY ARTHRITIS

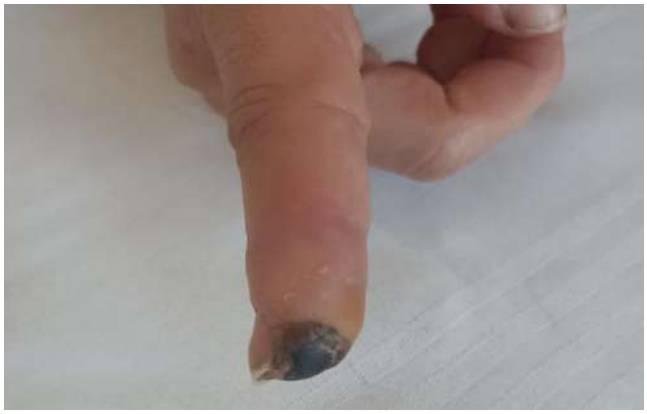
Dupuis A., Racca G., Canta R., Brignone C., Gollé G., Migliore E., Bracco C., Fenoglio L.M.
S.C. Medicina Interna Cuneo

We present the case of a 47-year-old woman who presented with refractory arthritis of the small joints of the hands, limiting her daily activities and work for one year. She had been treated with steroids, methotrexate, and adalimumab without any improvement. She presented to our emergency department due to the appearance of necrotic lesions on her fingertips and confluent petechiae on the skin of her right calf. During hospitalization, blood tests were conducted to assess autoimmune markers and serology for HBV, HCV, and HIV, all of which came back negative. Serum and urine immunofixation revealed a monoclonal IgG K component, and testing for cryoglobulins was positive, indicating type I cryoglobulinemia. Renal function was normal, and there was no proteinuria. A total body CT scan was performed to exclude paraneoplastic cryoglobulinemia, and it yielded negative results. Osteomedullary biopsy revealed a population of monotypic plasma cells with kappa chains comprising 20-30% of the cellular composition. A diagnosis of smoldering myeloma IgG K with type I cryoglobulinemia was made. As the symptomatic cryoglobulinemia met treatment criteria, therapy with Dara-VTD (daratumumab, bortezomib, thalidomide, dexamethasone) was initiated for four cycles, autologous steam cell transplant was planned. There was a subsequent significant improvement in joint symptoms and necrotic lesions. Type I cryoglobulinemia in multiple myeloma is a rare entity. Payet et al.(1) described the largest series of seven cases of type I cryoglobulinemia associated with multiple myeloma (MM), six of the cases in the series were men aged 28-69 years. Clinical manifestations in this group included skin lesions, rheumatologic failure, neurological abnormalities, and renal defects. Joint involvement is a very unusual manifestation in patients with MM or monoclonal gammopathy. The pathophysiology includes local synovial precipitation of cryoprecipitated paraproteins or Ig crystals that may activate the inflammatory response, resulting in arthritis. Like our patient, the majority of patients in the series were treated because of symptomatic cryoglobulinemia and not because of MM evolution, assessed by "CRAB" criteria (calcium elevation, renal insufficiency, anemia, and bone abnormalities). Specific MM treatments were introduced at an early stage, and bortezomib and lenalidomide were the most effective therapeutic agents. Spizzo and colleagues (2) have explained the efficacy of bortezomib through its direct effects on malignant plasma cells but also through its anti-angiogenic activity, inhibiting angiogenesis in patients with vasculitis, as observed in cases of type I cryoglobulinemia. We present this case because diagnosis of multiple myeloma in a woman of 47 years old with refractory small joints arthritis was challenging. Specific MM treatment was effective in reducing arthritis and necrotico lesions, improving patient's quality of life.

References:

1 Payet J, Livartowski J, Kavian N, Chandesris O, Dupin N, Wallet N, Karras A, Salliot C, Suarez F, Avet-Loiseau H, Alyanakian MA, Nawakil CA, Park S, Tamburini J, Roux C, Bouscary D, Sparsa L. Type I cryoglobulinemia in multiple myeloma, a rare entity: analysis of clinical and biological characteristics of seven cases and review of the literature. Leuk Lymphoma. 2013 Apr;54(4):767-77. doi: 10.3109/10428194.2012.671481. Epub 2012 Apr 19. PMID: 22385269.1

2 Spizzo G, Mitterer M, Gunsilius E. Bortezomib for the treatment [6] of refractory type-1 cryoglobulinaemia. Br J Haematol 2010;150:235 – 237.



227. A DRUG INDUCED AUTOIMMUNE HEMOLYTIC ANEMIA: A CASE REPORT

Montagano M.[1], Matarazzo G.[1], Troiano F.[1], Caporale M.[1], Vizzarri P.[1], Gigante E.[1], Calisi A.[1], Panara G.[1], D'ardes D.[1], Bucci M.[1], Santilli F.[1], Cipollone F.[1], Guagnano M.[1], Pierdomenico S.D.[2]
[1]Clinica Medica" Institute, Department of "Medicine and Science of Aging", Università "G. d'Annunzio"; Chieti, Italy;; [2]Department of Innovative Technologies in Medicine & Dentistry, University "Gabriele d'Annunzio", Chieti-Pescara, Chieti, Italy.

Background: Anemia, defined as a reduction in the value of hemoglobin or hematocrit, is one of the most frequent problems in clinical practice.
Hemolytic anemia is defined as anemia due to reduced survival of circulating red blood cells following premature destruction of the same.
Autoimmune hemolytic anemia (AIHA) is caused by autoantibodies that react with red blood cells and induce their destruction. AIHA from hot antibodies (active at body temperature), is the most common type of AIHA.
Drug-induced AIHA are rare diseases with an incidence of about 1:1,000,000 that is likely to be underestimated due to non-recognition.
Materials and Methods: Patient of 66aa comes to the emergency room for fever and asthenia for about 1 week (T max 39, C) not responsive to standard therapy with Ceftriaxone. For swelling and pain in the left lower limb, performed by legs venous doppler ultrasound with evidence of deep venous thrombosis on left leg.In recent clinical history, eradication therapy with Pylera (Bismuth subsacrate Potassium + metronidazole + Tetracycline) for the detection of chronic gastritis HP + histological examination of gastric biopsy performed during EGD test. Hematochemical tests showed severe anemia (Hb 5.9 g/dl) and increased hemolysis indices (Reticulocytes: 315 x 109/L, LDH 1734 U/L, haptoglobin < 7 mg/dl, RPI 3.4); the peripheral blood smear showed anisopoichilocytosis of the erythrocyte and presence of erythrocyte fragments.
The direct and indirect Coombs test was positive (IgG specificity).Due to severe anemia, the patient underwent a transfusion of 1 unit of red blood cells, after administration of intravenous steroid therapy with temporary ascent of Hb to 7.9 g/dl. It was performed abdominal contrast CT, which excluded lymphoproliferative disease and/or other heteroformative processes; the osteomedullary biopsy carried out excluded the presence of alterations of medullary cellularity.Following hematologists recommendations, the patient started high-dose steroid therapy (Urbason 40mg x 3/day), obtaining only a discreet, initial and transient response. Therefore, intravenous immunoglobulin transfusion at high doses (IVIG) was carried out at a dosage of 52 g/day. In the light of the clinical picture presented, a diagnosis of autoimmune hemolytic anemia was made by hot antibodies with probable iatrogenic etiology (therapy with Pylera).At discharge was set therapy with high-dose glucocorticoids and Folin.
The patient continued her CBC screened at the DH of Hematology Hospital in Pescara; during the follow-up in the light of Hb values persistently not in range, Mycophenolate mofetil was added.
The current therapy prescribed by hematologists is: Deltacortene 25 mg ½ cp 8 hours + ¼ cp 16 hours + Mycophenolate Mofetil 500 mg 1 cp h 8-20.
Discussion: Autoimmune hemolytic anemia (AIHA) is caused by autoantibodies that react with red blood cells and cause them to be destroyed. AIHA from hot antibodies is the most common type of AIHA mainly characterized by IgG antibodies.
Diagnosis is carried out by a complete blood count, calculation of the absolute number of reticulocytes, peripheral blood smear and direct Coombs test.
First-line treatment costs high doses of corticosteroids at the initial dose ranging from 1 to 2 mg/kg oral prednisone per day or a dose from 60 to 100 mg per day. Corticosteroid therapy achieves a clinical response in 70-85% of patients whose only 30% will remain in long-term remission after discontinuation of therapy. In this sense some experts suggest to associate directly the Rituximab as initial therapy (The generally proposed dosage is 375 mg/m2 per week for 4 weeks).
The guidelines include as third line drugs several immunosuppressive agents including Azathioprine, Cyclosporine, Mycophenolate mofetil and Cyclophosphamide. High-dose intravenous immunoglobulins (IVIG) have limited efficacy as a single agent in AIHA but are often useful as an addition to other therapies. In patients still dependent on transfusions after two weeks from the start of therapy with prednisone and/or rituximab, sometimes there is indication to use IVIG (500 mg/kg per day for four days) to improve RBC survival and reduce the need for blood transfusions.
Drug-induced immunomediated hemolytic anemias are rare diseases; the basic physiopathological distinction is represented by the presence of drug-dependent antibodies (the most frequent mechanism), drug-independent antibodies. In the latter, the hemolytic mechanism becomes autonomous due to the presence of real autoantibodies, for which additional therapies like those used in AIHA by hot antibodies may be necessary.

228. CARFILZOMIB INDUCED HEMOLYTIC UREMIC SYNDROME

Seu M., Metcalf X., Cigoreanu A., Vivarelli C., Catena C., Sechi L.A.
Clinica Medica, Dipartimento di Scienze Mediche Sperimentali e Cliniche, Università di Udine, Udine, Italia

Background: Thrombotic microangiopathies (TMAs) are characterized by vascular damage, thrombosis, thrombocytopenia, hemolytic anemia and organ dysfunction. We distinguish two main syndromes: thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS). The first one is due to a reduced activity of the ADAMTS13 enzyme, which can be primary or acquired and it most often involves the central nervous system. The HUS, on the other hand, mainly involves the kidney. We can classify HUS into two main types: typical and atypical. The typical form is caused by E. coli O157:H7 or Shigella infections. The atypical form (aHUS) is characterized by hyperactivation of the complement system induced by a trigger in susceptible individuals (see Table 1). Activation of C5 leads to the formation of the membrane attack complex (MAC), endothelial damage, activation of the coagulation cascade and thrombotic microangiopathy. Eculizumab, a monoclonal antibody to C5, plays an essential role in the therapy of aHUS. HUS encompasses various forms, both hereditary and acquired (see Table 2). The complement system also plays an important role in the different forms of acquired HUS, whit possible benefits of eculizumab in some of these patients.
Clinical Presentation: A 73-year-old patient, affected by Multiple Myeloma in 3rd stage, in 3rd line therapy with carfilzomib and dexamethasone (infusion on 14/04/2023). She went to the ER on 15/04 for fever (T 38.2°C) and general malaise without any other sign. The labs showed acute anemia without any signs of bleeding (Hb 8.1 g/dL compared to the previous 11 g/dL) and thrombocytopenia (PLT 104,000/mcL), initial increase in creatinine (1.39 mg/dL vs 0.86 mg/dL), CRP 15 mg/dL. The culture exams were negative. We observed the onset of pulmonary edema (on the echo: white lung and IVC without collapse). She stayed in the ER for ventilatory support (NIV) and hemodynamic support with dobutamine. After that there has been a further drop in Hb e PLT until 6000/mcL, increasing creatinine (to 4.03 mg/dL) and diuresis decreased. The patient was transfused with 3 units of PRBC and 4 PLT transfusions. Analysis revealed hemolytic anemia (haptoglobin 7 mg/dL, LDH 1282 UI/L) and schistocytes (7.7%) on the peripheral blood smear. Two cycles of plasmapheresis were performed (without benefit) and dialysis was initiated. Then she was transferred to the Medical Clinic of the HUB Hospital. The medical History revealed that after the first infusion of carfilzomib (October 2022) a similar, but self-limiting clinical picture occurred. Then we suspected for acquired aHUS from Carfilzomib. Upon arrival in the ward Hb was 7.5 g/dL, then she was transfused with 1 unit of PRBC. Having performed the test for ADAMTS13 activity and inhibitor, the result showed an activity of 94% and ruled out TTP. We prescribed eculizumab. The patient was already vaccinated against Meningococcus B and A, C, Y and W135, Hemophilus, 13-valent and 23-valent Pneumococcus. We started prophylaxis with ciprofloxacin at a dose of 500 mg per day because of renal insufficiency. On 18/04 first infusion of eculizumab was administered and well tolerated. Recovery of platelet count and hemoglobin level, and improvement in renal function were observed (no further dialysis sessions were needed). Samples were sent to investigate complement abnormalities (negative). Subsequent infusions of eculizumab were administered, with complete recovery of renal function. The patient was discharged and referred to the hematology department on 05/05, with Hb 10.2 g/dL, PLT 114,000/mcL and creatinine 1.14 mg/dL.
Discussion: Acute hemolytic anemia presenting as TMA. AKI and the absence of neurological symptoms suggested HUS. Treatment with plasma exchange was ineffective. Normal ADAMTS13 activity ruled out TTP. The absence of gastrointestinal or respiratory symptoms made typical HUS less likely, so Shiga toxin testing was not performed. The clinical presentation suggested atypical HUS due to Carfilzomib (case reports of TMA/HUS induced by this drug or others in the same pharmacological class, responsive to eculizumab but not to plasma exchange). It seems reasonable in such patients to initiate eculizumab as first-line therapy (within 48 hours for greater efficacy) instead of plasma exchange, to prevent progression of renal damage.
Conclusions: Atypical hemolytic uremic syndrome is a rare disease characterized by AKI, microangiopathic anemia, and thrombocytopenia. It is often precipitated by an infectious or pharmacological trigger, in this case, Carfil-

zomib. It is an acute condition with a high risk of mortality. It is necessary to exclude other causes of microangiopathic anemia such as TTP and maintain a high level of suspicion in the presence of recent use of carfilzomib. The first-line therapy in these cases should be eculizumab, which has shown high efficacy when introduced early, unlike plasma exchange.

	CAUSES
HEREDITARY HUS	Mutations in complement genes
	Disorders of metabolism of cobalamin
	Mutations in the Diacylglycerol Kinase Epsilon (DGKE) gene
ACQUIRED HUS	Infections: Shiga-toxin producing E.coli (STEC), S.pneumoniae, HIV
	Autoantibodies against complement factors
	Drug toxicity (expecially in cancer patients or transplant recipients)
	Pregnancy
	Autoimmune diseases

TRIGGER OF AHUS	
NON SHIGA-TOXINS ENTERITIS	Norovirus, Campylobacter upsaliensis, Clostridium difficile
RESPIRATORY INFECTIONS	Boredetella pertussis, Streptococcus pneumoniae, Hemophius influenzae
VIRAL DISEASES	Varicella, CMV, influenza H1N1, Hepatitis A and C, HIV, Coxackie B, Epstein-barr, Dengue, HHV8, Parvovirus B19
PARASITES	Plasmodium falciparum
PREGNANCY	
MEDICATIONS	Cisplatin, gemcitabine, mitomycin, clopidogrel, quinine, INF-α/β, anti-EGFR drugs, alemtuzumab, cyclosporine, tacrolimus, ciprofloxacin, oral contraceptives, cocaine, ectasy, heroin
AUTOIMMUNE DISORDERS	Anticardiolipin antibodies, C3Nef, SLE
HEPATITIS B VACCINATION	
BONE MARROW TRANSPLANTATION	
MALIGNANCY	Gastric, brest, prostate, lung, colon, ovaries, pancreas, lymphoma

229. AN ATYPICAL ETIOLOGY OF ARDS: THE IMPORTANCE OF A CAREFUL EYE IN THE EVALUATION

Troiano F.[1], Caporale M.[1], Montagano M.[1], Matarazzo G.[1], Vizzarri P.[1], D'Ardes D.[1], Bucci M.[1], Guagnano M.T.[1], Cipollone F.[1], Pierdomenico S.D.[2], Simeone P.[1], Santilli F.[1]
[1]"Clinica Medica" Institute, Department of "Medicine and Science of Aging", "G. d'Annunzio"; University, Chieti, Italy.; [2]Department of Innovative Technolog. In Medicine & Dentistry; "G. D'Annunzio" University, Chieti, Italy

80-year-old man arrived in PS for ingravescent dyspnea from twenty days, worsened in the last week, referred also to rest, and desaturation with associated asthenia and nocturnal fever. Denied angor. Concurrently it was reported in pathological history a pancytopenia, under study c/ o hematology of another hospital and a hepatosplenomegaly, likely related to the haematological condition, found at ultrasound examination performed about 5 months before. Already excluded the presence of monoclonal gammapathy before arrival in PS. Haematochemical and hemogasanalytic tests were carried out, showing an important hypoxyemic respiratory insufficiency - po2 53 mmhg -, slightly hypercapnic - pCO2 48 mmhg - with a pH of 7.4 and Lactates 1.5 mmol/l; and a fair increase in PCR values 25 mg/l and d-Dimer 3.5, with associated considerable share of monocytes to CBC (15000 /ul) and severe thrombocytopenia (22000 /mmc). Initial supportive oxygen therapy was set up and then a radiological assessment of the chest was required by contrast CT examination, in suspected pulmonary embolism, which excluded opacification defects in the pulmonary arteries and their main branches, and highlighted multiple, focal areas of "ground glass" mixed with areas of parenchymal consolidation, some of which are confluent, prevailing at the bases with bilateral pleural effusion as per suspected ARDS.
From the caudal scans passing through the upper abdomen was also observed abundant abdominal effusion in the perihepatic and perisplenic sites. NIV was positioned with FiO2 60 % with Psupp 6 cmH20 and PEEP 7 cmH20. The patient was transferred to Internal Medicine stable hemodynamically, apiretic, where he also performed transfusions of platelet pool, with the consent of the patient himself. During the first part of the hospitalization several evaluations were carried out for the presence of urinary Ag for Legionella and Streptococcus Pneumoniae, CMV DNA, EBV DNA, VZV DNA, Ag. Mycoplasma and Chlamydia, Quantiferon, as well as antigen and molecular tests for Sars-COV2 and influenza viruses, and blood culture tests for aerobics and anaerobes with all negative results. It was also introduced steroid therapy ev using Methylprednisolone 40 mg twice /day and antibiotic cover with Ceftriaxone 2 gr/day. At the same time, the Haematology of the patient's reference unit was contacted to program a BOP, because of the marked increase in monocytosis and leukocyte count at subsequent blood counts and the finding of approximately 10 % myeloid blasts at peripheral smear examination. It started a therapy with Hydroxyurea 500 mg twice cp/day and Allopurinol 300 mg daily.
In addition, during the hospitalization the patient contracted an infection of the urinary tract, with a positivity for Pseudomonas aeruginosa to cultural examination of the urine and subsequently of the blood and an important increase in creatinine values (about 3 mg/dl) and PCT (about 9 ng/ml), for which was introduced empirically and subsequently continued antibiotic therapy with Meropenem 0.5 grams repeated 3 times/day. Not feverish episodes detected. There was no improvement in the clinical-radiological status with worsening respiratory failure and the appearance of severe hypotension with mPA < 65 mmhg, despite adequate fluid intake, for which vasoactive amine therapy was set.
At the same time, the histological report, sent to us, deposed for acute myeloid leukemia with differentiating aspects in a monocytic/monoblastic sense in a patient with flt3 D835 mutation. However, in view of the comorbidities and the age of the patient, he was not considered eligible for other therapy if not the best supportive one.
Finally, the patient, evaluated also by the colleagues resuscitators, died for septic shock complicated with MOF, not responsive to treatment. The relevance of the case report is closely related to this rare etiology of ARDS, presented in the patient as a complication of monocytic/monoblastic acute myeloid leukemia. In literature there is a fair number of papers and reviews describing the role in the pathogenesis of ARDS - AML related, played by leucostasis and the subsequent release of cytokines, mainly IL-1 and TNF-alpha.Cytokines themselves leads to increased expression of adhesion molecules on endothelial cells (such as selectins and ICAM-1), aggregation and activation of leukocytes and secretion of matrix metalloproteinases, causing endothelial damage, increased vascular permeability and resulting extravasation of fluid, blood and leukemic cells. This migration from intravascular to interstitial and alveolar spaces is the basis of the radiological opacities and hypoxic respiratory insufficiency that constitute the hallmarks of ARDS.

230.ANTIPLATELET-DRUGS FOR THE PRIMARY PREVENTION REDUCES THROMBOTIC RISK IN PATIENTS WITH IDIOPATHIC ERYTHROCYTOSIS

Cosi E., Bertozzi I., Benetti A., Gamba V., Randi M.L.
Clinica Medica 1, Dipartimento di Medicina - DIMED, Università degli studi di Padova

Background and Aims: Absolute erythrocytosis is characterized by persistently raised hemoglobin (Hb) over 165 g/l in men and 160 g/l in women or hematocrit (Ht) over 49% in men and 48% in women. Idiopathic Erythrocytosis (IE) is a primary form, that occurs when the increased red-cell mass has no identifiable cause. In spite of its relative frequency in clinical practice, few papers have focused on IE and on its clinical characteristics and natural history. In our recent studies we observed that the thrombotic risk in IE patients is lower than in Polycythemia Vera (PV), a form of primary erythrocytosis due to a clonal disease of hematopoietic stem cell, but higher than in general population. While low-dose aspirin in primary prevention has been demonstrated to clearly reduce thrombotic risk in PV, less is known about the indication of antiplatelet-drugs in IE.
In this study, we retrospectively analyzed a large monocentric cohort of patients with IE, evaluating clinical outcomes and therapeutical approach to determine the efficacy of antiplatelet-drugs in primary prevention in reducing thrombotic risk.
Methods: We studied 94 patients with IE, excluding other primary and secondary forms of erythrocytosis (JAK2 somatic mutations, complete medical history, other laboratory and instrumental evaluations where indicated). In all these patients, we collected disease-relevant parameters, thrombotic events and therapeutical approaches (antiplatelet drugs and/or phlebotomies). Phlebotomy has been performed in all patients to keep Ht < 50% or a lower target when indicated (coexisting cardiovascular risk factors and/or microvascular/hyperviscosity symptoms). Thrombosis-free survival has been calculated with Kaplan Meyer method and compared with Log rank test.
Results: Among our 94 patients (M/F 81/13; median age at diagnosis 56,6 y range 18 - 85,2), we observed 17 thrombotic events (12 arterial events, 5 venous) in 15 patients (16%). In 46 patients (48,9%) antiplatelet treatment was started in primary prevention at time of diagnosis of IE (44 with low-dose

aspirin, 2 with clopidogrel); among these patients, only 4 (8,7%) experienced a thrombotic event. Whereas, 11 patients (22,9%) among the 48 not administered with antiplatelet drugs, had a thrombotic complication. Thrombosis free survival resulted significantly poorer in patients not treated with antiplatelet drugs from diagnosis of IE (p = 0,04, Figure 1)
Conclusions: IE is a primary form of erythrocytosis diagnosed when all the other causes have been ruled out. Thrombotic risk in IE is higher than in general population but a clear therapeutic approach to prevent vascular complications in this disease has not yet been defined. Borrowing experience from PV, in which low-dose aspirin treatment in primary prevention significantly reduces thrombotic risk, patients with IE has been occasionally treated with antiplatelet drugs, although this approach has not been studied in this setting of patients. Present study suggests that primary prevention with antiplatelet drugs, in the absence of contraindications, should be considered in IE to reduce the thrombotic risk taking into account that most thrombotic events in this setting of patients are represented by arterial thrombosis.

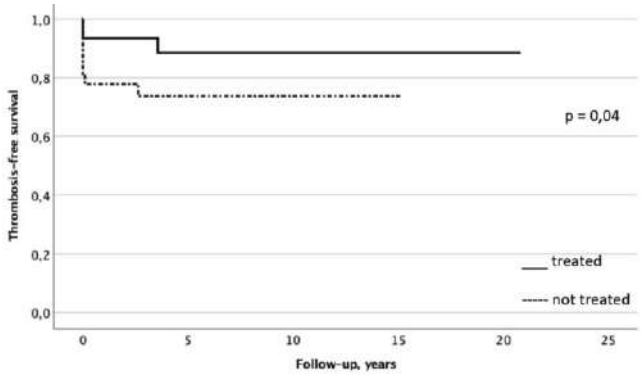


Figure 1. Comparison of thrombosis-free survival of patient treated or not treated on primary prevention with antiplatelet drugs from diagnosis of IE.

231. LATE ONSET OF MALT IN PATIENT WITH SJOGREN'S SYNDROME

De Gregorio
Dipartimento di Medicina Interna

A 78-year-old Caucasian woman originally from Sardinia, C. G., comes to our attention for pain in the right hypochondrium for about a month with lumbar irradiation.
In past pathological history: Sjogren's syndrome from the age of 18 treated before with corticosteroids and then with immunosuppressants and bilateral parotidectomy; spondylodiscoarthrosis; chronic relapsing gastroenteritis.

Diagnostic process and management: blood chemistry tests showed the following values:

WBC: 5.17 x 10^3/uL **Linfo: 0.9 x 10^3/uL**	ALT: 60 U/L	HBsAg: non-reactive	**B2M: 3.87 mg/L**
RBC: 4.39 x 10^6/uL	AST: 63 U/L	IgM: 280 mg/dL	CA 19.9: 62.6 U/mL
HGB: 13.2 g/dL	Total Bilirubin: 1,40 mg/dL	IgA: 670 mg/dL	CYFRA: 7.6 ng/mL
PLT: 94 x 10^3/uL	ALP: 183 U/L	IgG: 2012 mg/dL	**RF: 43 umol/L**
PT/INR: 1.09	GGT: 256 U/L	HCV-Ab: absent	ESR: 42 mm/h
Fibrinogen: 232	Albumin: 3.1 g/dL	**Complement C4: 9.6 mg/dL**	PCR: 0.13 mg/dL.

US exam showed a dysmorphic liver with coarse nodular pattern, irregular margins and two hypoechoic nodular lesions in the II and V segments characterized, after injection of contrast medium, by hyperenhancement in the arterial phase with a very late (> 3 minutes) and not particularly marked hypoenhancement in the lesion of the II segment while it appeared earlier and more intense in the lesion of the V segment (after 1 minute). US-guided needle biopsy of both nodular areas was also performed.
The chest-abdomen CT showed two lymphadenopathies bigger than 10mm, one retrosternal and the other paraesophageal, respectively. The liver was within the limits in size and characterized by an inhomogeneous densitometric structure. The gastric walls appeared thickened with two subcentimeter lymph node formations near the antral region. The size of the spleen was increased. Upper-abdomen MRI pointed out two pseudonodular areas with irregular margins located at the level of the II segment (37x25mm) and V segment (57x38mm); these lesions showed signal characteristics and contrastographic behavior to be referred to a replacement lesion with interstitial growth as likely to be lymphoproliferative in nature.
FDG-PET detected multiple areas of focal hyperaccumulation of the radiopharmaceutical in the liver in the II segment (SUV max 5.4) and V segment (SUV max 7.0). Concomitant further hyperaccumulation of the tracer was detected in the laterocervical area bilaterally (SUV max up to 3.2) and in the paraesophageal (SUV max 4.3), retrosternal (SUV max 2.7) and retropancreatic (SUV max 3.6) areas.
Finally, the result of US-guided fine needle biopsy showed a morpho-phenotypic finding consistent with hepatic localization of NHL derived from low-grade mature B lymphocytes. So, the diagnosis suggested was marginal zone lymphoma (MALT).
Subsequently, the patient performed EGDS showing gastropathy with the presence of subcardial erosion subjected to multiple biopsies: microscopic examination indicated the presence of intestinal-type columnar metaplasia of the esophagogastric junction compatible with Barrett's esophagus.
In the end, the hematologist consultant confirmed the diagnosis: systemic marginal NHL with perihepatic multiple extranodal infiltration (Ann Arbor stage IV) associated to an accompanying monoclonal component (IgG Kappa in serum, undetectable urinary Bence-Jones protein).
The patient was referred to oncohaematologists for therapy prosecution with Rituximab and follow-up.
Discussion: NHL has a prevalence of 4.3% in pSS (primary Sjögren's Syndrome) patients. Lymphoma development in the setting of SS is associated with increased overall disease mortality. A multistep process leads to the transition of reactive LESA (Lymphoepithelial sialadenitis) to lymphomagenesis. Chronic antigenic stimulation leads to abnormal B cell activation in the salivary glands of SS patients and the emergence of autoreactive B cell clones. Loss of immune control, ectopic GC formation and oncogenic events further drive the malignant transformation to lymphoma.
Schematically, pSS-associated NHL can be divided into two main categories: the first has an indolent course and is dominated by the extranodal marginal zone (MZ) B cell lymphomas of MALT-type (60% of cases), and the second corresponds to the high-grade lymphomas such as de novo or secondary diffuse large B cell lymphoma (DLBCL). In pSS patients, MALT lymphomas are preferably located in one or more extranodal sites such as SG, stomach, lung, liver, kidney, and only 10% of them might transform into a less differentiated (more aggressive) variety.
Biomarkers associated with the development of lymphoma represented by: parotid swelling, germinal centre-like lesions, palpable purpura, complement consumption (Low C3, C4), presence of cryoglobulinemia or monoclonal paraproteinemia, rheumatoid factor, increased β-2 microglobulin, lymphocytopenia, hypoglobulinemia, lymphadenopathy or splenomegaly.
Treatment of SS-associated lymphoma is related to stage at diagnosis, involved site(s) and histopathologic features and can vary from active monitoring strategy to multiple combined chemotherapy.

232. A CASE OF HYPERVISCOSITY SYNDROME AS ISOLATED CLINICAL PRESENTATION OF A MYELOPROLIFERATIVE DISORDER

Sordillo R.[1], Gamba L.[1], Paladini A.[1], Manfredi L.[2], Moroncini G.[2]
[1]Scuola di Specializzazione in Medicina Interna, Università Politecnica delle Marche, Ancona, Italy; [2]Clinica Medica, Dipartimento di Medicina Interna, AOUM, Ancona, Italy

Background: Hyperviscosity syndrome (HVS) refers to a condition with blood increased viscosity, resulted from increased circulating serum immunoglobulins (macroglobulinaemia, multiple myeloma) or from increased cellular blood components in hyperproliferative states, such as lymphoproliferative and myeloproliferative disorders. Hyperviscosity occurs from pathologic elevation of either cellular or acellular (protein) fractions of the circulating blood. In cellular fractions, significant elevation of any of the three primary blood cell lines may lead to clinical manifestations: erythrocytosis, leukocytosis and thrombocytosis. Classically, hyperviscosity presents with the triad of bleeding, visual disturbances (such as diplopia and nystagmus), and focal neurologic signs. Bleeding is the most common manifestation and typically arises from impaired platelet function; neurological manifestations are due to decreased blood flow to the central nervous system and deposition of paraproteins within the myelin sheath of peripheral nerves, while retinopathy and visual derangements such as blurred vision or double vision arise because of microvascular changes such as thrombosis or hem-

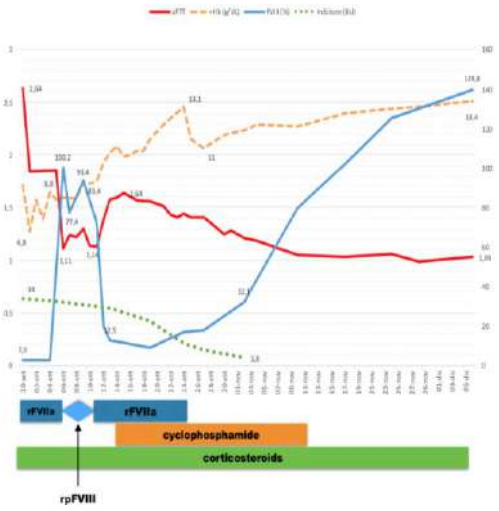
orrhage. Hyperviscosity can also cause headache, dizziness, and tinnitus. Hypergammaglobulinemia is the most common cause of HVS, specifically the monoclonal condition Waldenstrom macroglobulinemia. Much rarer is association of HVS to myeloproliferative disorders.
Objectives: We describe a clinical case of a 49 year old man in which pauci-symptomatic hyperviscosity syndrome is the first and unique manifestation of a JAK2 positive myeloproliferative disorder at the onset.
Clinical presentation: Patient referred to our department for a recent onset of tinnitus and acrocyanosis of fingers and lateral plantar areas of feet, associated with peripheral dysesthesias. Frank ischemic lesions were absent, and peripheral pulses were present. Hematological abnormality observed was incostant neutrophilic leukocytosis. In the first stage of the hospitalization, hemoglobin and platelet count were only to the upper limits of normal. Since the patient had a significant and protracted smoking habit, this is an important confounding factor which initially led the diagnosis towards macroangioapthia or Buerger's disease presenting with peripheral nerve and microcirculation involvement. However, progressive increase of platelet count and hemoglobin was observed during the hospitalization. Furthermore, a more detailed anamnesis revealed a familiarity with JAK2 positive myeloproliferative disorders. So, JAK2 gene mutation was detected.
Diagnosis: diagnostic tests evidenced a smoking related peripheral vascular occlusive disease, without hemodynamic impact. Peripheral polyneuropathy was excluded by electromyography (EMG). Autoimmune serology, serum cryoglobulins and antiphospholipid antibodies were negative, except for a dubious positive for anticardiolipin IgM antibodies, not subsequently reconfirmed. Total body CT-scan were negative for heteroproliferative lesions, but, interestingly, showed splenomegaly. So, hematological findings of leukocytosis, thrombocytosis and polyglobulia, associated with family history of JAK2 positivity and neurological and vascular symptoms have placed the clinical suspicion of an uncommon hyperviscosity syndrome presentation as epiphenomenon of a myeloproliferative disorder at the onset. This was supported by the following findings: suppressed serum levels of erythropoietin, detection of the JAK2 gene mutation and a widespread bone marrow hyperuptake at PET scan. Finally, definitive diagnosis was obtained with bone marrow biopsy which showed a pattern of myelofibrosis.
Conclusions: hyperviscosity syndrome (HVS) is a clinical condition which results from pathological increase in serum proteins, red and white blood cells, or platelets; it can presents as an oncologic emergency. Its association with myeloproliferative syndromes is infrequent. Our clinical case is an example of an unusual clinical presentation of HVS that, also if in absence of explicit visual changes, mucosal bleeding or neurological disorders, led to diagnostic hypothesis of an hidden JAK2 positive myelofibrosis myeloproliferative syndrome. These clinical aspects could be very useful for an early diagnosis of hematological disorder, also when typical myelofibrosis-related cytopenias had not yet appeared. After diagnosis, patient was started on prompt haematological treatment with janus kinase inhibitor ruxolitinib, achieving sharp clinical and laboratory improvement.

EMOSTASI E TROMBOSI

233. SUSOCTOCOG-ALFA, A RECOMBINANT PORCINE FACTOR VIII, AS RESCUE THERAPY IN ACQUIRED HAEMOPHILIA A: A CASE REPORT

Begali F.[1], Suardi S.[1], Giuffrida A.C.[2], Donini M.[1], Vitale S.[1], Lombini M.[1], Moruzzi S.[1], Pizzolo F.[1], Genesini S.[2], Gandini G.[2], Friso S.[1], Martinelli N.[1]
[1]Department of Medicine, Section of Internal Medicine – Medicina Generale B, University of Verona, Italy ; [2]Transfusion Medicine Department AOUI Verona, Italy

Background: Acquired haemophilia A (AHA) is a very rare bleeding disorder, whose pathogenesis is characterized by the production of auto-antibodies against coagulation factor VIII (FVIII) acting as inhibitors of coagulation. AHA should be suspected in patients with new-onset bleeding without either personal or family history of bleeding. In such clinical settings laboratory analysis showing an isolated prolonged activated partial thromboplastin time (aPTT) with normal prothrombin time (PT) may be suggestive for AHA. Further examinations with mixing test and specific assays for FVIII activity and FVIII inhibitors can confirm AHA diagnosis. The management of AHA includes 3 main cornerstones: i) restore haemostasis and control bleeding by means of haemostatic agents, ii) eradicate the FVIII inhibitors by means of immunosuppressive therapies and iii) identify and treat any underlying diseases. Among haemostatic agents, the first-line options for acute bleeding include bypassing agents, like activated prothrombin complex concentrates (aPCC) or recombinant activated factor VII (rFVIIa). Susoctocog-alfa, a recombinant porcine FVIII (rpFVIII), has been also licenced for the treatment of AHA. Noteworthy, rpFVIII activity can be monitored with one-stage clot-based FVIII assays, thus representing an advantage over the treatments with aPCC or rFVIIa which cannot be monitored with standard laboratory assays.
Case report: A 64-year-old man went to the Emergency Department for pain and swelling of his left knee after minor trauma. An arthrocentesis was performed, documenting a modest blood effusion, and the patient was discharged with antalgic therapy and thrombophylaxis (enoxaparin 4000 U/day). The symptoms did not improve and the patient returned the next day to the Emergency Department, from where he was admitted to the Orthopedic Department. Antalgic therapy and thrombophylaxis were continued, as well as antiplatelet therapy with low-dose aspirin for a history of previous minor stroke. In the following days there was a progressive increase in bruises in the left thigh, associated with a sharp drop in haemoglobin levels such as to require blood transfusions for a total of 6 units of concentrated red blood cells (RBC). A CT scan showed large haematomas in the anterolateral compartment of left lower thigh and in ipsilateral ileo-psoas. An internal medicine consultancy was requested. From the review of the medical records it was noted that since the first blood examinations the patient had an isolated prolongation of aPTT (1.92). No previous events of significant bleeding were reported in personal medical history. The clinical suspicion of AHA has been posed and the patient was transferred to our Internal Medicine Department. AHA diagnosis was confirmed by laboratory tests showing prolonged aPTT (2.64) without correction after mixing test, decreased FVIII activity (2.5%), and high titer of FVIII inhibitors (34 Bethesda Units). Haemostatic therapy with bypassing agent (rFVIIa 90 mcg/kg administered every 4 hours) as well as therapy with corticosteroids (prednisone 1 mg/kg/day) were started. Despite this treatment, bruises on the left lower limb continued to grow in size, haematuria appeared, and regular blood support (further 7 RBC units in 3 days) was required. The dosage of rFVIIa was increased to 90 mcg/kg administered every 2 hours, but without clear clinical benefit. Therefore haemostatic management was changed, stopping rFVIIa and switching to susoctocog-alfa with an initial bolus of 100 UI/kg. An excellent laboratory response was quickly obtained: after 30 minutes aPTT (1,1) and FVIII (100,2 %) were normalized. A dosage of 50 UI/kg every 8 hours was continued for 4 days leading to a substantial clinical improvement with stopping the progression of haematomas, resolving haematuria and stabilizing haemoglobin concentration. Subsequently, susoctocog-alfa was stopped and a low-dose "prophylactic" treatment with rFVIIa (90 mcg/kg every 12 h) was administered for further 2 weeks. No thrombotic complication was associated with haemostatic therapies. Meanwhile, diagnostic investigations did not identify clear secondary causes of AHA. Therapy with cyclophosphamide per os (1 mg/kg/day) was then started once viral infections and active cancer have been excluded. The progressive reduction of FVIII inhibitors was finally achieved. At the discharge, after about 1 month of hospitalization, the patient had normal aPTT (1,18), FVIII activity in safe range (32.1%), and low levels of FVIII inhibitors (3.8 Bethesda Units). Figure 1 summarizes the trend of the main laboratory parameters during hospital stay. After 6 months of follow-up, no recurrence of AHA has been reported.



Conclusions: AHA remains a still underdiagnosed disease for which a high index of suspicion is needed. Isolated prolonged aPTT should be carefully considered, especially when associated with newly occurring haemorrhagic diathesis. In this complex clinical setting, rpFVIII can be an effective tool to control AHA-associated bleeding, even after the failure of treatment with bypassing agents.

234. SHORT AND LONG-TERM RENAL FUNCTION CHANGES WITH DIRECT ORAL ANTICOAGULANTS IN ELDERLY PATIENTS WITH ATRIAL FIBRILLATION

Armentaro G.[1], D'Arrigo G.[2], Bo M.[3], Cassano V.[1], Miceli S.[1], Pitino A.[4], Tripepi G.[2], Sesti G.[5], Lip Y.H.G.[6], Pastori D.[7], Gori M.[4], Sciacqua A.[1]
[1]Department of Medical and Surgical Sciences, University Magna Grœcia of Catanzaro, 88100 Catanzaro, Italy; [2]Institute of Clinical Physiology (IFC-CNR), Section of Reggio Calabria, 89124 Reggio Calabria, Italy.; [3]Section of Geriatrics, Department of Medical Sciences, University of Turin, Città della Salute e della Scienza, Molinette hospital, Corso Bramante 88-90, 10126 Turin, Italy; [4]Institute of Clinical Physiology (IFC-CNR), Section of Rome, 00185 Rome, Italy.; [5]Department of Clinical and Molecular Medicine, University Rome-Sapienza, viale Regina Elena n. 324, 00161, Rome, Italy; [6]Liverpool Centre for Cardiovascular Science, University of Liverpool, Liverpool John Moores University and Liverpool Heart and Chest Hospital, Liverpool, UK; Department of Clinical Medicine, Aalborg University, Denmark.; [7]Department of Clinical Internal, Anesthesiological and Cardiovascular Sciences, Sapienza University of Rome, Viale del policlinico 155, 00161, Rome, Italy

Background: Atrial Fibrillation (AF) and chronic kidney disease (CKD) frequently coexist in elderly patient. Previous evidence showed that vitamin K antagonists (VKAs) may be associated with an accelerated decrease of estimated glomerular filtration rate (eGFR) compared to direct oral anticoagulants (DOACs). However, there is little evidence on DOACs in the elderly population and in real life settings; the evidence available to us comes from randomized clinical trials with younger populations.
Purpose: The main objective of this study was to investigate the medium to long term renal function changes in older AF patients treated with DOACs and VKAs.
Methods: Enrolled patients underwent 3 eGFR measurements during follow-up, and the between arms difference in eGFR lost over time was investigated by 1) the Linear Mixed Models (LMM) and 2) group-based trajectory model (GBTM) analyses. Analysis was done according to short-term (3.2 years) and long-term follow-up (6.7 years). During the study period 420 enrolled AF patients (77.0±6.0 years, 136 on VKAs and 284 on DOACs) underwent 1260 eGFR assessments.
Results: After a median follow-up of 4.9 years, in the whole sample eGFR decreased from 67.4±18.2 ml/min/1.73 m2 to 47.1±14.3 ml/min/1.73 m2, p<0.001. Patients on DOACs experienced a significantly lower eGFR decrease that those treated with VKAs (-21.3% vs -45.1%, p<0.001). The benefit of DOACs compared with VKAs was evident both in the short term (eGFR decline -6.6 (95% CI: -9.1 to -4.0) ml/min/1.73 m2 vs -19.9 (95% CI: -23.6 to -16.2) ml/min/1.73 m2 respectively) and in the long-term, (eGFR -13.5 (95% CI: -16.1 to -11.0) ml/min/1.73 m2 in DOACs group vs -34.2 (95% CI: -37.9 to -30.5) ml/min/1.73 m2), respectively). After stratifying our study population into 5 groups according to trajectories of renal function decline, from the first (lowest decline in eGFR) to the fifth (greatest decline in eGFR), the first trajectory consisted of 80% patients on DOACs therapy. Logistic regression showed that the group on DOACs therapy was 3.03- to 4.24-fold more likely to belong to the trajectory with less eGFR decline than the VKAs group.
Conclusions: In conclusion, DOACs were associated with less long term decline in renal function in elderly patients with AF compared with VKAs.

235. ORAL ANTICOAGULANT THERAPY AND RISK OF MACE IN ELDERLY PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION: REAL WORLD EVIDENCE DATA

Armentaro G.[1], Crudo G.[1], Clausi E.[1], Cuda P.[1], Scarcelli M.R.[1], Scozzafava A.[1], Cassano V.[1], Condoleo V.[1], Miceli S.[1], Maio R.[1], Perticone M.[1], Sesti G.[2], Sciacqua A[1]
[1]Department of Medical and Surgical Sciences, University Magna Grœcia of Catanzaro, 88100 Catanzaro, Italy.; [2]Department of Clinical and Molecular Medicine, University Rome-Sapienza, viale Regina Elena n. 324, 00161, Rome, Italy

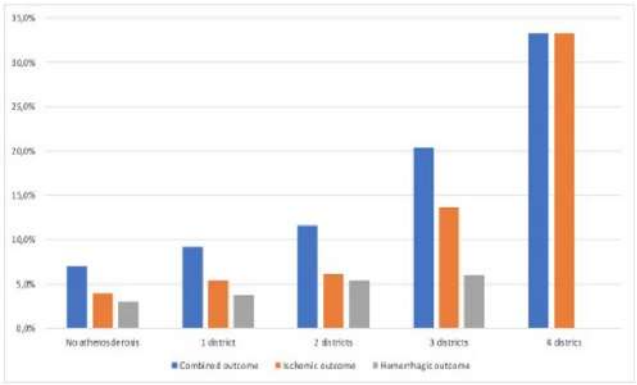
Background: Atrial fibrillation (AF) is the most common cardiac arrhythmia globally and is associated with a five times greater risk of stroke than in patients without AF. AF and major adverse cardiac event (MACE) share some very frequent risk factors in the elderly population: type 2 diabetes mellitus (T2DM), insulin resistance, dyslipidemia. Efficacy and safety of direct oral anticoagulants (DOACs) have been studied in patients with AF in association with other several critical conditions, including elderly, chronic kidney disease, or history of intracranial haemorrhage. Current international guidelines recommend the use of DOACs as an effective, safer, and more affordable alternative to vitamin K antagonists (VKAs), especially in the elderly (1). Although large clinical trials have demonstrated the non-inferiority of DOACs compared to VKAs in the prevention of stroke and systemic thromboembolism, and the reduction of major bleeding, especially in the brain, the role of antithrombotic therapies on the risk of MACE in a high-risk population, such as that elderly, is still controversial. It is probably related to the different impact of the numerous comorbidities on MACE (2). The aim of the present work is to evaluate any differences on the appearance of MACE between patients treated with DOACs compared to VKAs in an elderly population with AF and other critical comorbidities.
Materials and Methods: 420 caucasian patients, aged ≥ 65 years, were enrolled at the Department – "Magna Graecia" University of Catanzaro, suffering from non-valvular AF, 136 in treatment with VKAs and 284 with DOACs, with mean age 76.7 ± 5.7, 55 women in the VKAs group (40.4%) and 133 in DOACs (46.8%) (p = 0.217). A clinical-instrumental and laboratory evaluation was performed for a follow-up of 93.9 (30) months. Data were expressed as standard deviation or as median and interquartile range, when appropriate. Wicoxon's test and Student's t-test were performed for unpaired data, and chi-squared test was performed when appropriate. Furthermore, a log rank test was performed comparing the estimates of risk functions of two groups at each time point of the observed events, and, subsequently, a univariate Cox regression model about incidence of MACE; variables that significantly related with the occurrence of MACE were included in a multivariate Cox regression model in order to calculate the hazard ratio (HR) for independent predictors associated with the incidence of MACE.
Results: The two groups were overlappings for sex, smoking, type 2 diabetes mellitus. The group in treatment with DOACs had a higher prevalence of: heart failure (110 vs 32, p=0.002), COPD (127 vs 39 p = 0.001), arterial hypertension (266 vs 112, p = 0.0003) and they were older than the patient of the other group (78.4 ± 4.7 vs 73.2 ± 5.9 years); p <0.0001. In the whole general population at baseline, the following values were detected: estimated glomerular filtration rate (eGFR) 64.6 ± 18.2 ml/min/1.73 m2, Systolic blood pressure (SBP) 132.5 ± 11.6 mmHg, diastolic blood pressure (DBP) 76.6 ± 9.5 mmHg, BMI 29.4 ± 4.8 Kg/m2. In patients treated with DOACs, MACEs observed were 44 (2.4 events /100 patient-years), while in the group treated with VKAs were 76 (7.2 events/100 patient-years) (p <0.0001). A Cox's stepwise multivariate regression model showed that an enhancement of 1g/dl of albuminemia value (HR 0.565, p = 0.033), β-blockers therapy (HR 0.621, p = 0.013), ACE inhibitors or ARBs (HR 0.695, p = 0.024) were protective factors for the onset of MACE, while VKAs therapy (HR 2.596, p <0.0001) and heart failure (HR 1.471, p <0.0001) increased the risk of MACE in patients with AF.
Conclusions: The data of present study confirm a better safety profile of DOACs compared to VKAs on the occurrence of MACE in an elderly population with critical comorbidities, even though patients treated with DOACs were older and had a greater burden of comorbidities that negatively affect the risk of MACE such as: arterial hypertension, COPD and heart failure.

236. THE IMPACT OF ATHEROSCLEROTIC BURDEN ON VASCULAR OUTCOMES IN PATIENTS WITH STROKE AND ATRIAL FIBRILLATION (ATHENA)

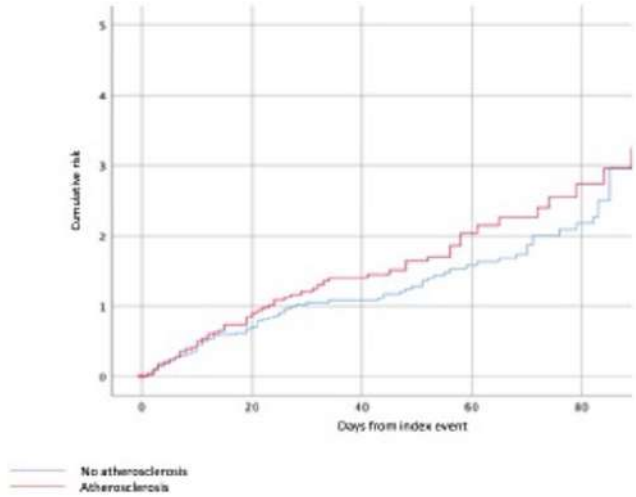
A.Galeazzo Rigutini, A.Bufi
Dipartimento di Medicina interna e vascolare, Università di Perugia

Background: Patients with prior ischemic stroke (IS) and atrial fibrillation (AF) are at high risk for recurrent vascular events. Atherosclerotic vascular disease is included in the CHA2DS2-VASc score. Vascular disease in more than one arterial district increases the vascular burden and is associated with a worse prognosis than single-vessel disease. This study aimed to evaluate the effect of various atherosclerotic vascular disease burdens on the risk of vascular events among stroke patients with AF.
Methods: This observational study used data from a prospective international multicenter cohort study (International RAF-network). We included patients with ischemic stroke and atrial fibrillation who were prospectively followed up for 90 days. Atherosclerosis was defined as the presence of at

least one of the following: 1) history of symptomatic ischemic heart disease 2) history of symptomatic peripheral artery disease, 3) presence of internal carotid stenosis 50% and 4) presence of plaques throughout the course of the aorta (ascending,arch,descending and abdominal aorta). The primary outcome of this multicenter study was the composite of stroke, transient ischemic attack, symptomatic systemic embolism, symptomatic cerebral bleeding, and major extracranial bleeding within 90 days from acute stroke.
Results: A total of 2148 patients were included; 744 (34,6%) had atherosclerosis. In the univariate analysis, male sex, 407 (54,7), diabetes 236 (31,7%), hypertension 652 (87,6%), hyperlipidemia 342 (46,0%,) and history stroke/TIA 237 (31,5%), were statistically significant in atherosclerotic patients. On the multivariate analysis, the presence of the atherosclerotic was statistically significant for the combined outcome events OR 1.56 (1.14-2.13,95% CI; P=0,006) and the ischemic outcome OR 1.62 (1.08-2.42, 95% CI; P=0,0018). The presence of more than two districts was an independent variable for ischemic (OR 2.88, 1.04-7.95; P=0.04) and combined outcomes (OR 2.80, 1,20-6,52; P< 0,01).
Conclusions: In our study cohort, atherosclerosis is an important marker for vascular burden. The more vascular districts are involved, the higher the risk for ischemic events. These patients need tailored treatment in order to reduce the vascular burden.



Outcomes in patients with atherosclerosis according to the number of districts involved



KM curves with combined outcome in patients with and without atherosclerosis

	Adjusted Odds Ratio (95%CI)	P value
Combined outcome		
No atherosclerosis	1 (Reference)	
Atherosclerosis		
1 district	1.08 (0.74-1.58)	0.6
2 districts	1.39 (0.77-2.49)	0.2
3 districts	2.80 (1.20-6.52)	0.01
4 districts	6.81 (1.02-36.24)	0.04
Ischemic outcome		
No atherosclerosis	1 (Reference)	
Atherosclerosis		
1 district	1.14 (0.70-1.85)	0.5
2 districts	1.17 (0.54-2.52)	0.6
3 districts	2.88 (1.04-7.95)	0.04
4 districts	7.76 (1.22-49.23)	0.03
Hemorrhagic outcome		
No atherosclerosis	1 (Reference)	
Atherosclerosis		
1 district	1.08 (0.62-1.89)	0.7
2 districts	1.72 (0.75-3.93)	0.2
3 districts	2.16 (0.56-8.26)	0.2
4 districts	NA	

Adjusted OR for outcomes in patients with atherosclerosis according to the number of districts involved

	ATHEROSCLEROSIS N=744	NO ATHEROSCLEROSIS N=1404	Odds ratio (95%CI)	P value
Combined outcome	77 (10.3%)	97 (6.9%)	1.56 (1.14-2.13)	0.006
			Adjusted 1.22 (0.87-1.92)	0.2
Ischemic outcome*	46 (6.2%)	55 (3.9%)	1.62 (1.08-2.42)	0.018
			Adjusted 1.24 (0.80-1.92)	0.3
Hemorrhagic outcome**	31 (4.1%)	42 (3.0%)	1.41 (0.88-2.26)	0.135
			Adjusted 1.22 (0.74-2.03)	0.4

*Ischemic outcomes (ischemic stroke and systemic embolism including myocardial infarction);
**hemorrhagic outcomes (intracranial hemorrhage and severe extracranial bleeding)

Outcomes of patients with and without atherosclerosis

237. EFFICACY AND SAFETY OF LOW-DOSE ACETYLSALICYLIC ACID FOR THE PREVENTION OF THROMBOEMBOLIC EVENTS IN PATIENTS WITH ELEVATED ANTIPHOSPHOLIPID ANTIBODIES: A SYSTEMATIC REVIEW AND META-ANALYSIS.

De Pascali F.[1], Aleksandrovna Filippova Y.[2], Donadini M.P.[3], Squizzato A.[4]
[1]Residency program in Internal Medicine, School of Medicine, University of Insubria, Varese-Como, Italy; [2]School of Medicine, University of Insubria, Varese-Como, Italy; [3]Thrombosis and Heamostasis Center, Ospedale di Circolo, ASST Sette Laghi, Varese; [4]Research Center on Thromboembolic Disorders and Antithrombotic Therapies, ASST Lariana, University of Insubria, Como, Italy

Background: Anti-Phospholipid Antibodies (aPLAb) are a group of autoantibodies directed against phospholipids, which predispose to an increased risk of thromboembolic events. The net clinical benefit of antithrombotic prophylaxis in aPLAb carrier is still unclear since controversial data are available. We performed a systematic review to assess the efficacy and safety of antiplatelet drugs for the primary prevention of thromboembolic events in aPLAb carriers.
Methods: Studies evaluating primary thrombotic prevention with antiplatelet drugs in aPLAb carriers were identified by electronic search of MEDLINE and EMBASE database until May 2023. The differences in the outcomes among groups were estimated as pooled odds ratio (OR) and corresponding 95% confidence interval (CI). Statistical heterogeneity was evaluated using the I2 statistic.
Results: A total of 1056 participants were included in the 10 studies, 2 RCTs and 8 cohorts. Low-dose acetylsalicylic acid (LDA) was the antiplatelet drug in treated patients. Overall thromboembolic events were significantly reduced in th LDA group compared to the control group [OR 0.46 (95% CI 0.30 – 0.71), I2 27%, fixed-effects model]. Arterial thromboembolic events were significantly reduced in the LDA group compared to the control group [OR 0.47 (95% CI 0.26 – 0.86), I2 0%, fixed-effects model]. Venous thromboembolic events were significantly reduced in the LDA group compared to the control group [OR 0.44 (95% CI 0.21 – 0.89, I2 1%, fixed-effects model]. No major bleedings occurred in the two studies reporting them.
Conclusions: aPLAb carriers receiving long-term LDA had a significant reduction of thromboembolic events, without a significant increased in major bleedings. It remains unclear if LDA has the same benefit/risk profile in all aPLAb profile, i.e. single, double, or triple positivity

238. FIBRINOGEN SANT'ANTIMO: A NOVEL MUTATION FGG C.952G>T (P.GLY318>CYS) CAUSING HYPODYSFIBRINOGENEMIA

Casoria A.[1], Miele C.[2], Capasso F.[2], Mormile R.[2], Bisceglia L.[3], Vecchione G.[3], Conca P.[1], Cimmino E.[1], Cirillo F.[1], Frangipane I.[1], Di Minno M.D.[1], Tufano A.[1]
[1]Dipartimento di Medicina Interna, Università Federico II di Napoli; [2]UOC Laboratorio di ematologia ed emostasi, Università Federico II di Napoli; [3]Divisione di Genetica Medica IRCCS casa sollievo della sofferenza, San giovanni Rotondo

Background: Fibrinogen, a 340 kDa glycoprotein, consists of three homologous polypeptide chains (A , Bß, and), encoded by FGA, FGB, and FGG genes. Genes coding for fibrinogen chains are situated at chromosome 4 gene map (locus 4q28). A chain with an aminoacid residue change is either not expressed in plasma or its half-life in blood is too short. Congenital fibrinogen disorders may be classified into Type I and Type II disorders. Type I disorders (Afibrinogenemia and Hypofibrinogenemia) affect the quantity of fibrinogen in circulation (fibrinogen levels lower than 1.5 g/L). Type II disorders (Hypo-dysfibrinogenemia or Dysfibrinogenemia) affect the quality of circulation fibrinogen. Phenotypic manifestations include arterial and venous thrombotic events in addition to bleeding. Herein, we report a novel missense mutation in the FGG gene identified in a 62 years-old female and her family with eight affective members, with hypo-dysfibrinogenemia, arterial thrombotic events, bleeding and obstetric complications.
Case report: The patient a 62- year-old female from Naples was admitted to our department for the evaluation routine coagulation test. In 1979 she had an abnormal bleeding after a caesarean section, in 1981 after a second caesarean section she had a life-threatening bleeding and hysterectomy. The clinical history included arterial hypertension, dyslipidemia, polycythemia, MGUS and smoking habit. Laboratory examination showed a hypo-dysfibrinogenemia. The family clinical history showed that the proband's mother was death for a bleeding during the third birth. The proband and seven family members had a routine parameters of coagulation pattern peculiar of hypodysfibrinogenemia, characterized by discrepancy between clottable and immunologic fibrinogen levels (ratio < 0.7 suggestive of congenital hypo-dysfibrinogenemia). We drew and study the family tree through the birth registry office and identified eight living members with hypo-dysfibrinogenemia.All have the same missense mutation c.952G>T (p.Gly318>Cys) in exon 8 gene FGG in heterozygosity. One family member clinical history was positive for arterial thrombosis and another family member clinical history was positive for cerebral gliosis. The other five member were asymptomatic for vascular disease.

Patients Age/Gender	Fg Act (v.r. 169- 358)	Fg Ag (v.r. 166-358)	Ratio Act/Ag (v.r. < 0,7)	PT (v.r. 0,8-1,20)	aPTT (v.r. 0,8-1,20)	TT (v.r. 0,8-1,20)	Mutation c.952G>T	Phenotype
P.G. (F. 62 y/female)	244	1564	0,15↓	1,27↑	1,06	1,99↑	Present	Bleeding
M.J. (F. 15 y/female)	303	357	0,85	1,10	0,94	0,98	NT	NA
M.M. (F. 17 y/female)	334	1124	0,29↓	1,27↑	1,01	1,80↑	Present	Asymptomatic
M.G. (M. 44 y/male)	354	1304	0,27↓	1,14	1,04	1,78	Present	Thrombotic
P.C. (M. 84 y/male)	347	433	0,80	1,09	1,15	0,93	NT	NA
P.G. (M. 60 y/male)	644	194	0,33↓	1,03	1,07	1,49↑	Present	Thrombotic
P.L. (M. 21 y/male)	344	1554	0,22↓	1,25↑	0,98	1,64↑	Present	Asymptomatic
M.C. (M. 42 y/male)	304	1044	0,29↓	1,29↑	1,06	1,92↑	Present	Asymptomatic
M.V. (M. 19 y/male)	223	292	0,76	1,14	1,13	1,00	NT	NA
M.C. (F. 13 y/female)	334	894	0,37↓	1,35↑	1,10	2,09↑	Present	Asymptomatic
M.J. (F. 8 y/female)	324	1124	0,28↓	1,29↑	1,18	2,02↑	Present	Asymptomatic
M.V. (M.65 y/male)	310	382	0,81	1,01	1,13	0,96	Absent	NA

Tabel I. *Summary of coagulation test and phenotypic characteristics according to traditional fibrinogen analyses. Fg Act – Functional Fibrinogen; Fg Ag – Fibrinogen Antigen; PT – Prothrombin Time, aPTT – Activated Partial Thromboplastin Time; TT – Thrombin Time; NA – Unaffected; NT – Not tested*

Methods: Citrated plasma from the proband and her family members was collected in a 2,7 mL vacuum tubes containing buffered sodium citrate solution (0.109 M, 3.2%), from a venous blood vessel in a 1:9 ratio. Specimens for screening and confirmatory coagulation tests were centrifuged at 1.500 g for 15 min to obtain platelet-poor plasma. Both clotting assays, such as PT, aPTT, Thrombin Time, Clauss fibrinogen and immuno-turbidimetric assay for antigenic fibrinogen, were assessed using an ACL TOP 550 spectrophotometric hemostasis equipment (Instrumentation Laboratory Company, Bedford, MA, USA). To provide more information on the global coagulation process, we evaluated Rotational Thromboelastometry on whole citrated blood with a computerized ROTEM Delta device (Instrumentation Laboratory Company, GmbH, Munich, Germany). For genetic analysis, DNA from the proband and the family members was obtained from peripheral blood samples. The purified genomic DNA extracted was then amplified by PCR and sequencing was performed to find the causative mutation.
Discussion: Hypo-dysfibrinogenemia is a rare disorder characterized by a reduced fibrinogen antigen level, associated with a disproportionately low functional activity. Fibrinogen has a central role in hemostasis, contributing to platelet aggregation, clot formation and fibrinolysis. The data that emerged thanks rotational thromboelastometry (ROTEM) and Generation of Thrombin appear to be influenced by the reduction of fibrinogen functional levels, as already described in the literature, proving an increase in clot formation times; on the contrary the generation of thrombin evaluating the dynamism of the formation and the thrombin inhibition, is influenced by circulating thrombin levels. This novel mutation has an autosomal dominant inheritance and is absent in the consultation databases (gnomAD). This heterozygous mutations probably destabilize the fibrinogen molecule and the resulting abnormal fibrinogens are either not expressed in plasma or their plasma half-life is extremely short. The novel mutation was named "Fibrinogen Sant'Antimo" after the town of its discovery.

239. SKIN ERYTHEMATOUS MIGRANT PLAQUES CONSISTENT WITH HISTOLOGICALLY CONFIRMED DERMAL ARTERIOLAR THROMBOSIS CONNECTED TO APS

Croce J.[1], Suardi S.[1], Moruzzi S.[1], Tinazzi E.[1], Maiolini F.[1], Mazzi F.[1], Colato C.[2], Rizzo P.C.[2], Martinelli N.[1], Friso S.[1], Pizzolo F.[1]
[1]Department of Medicine, Unit of Internal Medicine B, University of Verona School of Medicine; [2]Department of Diagnostics and Public Health, Section of Pathology, University of Verona

Background: Antiphospholipid syndrome (APS) is characterized by venous or arterial thrombosis and/or an adverse pregnancy outcome in the presence of persistent laboratory evidence of antiphospholipid (aPL) antibodies. APS occurs either as a primary condition or in the setting of an underlying disease, usually systemic lupus erythematosus (SLE), but also other autoimmune diseases, infections or medications. Antibody testing in patients with suspected APS involves two immunoassays and a functional coagulation assay (Anticardiolipin antibodies IgG and IgM by ELISA, Anti-beta2 glycoprotein I antibodies IgG and IgM by ELISA and LAC functional coagulation assay) followed by confirmatory testing at least 12 weeks later. Skin lesions, although not diagnostic, are a relatively common manifestation of antiphospholipid (aPL) syndrome and occur in 50% of patients with APS. Skin disorder is usually due to vascular thrombosis involving the dermal layer and more rarely the subcutaneous tissue; it can be limited or widespread and it may cause skin necrosis and/or ulceration without evidence of histologically confirmed vasculitis. The treatment is generally based on anticoagulation, usually with Warfarin but also with DOAC in selected patients. Antiplatelet therapy with aspirin can be considered if arterial involvement is present. There are insufficient data in scientific literature about the specific treatment of the skin involvement in APS that has to be individualized according to the patient's bleeding risk (some experts recommend dual antiplatelet therapy or Warfarin +/- ASA) with conflicting results.
Case Report: A 58-year-old woman originally presented to our Unit with a medical history of arterial and venous thrombosis (one episode of cerebral venous thrombosis and 2 episodes of CNS arterial ischemia – cerebellar and nucleobasal) and the evidence of a low-title positivity of anticardiolipin IgG in 2 different determinations. She did not demonstrate any clinical or biochemical features suggestive of SLE or any other autoimmune diseases, except for 1:320 ANA positivity with cytoplasmic pattern. She had a mild, JAK2-negative, polyglobulia, with no familiar history of thrombosis. She had a mild hyperhomocysteinemia (in a composite heterozygosity 677C>T-1298A>C), treated with folic acid. She did not have any known thrombophilic condition.
The patient was already taking ASA 100 mg because of the previous CNS insults. A diagnosis of primary APS was made, so we decided to add Warfarin in order to prevent any other thrombotic complication. After one month of combined anticoagulant and antiplatelet therapy, the patient had persistent haematuria so ASA was suspended and the patient only continued to take Warfarin. Two years later, she started to develop erythematous, painful, non-palpable, migrant, evolving to purple and spontaneously remitting plaques, located mainly in the abdominal region. The skin biopsy documented intravascular thrombi with mild perivascular infiltrate of lymphocytes and eosinophils but without evidence of vasculitis. Immunofluorescence showed CD61-positive thrombi. She restarted to take ASA therapy in combination with Warfarin with an improvement of the lesions, and no others appeared

in the 9 months follow-up.
Conclusions: This case demonstrates an atypical cutaneous manifestation of aPL syndrome, but with aspects in common with other APS skin manifestations such as dermal thrombosis without the evidence of vasculitis. Our experience would suggest the use of antiplatelet therapy in combination with warfarin to be preferred to warfarin alone for the management of cutaneous intermediate-deep dermal arteriolar platelet-mediated thrombosis, particularly in the setting of APS with a previous arterial involvement.

240. ARE PLASMA OXIDATIVE STRESS AND HEPCIDIN INCREASED IN THE VENOUS THROMBOEMBOLISM?

Maiuzzo R., Scebba S., Di Tomasi G., Manzitto L., Dipasquale M., Campanelli L., Frazzetto E., Privitera G., Sapuppo T., Incognito C., Platania I., Signorelli S.S.
Dipartimento di Medicina Interna Policlinico G. Rodolico Catania

Introduction: Venous thromboembolism (VTE) is a preventable disease with higher morbidity and mortality characterized by diagnostic difficulties and recurrence risk. In VTE there are venous circulation instability, hypoperfusion, hypoxia, and ischemia. All these conditions are able to induce oxidative stress (Oxs). Oxs is a disturbed balance between oxidant and antioxidant systems leading to protein oxidation and lipid peroxidation. Robust evidences have showed that blood levels of transitional metal, particularly the iron, can play a role in the VTE.
Hepcidin is the homeostatic regulator of iron that ensures the balance of circulating and stored iron levels. Since hepcidin can activate membrane oxidation, the aim of our study was to examine activated OxS in VTE and relationship between OxS and hepcidin (Hep).
Malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) are considered as common surrogate markers to validate OxS. The superoxide-dismutase enzyme (SOD) is considered marker to evaluate as the defence against OxS.
Methodology: We performed a case-control observational study in evaluating MDA, 4-HNE, SOD and Hep in VTE patients and in controls.
We enrolled twenty patients admitted to the Internal Medicine University Hospital G. Rodolico (Catania, Italy) affected by pulmonary embolism (PE) and deep vein thrombosis (DVT) of the lower limbs. 12 out 20 were men and 8 women (aged between 56 and 73, mean 63.5 years). Ten healthy individual (5 men and 5 women aged between 43 and 68, mean 45 years) were controls. PE diagnosis was given upon admission at the hospital by the computed tomography examination. Patients underwent an ultrasound evaluation of the venous circulation in the lower limbs. The DVT diagnosis was based on evidence from an intraluminal echogenic image of one or more veins, and on the positivity of the wave-compression test (CUS test). Following patients consented to a venous blood sample to measure the levels of MDA, 4-HNE, SOD and hepcidin.

	Markers	VTE	Controls
Weighted Average	MDA (microM/l)	8,38±0.5	5,5±0.6
	4-HNE (microM/l)	2,75±0.03	2,24±0.021
	SOD (U/ml)	0.025±0.01	0.08±0.01
	Hep (ng/ml)	4,77±0.52	2,1±0.55

Results revealed that patients presented higher levels of surrogate biomarkers of the OxS and Hep and lower level of SOD compared with controls.

Considerations:Iron can induce the Oxs, reduces the bio-availability of nitric oxide (NO) producing two critical pathways for pro-thrombotic activation: endothelial dysfunction and platelet activation. On the contrary, SOD enzyme plays a role in the fluidity of the platelet membranes and in preventing the clot. The imbalance between oxidative and anti-oxidative systems plays a crucial role in determining pro-thrombotic activation and in increasing or determining the VTE risk. Differences about MDA and 4-HNE found patients compared to controls elicite that the OxS is activated, whereas the lowered levels of SOD indicate the reduced capacity of the redox system. To explain on the Hep, it should be remembered that hepcidin is the main regulator of iron homeostasis. Hep internalise the ferroportin-ceruloplasmin complex, inhibits iron degradation and prevents iron exportation. The increased synthesis of Hep is produced by blood iron overloading and inflammation processes.
Conclusions: To sum up, the results of our study, in line with other published data, suggest that in VTE there are both activated OxS and over-production of Hep. This last, points to iron deregulation, which in itself is a potent inducer of OxS in turn sensitive to inflammation and a potent activator of clot and of pro-thrombotic condition. It is intriguing to consider both as potential indicators of the risk of VTE.
References:
Bilal Halici, Sevinc Sarinc Ulasli, Ersin Günay, Serkan Nural, Serkan Sen, Olcay Akar, Sefa Celik and Mehmet Unlu. Assessment of Inflammatory Biomarkers and Oxidative Stress. Springer Science, Business Media New York, 2014
Tomas Ganz. Hepcidin. Elselvier, 2004.
Trygve S. Ellingsen, Jostein Lappegard, Thor Ueland, Pal Aukrust, Sigrid K. Brækkan and John-Bjarne Hansen. Hepcidin and risk of VTE. Blood advances, 2018.

241. DIRECT ORAL ANTICOAGULANTS IN ATYPICAL SITE VEIN THROMBOSIS: EXTENDED FOLLOW-UP

Guida A., Vitale P.[1], Mazzarelli U.[1], Sottolano A.[1], Agrelli L.[1], Carrieri I.[1], Amato M.[1], Marotta P.[2], Pagliuca A.L.[1], Madonna P.[3], Triggiani M.[1]
[1]Centro per le Malattie Emorragiche Congenite e Malattie Trombotiche UOC Immunoreumatologia Dipartimento delle Scienze Mediche University of Salerno; [2]UOC Nefrologia AOU San Giovanni di Dio e Ruggi d'Aragona; [3]UOC Medicina Interna Ospedale del Mare ASL Napoli 1 centro

Background: Direct oral anticoagulants (DOAC) are currently recommended as initial treatment of Venous Thromboembolism (VTE). Although the evidence on the use of these drugs in patients with unusual-site venous thromboembolism (VTE) is limited to a few, small studies, these drugs are currently used in clinical practice. Aim of our survey was to evaluate the efficacy and safety of anti Xa-direct oral anticoagulants (aXa-DOAC s) in treatment and secondary prevention of VTE in 9 non neoplastic patients.
Methods: we enrolled 9 patients (2F, 7Mmean age 53,44) referred to Ospedale del Mare thrombosis centre and Centro malattie emorragiche congenite of University Hospital of Salerno since march 2019 to march 2022. All patients were screened for inherited and acquired thrombophilia, Jak-2 polymorphism, autoimmunity and neoplasm. Diagnosis of VTE was obtained with contrast-CT-Scan. 5 patients experienced splanchnic vein thrombosis, in 3 cases secondary to abdominal infection (diverticulitis, cholecystitis)3 patients had vena cava thrombosis, 2 cases were provocked VTE (1 spondilodiscitis, sepsis and inferior vena atresia) 1 patients presented FII-G20210A heterozigousity, 1 patient Factor V Leiden heterozigousity no other thrombophilic abnormalities were detected. All patients performed a Total body CT-Scan and endoscopy was done in 5/9 patients no solid tumors emerged. 3/9 were prescribed apixaban the others received edoxaban.
Conclusions: in our population only one patient presented menorrhagia with anaemia, we reduceded the dose of apixaban in the first two days of menstrual period, resolving anemia ed reducing the bleeding symptoms without thrombotic complications. All patients were prescribed longterm anticoagulant therapy after informed consent. In a our small case series we observed effectiveness and safety of anti Xa-DOACs in patients with atypical site vein thrombosis.

242. DIRECT ORAL ANTICOAGULANTS IN PATIENTS WITH VENOUS THROMBOEMBOLISM AND SEVERE THROMBOPHILIA.

Madonna P.[1], Guida A.[1], Mocerino L.[2], Calcaterra I.[2], Amitrano M.[3], Casoria A.[3], Di Minno M.[2], Tufano A.[2]
[1]Thrombotic Unit, Ospedale del Mare, Naples, Italy; [2]Department of Clinical Medicine and Surgery, University of Naples, Federico II; [3]UOC Medicina Interna, AORN Moscati Avellino

Introduction: The role of direct oral anticoagulants (DOAC) in the management of patients with venous thromboembolism (VTE) and severe thrombophilia is controversial.
Patients and methods: We evaluated 50 patients (27 M, 23 F; age at first event 38 ± 13.7 years) with a history of VTE [deep vein thrombosis (DVT)

and/or pulmonary embolism (PE)] and thrombophilia, referred between March 2014 and March 2022 to 3 Centers: Thrombotic Unit, Ospedale del Mare, Naples; Department of Clinical Medicine and Surgery, Federico II University, Naples; and UOC Medicina Interna, AORN Moscati, Avellino.
All patients were affected by thrombophilia [AT, PS, PC deficiency, FV Leiden (FVL) homozygosis, FIIG20210A homozygosis, combined heterozygosis of FVL+ FIIG20210A, and homocystinuria], and treated with DOAC (rivaroxaban, edoxaban, apixaban) for at least 3 months. **Each patient underwent clinical/instrumental/laboratory follow-up every 3 months.**
Results: In our setting of 50 patients, we identified: 5 AT deficiencies, 3 PC deficiencies, 10 PS deficiencies, 22 combined heterozygosis for FV Leiden+FII20210A, 5 FVL homozygosis, 5 FII20210A homozygosis, 2 combined heterozygosis FVL+ homozygosis FII20210A, 1 combined heterozygosis FVL+homozygosis FII 20210A+PS deficiency, 1 homocystinuria. Twenty-seven patients received long-term rivaroxaban, 10 edoxaban and 13 apixaban; 9 patients switched from warfarin to DOAC. Provoking factors (surgery, trauma, estrogens) were present in 11 cases, the others were unprovoked. Patients were treated for 104,34 ± 281.94 months (mean). During this time, no recurrences nor major bleedings were observed. No differences for sex, type of thrombophilia, or drug were observed.
Conclusion: This study suggests that DOACs are an appropriate and safe option for treatment/secondary prophylaxis of VTE in hereditary thrombophilia. During the observation, in our setting, no thrombotic recurrences or major bleedings were observed.

243. A COMPLEX CASE OF CEREBRAL VENOUS SINUS THROMBOSIS

Rufolo P., Strano F. , Cimino E., Tufano A.
Department of Clinical Medicine and Surgery, University of Naples, Federico II

Background: Cerebral vein thrombosis (CVT) is a manifestation of unusual site venous thromboembolism (VTE). CVT encompasses thrombosis of the cerebral veins (cortical or deep veins) and dural venous sinuses, has an estimated annual incidence of 3 to 4 cases per million adults, and is the cause of 0.5–1% of strokes. CVT usually shows a clear prevalence of females (approximately 75% of cases). Among the main conditions favouring CVT are thrombophilia (about 38% of cases), oestrogen-progestin therapy (about 33% of cases), pregnancy/puerperium, cancer, and myeloproliferative syndromes. Local risk factors for CVT have also been reported, such as mechanical causes (e.g., head injury, central venous catheter placed into the jugular vein, or neurosurgical procedures, reported in 3–5%) or infections (e.g., otitis, mastoiditis, meningitis, reported in about 10% of cases). Early diagnosis and adequate anticoagulant therapy represent the main challenges for the clinician, to avoid long-term neurological sequelae.
Case report: a 28-year-old woman, admitted for severe headache, not responsive to NSAIDs, and left weakness, underwent MR of the brain with evidence of thrombosis of the superior longitudinal sinus, the bilateral sigmoid sinus, associated with infarction in the right fronto-parietal white matter, with evidence of abnormal impregnation of the walls of the sagittal sinus (characteristic sign of the "delta"), straight sinus and part of the transverse. Approximately three months before she reported fleeting episodes of diplopia and concomitant finding of bilateral papilledema at an ophthalmological evaluation. At that time, the neuroradiological findings, including MR angiography, were negative and a diagnosis of pseudotumor cerebri was therefore made. Interestingly, she had performed lumbar puncture (LP) with cerebrospinal fluid pressure measurement about two weeks before admission, which showed a value of 340 mmH2O. After the LP she had presented exacerbation of the headache. Pulsating headaches were also reported in previous years. She had never taken oestrogen-progestin therapy. Laboratory tests revealed thrombocytosis (643,000/mL). The search for the V617F mutation on the pseudokinase domain (JH2) of the JAK-2 gene was positive and, following specialist haematological evaluation, the diagnosis of JAK-2 positive essential thrombocythemia was done. The laboratory investigation also revealed the presence of the G20210A mutation of the prothrombin gene in heterozygosity. Treatment with warfarin (target INR 2-3), oncocarbide, and acetazolamide, was started. The patients stopped warfarin after some months, due to warfarin resistance, and rivaroxaban 20 mg daily was started and continued for long term, without major/minor bleedings and without recurrences.
Conclusions: CVT after **LP** is a well-known phenomenon, and a CVT should be suspected in any patient who undergoes LP and develops refractory and transformed headache. The guidelines for the treatment of CVT suggest a therapeutic conduct like that established for VTE in typical sites: oral anticoagulants for at least 3 months, to be maintained for long term in patients with recurrent thrombosis or with conditions at high risk of recurrences such as in the case of the patient described. There is growing evidence on the use of DOACs (direct oral anticoagulants) in CVT. In this case, the patient was treated with rivaroxaban 20 mg for about 3 years, without bleeding complications or thrombotic recurrences.

244. PREVALENCE AND RISK FACTORS FOR THOMBOTIC EVENTS IN OUT-PATIENTS AFFECTED BY INFLAMMATORY BOWEL DISEASE.

Rufolo P., Rispo A., Testa A., Patturelli M., Casoria A., Vitale A., Strano F., Guarino A.D., Leo C., Castiglione F., TufanoA.
Department of Clinical Medicine and Surgery, University "Federico II" of Naples

Background: Patients affected by inflammatory bowel diseases (IBD), namely Crohn's disease (CD) and ulcerative colitis (UC) are at risk for thrombotic complications. Patients with active and relapsing disease and those needing steroids, hospitalizations and surgery show the highest risk. On the contrary, the thrombotic risk in the IBD out-patient population is underestimated and poorly investigated.
Aims: starting from these considerations, we decided to perform a study to better define and assess the prevalence and features of thromboembolic (TE) events in out-patients affected by IBD, a population normally considered at low risk for thromboembolic events.
Methods: From May 2019 to September 2022, all consecutive IBD patients afferent to the third level IBD ambulatories of University "Federico II" of Naples, were evaluated. All subjects were examined for the presence of the common risk factors associated to TE (smoking habit, systemic hypertension, diabetes, dyslipidaemia, neoplasms, estro-progestogen assumption, traumas, etc). Patients with a history of thromboembolic events (arterial thrombosis, heart attack, ischaemic stroke, TIA, deep vein thrombosis, superficial vein thrombosis, pulmonary embolism) were studied for prothrombotic susceptibility by testing the plasmatic levels of antithrombin, protein C, Protein S, FV, FVIII, FXII, FXIII, anticardiolipin antibodies (aCL) and LA, and for the presence of the genetic polymorphisms (MTHF C677T, FV Leiden, FII G20210A).
R**esults:** At the end of the period of observation, 303 IBD patients were enrolled in the study (153 CD; 150 UC; M/F: 176/127; mean age: 41 years; mean BMI 23). Twenty-three IBD patients (7.5%) showed a TE event. Specifically, we observed 14 patients with TE events (9.3%) and UC and 9 patients with TE events (5.8%) and CD. About the specific type of TE, we recorded: 5 cases of arterial thrombosis, 3 heart attacks, 1 stroke, 3 cases of TIA, 8 deep vein thromboses (in 2 cases associated with pulmonary embolism), 3 patients with superficial vein thrombosis. When considering the main risk factors associated to TE, 60 patients were active smokers, while 66 patients were exsmoker; 70 IBD patients showed systemic arterial hypertension, 26 subjects were obese, 16 patients showed dyslipidaemia, 8 patients assumed estro-progestogens pills. At the univariate analysis, only systemic arterial hypertension ($p<0.01$; OR 5.1), obesity ($p<0.01$; OR 4.6) and dyslipidaemia ($p<0.01$; OR 4.7) were significantly correlated to TE occurrence. No differences were observed between the CD and UC population. When considering the serological/genetic prothrombotic profile of IBD patients with TE events, 2 patients showed homozygosity for MTHF C677T, 1 patient FV Leiden in heterozygosity, and no cases of FII G20210A mutation. Furthermore, no significant alterations were found in the levels of anticardiolipin antibodies (aCL) and LA, levels of FV, FVIII, FXII and FXIII.
Conclusions: Out-patients with IBD presented a low but not negligible risk of TE events, which are mainly correlated to the common risk factors described in general population. Clinicians should not underestimate TE risk in IBD out-patients to promptly identify and correct the main risk factors for this severe complication.

245. THERAPEUTIC PLASMA EXCHANGE-RELATED COMPLICATIONS IN PATIENTS WITH IMMUNE-MEDIATED THROMBOTIC THROMBOCYTOPENIC PURPURA

Agosti P.[1], Cardone C.[2], Mancini I.[1], De Leo P.[3], Bichard C.[1], Artoni A.[3], Ferrari B.[3], Giannotta J. A.[3], Fantini N. N.[4], Mocellin M. C.[4], Peyvandi F.[5]
[1]Università degli Studi di Milano, Department of Pathophysiology and Transplantation, Milan, Italy.; [2]Department of Healthcare Professions, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [3]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Milan, Italy.; [4]Transfusion Medicine and Cell Therapy Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.; [5]Università degli Studi di Milano, Department of Pathophysiology and Transplantation, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Milan, Italy

Background: Thrombotic thrombocytopenic purpura (TTP) is a rare and life-threatening thrombotic microangiopathy (TMA), which manifests as an acute episode of thrombocytopenia, microangiopathic hemolytic anemia and disseminated microvascular thrombosis with variable and multiple organ involvement. TTP is caused by a severe deficiency of the von Willebrand factor cleaving protease ADAMTS13 (a disintegrin metalloproteinase with thrombospondin type 1 motif 13). The most common form of TTP (95% of cases) is acquired immune-mediated TTP (iTTP), an autoimmune disease caused by immunological tolerance loss in ADAMTS13. Daily therapeutic plasma exchange (TPE) is the cornerstone of treatment for iTTP. However, TPE is not a risk-free procedure and there is scarce evidence regarding its safety in iTTP.
Aims: This study aims to describe the TPE-related clinical complications occurred in a cohort of patients hospitalized for an acute iTTP episode.
Methods: In this cross-sectional study, patients hospitalized for an acute iTTP episode at the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (Milan) between January 2016 and April 2022 undergoing a central venous catheter (CVC) placement to start TPE were enrolled. We defined major clinical complications as those requiring transfer to an intensive care unit, an invasive procedure (e.g. CVC replacement), TPE interruption, systemic treatment, or blood transfusion. We distinguished between CVC- and TPE-related complications. Age, sex, clinical manifestations, laboratory parameters, chronic diseases and treatments, episode management and outcomes were collected.
Results: Thirty-three iTTP episodes from 32 patients were included, 20 (61%) first episodes. The majority of CVCs were placed in a common femoral vein. The most common CVC-related complications were minor, including 19 CVC-related bleeds (in 16 episodes), which required only local hemostatic medications. Among the major CVC-related complications, 5 were venous thromboses (VTs) requiring heparin and CVC removal, and 3 infections (2 systemic) requiring systemic antibiotic treatment with CVC removal. The two systemic infections were methicillin-resistant Staphylococcus aureus (MRSA)-related. Fifteen iTTP episodes (46%) presented at least one major TPE-related complication. Among major TPE-related complications, the most common were allergic reactions (49%), mostly urticarial rashes requiring systemic steroids and antihistamines, followed by symptomatic hypocalcemia requiring systemic treatment (24%), and hypotension or heart failure (21%). The episodes complicated with CVC-related VT or infection required a higher median number of days of hospital stay (30 [interquartile range, IQR, 17-35] and 30 [IQR, 27-34], respectively), compared with the whole cohort (14 [IQR, 11-23]). Those complicated with CVC-related infection required also a higher median number of TPE procedures to achieve clinical response than the whole cohort (16 [IQR, 10.5-19] vs 8 [IQR, 7-14]). No other major differences were observed among episodes with and without CVC-related complications.
Conclusions: TPE was well tolerated in our cohort of acute iTTP patients, with CVC-related minor bleeds and allergic reactions being the most common complications (48.5%). The occurrence of CVC-related major complications, as VT or infections, may lead to a longer hospitalization, also independently of patients' characteristics and disease severity.

246. GENETIC AND IMMUNOINFLAMMATORY SIGNATURES OF ISCHEMIC STROKE AND ITS PROGNOSIS: RELATIONSHIP BETWEEN SINGLE NUCLEOTIDE POLYMORPHISMS (SNPS) OF PROINFLAMMATORY AND PROTHROMBOTIC GENES FREQUENCY AND SERUM LEVELS OF INFLAMMATORY CYTOKINES IN THE ACUTE PHASE OF ISCHEMIC STROKE AND TOAST SUBTYPE, THE METABOLIC PROFILE AND STROKE RECURRENCE

Daidone, M.[1], Pacinella, G.[1], Ciaccio, A.M.[1], Casuccio, A.[2], Puleo, M.G.[1], Restivo, V.[2], Del Cuore, A.[1], Di Raimondo, D.[1], Di Chiara, T.[1], Tuttolomondo, A[1]
[1]U.O.C di Medicina Interna con Stroke Care, Dipartimento di Promozione della Salute, Materno-Infantile, di Medicina Interna e Specialistica di Eccellenza "G. D'Alessandro"(PROMISE), University of Palermo, Italy; [2]Dipartimento di Promozione della Salute, Materno-Infantile, di Medicina Interna e Specialistica di Eccellenza "G. D'Alessandro"(PROMISE), University of Palermo, Italy

Background: Genetics contribute significantly to stroke risk through several mechanisms. Some genetic polymorphisms have been associated with the risk of stroke, although the individual contribution of such polymorphisms is considered modest. Furthermore, since most ischemic strokes are due to thrombotic or thromboembolic occlusion, a role of polymorphisms in the genes that code for factors involved in the coagulation cascade, and in particular, in maintaining the balance between fibrinolysis and thrombosis.
Aims: The purpose of this prospective observational study is to evaluate:1. The frequency of some single nucleotide polymorphisms (SNPs) of genes encoding pro-inflammatory cytokines and coagulation factors in stroke patients.2. The relationship between each identified SNP and TOAST stroke subtype.3. The relationship between each SNP frequency and prognosis, defined through the degree and type of neurological deficit in the acute phase evaluated by means the NIHSS, the degree of disability at discharge assessed by means of the modified Rankin score (mRS), the recurrence of major vascular events (new ischemic stroke, new acute myocardial infarction and or death for vascular causes) 4. The relationship between the serum levels of the cytokines analyzed and the diagnostic subtype of ischemic stroke;5. The relationship between the serum levels of the analyzed cytokines and stroke prognosis in terms of event recurrence, AMI recurrence and mortality.
Material and Methods: All patients aged> 18 years admitted for acute ischemic stroke in the period between 2011 and 2021 were prospectively enrolled at the Internal Medicine and Stroke Care Ward of University Hospital of Palermo, The Stroke Care Unit and Neurovascular Therapies of the San Camillo Hospital in Rome, the Neurology ward of the Civic Hospital of Palermo and the Emergency Department of the Giglio Hospital in Cefalù (PA). Blood samples have been collected within 72 hours of the onset of signs / symptoms referable to ischemic stroke. Each patient was subjected to genetic analysis for the evaluation of various genetic polymorphisms and to the analysis of the levels of cytokines circulating in the different collection times (T0, T1 and T2). The biochemical and genetic analyzes were conducted at the genetic and biomolecular analysis laboratory of the center for genetic vascular diseases of the Gemelli Polyclinic in Rome and at the molecular analysis laboratory of the UOSD of Immunology and Clinical Allergology of the University of Bari. IL1-β, TNF-α, IL-6 and IL-10 and were measured using a "sandwich ELISA-kit". Three different biallelic polymorphisms, rs1800896 (-1087G / A), rs1800871 (- 824C / T) and rs1800872 (-597C / A) of the IL-10 gene were identified. The IL-1RN exon 2 polymorphism, characterized by a variable number of 86 bp repeats was analyzed. The SNPs of PTGS2, MMP2 and MMP9 were selected and retrieved from the dbSNP database of the National Center for Biotechnology Information.
Results: 624 subjects were enrolled in this cross-sectional study, including 429 patients with ischemic stroke and 195 controls. Among patients with ischemic stroke, 47% LAAS, 27% LAC and 26% CEI. Regarding the immunoinflammatory variables, patients with CEI showed significantly higher levels of glycemia and of all the cytokines analyzed, therefore IL-10, TNF-alpha and IL-16 compared to patients with both LAC and LAAS. Logistic regression analysis revealed that elevated values of IL-10, TNF-alpha, IL-6 and IL-1beta are predictive of LAAS and CEI subtypes respectively. Furthermore, IL-10 levels were lower in patients who developed stroke during follow-up, whereas TNF-alpha, IL-1 and IL-6 levels significantly higher in patient with recurrent stroke at follow-up. Similarly, the levels of TNF-alpha and IL-6 IL-10, TNF-alfa, IL-1 beta) and IL-6 were increased in patients who developed a new vascular event or who experienced death during follow-up. From the analysis of the distribution of the genotypic frequencies of the polymorphisms analyzed, a statistically significant difference emerged between the cases and the controls for all the polymor-

phisms in the genes that code for pro-inflammatory cytokines, for TPA and PAI-1. Of the three polymorphisms in the gene encoding PTSG2, the haplotypes rs6275 and rs20417 showed a different distribution between cases and controls.
Discussion: In light of the close association between ischemic stroke and immune-inflammatory variables, we wondered if there was a relationship between the distribution of some SNP of the genes involved in inflammation and thrombosis / fibrinolysis and the risk of ischemic stroke.
These results are in agreement with other authors who had previously demonstrated an association between some pro-inflammatory and prothrombotic polymorphisms with the risk of ischemic stroke. However, it must be considered that the contribution of individual SNPs to the risk of stroke is small and therefore should be evaluated in relation to other factors, such as diabetes, hypertension, dyslipidemia, etc.

247. LIVER TRANSPLANTATION IN A PATIENT WITH HAEMOPHILIA A

Rufolo P., Cimino E., Conca P., Strano F., Pontoriero M., Donnarumma S., Palermo V., Schiano N.
Department of Clinical Medicine and Surgery, University of Naples, Federico II.

Background: Hepatocellular carcinoma (HCC) may represent an important complication in haemophiliacs with long-standing hepatitis C virus infection. In most cases, liver transplantation is the only treatment option available for patients with end-stage liver disease (decompensated liver cirrhosis and/or HCC).
Case report: a 62-year-old man with severe haemophilia A (Factor VIII = 0.8 %), with no history of anamnestic specific inhibitor, and in secondary prophylaxis with plasma-derived factor VIII (FVIII) concentrate and then with recombinant FVIII. The genetic investigation showed the mutation in hemizygosity c.1336 C>T, p.R427X, classified as pathogenic. Since childhood he had presented spontaneous and post-traumatic haemorrhages, affecting the osteo-articular system (knees, ankles, elbows, even bilaterally). He underwent left total knee and total hip replacement. For the past use of plasma-derived products not subjected to viral inactivation techniques, the patient had contracted HCV infection (genotype 3), relapsing after 3 cycles of standard antiviral therapy combined with pegylated a/b IFN alpha 2 a/b and ribavirin (last cycle in 2011) and subsequent long-term response with direct-acting antiviral drugs (sofosbuvir and ribavirin for 24 weeks - 2015). The comorbidities included previous duodenal ulcer and prostatic hypertrophy. During the follow-up for the HCV infection, a 16 mm unifocal nodule was found (2010) on ultrasound (US) valuation, in the fifth hepatic segment, close to the posterior wall of the gallbladder. The patient then underwent periodical clinical and instrumental monitoring with an annual US with contrast medium (CEUS), with evidence of progressive size increase (28 x 20 mm) and a diagnosis of HCC (G3 with G4 areas according to Edmondson), at MR in 2015, that was surgically enucleated in 2016. For MR recurrence evidence of unifocal HCC at the VIII-IV segment transition (2019), the patient underwent liver transplantation in 2019, with adequate peri- and post-operative haemostatic prophylaxis and without significant bleeding complications. Following liver transplantation, normal coagulation FVIII values were found (about 74%), which remained stable 3 years after the operation, with a significant improvement in the patient's quality of life.
Conclusions: liver transplantation in the reported case allowed the oncological radicality of the HCC and the contextual normalization of the FVIII levels, to allow the withdrawal of the secondary prophylaxis. The liver is the main site of synthesis of coagulation factors. A long-term follow-up for surveillance of any complications related to the graft is of course needed.

248. A SYSTEMATIC-REVIEW AND META-ANALYSIS OF INHERITED THROMBOPHILIA IN CEREBROVASCULAR, CORONARY, AND PERIPHERAL ARTERY DISEASE

Valeriani E.[1], Pastori D.[2], Astorri G.[2], Porfidia A.[3], Menichelli D.[4], Pignatelli P.[2]
[1]Department of General Surgery and Surgical Specialty, Sapienza University of Rome; Infectious Disease Department, Umberto I Hospital, Rome; [2]Department of Clinical Internal, Anesthesiological and Cardiovascular Sciences, Sapienza University of Rome; [3]Department of Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome; [4]Department of General Surgery and Surgical Specialty, Sapienza University of Rome

Background and aims: The role of inherited thrombophilia in arterial disease is uncertain. In this systematic review and meta-analysis we provided comprehensive values of prevalence and odds of having prespecified inherited thrombophilia in patients with cerebrovascular disease (CVD), coronary heart disease (CHD), and peripheral artery disease (PAD). Methods: This study-level systematic review and meta-analysis was performed following the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guidelines (PROSPERO registration ID, CRD42022308466). MEDLINE and EMBASE were searched from inception up to February 2022 for studies reporting data on prespecified inherited thrombophilia (Factor V Leiden -G1691A-, Factor II -G20210A-, MTHFR C677T, MTHFR A1298C, PAI-1 4G/5G mutations) in CVD (i.e., acute and recurrent ischemic stroke or transient ischemic attack), CHD (i.e., acute and recurrent myocardial infarction or stable coronary artery disease), and PAD. The risk of bias was evaluated using the Cochrane tool for randomized controlled trials and the Newcastle-Ottawa scale for observational studies. Pooled prevalence (PPs) and odds ratios (ORs) with 95% confidence intervals (95%CI) were calculated in a random-effects model. Subgroup analyses were performed in patients with different age (i.e., mean age of 18 to 55 years and > 55 years), belonging region (i.e., African, American, Asiatic, European, Oceanic regions), and considering those studies in which cases and controls shared a similar proportion of patients with at least one cardiovascular risk factor (i.e. arterial hypertension, diabetes mellitus, dyslipidemia, obesity, and smoking history).Results: A total 377 studies with 98,146 patients (32,791 with CVD, 62,266 with CHD, and 3,129 with PAD) and 108,569 controls were included in the analysis. Overall, 37,249 patients had G1691A, 32,254 G20210A, 43,211 MTHFR C677T, 8,889 MTHFR A1298C, and 19,861 PAI-1 4G/5G mutations. In CVD patients, PPs was 6.5% for G1691A, 3.9% for G20210A, 56.4% for MTHFR C677T, 51.9% for MTHFR A1298C and 77.6% for PAI-1. In CHD, corresponding PPs were 7.2%, 3.8%, 52.3%, 53.9%, and 76.4%. In PAD, the PPs were 6.9%, 4.7%, 55.1%, 52.1%, and 75.0%, respectively. Relevant ORs for CVD were 2.77 (95% CI 1.83-4.18) for homozygous G1691A, and 3.96 (95% CI, 2.05-7.64) for homozygous G20210A. Relevant ORs for CHD were 1.79 (95%CI, 1.09-2.93) for homozygous G1691A and 1.53 (95% CI, 1.26-1.86) for heterozygous G20210A and 1.54 (95% CI, 0.79-2.99) for homozygous G20210A. The OR for PAI-1 4G/4G in PAD was 5.44 (95% CI, 1.80-16.43). Higher PP and ORs were identified specific subgroup of patients according to age and region. Conclusions: Patients with arterial disease appeared to have an increased prevalence and odds of having some inherited thrombophilia. Some thrombophilia testing may be considered in specific subgroups of patients with arterial disease.

Table. Odds ratios for inherited thrombophilia in patients with cerebrovascular, coronary heart, and peripheral artery disease.

Dominant Model		G1691A	G20210A	MTHFR C677T	MTHFR A1298C	PAI-1 4G/5G
Cerebrovascular disease	Odds ratio, 95% CI	1.50 (1.30 to 1.73)	1.60 (1.31 to 1.95)	2.04 (1.84 to 2.27)	1.21 (0.83 to 1.77)	1.03 (0.86 to 1.24)
Coronary artery disease	Odds ratio, 95% CI	1.39 (1.19 to 1.63)	2.31 (1.34 to 3.99)	1.07 (1.00 to 1.15)	0.95 (0.85 to 1.08)	1.17 (1.05 to 1.31)
Peripheral artery disease	Odds ratio, 95% CI	1.22 (0.65 to 2.29)	2.00 (0.69 to 5.80)	1.15 (0.89 to 1.48)	1.07 (0.18 to 6.53)	0.21 (0.07 to 0.65)

249. CAVERNOMA DEVELOPMENT IN SPLANCHNIC VEIN THROMBOSIS: CLUES OF PATHOGENIC MECHANISM

Rosati G., Camerlo S.
Dept. Clinical and Biological Sciences, University of Turin

Background and aims: Cavernous transformation of the portal vein is a sequela of portal vein thrombosis and involves the replacement of the vessel with numerous tortuous venous channels. The pathophysiology is still unknown, but it appears to be a consequence of delayed recanalization and is associated with different amounts of time to be completed. Portal cavernomas are generally associated with clinical manifestations, due to overt portal hypertension. Deciphering the mechanisms of cavernoma formation is advisable to better stratify SVT patients and to adopt strategies to prevent cavernomas formation and optimize the treatment. This study will describe cavernomas development in an institutional cohort of SVT according to clinical and laboratory evaluations, and attempt to correlate cavernoma formation to specific biological determinants.
Methods: We assessed a cohort of 36 consecutive SVT-patients admitted to our Internal Medicine Division. All patients were assessed to determine the SVT origin, classified as secondary to cirrhosis, myeloproliferative neoplasm (MPN), cancer, infection, autoimmunity, surgery, and antiphospholipid syndrome (APS). For all patients, occlusion type (total vs partial) and thrombosis site (portal, mesenteric, or splenic vein) were recorded. Besides common blood tests (CBC, liver and renal function, electrolytes levels, iron

state, coagulation tests, lipidic state, and serum immunoglobulin levels), thrombophilia screening was included when available. Furthermore, anticoagulant drugs and their duration were reported, as well as the continuation of prophylactic dosage therapy. The presence of varices, their site, and the spleen dimension were included too.
Results: Our cohort includes 36 SVT patients, 18 males (mean age 59 years, SD 11 years) and 18 females (mean age 55.6 years, SD 17.7 years). Of the thromboses investigated, 27 involved the portal vein, 16 the mesenteric vein, and 14 the splenic vein. 9 out of 38 SVTs were associated with MPN, 7 to cancer, 7 to infection, 5 to liver cirrhosis, 4 to surgery, 3 to autoimmunity, 3 to hemoglobinopathy or dyserythropoiesis, 1 to APS, and 6 were idiopathic. Among the latter, 5 were associated with clonal hematopoiesis of indeterminate potential (CHIP), as we recently published. Overall, 8 patients (22.2%) developed cavernomas. 3 were associated with MPN, 1 to cirrhosis, 1 to colangitis, 1 to hemoglobinopathy/dyserythropoiesis, and 2 were idiopathic (both associated with CHIP). Interestingly, both patients with CHIP and cavernomas were positive for mutations in the gene DNMT3A. Notably, the median time from the thrombosis diagnosis to the cavernoma diagnosis was 4.33 months (range, 0–7.2). 6 months after SVT diagnosis, cavernoma-free survival was estimated at 24% (CI95% 4–100%). Patients with cavernoma were associated with longer treatment time (mean difference 38.6 months, CI95% 24–45.4 months), varices occurrence (OR 5.83, CI95% 1.07–31.8), and higher serum iron levels (mean difference 38 mcg/dL, CI95% 2–70 mcg/dL).
Conclusion: Due to the phenomenon's rarity, our data require further evaluations in an extended patient cohort, but provide clues on potentially relevant determinants of cavernoma development. CHIP and MPN patients with SVT appear to have higher risk of cavernoma formation, suggesting that the portal vein thrombus could be associated with a pro-angiogenic feature in the splanchnic territory. Mutation of the DNMT3A gene should be assessed in all patients with idiopathic SVT, as potentially at higher risk of developing cavernomas. Accordingly, we observed a rapid cavernoma development in our cohort of patients, even if anticoagulation was promptly administered. Further biological analyses to provide a pathological explanation of these correlations are ongoing.

250. HEREDITARY THROMBOPHILIA: A SYMBOLIC CASE

Di Tomasi G., Maiuzzo R., Scebba S., Risicato A., Platania I., Curto I., Incognito C., Signorelli S. S.
Department of Clinical & Experimental Medicine. University of Catania. Internal Medicine Unit University Hospital G.Rodolico, Catania , Italy

Background: Hereditary thrombophilia includes various genetic risk factors which predispose individuals to developing vein thromboembolisms (TEV). Mutation of the Leiden factor V (LFV) is the most frequent congenital condition. The examined clinical case represents an example of hereditary thrombophilia, presenting LFV mutation, which remarks the constant evolution of clinical evidences. It consists in a F5 gene mutation affecting protein factor V in the coagulation cascade. The mutation taken in exam affects the factor V anti-coagulation Activity related to activated protein C (aPC). LFV is a prevalently autosomal dominant condition (99% of individuals are heterozygous for this variant). Only the 1% of individuale are homozygous or pseudo-homozygous showing the highest thrombotic risk.
Clinical case: A patient, a 60 year-old Caucasian male, was admitted for worsening shortness of breath. Case history: hereditary thrombophilia (homozygous mutation of Leiden factor V); two episodes of pulmonary thromboembolism (TEP) treated with thrombolysis; previous DVT; anterior wall STEMI (2 weeks prior) treated with primary PCI throught two DES implant in the left anterior descending coronary artery.
The patient underwent a double anti-platelet therapy with Clopidogrel and Ticlopidine (ASA not prescribed because of allergy to the active principle). The patient had been taking Warfarin irregularly and without continuous monitoring by the INR. On admission to the ward, the patient was alert and well-oriented. He denied angina, but descrived dispnea upon light effort.
The patient had stable blood dynamics. Diagnostic route: arterial gas analysis revealing hypoxia and hypocapnia; the ECG revealed sinusoidal rhythm and average frequency of 100bpm with left-oriented cardiac axis. Block of the right branch, negative T-waves in D2, D3, AVF and from V3 to V5; blood test with D-dimer 605 microg/L. The echocardiography highlited an overall depressed contractile function and a slightly dilated right ventricle coupled to normal kinetic. Suspecting TEP, clinical probability was evaluated using both simplified Wells score (3 points for previous DVT and PE, tachycardia and bed-rest in the prior 4 weeks) and simplified Geneva score (3 points for cardiac frequency >95 bpm and previous DVT/PE). The analysis showed a probable pulmonary thromboembolism. The patient underwent to thoracic arterial computerized tomography which showed small defects of intraluminal refilling by the pulmonary artery branches of the lower lobes close to the segmentary branching out of the bilateral basal pyramid, caused by thromboembolic phenomena and defective thrombotic intraluminal refilling by the lower vena cava. Considering the acquired data, pharmacological therapy was re-modelled suspending the Warfarin and administering an anti-coagulant such as low molecular weighted heparin (dose: 100UI/kg 2 times a day). After 5 days, the patient was released with the following home therapy: Edoxaban + Clopidogrel + Ticlopidine. After 30 days monitoring activity, the pulmonary thromboembolism remained the same whereas the cava thrombosis was reduced by extension and dimension. During follow-up, patient continued with the prescribed therapy until release, without further complications or relapse.
The described clinical case allowed the reporter following considerations:
References

251. ACQUIRED HEMOPHILIA A IN A CASE OF PURPLE URINE BAG SYNDROME.

Gammaldi V.[1], Mocerino L.[1], Fierarossa C.[1], Tartaglia B.[1], Petrosino C.P.[1], Boccia R.[1], Zarrella A. F.[1], Tramontano A.[2], Rainone C.[3], Modestino M.R.[3], Guida A.[4], Madonna P.[5]
[1]Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy; [2]Department of Clinical Pathology, Laboratory Diagnostics and Virology, Federico II University, Naples, Italy; [3]Department of Translational Medical Sciences, Federico II University, Naples, Italy; [4]Congenital Hemorrhagic and Thrombotic Diseases Center, AOU San Giovanni di Dio Ruggi d'Aragona, Salerno, Italy; [5]Internal Medicine Unit, Ospedale del Mare, ASL Napoli 1 Centro, Naples, Italy

A 90-years-old woman was admitted to the emergency department due to marked asthenia caused by severe anemia. Vital signs were normal and she had no fever. Her previous medical history included arterial hypertension with hypertensive heart disease, renal failure and previous right femur fracture, no personal history of hemorrhage or thrombosis were reported. At the admission, laboratory tests showed: Hb 5.8 g/dl, MCV 86 fl, MCH 27 pg, GB 10.42 10 3 /mm3 , PLT 336,000 10 3 /mm3 , creatinine 3.8 mg/dl, C-reactive protein 3.86 mg/dl, d-dimer 2178 microg/L, fibrinogen 502 mg/dl, prothrombin activity 107%, INR 0.96, aPTT 45 sec with ratio 1.49. At physical examination, the patient appeared drowsy, arousable to algic and verbal stimuli, with dehydrated skin and mucous membranes, with sarcopenia mainly in the lower extremities. No active sources of bleeding were objectified, except for the presence of ecchimosis at the venipuncture siets. At the bladder catheterization purple urine outputted, for this reason an urine sample for urgent culture was performed, in the suspicion of urinary tract infection (UTI), broad-spectrum antibiotic therapy with piperacilline/tazobactam was started corrected for renal function, and two units of compatible packed red blood cells were transfused. At routine laboratory tests, a steady prolongation of the partial thromboplastin time (aPTT: 50 sec, Ratio 1.67) was observed, in the absence of heparin therapy. Therefore, in the hypothesis of acquired coagulopathy, the following blood tests were prescribed: APTT Plasma mixing test, assay of intrinsic coagulation pathway factors (FVIII, FIX, FXI, FXII), lupus anticoagulant (LAC), Von Willebrand factor (vWF) antigen (vWF:Ag) and ristocetin cofactor (vWF:RCo). The APTT mixing test (after incubation for two hours at 37°C of the patient's plasma with normal plasma) APTT remained prolonged (2-hrs mixing test ratio 1.47), suggesting the presence of a direct inhibitor against FVIII. The diagnosis of acquired A haemophilia (AHA) was confirmed by low concentration of FVIII 30% with the presence of factor VIII antibodies at a titer of 4 U.B./ml (Bethesda Units). The other intrinsic pathway factors, vWF and vWF:Rco were found to be normal. Due to lack of severe bleeding symptoms and the high thromboembolic risk (sepsis,immobilization,older age) we refrained to prescribe antihaemorrhagic therapy,while immunosuppressive therapy with steroids (Prednisone 1 mg/kg) was started. 48h after admission the urine culture showed the presence of Linezolid-sensitive Enterococcus Faecalis, so antibiotic therapy was modified according to the antibiogram. In order to rule out a neoplastic disease, at the day 3 the patient underwent a total body-CT scan that resulted negative for neoplasm except for a bladder mass of undetermined origin. She also tested negative for autoimmune disease. At day-7 of hospitalization, the patient presented severe haematuria, therefor an antihemorrhagic therapy with recombinant activated factor VII (FVIIa) at a dosage of 90 mcg/kg was prescribed successfully, resulting in rapid cessation of bleeding. Subsequent cystoscopic examination was negative for exophytic endoluminal neofor-

mations, and showed the presence of an ulcerated lesion due to catheter decubitus at the posterior wall of the bladder and a voluminous floating clot. Ruled out the neoplastic and autoimmune causes, according to the patient's clinical and laboratoristic picture, the diagnosis of acquired hemophilia A secondary to Enterococcus faecalis infection was made. Acquired hemophilia A (AHA) is a rare hemorrhagic syndrome (1.5 in 1x10 6 patients/year) with autoimmune pathogenesis, due to the development of autoantibodies directed against various epitopes of the factor VIII (FVIII) molecule that neutralize its coagulant activity (inhibitors). In 50% of cases it is idiopathic, in secondary forms the most frequent cause, especially in the elderly, are neoplasms, while infections account for less than 10% of cases. In this case, the patient had a UTI caused by an Enterococcus Faecalis, a Gram-negative agent, which had also caused the peculiar purple coloration of the urine, which is referred to in literature as Purple Urine Bag Syndrome (PUBS). PUBS is a rare syndrome caused by increased levels of indigo and indirubin, two pigments related to the metabolism of the amino acid tryptophan, and is most common in female and older persons with dementia, chronic renal failure, dehydration, urinary catheter wearers, and long-time bedridden.

252. INCIDENCE AND RISK FACTORS OF MAJOR ADVERSE CARDIOVASCULAR EVENTS IN PATIENTS WITH IMMUNE-MEDIATED THROMBOTIC THROMBOCYTOPENIC PURPURA DURING REMISSION

Boggio F.[1], Agosti P.[1], De Leo P.[2], Truma A.[1], Giannotta J.A.[2], Artoni A.[2], Ferrari B.[2], Mancini I.[1], Peyvandi F.[1]
[1]Università degli Studi di Milano, Department of Pathophysiology and Transplantation; [2]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Milan, Italy

Background: Immune-mediated thrombotic thrombocytopenic purpura (iTTP) is an acquired thrombotic microangiopathy caused by deficiency of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13), an enzyme that cleaves von Willebrand factor. An increased risk of major adverse cardiovascular events (MACE) during remission has been reported; however, data on MACE prevalence and related risk factors are scarce.
Aims: To evaluate the rate of MACE during remission in Italian iTTP survivors and related risk factors.
Methods: In this cohort study, we enrolled patients from the Milan TTP Registry surviving the first acute episode of iTTP and followed-up at the Angelo Bianchi Bonomi Hemophilia and Thrombosis Center for at least six months. Patients with history of ischemic stroke (IS) or acute coronary syndrome (ACS) and lost to follow-up before 2012 were excluded. MACE was defined as occurrence of ACS or IS. ACS was defined as the occurrence of ST-elevation myocardial infarction (STEMI), non-STEMI or unstable angina. IS was defined based on the evidence of new ischemic lesions on neuroimaging.
Results: We included 238 patients, of whom 8 (3.4%) had at least one MACE, with a total of 11 MACE, mostly IS (3 ACS, 7 symptomatic IS and 1 silent IS). We found the following age-stratified MACE rates: 5/169 (3%) at ages<50 years, 2/63 (3.2 %) in patients aged 50-69 years, 1/7 (14.3%) in patients older than 70 years. These rates were consistent with a population of moderate-high cardiovascular risk. Except for a patient having atherosclerotic cardiovascular disease, the other 7 were apparently healthy people, according to European Society of cardiology (ESC) definition. Two patients had 2 and 3 MACE, respectively. A woman presented an IS 11 months after the fourth TTP episode, an ACS and an IS at 22 and 25 months after the seventh TTP episode, respectively. The other patient had an IS and an ACS at 228 and 250 months after the first TTP episode, respectively.
Patients presenting with MACE were slightly older than those without, with a higher proportion of males. Regular ADAMTS13 testing during remission was unavailable before MACE, although six patients (75%) showed persistently reduced ADAMTS13 activity later in life (Table 1). Compared with an Italian population study with a similar age and sex distribution, our cohort showed higher IS rates despite a lower prevalence of atherogenic risk factors (Table 2).
Conclusions: In our cohort of Italian iTTP patients, we found a MACE rate of 3.4% during remission. ACS and IS rates were similar and 3-fold higher than in an Italian population, respectively, supporting a possible major role of microvessels dysfunction over atherosclerosis progression in iTTP.

Table 1.

variables	iTTP patients with MACE during clinical remission N=8	iTTP patients without MACE during clinical remission N=220
Age at the first TTP event, years, median (IQR)	44 (31-58)	39 (29-51)
<50 years, n (%)	5 (62.5)	164 (71.3)
50-69 years, n (%)	2 (25)	61 (26.5)
≥70 years, n (%)	1 (12.5)	6 (2.6)
Female sex, n (%)	4 (50)	175 (76.1)
White ethnicity, n (%)	8 (100)	224 (97.4)
Time of observation, months, median (IQR) 1-2	95 (66-141)	82 (45-138)
Number of iTTP episodes, median (IQR)3	1 (1-2)	1 (1-3)
Age at MACE, median (IQR) 2	56 (44-66)	NA
Neurological/cardiovascular signs/symptoms at the onset of the TTP episode before MACE, n (%)	3 (50)4	NA
Time to MACE from the first iTTP episode, months, median (IQR) 2	95 (66-141)	NA
Normal ADAMTS13 activity level at MACE, n (%)	4 (100)5	NA
Evidence of persistently reduced ADAMTS13 activity during remission after MACE	6 (75)	NA

1 from enrolment date (iTTP onset of the first episode) to the date of MACE, or the last follow-up or the study end date (December, 31, 2022), whichever occurred first; 2 for patients with two or more MACE, the first MACE has been considered; 3 in life up to the date of MACE, or the last follow-up or the study end date; 4 available in 6/8 patients; 5 available in 4/8 patients; NA: not available.

Table 2.

	Our cohort n=238	Brodsky et al cohort* n= 181	Patients with MACE in Santoro et al** n= 132,598
Population	iTTP survivors	iTTP survivors	Italian general population
MACE rate 1, %	3.4	28.6	NA
IS rate 1, %	2.9	22.1	0.8
ACS rate 1, %	1.3	9	1.9
	Patients with MACE in our cohort n=8	Patients with MACE in Brodsky et al* n=43	Patients with MACE in Santoro et al** n=6545
white ethnicity, %	100	32.6	95
female sex, %	50	74.4	43
age at enrolment, years, median (IQR)	44 (31-58)	45 (34-53)	range: 18-69
overweight/obesity, % 3-4	33.3	55.85	61.1
current/former smoker, % 3-4	66.7	NA	56.9
type 2 diabetes, % 3,5	0	53.5	18.6
hypertension, % 3,6	28.6	74.4	55.9
hyperlipidemia, % 3,6	28.6	51.2	44.2
chronic kidney disease, % 3	0	41.9	NA
ASCVD, % 3	12.5	NA	NA
concomitant autoimmune disease, % 3	12.5	14	NA

*Brodsky MA et al. Am J Hematol. 2021; ** Santoro V et al. Ann Ist Super Sanita. 2022
1 For patients with two or more MACE, the first one was considered; 2 for iTTP patients (our cohort and Brodsky et al), age at the first TTP episode onset was considered; 3 at the closest visit before MACE (before the first MACE, for patients with two or more MACE); 4 available in 6/8 patients; 5 referred to obesity; 6 available in 7/8 patients; NA: not available

253. EFFICACY OF DOAC IN SPLANCHNIC VEIN THROMBOSIS: A POOLED ANALYSIS OF LITERATURE STUDIES

Strano F. , Calcaterra I., Tufano A., Rufolo P., Donnarumma S., Palermo V., De Ruberto F., Cimino E., Iannuzzo G., Di Minno M.
Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy

Background and Aims: Limited and contrasting evidence are available on management of splanchnic vein thrombosis (SVT). We performed a meta-analysis to evaluate safety and efficacy of Direct Oral Anticoagulants (DOACs) for the treatment of SVT patients.
Methods: Studies were systematically searched in the PubMed, Web of Science and Scopus databases according to PRISMA guidelines. Results were reported as weighted mean prevalence (WMP) with 95% Confidence Intervals (95%CI) and differences between different treatment groups were presented as Odds Ratios (OR) with 95%CI.
Results: We included a total of 20 studies on 741 SVT patients receiving DOACs. We found any recanalization in 69.1% (95% CI 53.7%–81.2% I 2 84.6%, P<0.001), full recanalization in 52,7% (95% CI 37,2%–67.6% I 2 87.4%, P<0.001). Recurrent VTE occurred in 3.0% (95%CI: 1.5%-5.7% I 2 0%, P = 0.910) and death in 3.1% (95%CI: 1.4%-6.6% I 2 29.8%, P = 0.180) of patients. Major bleeding was reported by 6.5% (95% CI 4.4%–9.3% I 2 24,9%, p = 0.151) of patients. When compared to traditional anticoagulant treatment, DOACs showed a higher prevalence of any recanalization (OR: 4.82, 95%CI: 2.06-11.29) and full recanalization (OR: 2.86, 95%CI: 1.51-5.43),

lower mortality (OR: 0.37, 95%CI: 0.14-0.96) and lower prevalence of major bleeding (OR: 0.41, 95%CI: 0.20-0.88). Conclusions: The present study provides evidence on the efficacy and safety of DOACs in SVT patients. Use of DOACS in patients with SVT is associated with significant reduction of mortality, higher probability of recanalization, and lower risk of major bleeding as compared to standard treatments.

254. A CASE OF MAY-THURNER SYNDROME

Scebba S. , Sciacca O.R., Sanfilippo G., Russo J., Frazzetto E., Privitera G., Campagna C., Incognito C., Di Tomasi G., Manzitto L., Signorelli S.S.
Department of Clinical & Experimental Medicine. University of Catania. Internal Medicine Unit University Hospital G.Rodolico, Catania , Italy

Background: The May-Thurner syndrome is a pathological and anatomical variable in which left iliac vein are compressed between the lumbar vertebra and the overlyng right common iliac artery, leading to iliac venous outflow obstruction which and subsequent deep vein thrombosis (DVT).
Clinical case: A 37 year-old Caucasian man presented at the first aid (FD) of the Hospital G. Rodolico for sudden onset of edema and pain in his left leg. The patient showed no signs of pathology worth noting. In FD they carried out an arterial gas analysis in ambient air (normoxyemic, normocapnic), ECG (sinus rhythm, 67 bpm, norm-oriented axis, no alterations in re-polarization). The patient underwent an eco-color-doppler exam of the lower limbs which showed: "DVT of the left common femoral vein (CUS positive)". The patient began anti-coagulant therapy with subcutaneous pentasaccharide (7.5mg) and admitted to our department.
Upon entering the ward, the patient was vigilant, oriented, collaborative, free-breathing and hemodynamically stable. He admitted habitual consumption of cocaine and alcohol, being a heavy smoker, and having lost about 10 kg in the last year with bowel function alternating between constipation and diarrhea. An examination of his left limb showed swelling, warm to the touch and tender to palpation with signs of Bauer and Homans.
During hospitalization, the causes of this thrombosis were sought considering patient's age and medical history. We excluded MICI, autoimmune pathologies and genetic or acquired thrombophilia. Given the medical history of drug-taking, we assumed there might be trauma phlebitis, but no lesions were found.
Supposing there might be anatomical alterations that may have caused vein stasis or occult neoplasm the patient underwent thoracic and abdominal computerized tomography that showed: […] vein thrombosis induced by a reduction in the space between vertebral column and the right common iliac artery with consequent compression of the left iliac vein. Stenosis at the base of the celiac trunk due to the arcuate ligament associated with modest post stenotic vascular dilation". Based on these findings, we were able to diagnose 'May-Thurner Syndrome' (MTS) with the concomitant 'Dunbar Syndrome'. We have requested a interventional radiology advice to place stents in the compressed vein. The patient was discharged with an oral anticoagulant therapy (Edoxaban 60mg.). The patient was re-evaluated by eco-colour-doppler exam, which showed almost a total resolution of the thrombosis. The patient underwent angioplasty and stent placement at the level of the common femoral vein and the left external iliac vein during a phlebografy. The patient was discharged again with indications for anti-platelet (Asa 100mg) and antithrombotic therapy (Edoxaban 60mg).

255. THE ROMA ETHNIC POPULATION'S UNFAVORABLE GENETIC LOAD: CONGENITAL ATRESIA OF THE INFERIOR VENA CAVA AND ANTITHROMBIN III ABNORMALITIES.

De Fortuna U., Abate M., Cappuccia F., Giardino F. , Arcopinto M., Cittadini A.
Dipartimento di Scienze Mediche Traslazioni

We report the clinical case of a 35-year-old Roma patient with a history of recurrent deep vein thrombosis (DVT) of the lower limbs at the age of 25 and 35 with no evident causative factors. At the hospital admission, our patient showed bilateral leg ulcers in the presence of a history of recurrent and recent DVT, which was verified by color Doppler ultrasound describing internal saphenous vein thrombosis and valvular incontinence from previous DVT. On physical examination, tortuous and swollen veins could also be observed at the abdominal level, mainly in the left lower quadrant. Cardiac ultrasound, showed the presence of a fibrous labrum of the vena cava at the level of the outlet into the atrium **(Fig. 1)**, partially obstructing the venous tract. To better investigate the finding, we performed a contrast-enhanced abdominal tomography, and we were able to detect the atresia of the inferior vena cava (AIVC) and iliac veins with evidence of superficial venous ectasias draining the lower limbs and the abdominal wall with secondary ectasia of the hemiazygos and azygos systems **(Fig. 2)**. Blood tests showed an antithrombin III deficiency (34% antithrombin activity), a condition associated with a greater risk of thrombotic events and an inadequate therapeutic response to Low Molecular Weight Heparin (LMWH). At the admission, the patient was on 6000 UI bid of Low Molecular Weight Heparin (LMWH); antithrombin III supplementation was added to the therapy (initial dose of 2000 UI/die for three days, then dose of 2000 UI/die three times a week), but despite this supplementation (AT III activity from 34% to 89%) and an increase in heparin dosage there was no adequate response to the drug monitored through anti-Xa test (anti-Xa: 0,27 IU/ml). At the discharge, vitamin K antagonist has been prescribed to the patient for the long term, with indication to close ultrasound follow up. Congenital absence or agenesis of the inferior vena cava (AIVC) is a rare vascular anomaly with an estimated incidence in the general population ranging from 0.0005 to 1%; however this condition represents about 5% of unprovoked DVT in patients < 30 years of age. Few other cases of AIVC-related extensive DVT are reported. Another case of congenital absence of the inferior cava (AIVC) associated with a history of superficial and deep vein thrombosis has been observed in a patient with intrahepatic AIVC. Among the defects of the cava, the suprarenal region is the most common anomaly. Another point taken into consideration is that often the AIVC can remain asymptomatic and undetected if there is an adequate compensation of the azygous and hemiazygous system. However, the venous drainage of the lower limbs is often not sufficient, favoring venous stasis and thrombosis and then DVT. This condition can be promoted by additional risk factors such as coagulation abnormality: as observed in another case report,2 a suprarenal AIVC was associated with antithrombin III deficiency as in our case with a subsequent extensive thrombosis of the right renal vein, the infrarenal IVC and iliac veins bilaterally.
It is clear how in this patient AIVC and ATIII deficiency act as compound risk factors, since ATIII is a coagulation modulator and represents the most important physiological inhibitor of thrombin (IIa) and its deficiency favors thrombotic phenomena, especially in patients with AIVC in which the venous circulation is compromised and venous stasis is greater.
Among the Antithrombin III deficiencies we can find patients with mutations such as AT Budapest 3 (ATBp3) which is a prevalent deficiency of the type II heparin binding site (IIHBS) due to the founder effect and which presents a high prevalence and specificity in the Roma population, with an estimated prevalence of 3% which is very high compared to the general population. The age of the mutation, in this study, was calculated from the analysis of 8 short tandem repeat sequences deriving from SERPINC1 gene, and was dated back to the 17th century, when Roma migration in Central and Eastern Europe occurred. This condition would explain our patient's lack of response to LMWH therapy despite antithrombin III supplementation, given that ATBp3 is a prevalent deficiency of the type II heparin binding site (IIHBS). Consequently, the exogenous antithrombin III was able to bind the LMWH leading to a slight increase of the Anti-Xa (from 0 IU/ml to 0.27 IU/ml), while the endogenous AT III, given the deficiency of the site of binding, did not contribute to an adequate therapeutic response.
Interestingly, another study4 supported a link between AIVC and ATBp3 polimorphism: using a cohorts of 61 patients homozygous for the Budapest 3 variant selected from 1118 patients with congenital antithrombin deficiency, the Authors showed the specific association of IVC system atresia with SERPINC1 mutations. It is also supported the possibility that the AIVC may not be an actual congenital anomaly; a thrombosis in the developing fetal vessels could represent the reason for this condition.

256. EGYPTIAN SOUVENIR: PULMONARY EMBOLISM WITH MULTIPLE INFARCTS

Di Stasio P., Carapellese R., Lo Buglio A. , Bellanti F., Vendemiale G.
Department of Medical and Surgical Sciences, University of Foggia

Introduction: Pulmonary embolism (PE) is a relatively frequent occurrence in hospitalized internal medicine patients. On the other hand, pulmonary and hepatic infarctions are rarer events due to the presence of a double organ blood supply. We describe the case of a patient with the simultaneous presence of PE, pulmonary, hepatic and splenic infarctions, in the absence of known thromboembolic risk factors.
Case Report: 79-year-old woman, former smoker, with preserved functional autonomy (she also refers to frequent trips abroad, in particular to North Af-

rican countries; she has just returned from Egypt), suffering from hypertensive heart disease under treatment, class I obesity, chronic obstructive pulmonary disease, with a history of bladder papilloma excision in 2012, cholecystectomy in 2018, and a single event of spontaneous abortion. In the 7 days prior to admission, she reported the appearance of exertional dyspnea and a single episode of hematuria. Laboratory examinations at entry revealed moderate normocytic normochromic anemia, stage IIIb acute renal failure, Fibrinogen 2 x 450 mg/dl, D-dimers 4.2 x 500 ng/ml, C-reactive protein 10.6 x 5 mg/l, proBNP 3.2 x 450 pg/ml, and bacteriuria without leukocyturia. Echocardiography showed left ventricular hypertrophy, with ejection fraction 55% and lipomatosis of the interatrial septum. CT of the chest and abdomen described a thromboembolic component in some segmental branches of the lower pulmonary lobes, two areas of pulmonary consolidation in the left lower lobe, lingula, and right supra-diaphragmatic region, hypo-vascularized, of possible infarct significance; furthermore, other hypodense areas referable to hepatic and splenic infarctions were found. After making diagnosis of unprovoked PE, was performed comprehensive thrombophilic screening which showed heterozygous mutation of the MTHFR gene. In the suspicion of vasculitis of the medium and/or small vessels, a complete autoantibody screening and a renal biopsy were performed, both with negative results. Urine research was also carried out for Schistosoma haematobium, wich ruled out bilharzia. The result of the respiratory virus genomes panel carried out on a nasopharyngeal swab was positive for human Bocavirus (HBoV). The search for the virus also gave positive results on fecal and blood samples. After supportive therapy and clinical-laboratory improvement (resolution of renal failure and anemia), the patient was started on anticoagulant therapy and discharged home in stable conditions. Discussion: We descrive a case of PE and multiple infarcts associated with an infection caused by an emerging pathogen. HBoV was described for the first time in 2005. (1). This virus is responsible for respiratory and enteric infections in children, while it is rarely isolated in adults, probably due to the lack of systematic research in samples other than the respiratory one. To date, the virus has been isolated in the blood of subjects with a positive respiratory or fecal sample (2,3). HBoV reaches the circulation both by crossing the respiratory wall and after the secretions are ingested (7) by crossing the duodenal mucosa, where it replicates (4), causing a local cytopathic effect that can manifest itself with gastrointestinal symptoms. The presence of viral loads in blood, respiratory and fecal samples demonstrates that this virus may be responsible for systemic infection (5,6). Our hypothesis is that HBoV may have contributed to hypercoagulability leading to the occurence of multiple infarctions (pulmonary, splenic, and renal) and PE. This case aims to highlight the role of HBoV in the adult population, where only sporadic cases have been described, suggesting to proceed with the research for the virus in other biological samples even after a positive respiratory sample, in order to better understand its still poorly-known effects on other organs and systems.

References: (1):Clinical and epidemiological aspects of human bocavirus infection; Juha Lindner, Lüdya Karalar, Sven Schimanskia et al.– (2):Human Bocavirus, a Respiratory and Enteric Virus; Diego Vicente, Gustavo Cilla, Milagrosa Montes et al. – (3):Human Bocavirus: Multisystem Detection Raises Questions about Infection; Ian M.Mackay, Queensland Paediatric Infectious Diseases Laboratory – (4):Human Bocavirus and Gastroenteritis Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 13, No. 10, October 2007- (5):Human bocavirus: clinical significance and implications; Jeffrey Kahn, Division of Infectious Diseases, Yale University School of Medicine – (6):Infections à Bocavirus humain, Revue gènèrale; C.Catalano-Pons, C.Vallet, P.Lebon, D.Gendrel - (7):Viral Respiratory Pathogens and Lung Injury; Nicola Clementi, Sreya Ghosh, Maria De Santis, Matteo Castelli et al.

257. ACQUIRED HAEMOPHILIA AN INSIDIOUS PATHOLOGY IN THE ELDERLY PLURIPAROLOGICAL PATIENT

Pontoriero M., Schiano Di Cola N., Donnarumma S., Palermo V., Rufolo P., Calcaterra I., Conca P., Cimino E., Di Minno M.
Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy

Introduction: Acquired haemophilia A (EAA) is a rare hemorrhagic syndrome with an autoimmune pathogenesis, due to the development of autoantibodies directed towards epitopes of the factor VIII (FVIII) molecule, which neutralize its coagulant activity (inhibitors) and/or induce one faster clearance. EAA has an incidence in the general population of about 1.5 cases per million inhabitants/year. The incidence increases with age and is more frequent in patients after 65 years of age.
The largest cases reported in the literature have secondary causes as the condition responsible for the onset of the autoimmune phenomenon, among which the most numerous are associated with solid and oncohaematological neoplasms, autoimmune diseases, infections, dermatological diseases and pharmacological intake.The hemorrhagic manifestations are mainly mucocutenea and not articular as in the congenital form.
Clinical case: A 89 years patient arrived from the ER where he was hospitalized for thoracic pain in the context of congestive heart failure on severe mitral insufficiency found two years ago, surgical indication and permanent AF on therapy with Edoxaban 30 mg, suspended at the time of admission. In anamnesis, autoimmune background for rheumatoid arthritis and Hashimoto's thyroiditis, CRF stage IIIb and type II diabetes on insulin therapy. During her hospitalization she presented localized skin hematomas on the upper limbs, neck and upper trunk. From a laboratory point of view, an aPTT lengthening was found that was incorrect in the mixture test, , on subsequent investigation, negative LAC, FVIII <1%, FVIII INHIBITOR 101 UB. The clinical and laboratory findings were consistent with a diagnosis of high title inhibitor EAA, for wich steroid immunosuppressive therapy was started.
At the time of admission, the patient was alert and cooperative, with BP 100/60 mmHg, arrhythmic HR of 65 bpm and SpO2 98% in AA.
The haematochemical tests revealed alterations in the indices of renal function (worsening compared to the previous ones practiced in another facility). Creatinine 3.89 mg/dl, Urea 302 mg/dl with eGFR 10 ml/min/1.73 m2); Hypoalbuminemia (2 g/dl) and, aPTT ratio 3, Hb of 7.7 g/dl. Given the severe anemia we proceeded to the transfusion of concentrated red blood cells. Furthermore, to manage the haemorrhagic complications, mainly represented by large skin haematomas, antihaemorrhagic therapy was administered with bypassing agents (recombinant FVIIa at a dosage of 90 micrograms/kg) associated with an antifibrinolytic (tranexamic acid 20 mg/kg iv). Despite the therapy, the patient's heart failure condition worsens with the appearance of edema and dyspnea. Thus, it was practiced follow-up echocardiography reconfirming severe mitral regurgitation associated with moderate concentric left ventricular hypertrophy and grade II diastolic dysfunction associated with increased filling pressures. The most significant finding , were signs of severe right heart failure (moderate to severe tricuspid valve regurgitation with severe pulmonary hypertension, right chamber dilatation with decreased right ventricular systolic function). Complicating the situation, the development of an IRA framework on IRC with oliguria; therefore, treatment with Albumin 20 g/100ml iv associated with furosemide 250 mg 1 fl was practiced, followed by hydration, with good recovery of diuresis and improvement of dyspnea. 10 days after hospitalization due to immunosuppression, the patient shows infectious complications with reactivation of CMV replication with values of 36,000 and fever peaks of 38°C, therefore, after infectious disease advice, we started treatment with Ganciclovir 1.25 mg every 24 h iv associated with empiric antibiotic therapy with piperacillin/tazobactam dose adjusted by glomerular filtration rate. Nonetheless, the patient's condition worsened with new onset of dyspnea and wet chest sounds with contraction of diuresis and hypotension (SPO2 82% in AA, P/F ratio of 100), sleepy, with a GCS of 10. Oxygen set therapy with 40% venturi mask with 8 l/min of O2, high dose diuretic, albumin and vasoactive amines after an initial improvement we find a worsening of the clinical condition ,up to the exitus mainly caused by congestive failure on severe mitral insufficiency , not treated over time.
Conclusions: This clinical case shows that, although the pathology was recognized in a short time and prompt therapy was started, to contain the bleeding, the complications during the immunosuppressive treatment and the patient's comorbidities did not avert the worst. It should be underlined that, although there are effective strategies for bleeding control and inhibitor eradication, acquired haemophilia A can be a very insidious pathology in an elderly patient, as very often immunosuppressive therapy involves risks of infectious complications that can expose patients to an unfavorable course of the pathology ,especially if there are comorbidities such as in this case type, I cardio-renal syndrome, in the context of severe congestive heart failure.

258. EFFECTS OF GASTROINTESTINAL RESECTION AND/OR OSTOMY SURGERY ON THE PLASMA CONCENTRATION OF APIXABAN

Caprari R.[1], Talerico R.[1], Porfidia A.[1], Fondi E.[1], De Candia E.[2], Pola R.[1]
[1]Unità di Medicina Interna e Malattie Tromboemboliche, Dipartimento di Medicina Interna - Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore - Largo F. Vito, 1, 00168 Roma;
[2]Dipartimento di Diagnostica per Immagini, Radioterapia, Oncologia ed Ematologia, Centro di Malattie Emorragiche e Trombotiche - Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore - Roma

Background and Aims: Gastrointestinal resections (GIR) and/or ostomy

surgery (OS) may result in altered absorption of orally administered drugs. No data are available on the plasma concentration of direct oral anticoagulants (DOAC) in subjects with history of GIR and/or OS. In this study, we measured the plasma levels of apixaban in this category of patients.
Methods: We designed an observational study on patients with previous GIR and/or OS who were receiving apixaban for the treatment and/or secondary prevention of venous thromboembolism (VTE) or the prevention of cardioembolic stroke and systemic embolism (SSE) in non-valvular atrial fibrillation (NVAF). Inclusion criteria were gastric, small and/or large bowel resection up to the descending colon and/or ostomy surgery. Patients with history of isolated resection of sigmoid colon and/or rectum were excluded. Apixaban plasma concentrations were measured at peak and trough (2-3 and 12 hours upon taking the drug, respectively). The primary outcome was to assess whether apixaban peak and trough plasma concentration was within the expected value for the respective therapeutic indication (either treatment of VTE, prevention of VTE, or NVAF), as established by the European Medicines Agency (EMA). The secondary outcome was to assess the incidence of thrombotic (SSE or symptomatic VTE recurrence) and bleeding events during the study period. Bleeding events were distinguished in major (MB) or clinically relevant non-major bleedings (CRNMB), according to the criteria of the International Society on Thrombosis and Haemostasis.
Results: 38 patients were enrolled: 12 on apixaban 5 mg BID for VTE treatment, 5 on apixaban 5 mg BID for NVAF, and 21 on apixaban 2.5 mg BID for prevention of VTE recurrence. The characteristics of the population are reported in Table 1.
Regarding surgeries, 3 patients (8%) had resection of the stomach, 8 (21%) resection of the small bowel, and 23 (61%) resection of the large bowel. Additionally, 4 (10%) patients had multiple GIR.
The peak and trough plasma concentrations were:
There were 2/38 patients with peak concentration above the reference range. Both patients were on apixaban 5 mg BID for VTE treatment. There was 1/38 patient, on therapy with apixaban 5 mg BID for VTE treatment, with trough concentration below the reference range. Finally, there was 1/38 patient, on therapy with apixaban 2.5 mg BID for VTE secondary prevention, with trough concentration below the reference range.
During a total observation period of 25.5 patient-years (PY), neither thrombotic nor MBs events were reported. One CRNMB occurred (Incidence Rate [IR] of 3.9 per 100 patient-years). Four patients died (IR of 15.7 per 100 patient-years), due to progression of cancer disease.
Conclusions: almost all patients achieved apixaban plasma concentrations within the reference range. No thrombotic or bleeding events were recorded among patients with out-of-range concentrations. Despite the limitations of the study, undoubtedly due to the small sample size and the variety of surgeries, these results suggest that the use of apixaban should not be ruled out a priori in patients with previous gastrointestinal resection.

Table 1. Characteristics of the population

	Study population (n=38)
Demographic characteristics	
Age ± DS	63,5 ± 12,4
Male - n° (%)	19 (50%)
BMI ± DS	25 ± 3,8
GFR (according to Cockcroft-Gault) ± DS	79,7 ± 25,4
Ethnicity (Caucasian) - n° (%)	38 (100%)
Clinical characteristics	
Indication for apixaban intake	
AF - n° (%)	5 (13%)
VTE - n° (%)	33 (87)
Apixaban dosage	
5 mg BID for AF - n° (%)	5 (13%)
5 mg BID for VTE treatment- n° (%)	12 (32%)
2,5 mg BID for VTE prevention - n° (%)	21 (55%)
Months of apixaban intake before dosing	
≤ 1 month - n° of patients	14 (37%)
>1 to ≤6 months - n° of patients	20 (53%)
>6 to ≤12 months - n° of patients	4 (10%)
>12 months - n° of patients	0 (0%)
Drug interactions	
Ongoing chemotherapy - n° (%)	23 (61%)
Chemotherapies potentially interacting with apixaban - n° (%)	3 (8%)
Other drugs potentially interacting with apixaban - n° (%)	0 (0%)
Surgeries	
Resection due to malignancy, n° (%)	33 (87%)
Resection due to other pathology, n° (%)	5 (13%)
Portion of the gastrointestinal tract excluded	
Stomach - n° (%)	**3 (8%)**
Biliopancreatic diversion - n° (%)	1 (3%)
Partial gastrectomy - n° (%)	2 (5%)
Total gastrectomy - n° (%)	0 (0%)
Small bowel - n° (%)	**8 (21%)**
Resection of duodenum - n° (%)	2 (5%)
Resection of jejunum - n° (%)	0 (0%)
Resection of ileum - n° (%)	6 (16%)
Large bowel (not isolated sigma and/or rectum) - n° (%)	**23 (61%)**
Right hemicolectomy - n° (%)	5 (13%)
Left hemicolectomy - n° (%)	2 (5%)
Resection of transverse colon - n° (%)	0 (0%)
Total colectomy - n° (%)	0 (0%)
Ileostomy - n° (%)	13 (34%)
Colostomy - n° (%)	3 (8%)
Multiple resections - n (%)	**4 (11%)**
Partial gastrectomy + duodenum resection + right hemicolectomy - n° (%)	1 (3%)
Total gastrectomy + small bowel resection - n° (%)	1 (3%)
Right hemicolectomy + left hemicolectomy - n° (%)	1 (3%)
Right hemicolectomy + transverse colon resection - n° (%)	1 (3%)

259. ACUTE MANAGEMENT OF GASTROINTESTINAL BLEEDING AND ENDOSCOPIC FINDINGS IN PATIENTS RECEIVING DIRECT ORAL ANTICOAGULANTS: RESULTS FROM PROSPECTIVE COHORT STUDY

Verso M.[1], Maraziti G.[1], Morelli O.[2], Castellani D.[2], Bassotti G.[2]
[1]Internal, Vascular and Emergency Medicine – Stroke Unit, University of Perugia, Perugia, Italy ; [2]Gastroentorology Division, University of Perugia, Perugia, Italy

Introduction: Direct oral anticoagulants (DOACs)are reported to be associated with a high risk for gastro-intestinal bleeding (GIB). Limited data are available concerning the endoscopic features in patients with DOACs-associated GIB. The aim of our study was to prospectively collect real-world data concerning acute management of bleeding and endoscopic features in patients with DOACs-associated GIBs**. Materials and Methods**: Consecutively patients admitted to the hospital for DOAC-associated GIB were enrolled. Information about clinical characteristics of patients and GIBs, endoscopic features and acute management of bleeding were captured by an electronic database at the time of the index event. **Results**: 208 patients were included. At entry, the mean patient age was 81.7± 8.9years (range 51 –95 years),58.7% were male. 63 (30.1%%) patients presented GIB on dabigatran (of which 45 patients on 110mg twice daily), 73 (35.1%) on rivaroxaban (of which 35 patients on 15 mg daily) 48 (23.1%) on apixaban (of which 15 on 2,5mg twice daily) and 24 (11.5%) on edoxaban (of which 10 on 30 mg daily). 20 patients (9.6%) received inappropriate doses of DOACs. The indication for DOAC treatment was atrial fibrillation in 87.5% of patients, venous thromboembolism in 9.1% and both indication in 3.4% of patients. According with ISTH criteria, GIB was defined as major in 161(77.4%) patients, of which 32 (9.8%) defined as life-threatening and 2 (0.62%) as fatal bleedings, and clinically relevant non-major bleeding in 47 (22.6%) patients. All patients discontinued the DOAC administration, except one. 143 patients were transfused with packed red cells, with a median number of blood transfusions of 2.4. A re-

versal strategy with prothrombin complex concentrates, fresh frozen plasma, or antidote was adopted in 10.6% of patients. 198 (95.2%) patients underwent to at least one endoscopic procedure. The bleeding source was identified in the upper GI tract in 109 patients (52.4%) and in the lower GI tract in 84patients (40.4%). More frequent endoscopic findings were mucositis(30.5%) and vascular lesions (17.6%). Malignancy was documented in 29 patients (15.0%).According to the Saurin's classification, lesions were classified as at high bleeding risk in 85 patients (40.9%) and at very-high bleeding risk or as with active bleeding in 61 patients (29.3%).Local haemostasis or polypectomy were performed in 55 patients (26.4%) and 11 patients (5.3%) respectively. An acute reversal strategy for anticoagulation was performed before endoscopy in 22 patients (10.6%) During the 6-month FUP, 12 patients had a bleeding recurrence and 8 patients had thrombotic complications. Six patients died during hospitalization and 45 during 6-month FUP.
Conclusions: Patients with DOAC-associated GIBs were found to have more frequently mucosal diseases. The endoscopic procedures identified lesions at high bleeding riskor active bleeding in 70.1% of cases. An interventional endoscopy was performed in about 30% of cases.

260. ANTI-PHOSPHATIDYL SERINE (APS) ANTI-PROTHROMBIN (APT) ANTIBODIES IN IMMUNE THROMBOCYTOPENIA (ITP): SPACE FOR A MISDIAGNOSED AND UNDERESTIMATED FORM OF SECONDARY ITP?

Camerlo S.[1], Rosati G.[1], Montaruli B.[2], Radin M.[1], Sciascia S.[1], Morotti A.[1]
[1]University of Turin; [2]AUO Mauriziano

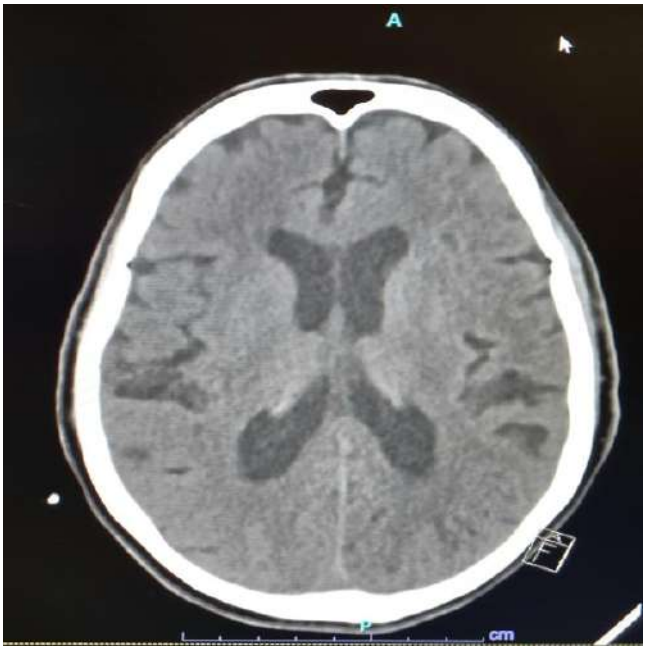
Background and aims: Antiphosphatidyl serine (aPS), antiprothrombin (aPT) antibodies are recognized as markers for antiphospholipid syndrome (APS). While LAC, anti cardiolipin and anti-beta2-glycoprotein antibodies are frequently tested to assess the presence of APS, aPS/aPT are very rarely evaluated. Immune thrombocytopenia (ITP) is an autoimmune disorder which can be idiopathic (primitive ITP) or secondary to other conditions, such as other immunological disorders as APS. ITP diagnostic workup requires to rule out an underlining APS, due to the potential pro-thrombotic risk of this disease which should be potentially augmented by TPO-mimetic treatment. The classical screening with LAC/ACA/antiBeta2GPI determination could however underestimate the presence of antibodies with antiphospholipid activity and therefore it could misdiagnose an ITP as primary instead of secondary. In this report, we aimed to investigate the frequency of aPS and aPT in a cohort of patient with ITP mostly focusing on those patients with a potential diagnosis of primitive ITP.
Methods: We analyzed a cohort of 68 consecutive patients, admitted to our Division of Internal Medicine – Hematology, with a diagnosis of ITP. For each patient, the positivity to LAC, anti-cardiolipin (ACA) IgG/IgM, anti-Beta2glycoprotein I (GPI) and aPS/aPT were evaluated, together with the determination of peripheral blood counts, C3-C4 dosage and ANA, ENA, anti-ds-DNA positivity. A systemic screening with chest radiography/abdominal sonography was performed for all patients, with further radiological evaluation. Bone marrow biopsy was also performed accordingly to the age of patients and/or the clinical suspect of a primitive hematological disorder.
Results: Our ITP cohort includes 68 patients, 41 (61%) were female (average age 60.5 yrs, 19.5 std), 27 (39%) male (average age 72.1 yrs, 17.2 std). As first line treatment, 31% patients received only steroids therapy, while 63% patients required also IVIG. During the follow up period 54% required treatment with TPO mimetics. Overall, 60.29% patients were classified as primitive ITP and 39% secondary ITP.
In the attempt to assess the presence of antiphospholipid antibodies, 24% of the patients with secondary ITP were positive for LAC or ACA and anitbeta2GPI antibodies. Very interestingly, while assessing the frequency of aPS/aPT antibodies in the sub-cohort of patient with unclassified ITP, we discovered the positivity to these antibodies in 16% of the caseas.
Conclusion: While an extended analysis is mandatory, our work points to utility of the determination of aPS and aPT in the diagnostic workup of ITP patients. aPS/aPT determination allows to identify a potential subgroup of otherwise misdiagnosed secondary ITP patients which should require a specific diagnostic and therapeutic approach, due to the potential pro-thrombotic risk that could be emphasized by TPO mimetic treatment and/or the need of investigation of additional organ dysfunctions.

261. RECURRENT ITTP IS NOT ALWAYS BETTER THAN THE FIRST EVENT

Truffelli P., Ferrari B., Giannotta J.A., Artoni A., Peyvandi F.
Fondazione IRCSS Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Milan, Italy

Immune-mediated Thrombotic Thrombocytopenic Purpura (iTTP) is a potentially life-threatening thrombotic microangiopathy caused by ADAMTS13 deficiency: in acute phase, it is characterized by widespread microvascular thrombosis, leading to tissue ischemia and variable organ failure. The disease may have a recurrent course and relapses are usually milder than the first acute episode.
Case report: G.L.S is a 56-year-old woman, with a personal history of idiopathic iTTP since 2005, treated with a long-course of immunosuppressive agent (cyclosporine) due to ADAMTS13 severe deficiency in remission phase. In 2021 she was diagnosed with two concomitant solid cancers (poorly differentiated lung adenocarcinoma and locally advanced uterine cervical carcinoma) and therefore appropriately treated (with lobectomy and CT/RT combination therapy, respectively). Due to these oncological problems, cyclosporine was interrupted and the patient lost to haematological follow-up. In may 2023, she was admitted to the emergency department for hyperacute clinical deterioration, with rapid onset of cognitive impairment after repeated vomiting. Blood tests showed thrombocytopenia (PLT 26'000/mmc) and hemolytic anemia (Hb 12.9 g/dL, LDH 4'777 U/L, HP 30.1 mg/dL, total bilirubin 2.52 mg/dL), associated with renal damage (creatinine 2.69 mg/dL). The ECG was normal and brain CT scan did not reveal any focal lesion. Despite a prompt diagnosis of iTTP relapse and correct treatment with plasma exchange (TPE) and systemic corticosteroids, both clinical and biochemical data worsened the following day, with a drop in platelets and hemoglobin levels (14'000/mmc and 9.9 g/dL, respectively). In addition, a second brain CT scan revealed multiple bilateral ischemic lesions, including hypodense foci in the cerebellum bilaterally, temporal-occipital-basal left lobes, and occipito-polar and frontal right lobes. Due to the number and bilateral distribution of the ischemic lesions, the radiologist described them as of possible cardioembolic origin. Unexpectedly, the neurological examination only showed confusion.
Due to the severity of disease, the patient was transferred to our Hospital and admitted to the intensive care unit: in addition to brain lesions, an acute cardiac involvement was demonstrated by the presence of ECG alterations and the marked increase of troponin T levels (up to 4'900 ng/L, that is 350-fold greater than the upper limit of normal); however, despite the echocardiogram showed left ventricle global hypokinesia with a reduced EF (40%), no endoventricular thrombi nor atrial enlargement were detected. Albeit atypical for their large size, the cerebral ischemic lesions were therefore presumed to be TTP-related. Moreover, the patient developed progressive acute kidney failure, with the need of hemodialysis.
Caplacizumab was added to the ongoing treatment (TPE and steroids), without hemorragic evolution of brain lesions. In the following days, the patient's conditions ameliorated with complete restitution to normal neurological status, normalization of cardiac function (as assessed by troponin T levels, ECG and echocardiography), and also kidney function improved and hemodialysis was interrupted. As the patient blood tests confirmed biochemical remission, TPE were stopped, without recrudescence of disease on caplacizumab and steroids. Even after platelets normalization, the patient did not receive any anticoagulant drug, not only for the absence of clear cardioembolic genesis of the brain ischemic lesions but also for high risk of their hemorragic evolution due to concomitant use of caplacizumab. After exclusion of ongoing oncological disorders, a course of rituximab was planned, since ADAMTS13 levels were still severely reduced (< 10%). We concluded for a very severe relapse of iTTP, with multi-organ damage (brain, heart, kidney) and successfull recovery with appropriate intensive treatment.
Discussion: iTTP tipically affects the central nervous system, with variable neurological impairment [encephalopathy (69%), motor symptoms (42%), generalized weakness (28%), focal motor deficit (19%), visual changes (23%), seizure (14%), dysarthria (11%), aphasia (11%) [1]. This large variability is related to complex and multiple pathophysiological mechanisms, such as microthrombi formation, endothelial injury, and also hemorrhage, coexisting in acute TTP. The complexity and variability of this condition is evident also in brain imaging studies, such as CT scans and MRI scans [2]. Acute Kidney Injury requiring dialysis is present only in 4-15% of patients. Moreover, high levels of troponin in acute phase correlate with an increased risk of mortality [3].
Conclusions: acute TTP may manifest with heterogeneous neurological features, with neuroimaging findings not always clearly correlated to neurologic clinical impairment. In case of macroscopic brain ischemic lesions, especially if atipycal for site and size, a proper differential diagnosis has to be done in

order to provide the proper management. Even if recurrences are usually milder than the first TTP event, a prompt treatment is always needed, since the risk of morbidity and mortality is high.



262. INCIDENCE OF FRACTURES AND PREDICTIVE ROLE OF BONE MINERAL DENSITY IN HEMOPHILIC PATIENTS: OUR SINGLE-CENTER EXPERIENCE

Giachi A.[1], Agosti P.[1], Marino S.[2], Hassan S.[3], Suffritti C.[4], Gualtierotti R.[5], Peyvandi F.[5]
[1]Department of Pathophysiology and Transplantation, Università degli studi di Milano, Milan, Italy.; [2]Department of Biomedical Surgical and Dental Sciences, Università degli studi di Milano, Milan, Italy; Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico di Milano, Centro Emofilia e Trombosi Angelo Bianchi Bonomi, S.C. Medicina – Emostasi e Trombosi, Milan, Italy; [3]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands; [4]Department of Biomedical Surgical and Dental Sciences, Università degli studi di Milano, Milan, Italy; [5]Department of Pathophysiology and Transplantation, Università degli studi di Milano, Milan, Italy; Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico di Milano, Centro Emofilia e Trombosi Angelo Bianchi Bonomi, S.C. Medicina – Emostasi e Trombosi, Milan, Italy

Introduction: Hemophilia is a rare bleeding disorder characterized by the partial or complete deficiency of clotting factor VIII or IX. Hemophilic patients are burdened by many complications, the most common being joint bleeding (hemarthrosis) which leads to the development of hemophilic arthropathy.
Bone mineral density (BMD), measured by dual-energy x-ray absorptiometry (DXA), is a standard-of-care screening tool used to assess fragility-fracture risk. According to two metanalyses, in hemophilic patients a reduction of BMD both in hips and vertebrae is observed since young age.
Aside from many common factors, such as vitamin D deficiency or concomitant HCV or HIV infections, a possible explanation for this loss of BMD in hemophilic patients could be also ascribed to the lack of physical activity due to the presence of hemophilic arthropathy or to a biological role of factor VIII beyond coagulation. However, the role of BMD in predicting the occurrence of fractures in hemophilic patients is still debated.
Aim: To investigate in a cohort of hemophilic patients the incidence of fractures, as well as to assess the role of BMD in predicting their fracture risk.
Methods: In this retrospective study, 115 adult patients with hemophilia A or B, followed at the Angelo Bianchi Bonomi Hemophilia and Thrombosis center and undergoing a DXA between July 2013 and August 2021 were included. Exclusion criteria included history of fractures, use of drugs that could influence BMD such as corticosteroids, antiresorptive agents, anticonvulsants, proton pump inhibitors, aromatase inhibitors, pioglitazone, heparin and levothyroxine, and history of tumors or diseases that directly affect bone health like multiple myeloma, lung and liver cancer, inflammatory bowel diseases and endocrine conditions such as hyperparathyroidism, hyperthyroidism, glucocorticoids excess, hypogonadism and hyperprolactinemia.
Results: Median age of our study population was 43 years (interquartile range, IQR, 36 – 51). Ninety-seven (84%) patients were affected by hemophilia A, 18 by hemophilia B. Out of 115 patients, 89 (77%) had a severe disease. Among the whole cohort, 105 (91%) showed a certain degree of BMD loss, defined as a T score ≤1 (osteopenia) or ≤2.5 (osteoporosis), with a median T-score of -1.5 [IQR, -2.3; -0.6]. Fourteen patients experienced a fracture during the observation period, of whom 2 (14%) had osteoporosis. We found an incidence rate of fractures of 0.015 (95% confidence interval, CI: 0.008 – 0.025) fractures/year. BMD resulted to be not a good predictor of fracture risk with an area under the curve (AUC) of 0.64, as shown by means of the receiver operator characteristic (ROC) curve model.
Conclusions: Compared to the Italian general population, hemophilic patients have an earlier and higher incidence rate of fractures. BMD does not seem to be a reliable tool to identify hemophilic patients at higher risk of fracture. A possible explanation is related to the intrinsic nature of BMD, which is measured by proxy based on the optical density per square centimeter of bone surface upon imaging. This kind of measurement is useful in detecting BMD reduction due to a direct loss of bone structure, whereas it is less valid in some kind of secondary osteoporosis, characterized by bone microarchitectural alterations without a significant density reduction. Our findings pave the way to prospective studies properly designed to deeply explain the contribution of all main hemophilia-related risk factors of bone fractures.

263. EFFECTS OF TOFACITINIB ON PLATELET ACTIVATION IN PATIENTS WITH RHEUMATOID ARTHRITIS

Simeone P., Liani R., Celletti E. , Sabatini E., Di Penta M., Frezza M., Catitti G., Lanuti P., Cipollone F., Santilli F.
Department of Medicine and Aging, and Center for Advanced Studies and Technology (CAST), "G. d'Annunzio" University of Chieti-Pescara, Chieti, Italy

Background: Atherothrombosis is a common comorbidity associated with arthritis and inflammation and represents the cornerstone of increased cardiovascular (CV) risk in these patients. We hypothesized that Tofacitinib, a JAK inhibitor, may affect platelet activation, either directly through the downstream consequence of JAK-2 inhibition on thrombopoiesis and platelet hyperresponsiveness, or indirectly, through modulation of the inflammatory cytokine network and the activation of inflammatory/immune cells.
Objectives: To evaluate, in patients with RA, the effects of treatment with tofacitinib for 6 months on markers of platelet activation and on markers of platelet turnover/regeneration and to correlate the change in markers of platelet activation/turnover/regeneration with: a) change in systemic inflammation; b) response to disease.
Methods: Twenty-four patients diagnosed with RA according to the 2010 ACR-EULAR classification criteria, who were intolerant to or had an inadequate response to at least one csDMARD drug, were enrolled in a prospective observational study.
Urine and blood sampling was performed at baseline (T0M) and after 3 (T3M) and 6 (T6M) months of tofacitinib therapy (5 mg twice daily).
Patients were evaluated for clinical assessment (including RA response criteria), systemic inflammation (HS-CRP), TX-dependent platelet activation (11-dehydro-TXB2); platelet-derived inflammation (CD40L and P-selectin); pro-thrombotic phenotype (TF expression on platelets and platelet-leukocyte complexes, P-selectin and GPIIbIIIa expression on platelets; circulating extracellular vesicle), platelet turnover and production/destruction balance (platelet count, platelet mass, mean platelet volume, immature platelet fraction, thrombopoietin, glycocalycin, glycocalycin index).
Results: Tofacitinib treatment was associated with:
- altered platelet turnover, with higher rate of platelet destruction, as reflected by higher circulating glycocalicin, and a trend for higher immature platelet fraction (**Figure 1**). Whether lower circulating thrombopoietin reflects lower production or increased uptake by megakaryocytes/platelets, is not unraveled.
-a transient increase in platelet activation after 3 months, as reflected by higher urinary 11-dehydro-TXB2, plasma CD40L and platelet-derived extracellular vesicles, which normalized at 6 months of tofacitinib treatment **(Figure 2)**.
-reduced inflammation, as reflected by lower CRP, leukocyte-derived Evs and endothelial-derived Evs (**data not shown**).

-a less prothrombotic platelet phenotype, as reflected by a reduced percentage of platelets expressing p-selectin (after activation with ADP), both superficial and intraplatelet TF (**data not shown**).
-increased percentage of platelet-leucocyte aggregates, with decreased percentage of TF-expressing aggregates although with increased MFI (**data not shown**).
Conclusions: Overall, our study shows that tofacitinib favorably affect the prothrombotic phenotype of platelets, with particular reference to the expression of tissue factor, one of the main drivers of platelet activation and coagulation. Our findings shed light on a possible early, transient increase in platelet activation, translating into increased circulating concentrations of thromboxane, CD40L, and platelet-derived extracellular vesicles, and increased expression of the platelet receptor GPIIbIIIa. Interestingly, all these abnormalities return to baseline after six months of treatment. Further, larger scale studies, are needed to ascertain the long-term effects of tofacitinib, and to characterize clinical and molecular predictors of adverse cardiovascular events during treatment.

Figure 1

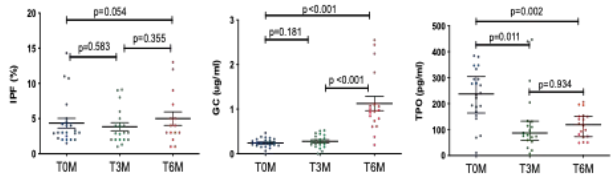
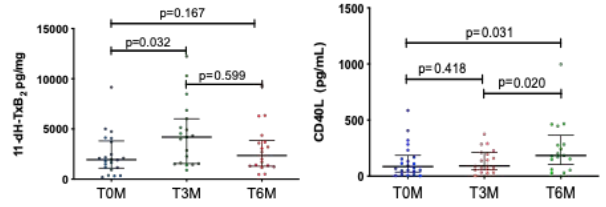


Figure 2



264. INTERNAL CAROTID ARTERY THROMBOSIS IN IRON DEFICIENCY ANEMIA

Ruocco I.[1], Bracco C.[2], Brignone C.[2], Migliore E.[2], Morgillo T.[2], Serraino C.[2], Fenoglio L.[2]
[1]Scuola di specializzazione in Medicina Interna, Università degli Studi di Torino; [2]Dipartimento di Medicina, Ospedale S.Croce e Carle Cuneo

Introduction: Iron deficiency anemia is a frequent condition: it has been estimated to affect about 20% of human population at any given time[1]. Iron deficiency anemia can lead to reactive thrombocytosis, a known cause of venous thromboembolism (VTE). However, arterial thrombosis in the context of iron deficiency anemia is rare. We present a case of repeated internal carotid artery occlusion in a young woman, attributed to thrombocytosis due to iron deficiency anemia after exclusion of known prothrombotic risk factors.
Case presentation: A 49-year-old woman was admitted to Emergency Department with acute onset of left-sided limb weakness accompanied by facial palsy, which lasted 45 minutes and reversed spontaneously. Her past medical history was negative for previous thrombotic events nor cardiologic risk factors. She had not yet reached menopause. She didn't assume medications at home on regular basis. The Angio computed tomography (AngioCT) scan showed a free-floating thrombus in the rnternal carotid artery (ICA). The patient was diagnosed with a transient ischemic attack (TIA) and underwent urgent thromboendarterectomy. The diagnostic workup excluded cardioembolic pathogenesis via an Holter ECG and a transthoracic echocardiography. A patent foramen ovale was ruled out by contrast echocardiography and transcranial doppler. The patient started taking low-molecular weight heparin (LMWH) at therapeutic dosing in addition to acetylsalicylic acid (ASA) 100 mg/die and was discharged. Heparin was interrupted at the follow-up visit at 4 weeks, when results of anti-phospholipid antibodies were negative. A few days after discontinuation of heparin, a new TIA with identical symptoms occurred. On this admission, laboratory workup showed a hemoglobin level of 5.2 g/dL, mean corpuscular volume of 62 fL, white blood cell count of 6.58 x 10^3/uL and platelet count of 933 x 10^9/L. Iron studies showed an iron level of 37 ug/dL, a ferritin level of 8.6 ng/mL, a transferrin level of 425 mg/dL with a transferrin saturation of 6%, which established the diagnosis of severe iron deficiency anemia. An AngioCT was repeated, which showed a small thrombotic residual on the origin of right ICA. The patient was treated non-operatively with therapeutic dose of LMWH and blood transfusion. We performed a workup to rule out malignancies, including a thoracoabdominal CT scan, gastroscopy, colonoscopy and mammography, all negative. The patient's iron deficiency anemia was attributed to chronic excessive menstrual losses secondary to uterine fibroid. Screening for rheumatologic conditions, homocysteine value, hereditary mutations of thrombin and coagulative factor V, dosage of antithrombin and C and S proteins were negative for thrombophilic conditions. JAK2 and calreticulin mutations were researched and found negative. Excluded other causes of thrombophilic conditions, we concluded for ICA thrombosis in thrombocytosis due to iron deficiency anemia.
Discussion: Our patient presented with severe reactive (or secondary) thrombocytosis, that can be caused by iron deficiency, sepsis, neoplasms, asplenism and chronic inflammatory diseases. Thrombocytosis can occur also as a primary event in myeloproliferative neoplasms, including essential thrombocythemia, polycythemia vera, chronic myeloid leukemia and myelodysplastic syndromes. Although secondary thrombocytosis is more frequent, the risk of thrombotic events is higher in patients with primary thrombocytosis[2]. Iron deficiency anemia has been identified as risk factor for venous thromboembolism, but seldom for acute arterial thrombosis. A recent large cohort study on 6 million patients found a rate of 32.6% thrombocytosis in patients with iron deficiency anemia, of which 15.8% developed thrombotic events, mainly of the venous type. However, thromboses occurred in 7.8% of patients with iron deficiency but without an increased platelet count[2]. Pathogenetic aetiology of thrombocytosis in iron deficiency involves expansion of common progenitor cells and augmentation of megakaryocyte differentiation. The increased thrombotic risk may result from comorbidities associated with the anemia; however, it is likely multifactorial. It has been demonstrated that in vitro, thrombocytosis leads to augmented thrombin generation, as well as abnormal platelet activation and aggregation. Moreover, it has been suggested that iron deficiency may play a role in low-grade chronic inflammation, a known prothrombotic status, and in endothelial amage via hypoxia[3].
Conclusion: This case shows how thrombocytosis due to iron deficiency can be regarded as a reversible risk factor for arterial thrombosis. Prevention and prompt treatment of low iron levels in the blood are important to prevent venous and arterial thrombotic events.

ENDOCRINOLOGIA

265. CUSHING'S SYNDROME: THE REASON OF MANY PROBLEMS

Rosellini V., Mattei M., Morettini A., Martini L., Ciurleo G., Iozzia M., Coppola A., Giovagnini E., Menicacci L., Simonetti V., Puma A., Rossi Ferrini G., Hennig M., Abatangelo S.
Dipartimento di Medicina Interna 2, AOUC

Introduction: we present the case of G.M., a 59-year-old female patient who was brought to the emergency department for hyperglycemia and tremors of new onset. She was pyretic (T 38°C), with pyuric urine, blood sugar 553, acute kidney injury (creatinine 4.23) on chronic disease, procalcitonin 8.87, respiratory failure with Po2 57.9, Pco2 29.7, Na 118, k 6. 5, Hco3 12. Oxygen therapy, ev insulin with subsequent switch to basal bolus, correction of hypervolemic hyponatremia, and antibiotic therapy was set for finding pyelonephritis in the course of MSSA sepsis. Adequate infusion therapy with diuretic and bicarbonates and correction of hyperphosphoremia with progressive and slow improvement of AKI was also performed.
Background: The patient presented past medical history positive for grade 2 obesity; DM2 since 2012 with poor therapeutic compliance followed by the diabetes department, treated with dulaglutide 1 time/week and lantus 22 IU; hypertension treated with norvasc and losartan; dyslipidemia treated with atorvastatin and also ASA; anxious-depressive syndrome treated with citalopram and alprazolam; previous hystero-annessiectomy for cervical cancer in negative follow-up; functional monorene (left contracted kidney).
Differential Diagnosis: secondary to the striking septic picture that had precipitated kidney failure in the context of a hitherto uncharacterized known metabolic syndrome, we focused on the patient's peculiar clinical presentation that guided our diagnostic suspicion: in view of the clinical hyperan-

drogenism (hirsutism, hairline rarefaction, Prader 2 cytorehydomegaly), testosterone, FSH, LH were dosed and thus we confirmed a picture of biochemical hyperandrogenism with gonadotropin suppression with clearly age-inappropriate values. We therefore assayed morning free and urinary cortisol, ACTH, thyroid hormones, and IGF-1, superseding the two-step prolactin assay. The tests showed a picture of hypercortisolism associated with elevated ACTH values, with suppression of other pituitary hormones. To rule out ACTH-independent hypercortisolism, an abdominal CT scan was performed, which showed adrenal hyperplasia in the absence of focality. In suspicion of Sd. of Cushing's, first among the causes of central endogenous (ACTH-dependent) hypercortisolism, suppression test with dexamethasone 1 mg overnight (Nugent's screening test) was performed, which showed no suppression of cortisol. Therefore, classical Liddle diagnostic test (suppression with dexamethasone 2 mg/day for 2 days) was performed, which showed inadequate cortisol response. The tests supported the initial hypothesis of metabolic Sd. secondary to Sd. Cushing's, therefore MRI of the sella turcica was performed, which confirmed the presence of 3 mm microadenoma of the posterior pituitary portion. In consideration of the previous bilateral hystero-annexectomy and the absence of suspected adrenal or ectopic nodularity (except for two nodular areas of the left lung found on chest CT), the picture of chemical hyperandorgenism associated with inadequate pituitary hormone production was attributed to central ACTH-dependent stimulus. To confirm this suspicion and exclude hypercortisolism secondary to ectopic tumor, petrous sinus catheterization was scheduled.
Conclusions: the laboratoristic-instrumental findings were highly suggestive of ACTH-secreting pituitary adenoma in Sd. Cushing's disease, with indication for medical therapy with ketoconazole, found in the course of sepsis by MSSA determinant picture of pre-dialytic AKI in known CKD.

266. REPEATED COLD-INDUCED SHIVERING PROMOTES MITOCHONDRIAL NETWORK CONNECTIVITY AND REDUCES SUBSARCOLEMMAL INTRAMYOCELLULAR LIPID CONTENT IN TYPE II MUSCLE FIBERS IN INDIVIDUALS WITH OVERWEIGHT OR OBESITY

De Lorenzo R.[1], Gemmink A.[2], Schaart G.[2], Kornips E.[2], Sellers A.J.[2], van Beek S.M.M.[2], Hashim D.[2], van Marken Lichtenbelt W.D.[2], Schrauwen P.[2], Hesselink M.K.C. [2], Hoeks J.[2]
[1]San Raffaele University, Milan, Italy; [2]Department of Nutrition and Movement Sciences, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Centre, Maastricht, The Netherlands

Background: Cold exposure is gaining increasing attention as a novel lifestyle strategy to counteract obesity and its negative metabolic consequences via its impact on energy metabolism. Recently, we found that overweight/obese individuals that were intermittently exposed to cold for ten days, with at least one hour of shivering per day, displayed significantly improved glucose tolerance and reduced circulating fasting glucose and lipid levels. Most likely, these metabolic benefits are linked to the activity of the skeletal muscle as a result of shivering. Indeed, structured exercise is known to exert similar metabolic benefits which have been associated to the dynamics of mitochondrial network connectivity and lipid droplet (LD) number, size and subcellular distribution in the skeletal muscle. Hence, we examined whether ten days of repeated cold-induced shivering induced morphological changes in mitochondrial networks and LDs and their putative relation to the response to an oral glucose tolerance test (OGTT).
Methods: Eleven overweight/obese men (mean age ±SD 62 ±7 years; mean body mass index ±SD 30.6 ±3.1 kg/m2) underwent cold-induced shivering through a cold-water (10°C) perfused suit for 10 consecutive days, with at least 1 hour of shivering per day. Quantitative immunofluorescent confocal laser scanning microscopy was performed on muscle biopsies taken before and after the intervention to evaluate mitochondrial network connectivity and LD morphology and subcellular localization in both type I and II muscle fibers. Muscle biopsy sections were stained for membranes, type I muscle fibers, and mitochondria using antibodies against caveolin, myosin heavy chain type I (MHC1), and translocase of the outer mitochondrial membrane 20 (TOMM20). Lipid droplets were visualized using Bodipy 493/503 and LD size, number, and subcellular localization (subsarcolemmal (SS) or intramyofiber (IMF) region) were examined. Mitochondrial network connectivity was measured in longitudinally cut fibers as mitochondrial fragmentation index (MFI), which is computed as the ratio of total number of mitochondrial network particles to total mitochondrial area, a lower MFI indicating a more fused (connected) mitochondrial network. Paired Wilcoxon rank sum test was used to detect changes in MFI, LD content, LD size, and LD number upon repeated cold-induced shivering. Spearman correlation test was employed to correlate MFI and LD characteristics with changes in the area under the curve (AUC) for glucose and insulin obtained during the OGTT performed before and after the cold intervention. **Results:** In type II fibers, we observed a more fused mitochondrial network after 10-day cold-induced shivering (MFI 0.84 ±0.32 vs. MFI 0.55±0.20, p<0.01). Mitochondrial network connectivity as well as LD content, morphology (size and number) and localization in type I fibers were unaffected by repeated cold exposure with shivering. Interestingly, however, in type II fibers the cold intervention induced a significant reduction in LD content, LD size, and LD number, specifically in the SS region, by 61.5%, 28.2%, and 47.5% (all p<0.05), respectively. LD number also decreased in the IMF region in type II fibers (0.016±0.0053 vs. 0.011±0.0058 count/μm2, p<0.05). Jointly, these data suggest that repeated cold exposure with shivering induces a net loss of lipids from LDs in skeletal muscle. The decrease in MFI in type II fibers (reflecting a more fused mitochondrial network) upon repeated cold-induced shivering also positively correlated with the improvement in glucose tolerance, as reflected by a decrease in glucose AUC during OGTT (R coefficient 0.82, p <0.05). No correlations were found between changes in LD morphology in type II fibers and AUCs of glucose or insulin during OGTT.
Conclusion: Ten days of repeated cold exposure with shivering resulted in a more densely connected mitochondrial network and decreased lipid content in LDs in type II skeletal muscle fibers. These findings suggest that changes in mitochondrial network connectivity and LD morphology in skeletal muscle might at least in part contribute to the metabolic benefits of cold-induced shivering.

267. IMPLEMENTATION OF A MULTIDISCIPLINARY FRACTURE LIAISON SERVICE (FLS): EARLY INSIGHTS FROM PADOVA EXPERIENCE

Arcidiacono G.P.[1], Sella S.[1], Sergi G.[2], Camozzi V.[3], Bertocco A.[2], Zanchetta F.[1], Torres M.O.[1], Cannito M.[3], Ruggieri P.[4], Rodà M.G.[4], Sartorello E.[5], Romanato G.[5], Venturin A.[6], Cianci V.[7], Boemo D.G.[8], Nesoti M.V.[8], Degan M.[9], Cecchinato A.[1], Ceolin C.[2], Diogo M.[1], Ferrarese M.[3], Masiero S.[6], Peleg Falb M.[1], Pizziol A.[10], Savino S.[11], Giannini S.[1]
[1]UOC Clinica Medica 1, Azienda Ospedale-Università di Padova; [2]UOC Geriatria, Azienda Ospedale-Università di Padova; [3]UOC Endocrinologia, Azienda Ospedale-Università di Padova; [4]UOC Clinica Ortopedica Traumatologica, Azienda Ospedale-Università di Padova; [5]UOC Ortopedia e Traumatologia OSA, Azienda Ospedale-Università di Padova; [6]UOC Riabilitazione Ortopedica, Azienda Ospedale-Università di Padova; [7]UOC Accettazione e Pronto Soccorso, Azienda Ospedale-Università di Padova; [8]UOC Direzione Medica Ospedaliera, Azienda Ospedale-Università di Padova; [9]UOC Direzione delle Professioni Sanitarie, Azienda Ospedale-Università di Padova; [10]UOSD Accettazione e Pronto Soccorso OSA, Azienda Ospedale-Università di Padova; [11]Dipartimento di Medicina, Università degli Studi di Padova

Introduction: Osteoporosis and fragility fractures represent a major public health problem worldwide. Fragility fractures are defined as low-energy fractures that occur in the absence of significant traumas. Fragility fractures have serious consequences in terms of both morbidity and mortality, the latter with a rate of up to 20-24% in the first year after a hip fracture. Patients who experience a fragility fracture also have at least a two-fold increase in the risk of subsequent fractures, triggering a vicious circle that can lead to loss of independence, disability, and admission to long-term care facilities, with a significant increase in healthcare costs. In Italy, as in other European countries, the incidence of fragility fractures is expected to increase in the coming years, due to the progressive ageing of the general population. However, despite the availability of many treatment options which are effective in reducing fracture risk, a large treatment gap exists, with only a small proportion of patients receiving appropriate therapy even after a hip fracture. The Fracture Liaison Service (FLS) is a model of care designed to address this gap by identifying patients at high risk of fractures, assessing their bone health, and providing appropriate treatment and follow-up care. We here present data on the initial activity of the recently instituted FLS at our University Hospital.
Methods: In March 2023 we implemented a FLS within the "Azienda Ospedale-Università di Padova" with the aim of automatically identifying all patients aged 50 years or older referred to the Emergency Department for a fragility fracture of the hip and because of this admitted to the Orthopedic ward. Patients with fractures related to major trauma or pathological fractu-

res due to pre-existing neoplastic bone lesions were not considered. The FLS team includes several figures of physicians, such as those trained in bone and mineral disorders diagnosis and treatment (Internal Medicine physicians, Geriatricians, and Endocrinologists), Orthopaedic Surgeons, Rehabilitation Specialists, and Emergency Department physicians. The organisation of FLS included an inpatient evaluation in order to identify the main comorbidities as well as the general prognosis by using a multidimensional score (Multidimensional Prognostic Index, MPI). Data on patient demographics, risk factors for skeletal fragility, and laboratory as well as imaging tests were collected. Informations on pre-admission treatments for any possible clinical condition, including osteoporosis were also recorded. All data werecollected in a dedicated management database system.
Results: Here we present data from the first two months of activity (March-April 2023). A total of 122 patients aged 50 years or older with a fragility fracture of the hip were automatically identified and referred to the Project Coordination Center. Of these, 92 were female (75.4%) and 30 were male (24.6%), with a mean age of 82.2±9.1 years (range 53-100 years); the majority of patients (44.2%) were in the age group 80-89 years. Several patients were previously diagnosed as having arterial hypertension (68.0%), hypercholesterolemia (21.3%), diabetes mellitus (18.9%), heart failure (16.4%), carotid or peripheral artery disease (13.9%), previous myocardial infarction (12.3%), stroke or TIA (9.8%) and venous thromboembolism (7.4%). Thirty-four patients (27.9%) had a diagnosis of severe cognitive impairment. Despite the high comorbidity burden observed in the entire cohort, a large proportion of patients (53.7%) had a low MPI score (0.00-0.33), suggesting a relatively low risk of one-year mortality. On the other hand, many patients had a very high risk of subsequent fractures, with a mean DeFRA score (an Italian-developed risk assessment tool for the prediction of major osteoporotic fractures in the female population) of 36.5±15.3%, with 41.1% of patients having a DeFRA score greater than 50% and 35.2% of patients having experienced at least one previous fragility fracture. Prior to admission, only 11.2% of the patients were receiving anti-osteoporosis drugs and 31.9% vitamin D supplements; after the evaluation, treatment rate increased to 77.8% for anti-osteoporosis drugs and 86.5% for vitamin D supplements, and all the patients were referred to a bone specialist for future follow-up.
Conclusions: The implementation of the FLS model worldwide has demonstrated promising results in improving refracture prevention, reducing fracture-related complications, and lowering mortality rates. Our initial findings confirm that the adoption of this model was effective in increasing treatment rates and has the potential to achieve positive results on refracture prevention also in our context. However, a prospective analysis is necessary to assess adherence to treatment, refracture rate, residual disability, and mortality in the coming months or years.

268. BASEDOW'S DISEASE AND AUTOIMMUNE THROMBOPENIC PURPURA: AN INTRIGUING PATHOGENETIC ASSOCIATION

Prencipe A.[1], Leone P.[2], Susca N.[3], Guastadisegno C.M.[1], Racanelli V.[4], Vacca A.[1], Prete M.[2]
[1]Department of Precision and Regenerative Medicine and Ionian Area, Section of Internal Medicine, School of Medicine, 'Aldo Moro' University of Bari; [2]Department of Interdisciplinary Medicine, Section of Internal Medicine, School of Medicine, 'Aldo Moro' University of Bari; [3]Department of Interdisciplinary Medicine, Emergency Department Unit, School of Medicine, 'Aldo Moro' University of Bari; [4]Department of Cellular, Computational and Integrative Biology - CIBIO, University of Trento, Trento, Italy

The association of Basedow's disease with immune thrombocytopenic purpura (ITP) is uncommon, and a very few case reports have been reported so far. ITP and autoimmune hyperthyroidism can simultaneously occur or the diagnosis of the two diseases can vary from months to years. Treatment with corticosteroids, immunosuppressants and antithyroid drugs usually results in complete normalization of platelet counts.
Here, we report the case of a 33-year-old Caucasian male presented to our hospital's emergency department with a complaint of palpitations, fever, bilateral exophthalmos, difficulty breathing, easy fatigue, headaches and weight loss of 6 kg in few months. Laboratory findings documented hyperthyroidism: low thyroid stimulating hormone (TSH) (0.0083 mIU/mL), elevated serum-free T3 (>10 pmol/L) and serum-free T4 (15,4 pmol/L). Thyroperoxidase antibodies (TPOAb) levels were >2000 IU/mL, TSH receptor autoantibodies (TRAb) levels were 12.48 IU/L and thyroglobulin antibodies (TgAb) levels were 1666 IU/mL. Thyroid ultrasound revealed diffuse heterogeneous and hyperechoic enlargement of thyroid gland with a high increase in vascularity (patter type IV). A diagnosis of Basedow's disease was made and he received oral propranolol 40 mg twice daily and oral methimazole 20 mg daily. Two weeks after, for the onset of purpura, a full blood count was performed, with the finding of severe thrombocytopenia (PLT 9000). Methimazole was withdrawn in the suspicion of an iatrogenic effect and therapy with prednisone 1 mg/kg and IV IgG 25g/day for 5 days was undertaken, with a partial response and an increase of the platelet count at 48000.
Two months later, he returned to our observation complaining of fever, cough, epistaxis and headache. Laboratory tests confirmed values of severe hyperthyroidism, PLT 17,000, ANA positivity 1/160 with nuclear speckle pattern, polyclonal hypergammaglobulinemia equal to 30.9%, bone marrow biopsy revealed isolated megakaryocytic hyperplasia. A diagnosis of idiopathic autoimmune thrombocytopenia (PTI) was made and therapy with azathioprine was started (100 mg/die) associated with corticosteroids and methimazole.
Five months later, for persistent hyperthyroidism and fluctuation of PLT values under 40.000, he underwent surgery to remove the thyroid gland.
Subsequent blood counts documented PLT values within normal limits (PLT 145.000), which still persist.
In this case, although the clinical, hematological and bone marrow features were indistinguishable from immune thrombocytopenic purpura, we observed that there was no improvement in platelet count with corticosteroid and immunosuppressant use alone (or standard ITP treatment protocols) until the complete control of thyroid function by surgical removal of the gland.

269. TRICK OR TREAT: MSSA AS TRIGGER OR COMPLICATION OF LATENT AUTOIMMUNE DIABETES PATIENT

Palumbo F.[1], Finelli M.[1], Palumbo A.[1], Fischetti S.[1], Giordano M.[1], Paolisso G.[2]
[1]Università degli studi della Campania "Luigi Vanvitelli"; [2]Università della Campania "Luigi Vanvitelli"

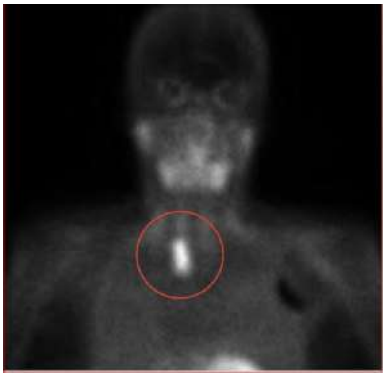
We described a case of 47-years old Caucasian man with decreased consciousness**,**diffuse abdominal pain and nausea. He past medical history was significant for Subacute sclerosing panencephalitis with neurogenic bladder and hyposthenia of lower limbs post COVID-19 vaccine, high blood pressure, chronic kidney disease, was not taking any madication. He reports consumption of alcohol. The man was admitted in hospital due to worsening of abdominal pain, hyperglicemia, polyuria, polydipsia and fever. On admission the patient appeared in substantial discomfort with fever (TC 38°C), blood pressure 150/90 mmHg, heart rate 90 bpm, SpO2 94%, Glasgow Coma Scale of 12 points, because he appeared soporous and confused accompanied by rapid and deep breathlessness; ispection revealed paleness and subcutaneus abscess in the posterior region of the right thigh. Arterial blood gas test detected high anion gap metabolic acidosis with hyperglycemia, superior to > 400 mg/dl. The abdominal wall was not tense, bronchovesicular breath crackles were present in both lower lung fields, cardiac examination resulted regular. Neurological evaluation showed no abnormalities of cranial nerve and preserved stretch reflexes, intact somatosensory system. ECG exhibited sinus rhytm at 90 b.p.m with normal intervals and waves. Laboratory data highlighted: WBC 23.3 x 103/ul (Neut 20.1x 103), creatinine 2.85 mg/dl, urea 119 mg/dL, Glu 201 mg/dL, Hb1Ac 77 mmol/mol, PCR 18,09 mg/dL and urinary ketone bodies was > 5 mg/dl. The clinical and laboratory signs were conistent with diabetic ketoacidosis (DKA) and subcutaneous abscess, so was started an empiric antibiotic therapy and correction of fluid deficits with saline 0.9% and glucose 5%, insuline therapy and potassium repletion. On the second day, the treatment of DKA was resolved and continued with the administration of short-acting insulin and regular long-acting. Further laboratory tests revealed: presence of Ab GAD (13U/ml), C-peptide 11 ng/ml and Hb1Ac 77 mmol/mol. Blood culture and abscess fluid colture were positive for Staphilococcus Aureus MSSA, so the abscess was drained and the ampicillin/sulbactam 3mg, dosing adjustment for renal function, was started. At this poin basal bolus insuline was started. Two week after hospitalized a significant improvement in symptomatology and laboratory markers (WBC 8.3x103/uL, Neut 5.2x103/uL, PCR 0.5 mg/dl and glucose 100 mg/dl) was observed. The patient was discharged with a diagnosis of "Latent autoimmune diabetes of adults (LADA)".
Discussion: A diagnosis of Latent Autoimmune Diabetes in Adults (LADA) may be considered a slowly progressive variant of type 1 diabetes. Patients with LADA are a heterogeneous group with variable titers of antibodies, body mass index (BMI), and rate of progression to insulin dependence. According

to the Immunology of Diabetes Society, patients diagnosed with LADA are defined by adult age of onset (>30 years) and insulin indipendence for at least 6 months after diagnosis plus positvity for circulating islet-cell autoantibodies. At diagnosis, the clinical presentation of autoimmune diabetes is extremely broad, ranging from diabetic ketoacidosis to hyperglycemia controlled with diet alone or hypoglycemic agents. In this setting, subjects defined as having LADA who do not require insulin at first, encompass a wide spectrum of phenotypes from prevalent insulin resistance to prevalent insulin deficiency, sharing halfway clinical and metabolic features of T1DM and T2D. the most prevalent islet autoantibody utilized is GAD. Presence of Glutamic acid decarboxylase antibody GADA, N- terminally truncated GAD65 autoantibody and IA-2A presence determine the future need for insulin therapy. There is no specific protocol for the management of LADA. The main aim of treatment in these patients is to preserve the residual pancreatic beta cell function and to decrease long term risk complications. Insulin therapy is safe and effective in these patients as it preserves beta cell function. Infections are still the main cause of morbidity and mortality in diabetics patient. Diabetes could increase the risk of developing infections and sepsis to the patient. Organ systems where bacterial infections predominate as well as fungal diseases were associated with substantial increases in magnitude among patients with both T1DM and T2DM, but risks were consistently higher for T1DM. Patients with T1DM have approximately double the risk of patients with T2DM for infection-related to death. Thus, sepsis may represent a risck factor to develop DKA in patient with LADA.

270. ABDOMINAL PAIN AND ACUTE PANCREATITIS AS RED FLAGS FOR PRIMARY HYPERPARATHYROIDISM. A CASE REPORT

Salmeri C., Regolo M., Losio A.G., Cassisi G., Munno G., Castelletti F., Cardaci N., Lanzafame A., Fiorenza P., Torrisi E., Malatino L.
Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy

Background: Primary hyperparathyroidism (PHPT). in the 80-85% of cases is due to single parathyroid adenoma causing calcium, phosphorus and bone metabolism disorders.
PHPT is often asymptomatic and incidentally diagnosed, even if hypercalcemia could determine a systemic involvement (anorexia, polyuria, dehydration, polydipsia, constipation, abdominal pain, drowsiness), rarely associated with acute pancreatitis. a higher prevalence of hypertension, arrhythmias (often bradiarrhythmias), left ventricular hypertrophy, heart failure and endothelium dysfunction was also reported, leading in turn to increased cardiovascular morbidity and mortality.
The association p of PHPT with acute pancreatitis is still controversial.
We herein report a case of acute pancreatitis associated with severe and hypercalcemia.
Case Description: A 63-year-old woman was first admitted to the Emergency Room for reported chest pain with electrocardiographic changes suggestive of STEMI. A coronary angiogram showed occlusion of the anterior interventricular artery (AIV), treated with percutaneous coronary intervention (PCI) with drug-eluting stents (DES). During hospitalization in the unit of Cardiology, she manifested a marked sinus bradycardia (heart rate 28 bpm), so that it was necessary to first insert a temporary pacemaker and then an implantable cardioverter-defibrillator (ICD). The echocardiovision revealed hypertrophic left ventricle with areas of regional asynergy and depressed ejection fraction (EF=32%). The patient was classified according to the severity of her symptoms as NYHA class III, ACC-AHA stage C.
Two months later, for the occurrence of intermittent nausea, vomiting and upper abdominal pain, the patient was admitted to our Department of Clinical Medicine at Cannizzaro Hospital, Catania, Italy.
The patient had a past history of nicotine dependence (smoker of 30 pack-years), chronic kidney disease (KDIGO III) and right carotid stenosis. She had never consumed alcohol. Biochemical investigations revealed elevated serum amylase (136 U/I) and lipase (161 U/I). Lipid profile was altered (total cholesterol 317 mg/dL, LDL 210 mg/dL, triglycerides 409 mg/dL). Serum calcium was 15.3 mg/dL (normal range 8.2-10.6 mg/dL), phosphoremia was 1.3 mg/dl (normal range 2.5-4.5 mg/dL), and serum albumin was 3.5 g/dL.
Abdominal ultrasound showed an enlargement of pancreas, presenting with a diffusely uneven structure, confirmed by computed tomography (CT) scan. After the remission of acute pancreatitis, routine haematochemical tests were repeated. Hypercalcemia and hypophosporemia were confirmed by multiple samples (maximum value of serum calcium found 15.3 mg/dl) and serum showed a maximum peak of 2547.90 pg/ml (normal range 12-88). Adequate l saline infusion and frusemide was started. According to the American College of Radiology (ACR) Appropriateness Criteria, the patient underwent the following imaging: parathyroid ultrasound (hypoechoic nodular area extending caudally in the right paratracheal retro-jugular site, to be referred to parathyroid hypertrophy); neck CT (pseudo-nodular area with contrast enhancement in the right parotid region); and SESTAMIBI dual-phase parathyroid scan (late hypercaptation in the right thyroid lobe compatible with parathyroid adenoma). While waiting for surgery, a therapy with Cinacalcet 30 mg 1 cp per day was set up. The patient was discharged with a diagnosis of acute pancreatitis secondary to hypercalcemia due to PHPT.
Conclusions: This case-report underscores the possibility that abdominal pain and pancreatitis could be a complication of severe hypercalcemia, that is a rare extra-biliary cause of pancreatic cell leakage, moreover, longstanding hypercalcemia is often due to parathyroid adenoma/hyperplasia, leading to calcium deposition in the heart and arteries, so potentially amplifying the occurrence of cardiovascular complications.

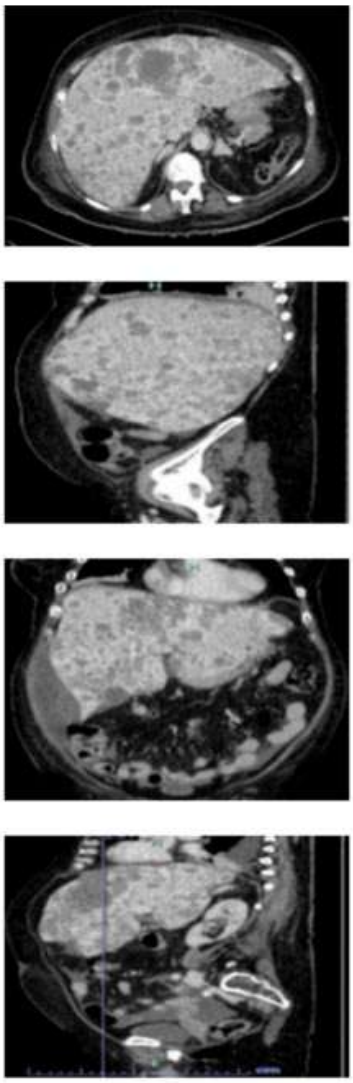


271. A CASE OF NEUTROPHILIA: AN HOLISTIC APPROACH

Lavorato S., Semproni E., Morena M., Tafuri F., Bitto N., Peyvandi F.
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Milan, Italy

Introduction: Neutrophilia refers to an increase of peripheral blood neutrophils at least two standard deviations above the mean. For adults, this generally corresponds to >7700 neutrophils/microL (typically seen in patients with >11,000 white blood cells/microL). Neutrophilia may be due to increased bone marrow production and/or demargination of peripheral blood neutrophils. Increased production of neutrophils may be primary (ie, due to malignant disorders such as myeloproliferative neoplasms) or reactive (ie, in response to infection, inflammation, cytokines or hormones).
Case Report: The patient is a 69-year-old female, former smoker, admitted to ED for persistent neutrophilia, weight gain and mood disorders. She was overweight (BMI=28.8) with a high blood pressure and type two diabetes mellitus (DM) receiving metformin. For two months the patient asked for medical attention for persistent neutrophilia. She was evaluated by a hematologist for neutrophilia which prescribed specific examinations such as BCR-ABL and JAK2 research and abdominal ultrasound with negative results. Systemic physical examination revealed muscle weakness and peripheral oedema and blood tests showed leukocytosis predominantly neutrophilic (17'000/mm3), hyperglycemia, severe hypokalemia and mild increase of transaminases while C-reactive protein, renal and clotting function were normal. Patient was therefore admitted to our ward. Considering the presence of recent hyperglycemia, hypertension with hypokalemia and neutrophilia associated with mild clinical changes (mild round face, central obesity, initial subtle hump) we suspected a one-for-all cause of the syndrome. The patient underwent a screening for hypercortisolism: serum cortisol (138 mcg/dL), cortisol response to low-dose dexamethasone, CRH and ACTH (407 pg/dL). These findings confirmed a diagnosis of ACTH-dependent hypercortisolism. A computed tomography (CT) had already been performed and revealed an invasive tumoral mass at the level of the pancreatic tail, 47/43 mm, and multiple nodules disseminated throughout the liver parenchyma, spontaneously hypodense, compatible with liver metastasis. Percutaneous liver biopsy from one of the nodules was obtained. The histopathological examination was compatible with liver localization of poorly-differentiated neuroendocrine carcinoma of pancreas. Immunohistochemistry (IHC) was strongly positive for synaptophysin, negative for CgA, CDX2 and TTF1 with a Ki-67 prolife-

ration marker of 80-90% in the hotspot areas. After biopsy her condition declined and she passed away.
Discussion: We present a case of ACTH-dependent hypercortisolism caused by a neuroendocrine carcinoma of the pancreas. Among ectopic ACTH-producing lesions, approximately 50% originate from intrathoracic tumors, usually small cell carcinomas [1]. Other well-described tumors of ectopic ACTH-production include medullary thyroid carcinoma, pheochromocytoma, as well as carcinomas of the thymus and pancreas [2]. Endocrine tumors may or may not produce and/or secrete hormones. Diagnosis is often difficult because none of the dynamic biochemical tests achieves 100% accuracy. In our case, however, all tests suggested hypercortisolism, since a) the decline of serum cortisol was less than 50 % in the overnight 8-mg dexamethasone suppression test as compared to basal values and b) the increase in serum cortisol and plasma ACTH was less than 20 % and 35 %, respectively, after CRH stimulation.
Conclusions: We report a case of a 69-year-old female with neutrophilia as a first sign of ectopic ACTH secretion due to a neuroendocrine carcinoma of pancreas. Neutrophilia associated with hypercortisolism is due to central mobilization of the marginated pool. The cancer presented itself with a very rapid evolution since the liver was spared at ultrasound examination a month before. In this rapid evolution of disease the patient didn't have time to develop proper physical stigmata typical of the Cushingoid phenotype.
1.Wajchenberg BL, Mendonca BB, Liberman B, Pereira MA, Carneiro PC, Wakamatsu A, Kirschner MA: Ectopic adrenocorticotropic hormone syndrome. Endocr Rev. 1994
2. Doppman JL, Nieman LK, Cutler GB, Chrousos GP, Fraker DL, Norton JA, Jensen RT: Adrenocorticotropic hormone-secreting islet cell tumors: are they always malignant?. Radiology. 1994



Figures 1, 2, 3 and 4: CT scan: late venous phase showing enlarged liver with multiple lesions in all segments with venous washout of contrast medium, partly confluent with focal necrosis.

272. TWENTY-FOUR HOUR HOLTER ECG RECORDINGS IN NORMOCALCEMIC PRIMARY HYPERPARATHYROIDISM DIFFER FROM HYP ERCALCEMIC HYPERPARATHYROIDISM

Pepe J., Magna A., Sonato C., Sgreccia A., Colangelo L., Cipriani C., Cilli M., Minisola S.
Department of Clinical Sciences, Anesthesiology and Cardiovascular Disease, "Sapienza" University of Rome

Background: There are no data regarding the prevalence of arrhythmias in patients affected by normocalcemic primary hyperparathyroidism (NC-PHPT) in daily life. Hypercalcemia may induce arrhythmias and shortening of QT. High PTH serum levels may also induce arrhythmias in murine models.The aim of the study was to investigate the occurrence of arrhythmias in patients with NC-PHPT compared to hypercalcemic patients with primary hyperparathyroidism (PHPT) and control subjects evaluated with 24-hour Holter ECG.
Methods: Thirteen NC-PHPT postmenopausal women were enrolled and matched with both thirteen sex and age-matched hypercalcemic PHPT patients and 13 controls, previously reported.
Every subject underwent basal ECG, 24-hour Holter ECG and mineral metabolism biochemical evaluation. QT was corrected with Bazett formula (QTc).
Exclusion criteria were as follows: left bundle branch block, pre-excitation and presence of pacemaker, history of severe valvular disease, hypertrophic cardiomyopathy. To exclude hypertrophic cardiomyopathy, we utilized a Sokolow–Lyon index higher than 3.5 mV, which has been defined as a threshold to diagnose left ventricular hypertrophy. None of the patients enrolled were treated with drugs that could interfere with the QT interval. Other exclusion criteria were: known coronary artery disease, diabetes mellitus type 1 and type 2, hypothyroidism and hyperthyroidism, history of hypo-hyperkalemia, hypo-hypermagnesemia, renal disease with a serum creatinine higher than 1.35 mg/dl, and body mass index >30 kg/m2.
Results: We found no difference in anthropometric measurements among the three groups. PHPT patients had higher mean serum calcium levels compared to NC-PHPT patients and to controls (10.9±0.5 vs 9.57±0.53 mg/dl, and vs 9.39±0.45 mg/dl, respectively, both p<0.0001). There was no difference in mean serum calcium levels between NC-PHPT patients and controls. Both NC-PHPT and PHPT patients had higher mean PTH levels compared with controls (97.8± 55.4 vs 42.5±6.92 ng/L, p=0.001; 84.06±17.91 vs 42.5 ±6.92 ng/L, p<0.0001). Mean PTH levels did not differ between NC-PHPT and PHPT patients.
There were no differences in ECG parameters between NC-PHPT and PHPT patients compared to controls, except for QTc. PHPT patients had normal QTc values , but significantly shorter compared with controls (400.6± 14.9 vs 413.61±16.55 ms, (p=0.04) and compared to NC-PHPT patients 412.69±14.50 ms (p=0.04).
A higher prevalence of both supraventricular (SVBPs) and ventricular premature beats (VPBs) during 24-hour Holter ECG monitoring in PHPT was observed compared to both controls and NC-PHPT patients. However, no difference was observed between NC-PHPT patients and controls. In particular, 100% of PHPT had SVPBs, compared to 46% of NC-PHPT (p=0.005), and to 53% of controls (p=0.01). There was no difference between the number of patients with SVPBs in NC-PHPT and controls subjects. 69.2% of PHPT patients experienced VPBs during 24- hour Holter ECG recording vs 15% of NC-PHPT patients (p=0.01) and 23% of controls (p=0.04). We found no difference between in the number of patients with VPBs in NC-PHPT and controls subjects.
Conclusions: NC-PHPT patients displayed no increased prevalence of SVPBs and VPBs compared to controls, while PHPT patients had an increased prevalence of both SVPBs and VPBs compared to controls and NCPHPT patients during 24-hour Holter ECG recordings. This result is probably relates to the short QTc caused by hypercalcemia of PHPT patients, not present by definition in NC-PHPT patients.

273. NOT ONLY A MATTER OF "MIDLIFE CRISIS"

Moriglia S., Giulietti F., Avitabile E., Spannella F., Sarzani R.
Clinica Medica e Geriatrica, INRCA, Ancona

An 86-year-old man with an history of hypertensive and valvular heart failure (HF) with reduced ejection fraction (HFrEF, EF <30%), permanent atrial fi-

brillation and chronic kidney disease (basal creatinine 2 mg/dl, eGFR-CG 35 ml/min/1.73mq), treated with Apixaban 2.5 mg BID, Furosemide 150 mg/day, Bisoprolol 1.25 mg/day, Telmisartan 80 mg/day and Canrenone 50 mg/day (mineralocorticoid receptor antagonist, MRA) was admitted to our Medical Unit from the emergency room for dehydration syndrome in severe acute gastroenteritis.
Since the admission, he was lethargic with hypotension (mean arterial pressure: 70 mmHg) but with preserved peripheric perfusion and active diuresis. No fever nor episodes of diarrhoea and/or vomit occurred during the hospitalization excluding the possibility of microbiological testing.
At the physical examination he had cutaneous hyperpigmentation, hypotension, tachycardia, normal oxygen saturation and peripherical oedema due to HF exacerbation.
Blood tests and ABG results showed severe hypoglycaemia (15 mg/dl), metabolic acidosis, hyperkalaemia (5,6 mmol/L), severe hyponatremia (107 mmol/L) and pre-renal acute kidney injury (AKI, creatinine 4 mg/dl, urea 319 mg/dl). While AKI improved with hydration therapy (creatinine 4à 1 mg/dl), electrolyte imbalance was resistant to intravenous treatment base on fluid therapy and loop diuretics, and suspension of Canrenone treatment and episodes of hypoglycaemia persisted over intravenous glucose perfusion.
In the suspicion of an adrenal crisis (AC), empiric hydrocortisone replacement was started (100 mg iv bolus followed by 50 mg every 6 hours). The diagnosis was supported by a basal serum cortisol of 10 mcg/dl (indeterminate between 3-18 mcg/dl), with normal ACTH and aldosterone. The patient responded favourably to cortisol replacement with normalization of sodium, potassium, glucose and pressure values and fast neurological recover to a normal state of consciousness.
Regarding aetiology, no corticosteroid treatment was administered or suspended before the admission; active infections, ischemic-haemorrhagic events and neoplasm were excluded as biological indices of inflammation and total-body Computed Tomography (CT) scan were all negative. Autoimmune causes were not investigated given the low pre-test probability. Cerebral CT scan revealed senile hypotrophy of the pituitary parenchyma in a context of global atrophy but with preserved thyroidal function (normal values of ACTH and TSH). As a diagnosis of exclusion, we hypothesized a relative AC related to the previous acute gastroenteritis, favourited by iatrogenic adrenal insufficiency due to MRA treatment. Canrenone was suspended long-term and hydrocortisone was slowly tapered to oral glucocorticoid maintenance dose.
CONCLUSIONS: AC is an acute life-threatening emergency that increases the risk of mortality in patients with adrenal insufficiency (AI), if not early identified and treated. In the past two decades, age-adjusted admission rates for AI and AC increased by 62.0% and 90.1%, respectively, partially due to an increase of iatrogenic AI mainly in older men1. Most causes of AI are related to immunotherapies for malignant disease or suspension of corticosteroid treatment. This case enhances how in a comorbid older patient, any stressogenic trigger can uncover acute AI with its related systemic symptoms.

274. WHEN HYPONATREMIA IS A TIP OF AN ICEBERG

Cardaci N., Castelletti F., Lanzafame A., Fiorenza P., Torrisi E., Regolo M., Salmeri C., Losio A.G., Munno G., Cassisi G., Malatino L.
Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy

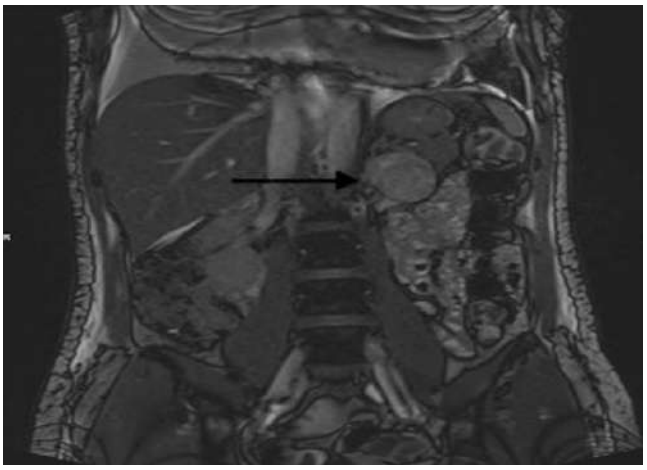
Background: Hyponatremia, an electrolyte disorder in which plasma sodium concentration is lower than normal (135-145 mmol/L), may be triggered by several determinants, including hypocortisolism, which may occur as an isolated condition or in the context of a complex syndrome, as in this case-report.
Case Description: A 76-year-old woman was admitted to our hospital for confusional state, asthenia and hypotension, occurring during last week. Hypothyroidism on levothyroxine, Crohn's disease, a recent pelvic fracture and a surgically treated cataract were her anamnestic features. The inspection identified a dry, thin and "bronze" hyperpigmented skin. Blood chemistry tests revealed severe hyponatremia (111 mmol/l), which was likely responsible for her altered state of consciousness. Sodium chloride infusion was given. The patient also presented with several severe hypoglycaemic episodes, treated with intravenous hypertonic glucose solutions. In order to recognize the etiopathogenesis of hyponatremia several tests were performed, from which a severe state of hypocortisolism (3.90 μg/dl) was discovered. On the basis of the association with hypothyroidism, a possible polyglandular involvement was suspected. Hence, anti-thyroid peroxidase, anti-thyroglobulin, and anti-adrenal antibodies were assayed. The positivity of autoantibodies allowed us to confirm the diagnosis of Schmidt's Syndrome. Thus, replacement therapy was prescribed, first with hydrocortisone and then with cortisone acetate. In the following days, two episodes characterized by hyperpyrexia, shaking chills, hypotension, nausea, vomiting and abdominal pain occurred, for which blood cultures and urine culture were performed, showing positivity for Stenotrophomonas Maltophila and Candida Albicans, respectively. These events, interpreted as Addisonian crisis, triggered by the underlying infectious process, were promptly treated with vasoactive amines and additional doses of hydrocortisone until the patient's hemodynamic stabilization was reached. Targeted antibiotic and antifungal therapy was also prescribed. After the recovery from the acute phase, the patient was discharged and a maintenance glucocorticoid replacement therapy was prescribed.
CONCLUSIONS: Hyponatremia is associated with unspecific symptoms and signs such as general malaise, nausea, vomiting, anorexia, asthenia, headache, and altered state of consciousness. These findings are frequently found, especially among the geriatric population. However, since such dysionia may be a sign of underlying syndromic or isolated conditions, it is important not to just treat the electrolyte imbalance alone, but to integrate it in the context of a more complex pathophysiological state. In this case-report, hyponatremia correlated with hypoglycaemic episodes, arterial hypotension and skin hyperpigmentation, allowed us to hypothesize and then to confirm the diagnosis of hypocortisolism. Furthermore, the past medical history is crucial, as it can be a cue for the diagnostic conclusion. In our case, the association with the already known hypothyroidism led us to suppose a polyglandular involvement on autoimmune basis, despite the old age. Therefore, it is important not to exclude *a priori* these nosological entities, generally associated with a younger age, as some of them may occur later in life.

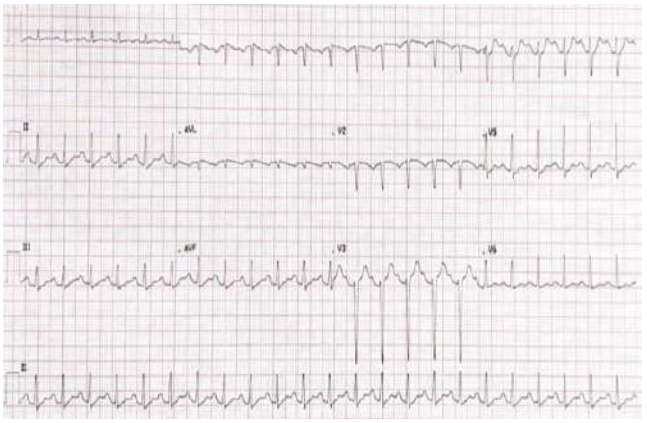
275. THE HIDDEN DIAGNOSIS: A CASE REPORT OF UNDIAGNOSED PHEOCHROMOCYTOMA

Ferrari V., Mazzanti C., Galastri S., De Biase L.
Department of Clinical and Molecular Medicine Sant'Andrea University Hospital, Sapienza University Rome

Pheochromocytoma is a rare neuroendocrine catecholamine-secreting tumor derived from chromaffin cells of the adrenal medulla. The clinical presentation could be vague with symptoms like headache, tachycardia and diaphoresis. The overproduction of these hormones could be related with specific triggers such as stressful situation, exercise and drugrelated. An example of dangerous drugs is metoclopramide, a dopamine D2 antagonist that can induce pheochromocytoma crisis with excess sympathetic stimulation, myocardial stunning, ischemia caused by coronary artery spasmand direct toxic effects of catecholamines on myocytes. 47-year-old women, with no previous relevant medical history, except for spontaneous diaphoresis in the past, who was admitted to the endocrinology clinic for the execution of thermal ablation of a non-secreting thyroid nodule. After the procedure, the patient reported nausea that was treated with metoclopramide i.v. Following this, sudden chest pain, dyspnea with acute respiratory failure and acute pulmonary edema occurred, associated with hypertensive crisis (PA 170/120 mmHg) and tachycardia (FC 115 bpm). The ECG documented widespread alterations of the S-T tract in all branches with the trend of rapidly rising troponins in few hours. The echocardiogram showed diffuse and severe hypokinesis. Urgent coronary angiography has been performed and it showed no epicardial obstructive lesions with a ventricular aspect as mid-ventricular and basal severe hypokynesis. In order to consider a clinical suspicion of iatrogenic adrenergic crisis due to an underlying pheochromocytoma, the 24hour urinary collection was performed that showed the presence of high level of vanilmandelic acid, adrenalin and noradrenaline, normetanephrine and methanephrine. When clinical conditions improved, a CT and then an NMR were performed and both of the exams characterized, in the left adrenal gland, an inhomogeneous high signal intensity referred to pheochromocytoma. In the case reported it is described the case of an Inverted Takotsubo Syndrome triggered by a pheochromocytoma crisis due to iatrogenic cause. This variant of Takotsubo Syndrome is characterized by the evidence of severe basal and mid-left ventricular hypokinesia sparing the apex. The pathogenesis of Takotsubo is still unclear but currently catecholamine-induced cardiotoxicity and microvasculature dysfunction are the most supported theories. According to InterTAKDiagnostic Criteria (2018), one of the possible causes of Takotsubo Syndrome could be the presence of Pheochromocytoma. The diagnosis may be missed during life. Massive secretion of catecholamines can lead to increased morbidity and mortality. For this reason, it is extremely important an early diagnosis to know and to avoid the

use of certain drugs that could break out life-threatening endocrine emergency. Takotsubo syndrome can be the manifestation of the presence of a pheochromocytoma and lead to its diagnosis. We must always suspect the presence of PPGLs and investigate not to commit therapeutic actions and use drugs that could trigger the pheochromocytoma crisis and severe cardiovascular complications.





276. ADRENAL CRISIS DURING COVID-19: DELAYED DIAGNOSIS OF AUTOIMMUNE ADDISON'S DISEASE IN THE ELDERLY

Guandalini G.[1], Davì M. V.[2], Calabria L.[1], Campagnari S.[1], Chesini F.[1], Girelli D.[1], Piccinno E.[2]
[1]Dipartimento di Medicina, UO Medicina d'Urgenza, Azienda Ospedaliera Universitaria Integrata di Verona; [2]Dipartimento di Medicina, UO Medicina d'Urgenza, UOS Endocrinologia, Azienda Ospedaliera Universitaria Integrata di Verona

Primary adrenal insufficiency (PAI), or Addison's disease, is a rare endocrine disorder characterized by impaired secretion of glucocorticoids and mineralocorticoids by the adrenal cortex. The most common cause of PAI, especially in Western countries, is autoimmune adrenalitis. The age of onset of the disease is typically between 20 and 50 years. The signs and symptoms of PAI are nonspecific, often underestimated and misinterpreted, leading to a delayed diagnosis. The most severe complication of PAI is adrenal crisis, an endocrine emergency that can be life-threatening if not promptly treated. This complication is characterized by severe cortisol deficiency or relative cortisol deficiency in the time of a major stress, such as infections or major surgical procedures.
An 82-year-old woman presented to the emergency department in a lethargic state, with severe arterial hypotension and tachypnoea. In the preceding days, she had flu-like symptoms with the onset of fever and gastrointestinal disorders such as nausea, vomiting, diarrhoea, and abdominal pain. Upon arrival at the emergency department a molecular nasal swab test revealed a SARS-CoV-2 infection. Additionally, a chest-abdomen CT scan showed bilateral pneumonia. Laboratory test showed hyponatremia (128 mmol/L), elevated creatinine (2 mg/dL), and hypoglycaemia (50 mg/dl) The patient was admitted to the intensive care unit for septic/hypovolemic shock in the setting of suspected aspiration pneumonia, acute renal failure, and COVID-19 infection. Broad-spectrum antibiotic therapy was initiated, and due to hemodynamic instability, volume replacement and circulatory support with amines were administered. Initially, high-dose norepinephrine was given, followed by the addition of vasopressin with inadequate response. Based on the clinical picture of severe hypotension with refractory shock, gastrointestinal disturbances, hyponatremia, hypoglycaemia, natriuresis (urinary sodium 139 mmol/L), and phenotypic signs of cutaneous hyperpigmentation in non-sun-exposed areas (palms, soles, axillary region, oral mucosa), suspicion of undiagnosed adrenal insufficiency arose. To confirm the diagnosis, a blood sample for plasma cortisol and adrenocorticotropic hormone (ACTH) was immediately performed. The patient was promptly treated with a bolus of hydrocortisone 100 mg iv, followed by 50 mg iv every 6 hours. The cortisol level was inappropriately normal in consideration of the ongoing stressful event (7.38 μg/dL [n.v. 4.78-19.33]), while ACTH was markedly elevated (1.028 pg/mL [n.v. 8-59]). Additionally, aldosterone levels were reduced (37.6 ng/L [n.v 70-300]), while renin was increased (62.5 mU/L [n.v 4.2-45.6]). The clinical picture consisted in a COVID-19 infection which precipitated an Addisonian crisis occurring in a patient with unrecognized adrenal insufficiency. After hemodynamic stabilization, the patient was transferred to our department for further diagnostic investigations. Morphological irregularities of the adrenal glands were excluded as the CT scan performed in the emergency department showed normal findings. Therefore, anti-adrenal antibody levels were measured, and the positive result confirmed the diagnosis of autoimmune adrenalitis. Additionally, the patient's medical history included Hashimoto's thyroiditis. The association between a form of autoimmune thyroiditis and PAI was compatible with autoimmune polyendocrine syndrome type 2 (APS2). Other autoimmune conditions typically associated with APS2, such as celiac disease and type 1 diabetes mellitus, were absent in this patient's case. Therapy with hydrocortisone led to a significant clinical improvement, followed by maintenance hormone therapy with cortisone acetate (25+12.5 mg/day) and fludrocortisone (0.1 mg/day). Considering the significantly elevated ACTH levels, a pituitary MRI was performed, which showed a pituitary gland hyperplasia without focal adenoma.
This case highlights how adrenal insufficiency remains a diagnostic challenge that requires an holistic view of the clinical and biochemical picture. Due to the insidious onset and nonspecific symptoms, the diagnosis is often delayed, and it cannot be excluded in elderly patients. Additionally, knowledge and timing of the treatment for Addisonian crisis are essential: volume resuscitation with crystalloids and intravenous hydrocortisone should be started as soon as the diagnosis is suspected. This case report is useful as a reminder that isolated autoimmune adrenalitis accounts for only 30-40% of cases, while in 60-70% of cases, it develops within the context of autoimmune polyglandular syndromes (APS), usually APS type 2 and less commonly APS type 1. This reported case also suggests an association between COVID-19 and Addisonian crisis in chronic adrenal insufficiency in different ways. First of all, the infection can precipitate a PAI as a relative cortisol deficiency during stressful event. Furthermore, SARS-CoV2 could determine a direct cellular damage or microvascular haemorrhagic/thrombotic complications which could contribute to adrenal dysfunction.

277. HYPOTHYROID PATIENTS HAVE MORE STABLE TSH LEVELS UNDER A LIQUID LEVOTHYROXINE THERAPY

Fallahi P.[1], Ferrari S.M.[2], Elia G. [3], Ragusa F. [3], Paparo S.R.[3], Balestri E.[3], Botrini C.[3], Patrizio A. [4], Mazzi V. [3], Antonelli A. [3]
[1]Department of Translational Research of New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy; [2]Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; [3]Department of Surgical, Medical and Molecular Pathology and Critical Area, University of Pisa, Pisa, Italy; [4]Department of Emergency Medicine, Azienda Ospedaliero-Universitaria Pisana, Italy

Objective: Hypothyroidism affects about 5% of the population, in particular women and people over 60 years of age. In the clinical practice once reached stable thyroid-stimulating hormone (TSH) levels in the normal range, patients are monitored with an annual test of the TSH levels in order to adjust the therapy, if necessary. Levothyroxine (L-T4) is the standard treatment for hypothyroidism and it is dispensed under different formulations. The most used and common formulation is the tablet ones. Our objective is to assess if hypothyroid patients have more stable TSH levels under a L-T4 therapy in a liquid formulation, with respect to the tablet one.

Methods: We compared two groups one including 700 hypothyroid patients in treatment with liquid L-T4, matched by age and gender with another group of 350 hypothyroid patients receiving tablet L-T4. All patients did not report any malabsorption or drug interference issues, and had normal circulating TSH levels at the basal evaluation. They were monitored for two years, and their serum TSH, FT3, FT4 levels were assessed after one and two years.
Results: Age, gender, body mass index, history of chronic autoimmune thyroiditis, initial TSH, and L-T4 dosage were evaluated at the first abnormal TSH value. At the time of initial normal TSH, these parameters were not significantly associated with time to abnormal TSH values. We observed that after 1 year, TSH values were normal in 84% of the patients who received L-T4 liquid formulation, and only in 77% of patients treated with tablet L-T4; after 2 years, TSH values resulted normal in 82% of patients receiving L-T4 liquid formulation, and only in 73% of those with tablet L-T4 ($p<0.05$).
Conclusion: Large population studies showed an increased mortality in people with TSH in the hypothyroid range, therefore the maintainment of a stable TSH level in the normal range is very important. We showed in the long term follow-up a better control of TSH levels in hypothyroid patients who received a liquid L-T4 therapy.

278. NORMALIZATION OF SERUM TSH LEVELS AFTER THE SWITCH FROM ORAL TABLET L-THYROXINE (L-T4) TO THE LIQUID FORMULATION IN PATIENTS WITH ENTERIC LT-4 MALABSORPTION ISSUES

Ferrari S.M.[1], Fallahi P.[2], Elia G.[3], Ragusa F.[3], Patrizio A.[4], Paparo S.R.[5], Balestri E.[3], Botrini C.[3], Mazzi V.[3], Antonelli A.[3]
[1]Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; [2]Department of Translational Research of New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy; [3]Department of Surgical, Medical and Molecular Pathology and Critical Area, University of Pisa, Pisa, Italy; [4]Department of Emergency Medicine, Azienda Ospedaliero-Universitaria Pisana, Italy; [5]. Department of Surgical, Medical and Molecular Pathology and Critical Area, University of Pisa, Pisa, Italy

Objective: L-thyroxine (L-T4) absorption can be impaired by many different factors, such as by enteric diseases (ED). In fact, it has been showed that patients with enteric diseases (ED) such as ulcerative colitis, Crohn disease, colectomy performed for different disorders can suffer from L-T4 tablets malabsorption.
Our objective is to investigate if these issues can be overcame by using a different formulation of L-T4.
Methods: We enrolled thirty-five patients, who received L-T4 in the tablet formulation with ED and reported elevated serum thyroid-stimulating hormone (TSH) levels. All the patients were switched to the oral liquid L-T4 formulation at the same dose.
Results: We observed a normalization, or reduction, of circulating TSH levels after the switch to the L-T4 liquid formulation (at the same tablet dose). Moreover, ten patients were switched again to L-T4 in tablets (at the same dosage) for different reasons, and TSH levels got worse (reaching the hypothyroid range).
Conclusion: Our findings sustain the use of L-T4 liquid formulation in overcoming the issues of the LT-4 absorption impairment in ED. Other conditions of altered L-T4 absorption need to be investigated in order to evaluate if the liquid L-T4 formulation can perform better in the management of this kind of issues.

279. RAMADAN INTERMITTENT FASTING AMELIORATES GASTROINTESTINAL MOTILITY AND METABOLIC PROFILES IN HEALTHY SUBJECTS

Abdallah H.[1], Khalil M.[1], Farella I.[1], JohnBritto S.[1], Lanza E.[1], Santoro S.[1], Garutti G.[2], Portincasa P.[1], Di Ciaula A.[1], Bonfrate L.[1]
[1]Department of Precision and Regenerative Medicine and Ionian Area (DiMePre-J), Clinica Medica "A. Murri", University of Bari "Aldo Moro" Medical School, Bari, Italy; [2]Department of Precision and Regenerative Medicine and Ionian Area (DiMePre-J), Section of Internal Medicine, Endocrinology, Andrology and Metabolic Diseases, University of Bari " Aldo Moro" Medical School, Bari, Italy

Background: Previous studies documented several beneficial metabolic effects of intermittent fasting. Ramadan can be considered a model of intermittent fasting and consists of prolonged fasting practised by Muslims for 24-30 days. The effects of Ramadan intermittent fasting (RIF) on the gastrointestinal tract are not properly investigated. We, therefore, explored noninvasively the effects of Ramadan on gastrointestinal dynamics in healthy subjects.
Methods: In 21 healthy Muslims (M: F 10:11, age 30.7±1.6, BMI 23.3±3.5), we assessed the impact of RIF on caloric intake, physical activity, gastrointestinal symptoms and motility (gastric/gallbladder emptying by ultrasonography, orocaecal transit time by lactulose H2-breath test (Medimar SrL, Milano, IT), anthropometric indices, ultrasonographic quantification of subcutaneous and visceral fat thickness (Sonoscape E2 Exp by Fujifilm by Eurisko Technology srl, Modugno Italy), glucose and lipid homeostasis
Results: Mean caloric intake decreased from a median of 2069 kcal (range 1677–2641) before Ramadan to 1798 kcal (1289–3126) during Ramadan and increased again to 2000 kcal (1309–3485) immediately after Ramadan. Although physical activity remained stable before, during, and after RIF, body weight, body mass index and waist circumference decreased in all subjects and in both genders, together with a significant decrease in subcutaneous and visceral fat thickness and insulin resistance. Compared to baseline, a significant reduction after Ramadan occurred with fasting volume (from 22.4± 4.7 to 20.9 ± 4 mL, P=0.006), postprandial residual volume (from 9.3 ± 2.4 to 6.8 ± 2.1 mL, P=0.0002), gastric half-emptying time (from 67.1 ± 12.1 to 57.8 ± 9.4 min, P=0.007), and OCTT (from 105.7 ± 16.6 to 84.8 ± 5.3 min, P=0.0006). Gallbladder refilling rate increased after Ramadan (from 0.47±0.15 % to 0.67 ± 0.11 P<0.0001).
Conclusion: Ramadan fasting generates, in healthy subjects, multiple systemic beneficial effects in terms of fat burden, metabolic profile, gastrointestinal motility. Further comprehensive studies should assess the potential beneficial effects of RIF in metabolically ill individuals.

280. EVIDENCE OF REDUCED MUSCLE MASS NOT ALWAYS ASSOCIATED WITH REDUCED MUSCLE STRENGTH IN POST COVID-19 PATIENTS: IS THIS PICTURE INDICATIVE OF A RECOVERY FROM ACUTE SARCOPENIA?

Damanti S.[1], Frara S.[1], Villanova M.[1], Vitali G.[2], Canti V.[3], Magnaghi C.[3], Giustina A.[1], Rovere Querini P.[1]
[1]Università Vita Salute San Raffaele; [2]Ospedale San Raffaele ; [3]Ospedale San Raffaele

Background: Sarcopenia is a disease [1] characterized by a progressive reduction in both muscle mass and function [2] which is associated to an increased risk of developing adverse clinical outcomes [3,4].
Acute illnesses, like COVID-19, can act as a catabolic stimulus altering muscle homeostasis and increasing muscle degradation [5,6]. Indeed, weight loss has been reported to be pronounced in COVID-19 patients [7,8] who are at high risk of developing acute sarcopenia.
Acute sarcopenia has been poorly characterised so far. During the first days of immobilisation two mechanisms (increased muscle protein breakdown and reduced muscle synthesis), seem to converge rapidly bringing to an elevated muscle mass reduction (0.5-0.6% per day) [9]. Impairment of muscle synthesis persists over time [9-11] whereas the up-regulation of the ubiquitin proteasome system (responsible for the increased muscle catabolism) [9], though precocious, fast returns to its basal levels [10,12].
To date no data are available on the recover from acute sarcopenia and in particular whether muscle strength is recovered earlier than muscle mass.
We evaluated the prevalence of sarcopenia in a cohort of post COVID-19 patients one month after hospital discharge for SARS-CoV-2 pneumonia.
Design:
Retrospective study using data on muscle mass and function and bone mineral density collected during the routine follow-up of post-COVID-19 patients. The present project was part of the COVID-BioB protocol "*Studio Osservazionale per la fenotipizzazione dei pazienti dei pazienti con infezioni da SARS-Cov-2 e la costituzione di una banca biologica per l'identificazione di fattori predittivi di gravità di malattia, mortalità e risposta al trattamento*" [13].
Population:
We studied a cohort of COVID-19 survivors visited at a dedicated post-COVID-19 clinic one month after hospital discharge for SARS-CoV-2 pneumonia.
INCLUSION CRITERIA
- Ability to walk independently

EXCLUSION CRITERIA
Medical visits took place one month after hospital discharge for SARS-CoV-2 pneumonia. During the visits patients underwent a complete medical evaluation including: anamnesis, physical examination, administration of the following scales: SARC-F [14], EQ 5D-5L [15], ADL [16], IADL [17], MNA-SF [18], evaluation of muscle mass and quality through lower limb ultrasound, evaluation of muscle strength through hand grip, evaluation of muscle performance through SPPB [19]. Two weeks after the medical visits, patients were examined with a body dual energy x ray absorptiometry (DEXA) at the endocrinology clinic of the San Raffaele Hospital.
The diagnosis of sarcopenia was performed according to the European Working Group on Sarcopenia in Older People definition [20].
Results
The sample was composed by 15 patients (8 males) with a median age of 73 years [IQR 70 - 75]. *Table 1* describe the main characteristics of the study population.The mean weight after covid was 8 kg less then the weight before COVID-19 ($p = 0.012$). In 6 patients (40%) the reduction of muscle mass was not associated with a reduction of muscle strength. Only 1 patient (6.7%) had presarcopenia (i.e. reduction of muscle strength not associated with a reduction in muscle mass). Two patients (13.3%) were sarcopenic. *Table 2 describes the Spearman correlations among muscle mass and bone mineral density*
Discussion: In a small sample of 15 post COVID-19 patients we found a reduction of muscle mass not associated with a reduction of muscle strength in nearly half of the sample.
The sample had an important weight loss during hospital stay, therefore we can speculate that even if we did not have measures of muscle mass and strength before COVID-19 a reduction of muscle mass happened during the acute illness, possibly leading to acute sarcopenia. Indeed, the studied patients were not frail (median frailty index 0.10), therefore is improbable that they suffered from chronic sarcopenia.
The fact that we found a higher prevalence of reduced muscle mass compared to a reduction of muscle strength is in contrast with the data typical of the pathogenesis of sarcopenia in which the decline of muscle mass precedes the loss of muscle mass [2]. To date, no data are available on the recover from acute sarcopenia. However, if the recover of muscle strength precedes the recover of muscle mass as it is for their loss, this could explain the picture that we found in our cohort of post COVID-19 patients.
Finally, the absence of a correlation between muscle mass and mineral density could indicate that acute sarcopenia does not correlate with osteopenia, but further studies are needed also to shed light on this point.

281. A RAPID COGNITIVE DECLINE IS ALWAYS A DEMENTIA?

Montozzi G.[1], Ferraioli Y.[1], Tana C.[1], Bigoni S.[1], Claudi I.[2], Curina L.[1], Pagliarecci G.[1], Manfredi L.[3], Fraticelli P.[3], Moroncini G.[3]
[1]Scuola di Specializzazione in Medicina Interna, Università Politecnica delle Marche, Ancona, Italy ; [2]Scuola di Specializzazione in Allergologia e Immunologia clinica, Università Politecnica delle Marche, Ancona, Italy; [3]Clinica Medica, Dipartimento di Medicina interna, AOUM, Ancona, Italy

Clinical case: A 71 years old man was referred to the emergency department for progressive asthenia, cognitive decline, recent appearance of edema in the lower limbs and fever (T max 38°C). One month before the onset of these symptoms, a single episode of headache lasting three days was reported. These clinical aspects were attributed, after a neurological evaluation, performed some days before, to an initial dementia. Blood examinations revealed anemia (Hb 9.9 g/dl), biological inflammation syndrome (C-reactive protein 2.98 mg/dl with a normal value < 0.5 mg/dl), moderate hyponatremia (126 mEq/l) and low level of TSH (TSH 0.187 mcU/ml). In his past medical history the patient reported suffering from congenital deficiency of coagulation factor VII (use of recombinant activated factor VII in case of invasive procedures/surgery), ventricular extrasystole in amiodarone therapy, OSAS in nocturnal C-PAP and hypercholesterolemia.
On the emergency department an empiric antibiotic treatment with ceftriaxone was started associated to intravenous sodium reintegration. A refractory hypotension was treated with norepinephrine infusion, with progressive recovery of basal blood pressure values.
During the admission in our department, the patient was pyretic (37.6°) with slowed speech and non-markable diffuse edema.
In the suspicion of an endocrinological pathology, due to the ideational and motor slow down, thyroid function was checked with evidence of low levels of TSH, FT3 and FT4 (TSH 0.187 mcU/ml, fT3 1.7 ng/dl, fT4 0.54 ng/ml), consistent with central hypothyroidism, therefore all pituitary hormones were dosed with evidence of panhypopituitarism (serum cortisol 0.4 mcg/dl, ACTH 5 pg/ml, FSH 0.8 m/U/ml, LH 0.3 m/U/ml, vasopressin 5.24 pml/l , prolattin 11.8 ng/ml, SHBG 129.1 mmol/l, testosterone 0.03 ng/ml) so a replacement therapy with cortisone acetate and levothyroxine was immediately started. In the following days, while the general clinical conditions of the patient improved, we recorded the appearance of polyuria, secondary to the involvement of the posterior pituitary with subsequent central diabetes insipidus treated with benefit with oral desmopressin.
In order to identify potential causes of panhypopituitarism, a brain magnetic resonance with gadolinium was performed with evidence of an expansive cystic process in the sellar region compatible with Rathke's cyst, which raised the sellar diaphragm and marked the pituitary parenchyma with associated asymmetry of the pituitary gland, without any other alterations of the cerebral parenchyma. Radiological features were evaluated by neurosurgeons but a surgical treatment was not indicated, since optic chiasm was not compressed. At the radiological evaluation a clear lesion of the pituitary did not appear evident except for a gland distortion: cystic lesion showed slight phenomena of enhancement which could be explained as recent modification due to an expansive process or bleeding; alternative hypotheses were an adenoma undergoing apoplexy, malignant nature of the cyst or acute autoimmune hypophisitis.
Furthermore, to exclude a systemic process with pituitary gland localization (like granulomatous disease), a chest/abdomen CT scan was performed with evidence of a "ground glass" hyperdensity of the left lung parenchyma associated with a slight ipsilateral pleural effusion, densitometric disomogeneity of the thyroid gland with small hypodense focus of the right lobe; ACE, IGG4, gamma globulins, LDH were all normal.
Conclusions: Clinical aspects and laboratory abnormalities were rapidly corrected with replacement therapy without evidence of an inflammatory or infectious process, so a definite cause was not found. Therefore, close pituitary and systemic follow-up will be required for a complete definition. The clinical case underlines the central role of the internist in the correct classification of a clinical problem through a correct anamnesis, physical examination, serological and diagnostic evaluations. If the diagnosis of dementia has not been refuted, and a simple search for major blood tests with thyroid function has not be done, the patient would have been mistreated as demented.

282. PROMISING INNOVATIVE BIOMARKERS FOR FRAILTY AND SARCOPENIA: DATA FROM THE FRASNET STUDY

Damanti S.[1], Lanzani C.[1], Zagato L.[2], Citterio L.[2], Manuta P.[1], Rovere Querini P.[1]
[1]Università Vita Salute San Raffaele; [2]Ospedale San Raffaele

Introduction: The number of older individuals is progressively growing: people aged 65 years living in the European Union are predicted to increase from 18.5% in 2010 to 28.7% in 2060. In parallel to this ageing process there is an increment of the number of pre-frail and frail people who are at risk of developing disability and other adverse events. Estimates of the prevalence of frailty vary between 4 and 59.1% of the population over 65 years depending on its definition. Frailty is a multidimensional dynamic condition, whose prevalence increases with age, but is independent of chronological age, characterized by decreased physiological resilience and a weakened response to stressors.There are many definitions of frailty, but the two main broad constructs used in the clinical practice are the Cardiovascular Health Study phenotype model, also known as Fried's phenotype model, and the Canadian Study of Health and Aging cumulative deficit model, commonly known as Rockwood's frailty index. Fried's phenotype describes frailty as a biological syndrome resulting from deficits in five physiological domains: global weakness, overall slowness, exhaustion, low physical activity and unintentional weight loss. Though being focused on a physical dimension, Fried's criteria may be influenced by psychological condition like depression thus equal scores may not identify people having the same level of frailty. Anyway, Fried's criteria have the merit of underling the dynamic aspect of frailty. Indeed, frailty is a continuum which can progress from a pre-frail to a frail status but can also reverse to even a robust condition if adequate intervention are adopted. Rockwood's index, proposing a measure of frailty as a risk state in terms of the number of health 'deficits' that are manifest in the individual, has the advantage of being more multidimensional than Fried's criteria. Indeed, it incorporates polypharmacy, cognition, mental health and activities of daily living in addition to physical weakness. However, it is more time spending to perform and more difficult to apply in clinical practice. Frail in-

dividuals, having a weakened response to stressors, are predisposed to poor clinical outcomes (disability, dementia and falls) and adverse events (hospitalization, institutionalization and mortality).Identifying biomarkers to predict frailty and age-related disease progression would be of paramount importance to adequately manage complex chronic patients. In this study we aimed at assessing the association between cytokines and single nucleotid polymorphisms (SNPs) with frailty and presarcopenia in a cohort of community dweeling volunteers by taking advantage of the data collected in the Frailty and Sarcopenia Network (FRASNET) study.
Materials and methods: The FRASNET study was a cross-sectional observational cohort study involving healthy volunteers. The study was performed between the April 2017 and July 2019 in the recreational and cultural centres and retirement homes in Milan and Monza Brianza areas. Participants underwent multidimensional geriatric assessments. Frailty was measured with both the Fried Phenotype and the frailty index created using the criteria defined by Searl et al. Fourty-six variables were included in the computation of the FI thus conferring it a sufficient robustness. The number of deficits recorded for each patient was summed to create the numerator of the FI and then divided by the total number of possible deficits included in the computation of the FI. In cases of missing data, the frailty index was calculated by using an adequately reduced denominator excluding the items for whom data were missing. Participants having more than 20% of missing variables were excluded from the computation of the FI. The score of the FI ranges from 0 to 1, with lower levels identifying fitter individuals. Rockwood et al. proposed a cut-off point of ≥ 0.25 to define 'frail' individuals. However, this value that do not take into account the relative weight of deficits in relation to age and the fact that FI increases with age because deficits tend to accumulate with ageing. Therefore, cut-off proposed by Romero-Ortuno et al that considered as frail people with a FI above the upper 50% CI of the FI distribution in a large longitudinal cohort were also considered. 11.Participants underwent also blood samples. Simultaneous assessment of plasma concentrations of a series of twenty-five cytokines was performed on a subset of the FRASNET cohort, 75 samples. Genotyping of targeted single nucleotide polymorphisms (SNP) was performed on genomic DNA from the entire cohort.
Results: Table 1 describes the characteristics of the sample and of the presarcopenic and robust individuals. Table 2 shows the concordance between the different frailty definition. Table 3 shows the correlation among cytokines and frailty index and muscle strength Table 4 shows the associations among SNPs and frailty index.
Discussion: If our results will be confirmed in future studies cytokine and SNP could be used in association with multidimensional geriatric evaluations to predict frailty and presarcopenia in older people.

283. TYPE 2 AUTOIMMUNE POLYENDOCRINE SYNDROME: THE IMPORTANCE OF EARLY DIAGNOSIS AND TREATMENT

Ascione G., Tozzetti C., Nardi C., Ferrentino F., Campana S., Nesi I., Guerrini S., Rostagno C.
Dipartimento di Medicina, Università degli studi di Firenze

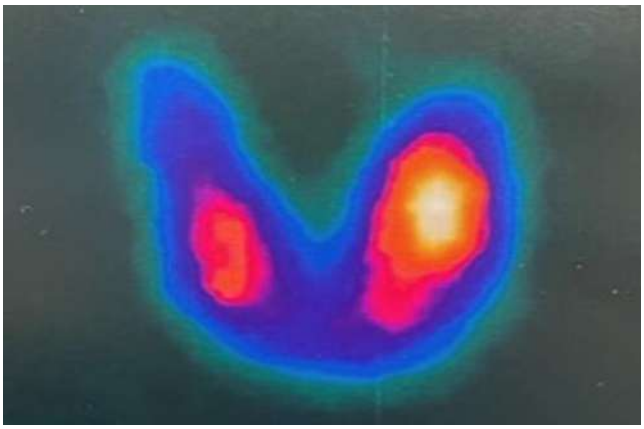
Background: Autoimmune polyendocrine syndromes (APS) are a group of rare diseases characterized by the coexistence of various endocrine glandular deficits with autoimmune pathogenesis. Type 2 APS (Schmidt syndrome), is characterized by the obligatory occurrence of autoimmune Addison disease in combination with thyroid autoimmune disease (usually Hashimoto thyroiditis or Graves' disease) and/or type 1 diabetes mellitus; other organ specific autoimmune disorders, such as primary hypogonadism, vitiligo, pernicious anemia, autoimmune chronic hepatitis and celiac disease may be associated. Therefore, in suspicion of type 2 APS, screening for other associated autoimmune diseases is recommended. APS type 2 has a prevalence of 1 in 20.000, occurs more frequently in women (1:3 male:female ratio) and has a peak incidence at ages 20–60 years, while is rare in children. It has well-identified genetic imprinting, including genes associated with an increased risk of autoimmunity such as HLA-DR3 and HLA-DR4 genes.Autoimmune Addison's disease occurs in 100% of patients with type 2 APS. Clinical presentation of Addison disease includes fatigue, muscle weakness, weight loss, vomiting, abdominal pain and hyperpigmented skin, particularly in sun-exposed areas. The acute presentation includes severe hyponatremia and hypokalaemia, hypotension progressing to shock, coma, and death, if not immediately treated (Addison's crisis). Diagnosis is confirmed by the presence of elevated plasma levels of adrenocorticotropic hormone (ACTH) associated with low levels of plasma cortisol; in addition, the main specific characteristic of autoimmune Addison disease is the presence of serum antibodies directed to adrenal steroidogenic enzymes, more often antibodies directed to 21-hydroxylase. The treatment of APS consists of hormone replacement therapy.
Case report: We reported a case of a 46-year-old woman presenting to the emergency department (ED) for fatigue, vomiting and weight loss. Her past history was notable for hypothyroidism in replacement therapy with levothyroxine (100mcg for 4 days + 125mcg for 3 days per week), and recent diagnosis of renal failure with hyperkalemia, on kayexalate therapy. Clinical examination showed hypotension and hyperpigmentation of sun-exposed skin. Laboratory tests showed renal failure (serum creatinine 1.33mg/dl), normocytic anemia (hemoglobin10.4 g/dl, mean corpuscular volume 90.4 fL), hyponatremia (131 mEq/dl) and hypoglycemia (42 mg/dl); kalemia was in normal range. In suspicion of primary adrenal insufficiency, specific laboratory tests were requested, which showed non doseable serum cortisol, elevated ACTH levels (1235 ng/L) and renin levels (200.5 mU/L), hypoaldosteronism (1.1 ng/dl) and hypoandrogenism (non doseable dehydroepiandrosterone). Abdominal ultrasonography showed normal kidney echotexture and size. Anti-adrenal antibodies resulted positive, confirming the autoimmune etiology of Addison disease. Replacement therapy with cortisone acetate (37.5mg/day) and fludrocortisone (0.1 mg/day) was initiated, with clinical benefit and normalization of glycemia, electrolytes and renal function.Considering the history of hypothyroidism, thyroid ultrasonography was performed, showing inhomogeneous echotexture thyroid with multiple nodular areas; laboratory tests also showed elevated levels of anti thyroperoxidase antibodies (243 IU/ml), confirming the presence of autoimmune thyroiditis in the context of type 2 APS. Under replacement therapy with levothyroxine, thyroid stimulating hormone (TSH) and thyroxine (T4) resulted within normal range, while triiodothyronine (T3) was reduced (2.8 pmol/L). Screening for type 1 diabetes mellitus was not performed because of hypoglycemia due to Addison's disease.
Considering the anemia and the diagnosis of type 2 APS, a search for gastric mucosal autoantibodies was performed, which resulted positive. However, further blood tests ruled out vitamin B12 deficiency, showing increased reticulocytes (2.3%), negative hemolysis indexes and no iron or folic acid deficiency. Screening for celiac disease was also negative. On abdominal ultrasound, gastric tumefaction had also been reported, therefore, in suspicion of a bleeding gastric tumor lesion, esophagogastroduodenoscopy was performed, with evidence of a 4-cm sessile polyp undergoing excisional biopsy, without signs of gastritis. Histology showed aninflammatory fibrous polyp. Therefore, the patient was discharged in good clinical condition and referred to the endocrinologist for follow-up. Blood tests performed 3 months later showed mild hypothyroidism (TSH 7.06 mU/L), for which levothyroxine dosage was increased (125mcg for 5 days + 100mcg for 2 days per week), normal parathormone and calcium, decreasing ACTH (186.3 pg/ml), normalized renin (28.4 mU/L), sodium 138 mEq/L, potassium 5.1mEq/L.
Conclusion: This case report underlines importance of early recognition and treatment of acute endocrine diseases, and the necessity to investigate patients with autoimmune diseases for coexisting conditions. Appropriate management may reduce morbidity and mortality significantly in patients with autoimmune poly-glandular syndrome.

284. MULTIPLE RELAPSES OF BASEDOW-GRAVES' DISEASE

Piacevole A., Alfano M., Sasso F.C.
Università della Campania L. Vanvitelli

A 36-year-old female patient comes at our clinic with tachycardia and restlessness. In her past medical history, she presented neuropathy of small fibers, non-alcoholic steatohepatitis, and dyslipidemia. On clinical examination appeared to be in good clinical condition, afebrile; reported regular diuresis and bowel function but difficulty sleeping. Fine tremors in the upper limbs were also present, but there were no evidence of exophthalmos. The electrocardiogram (ECG) showed sinus tachycardia; haematochemical investigations revealed a high thyroid hormones value with suppressed Thyroid Stimulating Hormone (TSH) and thyroid ecocolordoppler displayed a multinodular goiter (increased thyroid volume with multiple nodular forms). The positive results of antibodies to TSH (TRAb) validate the previously clinical suspicion of Basedow-Graves' disease, not aggravated by ophthalmopathy. Therefore, therapy was set with Propylthiuracil 50 mg 1 pill three times a day (in anticipation of pregnancy) and Propranolol 40 mg ¼ pill twice a day. At the end of the therapy, which is prolonged for 18 months, the patient presented euthyroidism (TSH 0.48, ft3 2.98, fT4 8.2) and a TRAb value within the reference limits. The patient remained asymptomatic for 18 months,

interrupted by onset of cardiopalms and tachycardia, for which she returned to outpatient evaluation where a suppression of TSH was observed (0.0002) with an increase in the value of thyroid hormones (fT3 24 and fT4 54). The title of TRAb was increased (40.62) and a new thyroid ultrasound showed a volumetric growth of the thyroid gland, inhomogeneous, hyperechoic, micronodular, with a moderate improvement in intraglandular vascularity. Graves' disease relapse was diagnosed and attack therapy with Metimazole (2 pills three times a day) was set for six months, in absence of benefit. Therefore, treatment with radioactive iodine was established after discussing the risks and benefits of alternate therapy with the patient. Following treatment, the patient experiences an initial phase of euthyroidism followed by hypothyroidism, which is managed for about a month with Levothyroxine 50 mcg 1 pill a day. About three months from the radiometabolic treatment, the patient reports a slight weight loss, increased heart rate and agitation. Thyroid hormone levels are as follows: ft3 4.96, fT4 12; TSH 0.002, TRAb 5.32, with thyroid ecocolordoppler overlapping the preceding values. A thyroid scintigraphy was therefore performed which showed an overuptake of the gland. This is a second relapse of Basedow- Graves' disease. The patient also has exophthalmos, which was not evident in earlier examinations. For this reason it is decided to undergo surgical treatment with thyroidectomy.
Conclusions: Basedow-Graves' disease is a syndrome defined by hyperthyroidism and goiter, sometimes complicated by ophthalmology and rarely by pretibial myxedema, with a peak of incidence in women, between the fourth and sixth decades of life. There are several predictive factors of recurrence risk, including goiter size, positive antibody titer at the end of treatment, young age at the time of diagnosis, short duration of antithyroid medical treatment. Some of these are combined together to form the GREAT score (Graves' Recurrent Events After Therapy). The size of the goiter is the most important predictor. The disease was more aggressive than expected, despite the patient's minimal chance of recurrence. In this case thyroidectomy may have been the only option from beginning for achieving total pathological remission.



EPATOLOGIA

285. EFFECTS OF A COMBINATION OF EMPAGLIFLOZIN PLUS METFORMIN VS. METFORMIN MONOTHERAPY ON NAFLD PROGRESSION IN TYPE 2 DIABETES: THE IMAGIN PILOT STUDY

Caturano A.[1], Galiero R.[1], Loffredo G.[1], Vetrano E.[1], Medicamento G.[1], Acierno C.[1], Rinaldi L.[1], Marrone A.[1], Salvatore T.[2], Monda M.[3], Sardu C.[1], Marfella R.[1], Sasso F.C.[1]
[1] Department of Advanced Medical and Surgical Sciences, University of Campania Luigi Vanvitelli, I-80138 Naples, Italy; [2] Department of Precision Medicine, University of Campania Luigi Vanvitelli, I-80138 Naples, Italy; [3] Department of Experimental Medicine, University of Campania Luigi Vanvitelli, I-80138 Naples, Italy

Non-alcoholic fatty liver disease (NAFLD) comprises a heterogeneous group of metabolic liver diseases and is characterized by the presence of steatosis in at least 5% of hepatocytes. The aim of our study was to assess the effect of the combination therapy of empagliflozin + metformin vs. metformin monotherapy on NAFLD progression in type 2 diabetic (T2DM) patients. Sixty-three metformin-treated T2DM patients who were SGLT2i-naïve and had an ultrasound diagnosis of NAFLD (aged 60.95 ± 11.14 years; males, 57.1%) were included in the present analysis. Thirty-three started the combination therapy. All patients were observed for 6 months and routinely monitored with anthropometry, blood biochemistry, and FibroScan®/CAP. At the 6-month follow-up, the combination therapy group presented a significant reduction in BMI (30.83 ± 3.5 vs. 28.48 ± 3.25), glycated hemoglobin (8.2 (7.4–8.8)) vs. 7.2 (6.8–7.9), ALT (68.5 (41.5–88.0) vs. 45.00 (38.00, 48.00)), CAP parameter (293.5 (270.0–319.25) vs. 267.00 (259.50, 283.75)) and steatosis degree ($p = 0.001$) in comparison with the control group, whose parameters remained almost stable over time. In patients affected by T2DM, the combination of empagliflozin + metformin vs. metformin monotherapy ameliorated liver steatosis, ALT levels, body weight, and glycated hemoglobin after a 6-month follow-up.

286. CO-STIMULATORY SIGNALS MEDIATED BY ICOS INFLUENCE THE HEPATIC EXPANSION AUTO-AGGRESSIVE CD8+ T CELLS IN NASH

Smirne C.[1], Crobu M.G.[2], Provera A.[3], Dianzani U.[3], Colangelo D.[4], Albano E.[3], Sutti S.[3], Pirisi M.[1]
[1]Internal Medicine Unit, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy; [2]Laboratory of Molecular Virology, Maggiore della Carità Hospital, Novara, Italy; [3]Department of Health Sciences and Interdisciplinary Research Centre for Autoimmune Diseases, University of Piemonte Orientale, Novara, Italy; [4]Laboratory of Pharmacology, Department of Health Sciences, University of Piemonte Orientale, Novara, Italy

Background and aims: Recent evidence indicated that cytotoxic CD8+ T-lymphocytes play important role in the progression of non-alcoholic steatohepatitis (NASH) toward hepatic fibrosis. The Inducible T-cell Co-Stimulator (ICOS) present on T lymphocytes and its ligand ICOSL (B7h) expressed on myeloid cells are member of the B7/CD28 family and play multiple roles in immunity by regulating T-cell activation/survival. From the observation that ICOS-expressing CD8+ T-cells are important in driving liver healing following acute injury, we have here investigated the possible involvement of ICOS-ICOSL dyad in modulating T-cells functions during NASH evolution.
Methods: In this research, ICOS and ICOSL were investigated in experimental model of NASH based on mice feeding with choline/methionine deficient (MCD) or a cholesterol-enriched Western (WD) diets. Soluble ICOS (sICOS) and ICOSL (sICOSL) were then dosed in a group of 81 Caucasian NASH patients aged ≥18 years and including all consecutive subjects undergoing a liver biopsy as part of their normal clinical practice at a single liver clinic of an academic hospital and willing to donate a blood sample.
Results: The results obtained showed that liver CD8+ T cells expressing ICOS expanded in animal models of NASH in parallel with an up-regulation of ICOSL in CD11bhigh/F4-80+ monocytes/macrophages (MoMF). Mice deficient for ICOS receiving the MCD diet for 6 weeks had milder steatohepatitis. This effect was confirmed in mice fed with the WD diet for 24 weeks that also showed reduced hepatic fibrosis. The characterization of ICOS+/CD8+ T-cells in WD-fed mice showed that they featured C-X-C Motif Chemokine Receptor 6 (CXCR6) and Programmed cell Death Protein-1 (PD-1), previously associated with the capacity of killing hepatocytes. Conversely, ICOSL+ MoMFs expressed CD9 and the Triggering Receptor Expressed on Myeloid cells-2 (TREM-2) that characterize NASH-associated macrophages (NAMs). ICOS deficiency strongly reduced CD8+ T-cell expansion and prevented PD-1 upregulation. Such effect also associated with a lowering in the expression of CD122, the β-chain, component of both IL-2 and IL-15 receptors responsible for CD8+ T-cell proliferation and survival. With regard to NASH patients, sICOS and sICOSL concentrations were significantly higher compared to a group of age- and sex-matched healthy controls, but did not vary amongst the different histological stages of the disease.
Conclusions: Altogether these data indicate that, at least in preclinical animal models, ICOS signals are critical for the expansion of auto-aggressive CD8+ T cells in NASH and suggest a possible interaction between these lymphocytes and NAMs, thus hinting at the ICOS/ICOSL dyad as a possible target for therapeutic interventions. However, their possible role as reliable biomarkers of the severity of liver damage in humans needs further validation.

287. DAA-TREATED HCV-INFECTION IN PATIENTS WITH G6PD DEFICIENCY: A PROSPECTIVE OBSERVATIONAL STUDY

Smirne C.[1], Gerevini C.[1], Crobu M.G.[2], Colangelo D.[3], Pirisi M.[1]
[1]Internal Medicine Unit, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy; [2]Laboratory of Molecular Virology, Maggiore della Carità Hospital, Novara, Italy; [3]Laboratory of Pharmacology, Department of Health Sciences, University of Piemonte Orientale, Novara, Italy

Background: Treatment of hepatitis C virus (HCV) infection is now rarely a challenge because direct acting antivirals (DAA) are safe and effective in most patients. However, data are still very limited concerning DAA use in patients affected by glucose-6-phosphate dehydrogenase (G6PD) deficiency (d), an X-linked genetic disorder caused by mutations in the G6PD gene. According to World Health Organization (WHO) estimation, 7.5% of the world population are carriers of G6PDd and 2.9% are G6PD deficient. Although most variants have only slightly subnormal red blood cell survival, the Mediterranean variant observed in Africa, Southern Europe to which Italy belongs, and several Middle Eastern countries renders the cells highly susceptible to oxidative stress.
Historically, previous hepatitis C standard of care with (pegylated) interferon was generally considered safe in G6PDd patients, although most studies were centered on combination therapies (which included ribavirin, in turn a well-known factor for dose-dependent intravascular hemolysis). Concerning current DAA regimens, while patients with comorbid G6PDd may have been included in the clinical trials, specific information on the efficacy and safety in these patients is not available. To the best of our knowledge, current literature cites only two genotype 4 children treated with ledipasvir/sofosbuvir for 12 weeks, in which no treatment-related serious adverse events were reported.
Aims: Based on these considerations, the goal of this study was to evaluate the effectiveness and safety of HCV treatments in this special subpopulation.
Methods: A prospective observational study (from March 2022 to March 2023) was conducted at a single liver clinic of an academic hospital on all consecutive patients treated with second-generation DAAs and with a definite diagnosis of G6PDd at medical history. Three Caucasian subjects were identified. In all cases, the disease was confirmed with a quantitative testing for G6PD activity before any antiviral treatment and after checking that there were no current or recent hemolytic episodes in order to minimize the risk of false negative results.
Results: Patient's sex, age, METAVIR fibrosis stage, HCV genotype, DAA regimen(s) and virological outcome(s) were as follows, respectively: #1: F, 75 years, METAVIR fibrosis stage F1, HCV genotype 2, sofosbuvir/velpatasvir for 12 weeks, sustained virologic response (SVR); #2: M, 49 years, stage F0, genotype 3, glecaprevir/pibrentasvir for 8 weeks, SVR; #3: M, 68 years, stage F2, genotype 2, glecaprevir/pibrentasvir for 8 weeks with no response followed by sofosbuvir/velpatasvir/voxilaprevir for 12 weeks with SVR. At the treating clinician's discretion, an enhanced clinical and laboratory follow-up was performed, generally on a monthly basis both during treatment and up to 3 months after the end of it. In all cases, no treatment-related adverse events were reported. Patient #3, who had a persistent mild predominantly unconjugated hyperbilirubinemia preceding the initiation of antiviral treatment, was then diagnosed with a concomitant Gilbert syndrome, as confirmed by the homozygous polymorphism A(TA)7TAA in the promoter of the UDP-glucuronosyltransferase 1A1 gene.
Conclusions: In a single-center experience, treatment of HCV hepatitis with different DAA regimens in patients with G6PDd as a comorbidity a common occurrence in countries such as Italy proved to be highly effective and safe.

288. LOW PREVALENCE OF HEPATITIS B AND HEPATITIS C VIRUS SERUM MARKERS IN A COHORT OF PREGNANT WOMEN FROM NORTHERN ITALY

Smirne C.[1], Crobu M.G.[2], Colangelo D.[3], Rapetti R.[1], Remorgida V.[4], Pirisi M.[1]
[1]Internal Medicine Unit, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy; [2]Laboratory of Molecular Virology, Maggiore della Carità Hospital, Novara, Italy; [3]Laboratory of Pharmacology, Department of Health Sciences, University of Piemonte Orientale, Novara, Italy; [4]Obstetrics and Gynecology Unit, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy

Background and aims: Mother-to-child transmission is still considered a major factor in the spread of hepatitis viruses. Nevertheless, epidemiological data on hepatitis B virus (HBV) and hepatitis C virus (HCV) in reproductive-age women are limited even in areas like Italy where both viruses have been widespread. Moreover, the changing migration patterns dramatically involving Italy in the last decades which transformed a traditionally country of emigration in a land of immigration may have contributed to invert, or at least slow, this trend toward lower prevalence rates of hepatitis, taking into account that most of migrants are of reproductive age and come from geographical areas with a high or intermediate HBV/HCV endemic. The aim of this study was to investigate the prevalence of HBV and HCV serum markers in a large cohort of pregnant women admitted to a tertiary Obstetric Department in Northern Italy, focusing on possible prevalence differences based on geographical provenance. In other words, it was the authors' interest to try to intercept -at least indirectly- possible migratory flows because of their contribution to viral hepatitis epidemiology.
Methods: Data concerning 33862 pregnant women consecutively admitted to Novara University Hospital over a seventeen-year period (January 2006–December 2022) were retrospectively collected from clinical notes.
Results: A large and increasing prevalence of subjects born outside abroad was found over the years, to the point that in the time frame analyzed women born in 116 countries or territories other than Italy were detected. The overall positivity for both HBV s-antigen (HBsAg) and antibodies to HCV (anti-HCV) was quite low (0.9% and 0.1%, respectively). HBsAg prevalence was significantly higher in non-Italian than in Italian women (2.5 vs. 0.4%, respectively; p<0.001). Similarly, the majority of the anti-HCV positive cases was found in non-Italian subjects compared to females born in Italy, although to a lesser extent (0.9 vs. 0.4%, respectively; p<0.001). Non-Italian HBsAg positive women were significantly younger compared to the HBsAg positive Italian ones (31.0 vs. 37.1 years, respectively; p <0.001). The same result was obtained concerning HCV-positive subjects (32.4 vs. 34.7 years, respectively; p=0.05). Unexpectedly, 32% of HBsAg positive Italian women were born after 1979, and thus should have been vaccinated, according to the Italian massive anti-HBV vaccination program.
Conclusions: These results confirm the dramatic decline of HBV and HCV prevalence that recently occurred in Italy, and highlight the importance and cost-effectiveness of systematic HBV and HCV screening in childbearing age women in order to properly apply the available preventive measures and definitively eliminate the risk of vertical transmission for both viruses.

289. PLASMA PATTERN OF EXTRACELLULAR VESICLES ISOLATED FROM HCV PATIENTS AND THEIR EFFECTS ON HUMAN VASCULAR ENDOTHELIAL CELLS

Smirne C.[1], Coratza G.[1], Greco A.[1], Crobu M.G.[2], Grossini E.[3], Venkatesan S.[3], Tonello S.[1], D'Onghia D.[1], Colangelo D.[4], Tanzi A.[5], Bussolati B.[5], Pirisi M.[1]
[1]Internal Medicine Unit, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy; [2]Laboratory of Molecular Virology, Maggiore della Carità Hospital, Novara, Italy; [3]Laboratory of Physiology, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy; [4]Laboratory of Pharmacology, Department of Health Sciences, University of Piemonte Orientale, Novara, Italy; [5]Molecular Biotechnology Center "Guido Tarone", Department of Molecular Biotechnology and Health Sciences, University of Torino, Turin, Italy

Background: The chronicity of hepatitis C virus (HCV), as well as the presence of the virus in non-hepatic tissues, may create a favorable milieu for the development of potential pathogenic impact on extrahepatic systems and organs, which can be found in up to 50% of infected patients. In particular, the association between the HCV infection and a higher incidence of major adverse cardiovascular events like coronary artery disease, heart failure, stroke and peripheral artery disease has been recently highlighted. Although there is much knowledge about cardiovascular disease (CVD) and HCV infection, studies aimed at identifying the precise role of HCV in the onset of CVD are needed. In addition to a direct pathogenic effect of the virus, it is conceivable the presence also of circulating factors, released in response to HCV infection by different tissues and capable of maintaining and perpetuating cardiovascular damage even beyond the acute event. In this context, good promising candidates could be extracellular vesicles (EVs), which have been proven to transmit HCV infection and contribute to viral spread.
Aims: In this study conducted in mono-infected HCV patients with detectable viremia and native livers, we intended to examine the circulating pattern of EVs and their role in inducing damages to vascular endothelial cells (HUVEC).

Methods: Sixty-five subjects with all the different stages of HCV-related chronic liver disease were enrolled in this case series and compared with a group of age- and sex-matched healthy controls. Their plasma EVs were characterized and used to stimulate human vascular endothelial cells (HUVEC), which were then examined for cell viability, mitochondrial membrane potential and reactive oxygen species (ROS) release.
Results: The results obtained showed that EVs from HCV patients had a mean higher size than that of healthy controls ($p<0.05$); moreover, amongst HCV-positive subjects, EVs were larger in those with advanced fibrosis compared to mild/absent fibrosis ($p<0.02$). Instead, no differences were observed between HCV patients and healthy controls as regarding the concentration of EVs; the same results were also found between different hepatitis C stages. The expression of the surface antigens of EVs isolated from hepatitis C subjects and normal controls showed was analyzed through a exosome flow cytometry assay. EVs reacted with beads expressing CD9, CD63, and CD81, which are markers for exosomal origin; moreover, the mean fluorescence intensity in HCV patients was higher than healthy controls ($p<0.05$) as regarding the main endothelial, platelet and lymphocytic epitopes (respectively: CD105, CD62e; CD42a, CD41b, CD62p; CD3, CD4, CD8, CD14, HLA-DR, DC19, CD29, CD69).
After a dose-response study to analyze the effects of different EVs concentrations on HUVEC, a concentration equal to 50000 EVs/cell was chosen to test the treatment of HUVEC with EVs from HCV patients. We demonstrated that the latter ones were able to reduce HUVEC cell viability and mitochondrial membrane potential, while increasing ROS release. These results were partially related to the stage of liver disease, being more evident with advanced fibrosis. In any case, those harmful effects were reduced by the pretreatment of HUVEC with various blockers of the inflammasome NLRP3 (NLR family pyrin domain containing 3), AMPK (AMP-activated protein kinase) and Akt (protein kinase B) pathways, suggesting their involvement in the above effects. However, similarly to what described above, in severe disease these inhibitors reverted the effects of EVs to a significantly reduced extent compared to what was observed in the lower stages of hepatitis C.
Conclusions: In a real-world setting of HCV patients, we could highlight a circulating pattern of EVs mainly of endothelial and lymphocyte origin, which were capable of inducing damage to the endothelium. These data could represent a novel possible pathogenic mechanism underlying the reported increase of endothelial disfunction and resulting CVD occurrence in HCV infection, and thus could be of clinical relevance even now that diagnosis and treatment of HCV infection are rarely a challenge also in relation to the widespread use of antiviral drugs.

290. ASSOCIATION BETWEEN HEMOGLOBIN GLYCATION INDEX AND SEVERITY OF HEPATIC FIBROSIS RISK

Fiorentino T.V.[1], Natale R.[1], Dagostino A.[1], Sergi S.[1], Cosenza A.[1], Marinaro G.[1], De Vito F.[1], Succurro E.[1], Sciacqua A.[1], Sesti G.[2], Andreozzi F.[1]
[1]Department of Medical and Surgical Sciences, University Magna Graecia of Catanzaro; [2]Department of Clinical and Molecular Medicine, University of Rome-Sapienza, Rome

Hemoglobin glycation index (HGI), obtained by the difference between the observed value of HbA1 and the predicted HbA1c based on plasma glucose concentrations, represents a measure of the degree of hemoglobin non-enzymatic glycation, and it has been found associated with adverse outcomes in subjects with diabetes. We have previously demonstrated that higher HGI levels identify amongst non-diabetic subjects those harbouring a worse cardiometabolic profile and an increased risk of non-alcoholic fatty liver disease (NAFLD). Since an increased non-enzymatic protein glycation has been found to contribute to NAFLD development and progression, it is conceivable that subjects with higher HGI value have an increased risk of hepatic fibrosis. To test this hypothesis we studied 517 white non-diabetic individuals undergone to a complete anthropometric and biochemical evaluation including a 75 g oral glucose tolerance test. Subjects were stratified into quartiles according to HGI levels. The severity of liver fibrosis risk has been estimated by the validated Fibrosis-4 (FIB-4) score. Participants with FIB-4 < 1.3 were considered as having the lowest risk of advanced hepatic fibrosis, FIB-4 ≥1.3 to < 2.67 as having intermediate-risk, while those with FIB-4 ≥ 2.67 were classified at high risk of advanced hepatic fibrosis. The four study groups of HGI were well matched for age and gender distribution. Conversely, as compared to individuals in the low HGI group (1 quartile), those in the intermediate (quartile 2 and 3), and high (quartile 4) HGI groups have increased BMI and waist circumference. After adjusting for BMI, we found that subjects in the intermediate and high HGI groups exhibited a worse metabolic phenotype with progressively increased levels of total cholesterol, triglycerides, and higher concentrations of the liver damage biomarkers aspartate aminotransferase (AST) and C reactive protein (CRP) as compared to the lowest quartile of HGI. Conversely, no difference in glucose tolerance was found between the study groups. Notably, we observed a graded increase of FIB-4 score across the four HGI groups with subjects in the highest quartile of HGI showing significantly augmented values of FIB-4 score in comparison to the lowest quartile (0.99 ± 0.74 vs 0.85 ± 0.25, $p=0.01$). Proportion of subjects having intermediate or high risk of advanced hepatic fibrosis was progressively increased in the intermediate (11% and 0.8%, respectively) and high HGI (17.2% and 0.8%, respectively) groups as compared to the lowest quartile of HGI (5.5% and 0%, $p=0.002$). In a logistic regression analysis adjusted for gender, BMI, total cholesterol, triglycerides, CRP, subjects with higher HGI levels have a 3.88 fold increased risk of having intermediate/advanced fibrosis (95%CI 1.38-10.96, $p=0.01$) as compared to those in the lowest HGI quartile. In conclusion our results demonstrating the association between higher HGI levels and liver fibrosis independently of several potential confounders indicate that HGI may be a useful tool to identify a subset of non-diabetic individuals at increased risk of having hepatic fibrosis, and support the view that a greater degree of non-enzymatic glycation of intracellular proteins plays a pathogenic role in development and progression of NAFLD.

291. THE IMPACT OF SERPINB3-PD POLYMORPHISM ON THE PROGNOSIS OF PATIENTS WITH HEPATOCELLULAR CARCINOMA

Guerra P.[1], Martini A.[1], Sartori C.[1], Ruvoletto M.G.[1], Biasiolo A.[1], Cannito S.[2], Novo E.[2], Quarta S.[1], Tonon M.[1], Piano S.[1], Parola M.[2], Angeli P.[1], Pontisso P.[1]
[1]Unit of Internal Medicine and Hepatology, Dept. of Medicine, University of Padova, Italy; [2]Unit of Experimental Medicine and Clinical Pathology, Dept. of Clinical and Biological Sciences, University of Torino, Italy

Background and Aims: Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide. Although curative options can afford long-term survival in patients with early-stage tumours, the actual strategy for HCC surveillance misses over one-third of HCC at an early stage. Chronic inflammation and neoangiogenesis play a central role in the promotion of carcinogenesis. SerpinB3 (SB3) is a serine proteinase inhibitor involved in tumorigenesis and promoting a pro-inflammatory milieu. The polymorphic variant SerpinB3-PD (SB3-PD) presents a substitution in the reactive centre loop of the protein (Gly351Ala), determining an improved anti-protease activity. This study aims to investigate the role of SB3- PD as a predictor of mortality in patients with liver cirrhosis and HCC and to assess the effect of SB3-PD in the pro-inflammatory response in vitro.
Methods: SB3-PD polymorphism was assessed in 107 cirrhotic patients with HCC, followed up from HCC diagnosis to death or transplant for a median period of 21 months. The results were analyzed in relation to clinical, radiological, and laboratory data, BCLC stage at baseline, and treatments of HCC during follow-up. In vitro study was conducted on a human monocytic leukaemia cell line (THP-1) treated with recombinant protein SB3-wild type (WT) or the polymorphic variant SB3-PD. mRNA quantification of pro-inflammatory cytokines was performed by quantitative real-time PCR, whereas protein quantification was carried out by ELISA.
Results: Patients carrying SB3-PD polymorphism (n=38; 35.5%) at diagnosis showed larger tumours, higher alpha-fetoprotein levels and more frequent vascular invasion and metastasis, associated with significantly lower survival compared with patients carrying SB3-WT (34.3 vs 53.8 months, p=0.009). SB3-PD was proven to be an independent predictor of mortality in patients with HCC, together with BCLC stage, ALBI grade, alpha-fetoprotein values, N/L rate and ALP values. In vitro results showed that THP-1 cells treated with SB3-PD had a more abundant and prolonged cytokine production, compared to controls.
Conclusion: Patients with liver cirrhosis and HCC carrying SB3-PD polymorphism have a poorer prognosis and the SB3-PD variant determines a stronger pro-inflammatory response, supporting its greater carcinogenetic effect. The assessment of SB3-PD polymorphism could help to personalize screening strategies for HCC.

292. CHOLESTATIC HCV-RELATED CRYOGLOBULINEMIA, A NEW CLINICAL AND PATHOLOGICAL ENTITY: A CASE-CONTROL STUDY

Romeo S.[1], Dalbeni A.[1], Amendola S.[2], Cattazzo F.[1], Tomezzoli A.[2], Sacerdoti D.[3]
[1]University and Azienda Ospedaliera Universitaria Integrata of Verona, Division of General Medicine C, Department of Medicine, Verona, Italy; [2]University and Azienda Ospedaliera Universitaria Integrata of Verona, Department of Diagnostics and Public Health, Section of Pathology, Verona, Italy; [3]University and Azienda Ospedaliera Universitaria Integrata of Verona, Liver Unit, Department of Medicine, Verona, Italy

Background and Aims: Mixed cryoglobulinemia (MC), the most common extrahepatic manifestation in chronic hepatitis C virus (CHC), persisting even after virus eradication with direct-acting antiviral agents, can manifest clinically as a systemic vasculitis with manifestations ranging from purpura, arthralgia, and weakness to more severe neurological and kidney involvement and cirrhosis development. Up today, the relationship between MC and liver intrahepatic cholestasis is unknown. Our study aims to investigate a possible correlation between MC and intrahepatic cholestasis in CHC patients.
Method: 31 hepatitis C virus (HCV) + MC + patients were enrolled, matched

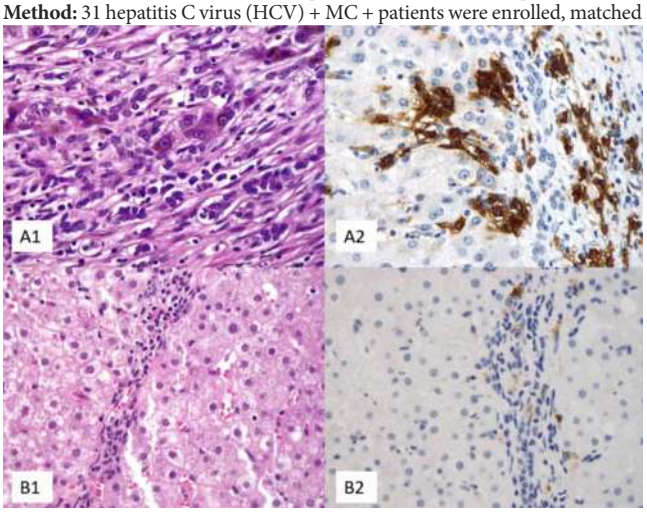


Figure 1.

293. AUTOIMMUNE HEPATITIS TRIGGERED BY SARS-COV-2 INFECTION

Ibba F.[1], Massaro M.G.[2], Pero E.[1], Pellegrino S.[1], Lipari A.[1], Rognoni F.[1], Agnitelli M.C.[1], Giustiniani M.C.[1], Gallo A.[1], Montalto M.[3]
[1]Policlinico universitario A. Gemelli; [2] Policlinico universitario A. Gemelli; [3]Policlinico universitario A. Gemelli, Università Cattolica del Sacro Cuore

In the last few years, much of medical interest has focused on Sars-Cov-2 infection; it is already known that, a part from pulmonary disease, it can causes a multiorgan involvement, including the liver. In particular, a few reports have reported an autoimmune hepatitis (AIH) triggered by SARS-CoV-2 infection, but no data are available about the specific liver inflammatory infiltrate and cluster of differentiation by immunohistochemical staining. We describe a case of AIH triggered by Sars-COV-2 infection, whose immunohistochemical examination was performed.
A 60-year-old man was admitted to our Emergency Department for alterations of hepatocellular necrosis and cholestasis indexes documented by the blood chemistry tests performed for asthenia. He did not report any chronic diseases and medications. A month earlier the patient reported a 10 days paucisymptomatic SARS-CoV-2 infection, treated at home with amoxicillin/clavulanate and ibuprofen. He completed vaccination for SARS-CoV-2 a year earlier. He reported intake of 4 alcohol units every day from youth, but he denied a recent increase. Family history resulted negative for autoimmune or liver disease. Blood chemistry tests confirmed the increase in bilirubin (3.1 mg/dl), in ALT (1390 IU/L) and in AST (1348 IU/L); ALP and GGT were also increased (317 UI/L and 353 UI/L respectively). Serum protein electrophoresis documented polyclonal hypergammaglobulinemia and IgG was increased (35 g/L). The INR (1.15) and blood counts were within normal limits (Hb 13.9 g/dL, MCV 86.9fL, PLT 134/mm3 and WBC 5.79/mm3). The serologies of hepatotropic viruses and for HIV were negative. Instead, the ASMA and ANA were positive (1:40 and 1:640, respectively). Anti-LKM and AMA were negative. An ultrasound of the abdomen ruled out signs of advanced fibrotic liver disease. An abdominal magnetic resonance imaging documented diffuse edema of the periportal-biliary spaces associated with periportal fluid and pericholecystic levels. Finally, for the persistent high hepatocellular necrosis and cholestasis indexes, a liver biopsy was performed. Hematoxylin-eosin staining highlighted severe portal inflammation with a rich CD38+ plasma cell component and interface epatitis (Fig. 1, A). Immunohistochemical staining showed low cell CD4+ count (Fig. 1, B) and prevalence of CD8+ (Fig. 1, C) and CD3+ (Fig. 1, D) throughout the whole lobule; CD38+ plasma cells concentration in the portal space (Fig. 1, E) with a lack in the whole lobule (Fig. 1, F). After biopsy, the patient started a corticosteroid therapy (methylprednisolone 1 mg/kg), with a progressive improvement in liver function indices and a relevant reduction of the polyclonal component in the gamma region of the protein electrophoresis; this allowed a progressive dose reduction and initiation of azathioprine. We can conclude that the patient developed a type 1 AIH triggered by SARS-CoV-2 infection. The presence of CD8 T-cells at immunohistochemical examination suggests different mechanisms from classic AIH.
Boettler et al. described a similar case, performing a cytometry on liver biopsy tissue, with a highly activated cytotoxic CD8 T-cell infiltrate with SARS-CoV-2 specificity, in a patient with an overlap syndrome, with both ANA and AMA positivity, occurring 2-3 weeks after SARS-CoV-2 vaccination. According to this result, *Lee et. al* described another overlap syndrome after SARS-CoV- 2 vaccination. It is known that CD8 T-cells are directly involved in the pathogenesis of primary biliary cholangitis; it might justify their presence at the immunohistochemical examination in an overlap syndrome. In both cases above mentioned, ANA and AMA positivity was found. In our case, AMA were negative; we observed just ANA and ASMA positivity, which suggests a diagnosis of type 1 AIH, without overlap. The presence at the immunohistochemical examination of CD8 T-cells, not typical in a classic AIH, suggests that SARS-CoV-2 triggers a specific T-cell immune response. In conclusion, our patient, after SARS-CoV-2 infection developed a type 1 AIH showing histological picture pretty similar to a classic AIH for the abundant presence of plasma cells, and immunohistochemical features similar to those described after COVID-vaccination.

294. LIVER FAT OVER-STORAGE IMPAIRS SINUSOIDAL EXTRACTION EFFICIENCY IN PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE (NAFLD) WITHOUT LIVER FIBROSIS

Di Ciaula A., Bonfrate L., Khalil M., Santoro S. , Abdallah H., Lanza E., Farella I., Portincasa P.
Clinica Medica "A. Murri", Department of Precision and Regenerative Medicine and Ionian Area (DiMePre-J), University of Bari "Aldo Moro" Medical School, Bari, Italy

Aim: The term nonalcoholic fatty liver disease (NAFLD) encompasses several conditions ranging from simple steatosis without inflammation to the necro-inflammatory form of nonalcoholic steatohepatitis (NASH), liver fibrosis, and ultimately cirrhosis. Accumulation of intracellular fat can derange the hepatocytes and sinusoidal space biomechanics resulting in abnormal liver phenotypes. It is still unclear whether simple intra-hepatocyte fat overstorage without liver fibrosis can generate measurable and subclinical liver dysfunctions in NAFLD patients.
Methods: We enrolled 42 subjects who underwent measurement of anthropometric indices, HOMA index, ultrasonography (diagnosis and grading of liver steatosis, extent of visceral fat), acoustic radiation force impulse shear wave elastography (ARFI, grading of fibrosis). Patients with a shear wave velocity above 1.19 m/s (i.e., fibrosis index >F0) were excluded. The infrared spectrometry stable-isotope (13C)-methacetin breath test (MBT) was employed to assess hepatocyte extraction capacity (DOB15 ‰) of methacetin from portal flow and hepatic microsomal metabolization (cPDR30).
Results: Twenty-one individuals had NAFLD and higher BMI, waist circumference, visceral fat thickness and insulin resistance, as compared to non-NAFLD individuals. NAFLD subjects had significantly decreased DOB15 ‰ and the lowest DOB15 occurred with the highest grade of steatosis. The microsomal metabolization efficiency (cPDR30) was comparable in subjects with- or without NAFLD.
Conclusions: Liver steatosis impairs the hepatocyte extraction capacity from portal flow at the level of sinusoidal channels. This finding points to an early, subclinical derangement of hepatocyte biomechanics in the absence of more advanced microsomal dysfunction. The (13C)-methacetin breath test be-

comes a novel dynamic diagnostic tool for the noninvasive detection of liver biomechanical dysfunction, and enriches the evaluation of liver steatosis and visceral fat by morphometric ultrasonography.

295. DIAGNOSTIC ACCURACY OF AGILE3+ SCORE FOR THE NON-INVASIVE IDENTIFICATION OF PATIENTS WITH ADVANCED FIBROTIC NON-ALCOHOLIC FATTY LIVER DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Dalbeni A.[1], Lombardi R.[2], Henrique M.[3], Zoncapè M.[1], Sacerdoti D.[4], Mantovani A.[5], Ravioli F.[6]
[1]Section of General Medicine C and Liver Unit, Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy; [2]Department of Pathophysiology and Transplantation, Unit of Metabolic and Internal Medicine, University of Milan, Italy; [3]Department of Internal Medicine, Federal University of Rio de Janeiro, Brazi; [4]Section of Liver Unit, Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy; [5]Section of Endocrinology, Diabetes and Metabolism, University and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy; [6]Department of Medical and Surgical Sciences (DIMEC), University of Bologna, I

Objective: Recently, a simple non-invasive score, the Agile 3+ Score, combining liver stiffness measurement (LSM) by transient elastography, aspartate aminotransferase/alanine aminotransferase ratio, platelet count, diabetes status, sex and age, has been proposed for identification of advanced fibrosis in patients with suspected non-alcoholic fatty liver disease (NAFLD). We performed a systematic review and meta-analysis of published studies to evaluate the diagnostic accuracy of the Agile 3+ score in identifying fibrotic NAFLD (F3-F4) patients.
Design: We systematically searched MEDLINE, Ovid Embase, Scopus, and Cochrane Library electronic databases for full-text published articles in any language from the inception to the 24th of April 2023. We included original articles reporting data on the sensitivity and specificity of the Agile 3+ score, according to previously described rule-out (≤0.451) and rule-in (≥0.679) cut-offs.
Results: We included 8 observational studies for a total of 7677 participants (mean age 54±6 years; mean BMI 31.4±2.1 Kg/m2; percentage of men 39.5%, percentage of patients with T2DM 48.5%) with biopsy-proven NAFLD. The pooled prevalence of fibrotic NAFLD (≥F3) was 47.6%. By the rule-out cut-off, the overall sensitivity and specificity were 88% (95% CI 84% to 91%; I2=80.4%) and 65% (95% CI 52% to 76%; I2=98.1%), respectively. Otherwise, for the rule-in cut-off (Agile 3+ ≥0.679), the overall sensitivity and specificity were 70% (95% CI 58% to 80%; I2=91.5%) and 88% (95% CI 80% to 93%; I2=98.0%), respectively; the positive LR was 5.64 (95% CI 3.79-8.41), the negative LR was 0.34 (95% CI 0.25–0.47), diagnostic odds ratio (DOR) was 16.5 (95% CI 11.6-23.3). Metaregression analyses reported that the diagnostic accuracy was partly mediated by BMI values (p<0.01) and sex (p=0.04).
Conclusion: Our systematic review and meta-analysis suggest that the Agile 3+ score has good diagnostic accuracy for the non-invasive diagnosis of advanced fibrosis NAFLD. Therefore, Agile 3+ could be used to identify patients who require a liver biopsy and/or consideration for treatment with emerging pharmacotherapies more efficiently.

296. A REAL-LIFE EXPERIENCE OF LONG-TERM ALBUMIN ADMINISTRATION IN ITALIAN PATIENTS WITH CIRRHOSIS AND ASCITES: THE REAL-ANSWER STUDY

Iannone G.[1], De Venuto C.[1], Piano S.[2], Lombardo A.[3], Bitetto D.[4], Gioia S.[5], Zaccherini G.[1], Gagliardi R.[2], Calvaruso V.[3], Pompili E.[1], Tonon M.[2], Baldassarre M.[1], Nardelli S.[5], Toniutto P.[4], Di Marco V.[3], Angeli P.[2], Caraceni P.[6]
[1]Department of Medical and Surgical Sciences - DIMEC, Alma Mater Studiorum University of Bologna, Italy; [2]Unit of Internal Medicine and Hepatology, Department of Medicine - DIMED, University and Hospital of Padova, Italy; [3]UOC di Gastroenterologia, Dipartimento di Promozione della Salute, Materno Infantile, Medicina Interna e Specialistica (PROMISE), University of Palermo, Italy; [4]Hepatology and Liver Transplantation Unit, University Academic Hospital, Udine, Italy; [5]Department of Translational and Precision Medicine, Sapienza University of Rome, Italy; [6]Unit of Semeiotics, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy

Background and Aims: Based on the results of the ANSWER randomized clinical trial, long-term albumin treatment (LTA) is currently standard of therapy along with diuretics in patients with cirrhosis and ascites in many Italian liver units. However, there are several open issues to clarify, such as a better definition of target patients suitable to LTA, schedules and doses of albumin administration, clinical trajectories of treated patients, and stopping rules of therapy. Thus, the main objective of this study is to assess how LTA has been performed in the real-life clinical practice.
Method: All patients with cirrhosis receiving albumin for at least one month to treat ascites in 5 liver units across Italy (Bologna, Padova, Palermo, Udine, Roma) were included in this multicenter retrospective observational study. Exclusion criteria were previous liver transplantation (LT) or other solid organ transplantation, previous TIPS placement, hepatocellular carcinoma beyond Milan criteria or active extra-hepatic malignancy, and severe extra-hepatic diseases or organ failures affecting prognosis. Data on patient's features, clinical and biochemical data, modalities and settings of albumin infusions, clinical trajectories and outcomes were collected.
Results: From January 2016 to January 2022, 323 patients (median age 63, males 69%) were included in the study and followed until February 2023. Main etiology of cirrhosis was alcohol (59%), followed by NASH (31%), viral (26%) and others (16%). At baseline, 55% had grade 2 and 36% grade 3 ascites, while 28% had a previous diagnosis of refractory; almost half patients had at least one paracentesis in the last 6 months. Prognostic scores were indicative of a relative advanced cirrhosis (MELD: 15, MELD-Na: 18, and Child-Pugh B9). Serum albumin concentration was 31 (27-35) g/dl. LTA was started in patients admitted to hospital for acute complications and then continued after discharge in 33% of cases, while it was initiated in outpatients in all the remaining cases (67%). Regarding the setting of infusion, albumin was infused in the outpatient clinic of the referral hospital in 46% of cases, in peripheral hospital and territorial services in 17% and at home in the remaining 38%. Median length of treatment in the entire cohort was 472 (209-1067) days. Median weekly dose was about 40 g and changes of the dose and schedule of administration occurred in about 65% of patients based on the clinical response. At the last observation, LTA was still ongoing in 34% of patients, while it was interrupted due to clinical improvement in 23%, LT in 15%, death in 17%, TIPS placement 6%, palliative care in 3% and other reasons in 1% of cases (Figure 2). In the 75 patients who interrupted albumin infusion for clinical improvement, median length of treatment was lower as compared to the entire cohort being 275 (145-473) days. At the time of albumin discontinuation, ascites regressed to grade 0-1 in 95% of patients; interestingly, 20% of these patients were diagnosed having refractory ascites. Prognostic scores significantly improved from baseline (MELD: 14 to 10; MELD-NA: 18 to 13; Child-Pugh: 9 to 7). Median serum albumin concentration was 39 (36-44) g/L. At inclusion, patients who interrupted albumin for clinical improvement were younger, more frequently had alcoholic cirrhosis and less hepatic encephalopathy. Finally, only 14% of these patients re-started albumin infusion due to ascites re-accumulation.
Conclusions: These initial results of the Real-ANSWER study show that: 1. LTA is frequently associated with diuretics for medical treatment of ascites in Italy; 2. albumin is infused not only in the referral hospital but also in territorial services or at home; 3. adherence to albumin treatment in real-life clinical practice is very high; 4. besides patients with grade 2-3 ascites, also those with refractory ascites can be responsive to LTA; and 5. interruption of LTA can occur due to resolution of ascites and improvement of liver function in almost one quarter of cases.

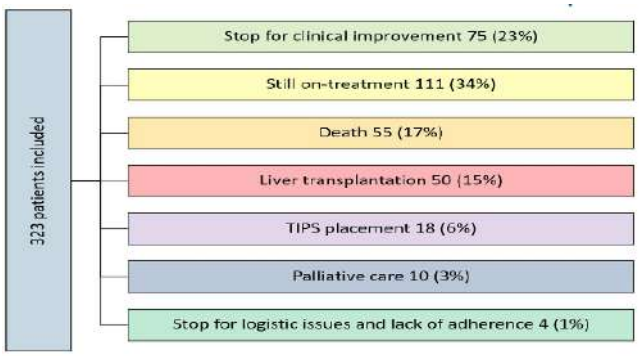


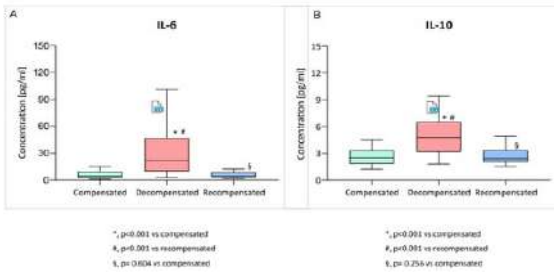
Figure 2. Outcome of the 323 patients at the end of treatment or at the end of follow-up

297. VALIDATING AND EXPANDING BAVENO VII CRITERIA OF RECOMPENSATION IN PATIENTS WITH DECOMPENSATED CIRRHOSIS

Tonon M. , Zilio G., Incicco S. , Calvino V., Accetta A., Zeni N., Gagliardi R., Gambino C.G., Barone A., Rigon L., Angeli P., Piano S.
Medicina Interna ad indirizzo Epatologico, Dipartimento di medicina, Azienda Ospedale Università di Padova, Padova

Background and aims: For decades, decompensation of cirrhosis has been considered an irreversible stage of the liver disease. However, recent evidences suggest that after etiological cure (removal of HCV, suppression of HBV and alcohol abstinence) patients with decompensated cirrhosis may experience an improvement of liver disease and disappearance of complications. This process, called recompensation, has recently been defined by the Baveno VII consensus in patients who achieve: 1) removal/suppression/cure of the primary aetiology of cirrhosis; 2) resolution of ascites (off diuretics), hepatic encephalopathy (off lactulose/rifaximin) and no recurrence of bleeding for > 12 months; c) Stable improvement of liver function tests (albumin, INR, bilirubin). The aims of this study were to evaluate the incidence and prognostic impact of recompensation in patients with decompensated cirrhosis. Biomarkers of inflammation were assessed in a subgroup of patients with different stages of the disease (compensated, decompensated and recompensated)
Methods: Outpatients with cirrhosis and curable etiology (alcohol, HCV, HBV) were included in the study and followed up prospectively for a median time of 35 months. Demographic, clinical, laboratory and endoscopic data were collected at the first outpatient visit and during follow up visits. Recompensation was defined according to Baveno VII criteria. Since withdrawal of treatment may be subjective, we evaluated expanded criteria of recompensation when patients cured the primary etiology of cirrhosis, had improvement of liver function tests and showed resolution of decompensating event for > 12 months while still on treatment for the decompensation (diuretics and/or lactulose/rifaximin). Predictors of decompensation were evaluated. In order to avoid immortal bias, recompensation was considered a time varying covariate for survival analysis. In a subgroup of 160 patients (62 compensated, 60 decompensated, 38 recompensated), inflammatory cytokines (IL-6, IL-10, IL1beta) were measured in plasma samples with a multianalyte Simple Plex cartridge kit run on an automated immunoassay system.
Results: 650 patients were enrolled (mean age 56±11 years, men 72%). Most common etiologies were alcohol (53%) and HCV (41%). At inclusion, 429 patients already had an episode of decompensation, and 60 decompensated during follow up. Overall, 387 patients achieved an effective etiological treatment and 21 (4.3%) achieved recompensation according to Baveno VII criteria, while 109 patients achieved recompensation according to expanded criteria (22.3%), with a 60-month cumulative incidence of recompensation of 16%. Among patients achieving etiological cure, MELD score was the only independent predictor of recompensation (adjusted HR=0.88; p=0.001). In univariable analysis, patients achieving recompensation (Baveno VII) had a significantly higher risk of mortality than those with compensated cirrhosis (HR= 2.99; p= 0.035), while the highest risk was observed in patients with decompensated cirrhosis (HR=9.08; p=<0.001). In multivariable analysis (Adjusted for age, sex, MELD albumin varices and further decompensation), mortality risk was not significantly different between patients achieving recompensation vs compensated patients (aHR=2.45; p=0.119). Mortality risk was not significantly different between patients with expanded recompensation criteria and Baveno VII criteria (HR= 1.03; p=0.954). Inflammatory cytokines were significantly higher in patients with decompensated cirrhosis than those with compensated cirrhosis (IL-6=21.9 vs 4.1 pg/ml, p<0.001; IL-104.5 vs 2.4 pg/ml, p<0.001). After recompensation, inflammatory cytokines significantly decreased (IL-6= 4.03 pg/ml, p<0.001 vs decompensated; IL-10=2.02, p<0.001 vs decompensated) and no difference was found vs compensated patients.
Conclusions: Baveno VII criteria of recompensation are accurate in identifying patients with cirrhosis with a prognosis similar to compensated patients, but less than 5% achieve recompensation. Expanding criteria to patients still on medical treatment for decompensation,allow to identify patients at low risk of mortality and an inflammatory profils similar to compensated patients.

Figure 1. Concentration of IL-6 (Panel A) and IL-10 (Panel B) according to the pattern of decompensation



298. ABEMACICLIB-INDUCED AUTOIMMUNE HEPATITIS IN ADVANCED BREAST CANCER

Feltrin S.[1], Ghinatti M.[1], Casu M.[1], Nobili G.[1], Dotta D.[1], Osmani M.[1], Ieni L.[1], Izzo D.[1], Babini P.[1], Lia M.[2], Pontremoli R.[1]
[1]Dipartimento di Medicina Interna, clinica medicina interna 2, Ospedale Policlinico San Martino; [2]Dipartimento di Medicina Interna, medicina interna ad indirizzo oncologico, Ospedale Policlinico San Martino

Drug-induced autoimmune hepatitis is a rare type of acute hepatitis, but with a poor prognosis if not promptly diagnosed and immediately treated. Clinically, it presents indistinguishable from an autoimmune hepatitis (often also with autoantibodies characteristic of autoimmune hepatitis and similar histological correlates), but the medical history represents a fundamental element. This case report describes the story of a 65-year-old woman diagnosed with infiltrating ductal carcinoma of the breast, estrogen receptor positive and HER-2 negative, presenting with advanced onset. In consideration of the volume of the tumor, the patient was candidated for therapy with a cycline inhibitor, abemaciclib, to obtain a volume reduction such as to allow surgery in the context of advanced carcinomatous mastitis. The patient's anamnesis was substantially negative, she did not take any other therapy. Few weeks after the start of therapy with abemaciclib, the patient presented in subjective well-being, but blood chemistry tests showed an increase in liver function indices up to 20 times over the upper range (AST/ALT 785/1064 U/L; ALP/GGT 132/206 U/L; LDH 425 U/L; total bilirubin 3.44 mg/dL conjugated bilirubin 2.40 mg/dL). Immediately suspended therapy with abemaciclib and hospitalized for examinations, the patient underwent a contrast enhanced abdominal CT scan, which did not show liver damage from biliary tract/intrahepatic stones. Subsequently we performed an in-depth study with liver MRI. Serologies for viral hepatitis were performed, resulting negative so as the research for typical autoimmune hepatitis marker. Since the severe impairment of liver function persisted even after the suspension of therapy with abemaciclib and other possible causes were excluded, the patient underwent a liver needle biopsy: the histological report was compatible with acute hepatitis from an adverse drug reaction. The patient was then treated with high-dose corticosteroid therapy (1 mg/kg/day prednisone per os as the initial dose), with complete recovery of liver function which allowed the patient to undergo mastectomy surgery and subsequently start chemotherapy of 1st line. After six months the patient is in good conditions with ongoing chemotherapy; she is still on low dose corticosteroid therapy with normal liver enzymes and function.

299. DEVELOPMENT AND INTERNAL VALIDATION OF A MULTIVARIABLE MODEL FOR THE PREDICTION OF 1-YEAR READMISSION TO THE EMERGENCY DEPARTMENT (ED) FOR ACUTE ALCOHOL INTOXICATION (AAI)

Benintende V.[1], Demartini C.[1], Palmese F.[2], Domenicali M.[2], Bedogni G.[2]
[1]Department of Medical and Surgical Sciences, Alma Mater Studiorum- University of Bologna; [2]Department of Medical and Surgical Sciences, Alma Mater Studiorum- University of Bologna, Department of Primary Health Care, Internal Medicine Unit addressed to Frailty and Aging AUSL Romagna Ravenna, Italy

Aim: To develop and internally validate a multivariable logistic regression model (LRM) for the prediction of 1-year readmission to the ED in patients with AAI.
Methods: We developed and internally validated the LRM on a retrospective cohort of 3304 patients admitted to the ED of the Sant'Orsola-Malpighi Hospital (Bologna, Italy) for AAI [1]. The development of the model began with the selection of a benchmark LRM, whose predictors were derived from available literature and expert opinion. The benchmark LRM employed readmission to the ED within one year as the binary outcome, age as a continuous predictor, and alcohol use disorder (AUD), substance use disorder (SUD), previous trauma, psychological disease, and homelessness as the binary predictors. Age was transformed using multivariable fractional polynomials with bootstrap evaluation of stability. The benchmark LRM was gradually simplified to get the most parsimonious LRM with a similar overall fit (scaled Brier score), discrimination (C-statistic), and calibration (calibration in the large, calibration slope, and calibration plot) [2]. All models were internally validated, i.e., corrected for optimism, on 100 bootstrap samples.
Results: The 1-year readmission rate was 16% (95%CI 14% to 17%, n = 518). A reduced LRM based on sex, age, AUD, psychological disease, and homelessness performed as well as the benchmark LRM. The reduced LRM had the following optimism-corrected metrics: scaled Brier score 18.3%, C-statistic 0.81 (95%CI 0.77 to 0.83), calibration in the large –0.004 (95%CI –0.093 to 0.090), calibration slope 0.987 (95%CI 0.859 to 1.100), and an acceptably accurate calibration plot (not shown).
Conclusion: An LRM based on sex, age, AUD, psychological disease, and homelessness can be used to estimate the probability of a 1-year readmission to ED for AAI. This model should be validated in external cohorts to prove its clinical usefulness.
References
1. Palmese F et al. Intern Emerg Med. 2023;18:257.
2. Collins GS et al. Ann Intern Med. 2015;162:55 (TRIPOD guidelines)

300. CASE REPORT: CIRRHOSIS IN BLOOM'S SYNDROME

Manganaro.G[1], Invernizzi F. [2], Cilla M.[2], Pedica F. [3]
[1]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy. Università Vita-Salute San Raffaele, Milan, Italy; [2]Unit of Hepatolgy, IRCCS Ospedale San Raffaele, Milan, Italy; [3]Unit of Anatomical Patology, IRCCS Ospedale San Raffaele, Milan, Italy

Bloom's syndrome (BS) is a rare autosomal recessively transmitted disease caused by a mutation in the BLM gene, which codes for the DNA repair enzyme RecQL3 helicase. Small body size, a sun-sensitive, erythematous facial skin lesion, an excess of well-demarcated hyper- and hypopigmented skin lesions, and increased numbers of bacterial infections due to immunodeficiency are typical features. Early cancer, chronic lung disease, and diabetes are complications. Only one case reported a particular liver disease pattern associated with BS.(ref) The clinical diagnosis is confirmed cytogenetically by demonstrating a characteristic chromosome instability.
Our patient was a 35-year-old white woman with BS diagnosed in 1994. About her health problems, she was affected by secondary amenorrhea, frequent respiratory tract infections, a lot of reactivations of Herpes Simplex Virus, cholelithiasis, basal cell carcinoma of the forehead and tubular adenoma of the transverse colon surgically removed in 2012, and since then the follow up always resulted negative.She had never drunk and smoken. On April 2022, she was hospitalized at our Hospital to remove another low-grade dysplasia tubular adenoma. Physical examination revealed a thin woman with the typical facies of Bloom syndrome (140 cm, 41 kg). Laboratory test: white blood cell count was 2.7 x 109/L, hemoglobin 9.4 g/L, aspartate aminotransferase 82 U/L, alanine aminotransferase 62 (hypertransaminasemia was known since 2019), glucose 73 mg/dL, International Normalized Ratio 1.8. Viral hepatitis A,B and C and the panel of autoantibodies were negative, total bilirubin 2.75 mg/dL (direct bilirubin 0.90 mg/dL). During the hospitalization she underwent a shear wave liver elastography which revealed a 14 kPa stiffness. An esophagogastroduodenoscopy diagnosed some small varices F2 without red signs and hypertensive gastropathy. Further, abdominal ultrasound revealed the presence of hepatosplenomegaly (spleen about 197 mm); portal venous flow was normal. She underwent an endoscopy ligation as primary prophylaxis and then she started non selective beta-blockers.
The liver biopsy specimen consisted of pieces of liver parenchyma measuring 1.3 cm overall, characterized by extensive areas of ductular proliferation with neutrophilic granulocytic infiltrate and hepatocytes that sometimes appear steatotic and balloniform (steatosis <5%), with Mallory bodies and numerous glycogenated nuclei. The portal spaces are expanded by fibrosis and marked ductular reaction including numerous neutrophilic granulocytes. There were foci of ductular metaplasia of the hepatocytes, discrete ectasia of the sinusoids, pericellular fibrosis and widespread capillarization. Vein centrilobular of reduced caliber, one of the branches with almost non-existent caliber. No martial deposits were observed; non-deposition of copper-related proteins. Due to advanced liver disease, she undertook an hepatological follow-up and she started low dose of diuretics.
Discussion: Idiopathic hepatitis and drug-liver toxicity have been reported in literature as frequent complications of cancer chemotherapy especially in case of leukemias and non-Hodgkin lymphomas, very common in these patients. Until now, only in 1997 a case report showed the presence of a great number of MBs that were mainly distributed in the centrilobular hepatocytes and the presence of central hyaline sclerosis which was similar to the spectrum of chronic liver disease. Mallory bodies, also known as alcoholic hyalin, are slightly refractile, eosinophilic, basophilic intracytoplasmic inclusions of hepatocytes that are never seen in normal tissue. They are typical of alcoholic liver disease and they can be also seen in nonalcoholic steatohepatitis, some of viral and drug hepatitis, hepatocellular carcinoma, obesity and jejunoileal bypass. In this case all other causes of liver damage were negative, so they did not explain the origin of MBjs. This pattern could suggest a metabolic etiology. Nonalcoholic fatty liver disease (NAFLD) might progress to metabolic-associated steatohepatitis (NASH), liver fibrosis, and hepatocellular carcinoma. Factors influencing NASH progression include lipotoxicity, endoplasmic reticulum (ER) stress, mitochondrial dysfunction, oxidative stress, gut endotoxins, and microbiota. It was demonstrated that in these patients oxygen radical production is dramatically elevated and the capacity to produce them contribute to the spontaneous chromosomal instability of BS cells. This leads oxidative stress may be the origin of susceptibility of somatic cells including hepatocytes. For the same reason BS patients night develop insulin-dependent diabetes and dyslipidemia in early adulthood. Insulin resistance of adipose tissue plays an important role indeed, despite clinically our patient had a normal glycemic and lipid asset.
Conclusion: The confirmation of this particular histological pattern of liver damage in a second patient affected by BS, indicates the need for liver histological examination among these patients to determine whether this is a consistent feature of the disorder as a consequence of somatic cell mutation.

301. EVOLUTION OF LIVER FIBROSIS IN DIABETIC PATIENTS WITH NAFLD IN A FOLLOW-UP STUDY: POSSIBLE HEPATOPROTECTIVE EFFECTS OF SODIUM-GLUCOSE CO-TRANSPORTER-2 INHIBITORS

Lombardi R.[1], Cespiati A.[1], Mantovani A.[2], Maffi G.[1], Del Zanna E.[1], Francione P.[3], Cinque F.[1], Santomenna F.[1], Currà J.[1], Maffeis C.[4], Colecchia A.[5], Passigato N.[6], Ferrarese A.[6], Caterina C.[6], Villani R.[7], Orsi E.[8], Grancini V.[8], Bignamini D.[9], Targher G.[2], Serviddio G.[7], Fargion S.[1], Fracanzani AL[1]
[1]Unit of Internal Medicine and Metabolic Disease, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano. Department of Pathophysiology and Transplantation University of Milan, Milan, Italy ; [2]Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy ; [3]UO di Medicina, Azienda Ospedaliera "Card. G. Panico" di Tricase, Italy; [4]Pediatric Diabetes and Metabolic Disorders Unit, Department of Surgical Sciences, Dentistry, and Pediatrics, and Gynaecology, University Hospital of Verona, Verona, Italy; [5]Gastroenterology Unit, Department of Medical Specialities, University Hospital of Modena, University of Modena & Reggio Emilia, Modena, Italy; [6]Gastroenterology Unit, University and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy ; [7]Centro C.U.R.E, Dept. of Medical and Surgical Sciences, University of Foggia, Italy;

[8]Department of Medical Science, Endocrinology and Diabetes Unit, Ca' Granda IRCCS Foundation, Policlinico Hospital, University of Milan Italy; [9]Unit of Internal Medicine and Metabolic Disease, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy

Introduction: Subjects with non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (T2DM) present high progression of liver disease to fibrosis, which is the main determinant of long-term adverse outcomes. Data are accumulating on the benefits of sodium glucose cotransporter 2 inhibitors (SGLT-2i) on hepatic fibrosis mainly in pharmacologic or retrospective studies.
Aim: to prospectively evaluate change in hepatic disease in patients with NAFLD and T2DM and predisposing factors, with particular regard to SGLT-2i.
Methods: 237 T2DM outpatients (mean age 67 ±9 years, 54% male) were enrolled at the diabetology outpatient clinics and re-evaluated after 52 + 10 months. At baseline and follow-up information about diabetic control, metabolic comorbidities and medications were collected. NAFLD and liver fibrosis (LSM) were detected by ultrasonography and Fibroscan®.
Results: During follow-up period no change in the prevalence of metabolic alterations except for hypertension (81% vs 73%, p<0.001) was observed, whereas an increase in LSM values (6.0 ± 2.8 vs 5.8± 2.7 kPa, p=0.02) was registered, despite stability of diabetic control. In particular, LSM worsened in 133(56%) subjects, 92 (39%) having a worsening >10% and 20 (8%) of at least 1 fibrosis stage at Fibroscan from baseline. At the end of follow-up, a higher prescription of SGLT2i was seen (20% vs 6%, p<0.001). Patients with worsening versus non worsening of LSM had higher prevalence of increase in BMI during follow-up (45% vs 32%, p=0.06), lower SGLT2i prescription (15% vs 27%, p=0.034) and higher of sulfonylureas (23%vs 11%, p=0.016). In multivariate analysis adjusted for age, sex, liver enzymes, HbA1c and weight gain, use of SGLT2-inhibitors at follow-up was independently associated with a reduced risk of worsening of LSM (HR 0.34, 95% CI 0.13-0.88), even when considered>10% from baseline. No impact of sulfonylureas was observed.
Conclusions: Despite a high prevalence of fibrosis progression in NAFLD subjects with T2DM, we showed a potential effect of SGLT2-inhibitors in reducing the risk of worsening of liver stiffness. Therefore, our data suggest that using this category of antidiabetic drug in NAFLD patients may prevent progression of fibrosis, especially if weight control is obtained in these patients.

302. RITIRATO

303. ACUTE COGNITIVE IMPAIRMENT IN PATIENTS WITH CHRONIC LIVER DISEASE: PROBLEMS OF DIFFERENTIAL DIAGNOSIS

Semproni E.[1], Reichenbach M.[1], Camisasca F.[1], Lavorato S.[1], Bregani E.R.[1], Bitto N.[1], La Mura V.[2], Peyvandi F.[2]
[1]Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Internal Medicine – Haemostasis and Thrombosis, Milan, Italy; [2]Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Internal Medicine – Haemostasis and Thrombosis, Milan, Italy - Department of Pathopysiology and Transplantation, University of Milan

Background: Cognitive impairment in internal medicine gives rise to problems of differential diagnosis. Hepatic encephalopathy (HE) is the typical cognitive dysfunction associated with cirrhosis; however, particularly in the acute setting, comorbidities, subtle neuro-psychiatric disorders, and social problems make the final diagnosis a challenge. We present three cases of acute cognitive dysfunction in patients with chronic liver disease managed in our unit of internal medicine.
Case Report: Case 1. A 63-year-old man was admitted to the emergency department (ED) because of a new episode of cognitive impairment. He was affected by alcohol-related cirrhosis complicated by recurrent ascites which had been successfully treated with TIPS six months before. Unfortunately, after the procedure, he had experienced several episodes of encephalopathy which were considered proper HE by his hepatologists. Therefore, the patient was a potential candidate to TIPS restriction to reduce the diameter of the stent and the risk of HE although this procedure would have exposed him to new complications of portal hypertension. On admission, he had behavioral alterations, with episodes of psychomotor agitation and aggressiveness, disorientation, alteration in the sleep-wake cycle. Ammoniemia, blood and urine cultures were all negative. There were no signs of bleeding neither electrolyte abnormalities. Treatment with lactulose and rifaximin was not effective. Therefore, we addressed the patients to a psychiatric evaluation to highlight potential alcohol-related disorders other than HE. The specialist concluded for delirium associated with altered behavior in a patient with a history of alcohol abuse. The patient was treated with promazine and olanzapine with clinical amelioration and TIPS restriction was not necessary.
Case 2. A 75-year-old man affected by metabolic cirrhosis had an acute appearance of unstable walking. He was on anticoagulation for atrial fibrillation. His general practitioner suggested contacting the liver-specialist to exclude HE. The patient had been addressed to TIPS three months before for recurrent esophageal rupture despite prophylaxis with medical and endoscopic therapy. He wrote detailed and accurate e-mails, suggesting an intact cognitive function. Contacted by phone, he presented a good level of interaction which was unusual for an acute episode of HE. Therefore, the patient was addressed to the ED. Ammonemia was negative and a brain CT-scan showed a subdural hematoma, which was surgically managed with gradual disappearance of the symptoms. In the end, the patient admitted that he had fallen two weeks earlier.
Case 3. A 79-year-old woman with no history of chronic liver disease was admitted to ED for lethargy which appeared during hospitalization for rehabilitation after ankle fracture. She was an overweight woman (BMI 26 kg/m2) affected also by arterial hypertension. Brain-CT scan was negative for acute events. In the suspect of hypokinetic delirium, she was admitted to our unit. During hospitalization, she was treated for an urinary tract infection and her neurological condition improved. Because of the detection of low proteins with normal kidney function and an increase of transaminases (2-3X), we performed an abdominal US-exploration which revealed liver nodular surface, caudate lobe hypertrophy and potential spleno-renal shunt suggestive of cirrhosis which was confirmed by the CT-scan. On day-7 she developed fever for a nosocomial pneumonia which triggered a new episode of encephalopathy associated with hyperammonemia. We considered it an episode of HE which responded to antibiotics and lactulose. In light of our recent diagnostic work-up, it is likely that also the episode of cognitive impairment on admission was a proper HE triggered by infection in a patient unaware of suffering from a metabolic cirrhosis.
Discussion: Our report shows three different cases of neurological impairment in patients with chronic liver disease but only one of them was an episode of HE.In Internal Medicine the diagnosis of HE is jeopardized by potential overlap with other forms of neuropsychiatric disorders even in patients with cirrhosis. TIPS and history of decompensated cirrhosis must induce physicians to consider HE as a potential diagnosis, however, ruling out any alternative neurological causes is an essential part of the diagnostic work-up. In case of doubts, a brain CT-scan/MRI should be performed to exclude acute vascular disorders. On the other hand, physicians should be aware that an acute cognitive impairment could also be the first episode of decompensation of an unknown advanced chronic liver disease, which must be investigated; in such cases, ammoniemia may be helpful, even though the diagnosis of HE remains clinical. Hence, the integration of anamnesis with the most common biochemical and instrumental tests allow to differentiate liver versus non-liver associated acute cognitive impairment.

304. HVPG ROLE IN CARDIOGENIC CIRRHOTIC PATIENTS PRESENTING WITH ASCITES, A SHORT REPORT

Zeni N.[1], Gagliardi R.[1], Incicco S.[1], Battistel M. [2], Gerosa G.[3], Angeli P.[1], Piano S.[1]
[1]Unit of Internal Medicine and Hepatology, Department of Medicine, University and Hospital of Padova, Padova, Italy; [2]Radiology Unit, Department of Medicine, University and Hospital of Padova, Padova, Italy; [3]Cardiac surgery Unit, Department of Cardio-thoraco-vascular sciences and public health, University of Padua

Background and aim: Heart surgery procedures in patients with cirrhosis and ascites are characterized by high risk of complications and mortality. However, in patients with cirrhosis and chronic heart failure, the occurrence of ascites can be due to wither the right heart failure (post-hepatic portal hypertension) or the liver cirrhosis (sinusoidal portal hypertension) or both. In the assessment of heart surgery eligibility, the dilemma is: "will the ascites resolve after heart surgery?". Available non-invasive tests are not useful in this setting. Herein we explored the potential use of hepatic vein catheterization with the measurement of hepatic venous pressure gradient (HVPG) to assess cardiac surgery eligibility and predict resolution of ascites. Three cases considered eligible because of HVPG < 10 mmHg and increase free hepatic vein pressure were reported.
Case presentations: *Case 1.* A 68 year-old man with medical history of positive Quantiferon test and prior AMI was referred to our unit because of refractory ascites and need for periodic paracentesis. An echocardiography showed abnormal movement of septal wall during diastole ("septal flattening") with signs of pericardial constriction. Bioumoral and CT-scan con-

firmed the presence of cardiogenic cirrhosis. With the suspicion of constrictive pericarditis right heart catheterization, thoracic CT scan as well as HVPG were performed. The right heart catheterization confirmed pericardial constriction, while HVPG excluded sinusoidal portal hypertension (HVPG 4 mmHg). Surgical pericardiectomy was performed with complete regression of ascites after surgery.
Case 2. A 45 year-old lady with a history of hypokinetic dilated cardiomyopathy with chronic heart failure was admitted for ascites. CT scan and liver-stiffness were suggestive for liver cirrhosis and no other etiology other than cardiogenic cirrhosis was found. Right heart catheterization showed increased pressure in inferior vena cava and hepatic veins (17 mmHg). The hepatic vein catheterization showed no sign of sinusoidal portal hypertension. For the end stage heat failure patient underwent a heart transplant with subsequent disappearance of ascites.
Case 3. A 29 year-old lady presented with refractory ascites with the need for periodic paracentesis and multiple episodes of spontaneous bacterial peritonitis in a known dilated cardiomyopathy with severe reduction in ejection fraction. The patient underwent several hospitalizations for heart failure and progressive clinical worsening. Right heart catheterization showed high inverior vena cava pressures. Since an abdominal ultrasound found radiologic signs of cirrhosis, HVPG as well as liver biopsy was performed. HVPG excluded sinusoidal portal hypertension while biopsy confirmed the presence of severe fibrosis and regenerative nodules. The patient underwent a heart transplant with complete regression of ascites.
Discussion: The main cause of ascites in patients with cirrhosis and or heart failure is portal hypertension. In patients with cirrhosis portal hypertension is mainly due to the increase in intrahepatic resistance and sinusoidal pressure, while in those with heart failure is inferior vena cava hypertension. The gold standard for assessing sinusoidal portal hypertension is the measurement of HVPG. HVPG values between 5 and 10 mmHg indicate sinusoidal portal hypertension, but ascites almost never appear if HVPD is not above 10 mmHg. Therefore we hypothesized that HVPG could be a relevant tool to predict the post heart surgery outcomes in cardiogenic cirrhosis with ascites. We cleared the indication to heart surgery according to HVPG value and all cases had ascites resolution after cardiac surgery.
Conclusion: HVPG measurement is a relevant tool that can aid clinicians to support indication to heart surgery in patients with cardiogenic cirrhosis and ascites. Cardiogenic ascites can be resolved by correction of heart structural defect when sinusoidal portal hypertension is ruled out by HVPG measurement.

	Case 1.	Case 2.	Case 3.
Type of cardiac defect	Constrictive pericarditis	End stage chronic heart failure	End stage chronic heart failure
Aetiology cirrhosis	Cardiogenic	Cardiogenic	Cardiogenic
Type of ascites	Refractory	Recurrent	Refractory
SAAG (g/dL)	1.3	unknown	< 1.1
Ascites total protein (g/L)	40	unknown	25
Catetere libero (mmHg)	17	13	21
Catetere occludente (mmHg)	21	18	24.5
Gradiente porto-sovraepatico (mmHg)	4	5	3.5
Pressioni atrio destro (mmHg)	16.5	12	20
Gradiente porto-atriale (mmHg)	0.5	1	1
Treatment	Pericardiectomy	Heart transplant	Heart transplant
Ascites resolution after treatment	Yes	Yes	Yes
Regression of liver stiffness in yearly follow-up	Unknown	Yes	Yes

305. BEYOND A RARE CAUSE OF ESOPHAGEAL BLEEDING: THE DICHOTOMIC BALANCE BETWEEN THROMBOTIC AND BLEEDING RISK.

Smith D., Cespiati A., Lombardi R., Pulixi E. A., Fatta E., Bertelli C., Fracanzani A.L.
SC Medicina -Indirizzo Metabolico, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy

Clinical Case: A 53-year-old woman was admitted to our ward of Internal Medicine due to episodes of melena with acute anemia.
Her past medical history was unremarkable for liver diseases, but she was diagnosed with adenocarcinoma of the colon with infiltration of the ileum in 2005, treated with surgery and adjuvant therapy with fluorouracil and oxaliplatin. At the emergency department she was conscious, pale, asthenic, and blood test revealed severe anemia (Hb 5 g/dL). Platelets were slightly reduced (140000/mm3), whereas liver function tests and coagulation profile were normal. She immediately underwent an esophagogastroduodenoscopy (EGDS) that revealed esophageal varices F3 with red signs and portal hypertensive gastropathy (PHG). The patient promptly underwent variceal banding and received blood transfusion with 4 units of packed red blood cells. Moreover, a non-selective beta-blocker (NSBB) was started (carvedilol 6.25 mg 1 tablet bid). After clinical stabilization the patient was transferred to our ward of internal medicine. To further investigate the reason for variceal bleeding, the presence of hepatic cirrhosis was excluded by both Fibroscan and liver biopsy, the latter showing only low-grade macrovesicular steatosis without significant fibrosis (stage 1C). The biochemical assessment highlighted normal coagulation parameters (PT 1.02, aPTT 0.98) and preserved liver function (albumin 4.1 g/dL, total bilirubin 1.06 mg/dL, pCHE 5611 U/L). An abdominal ultrasound showed reduced portal vein velocity (10 cm/s) with increased portal diameter, moderate splenomegaly (14.5 cm), and thrombosis of the right portal branch, configuring a condition of portal hypertension. A subsequent abdominal computed tomography highlighted the presence of two regenerative hyperplastic nodules, confirmed the presence of portal vein thrombosis (PVT) and contextually excluded mechanical causes of portal hypertension. In order to measure the portal pressure, the hepatic venous pressure gradient (HVPG), which is invasively calculated by subtracting the free hepatic vein pressure from the wedge hepatic vein pressure, was tested, obtaining normal values (1-3 mmHg). Based on the patient's oncologic history, presinusoidal portal hypertension caused by oxaliplatin therapy was suspected. During the observation, the patient developed paroxysmal atrial fibrillation (PAF) and anticoagulant therapy was started to address PVT and concomitant PAF, with only partial resolution of PVT despite a good patient's compliance to treatment and normal coagulation parameters. Because of clinical and biochemical stability (Hb level persistently around 12 g/dL), the patient was discharged and referred to a hepatology clinic. The outpatient follow-up was firstly complicated by the tendency of the patient to develop moderate iron-deficiency anemia (Hb 9.1 g/dL, MCV 81 fl, ferritin 12 ng/dL) consequent to chronic gastrointestinal loss from PHG, worsened by the anticoagulant therapy and requiring periodic intravenous iron administration. Moreover, the patient reported vertiginous and pre-syncopal episodes during the therapy with NSBB and 24-hours ECG showed symptomatic 3-second pauses, but the patient refused to implant a pacemaker. NSBB dosage was reduced with consequent suboptimal rate control and increased risk of new episodes of variceal bleeding. To overcome the risk of further life-threatening hemorrhage, a strategy of periodic variceal banding has been taken.
Discussion: We report a case of presinusoidal portal hypertension with regenerative nodular hyperplasia (RNH) induced by oxaliplatin therapy, presenting with esophageal bleeding and PVT, complicated by chronic anemia and beta-blocker intolerance. Presinusoidal portal hypertension is characterized by elevated portal venous pressure with normal HVPG and is caused by impaired flow in the presinusoidal portion of the hepatic venous vasculature. RNH is a rare cause of non-cirrhotic portal hypertension, especially in patients previously treated with oxaliplatin and it could be symptomatic even several years after chemotherapy. The management of our patient has been complicated by the development of chronic anemia due to gastrointestinal bleeding and by a NSBB intolerance. Indeed, the mismatch between the thrombotic and the bleeding risk that characterized our patient made their management difficult. Even though PVT, favored by the blood flow stasis typical of portal hypertension and to hypercoagulability needed anticoagulation, this therapy increased the bleeding risk of PHG and varices. NSBB is a cornerstone therapy of portal hypertension and variceal bleeding, but some patients interrupt the treatment due to its hypotensive effect. In conclusion, non-cirrhotic portal hypertension is challenging to diagnose, and patients often reach medical attention because of complications of portal hypertension. Accurate patients' history, including past drug exposure, is crucial for its suspicion. NSBB intolerance can be managed with alternative treatments, such as periodic variceal binding, transjugular intrahepatic portosystemic shunt (TIPS), cardiac pacemaker or, in selected cases, liver transplantation.

306. PREDICTIVE VALUE OF FATTY LIVER INDEX FOR LONG-TERM CARDIOVASCULAR EVENTS IN PATIENTS RECEIVING LIVER TRANSPLANTATION

Caturano A.[1], Albanese G.[1], Di Martino A.[1], Coppola C.[2], Galiero R.[1], Rinaldi L.[1], Monda M.[3], Marfella R.[1], Sasso F.C.[1], Salvatore T.[4]
[1]Department of Advanced Medical and Surgical Sciences, University of Campania Luigi Vanvitelli, I-80138 Naples, Italy.; [2]3 Area Stabiese Hospital, Naples, Italy; [3]Department of Experimental Medicine, University of Campania Luigi Vanvitelli, I-80138 Naples, Italy.; [4]Department of Precision Medicine, University of Campania Luigi Vanvitelli, I-80138 Naples, Italy

Introduction: Death from cardiovascular disease (CVD) is described as the main cause of early mortality after orthotopic liver transplantation (OLT), followed by infection, and graft failure. Fatty Liver Index (FLI) appears strictly associated with carotid and coronary atherosclerosis, and with cardiovascular mortality over traditional risk factors. Since data regarding the significance of FLI as predictor of cardiovascular events in OLT recipients are missing, we designed a study to investigate this topic.
Methods: We retrospectively evaluated 110 consecutive adult OLT recipients attending every three/six month (or more often when needed), from January 1995 to December 2020 and for at least two years after intervention. We collected anamnestic, clinical, anthropometric and laboratory parameters data. FLI was calculated for all patients.
Results: 110 eligible patients (median age 57 years [IQR: 50-62], 72.7% male) were followed for a median of 92.3 months (IQR: 45.7-172.4) after liver transplantation. During the follow-up, 16 patients (14.5%) developed at least an adverse CV event. The ROC estimated a cut-off value to predict post-OLT cardiovascular events of 66.0725 with an 86.7% sensitivity and a 63.7% specificity (68% vs. 31%; *P=0.001*). The Kaplan-Meier analysis showed a worse CV event-free survival in patients with FLI >66 compared to those with FLI £66 (*log rank: 0.0008*). Multivariable COX regression analysis showed that FLI >66 and the smoking habit in the pre-OLT were independently associated with cardiovascular risk.
Conclusions: FLI >66 and smoking habit pre-OLT emerged as a predictor of cardiovascular risk in a cohort of adult OLT recipients.

307. DISSOCIATION BETWEEN ACUTE LIVER DECOMPENSATION AND RADIOLOGIC RESPONSE IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA TREATED WITH ATEZOLIZUMAB-BEVACIZUMAB

Rosi M., Pellegrini E., Li Cavoli T., Winchler C., Vannini G., Adotti V., Campani C., Antonuzzo L., Marra F.
Dipartimento di Medicina Sperimentale e Clinica, Università degli Studi di Firenze

Background: The combination of atezolizumab (immunotherapic, anti-PD-L1) and bevacizumab (antiangiogenic) (Atezo-Bev) is the new first line treatment for patients with advanced hepatocellular carcinoma (aHCC). Aim of this study was to analyze the incidence of acute liver decompensation in a group of patients treated with Atezo-Bev, and its potential correlation with the oncologic response.
Methods: We collected data from patients followed by the hepato-oncology outpatient clinic of Careggi Hospital between December 2020 and May 2023. Patients with aHCC under Atezo-Bev with an available CT scan at 12 weeks after beginning of treatment were included in this study. The radiologic response (RR) was defined according to the mRECIST criteria. Patients with a stable disease (SD) or a partial response (PR) at the radiologic evaluation were considered 'responders'. Acute liver decompensation was defined as the occurrence of clinically significant ascites, overt hepatic encephalopathy (grade ≥2) and/or portal hypertensive bleeding during Atezo-Bev treatment.
Results: Thirty-two patients were included in the study. The majority were male (78.1%) with a median age of 69.3 years. 71% of patients had cirrhosis. The underlying etiology was HCV infection (43.8%), HBV infection (12.5%), alcohol use disorder (40.6%), NAFLD (31.3%). Twenty out of 25 patients with cirrhosis (80%) were in Child-Pugh class A. HCC stage was classified as BCLC C in 75% of patients and the ECOG performance status was 0 in 56.3% of cases and 1 in the remaining 43.8%. Seven patients (21.9% of the total, 28% of those with cirrhosis) developed at least one acute liver decompensation event during Atezo-Bev treatment. Three presented with clinically significant ascites, 3 developed hepatic encephalopathy and 1 had portal hypertensive bleeding. All these 7 patients had cirrhosis and six of them (85.8%) were in Child-Pugh class A. Considering the general population under study, 20/32 patients (62.5%) were responders at 12 weeks of treatment (PR in 9 cases, SD in the remaining 11), whereas the entirety of the decompensated patients showed a RR to the treatment. In particular, three patients had a partial response (PR) and 4 a stable disease (SD).
Conclusions: The development of acute liver decompensation during the treatment with Atezo-Bev is a frequent event in the population of cirrhotic patients. While the RR in the general population was 62.5%, the entirety of patients who developed a decompensation presented a RR at the 12-week radiologic evaluation. This dissociation between acute liver decompensation, that might be envisioned as a clinical progression, and oncologic response suggests a pathogenetic link between tumor lysis and worsening of hepatic function.

308. ACUTE VANISHING BILE DUCT SYNDROME: ALL OF A SUDDEN YELLOWER

De Francesco M.I., Carmignano D.F.P, Lo Buglio A., De Biase F., Bellanti F., Vendemiale G.
Dipartimento di Medicina Interna e dell'invecchiamento, Università degli studi di Foggia,Policlinico Riuniti Foggia

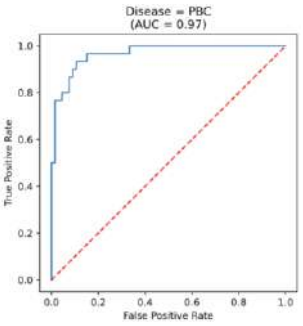
Background: Vanishing bile duct syndrome (VBDS) is a chronic pathological condition characterized by loss of bile ducts. Bile duct disruption is caused by an immunomodulated injury directed to the epithelium of interlobular tracts followed by inflammation and necrosis of cholangiocytes. This mechanism is very similar to that of primary biliary cholangitis1, graft versus host disease (GVHD) and other malignancies. Diagnosis of VBDS is clinical and histological. VBDS commonly develops within 1-3 years3 and prognosis depends on the degree of bile duct loss2. Here, we report a fatal case of acute VBDS.
Case report: we describe the case of a 77-year-old Caucasian male patient with sudden onset of jaundice, fever (max 39°C), fatigue and stabbing epigastric pain for two weeks before hospitalization. He was treated with amoxicillin/clavulanic acid for a week, without clinical benefit. His medical history included hypertensive heart disease; he underwent trans-urethral resection of the prostate (TURP) and radiotherapy for prostatic adenocarcinoma in 2016, appendectomy. He was on daily oral treatment with amlodipine and nebivolol. He referred healthy lifestyle with occasional alcohol intake (max 4 AU per month). Physical examination showed muco-cutaneous jaundice, body temperature 38.2°C, with vital signs within the normal range. Laboratory tests showed mixed component of total bilirubin >6 UL, procalcitonin 7 ng/ml, C-reactive protein >5 UNL, neutrophil number 30600/L, ALT >4.5 UNL, AST >2 UNL, GGT >4.15 UNL). Laboratory results ruled out viral and autoimmune hepatic diseases. Blood culture tested negative. Abdominal ultrasonography could not detect any bile duct alterations, and magnetic resonance imaging (MRI) found a kidney neoplasm. Empirical antimicrobial therapy with piperacillin/tazobactam and ciprofloxacin was started. Nevertheless, bilirubin, GGT and ALP levels progressively increased during the following days. After 13 days of hospitalization, total bilirubin increased > 42 UNL, so that three sessions of coupled plasma filtration and adsorption (CPFA) were administered, with poor clinical benefit. A second MRI was performed on day 24, showing stenosis of distal biliary tract with "rosary crown" appearance. Thus, liver histology was performed, describing severe drug-related cholestatic hepatic damage complicated with severe ductopenia, consistent with "vanishing bile duct syndrome". Roussel Uclaf causality assessment method (RUCAM) score was applied, indicating amoxicillin/clavulanate as the main drug suspected of causing cholestatic damage. In the following days, the patient developed progressive liver failure and died after 3 months from hospitalization.
Mechanisms of VBDS have not been completely defined yet. Nevertheless, immunological injuries may be determinant in the loss of bile ducts. Up to now, several drugs have been reported to cause VBDS2. Although it is impossible to prove the exact cause, several case reports showed that clavulanate more than amoxicillin could induce cholestatic damage with sudden elevation of gamma glutamyl transpeptidase and alkaline phosphatase3. Drug-induced cholestatic damage has been reported to cause liver insufficiency and progressive ductopenia within months or even years. In this case, loss of bile ducts led to end-stage liver disease and death in a few weeks. Ductopenia could be determined by severe inflammation with progressive fibrosis and sclerosing of bile ducts in the portal tract, with absence of interlobular bile ducts in at least 50% of portal tracts4. Recovery from ductopenia is slow and triggered by migration of progenitor cells to biliary channels, followed by reconstitutions of biliary tracts.5 There is no effective therapy that can induce regeneration of bile ducts. In this case, the patient developed stenosis of biliary ductuli in two weeks, as reported by MRI. Elevated eosinophil count and increased total IgE levels (>5 UNL) suggested an immunoallergic pathogenesis. The main hypothesis is that amoxicillin/clavulanate burst severe inflammation acting like a superantigen causing an uncontrolled immunological response with acute inflammation, resulting in massive bile duct disruption. Epigenetic or even genetic factors could have been determinant for the rapid progression of the disease, but also comorbidities such as an underlying septic state. In conclusion, this case reports that amoxicillin/clavulanate-induced cholestasis can be secondary to acute ductopenia, which is associated with severe clinical presentation and worse outcome. Liver biopsy is therefore important to helping identify patients with VBDS early in the disease process.
Bibliography
1.M. Visentin, 2018, Drug-induced bile duct injury

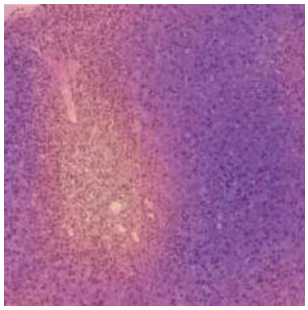
2.Zhao Z,2018 Acute vanishing bile duct syndrome after therapy with cephalosporin, metronidazole, and clotrimazole: A case report.
3.LiverTox: Clinical and Research Information on Drug Induced Liver Injury, 2020
4 Y. Zen, Bile Duct Diseases, MacSween's Pathology of the Liver 2024
5 M. Taghian, 2004, Acute vanishing bile duct syndrome after ibuprofen therapy in a child.

309. DEEP LEARNING CAN DISCRIMINATE BETWEEN AUTOIMMUNE HEPATITIS AND PRIMARY BILIARY CHOLANGITIS DIRECTLY FROM DIGITAL HISTOLOGY SLIDES

Gerussi A.[1], Saldanha O.L.[2], Verda D.[3], Bolis F.[1], Cazzaniga G.[4], Engel B.[5], Colapietro F.[6], Scaravaglio M.[1], Jiang M.[1], Rizzo M.[1], Cristoferi L.[1], Malinverno F.[1], Calvaruso V.[7], Cabibi D.[8], Lleo A.[6], Di Tommaso L.[9], Akpinar R.[9], Vigano M. [10], Rigamonti C.[11], Taubert R.[5], Pagni F.[4], Zucchini N.[4], Invernizzi P.[1], Kather J.N.[12], Carbone M. [1]
[1]Division of Gastroenterology, Center for Autoimmune Liver Diseases, Department of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy; [2]Else Kroener Fresenius Center for Digital Health, Medical Faculty Carl Gustav Carus, Technical University Dresden, Dresden, Germany; [3]Rulex Inc., Newton, MA, United States; [4]Department of Medicine and Surgery, Pathology, University of Milano-Bicocca, IRCCS Fondazione San Gerardo dei Tintori, Monza, Italy.; [5]Department of Gastroenterology, Hepatology, Infectious Diseases and Endocrinology, Hannover Medical School, Carl-Neuberg-Straße 1, 30625, Hannover, Germany; [6]Internal Medicine and Hepatology, Humanitas Clinical and Research Center IRCCS, Humanitas University, Milan, Italy.; [7]Gastroenterology and Hepatology Unit, University of Palermo, Palermo, Italy; [8]Anatomic Pathology Unit, Department of Health Promotion, University of Palermo; [9]Pathology Department, Humanitas Clinical and Research Center - IRCCS, Rozzano, Milan, Italy.; [10]Gastroenterologia 1 - Epatologia e Trapiantologia, ASST Papa Giovanni XXIII, Bergamo; [11]Department of Translational Medicine, Università degli Studi del Piemonte Orientale 'A. Avogadro', Novara, Italy; [12]Else Kroener Fresenius Center for Digital Health, Medical Faculty Carl Gustav Carus, Technical University Dresden, Dresden, Germany

Background and Aims: Autoimmune Liver Disease can have overlapping histological features, a challenge especially for non-expert pathologists. Deep Learning (DL) can identify histological patterns from digitalized specimens. The aim of this study was to investigate whether a validated algorithm for feature extraction from digital scans is accurate in discerning between Autoimmune Hepatitis (AIH) and Primary Biliary Cholangitis (PBC).
Methods: This is an observational, retrospective, multicenter study including patients affected by AIH and PBC. Diagnosis was confirmed by follow-up, without subsequent diagnosis of variant syndrome. Hematoxylin-Eosin (H&E)-stained liver samples of 333 AIH treatment-naive patients and 138 PBC treatment-naive patients, biopsied from 2000 to 2022, were digitalized using whole-slide imaging, after the review of an expert liver pathologist. Clinical and biochemical data were also available for each patient, but they were not included in the workflow to force the algorithm to differentiate by image features. High-resolution digital images were transformed into tiles by using Python end-to-end workflow. The cohort was split into a training set (70%), a test set (10%) for setting hyperparameters, and a validation set (20%). To visualize the DL predictions and make them understandable to human observers we rendered the tile-level soft predictions for each class as activation maps, visualizing prediction scores as a heatmap overlay on the original histology image. The primary endpoint to assess DL performance was the area under the receiver operating characteristic curve (AUROC). :
Results The analysis included 333 AIH patients, 274 (82.2%) female, with a mean age at diagnosis of 55 years; and 138 PBC patients, 128 (92.7%) female, with a median age of 51 years. The AUROC of the DL model was 0.97 for the classification of PBC in the hold-out validation set, which was not used during training (**Figure 1**). We investigated whether such prediction point to relevant diagnostic regions of the two diseases. Attention heatmaps were generated, normalized attention scores were assigned to their corresponding spatial location in the images. Without manual annotation, the model has learned how to discriminate between AIH and PBC in liver tissue. The regions with high attention scores correspond to diagnostically relevant morphology (**Figure 2**).
Conclusion: This is a proof-of-concept study showing the feasibility and accuracy of a DL pipeline in analyzing digital histology to support the differential diagnosis between AIH and PBC. Without human annotation, the DL algorithm is able to capture specific features of AIH and PBC.





310. PREDICTORS OF READMISSION AND 6-MONTH MORTALITY IN PATIENTS SURVIVING AN ACUTE DECOMPENSATION OF CIRRHOSIS

Gambino C.[1], Accetta A.[1], Buono R.[1], Incicco S.[1], Gagliardi R.[1], Zeni N.[1], Tonon M.[1], Calvino V[1], Barone A.[1], Angeli P.[1], Piano S.[1]
[1]Unit of Internal Medicine and Hepatology, Department of Medicine, University of Padova, Padova, Italy

Background and Aims: Patients surviving a hospitalization for an acute decompensation (AD) of cirrhosis (occurrence of ascites, GI bleeding, bacterial infection and/or hepatic encephalopathy [HE]) have an heterogeneous clinical course. Patients with unstable decompensated cirrhosis (UDC) have a higher risk for 3-month readmissions and mid-term mortality than those with a stable decompensated cirrhosis (SDC). The identification of patients with UDC could be crucial in their clinical management, however, predicting the clinical course at time of discharge is challenging. The aim of this study was to investigate predictors of: 1) readmission for AD of cirrhosis until 90-day after discharge from the index hospitalization; 2) 180-day mortality.
Methods: we included patients surviving an episode of AD of cirrhosis at the University Hospital of Padova from 2011 to 2020. We collected clinical, laboratory and pharmacological treatment data at admission, during hospitalization and at discharge. The same data were collected at first readmission. Patients were followed up until transplant, death, or 180 days.
Results: We included 353 patients (mean age: 62 ± 12 years; male: 64%; alcoholic etiology: 53%; MELD: 16 (12-21)). At 90-day after discharge, 93 (26%) patients required at least one hospitalization for AD of cirrhosis and 18 (5%) patients underwent OLT. At univariable analysis, the presence of any grade of HE (sHR 1.60; CI 1.07–2.40; p=0.023) and AKI (sHR 1.52; CI 1.00–2.31; p=0.05) during the first hospitalization, and a higher MELD at discharge (sHR 1.04; CI 1.02–1.05; p<0.001), identified patients at risk of readmission. In multivariable analysis (adjusted for age, gender, aetiology, MELD, presence of HE and AKI), the presence of HE during hospitalization (HR 1.58; CI 1.02-2.47; p=0.043) and higher MELD at discharge (HR 1.04; CI 1.02-1.06; p<0.001) were independent predictors of 90-day readmission. (Table 1)
At 180-days after discharge, 59 (17%) patients died, and 29 (8%) patients underwent OLT. In univariable analysis, older age (HR 1.03; CI 1.01-1.05; p<0.0015) and AKI during first hospitalization (HR 2.02; CI 1.21-3.38; p=0.007), together with higher WBC count (HR 1.10; CI 1.02–1.19; p=0.019), CRP levels (HR 1.02; CI 1.01–1.03; p<0.001), and MELD (HR 1.04; CI 1.00-1.08; p=0.007) at first discharge were associated with higher risk of 180-day mortality. In a multivariable model (adjusted for age, gender, aetiology, MELD, presence of AKI, WBC, CRP), older age (HR 1.04; CI 1.01-1.06; p<0.001), higher CRP (HR 1.02; CI 1.01-1.03; p=0.002) and MELD (HR 1.05; CI 1.01-1.08; p=0.014) at first discharge were independent predictors of 180-day mortality. (Table 2)
Conclusion: in our cohort, the presence of HE during hospitalization and higher MELD at discharge were independent predictors of 90-day readmission after hospitalization for AD of cirrhosis and requires stricter follow-up. Older age, a more advanced liver disease and higher grade of systemic inflammation at first discharge were independent predictors of 180-day mortality.

Table 1. Independent predictors of 90-day readmission.

	HR (CI 95%)	p-value
Age	1.01 (0.99, 1.04)	0.171
Gender (F vs M)	0.94 (0.58, 1.53)	0.803
Etiology		
Alcol	1.39 (0.73, 2658)	0.310
Autoimmune	0.79 (0.23, 2.73)	0.708
NASH	1.43 (0.72, 2.85)	0.312
HCV (before 2014)	1.84 (0.86, 3.92)	0.110
HCV (after 2014)	1.86 (0.95, 3.66)	0.071
HBV	1.09 (0.45, 2.62)	0.841
Other	1.33 (0.53, 3.31)	0.540
MELD at discharge	1.04 (1.02, 1.06)	<0.001
EPS	1.58 (1.02, 2.47)	0.043
AKI	1.34 (0.80, 2.24)	0.263

Table 2. Independent predictors of 180-day mortality

	HR (IC 95%)	p-value
Age	1.04 (1.02 - 1.06)	<0.001
Gender (F vs M)	1.03 (0.57 – 1.87)	0.930
Etiology		
Alcol	0.72 (0.29 – 1.79)	0.481
Autoimmune	1.01 (0.27 - 3.69)	0.998
NASH	0.78 (0.28 – 2.23)	0.653
HCV	0.79 (0.32 – 1.93)	0.609
HBV	0.75 (0.27 – 2.05)	0.572
Other	0.86 (0.33 – 2.22)	0.748
AKI	1.51 (0.85 – 2.70)	0.161
MELD at discharge	1.05 (1.01 - 1.08)	0.014
WBC at discharge	1.03 (0.91 – 1.17)	0.601
PCR at discharge	1.02 (1.01 – 1.03)	0.002

311. HEPATOFUGAL PORTAL FLOW IS ASSOCIATED WITH MORE ADVANCED LIVER DISEASE: A COHORT STUDY

Bevilacqua M.[1], De Marco L.[1], Stupia R.[1], Cattazzo F.[1], Zoncapè M.[1], Paon V.[2], Ieluzzi D.[2], Dalbeni A.[1], Sacerdoti D.[2]
[1]General Medicine C, Department of Medicine, University of Verona, Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy;
[2]Liver Unit, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy

Background and aims: Non-forward portal flow (NFPF), which is the presence of hepatofugal portal flow in main portal vein, is supposed to be a feature related to more severe portal hypertension in cirrhosis. However, scarce data exist about prevalence and clinical implications of NFPF. The aim of the study was to investigate the prevalence and the relationship between NFPF and liver disease severity.
Methods: 233 consecutive cirrhotic patients were included in the study. Color-Doppler ultrasound was used to assess portal vein patency, flow direction and significant porto-systemic shunts (SPSS, > 8 mm). Patients with hepatocellular carcinoma and severe non liver-related comorbidities were excluded. Clinical and biochemical data were collected. Chid-Pugh (CP) score and Model for End-Stage Liver Disease (MELD) score were also calculated.
Results: Twenty-four patients (10,3%) had baseline NFPF; they had predominantly alcohol-related cirrhosis. NFPF patients showed significantly worse liver function and major complications of cirrhosis as compared to patients with forward portal flow. In particular, when compared to forward portal flow patients, those with NFPF had higher CP score (9 [8-10] vs 7 [5-9], p<0,001) and MELD score (19 [14,5-30,5] vs 11 [8-15], p<0.001). Furthermore, NFPF patients had a higher prevalence of SPSS and hepatic encephalopathy but a lower rate of high risk varices (12,5 vs 32,2 p=0.038).
Conclusion: NFPF is a condition far from rare, present in nearly 10% of our cohort; it was found to be associated with worse liver function and higher risk of hepatic encephalopathy. Although there is no specific measure to reverse NFPF, patients with NFPF should receive prompt intensive management and urgent prioritization for liver transplantation.

312. A CASE OF ACUTE HEPATITIS IN A WOMAN WHO HAD RECEIVED METHYLDOPA IN PREGNANCY

Palumbo F., Criscuolo L., Gjeloshi K., Meo L.A. , Adinolfi L.E. , Marfella R., Marrone A.
Dipartimento di Scienze Mediche e Chirurgiche Avanzate, Università degli Studi della Campania "Luigi Vanvitelli"

We describe a case of 21-years-old Albanian woman with jaundice, diffuse abdominal pain and nausea. Four months earlier the patient gave birth to a child. During the last month of pregnancy she reported hypertension, so it was prescribed methyldopa 250 mg TID. Post-pregnancy cardiological visit demonstrated normalization of blood pressure, however the patient continued the drug until she noticed scleral icterus. Few weeks later, despite the withdrawal of methyldopa, the woman was admitted in hospital due to worsening of jaundice and appearance of gastrointestinal symptoms. She had no other significant past medical history, nor was taking any medications; she also denied consumption of alcohol, ingestion of suspected drugs or raw foods and recent vaccines. At admission the patient appeared in substantial discomfort, apyretic, with normal vital signs; there were no clinical features of hepatic encephalopathy. On physical examination the abdominal wall was not tense whereas the liver was enlarged; spleen, lung and cardiac examination resulted regular. ECG exhibited sinus rhythm at 75 b.p.m with normal intervals and waves. Chest X-ray didn't report any pathological sign. Abdominal US reported: "Liver of preserved volume, regular surface, finely patchy ecostructure with starry sky appearance, without visible solid lesions. Presence of at least one lymphonode with reactive appearance at the hepatic hilum. Bile ducts not dilated. Pancreas with finely coarse ecostructure, with increased thickness. Spleen volume within normal limits. Absence of ascites". Laboratory data highlighted: WBC 7000/μL, RBC 4.8 106/mm3, Hb 14 g/dL, preserved leukocyte composition, AST 52 x ULN, ALT 35 x ULN, GGT 2.9 x ULN, ALP 160 U/L, total bilirubin 12.6 mg/dL (direct 10.9), albumin 3.9 g/dL, INR 1.99, PTT 40 s, lipase 1.3 x ULN, IgG 1.7 g/dL, glycemia in range, normal kidney function, absence of markers of inflammation. The clinical and laboratory signs was consistent with acute hepatitis with hepatocellular injury, so methyldopa was definitely stopped and supportive therapy - based on i.v. fluids (saline 0.9% and glucose 5%), vitamin K1, glutathione and UDCA - was set up. Meanwhile, further laboratory tests were performed to investigate the cause of hepatitis: markers of HAV, HBV, HCV, EBV, CMV, HSV infections were negative, ceruloplasmin was normal, ANA (titer 1:1280) and ASMA (titer 1:160) were detected. At this point a liver biopsy was performed; the histological exam described "Partial subversion of lobular architecture by the presence of complete fibrotic septa, circumscribing initial hepatocyte nodules. Lymphoplasmacytic infiltration of portal spaces. Diffuse interface hepatitis, with plurifocal areas of lobular inflammation. Preserved features of intraportal biliary structures. Findings compatible with chronic active hepatitis in early fibrotic evolution". One week after admission, a significant improvement in symptomatology and laboratory markers (AST 19.1 X ULN, ALT 16.8 x ULN, GGT 1.7 x ULN, total bilirubin 6.0 md/dL) was observed. The patient was discharged with a diagnosis of "Methyldopa acute DILI with features of autoimmune hepatitis". Full resolution of the clinical and laboratory picture was observed at 1 month, with persisted normal liver indices at 6 months of follow-up. Acute hepatitis is referred as inflammation of hepatocites resulting in elevated transaminases that lasts ≤ 6 months. It can be determined by a wide variety of infectious (e.g. hepatotropic viruses) and non-infectious (drugs, toxins, alcohol, autoimmune, metabolism disorders, vascular, ischemia) causes. Drug-induced liver injury (DILI) is challenging clinical condition and leading cause of acute liver failure in Western countries. DILI is traditionally classified as direct or idiosyncratic. Direct hepatotoxicity is caused by agents that are intrinsically toxic to the liver and is typically dose-related; idiosyncratic DILI is unpredictable, not dose-dependent, with variable latency to onset. DILI is categorized as hepatocellular, cholestatic, or mixed according to ALT/ALP (R) ratio. DILI diagnosis relies on the exclusion of alternative causes and on causality assessment with an hepatotoxic drug. Methyldopa is an old antihypertensive agent with centrally sympatholytic action. Currently, its major use is treatment of hypertension during pregnancy. Two patterns of hepatotoxicity have been described (acute or chronic hepatitis), although some cases share features of both. The acute liver injury from methyldopa generally arises within 2 to 12 weeks of starting therapy and is typically hepatocellular, with marked elevations in ALT and AST. Symptoms resemble those of acute viral hepatitis, including jaundice, malaise, anorexia and nausea. Autoantibodies may be present. Liver biopsy shows an acute hepatitis-like picture with marked inflammatory infiltrates with variable amounts of necrosis. The use of methyldopa in pregnancy requires careful monitoring of liver enzymes.

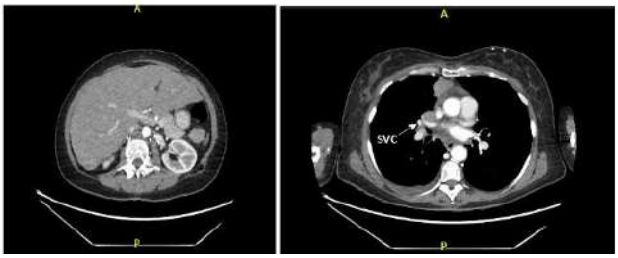
313. SMALL-CELL LUNG CANCER UNUSUAL PRESENTATION: CRUCIAL ROLE OF LIVER BIOPSY IN THE DIAGNOSIS

Bufano G.G, Chiarelli I., De Girolamo G., Iraci A., Petrozzi M.T., Villani R., Sangineto M., Serviddio G.
Liver Unit, University of Foggia

Small-Cell Lung Cancer (SCLC) is an aggressive neuroendocrine tumor characterized by early metastatic spread and responsiveness to initial therapy, representing the 15% of all lung cancer new diagnoses and affecting old male with a long history of smoke exposition. The metastatic dissemination mostly involves liver, brain and bones, although every organ can be affected. Onset symptoms usually are thoracic pain, cough, dyspnea, hemoptysis, and hoarseness. Whilst, an unusual clinical pattern is represented by Superior Vena Cava Syndrome (SVCS), which encompasses a collection of signs and symptoms due to Superior Vena Cava (SVC) compression by a mediastinal mass. A 59 years-old woman accessed to the Emergency Department of University

hospital of Foggia for face and neck edema, erythema and functional impairment (dysphagia and dyspnea) occurred within the last two hours after assuming Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). Steroids were administered in the suspicion of allergic reaction with no clinical improvement, hence further investigations were assessed. Blood test showed slight White Blood Cells (WBC) increase (14.000 uL), mixed hyperbilirubinemia (2.77 mg/dL), GOT and GPT x 4 ULN, GGT x 61 ULN; thorax X-rays and CT-SCAN showed respectively "*right paramediastinal consolidative area*" and "*dense superior mediastinal tissue probably of lymphomatous origin extending along lymph node stations until subcarinal region and prevascular space showing mass effect on VCS (..) enlarged liver with inhomogeneous echotexture and 'geographic' fatty change*". The patient was admitted to the Liver Unit for further investigations. Other hepatomegaly causes were considered: anti-hepatitis A virus immunoglobulin M (IgM), anti-hepatitis B core antigen IgM, hepatitis B surface antigen, anti-hepatitis C virus antibody, Epstein-Barr virus/cytomegalovirus immunoglobulin G, herpes simplex virus for viral hepatitis resulted negative; antinuclear antibody (ANA), ENA anti RNP, anti-mitochondrial (AMA), anti-LKM, C-ANCA, P-ANCA resulted negative, JAK2 negative. Considering the complexity of mediastinal biopsy procedure, ultrasonography-guided liver biopsy was performed for histological examination that showed features of SCLC liver metastases. The patient was consequently addressed towards proper cancer treatment.This case report showed an unusual clinical presentation of SCLC, and demonstrated the advantages of liver biopsy in the diagnosis of metastasized SCLC.

SMALL-CELL LUNG CANCER UNUSUAL PRESENTATION: CRUCIAL ROLE OF LIVER BIOPSY IN THE DIAGNOSIS



314. A RARE FORM OF ALCOHOLIC POLYNEUROPATHY

A.Mariniello, C.Matteo, A.Di Mauro, Giordano M., Paolisso G.
Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli"

We describe the case of Adam, a homeless polish man of 50 YO, that come in ED for a progressive hyposthenia of inferior limbs and loose of sphincter control for about two weeks. His anamnesis was mute for any notable disease except for a binge drinking history of beer and pure alcohol for 30 years. At neurological examination, the patient was alert, collaborated, oriented in space and time with areflexia and hypotrophies of inferior limb muscles but a preserved sensitivity. At general PE, Adam presented malnourished but anasarcatic with caput medusae and an abdomen dull at percussion. Among instrumental, he performed a total body CT scan that showed abundant ascites, splenomegaly, and a small, lumped liver with irregular margin. First it was performed a diagnostic and evacuative paracentesis, in which were removed 6 liters that showed a transudative ascites (SAAG > 1.1) without leukocytes. To control complication of cirrhosis he performed a EGDS which showed an esophageal candidiasis and a severe hypertensive gastropathy. In addition, CT scan evidenced swollen and dilated segments of bowel as paralytic ileus. At ABG there was a severe type I respiratory insufficiency explained by a bilateral pleural effusion with left pulmonary thickening. At laboratory analysis there were noted a macrocytic anemia (6,5 Hb) corrected with transfusions, increased index of flogosis, signs of hepatic dysfunction (low albumin, platelets, cholinesterase, and increased bilirubin) and an increased TSH 6 with low fT3 and fT4. It was imposed a therapy to contain cirrhosis (diuretics, lactulose, beta blockers, albumin); oxygen therapy to ameliorate respiratory insufficiency; antimicrobials (piperacillin/tazobactam) and antifungal (fluconazole) to treat infections, and levothyroxine to support chronic thyroiditis. After three-weeks Adam's conditions improved with a significative reduction of ascites and pleural effusion with a recovery of respiratory function but he continues to have difficulties in performing habitual activities like walking due to asthenia and hypotrophies of inferior limbs. First it was performed a blood sample to exclude autoimmune diseases for antibodies and HIV, HBV, HCV tests to exclude infective diseases which resulted negative. To exclude neurodegenerative and infective disease of brain and spinal cord he performed RMN that evidenced cortical atrophy; so the neurologist concluded to a long term dysmetabolic polyneuropathy due chronic assumption of alcohol.
DISCUSSION: It could seem trivial, but alcohol related peripheral neuropathy (ALN) is rarely discussed debilitating complication of alcoholism nevertheless about 66% of chronic drinker are affected. ALN has a slow, progressive onset over months to years characterized primarily by sensory symptoms like paresthesia, impaired vibration sensation and reduced proprioception. Motor features also occur, most often weakness with diminished or absent reflexes. Several risks of factors were involved in its development like male sex; type, and duration of alcohol consumption (more frequent in beer and pure alcohol consumers for several years than wines and occasional drinkers). Pathophysiological mechanism is still an item of debate. For years was thought that ALN was a nutritional neuropathy due to deficit of vitamin B, the brick for synthesis of myelin and alcohol interferes in its absorption in GI tract, its utilization by tissues and storage in the liver; today its increasingly frequent ALN with normal vitamin B, as our Adam. Hence was born the hypothesis that ALN is a toxic neuropathy in fact ROS produced by ethanol, inhibits IGF impairing myelinic sheath production, axonal transport and disrupt oligodendroglia and astrocytes inducing to white matter atrophy and decreased cognitive function. The best cure of this condition is total abstinence from alcohol and administration of complex of vitamin B even is normal but it's a long process not always reversible in severe cases. For this reason, we have decided to add in therapy chloridrate thiamine one intravenous administration per day, continuing alcohol abstinence, active and passive exercise. After three weeks Adam was able to maintain a sitting position and to walk accompanied by physiotherapists. ALN is often a misdiagnosed complication in chronic drink abusers, especially in those with normal vitamin B complex values. In this case, it'is important continuing administrate thiamine in alcoholists because this polyneuropathy is usually long term and may even take two years to reverse, in order to guarantee a better quality of life improving motor and sensory functions of limbs.

315. ASSOCIATION BETWEEN LIVER FIBROSIS SEVERITY AND IMPAIRED INSULIN-STIMULATED MYOCARDIAL GLUCOSE METABOLIC RATE IN SUBJECTS WITH DIFFERENT DEGREE OF GLUCOSE TOLERANCE

Succurro E.[1], Giofrè F.[1], Massimino M.[1], Marinaro G.[1], Fiorentino T.V.[1], Sciacqua A.[1], Veltri P.[2], Cascini G.L.[3], Andreozzi F.,[1], Sesti G.[4]
[1]Dipartimento di Scienze Mediche e Chirurgiche, Università "Magna Graecia", Catanzaro; [2]Dipartimento di Ingegneria Informatica, Modellistica, Elettronica e Sistemistica, Università della Calabria, Cosenza; [3]Dipartimento di Medicina Sperimentale e Clinica, Università "Magna Graecia", Catanzaro,; [4]Dipartimento di Medicina Clinica e Molecolare, Università Sapienza, Roma

Increasing evidence suggests that liver fibrosis in subjects with non-alcoholic fatty liver disease (NAFLD) is an independent risk factor for cardiovascular disease (CVD). It has also been shown that NAFLD is associated with decreased myocardial glucose uptake in subjects with type 2 diabetes. However, the association between myocardial glucose uptake and liver fibrosis is unsettled.
To elucidate this issue, we aimed to investigate the association between liver fibrosis severity and insulin-stimulated myocardial glucose metabolic rate in 57 subjects without coronary heart disease exhibiting different glucose tolerance status. Myocardial metabolic rate of glucose (MRGlu) was assessed using dynamic cardiac 18F-FDG PET combined with euglycemic hyperinsulinemic clamp, which allows to assess peripheral insulin sensitivity normalized for lean body mass (MFFM) and to standardize metabolic and hormonal conditions during PET. Liver fibrosis severity was estimated by the fibrosis-4 index (FIB-4), one of the most widely used non-invasive fibrosis test, which uses as variables age, levels of aspartate aminotransferase (AST), levels of alanine aminotransferase (ALT), and platelet counts. According to FIB-4 index, subjects were stratified into four groups: lowest risk of fibrosis (<1.3; n=37); low risk of fibrosis (≥1.3 to < 1.67; n=12); moderate risk of fibrosis (≥1.67 to < 2.67; n=4); high risk of fibrosis (≥2.67; n=4).
As compared with subjects with lowest risk of liver fibrosis, those with high risk of advanced fibrosis exhibited a decrease in myocardial MrGlu (21.7+11 vs 4.6+4.3 mmol/min/100g; P=0.005) No significant differences in glycemic and anthropometric parameters, in whole body insulin sensitivity, and in blood pressure were found between groups.
Univariate correlations showed that FIB-4 index was significantly negatively

correlated with myocardial MRGlu (r= -0.320, P=0.01), and positively correlated with waist circumference (r= 0.299, P=0.02). In a multivariable regression analysis, the only variable significantly associated with FIB-4 index was myocardial MrGlu (b -0.286; P=0.003) explaining the 28.6% of its variation. These data suggest that an impairment of insulin-stimulated myocardial glucose metabolism is associated with higher risk of liver fibrosis and may represent an early cardio-metabolic defect heralding future CV events in subjects with NAFLD and advanced fibrosis.

316. PUFAS AND MUFAS INTROITS CONTRIBUTION TO NONALCOHOLIC FATTY LIVER DISEASE PROGRESSION: NEW PERSPECTIVES FOR PREVENTION AND TREATMENT

De Girolamo G. , Sangineto M., Bianco R., Ciarnelli M., Frisoli I., Villani R., Romano A.D., Serviddio G.
Liver Unit, University of Foggia

Aim: Nonalcoholic fatty liver disease (NAFLD) is defined as the presence of fat in the liver, known by now as a metabolic and cardiovascular risk factor. Several components, such as excessive energetic introit and micronutrients deficiencies, can concur to its pathogenesis. Whilst Mediterranean diet (Md) is highly recommended for its cardiovascular and metabolic protection thanks to the high intake of fibers, complex carbohydrates, non-animal protein and Monounsaturated and Polyunsaturated fatty acids (MUFAs and PUFAs), NAFLD is progressively becoming a burden of Western Countries. Few studies investigated MUFAs and PUFAs role in prevention and treatment of NAFLD and steatohepatitis (NASH), and no relevant data are available about their role in the pathogenesis of NAFLD.
For these reasons, we questioned alimentary habits and adhesion to Md of a cohort of patients affected by NAFLD (including NASH), with a particular focus on MUFAs and PUFAs introits.
Methods: We enrolled 60 patients with NAFLD, referring to Centro Cure (Centre for diagnosis and treatment of hepatic diseases) of University of Foggia from November 2022 to February 2023. The average age was 56.4 (55% men, 45% women), with a mean BMI of 31.5 Kg/m2. The diagnosis of NAFLD and NASH was assessed by abdominal ultrasound and histological examination respectively. Subjects were divided into four groups according to steatosis severity and NASH diagnosis (L: mild, M: moderate, S: severe, N: NASH). Every patient filled a self-administered food frequency survey containing information about red and white meat, fish, wholegrain cereals, olive oil consumption. In particular, weekly consumption of MUFAs and PUFAs rich food such as extravirgin olive oil, seeds and oily fruits was recorded.
Results: Although 73% of patients declared to follow Md recommendations, only 5% of patients was truly adherent to Md principles. In fact, 87% of subjects reported to eat red meat at least twice a week, 18% ate white meat more than three times a week, while 80.8% and 48.3% reported to eat respectively wholegrain cereals and fish less than once a week. The weekly mean consumption of MUFAs and PUFAs-rich food decreased along with steatosis severity. We found a significant difference in weekly PUFA consumption between L and N groups (L 9 vs N 6.5). In addition, the intake of MUFAs rich food (especially EVO and olives) decreased by 34% in N patients compared to L subjects (L 9.1 vs N 5.93), with a daily consumption of EVO of about 30g in L and 15g in N patients. Overall, the mean omega-3-rich food consumption was 2.46/week. In detail, comparing L with N patients we observed a significant lower assumption of omega-3-rich food in N (L:3.1 vs N:1.28).
Conclusions: The analysis of survey revealed unhealthy alimentary habits of NAFLD patients, who reported to consume high quantity of meat, while wholegrain cereals, fish and EVO were underrepresented.
Further studies are needed to clarify the role of MUFAs and PUFAs assumption in the prevention of NASH, as these findings suggest that MUFAs and PUFAs-poor diets may be involved in the progression of NAFLD.

317. PLACEMENT OF A TRANS-JUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT (TIPS) MODIFIES THE EXPRESSION OF PROINFLAMMATORY CYTOKINES IN CIRCULATING MONOCYTES EXPOSED TO LIPOPOLYSACCARIDE (LPS)

Adotti V., Pastore M., Vizzutti F., Roccarina D., Navari N., Piombanti B., Rosi M., Cacciato V., Marra F.
Department of Experimental and Clinical Medicine, University of Florence, Firenze, Italy

Background/aims: Recent data have indicated that decompensated cirrhosis is characterized by an imbalance in the innate immune system, leading to low-grade systemic inflammation. In particular, inflammatory cytokines secreted by monocytes and macrophages have been implicated in the pathogenesis of portal hypertension and its complications. Additionally, MerTK-expressing monocytes participate in the determination of severity of acute liver failure. Trans-jugular intrahepatic portosystemic shunt (TIPS) is currently used for the treatment of complications of portal hypertension, but whether portosystemic derivation results in changes in the biology of inflammatory cell is currently unknown.
Methods: Fifteen patients with severe portal hypertension referred for TIPS placement were enrolled. During the TIPS procedure, blood from the portal and jugular vein was drawn, and at 4 weeks after TIPS placement a sample from a peripheral vein was repeated. Monocytes were isolated from peripheral blood mononuclear cells by adherence after Ficoll-Hypaque purification, and stimulated with LPS (1 μg/ml) for 2, 8 and 24 hours. Gene expression was evaluated by real-time PCR.
Results: Upon exposure to LPS, a significant increase in gene expression of IL-1beta, IL-6, TLR4 and MerTK was observed in monocytes isolated from either the portal or the jugular vein. Basal and LPS-stimulated mRNA levels of these molecules were markedly lower in the post-TIPS compared to pre-TIPS, in particular after exposure to LPS. Expression of the anti-inflammatory cytokine IL-10, was significantly increased after LPS stimulation for 2 and 8 hours. After TIPS, mRNA levels of IL-10 were reduced in unstimulated conditions but increased after LPS stimulation for 2 hours.
Conclusions: Reduction of portal pressure through TIPS placement is associated with reduced expression of pro-inflammatory mediators and modulation of anti-inflammatory IL-10. Increased portal pressure in cirrhotic patients may be a direct modulator of the complex changes in the inflammatory balance observed in these patients.

318. HERBAL, DIETARY SUPPLEMENT AND OLIGO-MINERAL CONSUMPTION AMONG CHRONIC LIVER DISEASE PATIENTS AND CAREGIVERS: AN OUTPATIENT'S SURVEY

Tulone O.[1], Cammilleri M.[1], Cilona L.[2], Fazzari A.[2], Chianetta R.[1], Veronese N.[2], Giannitrapani L.[1], Citarrella R.[1], Soresi M.[1], Barbagallo M.[3], Licata, A.[1]
[1]Internal Medicine & Hepatology Unit, PROMISE, University of Palermo; [2]Geriatrics Unit, PROMISE, University of Palermo; [3] Internal Medicine, Geriatrics Unit, PROMISE, University of Palermo

Background: Herbal and Dietary Supplements (HDS) consumption is widespread among chronic liver disease patients. Although they may have adverse effects and potentially interact with conventional medications, it is enough common the perception that they are "natural" products, free of side effects with no need for medical consultation or prescription. The purpose of this study was to investigate herbal and dietary supplement and oligo-elements consumption among patients with chronic liver disease and caregivers, their perceived benefits and modality of prescription.
Methods: During a six-month study period, patients with chronic liver disease followed at Internal Medicine and Hepatology Unit and caregivers, were assessed regarding HDS and oligo-minerals consumption. Data were collected using quantitative methods through a self-administered questionnaire with the following items: age, sex, housing, marital status, qualification, smoking habits, alcohol consumption, lifestyle, use of HDS, reason for taking HDS, type of HDS, benefit or not, type of prescriber, awareness of the general practitioner. A computerized database was constructed with all the variables included in the questionnaire and the statistical analysis was performed by SPSS.
Result: Out of 281 participants, 182 (64,76%) were chronic liver disease patients (chronic viral hepatitis 51.0%, MAFLD 46.7% and autoimmune liver disease 2.3%) and 99 (35,23 %) were the caregivers. Out of the entire cohort, 93 (33,3%) were HDS and oligo-elements consumers. Multivitamins (64.1%) were the most frequently reported type of supplement consumed, followed by oligo-elements (34.9%) and herbal (26.7%) products. The prevalence of HDS consumption among adults was 46.5%, whereas 36.9% reported regular and 63.1% occasional supplement use, respectively. Common reason for taking HDS were: anxiety and sleeping disturbance (14%), peripheral venous insufficiency of the lower limbs (10%), liver steatosis and menopausal symptoms (9%), constipation, dyslipidemia and personal well-being (8%), immune-stimulant action and urological disease (6%), osteoarticular pain, asthenia, headache (5%) and others (6%). Sixty-five (69,8%) out of 93 consumers admitted to benefit from HDS or oligo-elements intake. A third of the users (35.9%) admitted a self-prescribing dietary supplements without

seeking any professional or medical advice. Awareness of general practitioners was reported in 28.8% of cases. HDS consumption was associated with older age (p=0.003) and female gender (p = 0.02). In general, HDS consumers reported a healthy lifestyle (71,17%), only 19% showed smoking habits and the majority (91,46%) were urban area residents. None of the participants reported adverse events.
Conclusions: HDS and oligo-elements consumption is quite popular among older and female patients living in an urban area. Their use is generally exacerbated by perceived knowledge and the search for well-being. Further studies to explain better health education to prevent inappropriate or excessive use of HDS should be needed.

319. ISONIAZID HEPATIC INTOXICATION – ENVIRONMENTAL OR IDIOSINCRATIC MECHANISMS? TIPS AND TRICKS OF DETOXIFICATION.

A. Mariniello, C. Matteo, M.C. Giordano, A. Di Mauro, M. Giordano
Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli"

We describe the case of Luigi, a caucasian man of 60 years old, with an history of HBV and HCV-related cirrhosis, previous assumption of drugs and ankylosing spondylitis. Luigi attending rheumatologic ambulatory, during exams in starting secukinumab for ankylosing spondylitis, was found a positivity to quantiferon test. For this reason, his trusted rheumatology ambulatory, suggested to start a prophylactic treatment for TBC with isoniazid (INH). After 2 months, Luigi come to emergency department for sudden fever, unresponsive to ceftriaxone, and jaundice. The patient was in severe clinical conditions, tachypneic with respiratory insufficiency needing oxygen therapy, fever (38°C), BP 140/80 mmHg, HR 102 bpm. On general physical examination were relevant a globular tense abdomen, painful at palpation. His blood examination showed ALT 15x, PLT 16000, spontaneous INR 3, Total Bil 14 resulted compatible with a case of acute fulminant hepatitis. The most probable hypothesis seemed to be an iatrogenic hepatitis due INH, so he was hospitalized in the internal medicine department for diagnostic-therapeutic investigation. First were suspended INH and secukinumab, then was started a detoxification therapy with high doses of acetylcysteine (NAC) (300 mg/kg of loading dose, tapering until regression of the hepatotoxicity was obtained), 1 mg/kg of corticosteroids, Ursodeoxycholic acid, vikamin K, hydration, multicomplex vitamins and platelets transfusion. During hospitalization Luigi showed fever with a progressive increase of inflammatory index (PCR 8) and WBC (8900). In the suspect of viral hepatits reactivation and suppressed immune system considering the previous history of drug addiction, HBV-DNA, HCV-RNA and HIV tests were performed which resulted negative. Blood cultures were collected at peak febrile which resulted positive to Enterococcus Faecium resistant to vancomycin and Candida albicans. Excluding the presence of vegetations at transthoracic echocardiography, antibiotic treatment with 1000 mg of Daptomycin and antifungal treatment with Amphotericin B (preferential choice dictated by a lower hepatotoxicity compared to azoles and echinocandins) was imposed. After regression of phlogosis index, normalization of blood count exam and improvement of clinical condition, Luigi was discharged. DISCUSSION: In this case, Luigi, underwent a rare adverse effect of INH, present just in 1% of population. Its pathophysiological mechanisms were poorly understood for decades. Although the most probable cause is its induction in production of free radicals, that destroy hepatic cells and the production of metabolites as hydralazine, that cause mitochondrial injury; on the other side there are patient-specific determinants of susceptibility characterized by risks of factors as in the case of our patient (age above 50 years old, prior viral hepatic infections, alcohol and drugs addiction). As it is known, NAC is an antidot for paracetamol hepatic injury, it was chosen as detoxification therapy even in this case because it is considered the ancestor of hepatoprotective drugs. NAC has an antioxidation and anti-inflammation proprieties linking to free radicals and promoting hepatocytes regeneration. Interesting results its association with prednisone in patients with increased bilirubin inducing a significant improvement of ALT, AST and INR within two weeks. Finally, anticholestatic drugs are taken in consideration due its inhibition of cholesterol in intestine and reduction of cholesterol saturation index of bile gives hepatoprotective effect, anti-apoptotic and immunomodulatory effect. Even it is a rare condition, it's important to recognize as soon the INH toxicity of the liver and to use appropriate detoxification treatment in order to minimize the risk of hepatic failure.

320. THE EFFECTS OF VERY LOW-CALORIE KETOGENIC DIET (VLCKD) ON LIVER STEATOSIS IN PATIENTS WITH OBESITY

Natale M.R., Trapanese V., Giofrè F., Donato U., Cosentino F., Vatalaro C., Melina M., Fiorentino T.V., Andreozzi F., Arturi F.
Dipartimento di Scienze Mediche e Chirurgiche, Università degli Studi "Magna Graecia" di Catanzaro, Catanzaro, Italia

Background: Currently the treatment of metabolic dysfunction-associated fatty liver disease (MAFLD) is based on weight loss.
Aim: The aim of this study was to investigate the effects of Very Low-Calorie Ketogenic Diet (VLCKD) on liver steatosis and fibrosis in patients with obesity.
Materials and Methods: Ten patients treated with VLCKD have been enrolled. The inclusion criteria were a BMI > 30 kg/m² and a fatty liver index (FLI), a predictor of hepatic steatosis, > 60. At baseline and 3 months after VLCKD treatment, an antrhopometric (body weight, body mass index and waist circumference) and cardio-metabolic evaluation has been performed. Liver steatosis and fibrosis were assessed by using a transient elastography (FibroScan) to measure the controlled attenuation parameter (CAP) and liver stiffness measurement (LSM), respectively. Significant liver steatosis was defined as CAP ≥280 dB/m and significant liver fibrosis, as LSM ≥ 8.0 kPa. The insulin resistance was evaluated by HOMA-IR.
Results: Weight (kg) (105 ± 18.2 vs 83.7 ± 16.7, *P* <0.05), BMI (kg/m2) (40.1 ± 4.7 vs 31.8 ± 4.8, *P*= 0.002) and waist circumference (cm) (115 ± 13.6 vs 101.8 ± 12.4, *p* < 0.05) were significantly lower 6 months after VLCKD treatment. VLCKD improved also significantly fasting glucose (*P* <0.05), fasting insulin (*P* =0.004), HOMA IR (*P* <0.001), lipid profile and blood pressure. In addition, also the CAP values were significantly lower than at baseline (215,8 ± 62,33 dB/m vs 301,5 ± 68,31 dB/m, respectively; *P<0.05*) with a mean CAP reduction of 85,7 ± 33,11 dB/m. Similarly, LSM values were lower after 3 months of VLCKD than at baseline (4.56 ± 1.3 kPa vs 6 ± 2.9 kPa, respectively).
Conclusions: In conclusion, although preliminary, our data suggested that VLCK diet can induce a significantly reduction in body weight and an improvement in cardiometabolic parameters, in liver steatosis and fibrosis in patients with obesity. Then the VLCKD can represent a helpful approach for the treatment of MAFLD.

321. AIH AND SARCOIDOSIS MANIFESTING AS CHRONIC MYOPATHY

Paribello A.[1], Pes F.[1], Serra G.[2], Chessa L. [3]
[1]Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy; [2]Liver Unit, Department of Medical Sciences and Public Health, University Hospital of Cagliari, Cagliari, Italy; [3]Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy - Liver Unit, Department of Medical Sciences and Public Health, University Hospital of Cagliari, Cagliari, Italy

Autoimmune hepatitis is a chronic, inflammatory disease of the liver, characterized by a spectrum of clinical presentations, circulating autoantibodies and increased IgG serum concentrations. The disease may start as acute hepatitis and progress to chronic liver disease and cirrhosis or it can be completely asymptomatic. Here we discuss an unusual manifestation of AIH along with Sarcoidosis, that is a systemic disorder of unknown aetiology, characterized by the presence of noncaseating granulomas in the involved organs.
Case report: We reported the case of a 62-year-old Italian man presented with fatigue and muscular pain for six months, and with evidence of deranged liver function test (AST 95 U/l, ALT 200 U/I) and elevated CPK (3742 U/L). For the clinical suspicion of statin-related myotoxicity, he stopped taking Rosuvastatin without benefit. Persisting abnormal liver-related tests, laboratory evaluation of infectious and autoimmune process was done. His serum was negative for ANA, AMA, LKM, p-ANCA, c-ANCA, without any evidence of viral infections. The ultrasound images of the abdomen revealed inhomogeneous liver echogenicity. Subsequent liver biopsy showed chronic, non-granulomatous parenchymal inflammation with plasma cells in aggregates, compatible with an autoimmune aetiology.
To induce remission of the disease he started corticosteroids therapy with prednisone 50mg die, with an improvement of liver tests, but persistent increase of CPK and muscular pain. Myositis specific antibodies were negative (Ab mi2-alfa, Ab mi2-beta, Ab TIF1-gamma, Ab MDA5, NXP2, SAE1, Ku, PM-Scl100, PM-Scl75, jo-1, SRP, PL-7, PL-12, EJ, OJ, Ro-52).

To exclude a paraneoplastic syndrome, a chest and abdominal computed tomography (CT) were performed; these highlighted a 3cm pulmonary nodule, enlarged hilar-mediastinic adenopathy and bilateral sub centimetric hilar nodes. Subsequent bronchoscopy with transbronchial biopsy revealed chronic, noncaseating granulomatous inflammation that was consistent with sarcoidosis. Corticosteroids therapy with prednisone continued with gradual reduction to 10 mg, in association with Azathioprine 50 mg die. The serum transaminase and CPK levels returned to normal values within 5 months of treatment.
Conclusion: In conclusion, we described the case of a sarcoidosis manifesting as generalized chronic myopathy with autoimmune hepatitis, with full response to corticosteroid therapy, remission of muscular pains and fatigue, improvements in sarcoidosis (reduction of lung nodules in subsequent CT of chest 6 months later) and autoimmune hepatitis (normalization of liver biochemical abnormalities).

322. A CLINICAL CASE OF IGG4 HEPATHOPATY

Matarazzo G.[1], Ricciardi R.M.[1], Troiano F.[1], Caporale M.[1], Montagano M.[1], Vizzarri P.[1], D'Ardes D.[1], Santilli F.[1], Bucci M.[1], Guagnano M.[1], Cipollone F.[1], Pierdomenico S.[2]
[1]Institute of Clinica Medica, Department of Medicine and Science of Aging, "G. d'Annunzio" University of Chieti-Pescara; [2]Department of Innovative Technologies in Medicine & Dentistry, University "Gabriele d'Annunzio", Chieti-Pescara, Chieti, Italy

Introduction: IgG4 disease is a systemic disease characterized by increased serum IgG4 concentration and IgG4+ cell infiltration in multiple organs. The major diagnostic challenge today is to distinguish liver involvement as a manifestation of systemic IgG4-related disease (IgG4-related hepatopathy) or a subtype of Autoimmune Hepatits.
The gold standard diagnostic remains histological analysis, on liver biopsy.
We recognize 4 main clinical-pathological characteristics of autoimmune hepatitis from IgG4: 1.serum concentration of IgG4> 135 mg/dl, 2.increase in IgG4+ plasma cells in liver tissue greater than 10/FPF, 3.Chronic hepatitis with zonal and bridge necrosis with 4. metachronous or synchronous association of other manifestations of IgG4 disease.
In IgG4 related hepatopathy we find more frequently also the biliary tract involvement with eosinophilic infiltrate, obliterant phlebitis or pseudotumor and storiform fibrosis.
Clinical Evolution: 83-year-old male arrives in PS for jaundice and persistent hyperchromic urine about 10 days. History of ischemic heart disease treated with double BPAC 7 years before, FA in NAO, long history of psoriatic arthritis managed with Methotrexate recently suspended, on the advice of the doctor, in conjunction with the administration of vaccines against flu and Sars-Cov2.
The physical examination was normal except jaundiced skin and mild tenderness at deep palpation in right hypochondrium.
In ED, laboratory tests show mainly hepatocellular damage (R value: 9.2) with pancreatic cleavage, elevated cholestasis indices (predominantly direct bilirubin) and flogose indices.
Simultaneous ultrasound of the upper abdomen point out thickening of the walls of the gallbladder with biliary sludge in the absence of dilation of the bile tract and abdominal CT detect fibrosteatosis, distended gallbladder with imbibition of perivisceral adipose tissue, endoluminal lithiasic formations of the gallbladder and edema of the head of the pancreas.
In the suspicion of hepatocolangite the patient, hospitalized in our internal medicine department, undertakes antibiotic and fluid therapy with improvement of the flogosis indices. For further diagnostic analysis of the hepatitis picture, other tests are performed for viral hepatitis (in particular HAV, HBV, HCV, CMV, EBV, HSH, HIV all negative) and for autoimmune hepatitis with positive ANA (1/80) and hypergammaglobulinemia. Toxicological causes are also excluded.
Thus, autoimmunity is investigated with the search for Ig subclasses, with the demonstration of a significant increase in IgG4 (282 mg/dl, vn 1-104).
To complete diagnosis is carried out cholangium-MRI that shows thickened and oedematous walls of the gallbladder without lithiasic formation endoluminal and absence of significant distension of the cystic duct and choledochal with nothing to report at the pancreatic level.
Given the strong suspicion of IgG4-related hepatocolangite steroidal therapy (urbason 40 mg/day) was set with improved hepatocytonecrosis indices, and indication was given to the liver biopsy for diagnostic confirmation that however the patient, aware of the risk/benefit arising from the procedure, refused to execute.
Conclusions: In light of high serum IgG4 levels and positive ANA along with a good response to corticosteroid therapy, an autoimmune diagnosis of probable IgG4 hepatocolangite was made. Specifically, there was a clinical suspicion of slatentized autoimmunity caused by the suspension of methotrexate that the patient used to take for psoriatic arthritis.
For diagnostic confirmation, the biopsy may be considered histological differences in liver damage in IgG4 autoimmune hepatitis and IgG4-RD hepatopathy, but it would not have changed the therapeutic approach.

323. FOCUS ON SPONTANEOUS MUSCULAR HEMATOMA IN LIVER CIRRHOSIS: CASE REPORTS

Natola L. A., Dalbeni A., Sacerdoti D.
Division of General Medicine C and Liver Unit, Department of Medicine, University of Verona, Verona, Italy.

Background: Spontaneous hemostasis-related bleeding in cirrhosis, such as spontaneous muscular hematoma (SMH), is defined as an unprovoked hemorrhagic event of unexplained cause. This definition was recently introduced to distinguish bleeding occurring in patients with cirrhosis as a result of hemostatic abnormalities from bleeding related to portal hypertension, traumatic or iatrogenic vascular lesions, or peptic ulcers. The pathogenesis of SMH is still not clear but acute kidney injury, bacterial infections/sepsis, and progression from acute decompensation to ACLF are associated with an increased risk of bleeding. A review of the literature showed that high mortality is associated with SMH in alcoholic liver cirrhosis, which makes early recognition and prompt initiation of treatment a crucial part of managing such patients. We report 2 cases of patients diagnosed with SMH.
Case 1
In January 2023, a 68-year-old male patient, D.G., was admitted to our Liver Unit Verona for ACLF grade 3, Hepatic hydrothorax and urinary tract infection. His medical history included arterial hypertension, type 2 diabetes mellitus and hepatic cirrhosis with alcohol etiology. He reported withdrawal from alcohol from 2 months. Upon admission, the patient's liver function was assessed as MELD-Na score 38 and Child-Pugh score C 12. The patient received antimicrobial therapy and albumin infusions. The urine culture confirmed an infection caused by Escherichia Coli.Following the treatment, the patient showed clinical improvement. However, 15 days after admission, he developed a spontaneous muscular hematoma resulting in anemia. A CT scan showed a 17 cm long and 7 cm thick muscular hematoma on the left thoracic wall. Blood tests showed increased INR (2.6) and aPTT (1.9), piastrinopenia (32000/mmc) and hipofibrinogemia (1.2 g/L). No anticoagulant or antiplatelet treatments were ongoing. The bleeding could not be addressed by local measures and/or interventional radiology procedures because multiple muscular arterials were bleeding.The patient underwent treatment including blood transfusions, phytomenadione, fresh-frozen plasma (FFP), platelet transfusions and fibrinogen concentrate with poor efficacy. The possibility of a liver transplant was discussed and the patient was transferred to the Intensive Care Unit. Unfortunately, the patient deceased after 7 days.
Case 2
In January 2021, a 53-year-old male patient, P.M., was admitted to our Liver Unit for ACLF grade 2, bacterial pneumonia and severe anemia. His medical history included only hepatic cirrhosis with mixed etiology (alcohol and hepatitis C virus, eradicated in 2017), no other relevant comorbidities were reported. He reported withdrawal from alcohol from 4 months. No anticoagulant or antiplatelet treatments were ongoing. Upon admission, the patient's liver function was assessed as MELD-Na score 35 and Child-Pugh score C 12 and blood tests showed increased INR (2.49) and aPTT (1.45), piastrinopenia (25000/mmc), hipofibrinogemia (0.86 g/L) and decreased antithrombin 3 activity (24%). CT scan showed a 13 cm long and 3.5 cm thick muscular hematoma on the right thoracic wall. No trauma was reported. The patient received antimicrobial therapy and albumin infusions for the infection and the acute kidney injury. The bleeding could not be addressed by local measures and/or interventional radiology procedures because multiple muscular arterials were bleeding. For this reason, the patient was treated with blood transfusions, phytomenadione, fresh-frozen plasma (FFP), platelet transfusions, fibrinogen concentrate and tranexamic acid intravenous infusion. However, with poor efficacy. The patient underwent to liver transplant after 15 days. The postoperative course was without complications, and the patient was discharged in March 2021.
Conclusions: SMH is a clinical situation associated with high mortality. International guidelines currently lack clarity regarding the optimal medical treatment for cirrhotic patients experiencing active bleeding from a non-portal hypertensive cause. European guidelines recommend local measures

and/or interventional radiology procedures as the first-line therapy, although these recommendations are often not applicable. Literature reviews focusing on a limited number of SMH cases suggest that liver transplant may be the most effective option, with a high rate of survival. Our own experience supports this evidence. In conclusion, in accordance with the EASL (European Association for the Study of the Liver) guidelines, it is recommended to conduct large observational studies aimed at defining the precise incidence of spontaneous bleeding events and their impact on the clinical course and survival of patients with cirrhosis.

324. PREVALENCE AND CLINICAL FEATURES OF NON-CIRRHOTIC VS CIRRHOTIC HCC: RESULTS FROM A SINGLE-CENTER EXPERIENCE

Santoliquido M., Peluso A., Cicco A., Serviddio G., Villani R.
C.U.R.E. (University Centre for Liver Disease Research and Treatment), Liver Unit, Department of Medical and Surgical Sciences, University of Foggia, Viale Pinto 1, 71122, Foggia, Italy

Introduction: Liver cancer is the fifth common cancer and the second cause of cancer-related death in the world. Cirrhosis is the most important risk factor for HCC development, and it is linked to chronic viral hepatitis or alcohol abuse, metabolic diseases such as NAFLD, as well as genetic disorders such as haemochromatosis or alpha-1-antitrypsin deficiency. Overall, one-third of cirrhotic patients will develop HCC during their lifetime. The diagnosis is mostly late due the lack of symptoms in its early stages, and it is resistant to conventional systemic chemotherapy or radiotherapy. Previous studies showed that about 20% of HCC can occur in non-cirrhotic livers. In this subgroup, the diagnosis is generally delayed due to the lack of specific surveillance programs. However, the clinical phenotypes of non-cirrhotic HCC or specific clinical features have not been completely defined. Therefore, our aim was to establish the prevalence of HCC occurring in patients without cirrhosis in our Liver Unit and compare their clinical course and characteristics with cirrhotic HCC.
Methods: Data were retrospectively collected and included all HCC patients who referred to our Liver Unit from 2018 to 2023. Data on patient demographics, liver etiology, stage at presentation and clinical features were recorded. **Results:** 132 HCC patients were included in our analysis and 19 patients (25%) had no underlying cirrhosis. Age at diagnosis in non-cirrhotic HCC were not statistically different (median 68.2 years SD: 9.4 for non cirrhotic HCC vs 67.6 years SD 7.4 for cirrhotic ones; p=0.234). 84% of patients were male. Viral related liver disease was the most common underlying etiology in patients with non-cirrhotic HCC (36.8% vs. 50% in cirrhotic group), followed by NAFLD (26% of cases in the non-cirrhotic group vs. 11 % in cirrhotic patients) and unknown etiology (26% in non cirrhotic vs. 6% in cirrhotic population). The Barcelona Clinic Liver Cancer (BCLC)stage was assigned and confirmed using the collected clinical, radiologic, and laboratory data. 84% of the patients with non-cirrhotic liver were classified in BCLC stage 0-A and the remaining 16% of the patients were diagnosed in BCLC stage B (early HCC). In the cirrhotic group 46% was classified in BCLC stage 0/A, 15% in stage B and 11% in stage C. Liver resection was performed in 13.2% cirrhotic versus 42% non-cirrhotic whereas Radiofrequency Ablation (RFA) in 8.8% and 10% of cirrhotic and non-cirrhotic HCC, respectively. Transarterial chemoembolization (TACE) was used in 23% of cirrhotic HCC and in 21% of non-cirrhotic HCC. 21% and 3% of patients with cirrhosis and non-cirrhotic HCC, respectively, received supportive care only. AFP levels above the upper limit of normality (10 ng/ml) were observed in 10% of non-cirrhotic patients and 30% of cirrhotic livers; 47% of patients without cirrhosis had disease progression in 5 years. **Conclusion** In our study about 25% of HCCs occurred in patients without underlying cirrhosis. NAFLD is associated with a higher prevalence of non-cirrhotic HCC in comparison with other etiologies (viral or alcohol-related disease). Despite the lack of specific surveillance program, however a curative approach may be more often used in patients with non-cirrhotic HCC and this lower mortality compared to patients with cirrhotic HCC. A surveillance program may be useful for the early diagnosis of HCC in NAFLD patients.

EDIPEMIOLOGIA CLINICA

325. RENIN-ANGIOTENSIN SYSTEM INHIBITORS AND MORTALITY RISK IN PATIENTS WITH ATRIAL FIBRILLATION. INSIGHTS FROM THE NATIONWIDE START REGISTRY

Menichelli D.[1], Poli D.[2], Antonucci E.[3], Palareti G.[3], Pignatelli P.[1], Pastori D.[1]
[1]Department of Clinical Internal, Anesthesiological and Cardiovascular Sciences, Sapienza University of Rome; [2]Thrombosis Center, Azienda Ospedaliero-Universitaria Careggi; [3]Fondazione Arianna Anticoagulazione – Bologna

Background: Arterial hypertension (AH) is the most common cardiovascular comorbidity in patients with atrial fibrillation (AF). We want to investigate the relation between antihypertensive drugs and mortality risk in patients with AF.
Materials and Methods: . We analysed the use of single antihypertensive medications in 5769 AF patients included in the nationwide ongoing Italian START registry. We also investigated the association of antihypertensive drugs with mortality risk.
Results: Mean age was 80.8 years, 46.1% were women; 80.3% of patients were hypertensive. Furosemide (30.1%) was the most frequent diuretic followed by hydrochlorothiazide (15.4%) and potassium canrenoate (7.9%)**.** 61.1% received β-blockers: 34.2% bisoprolol, 6.2% atenolol. Additionally, 36.9% were on ACE-I: ramipril (20.9%), enalapril (5.3%) and perindopril (2.8%); 31.7% were on ARBs: valsartan (7.6%) and irbesartan (6.4%). Amlodipine and lercanidipine were prescribed in 14.0% and 2.3%, respectively. ACE-I ($p<0.001$), α-blockers ($p=0.020$) and D-CCB ($p=0.004$) were more common in men, while ARBs ($p=0.008$), thiazide diuretics ($p<0.001$) and β-blockers ($p<0.001$) in women. During 22.61±17.1 months, 512 patients died. Multivariable Cox regression analysis showed that ACE-I (Hazard ratio [HR] 0.677 95% Confidence Interval [95%CI] 0.545-0.841, $p<0.001$) and ARBs (HR 0.572, 95%CI 0.447-0.732, $p<0.001$), were inversely associated with mortality. ACE-I/ARBs were inversely associated with mortality in patients with diabetes, ACE-I also in previous cardiovascular disease, and ARBs also in HF. ACE-I/ARBs were inversely associated with death both in women and men.
Conclusion: ACE-I/ARBs are inversely associated with mortality in AF. Our data suggest that ACE-I/ARBs should be considered to optimise clinical management of AF patients.

326. TOUCH ME IF YOU CAN - THE IMPACT OF CONTACT ISOLATION STATUS ON HOSPITAL LENGTH OF STAY AND MORTALITY. PRELIMINARY DATA FROM A MULTICENTER STUDY IN LOMBARDY

Peta J.A.[1], Tirelli R.[1], Della Torre A.[1], Piantelli C.[2], Milani O.[1], Casazza G.[3], Berra S.[2], Pisetta C.[4], Birocchi S.[4], Benetti A.[5], Berra S. A.[6], Canetta C.[1], Colombo F.[7], Dentali F.[8], Magnani L.[9], Mazzone A.[10], Montano N.[1], Moreo G.[11], Muiesan M. L.[12], Podda G.[4], Rovere Querini P.[13], Squizzato A.[14], Cogliati, C.[2]
[1]Division of Internal Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [2]Division of Internal Medicine, Ospedale Luigi Sacco, ASST Fatebenefratelli Sacco, Milan, Italy; [3]Department of Clinical Science and Community Health, University of Milan, Milan, Italy; [4]Division of Internal Medicine, Ospedale San Paolo, ASST Santi Paolo e Carlo, Milan, Italy; [5]Division of Internal Medicine, ASST Papa Giovanni XXIII, Bergamo, Italy; [6]Division of Internal Medicine, Ospedale di Garbagnate Milanese, ASST Rhodense, Garbagnate Milanese, Italy; [7]Division of Internal Medicine, Ospedale Niguarda, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [8]Division of Internal Medicine, Ospedale di Circolo e Fondazione Macchi di Varese, ASST Sette Laghi, Varese, Italy; Department of Medicine and Surgery, University of Insubria, Varese, Italy; [9]Division of Internal Medicine, Ospedale Civile di Voghera, ASST Pavia, Voghera, Italy; [10]Division of Internal Medicine, Ospedale Nuovo di Legnano, ASST Ovest Milanese, Legnano, Italy; [11]Division of Internal Medicine, Clinica San Carlo, Paderno Dugnano, Italy; [12]Division of Internal Medicine, Spedali Civili Brescia, ASST Spedali Civili, Brescia, Italy; [13]Division of Immunology, Transplantation, and Infectious Diseases, IRCCS San Raffaele Scientific Institute, 20132 Milan, Italy; [14]Division of Internal Medicine, Ospedale Sant'Anna, ASST Lariana, Como, Italy, Department of Medicine and Surgery, University of Insubria, Varese, Italy

Background and aims: Patients admitted to internal medicine wards are characterized by high complexity of care, which can lead to difficulties in delivering effective assistance based on patients' needs. In this setting, the diffusion of multi-drug resistant (MDR) pathogens in the last years has demanded interventions aimed to reduce healthcare-associated infections, including contact isolation. There is still uncertainty around the net effect of this intervention on patients' outcomes, as evidence has shown that it may reduce the time healthcare personnel spend with the patients and increase adverse events and hospital length of stay.
The aim of this study was to evaluate the association between contact isolation, hospital length of stay and in-hospital mortality in a real-life, large cohort of patients hospitalized in Internal Medicine Units.
Methods: We retrospectively analyzed data from a prospective, multicenter study describing the complexity of care and social frailty of patients hospitalized in 15 Internal Medicine wards in Lombardy (Italy) during a one-year period. A prespecified enrollment date for each month was established and data for all patients hospitalized in each ward were recorded on that day. The study was approved by the local ethics committees and informed consent was obtained.
Data concerning anthropological features (age, sex and body mass index), comorbidities (Charlson Comorbidity Index), clinical instability (NEWS score), care dependency scale (mICD), social frailty, isolation status and length of hospitalization were collected.
Our primary endpoint was to evaluate if there was an independent association between contact isolation and hospital length of stay (LOS).
Our secondary endpoint was to evaluate if there was an independent association between contact isolation and in-hospital mortality.
All the analyses are purely descriptive. For primary and secondary outcomes, a univariate and multivariate logistic regression model was performed.
Results: Out of the 2471 patients enrolled in the primary study, 177 missed the isolation status, thus 2294 patients were included in the final analysis (median age 79, 46% female). Patients isolated by contact precautions were 227 (10%), 75 of whom (34%) were isolated in single rooms, and 92 (41%) were symptomatic for the isolated pathogen.
The most frequently involved microorganisms were Vancomycin-Resistant Enterococci (VRE) and Extended Spectrum Beta-Lactamase (ESBL) producing Enterobacteriaceae, with 74 (33%) and 59 (26%) of patients involved respectively, while 39 (17%) patients were colonized by Carbapenemase-producing Enterobacteriaceae. Forty-two (19%) patients were colonized by more than one microorganism.
Isolated patients appeared to have higher care dependency (p<0,001) and social frailty (p<0,001). Median hospital LOS was significantly higher in isolated patients (median of 24 vs 15 days, p<0,001) and they showed higher in-hospital mortality (12,8% vs 8,8%, p=0,046).
Charlson index, mICD, social frailty and isolation status were all associated with hospital LOS in the univariate logistic regression. Isolation status, social frailty and mICD were significantly correlated with hospital LOS also in the multivariate logistic regression model (image 1).
For the secondary endpoint, the univariate logistic regression demonstrated an association between in-hospital mortality and age, Charlson index, NEWS score, mICD, social frailty and isolation status. However, isolation status and age lost significance when performing the multivariate regression (image 2).
Conclusion: In our exploratory analysis contact isolation status seems to be independently associated with longer hospital stay, but not with mortality. We could not infer from this observational analysis if contact isolation per se could prolong hospitalization due to limited access to care or whether this condition is prevalent in more compromised patients with multiple recent hospitalizations. Ancillary, the absence of any independent association with mortality in this cohort, seems to be in contrast with the idea that colonization with MDR organisms could be associated with an increased risk of adverse events.

Image 1: Univariate and multivariate logistic regression for hospital LOS, considering median hospitalization as cutoff

	Univariate analysis		Multivariate analysis	
	OR (IC95%)	p value	OR (IC95%)	p value
mICD*				0,001
2 vs 1	2,094 (1,750-2,506)	<0,001	1,498 (1,205-1,862)	<0,001
3 vs 2	2,245 (1,732-2,910)	<0,001	1,340 (0,995-1,806)	0,054
Social frailty				<0,001
2 vs 1	1,873 (1,536-2,284)	<0,001	1,424 (1,126-1,801)	0,003
3 vs 1	2,971 (2,349-3,757)	<0,001	2,205 (1,675-2,904)	<0,001
4 vs 1	5,164 (3,349-7,964)	<0,001	4,098 (2,598-6,464)	<0,001
Isolation	2,224 (1,669-2,964)	<0,001	1,905 (1,417-2,561)	<0,001

* mICD was divided in 3 categories: 8-14 (1), 15-23 (2), 24-32 (3)

Image 2: Univariate and multivariate logistic regression for in-hospital mortality

	Univariate analysis		Multivariate analysis	
	OR (IC95%)	p value	OR (IC95%)	p value
Age*				0,088
2 vs 1	2,6 (1,789-3,783)	<0,001	1,591 (1,036-2,445)	0,034
3 vs 1	2,928 (1,965-4,362)	<0,001	1,552 (0,979-2,459)	0,062
Charlson > 5	3,267 (2,114-5,049)	<0,001	1,935 (1,175-3,188)	0,010
NEWS°				
2 vs 1	3,207 (2,155-4,771)	<0,001	2,169 (1,418-3,318)	<0,001
3 vs 1	12,914 (8,794-18,963)	<0,001	6,190 (4,004-9,572)	<0,001
mICD#				
2 vs 1	3,93 (2,524-6,118)	<0,001	2,433 (1,463-4,046)	<0,001
3 vs 2	14,636 (9,228-23,213)	<0,001	4,847 (2,742-8,566)	<0,001
Social frailty				<0,001
2 vs 1	3,556 (2,209-5,725)	<0,001	1,252 (0,716-2,190)	0,430
3 vs 1	4,835 (2,936-7,962)	<0,001	1,342 (0,741-2,495)	0,332
4 vs 1	12,759 (7,112-22,888)	<0,001	3,604 (1,797-7,229)	<0,001
Isolation	1,526 (1,004-2,319)	0,048	1,069 (0,683-1,721)	0,767

*Age was divided in 3 categories: age<75 (1), 75≤age≤85 (2), age>85 (3)
°NEWS was divided in 3 categories: 0-4 (1), 5-6 (2), ≥7 (3)
#mICD was divided in 3 categories: 8-14 (1), 15-23 (2), 24-32 (3)

327. GENERAL POPULATION UNIVERSAL CAPILLARY SCREENING FOR CHRONIC AUTOIMMUNE, METABOLIC AND CARDIOVASCULAR DISEASES (UNISCREEN): FEASIBILITY AND ACCEPTABILITY PILOT STUDY

Merolla A., Angiulli S., Peracino R., Bellino C., Manganaro G., Biasco F., Borgonovo E., Bongiovanni A., Calabrese C., Critelli S., Di Resta A., F arina F., Fici A., Mallus M., Melodia P., Menchi S., Morocutti G., Pata G., Rela E., Ruggiero M., Soggetti C., Spanò A., Stocchi M., Martinenghi S., Rovere-Querini P., Bosi E.
Vita-Salute San Raffaele University, Milan, Italy

Introduction: Diabetes mellitus, celiac disease, cardiovascular disease are among the most common chronic diseases across the population. Undoubtedly, their natural history is well known, having a recognizable early asymptomatic phase. However, they are often underdiagnosed, especially in some age groups historically thought to be unaffected. Moreover, diagnosis comes often at later stages in the disease course, when complications become clinically manifest. Delayed diagnosis places an increased burden on patients, caregivers and healthcare systems while leading to life-threatening complications, reduced quality of life and disability. In contrast, early detection and tailored intervention are of paramount importance to reduce morbidity and mortality. In an era of increasingly available therapeutic options and prevention strategies, making screening accessible on a large scale is an exciting challenge for clinicians and institutions. Commonly used screening methods require venous blood sampling, which can be traumatic in children. Moreover, barriers to screening can include high costs and time constraints. Simple, fast and less traumatic tests through capillary blood sampling might overcome these limitations and offer a potential and valid alternative. The use of capillary screening has been validated in previous trials. However, to our knowledge, this is the first study to propose a comprehensive capillary screening method for cardiovascular, metabolic and autoimmune diseases in all age ranges.
Aim of the study: The primary aim of our study is to assess the feasibility and acceptability of capillary screening for diabetes mellitus, celiac disease and dyslipidaemia in a prototype of general population, in order to justify its reproducibility on a larger-scale to enable widespread population screening program. Secondary outcomes are: measurement of the specific disease markers; estimation of the prevalence of the identified diseases within the population; correlation of study disease indicators with demographics, anthropometrics and clinical data; assessment of the total burden of cardiovascular risk factors.
Study design: This is a low-risk interventional, single centre, pilot study promoted by San Raffaele University Hospital and carried out in Cantalupo, a locality near to Cerro Maggiore (Milan) comprehensive of 3095 inhabitants. Screening is offered to the resident population aged 1 to 100 years on a voluntary basis. The choice of this small town comes from the desire of the Municipality and local Volunteering Associations to be involved in health promoting campaigns. The study started in April 2023 and has an expected duration of 10 months. The involved personnel is a pool of dedicated medical and nurse professionals from San Raffaele University Hospital, in collaboration with local volunteers. Screening activities will be held every week-end in the town main social aggregation facilities, such as schools and squares. The study procedures include: i) an interview collecting demographics, anthropometrics and medical history; ii) capillary blood sampling by point-of-care device, to test blood glucose level, glycated haemoglobin, lipid panel (i.e total

cholesterol, HDL-c, LDL-c, triglycerides) and specific autoantibodies for type 1 diabetes and celiac disease; iii) subsequent confirmatory venous blood sampling in case of positive autoantibodies; iv) blood pressure measurement; v) fulfilment of a structured questionnaire about feasibility and acceptability. We intend to screen at least 50% of the population in Cantalupo.
Discussion: The proposed study addresses the current and urgent need for prevention. Strengths of our program lies in the use of a rapid and very low risk method for a population-based screening design aimed at simultaneously assessing glicometabolic status and lipid panel by point-of-care technique, and autoantibodies status for two common autoimmune conditions. Moreover, identifying cardiovascular risk factors distribution across the population will provide an accurate estimate of cardiovascular risk. With the aim of early detection of chronic diseases, our study might pave the way to larger scale screening programs in a public health setting.

328. THE COMPLEXITY OF CARE OF INTERNAL MEDICINE PATIENTS AND ITS IMPACT ON HOSPITAL STAY LENGTH AND PROGNOSIS: AD INTERIM ANALYSIS FROM A MULTICENTER STUDY IN LOMBARDY (ITALY)

Donadoni M.[1], Banfi F. [2], Benetti A. [3], Berra S. [1], Berra S. [4], Brusco G.[5], Canetta C. [6], Casanova F.[7], Casazza G.[8], Ceriani E.[1], Colombo F. [9], Dentali F.[10], Lucini A.[11], Magnani L.[5], Mazzone A.[2], Montano N.[12], Moreo G.[13], Muiesan L.[14], Negro F.[15], Piantelli C.[16], Podda G.[7], Rovere Querini P.[11], Sbattella M. [9], Squizzato A.[15], Cogliati C.[1]
[1]Dipartimento di Medicina Interna, Ospedale L. Sacco, Milano; [2]Dipartimento di Medicina Interna, Presidio Ospedaliero Legnano; [3]Dipartimento di Medicina Interna, Ospedale Papa Giovanni XXIII, Bergamo; [4]Dipartimento di Medicina Interna, Presidio Ospedaliero Garbagnate Milanese; [5]Dipartimento di Medicina Interna, Ospedale Civile di Voghera, Pavia; [6]Dipartimento di Medicina ad Alta Intensità di Cura, Policlinico di Milano; [7]Dipartimento di Medicina Interna, Ospedale San Paolo, Milano; [8]Dipartimento di Scienze Cliniche e di Comunità, Policlinico di Milano; [9]Dipartimento di Medicina Interna, Ospedale Niguarda Ca' Granda, Milano; [10]Dipartimento di Medicina Interna, Ospedale di Varese; [11]Dipartimento di Medicina Interna, Ospedale Vita e Salute San Raffaele, Milano; [12]Dipartimento di Medicina Interna, Ospedale Policlinico di Milano; [13]Dipartimento di Medicina Interna, Ospedale San Carlo, Paderno Dugnano; [14]Dipartimento di Medicina Interna, Spedali Civili, Brescia; [15]Dipartimento di Medicina Interna, Ospedale Sant'Anna, Como; [16]Dipartimento di Medicina Interna, Ospedale L. Sacco, Milano
Background: in Italy, the organization of Internal Medicine wards is regulated by a ministerial decree of 1988 [1], which classifies Internal Medicine as a low intensity care specialty. However, the evolving demographic, epidemiological, and social context is fundamentally changing the complexity of care for patients in Internal Medicine departments [2]. The actual organization is probably not entirely adequate for the patients' needs so that a better patient characterization is critical to tailor future interventions.
Aims: primary endpoint of the study was to describe the complexity of care and the social frailty of patients hospitalized in Internal Medicine departments. Secondary outcomes were the evaluation of the impact of complexity of care and social frailty on the length of stay and prognosis.
Material and methods: we conducted a prospective, multicenter study in fourteen Internal Medicine wards in Lombardy (Italy) during a one-year observation period. Once a month, on a randomly selected working day, the census of hospitalized patients was performed. The complexity of care was defined by a multidimensional approach through the combination of clinical instability (NEWS score) and care dependency scales (mICD) into a unique index of caring complexity (ICC score) [3]. Social frailty was defined as absent, low, moderate or critical by a simplified BRASS scale [4].
Results: this represents an ad-interim analysis in which 2471 patients were enrolled (from May 2nd 2022 to January 12th 2023), 45.7% female, mean age 75 years (61% ≥ 75 years), 72.5% with Charlson Comorbidity Index ≥ 5. Complexity of care was high in 15.7%, medium in 44.3%, and low in 40%. A quarter of the patients presented at least moderate social frailty. At the univariate analysis NEWS, mICD, ICC and social frailty scores were predictive of in-hospital mortality. On the other side mICD, ICC and social frailty scores, but not the NEWS score, were predictive of hospital stay length.
Conclusion: Our study shows that patients hospitalized in Internal Medicine wards have different levels of clinical instability and dependency, with more than half of them characterized by at least medium complexity of care. Thus, organization models should consider the allocation of appropriate human resources, monitoring and equipment to allow a patient-centered assistance based on real needs.
Moreover, a better territorial net involving low intensity care structures is required since up to a quarter of the hospitalized patients has a significant social score which impacts the length and the outcome of hospital stay.
References
1. Decreto Ministeriale 13 settembre 1988 <<Determinazione degli standards del personale ospedaliero>> (G.U. 24 settembre 1988, n. 225)
2. FADOI-SIMI. *DOCUMENTO SULLA RIORGANIZZAZIONE FUNZIONALE DELLE UUOO DI MEDICINA INTERNA*
3. Salvatore F. P.; Fanelli S. Patient Related Complexity of Care in Healthcare Organizations: A Management and Evaluation Model. *Int. J. Environ. Res. Public Health* 2020.
4. Zarovska, A.; Evangelista, A.; Boccia, T.; Ciccone, G.; Coggiola, D.; Scarmozzino, A.; Corsi, D. Development and Validation of a Simplified BRASS Index to Screen Hospital Patients Needing Personalized Discharge Planning. *J. Gen. Intern. Med.* 2018, *33*, 1084–1091, doi:10.1007/s11606-018-4405-y.

329. ADHERENCE TO MEDITERRANEAN DIET, COMORBIDITIES, AND MAFLD OR NAFLD IN LEBANESE AND ITALIAN COHORTS

Khalil M.[1], Abdallah H.[1], Jaber N.[1], Mahdi L.[2], Daher A.[3], Shanmugam H.[4], Di Ciaula A.[4], Portincasa P.[4]
[1]Clinica Medica "A. Murri", Department of Preventive and Regenerative Medicine and Ionian Area (DiMePrev-J), University of Bari Aldo Moro, Piazza Giulio Cesare 11, 70124, Bari, Italy. ; [2]Rammal Rammal Laboratory, ATAC group, Faculty of sciences, Lebanese University, al-hadath campus, Beirut-Lebanon; [3]Rammal Rammal Laboratory, ATAC group, Faculty of sciences, Lebanese University, al-hadath campus, Beirut-Lebanon. Faculty of public health, Islamic University of Lebanon, Khaldeh, Lebanon; [4]Clinica Medica "A. Murri", Department of Preventive and Regenerative Medicine and Ionian Area (DiMePrev-J), University of Bari Aldo Moro, Piazza Giulio Cesare 11, 70124, Bari, Italy

Background: Epidemiological and clinical studies show that the use of Mediterranean diet (MD) is associated with decreased cardi-metabolic risk, including non-alcoholic- or metabolic associated- fatty liver disease (NAFLD/MAFLD). However, the existence of possible heterogeneous effects induced by both dietary habits and fatty liver subtype on the prevalence of comorbidities in people living in different Mediterranean areas is poorly explored.
Methods: Adherence to MD and presence of comorbidities were examined by specific and validated questionnaires in patients with a previous ultrasonographic diagnosis of fatty liver living in Italy and Lebanon. According to metabolic profile and alcohol consumption, enrolled subjects were classified as NAFLD (No metabolic alterations with no significant alcohol consumption), NAFLD/MAFLD (metabolic alterations with no significant alcohol consumption), or MAFLD (metabolic alterations with any alcohol consumption).
Results: A total of 61 Italian patients were enrolled at the policlinic of Bari, internal medicine division (Clinica Medica A. Murri) and 49 Lebanese patients were enrolled at the department of public health at the Islamic University, Lebanon. Italians were older than Lebanese subjects (48.6±1.5 vs 41.6±2.0 yrs, respectively, p=0.006). Body mass index was comparable in the two groups (Italy 32.1±0.7Kg/m2; Lebanon 31.1±0.9Kg/m2, P=NS). Italian patients had higher adherence to MD (score 9.1 vs 7.8 over 18 max; P=0.04) and a lower prevalence of comorbidities (56 % vs 78%, p=0.01) than Lebanese subjects. However, the prevalence of "pure" MAFLD was higher in the Italian (44%) than in Lebanese (2%, P<0.0001). Conversely, Lebanese subjects showed a trend towards increased NAFLD prevalence (13% vs 5% in Italians) and a significantly higher MAFLD/NAFLD prevalence (Italy:51%; Lebanon:85%; P=0.0002).
Conclusion: In patients with fatty liver**,** the adherence to MD can be variable in people living in different Mediterranean areas. Irrespective of BMI, a higher prevalence of comorbidities can be linked with a low adherence to MD and with the presence of NAFLD or NAFLD/MAFLD, rather than of "pure" MAFLD. Further studies are needed to better disentangle the role of diet and different subtypes of fatty liver in determining the individual health risk.

330. SECOND AND THIRD LINE ANTIMICROBIAL THERAPY IN INTERNAL MEDICINE DEPARTMENTS: A PROSPECTIVE ANALYSIS ON PRELIMINARY DATA FROM A MULTIPURPOSE HOSPITAL REGISTRY.

Donatoni M.[1], Senini E.[1], Rela E. [1], Marinosci A.[2], Di Terlizzi G.[2], Soddu D.[2], Sacco S.[1], Bellino C.[1], Soggetti C.[1], Damanti S.[1], Deonette G.[2], Bozzolo E.P.[2], Ramirez G.A.[3], Rovere-Querini P.[4], Tresoldi M.[2]
[1]Università Vita-Salute San Raffaele, Milan, Italy; [2]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy; [3]Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS Ospedale San Raffaele, Milan, Italy; [4]Unit of Medical Specialties and Healthcare Continuity IRCCS Ospedale San Raffaele, Milan, Italy

Background: Multidrug-resistant bacteria have increased at an alarming rate over recent decades, resulting in severe infections, prolonged hospitalization times and premature death . Previous hospitalization, history of antibiotic use and high comorbidity burden are common characteristics among patients admitted to internal medicine wards and several studies have shown that these factors are associated with a higher prevalence of multidrug-resistant microorganism infections. We investigated the use of antimicrobial therapies of distinct intensity in the general internal medicine ward setting.
Material and methods: We studied 319/439 patients admitted to the General Medicine Departments of our Institution from November 2022 to April 2023 and enrolled them in a prospective observational registry (Med-Cli protocol). We collected data about antimicrobial therapies administered during the Emergency department and General Medicine department stay, along with demographics and clinical features, including vital signs, anthropometrics and comorbidities. Patient complexity was assessed with the Charlson's Comorbidity Index (CCI), disability through the Barthel's score. We classified antimicrobial medications as 1st, 2nd and 3rd line treatments according to the ordinary clinical practice of our hospital (Table 1) and stratified patients by therapeutic strategies. Here, we show some preliminary data extracted from the registry. Data are expressed as median (interquartile range), unless otherwise specified.
Results: Data from only 315 out of 319 patients were available for analysis. 64% of all patients received at least one antimicrobial drug (AMD), and, among them, 42% received only 1st line AMDs, 39% 2nd line and 19% 3rd line AMDs. Patients treated with AMDs (n=202) had no difference with patients receiving no anti-infective treatment other than age [77 (69-84) vs 75 (64-81); p=0.023] and admission disability [Barthel = 75 (31-100) vs 45 (16-85); p=0.025]. When stratified by antimicrobial therapy intensity, patients receiving anti-infective drugs did not differ in terms of baseline characteristics. However, patients receiving 3rd line AMDs had a lower median Barthel score on discharge 18 (0-73] compared to patients with 1st [70 (13-95); p=0.022] and 2nd line treatment [65 (15-100); p=0.024]. 3rd line AMD-patients also had longer hospitalizations [26 (15-38) days] compared to patients with 1st [14 (11-18); p<0.001] and 2nd line treatment [16(12-23); p<0.001] and showed numerically lower survival rates (71% vs 92% vs 76%, respectively; p=NS).
Conclusions: Preliminary data from the registry suggest that most patients admitted to internal medicine wards receive antimicrobic therapy and a large proportion of them receive 2nd or 3rd line AMDs. Age, sex, anthropometrics and vital parameters do not correlate with the use of 1st, 2nd or 3rd line AMDs. While Barthel score on admission was not significantly different among patients who received different lines of antimicrobial therapies, Barthel score at discharge is significantly lower in patients who receive third-line antimicrobials, compared with those who received first- or second-line therapy, suggesting a significant impact of MDR-infections on patient's autonomy degree at the end of hospitalization, leading to difficult discharge. In-hospital mortality rates were higher in patients receiving 2nd and 3rdline AMDs vs patients receiving 1st line therapy, with almost 30% in patients receiving 3rd line AMDs, confirming that MDR pathogen-related infections are an important cause of mortality and morbidity in hospitalized patients.

Table 1.

First Line	Second Line	Third Line
Amoxicillin	Piperacillin-tazobactam	Ceftazidime-avibactam
Oxacillin	Daptomycin	Meropenem
Ceftriaxone	Linezolid	Cefiderocol
Azithromycin	Teicoplanin	Fidaxomicin
Clarithromycin	Ganciclovir	Tigecyclin
Ciprofloxacin	Voriconazole	Anidulafungin
Levofloxacin		Caspofungin
Trimethoprim-sulphamethoxazole		
Fosfomycin		
Nitrofurantoin		
Doxycyclin		
Vancomycin		
Clindamycin		
Fluconazole		
Aciclovir		

331. BED-BLOCKERS IN ACUTE HUB HOSPITAL: THE IMPACT OF AGE, COMORBIDITIES AND "PROTECTED" DISCHARGES IN AN INTERNAL MEDICINE WARD

Noto A., Belfiore A., Bonfrate L., Carratù P., De Luca A., Di Ciaula A., Giuliano A., Luglio C.V., Pugliese S., Portincasa P., Internal Medicine Recidency Group
Department of Precision and Regenerative Medicine and Ionian Area (DiMePre-J), Clinica Medica "A. Murri", University of Bari "Aldo Moro" Medical School, Bari, Italy

Background: The term "Bed Blocker" (BB) was coined in the mid of 1970s to indicate a hospitalized patient fit to discharge who continues to occupy a bed for non-clinical reasons (1). The estimated prevalence of BBs was 4.8%. About 40 years later available evidence points to an average prevalence of 22.8% (2), with a growing trend secondary to a variety of causes (mainly social isolation for lacking family support, progressive population aging, greater demand for "protected discharge" in residential facilities, increasing burden of disabilities, noncommunicable diseases and comorbidities). The main consequence of BBs is an increase in health care costs. Thus, a detailed knowledge and management of BBs is needed to maintain the sustainability of the National Health System (NHS). Aim of this study was to analyze the general characteristics of BBs in an internal medicine ward in a large university hospital in Southern Italy (AOUC Policlinico, Bari, Apulia).
Methods: We examined a cohort of 459 patients (F:M=164(36%):295(64%)) in a 12-months period (Jan-Dec 2022). Inclusion criteria were age>18 years and emergency admission. Planned hospitalization were excluded. We collected information on length of hospitalization, DRG cost, discharge modalities, principal diagnosis and comorbidities (Charlson index). Data are expressed as median [interquartile range] or as number and percentage. Subjects were divided in 2 groups according to length of hospitalization: delayed discharge (DD, >15 days of length of hospital stay) and regular discharge (RD, <15 days of stay).
Results: DD and RD groups were comparable in terms of gender balance (DD: n=105, 45 females (43%); RD: n= 354, 119 females (34%), P= 0.08) and median age (76 years [1.1] and 73.8 years [0.8] in DD and RD, respectively, P= 0.68). Overall, the average length of hospital stay was 8 [9] days. As expected, this index was longer in DD (30.5 [1.5] days) than in RD (6.9 [2] days, p<0.0001). The in-hospital death rate was comparable in DD and RD (17% and 15%, respectively, p=0.5). DD and RD showed a comparable prevalence of the most frequent chronic diseases (heart failure, diabetes mellitus, cancer, renal diseases). The prevalence of cognitive impairment was higher in DD than in RD (n=73 [69.5%] and n=89 [25%], respectively, p<0.0001). The rate of bed-ridden subjects in DD group was 28.6%, and 19% underwent a protected discharge (residential facilities, Hospice or dedicated home assistance). Waiting for discharge authorizations caused a longer length of stay in DD (38.5 [43] days)

than in RD (25 [15] days, p=0.006) and higher cost (5951 [1935] euros vs 4550 [1935], in DD and RD, respectively, p 0.007) despite the two subgroups showed a comparable burden of comorbidities, complexity, and prognosis (Charlson index 6 [3.25] and 6 [1.5] in DD and RD, respectively, p=0.46).
Conclusions: Delayed hospital discharges represent a growing, critical problem for the Italian national health system, due to high costs of hospital stay and reduced turnover in acute hospital beds. BBs are frequently elderly, with cognitive impairment. Due to the progressive aging of the general population, primary and secondary prevention measures oriented to obtain a healthy aging and a decrease of individual vulnerability (3) should certainly increase the sustainability of the NHS, possibly reducing the burden of BB. As expected in National Recovery and Resilience Plan (NRRP), it is needed to monitor the burden of BBs and to collect specific data to better direct future resources in hospital-territorial integration system, home care, and intermediate care.
References
(1) Rubin SG et al, *Age and Ageing*, 1975, 4.3: 142); (2) Landeiro F et al. *The Gerontologist*, 2019, 59.2: e86; (3) Di Ciaula A and Portincasa P, Mech Ageing Dev 2020 Jun;188:111244.

FARMACOLOGIA CLINICA

332. EFFICACY AND SAFETY OF DIRECT ORAL ANTICOAGULANTS IN THE PEDIATRIC POPULATION: A SYSTEMATIC REVIEW AND A META-ANALYSIS

Menichelli D.[1], Giossi R.[2], D'Amico F.[3], Idotta L.[3], Cirino M.[3], Scardoni L.[3], Furlanetto C.[3], Maggi M.[3], Bernocchi O.[3], Bosca F.[3], Girlando L.[3], Pignatelli P.[4], Pani A.[5], Pastori D.[4], Tozzo A.[2], Scaglione F.[5], Fornasari D.[3]
[1]Department of General Surgery and Surgical Speciality, Sapienza University of Rome; [2]ASST Grande Ospedale Metropolitano Niguarda; [3]Department of Medical Biotechnology and Translational Medicine, Postgraduate School of Clinical Pharmacology and Toxicology, Università degli Studi di Milano; [4]Department of Clinical, Internal, Anesthesiological, and Cardiovascular Sciences, Sapienza University of Rome; [5]Department of Oncology and Hemato-Oncology, Postgraduate School of Clinical Pharmacology and Toxicology, Università degli Studi di Milano

Background: Direct oral anticoagulants (DOACs) represent a cornerstone in the treatment of venous thromboembolism (VTE) in adults. Recently, randomized controlled trials (RCTs) to investigate DOACs use in the pediatric population have been performed.
Objectives: To evaluate the efficacy and safety of DOACs in the pediatric population.
Methods: We systematically searched MEDLINE (PubMed), EMBASE, and ClinicalTrials.gov from initiation up to 20 August 2022 (PROSPERO registration CRD42022353870) for RCTs comparing DOACs to standard of care (SOC) in patients aged <18 years according to PRISMA guidelines. The risk of bias was evaluated. Subgroup and sensitivity analyses were performed. GRADE was used to rate the quality of the evidence.
Efficacy outcomes were all-cause mortality and VTE. Safety outcomes were major bleeding (MB), clinically relevant non-major bleeding (CRNMB), any bleeding, serious adverse events (SAE), and discontinuation due to adverse events (AE).
Results: 8 RCTs with 1901 patients were included. The overall risk of bias was low. DOACs showed a reduction of VTE (OR 0.55; 95%CI 0.36-0.82), with similar mortality (OR 0.59; 95%CI 0.17-2.01) compared to SOC. Safety analysis showed non-significant differences in MB (OR 0.64, 95%CI 0.26-1.59), CRNMB (OR 1.34; 95%CI 0.57-3.13), any bleeding (OR 0.91; 95%CI 0.63-1.32). SAE (OR 1.05; 95%CI 0.83-1.32) and discontinuation due to AEs (OR 2.64; 95%CI 0.94-7.39). After subgroup and sensitivity analyses, no substantial differences from the primary analysis were found.
Conclusions: DOACs reduce VTE compared to SOC, without an increased risk of MB, CNRMB, any bleeding, SAE, and discontinuation due to AEs in the pediatric population

333. PATTERN OF PRESCRIPTION AND BENEFIT OF PCSK9 INHIBITORS IN FAMILIAL HYPERCHOLESTEROLEMIA IN ITALY: INSIGHTS FROM THE MONITORING PCSK9I AIFA REGISTRY

Arca M.[1], Celant S.[2], Olimpieri P.P.[2], Colatrella A.[2], Tomassini L.[2], D'Erasmo L.[1], Averna M.[3], Zambon A.[4], Catapano A.[5], Russo P.[2]
[1]Department of Translational and Precision Medicine, "Sapienza" University of Rome ; [2]Italian Medicines Agency, Rome, Italy; [3]Department ProMISE - Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, University of Palermo, Palermo, Italy; [4]Department of Medicine - DIMED, University of Padua, Padua, Italy; [5]Department of Pharmacological and Biomolecular Sciences Rodolfo Paoletti, University of Milan and IRCCS Multimedica, Milan, Italy

Background. Information on the real-world use of PCSK9 inhibitors (PCSK9i) in familial hypercholesterolemia (FH) are limited. We aimed to evaluate the pattern of prescription and the long-term efficacy of alirocumab and evolocumab in Italian FH patients in clinical practice.
Methods. The data set for analysis was extracted from the PCSK9i AIFA Registry and included 2484 patients with heterozygous (HeFH) and 62 patients with homozygous FH (HoFH), who were prescribed with PCKS9i from February 2017 to December 2021 and for which at least 2 years of follow-up could be reconstructed. As the follow-up schedules were not pre-specified and could vary, the persistence and adherence as well as LDL-C changes during treatment were analyzed in a cohort of patients with at least 24 months of potential follow-up and corroborated with a sensitivity analysis.
Results. At baseline, 53.8% of HeFH and 69.4% of HoFH were receiving maximally tolerated lipid-lowering therapies (LLTs), while 45.9% of HeFH and 30.7% of HoFH reported statin intolerance; mean LDL-C was 197.7 ± 52.3 mg/dl in HeFH and 252.0 ± 106.2 mg/dl in HoFH. Evolocumab and alirocumab were prescribed in 45.4% and 54.6% of HeFH, respectively, while HoFH received evolocumab only. The 6-month persistence and adherence to therapy were above 85% and LDL-C reduction reached 58.6% (to 79.7 mg/dl) in HeFH and 57.6% (to 95.1 mg/dl) in HoFH after 24 months of treatment. The EAS/ESC LDL-C goals were achieved in 43.3% of HeFH and 37.5% of HoFH.
Conclusion. PCSK9i prescribed to FH patients in routine clinical practice showed the same LDL-C lowering efficacy observed in controlled trials**.** Overall, 2 over 5 HeFH and 2 over 6 HoFH achieved the recommended LDL-C goals after 24 months of treatment. These results confirm the usefulness of PCSK9i in FH, even though the full achievement of EAS/ESC LDL-C goals should require a lower threshold for PCSK9i initiation and eventually multiple therapies.

334. PREVALENCE OF MUSCULAR SYMPTOMS BY STATIN-ASSOCIATED MUSCLE SYMPTOM CLINICAL INDEX IN A HYPERTENSIVE POPULATION CANDIDATE TO STATIN THERAPY.

Spannella F.[1], Giulietti F.[2], Allevi M.[1], Sarnari S.[1], Scorcella S.[1], Pepa M.[1], Di Agostini A.[1], Ortensi B.[1], Di Pentima C.[2], Landolfo M.[1], Sarzani R.[1]
[1]Dipartimento di scienze cliniche e molecolari, Università Politecnica delle Marche, Ancona, Italia. ; [2]Clinica Medica e Geriatrica, IRCCS INRCA, Ancona, Italia

Introduction: Statin-Associated Muscle Symptoms (SAMS) limits lipid-lowering therapy in clinical practice. SAMS Clinical Index (SAMS-CI) is a validated score to evaluate the correlation between the statin use and the muscular symptoms reported by patients. The study aimed to compare the prevalence and features of muscular symptoms through the SAMS-CI in a hypertensive population candidate to statin therapy.
Methods: We conducted a cross-sectional cohort study on 390 consecutive hypertensive outpatients candidate to statin therapy based on their cardiovascular risk profile. We divided the population into two groups according to statin intake. We performed the SAMS-CI for each patient. We compare the SAMS-CI results in terms of prevalence and features between the two groups.
Results: Mean age 60.5 ± 13.5 years, 54% males. 250 patients were already receiving a statin and 140 patients were statin-free but took at least one medication. The prevalence of SAMS by SAMS-CI did not differ between the groups (p = 0.217). The multivariate analysis showed that age and the total number of medication were associated to the muscular symptoms. The statin group scored higher but clinically not relevant SAMS-CI (p = 0.004) and no differences emerged regarding symptoms location between the two groups

(p = 0.170). Conversely, time to symptom onset and remission after the initiation and suspension of the therapy were associated to statin intake (p = 0.036 and p = 0.002, respectively).
Conclusions: The study evidenced that muscular symptoms are very common, especially in older, comorbid and often overmedicated patients. Statin-free patients often complain muscular symptoms considered specifically related to statin intake (SAMS) as well. When suspecting SAMS, after ruling out the nocebo/drucebo effects, particular attention should be paid to the timing of symptoms onset and remission.

335. EFFECTS OF LIFESTYLE CHANGES ASSOCIATED WITH A BEETROOT-BASED NUTRACEUTICAL ON DAILY ARTERIAL PRESSURE PROFILE IN A POPULATION WITH NORMAL-HIGH ARTERIAL PRESSURE OR GRADE 1 HYPERTENSION.

Spannella F.[1], Giulietti F.[2], Massaccesi A.[1], Poliseno C.[1], Rampino I.[1], Carrescia M.[1], Cavazzin E. [3], Sacco G.[3], Mazza A.[3], Landolfo M.[1], Sarzani R.[1]
[1]Dipartimento di scienze cliniche e molecolari, Università Politecnica delle Marche, Ancona, Italia.; [2]Clinica Medica e Geriatrica, "Hypertension Excellence Centre" della European Society of Hypertension, e Centro LIPIGEN della SISA, IRCCS INRCA, Ancona, Italia.; [3]"Hypertension Excellence Centre" della European Society of Hypertension, Dipartimento di Medicina Interna, Ospedale Generale di Rovigo, Rovigo, Italia

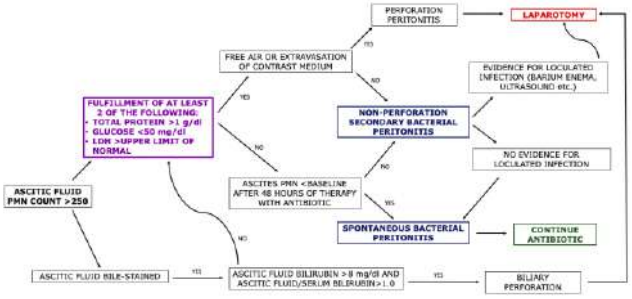
Introduction: 2018 European Society of Hypertension (ESH) guidelines support lifestyle changes as a first-line approach in patients with normal-high blood pressure (BP) or grade 1 hypertension and low cardiovascular risk. Recently, among nutraceuticals, some nitrate-enriched bioactive molecules have been demonstrated to reduce BP by exerting a vasoactive effect. The study was designed to evaluate the impact on the daily arterial pressure profile of adding a beetroot-base nutraceutical to lifestyle changes in mild hypertensive patients.
Methods: We conducted a prospective cohort study on 43 consecutive outpatients with normal-high BP or grade 1 hypertension on basal ambulatory blood pressure monitoring (ABPM). A daily dose of Beta vulgaris L. (500 mg of dry beetroot extract, a nitroxide source) was added to the lifestyle changes, and ABPM was repeated after three months for each patient. We assessed the differences between basal and three months ABPM.
Results: Mean age 50 ± 11 years, 54% males. Overweight and obese patients were 58%. At basal, the mean 24-hour BP was 127 ± 7 / 80 ± 6 mmHg, the mean daytime BP was 131 ± 8 / 83 ± 6 mmHg, and the mean nighttime BP was 118 ± 8 / 70 ± 5 mmHg. 63% of basal ABPM were diagnostic for grade 1 hypertension. After three months (median 98 days, IQR 92-121 days) of a daily dose of Beta vulgaris L., ABPM profiles significantly improved for all variables except for nighttime diastolic BP (-3 ± 6 / -2 ± 4 mmHg for 24-hour BP; - 4 ± 6 / - 3 ± 4 mmHg for daytime BP, and – 3 ± 7 / -1 ± 5 for nighttime BP). A more pronounced BP lowering was seen in grade 1 hypertensives and resulted independent of gender and nutritional status.
Conclusions: Adding a nitroxide nutraceutical source such as beetroot dry extract to lifestyle changes before any pharmacological treatment can be a helpful option to improve blood pressure profile in patients with normal-high arterial pressure or grade 1 hypertension and low cardiovascular risk.

GASTROENTEROLOGIA

336. DIAGNOSTIC TOOLS FOR A CHALLENGING PERITONITIS: TRUST THE GOOD OLD ONES

Butera. E., Metsovitis T., Tosoni A.
Department of Internal Medicine, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Rome, Italy

Secondary Peritonitis (SP) is an ascitic fluid infection from an intra-abdominal source. This condition can be a diagnostic challenge because of lack of clinical signs and symptoms, non-conclusive imaging studies and negativity of ascites cultures.
The distinction of SP from the spontaneous bacterical form (SBP) is crucial because mortality rate approaches 100% if treatment does not include emergency laparotomic intervention.We present the case of a young woman with new onset ascites secondary to portal vein thrombosis and consequent portal hypertension.
Ascitic fluid was sterile but analysis findings fulfilled Runyon's criteria (total protein >1 g/dL, glucose <50 mg/dL, LDH >upper limit of normal for serum), suggesting a form of SP with a total leukocyte count >10000 cells/mm3.
She had subtle symptoms and serial imaging studies resulted negative for intra-abdominal source of infection. After abrupt worsening of clinical condition, she has been diagnosed of splanchnic venous congestion with small bowel micro-perforation requiring emergency surgical intervention. Finally, blood exams revealed a JAK2-positive myeloproliferative disorder as cause of her prothrombotic state.
Distinction between SP and SPB is crucial. Despite development of advanced imaging techniques, the nature of this condition still makes diagnosis challenging in short time.
Our case is exemplary of the relevance of diagnostic algorithm based on Runyon's clinical criteria. To date, only five studies have indentified indicators of SP or SBP, focusing on cirrhotic patients. Further studies are needed to find early markers in order to help clinicians making prompt diagnosis preventing complications.



337. THE ROLE OF TRANS-ABDOMINAL ULTRASOUND FOR THE DIAGNOSIS AND CHARACTERIZATION OF BRANCH-DUCT INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS: A NEW TOOL FOR THE FOLLOW-UP OF LOW-RISK PATIENTS?

Migliori M., Ferronato M., Lizzio C.E., Marini D., Elia E., Trentini A., Potenza M.C., Andreetto L., Monfregola M., Rolla F.
Medicina Interna, Policlinico S. Orsola Bologna

Background: Cholangio-Wirsung Magnetic Resonance (CWMR) is widely recognized as the gold standard for diagnosis and follow-up of intraductal papillary mucinous neoplasms (IPMNs). Given the low risk of malignant transformation and the increasing number of IPMN patients under surveillance and consequent intolerable burden to health care system, there is growing interest in identifying less expensive techniques for the follow-up of these lesions. In this study we aim to evaluate the reliability of abdominal ultrasound (US) compared to CWRM.
Methods: Retrospective monocentric study among 79 patients with an incidental diagnosis of suspected BD- IPMN on US. Each patient underwent confirmatory CWRM within one year. We evaluated Cohen's kappa statistic agreement rate between CWMR and US, regarding cyst localization, size, and presence of radiological worrisome features.
Results: Of the 79 suspected BD-IPMN on US, CWRM identified 71 BD-IPMNs, one had other pancreatic lesion and in 7 patients did not reveal any lesion. Regarding cyst location and number, we identified a substantial agreement between US and CWRM (observed concordance rate and kappa of 77.5% and 81.7% and 0.66±0.08 and 0.62±0.11 respectively). We found a high agreement regarding cyst size (). Regarding the presence of worrisome features, we found a good agreement regarding the presence of Wirsung dilatation (concordance 95.7%, kappa 0.38±0.11), and good agreement for thickened septa (concordance 80.3%, kappa 0.38±0.12). We found that US is inferior to CWRM for the identification of mural nodules < 5 mm (observed concordance 97.2%, kappa 0). None of the patients presented other worrisome feature as distal atrophy or lymphadenopathy (concordance 100%, kappa 1).
Conclusions: Abdominal US presented a high agreement rate with CWRM regarding BD-IPMN location, number, and size. Moreover, there was a good concordance rate for Wirsung dilatation and for the presence of thickened septa, while US seems to underperform for the detection of mural nodules.

338. A CELIAC DISEASE COMPLICATION

Mattei M., Rosellini V., Ciurleo G., Iozzia M., Martini L., Giovagnini E., Coppola A., Puma A., Abatangelo S., Hennig M.C., Rossi Ferrini G., Simonetti V., Morettini A.
Medicina Interna 2- AOU Careggi

Introduction: We present the case of Mr. G.P., a 54 year old male admitted to the Infectious Diseases Department in December 2021 with bowel obstruction due to sigmoid volvolus treated with endoscopic derotation and concurrent asymptomatic SarS-CoV2 infection. One month after the patient came back to the E.R. with vomiting and diarrhea and was diagnosed with sigmoid volvolus again, and was once more treated with endoscopic derotation. The same happened again one month after the second episode, at which point the patient was treated surgically with laparotomic sigmoidectomy with colorectal anastomosis. The postoperative period was complicated by stercoraceous peritonitis due to dehiscence of the anastomosis, which is why the patient underwent distal colectomy and a colostomy was performed. Yet again the postoperative period was characterized by complications with an infection of the surgical site, treated with peritoneal revision and Vac-therapy and after that a total colectomy with terminal ileostomy was performed. A few days after his discharge the patient came to the ER again with symptoms such as fatigue and production of more than 2L of faeces through the ileostomy. The blood work showed prerenal acute kidney injury with severe metabolic acidosis and bicarbonate deficiency (pH 7,01, HCO3- 4,6, Lac 0,7, ABE -24,8). He was admitted to the Internal Medicine ward and required total parenteral nutrition and intravenous bicarbonates that were very difficult to downscale due to significant weight loss and persistence of metabolic acidosis. Background: the patient only stated a hernia-repair and bilateral saphenectomy, no other past medical history. Differential diagnosis: during the first few days the faecal volume was counted at 2,5L per day with liquid faeces partly mixed with undigested food. After nearly a month of hospitalization, complicated by numerous abdominal septic episodes, parenteral nutrition was stopped and the patient received first a low sugar diet in suspicion of metabolic acidosis due to lactic acid build up with little to no clinical response, and then a simple diet for patients with ileostomy. We ruled out other possible causes of chronic diarrhea with loss of bicarbonates: histological analysis of the specimens gained during the surgeries were negative; magnetic resonance enterography resulted negative for inflammatory disease but showed ileal dilation, which is why an ileoscopy was performed that did not show any signs of disease. We ruled out infectious causes with faecal culture tests. Faecal calprotectin resulted negative, same as the dosage of gastrin, 5-HIAA and VIP. We also performed measurment of celiac disease antibodies and found mild positivity of transglutaminase IgA (17,9U/ml) and antigliadin IgG (53,9U/ml) with normal IgA count. We then scheduled gastroduodenoscopy that confirmed histological findings compatible with celiac disease type 3C (destructive type) according to Marsh. Conclusions: even though the fecal volume was not optimally controlled and the patient still needed intravenous bicarbonates, he opted for home care with a gluten-free diet, blood gas analysis being performed every two weeks and daily intravenous bicarbonates. In the months to follow the patient maintained a gluten-free diet, he gained weight (72kg compared to the 63kg when he was hospitalized) and progressively reduced the need of intravenous bicarbonates

339. LONG-TERM OUTCOMES FROM A LARGE COHORT OF IGG4-RELATED AUTOIMMUNE PANCREATITIS PATIENTS

Lanzillotta M.[1], Dagna L.[1], Capurso G.[2], Falconi M.[2], Della Torre E.[1]
[1]Unit of Immunology, Rheumatology, Allergy and Rare Diseases, UnIRAR, IRCCS San Raffaele Scientific Institute, Milan, Italy; [2]Pancreato-Biliary Endoscopy and Endosonography Division, Pancreas Translational and Clinical Research Center, IRCCS San Raffaele Scientific Institute, Milan, Italy

Introduction: Autoimmune pancreatitis (AIP) is a rare form of pancreatitis that can lead to chronic pancreatitis. Type-1 AIP is part of the IgG4-related disease spectrum showing concomitant other organs involvement and a swift response to glucocorticoids(GC). Yet, relapses are common forcing multiple GC courses in a frail population, leading to metabolic derangements. A GC-based maintenance treatment appears to lower relapse rate, but data on the long-term safety of this strategy are lacking.
Purpose: Our aim was to report the long-term outcomes of a large cohort of AIP patients from a tertiary care center.
Materials and methods: We enrolled 75 patients in this unicenter retrospective study. AIP diagnosis was made according to the available criteria. The role of GC maintenance on long-term events was evaluated with Cox Regression analysis. Categorical variables were compared using Fisher's exact test. Patients presenting with diabetes at the time of diagnosis and those who underwent surgery were excluded for the analysis of long term metabolic outcomes.
Results: The male to female ratio was 4:1. The median age at diagnosis was 64 years (IQR 54-71). Median follow up was 32 months (IQR 17-42). Relapse occurred in 11 (33 %) out of 33 patients who underwent maintenance treatment and in 12 (52%) out of 23 who received only induction of remission treatment ($p > 0.05$). Median time to relapse was shorter in patients who did not receive maintenance therapy (13.5 months Vs 24 months, $p = 0.04$), A higher incidence of diabetes (41% Vs 9%)(HR 4.8 95%CI 1.05-22) and of infectious cholangitis (31% Vs 5%) occurred in those who received maintenance treatment with GC compared to others ($p< 0.05$).
Conclusions: Long-term treatment with GC in AIP patients might increase the risk of metabolic and endocrine complications. Steroids-sparing strategies are warranted.

340. CELIAC DISEASE IS CHANGING: EVOLUTION OF CLINICAL PRESENTATION OVER A 20-YEARS TIMESPAN

Pallotta D. P., Tovoli F., Raiteri A., GIamperoli A., Pratelli A., Monaco G., Boe M., Casadei F., Granito A.
University of Bologna, Department of Medical and Surgical Science, Bologna, Italy

Aim: to evaluate trends in epidemiology and clinical presentation of Celiac Disease (CD) between the year 2000 and the year 2019.
Methods: data from the records of 837 prospectively enrolled non paediatric (age > 16 years old) patients with diagnosis of CD referring to a tertiary centre were analysed. Univariate trend analysis was led via chi-square test, multivariate trend analysis was led via ordinal regression.
Results: our data showed an increasing trend across the time span for male frequency ($p<0.001$), age at diagnosis ($p<0.001$), and prevalence of seronegative CD ($p=0.043$), while a decreasing trend was observed for the frequency of weight loss at presentation ($p=0.006$) and low bone mass density at first DXA evaluation ($p<0.001$). Those trends are summarized in table 1.
Conclusion: our data highlighted two important changes in the epidemiology of CD, consisting of the increased the frequency of male patients in our population (without the inversion of the male:female ratio) and of the increased age at diagnosis. The decreasing trend in weight loss and low bone mass density at presentation may be related to the early recognition of milder and less malabsorptive form of CD. It appears reasonable that those changes in epidemiological and clinical presentation are not the results of intrinsic changes of CD presentation but should be related to the evolution of knowledge about CD in adults, with increased recognition of milder form of CD that would have not been recognized in the past.

Variable	Estimate (CI 95%)	p
Sex, male	0.46 (0.173; 0.755)	<0.001
Age, category	-1.15 (-1.74; -0.55)	<0.001
Weight loss at diagnosis	-0.43 (-0.74; -0.12)	0.006
Iron deficiency with or without anaemia	0.26 (-0.21; 0.739)	0.279
Iron deficiency anaemia	-0.30 (-0.78; 0.18)	0.219
Low bone mass density at first DXA evaluation	-0.62 (-0.87; -0.37)	<0.001
Villous atrophy	-0.58 (-0.74; 0.63)	0.868
Potential celiac disease	0.70 (-0.18; 1.58)	0.121
Seronegative celiac disease	0.90 (0.29; 1.763)	0.043

Table 1. Trends in epidemic and clinical presentation of patients with Celiac Disease.

341. A MYSTERIOUS ASCITES REVEALED A CASE OF UNRECOGNIZED WALDMANN SYNDROME!

Piccillo G.A.
Department Of Surgical And Medical Sciences And Advanced Technologies "G.F. Ingrassia", University Of Catania-Cannizzaro Hospital

Background: Waldmann's disease is a rare exudative enteropathy due to a congenital or obstructive malformation of the intestinal lymphatic drainage system and dilation of mucosal and submucosal lymphatic vessels. It can begin in childhood, in adolescence or even in adulthood. Symptomatology is represented by chronic diarrhea, lymphedema of the lower limbs, osteomalacia.

Case report description: A 43-year-old woman was admitted to our Department for chronic watery and fatty diarrhea with abdominal distension, ascites and oedema of the lower limbs. The laboratory tests, immediately executed, revealed the presence of microcytic hypochromic iron-less anaemia, and moreover disclosed a severe hypoprotidaemia with deep hypoalbuminaemia, hypocalcemia, low vitamin D but increased PTH, hypo-gamma-globulinemia, while normal resulted the research of Anti-endomysium antiboadies (EMA) and Anti-transglutaminase Antibodies (tTG). She underwent to thoraco-abdomino-pelvic CT scan which showed the presence of ascites and inflammatory digestive thickening. The ascites fluid analysis pointed out the presence of chylous rich in triglycerides. The gastro-duodenal-scopy (EGDS) revealed a congestive gastritis and creamy yellow of jejunal villi due to marked dilation of the lymphatics within the intestinal mucosa. Histological examination of duodenum-jejunum biopsies confirmed the presence of lacteal juice, dilated mucosal and submucosal lymphatic vessels with polyclonal normal plasma cells and no any alterations related to coeliac disease. Normal were Electrocardiography and Echocardiogram, while at X-ray of the lower limbs there was evidence of osteomalacia signs. The diagnosis of Waldmann's disease was made and the patient started a high-protein and a lifelong low-fat, calcium, iron, vitamin D and A, albumin infusions and monthly intramuscular injection of slow-release octreotide, multilayer compression bandages obtaining a dramatic clinical and biological improvement.
Conclusion: The diagnosis of Waldmann's disease is basedon clinical, biological, radiological, endoscopic and histopathological elements. The treatment is based on a diet free of long-chain lipids, and octreotide administration.

342. WORSENING DYSPHAGIA DISCLOSED A CASE OF UNRECOGNIZED COELIAC DISEASE

Piccillo G.A.
Department Of Surgical And Medical Sciences And Advanced Technologies "G.F. Ingrassia", University Of Catania-Cannizzaro Hospital

Background: Usually, patients with Coeliac Disease (CD) present with abdominal pain, diarrhea, steatorrhea, weight loss, growth failure, anemia, fatigue. A variety of diseases present with dysphagia: neuromuscular disorders, achalasia, systemic scleroderma, motility disorders, eosinophilic esophagitis (EoE), anatomical abnormalities such as esophageal web/rings, or obstructive lesions. Moreover, dysphagia is a known but an uncommon symptom for CD. In patients with dysphagia, CD should be considered in the differential diagnosis despite negative celiac serologies.
CASE REPORT A 58-year-old woman was admitted to our Dept for worsening dysphagia. Laboratory tests pointed out a slight microcytic, hypochromic, iron-less anaemia, normal resulted metabolic and thyroid panel, erythrocyte sedimentation rate, celiac serology (EMA e tTG), Helicobacter pylori test were normal. Esophagogastroduodenoscopy (EGDS) no showed any macroscopic alteration. Esophageal manometry revealed a normal low esophageal sphincter pressure, but she had an incomplete clearance of her fluid bolus. Her dysphagia continued to worsen with solid and soft foods and prolonged gurgling in her chest. Three months later, a new EGDS with duodenal biopsies showed villous blunting and focally increased intraepithelial lymphocytes in the duodenum as in CD, while serologies remained negative and celiac genetics showed DQ2 positive/DQ8 negative. The patient started a strict gluten-free diet (GFD) and bethanechol obtaining the complete resolution of her esophageal dysmotility and "gurgling."
Conclusions: Initial testing for CD includes serological testing for endomysial, tissue transglutaminase, and deamidated gliadin antibodies. These testing sometimes are negative in our patients (5%- 10% of patients with CD can have negative celiac serologies). Small intestinal biopsy remains the gold standard in diagnosing CD. Histological changes of the small intestinal mucosa include lymphocytic infiltration in the epithelium, increased depth of crypts, and flattening of the villi. Association of esophageal dysmotility has been reported in adult celiac patients. In subjects with esophageal symptoms and histological changes suspicious for CD, GFD is recommended. In serology-negative patients, repeat interval endoscopy on a GFD should be performed to assess for a histologic resolution to confirm the diagnosis of CD.

343. INTRAEPITELIAL LYMPHOCYTES COUNT IS A SIMPLE, YET USEFUL TOOL IN THE DIFFERENTIAL DIAGNOSIS OF SERONEGATIVE VILLOUS ATROPHY

Pallotta D. P. , Giamperoli A., Tovoli F., Raiteri A., Pratelli A., Monaco G., Casadei F., Boe M., Granito A.
University of Bologna, Department of Medical and Surgical Science, Bologna, Italy

Background and aim: differential diagnosis in the scenario of seronegative villous atrophy (SNVA) may represent a clinical challenge. We report a series of cases of SNVA from a tertiary centre, in order to identify features that may help in the differential diagnosis between the various conditions which can present with SNVA.
Methods: cases over a time span of 5 years (2016-2020) were reported. Comparison between group was led using chi-square analysis.
Results: over 280 patients with documented VA, 24 did not present serologic positivity for anti-TTG IgA and were classified ad SNVA. While the most common cause of VA in our series was CD (8 patients with seronegative CD and 2 patients with CD associated with IgA deficiency), over the half of our patients (14) with SNVA were not affected by CD. Aetiologies of non-celiac SNVA are reported in table 1. Increased intraepithelial lymphocytes (IELs >25/100 enterocytes) were associated with the diagnosis of CD (p=0.004), being observed in all patients with CD and, on the other hand in only one patient with non-celiac enteropathy. A similar association was observed for the presence of predisposing HLA (p=0.001). Comparison of baseline features between the two groups is reported in table 2.
Conclusion: the differential diagnosis of SNVA is troublesome, and several clinical, historical, biochemical, and histological features must be taken into account when navigating between the possible aetiology of SNVA. Our data highlight the role of increased IELs as a tool in the initial evaluation of SNVA.

Etiology	N° of patients
CVID-related enteropathy	3
Olmesartan-related enteropathy	3
Autoimmune enteropathy	2
Collagenous Sprue	2
Giardiasis	2
Crohn Disease	1
Lymphocytic Colitis	1

Feature	CD patients (10)	Non-CD patients (14)	P	All patients
Age - median (range)	46 (22-68)	51.5 (36-70)	0.5	47.5 (22-70)
Gender female – n (%)	8 (57%)	6 (60%)	1	14 (58%)
VA severity (according to Marsh-Oberhuber)			0.5	
3a – n (%)	7 (70%)	6 (43%)		13 (54%)
3b – n (%)	1 (10%)	6 (43%)		7 (29%)
3c – n (%)	2 (20%)	2 (14%)		4 (17%)
Predisposing HLA – n (%)	10 (100%)	4 (29%)	0.001	14 (58%)
IELs >25/100 enterocytes – n (%)	10 (100%)	4 (28%)	0.004	11 (46%)

344. A RARE CASE OF CHRONIC PANCREATITIS BY AB EXTRINSIC COMPRESSION

Massaro, M., Amati V.M., Vella F.S., Sabbà C.
Medicina Interna Universitaria "C. Frugoni" Dipartimento Interdisciplinare di Medicina, Università degli Studi di Bari "A. Moro"

On February 2023 a 87-years-old woman came to our attention for persistent diarrhea and elevation of phlogosis indices, with a single clinical history of arterious hypertension and dyslipidemia; in the absence of risk factors such as alcohol and smoking. Specifically, the patient reports, since May 2022, postprandial watery diarrhea (5-6 discharges/day), not associated with algic symptoms, resistant to antibiotic therapy, with concomitant weight loss of about 15 kg. During hospitalization, chest and abdominal X-ray was performed with findings of basal and bilateral pulmunary parenchymal thickening, for which she started antibiotic therapy, with resolution of indices of inflammation and respiratory clinic. To investigate the cause of diarrhea, the patient

performed laboratory tests including SOF search, coproculture, neoplastic markers, calprotectin assay, autoimmunity for celiac disease (negative results) and fecal pancreatic elastase (<50 micro/g; vn>200).
Chronic pancreatitis (CP) is a disease characterized by protracted pancreatic inflammation prolonged which causes a deterioration of the structure and functionality with fibrosis and atrophy of the parenchyma. Excessive alcohol consumption is the leading cause of chronic pancreatitis (about 44% to 65% of cases), followed by smoking, responsible for 46% of all cases. About 20% of cases are considered idiopathic CP. About only 10% of cases are associated with an obstructive cause: stenosis of the pancreatic duct (traumatic, iatrogenic, anastomotic); mass effect due to a tumor; a pancreas divisum (congenital anomaly causing division of the pancreatic duct). The most common symptom is abdominal pain, tipically epigastric with radiation to the back. Most cases are preceded by acute pancreatitis (AP), although it is increasingly recognized in patients without a history of AP or abdominal pain. Diagnosis is based on the presence of morphologic changes on TC o MRI. Among the most frequent complications (70% of cases) is exocrine pancreatic insufficiency: an inadeguate production and/or secretion of pancreatic enzymes necessary for nutrient digestion. The principal syntoms are related to malabsorption, ranging from abdominal bloating to steatorrhea and weight loss. It may develop even after decades, considering the rich reserve of the exocrine pancreas. Many patients presents commonly a obstruction of the pancreatic duct. The main and simplest method is fecal elastase-1 dosage on a random stool sample, costituiting an indirect measure of exocrine function. Treatment involves the use of pancreatic enzyme replacement therapy at a dose of 25.000-50.000 units of lipase at meals.
After ruling out all other causes of diarrhea, the diagnostic hypotheses more considered is chronic pancreatitis. However, the patient reported no past history of acute pancreatitis, let alone symptoms such as abdominal pain in the past that could explain it. Abdominal ultrasonography and abdominal CT scan was performed for further diagnosis, finding ectasic VBI and main biliary pathway (choledoco diameter about 12 millimeters), upstream area of altered morphologic of pancreatic head compatible with a duodenal diverticulum angulating Vater's papilla; diverticulosis of sigma and descending colon. In agreement with the clinic and reviewing the CT images, we placed indication for endoscopic evaluation to assess whether the duodenal diverticulum might be obstructing enzymatic outflow from the pancreas. The patient therefore underwent both colonoscopy, with confirmation of diverticulosis and conclusive EGDS for jatal slipped hernia and the presence of the perivaterian diverticulum with pancreatic and biliary tract dislocation and compression.
Chronic obstructive pancreatitis is a rare cause of pancreatitis; there are very few cases reported in the literature. Obstructive pancreatitis should always be considered in patients with no risk factors and no history of acute pancreatitis, confirming the structural alteration with CT and MRI. In this case, the diverticulum caused compression of the parenchyma to the point of pancreatic insufficiency, which caused the patient malabsorption and abrupt weight loss. Therefore, in accordance with strongly suppressed pancreatic elastase values, replacement therapy was started with Creon (lipase), the dosage of which was gradually increased to 25,000 IU 2 cp x3/day (at meals) with progressive reduction in the number of diarrhea discharges per day until resolution of symtoms. The patient was then discharged in good clinical condition, with indication to continue integration.

345. NATURAL HISTORY OF AUTOIMMUNE GASTRITIS IN A COHORT OF ITALIAN PATIENTS.

Gentile A., Miceli E., Pitotti L., Petrucci C., Lenti MV., Corazza G.R., Di Sabatino A.
Dipartimento di Medicina Interna, Fondazione Policlinico San Matteo di Pavia

Background and aim: Autoimmune gastritis (AIG) is a slowly progressive systemic disease, that leads to atrophy of the corpus-fundus mucosa of the stomach, with subsequent vitamin B12 and iron malabsorption.
The aim of this study was to describe clues leading to diagnosis, histopathological findings evolution and complications onset during prolonged follow-up. We also characterised a cohort of patients at risk for developing the disease and examined the evolution over time.
Material & Methods: All consecutive patients diagnosed with AIG at tertiary referred Gastroenterology outpatient clinic in IRCCS Fondazione Policlinico San Matteo were enrolled. We have collected and analysed data from laboratory investigations (gastrin and chromogranin A levels and presence of antiparietal cell antibodies) and gastric biopsy specimens. According to Newmann ed al. we classified disease in early stage, florid stage, end stage and complicated stage. As previously reported, potential AIG patients are characterized by the presence of positive anti-parietal cell antibodies in absence of histological alterations and normal levels of gastrin and chromogranin A.
Results: We collected 1620 gastric biopsy samples from 406 patients (mean age 58.2± 14.3 years, F/M ratio 2.3). Longest period of follow-up was 27 years, median of follow up was 5 years. Of these patients, 63 were classified as early stage, 64 as florid stage, 263 as end stage and 15 had a complicated stage at diagnosis (NET or dysplasia). Fifty percent (205/406) was affected by at least another autoimmune disease (39% had Hashimoto thyroiditis and 8,3% had more than one autoimmune comorbidity). According with histological stage, gastrin levels were significantly different (potential median 134 pg/ml, IQR 29-298 pg/ml; early/florid stage median 294 pg/ml, IQR 94-567 pg/ml, end/complicated stage median 605 pg/ml, IQR 333-979 pg/ml; p value < 0.05). Chromogranin A levels were not significantly different in the 3 subgroups of histological stage (potential median 86 ng/l IQR 30-228 ng/l; early/florid stage median 101 ng/l IQR 57-194 ng/l; and/complicated stage median 120 ng/l, IQR 199-61 ng/l; p value=0.3). Disease progression was documented in 144 patients and occurred more frequently within 2 years since diagnosis. Neoplastic complications occurred in 46 patients (11,3%). In particularly, NETG1 was found in 24 patients, NETG2 in 2 patients and dysplasia in 20. Recurrence of complications was observed in 14 patients.
Potential autoimmune gastritis was diagnosed in 84 patients (mean age 50 ± F/M ratio 2.8). Fifty percent of them was affected by at least another autoimmune disease, most frequently Hashimoto thyroiditis (71%). During the follow up 28 (33%) of them developed overt autoimmune gastritis in a median time course of 2 years. Two of them developed a complication (NETG1) in a median time of 9 years.
Conclusions: although AIG is a slowly progressive disease, it tends to progress towards more severe stages over the time and to develop complications. Patients affected by AIG must undergo to endoscopic surveillance to prevent the development of complications. In the meantime, it's important to detect potential AIG and follow up them in time, in order to avoid B12 deficiency, systemic manifestations and neoplastic complications.

346. DIAGNOSTIC DELAY OF COELIAC DISEASE IN CHILDHOOD

Varallo M.[1], Bianchi P.I.[2], Petrucci C.[1], Lenti M.V. [1], Aronico N. [2], Pozzi E.[3], Groppali E.[3], Siccardo F.[3], Di Leo G.[4], Zanchi C.[4], Cristofori F.[5], Francavilla R.[5], Aloi M.[6], Gagliostro G.[6], Montuori M.[6], Romaggioli S.[6], Strisciuglio C.[7], Crocco M.[8], Calvi A.[8], Auricchio R.[9], De Giacomo C.[10], Caimmi S.[11], Marseglia G.L.[11], Carrara C.[12], Staiano A.[13], Cenni S.[13], Congia M.[14], Schirru E.[14], Ferretti F.[15], Ciacci C.[16], Vecchione N.[16], Latorre M.A.[1], Resuli S.[1], Moltisanti G.C.[1], Canu P.[1], Quadrelli A.[1], Saglio S.[1], Ruggeri D.[1], De Silvestri A.[17], Gambini G.[17], Klersy C.[17], Corazza G.R.[1], Di Sabatino A.[1]
[1]First Department of Medicine, IRCCS Hospital Foundation San Matteo, Pavia, Lombardy, Italy; University of Pavia, Pavia, Lombardy, Italy; [2]First Department of Medicine, IRCCS Hospital Foundation San Matteo, Pavia, Lombardy, Italy; [3]Children Hospital Vittore Buzzi of Milan, Lombardy, Italy; [4]Gastroenterology Department, IRCCS Hospital Burlo Garofolo, Trieste, Friuli-Venezia-Giulia, Italy; [5]Paediatric Gastroenterology and Hepatology Department, Hospital Giovanni XXIII of Bari, Puglia, Italy; [6]La Sapienza University, Rome, Lazio, Italy; [7]AOU Luigi Vanvitelli, Naples, Campania, Italy; [8]Giannina Gaslini Institute, Genoa, Liguria, Italy; [9]Department of Paediatric Gastroenterology, AOU Federico II, Naples, Campania, Italy; [10]Paediatric Department, Grande Ospedale Metropolitano Niguarda of Milan, Lombardy, Italy; [11]Paediatric Department, IRCCS Hospital Foundation San Matteo, Pavia, Lombardy, Italy; [12]Paediatric Department, IRCCS Hospital Foundation San Matteo, Pavia, Lombardy, Italy; University of Pavia, Pavia, Lombardy, Italy; [13]Federico II Paediatric Department – UO Gastroenterology Department, Naples, Campania, Italy; [14]Hospital Brotzu – Paediatric Hospital Antonio Cao, Cagliari, Sardinia, Italy; [15]Gastroenterology - Hepatology and Nutritional Department, Paediatric Hospital Bambin Gesù, Rome, Lazio, Italy; [16]University of Salerno AOU San Giovanni di Dio e Ruggi d'Aragona, Salerno, Campania, Italy; [17]Clinical Epidemiology and Biometry Service, IRCCS Hospital Foundation San Matteo, Pavia, Lombardy, Italy

Backgrounds and Aims: Coeliac disease (CD) is a lifelong illness occurring from early childhood to old age. Clinical and laboratory presentation may be variable. Several studies show that there is a diagnostic delay (DD) for CD. DD may lead to lower quality of life, slower improvement of symptoms in GFD, increased medication, clinical complications in all population and

mortality in adults. Factors previously associated to DD were a low awareness of the disease, female sex, neurological or muscle-skeletal symptoms.
The first aim of our study was to investigate the overall, the patient-dependent and the physician-dependent DDs of CD in childhood. The second aim was to define the possible factors associated to DD.
Methods: In our multicentric study, data regarding 3171 CD paediatric patients (aged 0-18 years) diagnosed between 2010 and 2020 were retrospectively collected from thirteen Italian hospitals. The overall DD was described as the time lapse occurring from the first symptoms, laboratory alterations or other clues indicative of CD and diagnosis. Patient-dependent and physician-dependent delays were also assessed respectively as the time lapse within first symptoms or clues for CD and first visit of physician, and as the time lapse within the first visit and the diagnosis. Clinical and demographic data were collected. The DD was obtained as median (50' percentile) with 95% IC, calculating confidence intervals for non-parametric analyses and Wilcoxon test. Univariate regression models for factors affecting delay were fitted. We also analysed the extreme diagnostic delay (ED) defined as 75' percentile of results.
Results: In total, 3171 patients (mean age 6.16 ± 3.93 y, M:F=1:2, mean BMI 15.97 for both genders) were included. The median overall DD was 5 months (IQR 2-11), while patient- and physician-dependent DDs were respectively 2 months (IQR 0-6) and 1 month (IQR 0-3). However, concerning ED, the median overall (17%) was 11 months, patient-dependent (18%) was 6 months and physician-dependent (19%) was 3 months. Most of our patients (72%) had more than one symptom.
Patients who had first diagnosis at age < 3 y (21%), compared with all others, had higher rate of multiple symptoms (39 vs 28%), gastrointestinal symptoms (39 vs 28%), weight loss (19 vs 10%), failure to thrive (42 vs 30%), dysproteinemia (6 vs 2%), classic presentation of CD (68 vs 49%) and normal histological findings in Corazza-Villanacci classification (6 vs 3%).
Having first diagnosis at age < 3 y rather than between 3-18 y was associated with a lower DD, both overall (2 vs 5 months, p=0,0001) and physician-dependent (1 vs 2 months, p=0,0001). There was a slight but significant difference regarding to gender with overall and physician-dependent DDs higher in females, respectively 5 vs 4 months (p=0,018) and 2 vs 1 months (p=0,0013) than males.
HLA haplotype, endoscopic appearance and histologic grade of small-bowel lesions did not seem to interfere with time of diagnosis.
Patient-dependent ED was more common if there were multiple symptoms (32%), mainly gastrointestinal, failure to thrive (42%), previous misdiagnosis or if the diagnosis was not made by a paediatrician. On the other hand, physician-dependent ED was more common if patients had other possible diagnosis and less common if there were gastrointestinal symptoms, weight loss, dysproteinemia and if the diagnosis was made by a gastroenterologist.
Finally, previous misdiagnosis, assessed with multivariate analysis, was related to the presence of multiple symptoms, gastrointestinal symptoms, asthenia and blood panel abnormalities; as expected, having family history of CD was a protective factor from misdiagnosis.
Conclusions: The diagnostic delay of CD in paediatric patients in Italy has decreased in recent years and is confirmed to be shorter than in adults as highlighted from a comparison with data from our national multicentric study, which includes the same period of years, where overall, patient-dependent and physician-dependent DDs were respectively 8, 3 and 4 months. Lastly, by investigating ED and pointing out its associated conditions, we will try to correct the worst diagnostic paths in CD. However, there are several factors which still may increase the time lapse of diagnosis of CD in children.

347. EARLY-ONSET VS LATE-ONSET DIVERTICULAR DISEASE: RISK FACTORS AND OUTCOMES FROM AN ITALIAN TERTIARY REFERRAL CENTRE STUDY

Santacroce G.[1], Lenti M.V.[1], Abruzzese G.M.[1], Alunno G.[1], Di Terlizzi F.[1], Frenna C.[1], Gentile A.[1], Latorre M.A.[1], Petrucci C.[1], Ruggeri D.[1], Soriano S.[1], Bianchi P.I.[2], Aronico N.[2], Mengoli C.[2], Miceli E.[2], De Silvestri A.[3], Corazza G.R.[1], Di Sabatino A.[1]
[1]Department of Internal Medicine and Medical Therapeutics, University of Pavia, Pavia, Italy; [2]First Department of Internal Medicine, San Matteo Hospital Foundation, Pavia, Italy; [3]Scientific Direction, Clinical Epidemiology and Biometric Unit, San Matteo Hospital Foundation, Pavia, Italy

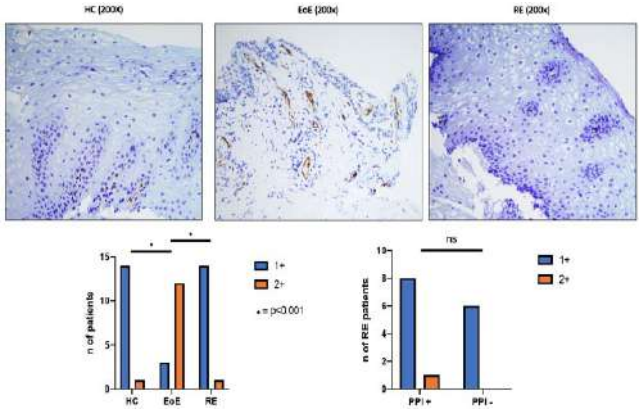
Background and aim: Diverticular disease is a spectrum of disorders including symptomatic uncomplicated diverticular disease, acute or chronic diverticulitis, with or without complications, and segmental colitis associated with diverticulosis. Although diverticular disease is prevalent in elderly, an increased incidence has been shown among younger individuals. Limited data are available concerning differences related to the age at disease onset. This study aims to compare demographic, clinical and prognostic features between early onset (EO) and late onset (LO) diverticular disease patients.
Methods: This retrospective study included adult patients with diverticular disease diagnosed between 2000 and 2022 at an Italian tertiary referral centre (San Matteo Hospital Foundation). Patients demographic and clinical data were retrieved, including diverticular disease features at onset, i.e. type, localisation, occurrence of complications, and hospitalization. Patients were divided into two groups: EO, defined as age <49 years (25th percentile of the population) and LO, defined as age ≥ 49 years. Univariate and multivariate analyses were performed to assess the association of collected variables with EO and LO disease. Also, survival analyses were performed to evaluate the correlation between the age at disease onset and outcomes -including disease recurrence, hospital access, surgery and death- at follow-up (2023).
Results: Data from 220 diverticular disease patients (median age 67 years, IQR 56-78; F/M 129/91) were collected, including 54 (25%) EO patients and 166 (75%) LO patients. EO patients had a significantly higher prevalence of male sex (57% vs 36%, p=0.006), active smoking (38% vs 14%, p=0.001) and alcohol consumption (54% vs 38%, p=0.03) compared to LO patients. Multivariate analysis confirmed male sex and active smoking as significant risk factors for the occurrence of EO diverticular disease. Conversely, relevant comorbidities (39% vs 69%, p=0.001), cardiovascular comorbidities (26% vs 50%, p=0.002) and history of neoplastic disorder of the gastrointestinal tract (2% vs 16%, p=0.015) resulted less frequent in EO than LO patients, being collinear with age. There were no significant difference between EO and LO patients regarding the specific type or localization of diverticular disease. Complications at diagnosis, particularly abscess and free perforation, occurred more frequently in EO compared to LO patients (18% vs 6%, p=0.04). Moreover, EO patients showed a higher rate of hospitalization (p=0.02) during follow-up (median 5 years, IQR 4-9).
Conclusion: Male sex, active smoking, and alcohol consumption were identified as risk factors for the occurrence of EO diverticular disease. EO patients should be carefully evaluated at diagnosis due to their higher risk of developing complications. Additionally, their higher rate of hospitalization during follow-up emphasizes the need for close monitoring and appropriate management strategies.

348. IMMUNOHISTOCHEMICAL EVALUATION OF ESOPHAGEAL VASCULAR BARRIER IN EOSINOPHILIC ESOPHAGITIS

Santacroce G.[1], Guerini C.[2], Rossi C.M.[1], Lenti M.V.[1], Merli S.[3], Vanoli A.[2], Aronico N.[3], Mauro A.[4], Pasini A.[3], Anderloni A.[4], Di Sabatino A.[1]
[1]Department of Internal Medicine and Medical Therapeutics, University of Pavia, Pavia, Italy; [2]Anatomic Pathology Unit, Department of Molecular Medicine, University of Pavia, San Matteo Hospital Foundation, Pavia, Italy; [3]First Department of Internal Medicine, San Matteo Hospital Foundation, Pavia, Italy; [4]Gastroenterology and Endoscopy Unit, San Matteo Hospital Foundation, Pavia, Italy

Background and aim: Eosinophilic esophagitis (EoE) is a TH2 antigen-driven disease which is characterized at the histological level by chronic eosinophil-rich inflammation. Its pathogenesis is multi-factorial, with the esophageal epithelium impairment playing a relevant role. Instead, at present little is known about the role of the vascular barrier, an anatomical structure which has been shown to control the systemic dissemination of resident bacteria and, according to previous evidence, may play a pathogenic role in other immune-mediated diseases of the gut, *i.e.* autoimmune gastritis and inflammatory bowel disease. The aim of this study was to evaluate the expression of plasmalemma vesicle-associated protein-1 (PV1), a marker of vascular barrier damage, in the esophagus of patients with EoE compared to healthy controls (HC) and patients with reflux esophagitis (RE).
Methods: We collected perendoscopic esophageal biopsies by 15 untreated patients with EoE, diagnosed according to the presence of 15 or more intraepithelial eosinophils per high-power field in hematoxylin and eosin stained biopsies, 15 patients with RE and 15 HC. Three-millimeter-thick paraffin sections were used for immunohistochemistry by the Dako Omnis automatic platform (Agilent, Santa Clara, CA, USA). An anti-PV1/PLVAP antibody (clone 174/2; LSBio, Seattle, WA, USA) was used. We evaluated PV1 staining within wall vessels in a semiquantitative manner, by using the following score: 0 (absence of PV1-positive vessels), 1+ (rare PV1-positive vessels), and 2+ (numerous PV1- positive vessels). Also, we assessed the use of proton-pump inhibitors (PPI) in RE patients before endoscopy, to evaluate their ef-

fect on vascular barrier.
Results: The immunohistochemical intensity of PV1 was weak in the majority of patients with RE (14 patients 1+ vs 1 patient 2+) and HC (14 patients 1+ vs 1 patient 2+), while it was more evident in the majority of patients with EoE (12 patients 2+ vs 3 patients 1+), regardless of the esophageal tract involved. No patient showed complete absence of PV1. The different PV1 immunohistochemical intensity between EoE and the other two groups was statistically significant at Fisher's exact test analysis (p<0.001). Moreover, in RE patients no significant difference in PV1 was found depending on the use of PPI. Results are summarized in Figure 1.



Conclusion: The esophageal vascular barrier appears to be disrupted in patients with EoE compared to HC and patients with RE. It can be assumed that the impairment of the vascular barrier could play a pathogenic role in EoE, just as in other immune-mediated conditions affecting the stomach and the bowel. PPI treatment does not seem to affect PV1 intensity at immunohistochemistry. Quantitative molecular studies of PV1 expression in patients with EoE and in controls are ongoing to confirm these immunohistochemical findings.

349. CHECKPOINT INHIBITOR-INDUCED COLITIS: A RETROSPECTIVE MULTICENTRIC INTERNATIONAL STUDY.

Broglio G.[1], Lenti M.V.[1], Bossetti C.[1], Schiepatti A.[2], Vernero M.[1], Felice C.[3], Blesl A.[4], Buda A.[5], Croitoru A.[6], Del Buono A.[7], Aranzazu Jaurgeu A.[8], Lasagna A.[9], Carvalho D.[10], Pugliese D.[11], Ribaldone D.G.[12], Dahl E.K.[13], Langholz, E.[13], Savarino E.[2], Agustoni F.[9], Borrelli De Andreis F.[14], Caprioli F.[15], Schaik F.[16], Sottotetti F.[2], Cammarota G.[17], Ianiro G.[17], Gröchenig H.P.[18], Koutroubakis I.[19], Geldolf J.[20], Argyriou K.[21], Foteinogiannopolou K[21], Bertani L.[22], Lobaton Ortega T.[20], Cappello M.[23], Delliponti M.[1], DeMarzo M.G.[24], Truyens M.[20], Van Ejis M.[20], Silvestris N.[25], Canu P.[1], Ellul P.[26], Pedrazzoli P.[9], Cannizzaro R.[27], Gabbiadini R.[7], Spagnuolo R.[28], Festa S.[17], Saglio S.[1], Stroie T.[6], Natalello G.[1], Varallo M.[1], La Torre M.A.[1], Petrucci C.[1], Klersey C.[29], Corazza G.R.[1], Di Sabatino A.[1]
[1]Internal Medicine Unit, IRCCS Fondazione Policlinico San Matteo Hospital, University of Pavia, Pavia, Italy; [2]Gastroenterology Unit, IRCCS Fondazione Maugeri, Pavia, Italy; [3]University of Padova, Italy; [4]University of Gratz, Austria; [5]Hospital of Feltre, Italy; [6]University of Bucarest, Romania; [7]Humanitas University Hospital, Milano, Italy; [8]University Hospital of Antwerp, Belgium; [9]Oncology Unit, IRCCS Fondazione Policlinico San Matteo Hospital, University of Pavia, Pavia, Italy; [10]University of Lisboa, Portugal; [11]IRCCS Fondazione Policlinico Gemelli, Roma, Italy; [12]A.O.U. Città della Salute e della Scienza di Torino, Molinette hospital, Torino, Italy; [13]University of Copenhagen, Denmark; [14]Internal Medicine Unit, IRCCS Fondazione Policlinico San Matteo Hospital, University of Pavia, Pavia, Italy; [15]Gastroenterology Unit, Policlinico Ospedale Maggiore di Milano, University of Milano, Italy; [16]University of Utrecht, The Netherlands; [17]Gastroenterology Unit, IRCCS Fondazione Policlinico Gemelli di Roma, Catholic University of Rome, Italy; [18]Hospital of the Brothers of St.John, Innsbruck, Austria; [19]University of Creete, Greece; [20]University Hospital of Ghent, Belgium; [21]University of Larissa, Greece; [22]ASL Toscana Nord-Ovest, University of Pisa, Italy; [23]Policlinico Paolo Giaccone - Palermo, Italy; [24]San Martino Hospital, Genova, Italy; [25]University of Messina, Italy; [26]University of Malta, Malta; [27]Oncology research Centre of Aviano, Italy; [28]"Magna Græcia" University, Catanzaro, Italy; [29]IRCCS Fondazione Policlinico San Matteo, UOC Biostatistica e Clinical Trial center, Pavia, Italy

Backgrounds and Aims: Anti–CTLA-4 (e.g., ipilimumab), anti–PD-1 (e.g., nivolumab, pembrolizumab), or anti–PD-L1 (e.g., atezolizumab) are immune checkpoint inhibitors (ICI) that have widened the treatment options for many cancer types. These drugs enhance the activity of T-cells that, while having an anti-tumoral activity, may induce autoimmune related adverse events (AIREs), of which colitis is one of the most common. Colitis has been defined by the Common Terminology Criteria for Adverse Events (CTCAE), as the presence of abdominal pain and blood in faeces. Phenotypically, inflammatory bowel disease (IBD)-like colitis is usually secondary to CTLA-4 therapies, while microscopic colitis is usually associated with anti-PD1/PD-L1 drugs. There is a paucity of data regarding the clinical and endoscopic presentation of ICI-induced colitis, as well as their outcome. Hence, we performed a retrospective multicentre study with the aim of describing the clinical characteristics across a large cohort of patients.
Materials and methods: This was a multicentric retrospective study which was approved by the European Crohn's and Colitis Organisation (ECCO) and funded by Fondazione IRCSS Policlinico San Matteo. Overall, 19 Italian and other 13 European centres took part to the study. Adult patients with an established, histopathological diagnosis of ICI-induced colitis were enrolled. A univariate analysis for factors associated with unfavourable outcomes was performed. Patients were enrolled from 2015 to 2022.
Results: Overall, 96 Caucasian patients (median age 65 years, IQR 55.7-71.2; 57 males) were included; half of them were either current smokers or past smokers (49, 51.5%), while a minority (12, 13.7%) had a pre-existing immune-mediated or autoimmune disease. Lung cancer (42, 40.6%), melanoma (34, 32.4%), and renal cancer (10, 10%) were the most common primary cancer sites. As for ICI, the most commonly used were anti-PD-1, particularly pembrolizumab (45, 42.7%) and nivolumab (24, 23.2%). At endoscopy, a diffuse inflammatory pattern was the most common finding at endoscopic assessment (51, 48.9%), followed by mucosal ulcerations in 28 cases (27%) while a normal endoscopic appearance was seen in 18 patients (17.5%). Interestingly, in the 78 patients with endoscopic signs of inflammation, this was associated to an IBD-like phenotype that resembled UC in 42 patients (53.8%), to CD with skip lesions in 10 (12%) cases while was unclassified in the remaining 26 (34.2%) cases. The left colon was the most frequent localization of the inflammation (36 patients, 45.5%). Among the other degrees of extension, the right and left colon were involved in 14 (17.5%) cases, the rectum in 9 (12.1%) and finally, an isolated localization in the ileum was found in 2 patients (2.5%). Among the 18 cases that presented as microscopic colitis, 19% of the overall cohort, collagenous colitis (10, 55%) was slightly more represented than lymphocytic colitis (8, 45%). Systemic steroids were the most common first line therapy (65, 67.4%), while infliximab and vedolizumab were needed in 18 patients (19%) as second line therapy. Further, 2 patients (2.5%) needed a third line therapy with vedolizumab. Oral budesonide was used in 6 cases (6.3%), all affected by microscopic colitis. The majority of patients reached remission with steroidal therapy (50, 52 %), though 11 (11%) were steroid-dependent; 18 patients were also still under ongoing biological/immunosuppressive therapy at the time of last data analysis and one patient was surgically resected. Interestingly, 20 patients (21.3%) remitted without need for therapy. At univariate analysis, diarrhoea severity (CTCAE ≥3) and IBD-like colitis were significantly associated to hospitalisation (p<0.001), need for ≥2 treatments (p=0.03 and p=0.02), and steroid-dependency/death (p=0.023 and p=0.036). Lastly, 31 patients died, with 5 deaths (5.2%) related to colitis.
Discussion and Conclusions: This is one of the first international studies on ICI-induced colitis. In our cohort, pre-existing autoimmune disorders in our patients was rare, highlighting how an AIRE may develop even in patients with no autoimmune predisposition. Importantly, clinical severity and IBD-like colitis were significantly associated with worse outcomes. It is mandatory to promptly recognize and treat these patients as soon as symptoms develop, in order to prevent complications. A prospective study is currently underway.

350. RAISED CA 19-9 LEVELS: CASES OF HORSES OR ZEBRAS?

D'Agruma A.[1], D'Agruma L.[2], Piscitelli P.[3], Castori M.[4], Parente P.[5], Graziano P.[5], De Cosmo S.[3], Vendemiale G.[6], Gasbarrini G.B.[7], Mirijello A.[3]
[1]SC di Medicina Interna, Policlinico Riuniti-Università degli studi di Foggia UOC di Medicina Interna, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG), Italia; [2] UOC di Genetica Medica, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG), Italia; [3]UOC di Medicina Interna, IRCCS Casa Sollievo della Sofferenza, San Giovanni

Rotondo (FG), Italia; [4]UOC di Genetica Medica, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG), Italia; [5]UOC di Anatomia Patologica, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG), Italia; [6]SC di Medicina Interna, Policlinico Riuniti-Università degli studi di Foggia; [7]UOC di Medicina Interna e Gastroenterologia, Università Sacro Cuore di Gesù, Roma, Italia

Background: Carbohydrate antigen 19-9 (CA 19-9) is a tumor marker used for prognosis and follow-up in several neoplastic conditions, such as biliary tract and pancreatic cancers. Its elevation can occur also in other malignant and non-malignant conditions, such as chronic pancreatitis, cholestasis, obstructive jaundice, and several other pulmonary, endocrinological and gynecologic diseases. The wide spectrum of raised CA 19-9 levels can make its interpretation troublesome, and it is at the basis for discouraging its use as diagnostic tool.
Case presentation: A 59-year-old Italian man with past history of left-sided abdominal wall melanoma (removed with wide local excision), hypertension, permanent atrial fibrillation, Hurtle cell's thyroid cancer (removed with thyroidectomy followed by ablation with I-131) and Gilbert syndrome, came to our observation for the finding of raised CA 19-9 levels (990.25 U/ml, n.v. < 37 U/ml). This exam had been required by his family physician within the laboratory follow-up of melanoma. Carcinoembryonic antigen (CEA) was also slightly elevated (2.77 U/ml, n.v. <2.5). He was on chronic treatment with bisoprolol, olmesartan, potassium canrenoate, edoxaban and levothyroxine.
Physical examination was unremarkable and the patient did not complain of any symptom, neither gastrointestinal.
A second CA 19-9 assay was performed confirming its significantly high levels (504.13 U/ml), even if its value was halved as compared to a week before. The laboratory workup included other laboratory exams and tumor markers: the neuron-specific enolase (NSE) was slightly raised (19.04 ng/l, n.v. < 18.3 microg/l), while other serum values were within the normal limits.
Due to these findings, a number of instrumental examinations was ordered, such as abdominal US-scan, lymph-nodes stations US-scan and contrast-enhanced total body computed tomography scan (CT-scan) which did not show any pathological finding. Thus, 18-FDG positron emission tomography was performed and did not evidence any increased metabolic activity.
The patient performed also upper gastrointestinal endoscopy and colonoscopy. While this latter was negative, gastroscopy showed the presence of erosive bulbitis and biopsies for H. pylori were carried out both in stomach and duodenum. Subsequently, pantoprazole 40 mg/day was started.
The CA 19-9 test was repeated showing, in few days, a progressive decline of its values (234.41 U/ml after 4 days). The patient was discharged with the prescription of proton pump inhibitors (PPI, pantoprazole 40 mg/day), awaiting for histology of endoscopic biopsies. With the suspicion of H. Pylori infection as the main cause of raised CA 19-9, anti-Helicobacter pylori IgG antibody serum titer and fecal Helicobacter pylori antigen test were requested: the first was positive (4.16 Index), while the second was negative (probably due to the concomitant treatment with PPI). After 14 days from the first assay, and 10 days after starting PPI treatment, CA 19-9 was constantly declining (132.91 U/ml). Meanwhile, histological exam performed over stomach biopsies showed: ''Chronic non-atrophic, active gastritis related to Helicobacter pylori ''. The patient received a prescription with quadruple-drug based treatment for H. Pylori eradication (bismuth subcitrate 140 mg tid, metronidazole 125 mg tid, tetracycline hydrochloride 125 mg tid) for 10 days together with pantoprazole 40 mg bid for 14 days and then 40 mg od for other 14 days. Two weeks after discontinuation of PPI therapy, Urea breath test was performed showing Helicobacter pylori eradication. At same day CA 19-9 was dosed, resulting within normal values (30.21 U/ml). Even NSE normalized (13.62 microg/l) and CEA was stable (2.77 ng/ml).
Conclusions: Helicobacter pylori is a gram-negative bacterium and represents the main cause of chronic gastritis and peptic ulcer disease, affecting billions of people worldwide. Increased CA 19-9 has been rarely reported as a consequence of this infection, although it does not represents a typical finding. Chronic gastric and/or duodenal mucosal inflammation can explain the raising of CA19-9 due to the continuous damage against gastric and duodenal epithelium.

351. GASTROINTESTINAL AUTOIMMUNE DISEASES IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY: A COHORT STUDY

Marasco G., Conti F., Cremon C., Montemitro P., Ferrari S., Barbaro M.R., Pession A., Stanghellini V., Barbara G.
Università di Bologna

Introduction: Common variable immunodeficiency (CVID) is the most prevalent primary immune deficiency. Two-thirds of CVID patients present concomitant autoimmune disorders, including gastrointestinal autoimmune disease, other than being at risk for gastric cancer.
Aims & Methods: We aimed to assess the prevalence of autoimmune gastrointestinal manifestation in patients with CVID and to evaluate the diagnostic yield of EGDS for the screening of gastric pre-neoplastic lesions in a prospective cohort of patients with CVID. From June 2020 to June 2022, we prospectively enrolled patients with CVID diagnoses from a tertiary referral center. At enrollment, patients underwent a gastroenterological screening consisting of clinical evaluation and laboratory tests for the screening of autoimmune gastrointestinal disease. Moreover, all patients were proposed to undergo an esophagogastroduodenoscopy (EGD) regardless of the presence of GI symptoms to rule out pre-neoplastic gastric lesions and upper gastrointestinal disease in the presence of clinical suspicion. Patients with lower GI symptoms were proposed for colonoscopy.
Results: We included 94 patients with CVID, of whom 58 (61.7%) were females, with a mean age of 44.3 years old [standard deviation (SD) 16.3]. Overall, 12 patients (12.8%) were diagnosed with one or more gastrointestinal autoimmune diseases. Eight patients (8.5%) had ongoing therapy with intravenous immunoglobulin, while 24 (25.5%) with subcutaneous immunoglobulin. Four patients (4.3%) had a previous celiac disease diagnosis, with a negative serology at screening, and only 1 (1.1%) patient had evidence of villous atrophy and duodenal inflammation at the time of EGD. Three (3.2%) patients were diagnosed with autoimmune atrophic gastritis with negative serology and evidence at biopsies taken during EGD of atrophic gastritis. One patient (1.1%) was diagnosed with ulcerative colitis, one patient (1.1%) with Crohn's disease, and 5 patients (5.3%) with autoimmune hepatitis. Sixteen (16, 17%) patients reported inhalant allergy, 5 (5.3%) reported food allergy, and 26 (27.7%) reported drug-related allergy. Eleven (11.7) patients reported previous Helicobacter pylori (HP) infection, while only 1 (1.1%) patient was diagnosed with an ongoing HP infection. Fifty-eight patients underwent EGD, with endoscopic evidence of esophagitis in 8 patients (13.8%), gastritis in 45 (77.6%), and duodenal atrophy/inflammation in 23 (39.7%), of whom 41.4% had histological evidence of duodenal lymphocytosis. No patient was diagnosed with gastric cancer. Twenty-three patients underwent colonoscopy according to clinical indication, which showed at biopsy sampling ileal nodular follicular hyperplasia in 2 patients (8.7%), microscopic (lymphocytic) colitis in 2 patients (8.7%), ulcerative colitis in 1 (4.3%) and Crohn's disease in 1 (4.3%).
Conclusion: Celiac disease, atrophic gastritis, and autoimmune hepatitis were the most common gastrointestinal autoimmune overlaps of patients with CVID. Autoimmune gastrointestinal diseases in patients with CVID may pose a particular diagnostic challenge since autoantibodies are often absent. Five percent of CVID patients screened with EGD were found with a gastric preneoplastic lesion. Further data are needed to define the optimal timing of endoscopic follow-up of these patients for the screening of preneoplastic and neoplastic lesions.

352. PANETH CELLS ABNORMALITIES IN DUODENAL MUCOSA OF PATIENTS WITH UNCOMPLICATED AND COMPLICATED COELIAC DISEASE AND OTHER ENTEROPATHIES

Quadrelli A.[1], Bianchi P.I. [2], Rossi C.[3], Vanoli A.[3], Neri G.[1], Betti E.[2], DeSilvestri A.[4], Paulli M.[3], Corazza G.R.[1], Di Sabatino A.[1]
[1]First Department of Medicine, San Matteo Hospital Foundation, Pavia, Italy, Department of Internal Medicine and Medical Therapeutics, University of Pavia, Pavia, Italy; [2]First Department of Medicine, San Matteo Hospital Foundation, Pavia, Italy; [3]University of Pavia, Anatomic Pathology Unit, Department of Molecular Medicine, San Matteo Hospital Foundation, Pavia, Italy; [4]Clinical Epidemiology and Biometry Service, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Introduction: Paneth cells are typically located at the base of the crypts of Lieberkühn in the intestinal mucosa, with an average count ranging from 5 to 12 per crypt. The estimated total number of Paneth cells is around 200 million units. These cells are secretory in nature, containing a high concentration of secretory granules filled with different types of proteins, with antimicrobial peptides (AMPs) being the most abundant. Normally, Paneth cells do not exhibit mitotic activity. Autophagy, a vital process in the life cycle of Paneth cells, involves the recycling of intracellular components through self-digestion. It has been observed that stressors can induce autophagy in Paneth cells, and defects in this process may be implicated in the pathoge-

nesis of certain enteropathies, such as Crohn's disease.
Materials and methods: Duodenal biopsies and clinical data were collected from 48 patients with different enteropathies, including 10 untreated coeliac disease (UCD), 10 treated coeliac disease (TCD), 9 refractory coeliac disease (RCD) RCD type I, 6 RCD type II (including also 3 ulcerative jejunal ileitis), 3 enteropathy-associated T-cell lymphoma (EATL), 13 common variable immuno-deficiency (CVID), 2 idiopathic villous atrophy (IVA), 2 autoimmune enteropathies, and from 6 controls. It was possible to recover biopsies only from the year 2015 onwards. Immunohistochemistry with Defensin-5 and with Polyclonal Rabbit Anti-Human Lysozyme antibodies was used to highlight Paneth cells, with Defensin-5 showing higher specificity, used at an optimal dilution of 1 to 5000. The images were captured with NanoZoomer-SQ C13140-0, analyzed with QuPath and reviewed by a blind expert operator who performed four observations on four different fields, each of one linear millimeter of mucosa.
Results: Out of the 54 enrolled patients, 3 presented 4/4 non-evaluable readings of Paneth cell count and were therefore excluded from in the study. The overall number of Paneth cells per millimeter of intestinal mucosa and the clinical outcome were assessed. A significant difference was found between CD (UCD and TCD) and RCD (RCD I and II) groups, with median Paneth cells count of 28.4/mm vs. 21 (p: 0.0333). A significant difference was also observed between RCD I and RCD II + EATL groups, with a median of 27 vs. 15 (p: 0.0487); between TCD and RCD II, with a median count of 34 vs. 13 (p:0.00789). RCD II and CVID groups also showed a significant difference, with a median count of 13 vs 27.4 (p:0.00372). No significant differences were found in other group comparisons. Among all the patients, 8 did not survive, and 8 were lost to follow up. Cox analysis indicated significant prognostic value for number of Paneth cells in patients as a whole (p: 0.00333) but not in each single group (p>0.05).
Conclusions: According to our findings, there was no significant reduction in Paneth cell number in patients with UCD, TCD, RCD type I and CVID compared to controls. Lower numbers were instead observed in patients affected by RCD type II, even compared to RCD type I. This could serve as an additional criterion of discrimination between them. Moreover, the prognosis varied, with all patients with UCD and TCD being alive during the follow-up period, while higher mortality rates were recorded in other groups where fewer numbers of Paneth cells correlated with a poorer prognosis regardless of the aetiology of villus atrophy.

353. EOSINOPHILIC COLITIS: AN EXTENSIVE DESCRIPTION OF A RARE DISORDER

Lo Bello A.[1], Lenti M.V.[1], Rossi C.M.[1], Di Terlizzi F.[1], Savarino E.[2], Vernero M.[3], Ribaldone D.G.[4], Marabotto E.[5], Corazza G.R.[1], Di Sabatino A.[1]
[1]First Department of Medicine, San Matteo Hospital Foundation, University of Pavia, Pavia, Italy; [2]Gastrointestinal Unit, Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy; [3]Department of General and Specialist Medicine, Gastroenterologia-U, Città della Salute e della Scienza di Torino, Turin, Italy; [4]Division of Gastroenterology, Department of Medical Sciences, Molinette Hospital, University of Turin, Turin, Italy; [5]Gastroenterology Unit, Department of Internal Medicine, University of Genoa, Genoa, Italy

Background and aim: Primary eosinophilic colitis (EC) is a rare, chronic, inflammatory, and immune-mediated disease characterized by the presence of an eosinophilic infiltrate within the colonic mucosa in association with gastrointestinal symptoms, more commonly abdominal pain, diarrhoea, and weight loss. EC remains an exclusion diagnosis. We herein aim to investigate the clinical characteristics of patients with EC, in comparison to other chronic gastrointestinal disorders.
Material and methods: this is a multicentre, retrospective study conducted in 2022. Data regarding patients with EC diagnosed and followed-up at 4 Italian centres were retrieved. Patients with eosinophilic esophagitis (EoE) and irritable bowel syndrome (IBS) were also enrolled as control groups. Several sociodemographic, clinical, laboratory, endoscopic and histological information were analysed; bivariate analyses were fitted when appropriate. The study aims to investigate different characteristic in a cohort of patients affected by EC and to evaluate demographic, clinical and laboratory differences between EC and other chronic gastrointestinal disorders. We also looked at potential links between colonic wall abnormalities and clinical manifestations, as well as possible factors that impact on diagnostic delay.
Results: Overall, 73 patients, 40 affected by EC (median age 39 years, IQR 25.5-59, F:M ratio of 2:1), 12 affected by EoE and 21 affected by IBS were included. EC was more frequent in female if compared to EoE (27 female patients, 93.1% vs 2 female patients, 6.9%; p= 0.003). Active and previous smoking were more frequently associated with EC as compared to IBS (80% vs 20%; p= 0.014). No statistically significant differences were noticed for age, familiarity, alcohol use or coffee intake. Significant laboratory abnormalities were found in patients with EC, namely serum eosinophilic count (p=0.0007), RCP level (p=0.0001), faecal calprotectin (p=0.004) and faecal occult blood (p=0.021), all increased in the EC cohort compared to the other control groups. Patients with a higher eosinophilic wall infiltration of the colon or rectum did not display a higher symptomatic burden. Similarly, no correlations were found between macroscopical abnormalities or eosinophilic infiltration of the colonic wall and weight loss, bowel movement alteration, and positive faecal occult blood test. The diagnostic delay were 3 months (IQR 2-8; patient-dependent), 8 months (IQR 6-12); physician-dependent), and 20 months (IQR 10-29; overall diagnostic delay), respectively. We identified three factors which were related to longer diagnostic delay, including the presence of atopy (p=0.008), a previous misdiagnosis (p=0.041), and weight loss (p=0.005).
Conclusion: The presence of gastrointestinal symptoms, along with peripheral eosinophilia, increased faecal calprotectin and history of atopy, should rise the suspicion of EC. Symptom burden is not related to the entity of mucosal eosinophilia. A better awareness of this condition is needed in order to improve the diagnostic delay.

354. BEWARE OF IMMUNE-RELETED ADVERSE EVENTS IN INTERNAL MEDICINE: A RARE CASE OF CHOLANGITIS AND PANCREATITIS DUE TO IMMUNE CHECKPOINT INHIBITORS

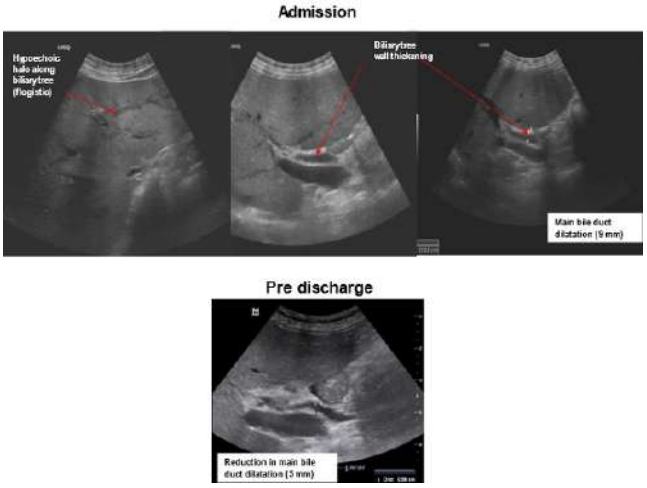
Bettazzoni L.[1], Sagrini E.[2], Palmese F.[3], Montepaone M.[2], Fuda D.[1], Domenicali M.[3]
[1]Department of Medical and Surgical Sciences, Alma Mater Studiorum-University of Bologna, Italy. ; [2]Department of Primary Health Care, Internal Medicine Unit addressed to Frailty and Aging, AUSL Romagna, Ravenna, Italy; [3]Department of Primary Health Care, Internal Medicine Unit addressed to Frailty and Aging, AUSL Romagna, Ravenna, Italy. Department of Medical and Surgical Sciences, Alma Mater Studiorum-University of Bologna, Italy

Introduction: In the last decade Immune checkpoint inhibitors (ICIs) had rapidly gained approval for the treatment of an increasing number of cancer types, due to their effect on patient survival(1). The antitumoral activity, obtained by stimulating the immune system, can also lead to a wide range of immune-related adverse events (irAE) that usually occur several months after the beginning of the therapy(2). Pancreatitis, acute cholecystitis and cholangitis have been reported as very rare irAE. Among patients treated with ICIs, pancreatitis is more common in those on combined immunotherapy(3).
Clinical case description: A 58-year-old man presented to the ED for epigastric pain without nausea or fever. Laboratory tests showed neutrophilic leucocytosis (18.2 10^9/L), elevated CRP (33.2 mg/L), GGT (1300 U/L), and ALT (183 U/L). At physical examination, Murphy's sign was positive while the point-of-care ultrasound showed biliary sludge in the gallbladder and a small gallstone (< 1 cm) along with mild common bile duct distension (9 mm) with thickened walls. Pancreas' echotexture was normal.
Past history: active smoker, non-drinker, diabetes, hypercholesterolemia, hypertension, recently diagnosed non-small cell lung cancer treated since 2 months with pemetrexed and carboplatin plus combined immunotherapy with nivolumab and ipilimumab (4 weeks of complete treatment followed by 4 weeks of immunotherapy).
Diagnosis of acute cholecystitis and cholangitis due to gallstone was made, no surgical indication was placed due to first episode. He was admitted to our internal medicine ward where treatment with bowel rest, hydration therapy, and piperacillin/tazobactam were given. Despite clinical improvement, on the following days we observed an increase in cholestasis (GGT 1964 U/L ALP 1559 U/L), total bilirubin (2.4 mg/dl), and lipases three times over the upper limit of normal (1670 U/L). A contrast CT scan was performed and confirmed thickened gallbladder walls with not obstructive gallstone, along with extrahepatic biliary walls thickening (9 mm). A minimal suffusion of the adipose tissue adjacent to the pancreas hooked process was also found, supporting the diagnosis of acute pancreatitis associated with cholangitis. No main bile duct stones nor dilatation of the Wirsung duct was evident.
Since patient was asymptomatic and hemodinamically stable, conservative therapy with hydration and antibiotics was continued. cANCA, pANCA and hepatic virus markers (HCV, HBV) were negative and no gallstones were detected in the biliary tree, nor gallbladder stones appeared obstructive. The

patient was started on immunotherapy in the weeks before admission, therefore ICI-induced pancreatitis and cholangitis were suspected. In accordance with the oncologist, indication to start treatment with 1mg/Kg iv corticosteroids was placed. At 48 hours abdominal ultrasound was performed, which showed a complete resolution of the cholecystitis and cholangitis, along with a reduction in cholestasis enzymes (GGT 627 U/L, ALP 777 U/L) and lipases (200 U/L). At discharge, patient was put on ursodeoxycholic acid (450 mg/die) and oral steroid (prednisone 50 mg/die). At one-month oncologic follow-up, the patient didn't present a clinical relapse of the disease. Laboratory exam shows: lipase 116 U/L, ALT 33 U/L, total bilirubin 0.28 mg/dl, ALP 151 U/L, and GGT 154 U/L. He also performed a full-body CT scan that confirmed the complete resolution of the condition. ICIs were stopped and chemotherapy with carboplatin and pemetrexed were resumed.

Conclusion: Gallbladder sludge and gallstones could represent a confounding factor in the aetiology of cholangitis and acute pancreatitis in patients treated with immunotherapy. Few cases of ICI-related cholecystitis have been described in literature so far, and they were acalculous event(2). Cholangitis appears to be an extremely rare irAE, and the few described by literature were characterized by extrahepatic bile duct dilation without obstruction, with diffuse hypertrophy of the bile duct wall(4). Acute pancreatitis is a rare but well-known irAE and the NCCN guidelines suggest treating moderate ICI-related pancreatitis, like our case, with 0.5-1.0 mg/Kg/die(5). The effectiveness of steroid therapy compared with standard treatment of these conditions is debated(6). However, we observed a rapid imaging resolution and laboratory improvement after the initiation of high-dose iv steroid. Given that positive response, we cannot rule out at least a dual component in the aetiology: cholecystitis due to gallstones and cholangitis with pancreatic injury due to immunotherapy.

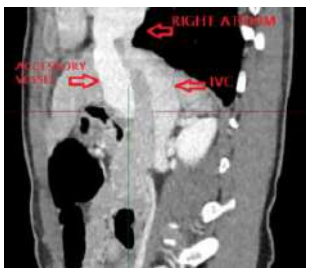
1.Bagchi, Yuan, Engleman. Immune Checkpoint Inhibitors for the Treatment of Cancer.2021
2.Abu-Sbeih, Wang. Hepatobiliary Adverse Events.2020
3.George et al. Incidence of pancreatitis with the use of immune checkpoint inhibitors (ICI) in advanced cancers.2019
4.Kawakami et al. Imaging and clinicopathological features of nivolumab-related cholangitis in patients with non-small cell lung cancer.2017
5.Thompson. New NCCN Guidelines.2018
6.Abu-Sbeih et al. Clinical characteristics and outcomes of immune checkpoint inhibitor-induced pancreatic injury.2019

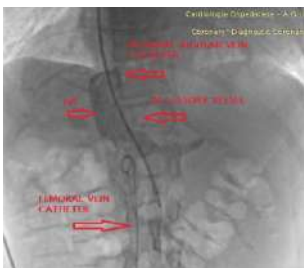


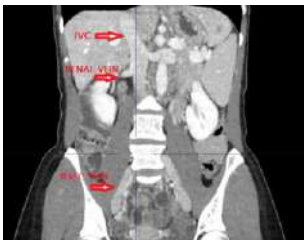
355. PULMONARY ARTERIAL HYPERTENSION UNVEILED IN A RARE ABERNETHY MALFORMATION CASE

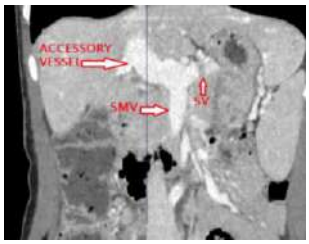
Graziadei M.[1], Amati V.[1], Tandoi F.[2], Camassa N.[3], De Tommasi E.[3], Rendina M.[3], 4 Vella F.S.[5], Sabbà C.[5]
[1]U.O. Medicina Interna "Cesare Frugoni" Policlinico di Bari, [2]U.O.S.D chirurgia epatobiliare e centro trapianti di fegato, policlinico di Bari, [3]Dipartimento di cardiologia ospedaliera, Policlinico di Bari, [4]U.O. gastroenterologia universitaria, Policlinico di Bari, [5]U.O. Medicina Interna "Cesare Frugoni" Policlinico di Bari

A 26-year-old woman was admitted to the Internal Medicine Unit "Cesare Frugoni" at Policlinico Hospital in Bari in December 2022, complaining of hemoptysis. Physical examination revealed elf-like facial features, hypertelorism, short stature, and bradypsychism. Her medical history included surgical ligation of the patent ductus arteriosus (PDA) at 5 months, nasal cautery for recurrent nosebleeds at 10 years, celiac disease, growth delay, polycystic ovary syndrome, Morgagni hernia, and visual disturbances. She had also experienced dyspnea on mild exertion and frequent lipothymic episodes. Laboratory tests showed mild iron-deficiency anemia, mild thrombocytopenia, elevated NT-proBNP levels (519 pg/mL, reference range <70 pg/mL), slightly elevated hs-TnI levels (39.4 pg/mL), D-dimer levels within the normal range (385 µg/L, reference range <500 µg/L), hyperbilirubinemia (2.30 mg/dL, reference range 0.3–1.2 mg/dL, predominantly indirect), and normal levels of C-reactive protein, ammonia, and transaminases. Electrocardiogram (ECG) revealed sinus tachycardia, right axis deviation, right ventricular hypertrophy, and T-wave changes in the precordial leads. Arterial blood gas analysis showed severe hypoxemia with combined hypocapnia (P/F ratio 230 mmHg). Abdominal ultrasonography revealed hepatomegaly and absence of an intrahepatic portal vein system, along with a dilated splenoportal axis. Echocardiography showed slight dilation of the right atrium and right ventricle, mild pulmonic regurgitation, and an estimated pulmonary arterial systolic pressure (PASP) of 47 mmHg (42+5 mmHg). CT angiography ruled out chronic thromboembolic pulmonary arterial hypertension, detected subpleural parenchymal consolidation in the right lower lobe, and revealed cardiomegaly, severe dilation of the pulmonary artery, and hepatomegaly with intrathoracic engagement of the left hepatic lobe through a right Morgagni's hernia. Contrast-enhanced computed tomography of the abdomen revealed a nodular liver and anomalous drainage of the portal vein directly into the right atrium. Right heart catheterization confirmed severe pulmonary artery hypertension (pulmonary arterial pressure PAP 64 mmHg, pulmonary capillary wedge pressure PCWP 4 mmHg, pulmonary vascular resistance PVR 11 WoodU), unresponsive to NO. Further angiography provided additional information about the shunt anatomy. Magnetic Resonance Imaging (MRI) showed an enlarged and inhomogeneous liver with multiple lesions, hypointense in the hepatobiliary phase, suspicious for regenerative nodules. It also confirmed the presence of an anomalous drainage of the dilated splenoportal axis (25 mm) directly into the right atrium. Based on instrumental examinations, clinical and laboratory findings, a diagnosis of Abernethy malformation with pulmonary arterial hypertension was established. Abernethy malformation, also known as congenital extrahepatic portosystemic shunt (CEPS), is a rare condition in which blood from the splanchnic circulation bypasses the liver and drains directly into the systemic circulation through a shunt. Due to its rarity, the diagnosis is often challenging and delayed, leading to serious long-term medical complications such as hepatic carcinoma, hepatic encephalopathy, severe pulmonary hypertension, hepatopulmonary syndrome, and diffuse pulmonary arteriovenous malformation. Patients with CEPS may also have associated cardiac anomalies such as atrial septal defect (ASD), ventricular septal defect (VSD), and patent ductus arteriosus (PDA). These patients often present to healthcare facilities when complications have already developed, as was the case with our patient, where the misdiagnosis of hemoptysis due to pulmonary hypertension (PAH) prompted further investigation. The pathogenesis of PAH caused by CEPS is multifactorial, involving an imbalance between vasoconstrictors and vasodilators that promote pulmonary vasoconstriction. The increased pulmonary blood flow may lead to endothelial injury and dysfunction, progressive vascular remodeling, and subsequent vasoconstriction. According to the pathophysiological theory, vasoactive substances present in the intestinal circulation bypass the liver without being metabolized and pass through the CEPS, directly affecting the pulmonary parenchyma. Abernethy malformation is classified into two types: Type I, with total aplasia of intrahepatic portal venous branches and complete extrahepatic shunting, further divided into type Ia and type Ib based on the drainage pattern of the superior mesenteric and splenic veins; and Type II, with hypoplastic intrahepatic portal venous branches and partial extrahepatic shunting. It is interesting to note that there is no specific subtype describing the anomaly pattern seen in our patient, with drainage of the splenoportal axis directly into the right atrium through its own ostium. Considering the need to halt the progression of hepatopulmonary syndrome, the patient is a candidate for liver transplantation.









356. LONG-TERM DIETARY AND BEHAVIORAL ATTITUDES OF PATIENTS WITH SELF-REPORTED NON COELIAC GLUTEN SENSITIVITY: A FOLLOW UP STUDY

Ruggeri D.[1], Bianchi P.I.[2], Volta U. [3], Quadrelli A.[1], Latorre M.A.[1], Aronico N.[2], Lusetti F. [4], Ferretti V.V.[5], Corazza G.R.[4], Di Sabatino A.[1]
[1]First Department of Medicine, San Matteo Hospital Foundation, University of Pavia, Pavia, Italy; Department of Internal Medicine and Medical Therapeutics, University of Pavia, Pavia, Italy; [2]First Department of Medicine, San Matteo Hospital Foundation, University of Pavia, Pavia, Italy; [3]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy; [4]Department of Internal Medicine and Medical Therapeutics, University of Pavia, Pavia, Italy; [5]Clinical Epidemiology and Biometry Service, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Introduction: Non-Coeliac Gluten Sensitivity (NCGS) was recognized as a specific entity between gluten-related disorders. There are still undetermined and debated aspects, as its natural history.
The aim of the study was to evaluate a long-term persistence of symptoms, GFD-adherence and its efficacy in NCGS patients.
Material and methods: Between 2012 and 2014, 59 adult patients complaining of NCGS symptoms were enrolled in a randomized doble blind placebo-controlled trial of one week assumption of small amounts of gluten vs placebo [DiSabatino, Clin Gastroenterol Hepatol 2015]. The severity of intestinal and extra-intestinal symptoms on gluten-challenge and on placebo was assessed; "Delta overall score" is the subtraction of the score of symptoms on placebo from the score of symptoms on gluten. In 2022 we recontacted these patients by a telephone interview on their actual symptoms, their diet and their medical history. Severity of intestinal and extra-intestinal symptoms was reassessed. Adherence to GFD was self-evaluated from 0 to 10. Median values were compared in patients with negative or positive delta score. Mann Whitney's test or Fisher's exact test were used.
Results: In 2014, 52,5% patients of the trial had comparable scores of symptoms with gluten or placebo. Only 3 (5,1%) patients demonstrated significantly worst symptoms on gluten, while 35,6% demonstrated worst symptoms on placebo (negative Delta score). We were able to interview 49/59 patients (31 with a positive and 18 with a negative Delta score; mean age 46,6 y, F:M = 44:5). Mean follow-up interval was of 8 years and 10 months (98-107 ms). At the end of the 2014 trial, 38 maintained a GFD, with no difference between groups. Twenty-eight patients (57%) are still on a GFD, with an average self-judged adherence of 9/10. The patients who abandoned the GFD reported an average adherence of 6/10. Of the 18 negative Delta score patients, 5 are on GFD while 13 are not, but 8 still complain of symptoms. The positive Delta score patients maintained a long-term GFD more frequently (p=0,008).
Conclusions: Our data of long-term follow up of patients with self-reported NCGS confirm those of Carroccio et al. (Gastroenterology 2017) about a strong long-term compliance of patients to the GFD and a rare clinical worsening both in the GFD than in gluten-containing group. These patients show frequently persistent/recurrent symptoms, even if different. There is a trend in the patients with worst symptoms from gluten to be more compliant of the others to the GFD.

357. MANAGEMENT AND FOLLOW-UP EVALUATION OF ANEMIA IN INFLAMMATORY BOWEL DISEASE: A MULTICENTER STUDY

Ferrami L.[1], Bergamaschi G.[2], Aronico N.[2], Lenti M.[2], Mengoli C.[2], Corazza G. R.[3], Di Sabatino A.[1]
[1]Internal Medicine Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy Department of Internal Medicine & Medical Therapy, University of Pavia, Italy; [2]Internal Medicine Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [3]Department of Internal Medicine & Medical Therapy, University of Pavia, Italy

Background: RIDART I is an observational, cross-sectional study on the prevalence of anemia in inflammatory bowel disease (IBD). Study results showed a 14% prevalence of anemia in italian IBD patients, with most cases due to iron deficiency anemia (IDA).
Methods: Changes in Hb concentration were prospectively investigated during a 24-week follow-up of anemic patients enrolled in RIDART I. Factors affecting Hb concentration, the impact of anemia on fatigue and quality of life (QoL), and its relation with treatment and disease complications were investigated.
Results: Hb increased from 108 g/L at baseline to 121 g/L at follow-up week 12 ($p<0.001$) and then stabilized until week 24, but most patients remained anemic, with ID, troughout the study period. Among patients whose Hb normalized during the study, anemia relapsed in 30%. IDA was characterized by lower baseline Hb than other types of anemia and by a larger improvement during follow-up. Improvement was greater in patients receiving either oral or parenteral iron supplementation, and oral iron was not associated with disease reactivation. At the tested time points lower Hb was associated with more severe disease (more patients had active disease, increased C-reactive protein, reduced kidney function, and clinical complications/hospitalizations), increased fatigue and reduced QoL. Anemia prevalence, however, remained >50% also in subjects with quiescent disease.
Conclusions: Our study shows that in patients with IBD anemia usually represents a long-lasting manifestation, with a high relapse rate and a negative impact on fatigue and QoL.

358. A PROSPECTIVE EVALUATION OF PATIENTS WITH GASTROINTESTINAL BEHÇET DISEASE: FINDINGS FROM AN ACADEMIC, TERTIARY REFERRAL CENTER

Bonfichi A.[1], Lenti M.V.[2], Scalvini D.[1], Lusetti F.[1], Alimenti E.[1], Borrelli De Andreis F.[2], Vernero M.[1], Rossi C.M.[1], Merli S.[1], Broglio G.[1], Anderloni A.[3], Corazza G.R. [1], Di Sabatino A. [1]
[1]Department of Internal Medicine and Medical Therapeutics, University of Pavia, Pavia, Italy; Department of Internal Medicine, IRCCS San Matteo Hospital Foundation, Pavia, Italy; [2]Department of Internal Medicine and Medical Therapeutics, University of Pavia, Pavia, Italy; Department of Internal Medicine, IRCCS San Matteo Hospital Foundation, Pavia, Italy.; [3]Gastroenterology and Digestive Endoscopy, IRCCS San Matteo Hospital Foundation, Pavia, Italy

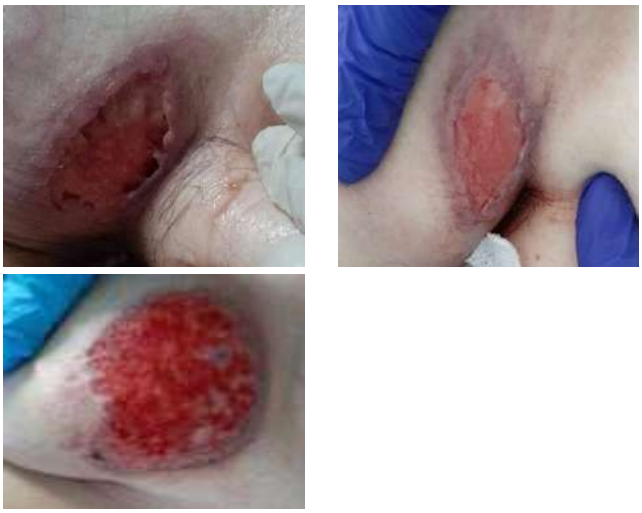
Background: Behet's disease (BD) is a multiorgan immune-mediated disorder involving skin, mucosa, eyes, joints, gut and the central nervous system. Several studies have shown the contribution of genetic factors to BD. The prevalence of gastrointestinal (GI) involvement in BD is estimated to be up to 10% in Asian populations, and its clinical presentation often mimics inflammatory bowel disease (IBD), leading to frequent misdiagnosis. Coeliac disease (CD) has been suggested as a potential association with BD, albeit, again, only in Asian populations. In this study, we aimed to elucidate the clinical, endoscopic, and histological manifestations of patients with BD gastrointestinal involvement who were enrolled at an Italian referral center.
Material and methods: From June 2018 to November 2022, we conducted a prospective evaluation of consecutive patients diagnosed with BD and gastrointestinal involvement who underwent endoscopic examination, by analyzing anamnestic, clinical, endoscopic, and histological findings. Baseline data, including age, gastrointestinal symptoms at the time of diagnosis, autoimmune comorbidities, and HLA status, were collected for all patients. CD diagnosis was established based on international guidelines. Furthermore, we collected endoscopic and histological findings from both the ileum and colon, as well as from gastroscopy when available.
Results: We enrolled 23 BD patients, of which 20 (86%) were female. The median age at BD diagnosis was 37 years, occurring 3 years before the onset of intestinal symptoms. HLA B51 was present in 17 (74%) patients. A total of 7 patients (30%) were diagnosed with CD, with 4 of those diagnosed according to paediatric guidelines (biopsy-free approach). The most commonly reported symptoms were abdominal pain (19; 82.6%) and diarrhoea (12, 52.2%). Upon colonoscopy, undetermined colitis (7; 30.4%) was the most frequent finding, followed by unspecific ileitis (1; 4%), unspecific ileo-colitis (2; 9%), microscopic colitis (2; 9%), BD-like colitis (3; 13%), ulcerative colitis (1; 4%), and Crohn's disease (1; 4%). Only two patients were correctly classified as BD-related colitis as a first diagnosis. Upon reviewing the cases, all IBD diagnoses were ultimately classified as manifestations of BD. Although two colonoscopies appeared macroscopically normal, microscopic inflammation was discovered. Follow-up colonoscopies were performed in 13 pa-

tients undergoing immunosuppressive or biological therapy. While the macroscopic mucosa was normal, histological inflammation was observed in 9 (39%) patients in the colon and ileum. Oesophagus involvement characterized by erosion and/or ulcers was found in 4 (17.4%) patients.
Discussion and conclusion: Our study represents the largest cohort of gastrointestinal BD in the Western world. We have confirmed the possible association between CD and BD. BD ileocolitis and microscopic colitis were frequently observed; however, a majority of ileitis/colitis cases were initially misclassified and not recognized as manifestations of intestinal BD, indicating a need for a better understanding of this condition. Despite achieving endoscopic healing through several treatments, persistent histological inflammation, similar to that often observed in patients with IBD, was observed.

359. A CHALLENGING DIAGNOSIS

Coppola R.[1], Longobardi F.[2]
[1]Università degli Studi di Salerno; [2]Università degli studi della Campania Luigi Vanvitelli

Introduction: pyoderma gangrenosum is a noninfectious neutrophilic dermatosis. Clinically, it begins with sterile pustules that progress rapidly and turn into painful ulcers. The most frequently affected areas are the legs, but it can involve any other part of the body. There are several subtypes, but the most common is the ulcerative subtype. The age of onset is between 20 and 57 years and women are more affected than men. In 74% of cases it is associated with other diseases: IBD, haematological diseases, arthritis. In 26% of cases, it precedes the clinical onset of the systemic disease, the diagnosis of which generally occurs within the following two years.
Patients and methods: we report on a case of a young 30-year-old woman who arrived in hospital for asthenia, menometrorrhagia (already under estrogen-progestogen treatment), and recent appearance of rapidly evolving skin lesions (one week). Blood tests revealed the presence of microcytic anemia (Hb 6.2 g/dl, MCV 67 fL), as well as neutrophilic leukocytosis (WBC 153000, 11670 neutrophils), increased number of platelets (1058000) and a marked increase in inflammatory indexes (CRP 22 mg/dl, VES 92). Because of anemia, the patient received 2 blood transfusions.The physical examination documented the presence of skin lesions with raised borders of erythematous - purplish colour, strongly painful and ulcerated, with variable width and depth located at the level of the breast fold, axillary fold, intergluteal groove, anterior surface of the legs. We did the swab and biopsies on the ulcers. The skin swab was negative, this indicated for sterile ulcers. The histological report showed dense neutrophilic and lymphocytic infiltration, reactive neoangiogenesis, and fibrosis. Furthermore, a total body CT revealed the presence of a thickening of the colon. In the following days, therefore, we proceeded with the dosage of faecal calprotectin and ASCA (anti-Saccharomyces cerevisiae antibodies). Anyhow, in the suspicion of a vasculitis, the search for anti-neutrophil cytoplasmic antibodies (ANCA) of subtypes c and p was carried out. We found the positivity of the c-ANCA (6.4 U/ml) associated with negative ASCA and increased faecal calprotectin (1550 mg/kg; reference value < 50 mg/kg). The patient then performed a colonoscopy which showed edema, hyperemia and reduction of the *haustra* of the rectosigmoid tract, with slight thickening of the walls. The biopsy concluded for an active phase of inflammatory bowel disease (IBD).
Results: patient response after about a month of therapy with sulfadiazine and VAC therapy,was encouraging; there was a progressive improvement of the ulcers, with a reduction in the inflammation indexes. The patient started therapy with asacol and deltacortene for ulcerative colitis and is currently in follow-up.
Conclusions: the pathogenesis of pyoderma gangrenosum is undetermined. The differential diagnosis includes all other causes of skin ulceration as there are no definitive laboratory or histopathologic criteria. Associated pathologies may precede, coexist or follow the onset of PG. It is therefore essential to search for associated pathologies in order to reduce the time to diagnosis to less than 24 months.



360. DIAGNOSTIC DELAY IN DIVERTICULAR DISEASE: AN ITALIAN TERTIARY REFERRAL CENTRE STUDY

Abruzzese G.M.[1], Lenti M.V.[1], Santacroce G.[1], Alunno G.[1], Di Terlizzi F.[1], Frenna C.[1], Gentile A.[1], Latorre M.A.[1], Petrucci C.[1], Ruggeri D.[1], Soriano S.[1], Bianchi P.I.[2], Aronico N.[2], Mengoli C.[2], Miceli E.[2], De Silvestri A.[3], Corazza G.R.[1], Di Sabatino A.[1]
[1]Department of Internal Medicine and Medical Therapeutics, University of Pavia, Pavia, Italy; [2]First Department of Internal Medicine, San Matteo Hospital Foundation, Pavia, Italy; [3]Scientific Direction, Clinical Epidemiology and Biometric Unit, San Matteo Hospital Foundation, Pavia, Italy

Background: Diverticular disease is a spectrum of disorders including symptomatic uncomplicated diverticular disease (SUDD), acute or chronic diverticulitis and segmental colitis associated with diverticulosis (SCAD). While several studies on diagnostic delay in other gastrointestinal diseases such as celiac disease and autoimmune atrophic gastritis have been conducted, there are no data regarding diagnostic delay in SUDD. The first aim of our study was to investigate the overall, the patient-dependent and the physician-dependent diagnostic delay in patient with diverticular disease. The second aim was to define which were the factors that increase the diagnostic delay of SUDD.
Materials and methods: Data regarding 71 patients diagnosed and followed up between 2015 and 2021 for diverticular disease were retrospectively collected. The overall diagnostic delay was described as the time lapse occurring from the first symptoms indicative of diverticular disease and the diagnosis. Patient-dependent and physician-dependent delay were described as the time lapse within the first symptoms and the first medical examination and the time occurring between the first visit of physician and the diagnosis, respectively. The delay was obtained as a median. The cohort was divided into two groups, one including patients who have been diagnosed within 24 months from the symptom onset, the other one including patients with a diagnostic delay greater than 24 months. This cut-off equates to the 75° percentile of the delay. Univariate and multivariate analysis were used to study the risk factors for a delayed diagnosis.
Results: The median overall diagnostic delay was 7 months (IQR 0-15), while the patient and the physician-dependent delay were 3 months (IQR 0-15) and 1 month (IQR 1-6), respectively. Regarding the risk factors for a diagnostic delay greater than 24 months, age (p-value=0,03), a high level of education (p-value=0,08) and a previous misdiagnosis of irritable bowel syndrome (IBS) (p-value=0,01) were positively correlated. At univariate analysis, there were no significant differences between the two groups (< or > 24 month-delay) in terms of localization of diverticula, complications, hospitalization rate, recurrence and need of surgery in the follow-up. At multivariate analysis, a previous misdiagnosis (p-value=0,03) and a high level of education (p-value=0,04) were confirmed as risk factors for a delayed diagnosis.
Conclusions: Diverticular disease is burdened by a late diagnosis, especially in patients who initially received a misdiagnosis of IBS that easily mimics SUDD. A high level of education may be associated to a lower use of healthcare resources, thus prolonging the delay. Clinical and laboratory predictors of diverticular disease need to be ascertained.

361. THE DIAGNOSTIC ROLE OF BOWEL ULTRASOUND FOR DIVERTICULAR DISEASE IN PATIENTS WITH IBS-LIKE SYMPTOMS

Frenna C., Lenti M.V., Lepore F., Mengoli C., Palumbo I., Abruzzese G.M., Alunno G., Di Terlizzi F., Gentile A., Latorre M.A., Petrucci C., Ruggeri D., Santacroce G., Soriano S., Corazza G.R., Di Sabatino A.
Department of Internal Medicine and Medical Therapeutics, University of Pavia, Pavia, Italy

Background. Diverticular disease is characterised by abdominal symptoms associated with the presence of diverticula in the large bowel. The proteiform clinical picture may lead to diagnostic delay. In particular, differential diagnosis with irritable bowel syndrome (IBS) is often challenging. Bowel ultrasound (US) is a low cost, quick, non-invasive exam which can diagnose diverticular disease. This retrospective analysis focuses on the potential, diagnostic, role of bowel US for diverticular disease in patients with IBS-like symptoms.
Methods and patients. We have reviewed the clinical course of 92 patients with IBS-like symptoms according to the Rome IV criteria (i.e., abdominal pain, bloating, diarrhoea, constipation, mixed bowel habits), who underwent bowel US followed by either a colonoscopy or an abdominal computerized tomography (CT) confirming the presence of bowel diverticula. The study comprises patients diagnosed at a tertiary referral, gastroenterology outpatient clinic, in 2020-2022. Bowel US was performed by experienced physicians (>3 years of abdominal US training).
Results. Out of 92 patients, 33 (35,9%) had diverticular disease as detected by both US and colonoscopy or CT; 12 (13%) had bowel US suggestive of diverticular disease, not proven by colonoscopy or CT; 10 (10,9%) had negative US and a positive colonoscopy or CT; 37 (40,2%) had both negative US and colonoscopy or CT. Accordingly, bowel US in diverticular disease had a sensitivity of 76%, a specificity of 75%, and an overall diagnostic accuracy of 76%. There were no significant differences as regards the diagnostic accuracy depending on age (≤ or > 50 years) or IBS subtype.
Conclusions. Bowel US could certainly demonstrate diverticulosis in three fourth of the cases. Indeed, considering the setting, this may represent a useful first-line diagnostic test in patients with IBS-like symptoms, while CT scan or colonoscopy could be indicated in case of a negative US, but a high clinical suspicious which would go beyond the Rome IV diagnostic criteria. This approach could reduce the rate of diverticular disease misdiagnosis, thus allowing to set a proper follow-up. A long term, prospective study is needed to confirm this assumption.

362. PRIMARY INTESTINAL LYMPHOMAS: DESCRIPTION OF A MONOCENTRIC SERIES FROM AN ACADEMIC TERTIARY REFERRAL CENTER

Moltisanti G.C.[1], Aronico N.[2], Bianchi P.I.[2], Alunno G.[3], Santacroce G.[3], Fraticelli S.[4], De Silvestri A.[5], Lucioni M.[4], Paulli M.[4], Corazza G.R.[6], Lenti M.V.[3], Di Sabatino A.[3]
[1]Department of Internal Medicine and Medical Therapeutics, University of Pavia; First Department of Medicine, Fondazione IRCCS Policlinico San Matteo; [2]First Department of Medicine, Fondazione IRCCS Policlinico San Matteo; [3]Department of Internal Medicine and Medical Therapeutics, University of Pavia; First Department of Medicine, Fondazione IRCCS Policlinico San Matteo; [4]Department of Molecular Medicine, University of Pavia; Unit of Anatomic Pathology, Fondazione IRCCS Policlinico San Matteo; [5]Clinical Epidemiology and Biometry Service, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [6]Department of Internal Medicine and Medical Therapeutics, University of Pavia

Background and aim: The gastrointestinal (GI) tract is the most common extra-nodal site involved in non-Hodgkin lymphomas (NHL). Primary GI NHL represent about 10-15% of all NHL and 30-40% of extra-nodal NHL. Among them, B-cell lymphomas are the most frequently observed, while T-cell lymphomas are less frequent, especially those with a primary bowel involvement. The aim of our study was to depict the clinical-pathological profile of a series of patients affected by primary intestinal B-cell lymphomas (PIBCL), comparing it to a series of patients affected by primary intestinal T-cell lymphomas (PITCL).
Material and methods: We retrospectively collected clinical and histopathological data of patients affected by PIBCL or by PITCL involving the small bowel, diagnosed at our centre in 2001-2021. We included a series of 226 cases of GI lymphomas. Among them, 48 were primary intestinal lymphomas, of which 20 were PIBCL and 28 were PITCL. Comparison of means or proportions were performed when appropriate. For PITCL only, a multivariate analysis for factors affecting survival was fitted.
Results: Among the group of B-cell lymphomas, we identified 20 patients with PIBCL (median age 58.5 years; 12 males), of which 11 were localized in the colon, 6 in the ileum, 2 in the jejunum, 3 in the duodenum, and 2 were multifocal. Regarding histotype, we found 6 Follicular Lymphomas, 8 Diffuse Large B-Cell Lymphomas, 4 Marginal Zone Lymphomas and 2 Mantle Lymphomas. Instead, considering the group of T-cell lymphomas, we identified 28 patients with PITCL (median age 59 years; 16 males), of which 17 enteropathy-associated T-cell lymphomas (EATL), 5 monomorphic epitheliotropic T-cell lymphomas (MEITL), 3 indolent T-cell lymphoproliferative disorder of the gastrointestinal tract (ITCLDGT) and 3 intestinal T-cell lymphoma-not otherwise specified (ITCL-NOS); clinical stage according to Lugano was I or II in 40% of cases and IV (disseminated) in 36% and coeliac disease (CD) was diagnosed in around 70% of the cases. B-symptoms were present in 15% of patients with PIBCL at diagnosis and GI complications (perforation, sub-occlusion and occlusion) occurred in 30%, while in PITCL more than 70% of patients presented with B-symptoms (p<0.0001) and around 35% showed GI complications (perforation, haemorrhage, fistula or obstruction; p=0.30). Serum LDH was slightly elevated in 30% of patients with PIBCL and in 89% of patients with PITCL (p=0.03), while serum β2-microglobulin was elevated in 100% of the patients with PITCL and only in 25% of PIBCL (p=0.01). As concerning therapy, the majority (12) of patients with PIBCL was treated with R-CHOP scheme, while the majority (22) of patients with PITCL were treated with either CHOP or CHOEP schemes. In the group of PIBCL, the mortality rate was 14%, while among the group of PITCL only 2 patients are still alive and the mortality rate is over 90% (p=0.01). In PIBCL, at diagnosis, increased neutrophils (p= 0.01), platelets (p= 0.003), beta2-microglobulin (p=0.01) and LDH (p=0.03) were significantly associated with treatment non-response. As concerning the PITCL, peripheral lymphocytosis, the absence of a previous diagnosis of CD, advanced Lugano clinical stage, and the histological subtype PITCL-NOS were significantly associated with poor survival at multivariate analysis.
Conclusions: We herein found some distinctive features that are associated with either poor survival or poor treatment response in PITCL or PIBCL, respectively. These features may be helpful in stratifying disease severity in this setting. Also, we observed a significant difference regarding mortality rate. PITCL is burdened by a high mortality rate as compared to PIBCL. In particular, in the group of PIBCL we observed an indolent clinical course in 8 patients which presented slight symptoms at diagnosis and a positive outcome and underwent annual clinical (LDH, β2-microglobulin) and radiological (TC/PET) follow-up. Our data support the need for timely diagnosis and treatment of these conditions and also the importance of a radiological and clinical follow-up.

363. EARLY-ONSET SMALL BOWEL ADENOCARCINOMA (EO-SBA) IS MORE FREQUENTLY ASSOCIATED WITH A PREDISPOSING CONDITION COMPARED TO LATE-ONSET SMALL BOWEL ADENOCARCINOMA (LO-SBA): AN INTERNATIONAL MULTICENTRIC STUDY

Latorre MA.[1], Lenti MV.[1], Arpa G.[2], Guerini C.[3], Quaquarini E.[4], Grillo F.[5], Fassan M.[6], Furlan D. [7], Graham RP.[8], Casadei Gardini A.[9], Antoci F.[10], Travaglino E. [11], Ferrante M. [12], Moens A.[12], De Hertogh G.[13], Vanoli A.[10], Corazza GR.[1], Di Sabatino A.[1]
[1]First Department of Internal Medicine, San Matteo Hospital Foundation, University of Pavia, 27100 Pavia, Italy; [2]Department of Molecular Medicine, Unit of Anatomic Pathology, University of Pavia, 27100; Unit of Anatomic Pathology, ICS Maugeri-IRCCS SpA SB, 27100 Pavia, Italy; [3]Department of Molecular Medicine, Unit of Anatomic Pathology, University of Pavia, 27100 Pavia, Italy; [4]Medical Oncology Unit, ICS Maugeri-IRCCS SpA SB, 27100 Pavia, Italy; [5]Pathology Unit, Department of Surgical and Diagnostic Sciences, University of Genoa and Ospedale Policlinico San Martino University Hospital, 16132 Genoa, Italy; [6]Surgical Pathology and Cytopathology Unit, Department of Medicine, DIMED, University of Padua, 35122 Padua, Italy; Veneto Institute of Oncology, IOV-IRCCS, 35128 Padua, Italy; [7]Pathology Unit, Department of Medicine and Surgery, University of Insubria, 21100 Varese, Italy; [8]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota 55902, USA; [9]Department of Oncology, Vita-Salute San Raffaele University, IRCCS San Raffaele Scientific Institute Hospital, 20132 Milan, Italy; [10]Department of Molecular Medicine, Unit of Anatomic Pathology, University of Pavia, 27100 Pavia, Italy; Unit of Anatomic Pathology, Fondazione IRCCS San Matteo Hospital, 27100 Pavia,

Italy; [11]Unit of Anatomic Pathology, Fondazione IRCCS San Matteo Hospital, 27100 Pavia, Italy; [12]Department of Gastroenterology and Hepatology, University Hospitals, KU Leuven, 3000 Leuven, Belgium; [13]Department of Pathology, KU Leuven University Hospitals, 3000 Leuven, Belgium

Background and objectives: The incidence of early-onset gastrointestinal cancers (i.e., age at diagnosis <50 years) is increasing and most of them are sporadic. However, data on early-onset small bowel adenocarcinoma (EO-SBA) are lacking. We aimed to investigate EO-SBA clinico-pathologic features.
Methods: A retrospective study was conducted on an international multicentric cohort of 208 SBA patients. EO-SBAs (i.e., SBAs with age at diagnosis <50 years) were compared to late-onset SBAs (i.e., age at diagnosis ≥50 years) in terms of predisposing conditions (hereditary syndromes and immune-mediated disorders), other clinico-pathological features, and cancer-specific survival. Mismatch repair status was assessed by immunohistochemistry.
Results: 41 EO-SBAs (mean age: 40 years; 20 males) and 167 LO-SBAs (mean age: 66.9 years, 109 males) were identified. A predisposing condition was significantly more common in EO-SBAs (76%) compared to LO-SBAs (52%, p=0.008). Association with coeliac disease, Crohn's disease, familial adenomatous polyposis and Lynch syndrome was reported in 13 (32%), 13 (32%), 2 (5%), and 3 (7%) EO-SBAs, and in 28 (17%), 45 (27%), 0 (0%), 14 (8%) LO-SBAs, respectively. Among such predisposing conditions, only coeliac disease proved to be significantly more frequent in EO-SBAs compared to LO-SBAs (p=0.047). No significant difference was found between the two groups for remaining clinico-pathologic features, cancer-specific survival, or mismatch repair status.
Conclusions: When compared to LO-SBAs, EO-SBAs showed a higher rate of cases associated with predisposing conditions, and the difference was mainly due to the association of EO-SBAs with coeliac disease. The present study emphasizes the importance of assessing potential predisposing conditions in all EO-SBA patients.
Bibliography: Ben-Aharon I, van Laarhoven HWM, Fontana E, Obermannova R, Nilsson M, Lordick F. Early-Onset Cancer in the Gastrointestinal Tract Is on the Rise-Evidence and Implications. Cancer Discov. 2023 Mar 1;13(3):538-551. doi: 10.1158/2159-8290.CD-22-1038. PMID: 36757194.

364. CLINICAL FEATURES OF ADULT COELIAC DISEASE ACCORDING TO THE AGE AT DIAGNOSIS: AN ITALIAN MULTICENTRIC STUDY

Latorre MA.[1], Bianchi PI.[2], Lenti MV.[1], Aronico N.[2], Petrucci C.[1], D'Agate CC.[3], Neri M. [4], Volta U.[5], Mumolo MG.[6], Astegiano M.[7], Calabrò AS.[8], Zingone F.[9], Latella G.[10], Di Sario A.[11], Carroccio A.[12], Ciacci C.[13], Luzza F.[14], Bagnato C.[15], Fantini M.C.[16], Elli L.[17], Cammarota G.[18], Gasbarrini A.[18], Portincasa P.[19], Quatraccioni C.[11], Iannelli C.[14], Vecchione N.[13], Broglio G. [1], Ianiro G.[18], Marsilio I. [9], Bibbò S.[18], Marinoni B.[17], Tomaselli D.[15], Abenavoli L.[14], Pilia R.[20], Santacroce G.[1], Lynch E.[8], Carrieri A.[19], Mansueto P. [12], Gabba M. [1], Alunno G. [1], Rossi C.[11], Onnis F.[16], Efthymakis K.[4], Cesaro N.[8], Vernero M.[7], Baiano Svizzero F. [6], Silano M. [21], Klersy C.[211], Corazza GR.[20], Di Sabatino A. [1]
[1]Department of Internal Medicine and Medical Therapeutics, University of Pavia, Pavia, Italy; First Department of Medicine, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [2]First Department of Medicine, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [3]University Hospital "G. Rodolico", Department of Gastroenterology and Endoscopy, Catania, Italy; [4]Department of Medicine and Ageing Sciences, 'G. d'Annunzio' University of Chieti-Pescara, Chieti, Italy; [5]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy; [6]Department of General Surgery and Gastroenterology, Pisa University Hospital, Pisa, Italy; [7]Città della Salute e della Scienza di Torino-Molinette Hospital, Turin, Italy; [8]Department of Biomedical, Experimental and Clinical Sciences "Mario Serio" University of Florence, Florence, Italy; [9]Department of Surgery, Oncology and Gastroenterology (DiSCOG), Gastroenterology Unit, University of Padova, Padova, Italy; [10]Gastroenterology Unit, University of L'Aquila, L'Aquila, Italy; [11]Department of Gastroenterology and Transplantation, Polytechnic Marche University, Ancona, Italy; [12]Internal Medicine Unit, "V. Cervello Hospital", University of Palermo, Palermo, Italy; [13]Department of Medicine and Surgery, Gastroenterology Unit, University of Salerno, Salerno, Italy; [14]Department of Health Sciences, Magna Græcia University, Catanzaro, Italy; [15]Madonna delle Grazie Hospital, Matera, Italy; [16]Department of Medical Science and Public Health, University of Cagliari, Cagliari, Italy; [17]Gastroenterology and Endoscopy Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy; [18]Digestive Disease Center, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica Del Sacro Cuore, Rome, Italy; [19]Department of Biomedical Sciences & Human Oncology, University of Bari Medical School, Clinica Medica "A. Murri", Bari, Italy; [20]Department of Internal Medicine and Medical Therapeutics, University of Pavia, Pavia, Italy; [21]Istituto Superiore di Sanità; [22]Clinical Epidemiology and Biometry Service, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Background: Heterogeneity in clinical presentation, according to the age at diagnosis, has been reported in coeliac disease (CD). Classical symptoms of CD are more frequent in early coeliac disease, whereas an atypical presentation occurs more often in late coeliac disease.
Objective: This study aimed to compare clinical characteristics of presentation in adult CD patients diagnosed at the age of 18-33 (early (E)) versus 50-65 (late (L)) versus >65 (aged (A)) years.
Methods: A total of 3094 CD adult patients from a 19 referral Italian CD centre database were included and divided in groups according to the age at diagnosis (early vs late vs aged). Relevant data comprised gender, method of diagnosis, clinical presentation, gastrointestinal (GI) symptoms, associated autoimmune diseases, dietary compliance after diagnosis. Statistical analyses were performed using the chi-square test.
Results: According to clinical presentation, silent presentation was more frequent in L-CD compared to E-CD (12 % vs 1 %; p< 0,05). Regarding GI symptoms, abdominal pain and bloating occurred more frequently in the early group compared to the aged group (47 % vs. 31 %, p <0,05; 36 % vs 21 %, p<0,05, respectively) whereas reflux occurred more frequently in the late group compared to the early group (16 % vs. 4 %, p<0,05). Weight loss was more frequent in the aged group compared to the early group (54 % vs 24 %, p<0,05). Concerning associated autoimmune diseases, multiple associated autoimmune disorders occurred more often in the late group (20% vs. 9%, p<0,05). Osteoporosis was more frequent in A-CD compared to E-CD (36% vs 6%, p<0,05). There were no other significant differences in symptoms, anaemia status, nor in dietary compliance from this multicentric database.
Conclusions: There are some significant differences in clinical presentation of CD according to the age at diagnosis. Some common symptoms and signs in patients older than 50-years, as oesophageal reflux, weight loss, osteoporosis and multiple autoimmune diseases, deserve an intelligent differential diagnosis, including CD not secondarily.
Bibliography:

365. VALPROIC ACID: MOOD STABILIZATION OR PANCREATIC DAMAGE?

Finelli M., Palumbo F., Schettini F., Di Sisto A.
Università degli Studi della Campania "Luigi Vanvitelli"

A 42-year-old man was admitted in emergency room with abdominal pain fever and vomiting. In remote pathological history he had hypertension, type II diabetes mellitus and schizophrenia. He lived in a psychiatric institute and he did drug therapy with Valproic Acid 500 mg tid, Aripiprazole 15 mg bid and Alprazolam 1 mg tid. He smoked until three monts ago, he didn't drink or use drugs. On admission he was hemodynamically stable, eupnoic with stable vital parameters, PA 130/80 mmHg, HR 95 bpm, SpO2 97% in AA, body temperature of 38°C. He was awake, oriented in time and space. On objective examination he presented a tense and painful abdomen in epigastrium on superficial palpation with bar irradiation; the lung examination detected a reduced vesicular murmur more at the bases bilaterally; a regular cardiac examination. Laboratory studies highlighted: WBC 4.8 *10^3 u/L Hb 8.2 mg/dl with MCV 91 fL and MCH 30.6 pg PLT 142 *10^3 u/L, amylase 193 mg/dl and lipase 254 mg/dl, which peaked at 471 mg/dl during hospitalization, acute renal failure of pre-renal type with urea of 230 mg/dl and creatinine of 5.42 mg/dl (eGFR 13 ml/min/1.73 m2 according to CKD-EPI), sideremia 17 mg/dl and TS of 7%, ferritin 932 mg/dl, PCR 31.9 mg/dl and PCT 6.13 mg/dl. Hematochemical examinations oriented us toward the diagnosis of acute pancreatitis. Supportive therapy was set with: Ringer's lactate 500 ml tid, light feeding, and his psichiatric therapy but Valproic Acid was discontinued on the hypothesis that it might be the etiologic agent. He practiced an abdominal CT scan without contrast medium, due to the renal insufficiency, which showed pancreas increased in volume with thickening of peripancreatic adipose tissue, peritoneal effusion in the periepatic region, perigastro-pancreatic and in the pelvic excavation, distended cholecyst with inhomogeneous content and presence of bilateral pleural effusion. To exclude the etiology of a biliary lithiasis he practiced Cholangio MRI which was negative. We observed a gradual clinical and laboratoristic improvement and after discontinuation of Valproic Acid normalization of amylase and lipase

was seen. At the follow-up abdominal CT with cm what had been seen previously was confirmed and a partial thrombosis of the splenic vein was evident for which he began anticoagulant therapy with Fondaparinux 7.5 mg. We also investigated normochromic normocytic anemia. He performed EGDS which was negative for bleeding sources and negative peripheral smear for immature or abnormal cells. Improvement in hemoglobin values after iron replenishment was observed.
Discussion: Acute pancreatitis is an acute inflammatory process of the pancreas. There is a breakdown in the synthesis-secretion coupling of pancreatic digestive enzymes; synthesis continues while there is a blockade of secretion. As a result, digestive enzymes leak out of acinar to the interstitial space and then enter the systemic circulation. Acute pancreatitis should be suspected in patients with severe acute upper abdominal pain. The diagnosis requires the presence of two of the following three criteria: acute onset of severe epigastricpain often radiating to the back, elevation in serum lipase or amylase to three times or greater than the upper limit of normal, and characteristic findings on imaging such as the presence of focal or diffuse enlargement of the pancreas (contrast-enhanced TC, RMN, or transabdominal ultrasonography). Serum lipase has a sensitivity for acute pancreatitis ranging from 82 to 100 percent. Lipase elevations occur earlier and last longer as compared with elevations in amylase and are especially useful in patients who present >24 hours after the onset of pain. The main etiological agents are biliary lithiasis, alcholol and drugs. Among the drugs there is the Valproic Acid. The first case of valproate-associated acute pancreatitis was reported in 1979. The mechanism is not clearly understood. The proposed mechanisms are a direct toxic effect of free radicals on the pancreatic tissue and a depletion of superoxide dismutase, catalase, and glutathione peroxidase. Management of the drug-induced pancreatitis involves withdrawal of the offending drug and supportive care to the patient. The development of pancreatitis has also been reported without association between dosage and serum levels of valproate. The dosage given to the patient was well within the maximum tolerated dose range. Similarly, the serum sodium valproate level on admission was 39.3 μg/ml, which was within the normal therapeutic range (50–100 μg/ml). A relatively commonvascular complication of pancreatitis is splenic vein thrombosis due to intimal inflammation leading to platelet aggregation and thrombosis and may present as a result of its proximity to the dorsal pancreatic surface. The use of an anticoagulation for three months, if there aren't permanent trombosis risk factors or a trombus extention into mesenteric veins, is associated with lower risk of recurrence and improved recanalization. Weighing the risks and benefits based on his psychiatric illness we preferred to discontinue the valproic acid and we observed full recovery of the patient.

366. DIAGNOSTIC CLUSTERS OF AUTOIMMUNE ATROPHIC GASTRITIS

Petrucci C.[1], Pitotti L.[1], Gentile A.[1], Coppola L.[1], Alunno G.[1], Brondino N.[2], Miceli E.[1], Lenti M.V.[1], Corazza G.R.[1], Di Sabatino A.[1]
[1]Department of Internal Medicine, San Matteo Hospital Foundation, University of Pavia, Pavia, Italy; [2]Department of Brain and Behavioral Science, University of Pavia, Pavia, Italy

Background and aim: autoimmune atrophic gastritis (AAG) is a chronic inflammatory disease causing progressive atrophy of fondus and corpus of the mucosa of stomach which leading deficit of B12 vitamin and iron. AAG is a systemic disorder, often underhand. Clinic presentation is heterogeneous causing challenge diagnosis. Several risk groups of patients were described for AAG. The aim of our study was to identify clinical clusters leading to diagnosis, in order to identify a useful tool for early diagnosis of AAG and prevention of complications.
Methods: data were retrospectively collected. All consecutive AAG adults patients diagnosed in 2010-2022 at the gastroenterology outpatient clinic of IRCCS Policlinico San Matteo Foundation were enrolled. We collected and analyzed demographic (age, gender, comorbidities) and laboratory data (Gastrin values, normal range < 108 pg/mL), histological stage at diagnosis (1=mild atrophy, 2=moderate atrophy, 3=severe atrophy, 4A=dysplasia, 4B=neuroendocrine tumors) and clinical features leading to diagnosis. Kruskal- Wallis test and Chi-square test were computed.
Results: overall 408 patients were included (median age 59±14 yrs). We identified 7 clinical clusters which led to diagnosis: histological evidence in patients affected by gastrointestinal symptoms (158 patients, median age 62 ±12 yrs)- cluster 1, hematological alterations (174 patients, median age 61±15 yrs)- cluster 2, autoimmune screening in patients affected by another autoimmune disease (43 patients, median age 49 ±13yrs)-cluster 3, family history of AAG (10 patients, median age 51±7 yrs)-cluster 4, neurological symptoms (11 patients, median age 56±14 yrs)- cluster 5, infertility or obstetric complications (7 patients, median age 47±13 yrs)-cluster 6, persistent anemia in patients affected by coeliac disease in gluten free diet (GFD) (5 patients, median age 71±15 yrs)- cluster 7. We found that age were significant different among different clusters (Kruskall-Wallis= 25.985 p<0.001), on particular cluster 3 was younger than cluster 1 and cluster 2. There was no difference between gender (Chi- square=6.75, p=0.34), gastrin levels (Kruskall-Wallis= 2.71, p=0.84) and histological stage at diagnosis, however we found different expression of stages. Focusing on complications at diagnosis, stage 4A was found in 5 patients of cluster 1, 1 patient of cluster 2, cluster 3 and cluster 6, while 4B was found in 5 patients of cluster 1, 2 patients of cluster 3, 1 patient of clusters 2 and 5.
Conclusion: we found 7 different diagnostic clusters for AAG. Different age at diagnosis may reflect the natural history of the disease: infertility and obstetric complications allowed to identify younger female patients, on the contrary persistent anemia in celiac patients in gluten free diet has been identified as the most muddled clue, as AAG was diagnosed in older patients in this cluster. Overall median age was 59 yrs, highlighting that AAG affects not only elderly patients. The seven described clinical clusters are a useful tool to early identification of AAG patients and a greater awareness should be raised among clinicians in order to improve diagnosis and prevent complications.

Table 1. Diagnostic clusters.

Diagnostic clusters	Age (Median)	F/M ratio	Early stage	Florid stage	End stage	Complicated stage	Total
1 Histological findings	62	1.5	27 (16.5%)	26 (16.5%)	95 (60.5%)	10 (6.5%)	158
2 Haematological complications	61	1.9	29 (16.7%)	27 (15.5%)	116 (67%)	2 (1.1%)	174
3 Autoimmune screening	49	3.3	7 (16.2%)	5 (11.6%)	30 (69.7%)	3 (6.9%)	43
4 Family history	51	2.2	2 (10%)	3 (30%)	5 (50%)	0 (0%)	10
5 Neurological symptoms	56	5.5	1 (9.09%)	1 (9.09%)	8 (72.7%)	1 (9.09%)	11
6 Obstetric ginecological complications	47	//	0 (0%)	1 (14%)	5 (71%)	1 (14%)	7
7 Persistent anemia in coeliac patients in GFD	71	3.5	0 (0%)	1 (20%)	4 (80%)	0 (0%)	5

367. IMMUNOHISTOCHEMICAL CHARACTERIZATION OF INTRAEPITHELIAL LYMPHOCYTES INFILTRATING THE OXYNTIC MUCOSA OF POTENTIAL AND OVERT AUTOIMMUNE ATROPHIC GASTRITIS

Soriano S.[1], Lenti M.V.[1], Bianchi P. I.[1], Aronico N.[1], Mengoli C.[1], Miceli E.[1], Gentile A.[1], Di Terlizzi F.[1], Santacroce G.[1], Pasini A.[1], Coppola L.[1], De Lisi G.[2], Guerini C.[2], Vanoli A.[2], De Silvestri A.[3], Klersy C.[3], Paulli M.[2], Corazza G. R.[1], Di Sabatino A.[1]
[1]Department of Internal Medicine and Medical Therapeutics, University of Pavia, Italy; [2]Department of Molecular Medicine, Unit of Anatomic Pathology, University of Pavia, Italy; [3]Unit of Clinical Epidemiology and Biometry, Istituto di Ricovero e Cura a Carrattere Scientifico (IRCCS) Fondazione Policlinico San Matteo, University of Pavia, Italy

Background: potential autoimmune gastritis (AIG) is defined by anti-parietal cell antibody (PCA) positivity in the absence of gastric atrophy. At present, there are no specific clinical, endoscopic and histopathologic features of very early, pre-atrophic AIG. We have recently described that a small group of patients with potential AIG (n=9) had increased deep CD3+ intraepithelial lymphocytes (IEL) infiltrating the oxyntic mucosa (>7/100 epithelial cells), compared to both healthy controls and active H. pylori gastritis. Nonetheless no difference was found in deep CD3+ IEL infiltration among potential, mild and severe AIG. The aim of this study was to confirm and validate these results in light of a larger sample size of potential AIG.
Methods: this was a single-centre study (Fondazione IRCCS Policlinico San Matteo, University of Pavia). The new potential AIG patients (n=9) were prospectively enrolled from September 2022 to May 2023 at the Department of

Internal Medicine, in a gastroenterology outpatient clinic dedicated to the diagnosis and treatment of AIG. The inclusion criteria were serum PCA positivity in the absence of gastric atrophy. The deep and superficial IEL CD3+ infiltration of the oxyntic mucosa was assessed at the time of enrollment through immunohistochemistry. CD3+ IEL were counted in 10 series of 100 contiguous gastric epithelial cells and reported as the mean number of IEL per 100 epithelial cells. IEL infiltrating the surface foveolar epithelium were considered superficial IEL, while the ones infiltrating the epithelium of oxyntic glands were reported as deep IEL. The potential AIG group (n=18, median age 53 years, 10 females) was thus compared with the following control groups: mild AIG (n=22, median age 65, 14 females), severe AIG (n=21, median age 61 years, 12 females), H. pylori gastritis (n=15, median age 50 years, 10 females), active coeliac disease (n=15, median age 45 years, 9 females), Hashimoto's thyroiditis (n=9, median age 55 years, 6 females), healthy controls (n=15, median age 56 years, 12 females). Deep and superficial CD3+ IEL were compared among all groups by means of Kruskall Wallis Test. The CD3+ cut-off point discriminating AIG patients from the other control groups was calculated by means of receiver operating characteristics (ROC) curves.
Results: according to our recent work, deep CD3+ IEL mean count in potential AIG (mean 8.5, SD 3.6) was significantly higher ($p<0.001$) than HC (mean 4.5, SD 1.1) and H. pylori gastritis (mean 4.7, SD 2.4), while no difference was found in deep CD3+ IEL infiltration among potential, mild AIG (mean 10.3, SD 4.5) severe AIG (mean 11.1, SD 3.2), Hashimoto's thyroiditis (mean 7.4, SD 2.3) and active coeliac disease (mean 8.6, SD 6.1). Furthermore, the deep CD3+ IEL cut-off point of 7/100 epithelial cells was confirmed as a discriminating value of any stage or severity of AIG.
Conclusions: to date, AIG is burdened by a significant diagnostic delay, mostly due to its diversified manifestations. Haematological, neuroendrocrinological and oncological complications of AIG, potentially irreversible, would be prevented by a reliable case finding strategy, in order to identify patients with AIG in its pre-atrophic stage. This study validates our previous work, and provides a better understanding of the immunohistochemical features of potential AIG. Our results suggest that increased deep CD3+ infiltration of the oxyntic mucosa in PCA serum positive patients could represent a marker of potential AIG. A better characterization of AIG histopathology and further prospective studies with a larger sample size are required.

368. EXTENSIVE SCREENING STRATEGY VS CASE FINDING STRATEGY IN AUTOIMMUNE ATROPHIC GASTRITIS

Coppola L.[1], Gentile A.[1], Pitotti L.[1], Petrucci C.[1], Alunno G.[1], Brondino N.[2], Miceli E.[1], Lenti MV.[1], Corazza GR.[1], Di Sabatino A.[1]
[1]First Department of Internal Medicine, San Matteo Hospital Foundation, University of Pavia, Pavia, Italy; [2]Department of Brain and Behavioral Scince, University of Pavia, Pavia, Italy

Background and Aim: Autoimmune gastritis (AAG) is an increasingly prevalent, organ-specific, immune-mediated disorder characterized by the destruction of gastric parietal cells, leading to the loss of intrinsic factor and reduced acid output. These alterations result in malabsorption of iron, vitamin B12 (pernicious anaemia) and other micronutrients. The diagnosis of AAG is made histologically through endoscopic biopsy, according to the updated Sydney System criteria. Serologic testing for anti-parietal celle autoantibodies (PCA) may help to make the diagnosis. There are few data about the prevalence of AAG. The aim of this study was to define the prevalence of AAG in gastroenterology outpatient population.
Material and Methods: We have enrolled 660 consecutive patients referred to two outpatient clinics of a tertiary referral gastroenterology clinic. All patients were tested for PCA by using two different approaches. In the extensive screening strategy, PCA were tested in all cases, while in the case-finding strategy PCA were tested only in patients with symptoms or laboratory tests alterations suggestive for AAG (i.e., anaemia, GI symptoms, autoimmune comorbidities, family history, neurological symptoms, infertility). PCA positive patients underwent upper endoscopy with biopsies for AAG confirmation. Patients with active *H. pylori* infection were excluded. All patients gave informed consent.
Results: The population of the extensive screening strategy consisted of 414 patients (F:M ratio 2:1), 31 of them had AAG (7.5%). Of these, 14 patients had a potential AAG with a female predominance (F:M ratio 2.5:1), while 17 patients had an overt AAG, with no gender predominance. The mean age of the patients was 55.1 (+ 15.5) years in the potential AAG group and 59.3 (+13.3) years in the overt AGG group. Altogether, 15 patients (50%) with AAG had at least an autoimmune comorbidity, mainly autoimmune thyroid disease. The most common diagnostic clusters were autoimmune comorbidity and anaemia. The population of the case finding strategy consisted of 246 patients (F:M ratio 3:1). Additionally, 39 patients (16%) had AAG (2 pontential and 37 overt AAG). The mean age of patients with overt disease was 60.1 (+15,8) years with higher prevalence of the female gender (F:M 2.7:1). Moreover 22 patients (57%) had at least an autoimmune comorbidity, mainly autoimmune thyroid disease. The most common diagnostic clusters were GI symptoms and anaemia. Potential AAG patients of both groups had normal gastrin and chromogranin levels, but all having low levels of vitamin B12; two of them evolved into overt AAG at the time of the last follow-up.
Conclusions: In the contest of the extensive screening strategy the prevalence of overt AAG is about 4% in agreement with the findings of our previous studies. Instead the prevalence of overt AAG in the case finding strategy is 15%, pointing out the importance to search this disease in gastroenterological patients with specific suggestive clinical manifestations (ie the so-called diagnostic). At last patients with potential AAG were younger and should be monitored over time because they evolve into overt AAG.

369. SMALL BOWEL CARCINOMAS COMPLICATING COELIAC DISEASE DESPITE MUCOSAL HEALING: A CASE SERIES FROM THE SMALL BOWEL CANCER ITALIAN CONSORTIUM

Aronico N.[1], Bianchi P.I.[1], Vanoli A.[2], Lenti MV.[3], Guerini C.[2], Arpa G.[4], Quaquarini E.[5], Grillo F.[6], Nesi G.[7], Furlan D.[8], Latella G.[9], Sessa F.[8], Mescoli C.[10], Rugge M.[10], Ferrero S.[11], Macciomei M.C.[12], Santini D.[13], Volta U.[14], De Giorgio R.[15], Caio G.[15], Calabrò A.[16], Ciacci C.[17], D'Armiento M.[18], Villanacci V.[19], Cannizzaro R.[20], Canzonieri V.[21], Florena A.M.[22], Ciardi A.[23], Elli L.[24], Vecchi M.[24], Zingone F.[25], Reggiani Bonetti L.[26], Astegiano M.[27], Sandri G.[27], Silano M.[26], Usai P.[30], Perfetti V.[31], Giannone A.G.[22], Barresi V.[32], Ciccocioppo R.[33], Corazza G.R.[3], Di Sabatino A.[3]
[1]First Department of Medicine, San Matteo Hospital Foundation, Pavia, Lombardy, Italy; [2]University of Pavia, Anatomic Pathology Unit, Department of Molecular Medicine, San Matteo Hospital Foundation, 27100 Pavia, Italy; [3]University of Pavia, First Department of Medicine, San Matteo Hospital Foundation, Pavia, Lombardy, Italy; [14]Anatomic Pathology Unit, Department of Molecular Medicine, San Matteo Hospital Foundation, University of Pavia, 27100 Pavia, Italy; [5]Medical Oncology Unit, IRCCS ICS Maugeri and Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy; [6]Pathology Unit, Department of Surgical and Diagnostic Sciences, University of Genoa and Ospedale Policlinico San Martino University Hospital, Genoa, Italy; [7]Division of Pathological Anatomy, Department of Surgery and Translational Medicine, University of Florence, Florence, Italy; [8]Pathology Unit, Department of Medicine and Surgery, University of Insubria, Varese, Italy; [9]Gastroenterology Unit, Department of Life and Environmental Sciences, University of L'Aquila, L'Aquila, Italy; [10]Pathology Unit, Department of Medicine, University of Padua, Padua, Italy; [11]Division of Pathology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy; [12]Pathology Unit, San Camillo-Forlanini Hospital, Rome, Italy; [13]Department of Experimental, Diagnostic and Specialty Medicine (DIMES), Institute of Oncology and Transplant Pathology, St. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy; [14]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy; [15]Department of Morphology, Surgery and Experimental Medicine, University of Ferrara, Ferrara, Italy; [16]Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence, Italy; [17]Department of Medicine and Surgery, University of Salerno, Salerno, Italy; [18]Public Health Department, Federico II University of Naples, Naples, Italy; [19]Institute of Pathology, Spedali Civili Hospital, Brescia, Italy; [20]Department of Gastroenterology, Centro di Riferimento Oncologico (CRO) di Aviano IRCCS, Aviano, Italy; [21]Pathology Unit, Centro di Riferimento Oncologico (CRO) di Aviano IRCCS, Aviano, Italy and Department of Medical, Surgical and Health Sciences, University of Trieste, Trieste, Italy; [22]Pathologic Anatomy Unit, Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, University of Palermo, Palermo, Italy; [23]Department of Radiological, Oncological, Pathological Sciences, Umberto I Hospital, La Sapienza University, Rome, Italy; [24]Gastroenterology and Endoscopy Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [25]Gastroenterology Section, Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy; [26]Section of Pathology, Department of Diagnostic Medicine and Public Health, University of Modena and Reggio Emilia,

Modena, Italy; [27]General and Specialistic Surgery, Città della Salute e della Scienza-Molinette Hospital, Turin, Italy; [28]Clinical Nutrition Unit, Sant'Eugenio Hospital, Rome, Italy; [29]Unit of Human Nutrition and Health, Istituto Superiore di Sanità, Rome, Italy; [30]Department of Internal Medicine, University of Cagliari, Cagliari, Italy; [31]Internal Medicine Unit, S.S. Annunziata Hospital, ASST-Pavia, Varzi, Italy; [32]Section of Anatomical Pathology, Department of Diagnostics and Public Health, University and Hospital Trust of Verona, Verona, Italy; [33]Gastroenterology Unit, Department of Medicine, AOUI Policlinico G.B. Rossi, University of Verona, Verona, Italy

Background and aim: Small bowel carcinoma (SBC) is an uncommon neoplasia which is 14-fold more frequent in coeliac disease (CD) than in the general population. In comparison to colorectal carcinoma, SBC diagnosis remains challenging and its prognosis worse. A recent epidemiologic study found that the risk of SBC persists for up to 10 years in CD and seems to be correlated with the lack of mucosal healing (Gastroenterology 2020;159: 1686–1694).
Material and methods: Cases of non-familial non-ampullary SBCs associated with CD (CD-SBCs) were retrospectively collected through the Small Bowel Cancer Italian Consortium; we excluded from the present investigation SBC cases diagnosed within the first year from the diagnosis of CD and those occurring in individuals with poor compliance to a gluten-free diet (GFD).
Results: Thirteen SBC cases in CD patients (6 males, 7 females) who were strictly adherent to a GFD were found, with a median interval between CD and SBC diagnosis of 5 years. The median age at CD diagnosis was 52 years, approximately 20 years more than the general median age at CD diagnosis, while the median age at SBC diagnosis was 60 years. Although none of such patients suffered from a *bona fide* refractory CD, most patients (8 out of 11 with sections including cancer-free small bowel mucosa available for review) showed histologic evidence of persistent mucosal lesions (Marsh2 in 50% of the cases and Marsh1 in all cases) at the time of surgical resection for SBC.
Conclusion: SBC may occur several years after CD diagnosis, especially in late-onset CD and may notbe associated to a poor adherence to a GFD; rather, it might be partly related to at least focally persistent mucosal damage despite strict GFD, a finding more frequently observed in follow-up biopsies of late-onset CD patients. These results stress the need for high-suspicious follow up in late-onset CD

370. SHORT STAY UNIT IN MANAGEMENT OF NON-VARICEAL UPPER GASTROINTESTINAL BLEEDING

Lumare M., Candelli M., Pignataro G., Spaziani G., Tullo G., Rozzi G., Novelli M., Pala M., Balsamo I., Piccioni A., Ojetti V., Franceschi F., Sacco Fernandez M., Gemma S.
Fondazione Policlinico Universitario Agostino Gemelli

Background: Emergency department overcrowding is health, political and economic problem of concern in the social sphere all over the world. The causes of overcrowding are many and varied. First and foremost, an aging population, but also an increase in chronic diseases, lack of access to primary care, a poor territorial outpatient network or lack of resources in communities increases the flow of patients to the ED. Overcrowding is fuelled by the shortage of hospital beds, which increases the length of stay in ED of patients requiring hospitalization. Overcrowding is a major problem, because it goes to increase the risk of patient mortality due to delayed care, which in turn can lead to increased care needs and the need for costly treatment and that burdens healthcare spending. Several solutions have been proposed around the world, such as the establishment of the Short Stay Unit (SSU), a functional unit of the Emergency department, established for conditions that cannot be managed at home, but that need treatment and hospitalization for up to 72 hours. SSU makes it possible to avoid the use of ordinary inpatient beds and contribute to the reduction of emergency department overcrowding. Several studies show how Short Stay Unit can significantly reduce hospital length of stay or reduce mortality for certain conditions, like chronic obstructive pulmonary disease or heart failure, head injury or pyelonephritis. Among the pathologies proposed for short stay unit are also non-variceal upper gastro-intestinal bleeding, which is one of the most frequent emergencies at the Emergency Department, with need, often, for urgent treatment. Currently, there are no studies addressing the safety and efficacy of short stay unit in the management of non-variceal upper gastrointestinal bleeding.
Objectives: Our study tries for evaluate the efficacy of short stay unit in decreasing the requirement of hospitalization, hospital length of stay, hospital readmission and mortality in the cases of non-variceal upper gastrointestinal bleeding, compared with admission to the regular ward.
Methods: This was a retrospective, single-centre observational study. Medical records of patients who presented to the Emergency Department with non-variceal upper gastrointestinal bleeding, April 1, 2021, and September 30, 2022, were analysed. The study population includes patients aged >18 years, of either sex, presenting to the Emergency Department with hematemesis or melena, defined as acute blood loss from the upper gastro-intestinal tract. The test population was divided into two groups: patients admitted to an ordinary inpatient ward (control) and patients treated at short stay unit (intervention). Clinical and medical history data were assembled for both groups. The hospital length of stay was the primary outcome. Secondary outcomes were time to endoscopy, number of blood units transfused, readmission to the hospital at 30 days, and in-hospital mortality.
Results: The analysis included 120 patients with a mean age of 69.6 +/- 0.7 years, 54% of whom were men. Sixty patients (50%) admitted to SSU, sixty (50%) did not. Patients admitted to the medical ward had a higher mean age and a higher likelihood of having a history of cerebrovascular disease and/or active cancer. Home treatment with proton pump was statistically lower in patients admitted to the short stay unit, compared to those admitted to an ordinary inpatient ward (p:0.01I). Among the laboratory data evaluated, only INR was slightly, but significantly, higher in patients admitted to inpatient wards, compared with patients admitted to SSU. Atrial fibrillation is associated with increased hospital length of stay with p<0.01. The Glasgow Blatchford blend score, used to assess bleeding risk in enrolled patients was similar in study and control groups. Mortality and hospital readmission at 30 days were also very low and similar among the groups. Multivariate analysis, after adjustment for confounders, establish that the only factor independently associated with reduced time in hospital (LOS) was admission to short stay unit (126 +/- 133 hrs, p<0.0001). Admission to short stay unit was independently and significantly associated with shorter time to endoscopy (31 +/- 39 hrs, p<0.001). The only other factor associated with a shorter time to endoscopy was creatinine level (p=0.05), while home treatment with proton pump inhibitors was associated with a longer time to endoscopy. Hospital length of stay, time to endoscopy, number of patients of requiring transfusions and number of units of blood transfused were significantly lower in patients admitted to short stay unit, than in the control group.
Conclusions: The results of the study show that management of non-variceal upper gastrointestinal bleeding in short stay unit can significantly reduce the time required for endoscopy, the hospital length of stay and number of transfused blood units, without increasing mortality and hospital readmission. Treatment of non-variceal bleeding in short stay unit, therefore, may help to reduce emergency department overcrowding, but multicentred randomized controlled trials are needed to confirm these data.

371. DERMATOLOGIC MANIFESTATIONS OF INFLAMMATORY BOWEL DISEASE: SIGNALS WE MUST LEARN TO RECOGNIZE.

Diesse Kamwa L. P. , Vannoni F. , Orlandi A. , Varocchi F. , Vannini F. , Gialloni S., Morrione A. , Bruni D.
Medicina Interna I, Nuovo Ospedale S. Stefano di Prato

There are several extraintestinal manifestations of inflammatory bowel disease (IBD). Data suggest that 6 to 40 percent of patients with IBD have one or more extraintestinal manifestation and up to 15 percent of patients have a cutaneous manifestation. The pathogenesis is incompletely understood and it is hypothesized that the diseased gastrointestinal mucosa may trigger an immune response at the extraintestinal site due to shared epitopes. While some extraintestinal manifestations parallel the disease activity of IBD (eg, erythema nodosum, Sweet syndrome), the course of others (eg, pyoderma gangrenosum) is independent of intestinal inflammation.
We report the case of a 76-year old woman non smoker presenting to the Emergency Room (ER) for diarrhea preceded by an erythematous rash in the previous month. Her personal history was notable for polymyalgia reumatica, hypokinetic heart disease and atrial fibrillation treated with apixaban for a few days. In the ER, she was hemodynamically stable and showed multiple erythematous macules and papules on the upper extremities and trunk and a deep ulcerate lesion in the left pretibial region. Blood tests showed neutrophilic leukocytosis, mild acute renal failure and hypoalbuminemia. Eosinophil and IgE values were normal, excluding an allergic reaction to recently prescribed anticoagulant therapy. Specific blood and stool tests excluded infectious pathologies. A Doppler ultrasound ruled out a venous or arterial pathology of the lower limbs, suggesting that the pretibial ulcerate lesion could be a pyoderma gangrenosum. Considering the worsening of the

clinical conditions, especially of diarrhea and dermatosis, an abdominal CT scan and a colonscopy were performed and diagnosed Crohn's disease. Therapy with mesalazine and corticosteroids was prescribed, but the patient got worse rapidly, developed an intestinal obstruction and died.
Dermatoses and skin lesions are often underestimated, but they can hide an underlying critical systemic disease, especially hematologic disorders and inflammatory bowel disease. It is essential to recognize these skin manifestations in order to start the appropriate therapy of the underlying pathology as soon as possible.

GERONTOLOGIA E GERIATRIA

372. VAC THERAPY: CASE REPORT

Ciancio L.[1], Ciammaichella M.M.[2], Pignata D.[2], Fanfarillo F.[2], Marzano M.A.[2], Ulissi A.[2], Di Castri C.[2], De Paola G.[2], Silvestrini S.[3]
[1]UOC Medicina Interna, Dipartimento di Medicina Interna, A.O. S. Giovanni-Addolorata, Roma; [2]UOC Medicina Interna ad Alta Intensità di Cure, Dipartimento di Medicina Interna, A.O. S. Giovanni-Addolorata, Roma; [3]UOC Geriatria, Dipartimento di Medicina Interna, A.O. S. Giovanni-Addolorata, Roma

Introduction: The Negative Pressure Wound Therapy (NPWT) is widely used in surgery and medicine for the treatment of surgical dehiscence or complicated skin lesions. Continuous technological instrument innovations have allowed a wide and effective application of the therapy also in complex cases, where the choice of filler is fundamental. A new innovative system that combines the benefits of NPWT with instillation therapy to help promote wound healing. Chronic, acute, infected wounds can be benefit from the automated delivery and drainage of solutions. The new NPWT system is indicated for patient with severe infected wounds, it combines the benefits of NPWT with the benefits of fluid instillation to help promote wound healing.
Case Report: A 82-yrs female patient arrives in our department as a transfer from one clinic to long-term care due to resistant high fever from about 15 days. Physical examination revealed the presence of cutaneous ulcerative lesions in the fourth degree with necrosis in the bottom and on the edges of the wounds in the both trochanters complicated about state septic. BP was 70/40 mmHg, HR 100 beats, breath rate 16/min, temperature was 40,9 °C. The wound were very painful and an huge bad-smelling purulent exudate, necrosis, undermining and serious slough, cellulitis around the wounds. The left trochanteric wound presented a 8 x 4 cm necrotic lesion and 7 cm of depth, while the right trochanteric wound presented 5 x 3 cm and 4 cm of depth. Cutaneous ulcer swabs are performed on the bottom and on the edges of the wounds and they was positive for Staphylococcus Aureus. The patient underwent antibiotic therapy by Piperacillin,Tazobactam and antipyretics. It was suggested to apply immediately NPWT with silver foam filler and instillation therapy about antiseptic solution from wound care specialist.
Material and Methods: We decided to treat these grade 4 pressure severe ulcer wounds with NPWT instillation therapy. We preferred to use a silver foam filler based NPWT with an innovative type of device which allowed both wounds to be connected to the NPWT machine at the same time. The connector (fitting) used used both lesions at the same time to receive instillation. In the lesions, antiseptic solutions alternating with saline solutions were instilled. Through the pad positioned on the surface as by ordinary technique, the instilled solutions were uniformly distributed on the ferrite bed for the direct contact of dressings with infected areas. The antiseptic used for instillation was 0.5% Polyhexamethilene Biguanide HCl (PHMB), alternating with saline 0.9% instillation. The selected instillation time was 20 seconds, with a 25 minute contact wound time and a suction time of 100 minutes. This cycle is repeated automatically without the need for operator manual intervention. The patient underwent this type of therapy for 7 days, the dressings were renewed three times. After the seventh day, a cutaneous swab was taken again at both ulcers, which was negative, ie no bacterial contamination was detected. After 7 days the patient is considered out of danger and no longer septic, no longer febrile, the pain is greatly reduced, the injuries were devoid of purulent material, to accelerate healing, continued traditional NPWT with foam at 125mmHg negative pressure for 35 days. As before, the injuries were both connected to the NPWT unit with the special 'Y' connector. At day 35, NPWT was discontinued and the treatment went on with advanced dressings, specifically three-layers polyurethane foam in mixed cells combined with alginate. The patient was discharged with an Home Care Center program, to continue dressing change every other day following the precise indications of the wound-specialist for a period of 25 days. Complete healing and functional recovery occurred at day 77.
Results: In the present paper V.A.C. Instill Therapy System ha offerto a dual therapy combining the benefits of V.A.C. Therapy with the benefits of instillation therapy, in particular we underline its efficacy in automatic delivery of instillation fluid into the infected wounds, an equal distribution of instillation fluid (soluzione antisettica alternata a soluzione salina) throught the foam dressing in the infected wounds, with instillation times programmed. The intermittent removal of used instllation fluid supports the cleaning and drainage of the wounds bed and the removal of infectious material. The V.A.C. Instill Therapy System privided to close moist woundshealing environment.
Discussion V.A.C.: Instill Therapy System allows automatic delivery of selected solutions by direct contact with the wound bed, enabling the removal of bacteria, absorbent and instillation fluid removed and instillation times can be freely programmed. This system has proved to be effective in terms of efficiency, allowing an unexpected tissue repair of these complex lesion
Conclusions: This case report has demonstrated that fluid delivery and removal is very effective and that this related to reduction in infection parameters.

373. OUTCOMES AND PREDICTORS OF IN-HOSPITAL MORTALITY AMONG OLDER PATIENTS WITH DEMENTIA

De Matteis G. [1], Burzo M.L.[2], Della Polla D.A.[3], Serra A.[1], Russo A.[4], Landi F[4], Gasbarrini A. [5], Gambassi G. [6], Franceschi F. [3], Covino M.[3]
[1]Dipartimento di Medicina Interna, Fondazione Policlinico Universitario A.Gemelli IRCCS, Roma, Italia; [2]Dipartimento di Medicina Interna, Ospedale Santo Spirito in Sassia, Roma, Italia; [3]Dipartimento di Medicina d'Urgenza e Pronto Soccorso, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italia; [4]Dipartimento di Scienze dell'Invecchiamento, Ortopediche e Reumatologiche, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italia; [5]Dipartimento di Medicina e Chirurgia Traslazionale, Università Cattolica del Sacro Cuore, Roma, Italia; [6]Dipartimento di Medicina e Chirurgia Traslazionale, Università Cattolica del Sacro Cuore

Dementia is associated with high rates of admission to hospital, due to acute illness, and in-hospital mortality. The study aimed to investigate the impact of dementia on in-hospital mortality and identify the predictors of in-hospital mortality in these patients. This was a retrospective study evaluating all the patients ≥65 years consecutively admitted to our Emergency Department (ED). We compared the clinical outcomes of the patients with dementia at ED admission with those who did not have dementia, using a propensity score-matched (PSM) paired cohort of controls. The patients were matched for age, sex, Charlson Comorbidity Index (CCI) value, and clinical severity at presentation (based on National Early Warning Score - NEWS ≥ 5). The primary study endpoint was all-cause in-hospital death. After the PSM, a total of 7118 patients, 3559 with dementia and 3559 in the control group, were included in the study cohort. The mean age was 84 years, and 59.8% were females. The overall mortality rate was higher for the demented patients compared with the controls (18.7% vs. 16.0%, p = 0.002). The multivariate-adjusted hazard ratio (HR) showed that dementia was an independent risk factor for death (HR 1.13 [1.01–1.27]; p = 0.033). In the patients with dementia, respiratory failure (HR 3.08 [2.6–3.65]), acute renal failure (HR 1.64 [1.33–2.02]; p < 0.001), hemorrhagic stroke (HR 1.84 [1.38–2.44]; p < 0.001), and bloodstream infection (HR 1.41 [1.17–1.71]; p = 0.001) were significant predictors of worse outcomes. Finally, the comorbidities and severity of illness at ED admission negatively influenced survival among the patients with dementia (CCI HR 1.05 [1.01–1.1] p = 0.005; NEWS ≥ 5 HR 2.45 [1.88–3.2] p < 0.001). In conclusion, among the hospitalized older patients, dementia was associated with a higher risk of mortality. Furthermore, among the older patients with dementia, respiratory failure and bloodstream infections were independently associated with an increased risk of in-hospital mortality.

374. CHRONIC NORMOCYTIC NORMOCHROMIC ANEMIA, HYPOGAMMAGLOBULINEMIA, AND HYPOMAGNESEMIA IN POLYMYALGIA RHEUMATICA: RANDOM ASSOCIATION? AN UNRESOLVED CASE REPORT IN ELDERLY PATIENT

Turrin M.[1], Fornasiero L.[2]
[1]former Department of Internal Medicine, Ospedali Riuniti Padova Sud, Monselice (Pd), Italy; [2]former Department of Laboratory Medicine, Ospedali Riuniti Padova Sud, Monselice (Pd), Italy

Case Presentation: A 74-years-old Caucasian man comes to us for an evaluation in March 2022. Anamnesis reveals: previous smoker, anal fistula operated, hypercholesterolemia, hyperuricemia, arterial hypertension, carotid and aorto-iliac atheromasia, livedo reticularis in lower limbs, chronic gastritis, cervical spondylarthrosis, mild chronic normocytic normochromic anemia and mild leukope nia, uncertain significance's mild hypogammaglobulinemia. His therapy consists in aspirin, esomepra zole, atorvastatin, candesartan, hydrochlrothiazide. Ten months earlier, polymyalgia rheumatica's (PMR) diagnosis formulated and treated with NSAIDs and dexamethasone. Test carried out in that period showed the persistence mild anemia's with leukopenia, variable increase in inflammatory indi ces, negative neoplastic markers, positive faecal occult blood. EGDS and colonscopy: erosive gastri tis, hyperplastic polyp of the stomach (H. pylori negative) and a tubulo-villous adenoma in sigma diver ticulosis. Abdominal US negative (reactive inguinal lymph nodes only). In mid-December the symp toms worsened with oedema's apparence in both lower limbs with marked accentuation of the livedo reticularis, feeling of facial, abdominal and scrotal swelling, dyspnea from physical exertion. The phy sical examination also revealed: symmetrical pitting oedema in both hands's dorsum, a deficit in the shoulder movement, an hydrocele, an hypertrophic right calf. Laboratory tests: RBC 3.70x10^12/L, Hb 9.5 g/dL, MCV 84 fL, MCH 26 pg, MCHC 302 g/L, RDW 16.9 %, Lymphocytes 1.13x10^ 9/L, eritropoi etin 22.7 U/L (nv 2.6-18.5), γglobulin 5.9 g/L, CRP 55 mg/L, haptoglobin 3.9 g/L (nv<2), D-dimer 2211 µg/L (nv <200), magnesium 0.56 mmol/l (nv 0.75-1.04)**,** IgA 1.8 g/L (nv 0.7- 4.0), IgG 8.7 g/L (nv 7-16), IgM 0.45 g/L (nv 0.4-2.3), 25(OH)D 59 nmol/L (insufficiency). Normal: IgE, CPK, LDH, nt-pro-BNP, RF, ANA, ENA, ACPA, calcium, phosphate, aPTT, INR, ferritin, folic acid, vitamin B12, fecal calprotectin, RBCOR, indirect Coombs, C3c, C4; cryoglobulins, anti-tTG IgA and EMA absent, anti-β2 GPI and ACL, HBV and HCV negative. V617F JAK2 mutation negative. Hands-X-ray: no erosions, soft tissue oedema (sausage fingers). Right shoulder US: sub acromial-subdeltoid bursitis. Scrotal ultrasound: bi lateral hydrocele. Lower limbs US: subcutaneous soft tissue oedema in legs, no deep vein thrombo sis, bilateral Baker's cyst, ematoma in the right medial twin muscle (from previous exertional muscle tear). In the remitting sieronegative symmetrical synovitis with pitting oedema (RS3PE) syndrome hypothesis the patient then treated with methylprednisolone orally (8 mg/daily), cholecalciferol, furose mide, enoxaparine, Mg pidolate 4.5 g/daily. The oedema in hands and legs quickly regressed, the weight reduced by 2 kg in a week, pain disappeared. After three weeks laboratory tests showed: RBC 4.2x10^12/L, Hb 10.6, MCV 83.8, MCH 25**,** Lymph 2.4x10^9/L, γglobulin 10.3, normal RCP, Mg 0.64-0.68. Hypomagnesemia has been related to prolonged therapy with the esomeprazole, increased D-dimer associated with right calf hematoma. In May, 20 cc of citrine liquid were extracted with knee ar throcentesis; the patient started on hydroxychloroquine therapy. Most recent laboratory tests showed: RBC 4.290.000**,** Hb 11.9, MCV 90, MCH 27, WBC 4.7x10^9/L, Lymph 0.87x10^9/L, HbA: 98.2% (nv 96-100), HbA2:1.6% (nv 2-3.2), HbF:0.2% (nv<1,5), Mg 0.73 mmol/L, 24-hour urinary Mg 1.1 mmol (nv 30-50), 24-hour urinary calcium 1.1 mmol (nv 2.5-7.5), 24-hour urinary phosphate 10 mmol (nv 12.9-42). Tests were performed after 10 days of suspension of oral Mg. Normal: Na, Cl, K, 24-hour urinary Na and K. Total IgG:7.89 g/L, IgG-1:6.09 g/L (nv 4.05-10.11), IgG-2:1.07 g/L (nv 1.69-7.86), IgG-3: 0.07 g/L (nv 0.11-0.85), IgG-4:0.657 g/L (nv 0.03-2.01). The lower than normal HbA2 value (1.6%), with normal RBCOR, could be compatible with delta thalassemia tract's anemia (not patholo gical and not detectable by our kits) or alpha thalassemia tract's. DNA analysis for defects (molecular typing of 22 alpha-globin gene mutations) was negative. Cortisone therapy did not significantly increa se blood count parameters**.**

Conclusion: Our clinical case currently leaves following questions open. The pre-existing's classifica tion, and persistent, mild normocytic normochromic anemia, in any case unrelated to these inflamma tory syndromes: a further in-depth research on blood counts and hemoglobin status not lead to defini tive diagnosis.The finding of persistent hypomagnesemia, it cannot be corrected with supplementa tion and it attributed to the prolonged intake of PPIs: unfortunately it wasn't possible to trace a pre vious magnesemia and it wasn't possible to suspend the intake of esomeprazole due to the exacerba tion of gastric disorder. The hypomagnesuria's finding associated with hypocalciuria and hypophospha turia suggests the alternative diagnosis of isolated-dominant hypomagnesemia, an anomaly that will in this case be studied with genetic investigations. The presence of hypogammaglobulinemia could have favored the onset of PMR and subsequent RS3PE syndrome.

375. ORAL ANTICOAGULANT THERAPY AND DECLINE IN COGNITIVE FUNCTION IN ELDERLY PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION: REAL WORLD EVIDENCE AND THE ROLE OF "GENDER"

Armentaro G.[1], Crudo G.[1], Rullo R.E.[1], Potenza G.[1], Daidone M.[2], Condoleo V.[1], Miceli S.[1], Maio R.[1], Perticone M.[1], Tuttolomondo A.[2], Sesti G.[3], Sciacqua A.[1]

[1]Department of Medical and Surgical Sciences, University Magna Græcia of Catanzaro, 88100 Catanzaro, Italy.; [2]Internal Medicine and Stroke Care Ward, University Hospital, Policlinico "P. Giaccone," Via del Vespro, 129, 90127 Palermo, Italy.; [3]Department of Clinical and Molecular Medicine, University Rome-Sapienza, viale Regina Elena n. 324, 00161, Rome, Italy

Background : Atrial fibrillation (AF) represents the most frequent cardiac arrhythmia in elderly, increasing the risk of stroke and cognitive decline (CD) regardless of the presence of previous stroke, with an estimated hazard ratio for CD or dementia of 2.43 and 2.70, respectively (1). AF and CD share common cardiovascular (CV) risk factors: aging, hypertension, and diabetes, and their association persists after adjustment for all possible confounders. Although large clinical trials have demonstrated the non inferiority of direct oral anticoagulants (DOACs) to vitamin K antagonists (VKAs) in preventing stroke and systemic thromboembolism, and reducing major bleedings especially cerebral bleedings, the role of antithrombotic therapies on the risk of CD is still controversial, probably due to the multifaceted pathophysiology of CD. The Mini-Mental State Examination (MMSE), is a simple and valid screening tool for the assessment and severity of CD, a score <24 indicates CD with a sensitivity and specificity of 87% and 82%, respectively (2). Despite this, the prognostic implications of different type of anticoagulation on the risk of CD assessed by MMSE in elderly AF patients are not defined. The purpose of the present work is to evaluate possible differences on the occurrence of new CD among patients taking DOACs versus VKAs in an elderly population with AF and major comorbidities.

Materials and Methods: 420 Caucasian patients aged ≥65 years were enrolled at the UOC of Geriatrics of the University Polyclinic of Catanzaro, suffering from non-valvular AF, 136 on VKAs and 284 on DOACs, with mean age 76.7±5.7, 55 women in the VKAs group (40.4%) and 133 in DOACs (46.8%) (p=0.217). A clinical-instrumental and laboratory evaluation was performed for a median follow-up of 93.9 months. Data were expressed as some mean and standard deviation or as median and interquartile range when appropriate. Wicoxon's test and Student's t-test were performed for unpaired data, chi-square test when appropriate. In addition, a log rank test was performed to compare the risk function estimates of two groups at each time point of the observed events, followed by a univariate Cox regression model on the incidence of CD; variables that correlated significantly with the occurrence of CD were included in a multivariate Cox regression model to calculate independent predictors associated with the incidence of CD.

Results: The two groups were overlapping in gender, smoking, type 2 diabetes mellitus. The DOACs treatment group had a higher prevalence of: heart failure (p=0.002), COPD (p=0.001), hypertension (p=0.0003) and a higher age (78.4±4.7 vs 73.2±5.9 years); p<0.001. In the entire general population at baseline, the following values were found: MMSE 25.6±2.0 pt, eGFR 64.6±18.2 ml/min/1.73 m2, SBP 132.5±11.6 mmHg, DBP 76.6±9.5 mmHg, BMI 29.4±4.8 Kg/m2; while at follow-up the mean MMSE values were: 25.1± 2.0 pt. In addition, the Delta of MMSE between follow-up and baseline was calculated and found to be -0.8±0.3 pt and the Delta of MMSE/year -0.2±0.06 pt. At follow-up, there was a higher incidence of CD in the VKAs group than in the DOACs group (2.41 events/100 patient-years vs 1.33 events/100 patient-years, p<0.0001). A Cox's stepwise multivariate regression model showed that DOACs therapy (HR 0.419, p<0.0001), less decline in renal function (HR 0.432, p<0.0001) and antiarrhythmic therapy (HR 0.572, p=0.001) were protective factors for the occurrence of CD, while smoking (HR 3.349, p=0.019), female sex (HR 2.244, p<0.0001), increased 1 kg/m2 of BMI (HR 1.087, p<0.0001), increased 1 year of age (HR 1.086, p<0.0001), and increased SBP (HR 1.065, p=0.001) increased the risk of CD.

Conclusions: The data from the present study confirm a better safety profile of DOACs compared with VKAs on the occurrence of cognitive decline in an elderly population with major comorbidities, despite the fact that patients on DOACs therapy were older with a higher burden of comorbidities that adversely affect cognitive function such as: hypertension, COPD, heart failure.

376. ROLE OF COMPREHENSIVE GERIATRIC ASSESSMENT IN ESTIMATING THE RISK OF COGNITIVE DECLINE AND FUNCTIONAL LIMITATION IN A COHORT OF ELDERLY NON-VALVULAR ATRIAL FIBRILLATION PATIENTS ON DOAC THERAPY.

Condoleo V.[1], Armentaro G.[1], De Marco M.[1], Pastura C.A.[1], Cordaro R.[1], Mesoraca D.[1], Clausi E.[1], D'Alterio N.[1], Benincasa C.[1], Cassano V.[1], Castagna A.[2], Ruotolo G.[3], Sesti G.[4], Sciacqua A.[1]
[1]Department of Medical and Surgical Sciences, University Magna Grœcia of Catanzaro, 88100 Catanzaro, Italy.; [2]Primary Care Department, Azienda Sanitaria Provinciale Catanzaro, Soverato, Italy; [3]Geriatrics Unit, "Pugliese Ciaccio" Hospital, 88100, Catanzaro, Italy.; [4]Department of Clinical and Molecular Medicine, University Rome-Sapienza, viale Regina Elena n. 324, 00161, Rome, Italy.

Introduction: Atrial fibrillation (AF) represents the most common supraventricular arrhythmia, with a prevalence of 1-3% in the world population. Growing evidences show that AF plays an important role as a risk factor for the development of cognitive decline and dementia, with the following mechanisms: stroke, small vessel disease, microbleeds and microembolism with silent ischemia, cerebral hypoperfusion due to a reduction in cardiac output, and inflammaging with brain atrophy. In addition, AF represents a risk factors for development of depression and functional limitation. The purpose of the study is to evaluate, in a large cohort of elderly hospitalized patients with nonvalvular AF (NVAF) on direct oral anticoagulant (DOAC) therapy, the prevalence of cognitive decline, depression, and functional limitation, and to assess the different variables that may be detrimental or protective on the risk of cognitive impairment or functional limitation.
Materials and Methods: We enrolled 1004 patients in a period between 2014 and 2021 in the Geriatrics Divisions of "Mater Domini" University Hospital and "Pugliese-Ciaccio"' Hospital of Catanzaro. At the time of enrolment, all patients underwent to an accurate anamnesis and a complete physical examination with the determination of the main anthropometric and hemodynamic parameters. Weight, height, and body mass index (BMI) were calculated. Routine blood tests and a 12-lead electrocardiogram (ECG) were detected. All patients underwent a Comprehensive geriatric assessment (CGA), cognitive function was assessed by the following tests: Mini-mental state examination (MMSE) and Montreal Cognitive Assessment (MoCA), depressive syndrome by the geriatric depression scale (GDS), and functional status was assessed by the short physical performance battery (SPPB).
Results: A number of 1004 elderly patients with NVAF receiving DOAC therapy were enrolled, 384 men and 620 women, with a mean age of 84±7.1 years. The two groups were comparable for the main study variables, except for age and prevalence of hypertension and chronic kidney disease, which were higher in women, while ischemic heart disease (IHD) was higher in men. In addition, men and women differed in the thromboembolic and bleeding risk, that was significantly higher in women than in men CHA2DS2VASc 5.3±1.3 vs 4.2±1.4 pts (p<0.0001); and HAS-BLED 2.5±0.7 vs 2.3±0.8 pts (p=0.009), respectively. The study population had a mean MMSE score of 24.3±5.2 pts and a MoCA score of 23.1±5.2 pts. The mean SPPB score was of 7.4±3.7 pts. A 39.9% of the population had a pathological MMSE (<24 pts) while 42.7% a pathological MoCA (<26 pts). Regarding the SPPB, 46.1% of the whole population was characterized by functional dysautonomia, and the mood status evaluated with the GDS was impaired in the 37.2% of the entire population. In a logistic regression model that considers pathological MMSE as the dependent variable, female gender (OR: 2.825, CI: 1.993-4.005; p<0.0001), one-point increase in CHA2DS2VASc score (OR: 1.139, CI:1.014-1.280; p=0.029), one-point increase in GDS (OR: 1.220; CI: 1.164-1.278; p<0. 0001), were associated with the risk of pathological MMSE; while antiarrhythmic drugs (AADs) (OR: 0.300, CI:0.153-0.588, p<0. 0001), statins (OR: 0.485, CI: 0.332-0.710; p<0.0001), and one-point increase in SPPB (OR: 0.864, CI:0.821-0.909; p<0.0001) were associated with reduced risk of pathological MMSE. Another logistic regression model assessing pathological MoCA score as the dependent variable showed that female gender (OR: 3.673, CI:2.437-5.535; p<0.0001), one-point increase in GDS (OR:1.220, CI: 1.162-1.281; p<0.0001) and were associated with risk of pathological MoCA score, while AADs (OR:0.255, CI: 0.128-0.506, p<0.0001), ACEi/ARBs (OR:0.694, CI: 0.481-0.999; p=0.049) and a one-point increase in SPBB (OR:0.852, CI: 0.803-0.903; p<0.0001) were protective. The third model had as endpoint the presence of functional disability assessed as SPPB<8 pts, showed that: 10-year increase in age (OR:4.46, CI:3.257-6.129; p<0.0001), one-point reduction in MMSE (OR:2.034, CI:1.410 -2.935; p<0.0001), the presence of IHD (OR:1.742, CI:1.109-2.736; p=0.016), insulin use (OR:1.731, CI:1.004-2.987; p=0.049), one-point increase in GDS (OR:1.288, CI:1.222-1.357; p<0. 0001), and the one-point increase in the CIRS-CI (OR:1.053, CI:1.022-1. 084; p=0.001). 084; p=0.001) increased the risk of functional limitation, while the use of Ca-channels blockers (OR:0.447, CI:0.233-0.861; p=0.016) and metformin (OR: 0.581, CI:0.353-0.956; p=0.033) were protective.
Conclusions: Our study revealed that in a cohort of elderly patients hospitalized with AF taking DOAC, cognitive impairment and disability are widely represented. Our study shows that female gender and different comorbidities increase the risk of being affected by cognitive decline, while AAD and other therapies are found to be protective. In addition, cognitive decline, depressive symptoms increase the risk of being affected by functional disability.

377. ASSOCIATION BETWEEN BLOOD PRESSURE VARIABILITY AND BIOMARKERS OF AGING IN COMMUNITY-DWELLING OLDER ADULTS: EVIDENCE FROM THE MAPT STUDY

Bencivenga L[1], Strumia M[2], Rolland Y[2], Vellas B[2], De Souto Barreto P[2], Rouch L[2]
[1]Dipartimento di Scienze Mediche Traslazionali, Università degli Studi di Napoli Federico II; [2]Gérontopôle de Toulouse, Institut du Vieillissement, CHU de Toulouse, France

Background: Aging is characterized by alterations of the neuro-cardiovascular mechanisms, which contribute to the impairment of the physiological models of homeostatic variability. Repeated evidence has demonstrated that increased blood pressure variability (BPV) is associated with organ damage and exerts an independent prognostic role on several outcomes: cardiovascular events, neurocognitive impairment, metabolic disorders and geriatric syndromes, such as sarcopenia and frailty. Consequently, increased BPV may constitute an epiphenomenon of the dysfunction of homeostatic mechanisms typical of late life. Vascular aging is associated with a low-grade chronic inflammation, known as "inflammaging", and with the stress-related "mitochondrial dysfunction", an antagonistic hallmark of aging. These factors in turn could contribute to an increase in BPV and the risk of cardiovascular disease.
The objective of the present study was to determine whether plasma levels of the stress-related pleiotropic mitokine Growth/Differentiation Factor 15 (GDF-15) and two inflammatory biomarkers, interleukin 6 (IL-6) and necrosis factor receptor tumor 1 (TNFR-1), are associated with long-term BPV in community-dwelling older adults.
Materials and methods: The study population consisted of 1,096 participants (mean age 75.3 ± 4.3 years; 699 females, 63.7%) selected from community-dwelling participants aged ≥70 years from the Multidomain Alzheimer Preventive Trial (MAPT) study. The selection criteria listed: reported memory disturbances, limitation in at least one instrumental activity of daily living and slow gait (<0.8 m/s). Individuals with Mini-Mental State Examination < 24, diagnosis of dementia, or deficit in basic activities of daily living were excluded. Biological sample (blood) was collected 12 months after enrollment and blood pressure was evaluated up to seven times over the following 4 years. Systolic BPV (SBPV) and diastolic BPV (DBPV) were determined using various indicators [among which the most common is coefficient of variation (CV%)], which take into account the variation of blood pressure over time, the order of measurements, even with formulas independent of the average values.
Results: Higher GDF-15 levels were significantly associated with an increase in SBPV (all indicators) after adjustment for demographics, body mass index, randomization group, baseline systolic blood pressure, use of antihypertensive drugs, presence of diabetes mellitus, cardiovascular and non-cardiovascular comorbidities [in the final model, for each 1-SD increase in GDF-15: β (SE)= 0.07 (0.04), p< 0.044, per %CV]. GDF-15 levels were not associated with DBPV. No significant associations were found between IL-6 and BPV, while TNFR1 was only partially related to increased DBPV.
Conclusions. Unlike biomarkers of inflammaging, higher levels of GDF-15 were associated with increased SBPV. Overexpression of GDF15 may constitute an adaptive response to stress and the body's reaction to counteract tissue damage and pro-inflammatory stimuli associated with aging. The higher values of GDF-15 detected in the present study can be understood as an early attempt to preserve the altered homeostasis, indicated by an increase in SBPV, and could help prevent inflammation. These results also support the role of mitochondrial dysfunction as an age-related process underlying blood pressure instability, confirming that BPV could be a potential early marker of aging.
References:Bencivenga L, et al (2023) Biomarkers of mitochondrial dysfun-

ction and inflammaging in older adults and blood pressure variability. GeroscienceBencivenga L, et al (2022) Blood pressure variability: a potential marker of aging. Ageing Res RevConte M, et al (2022) GDF15, an emerging key player in human aging. Ageing Res RevHartmann A, et al (2021) Ranking Biomarkers of Aging by Citation Profiling and Effort Scoring. FrontiersPaneni F, et al (2017) The Aging Cardiovascular System: Understanding It at the Cellular and Clinical Levels. J. Am. Coll. Cardiol.Rouch L, Cestac P, Sallerin B, et al (2020a) Visit-to-Visit Blood Pressure Variability Is Associated With Cognitive Decline and Incident Dementia. HypertensionRouch L, et al (2021) Visit-to-Visit Blood Pressure Variability and Incident Frailty in Older Adults. Journals Gerontol - Ser A Biol Sci Med SciTatasciore A, et al (2008) Awake blood pressure variability, inflammatory markers and target organ damage in newly diagnosed hypertension. Hypertens ResVellas B, et al (2014) MAPT STUDY: A MULTIDOMAIN APPROACH FOR PREVENTING ALZHEIMER'S DISEASE: DESIGN AND BASELINE DATA. J Prev Alzheimer's Dis

378. THE PREDISPOSITION TO NOCTURNAL CONTINUOUS POSITIVE UPPER AIRWAY PRESSURE (CPAP) THERAPY IN ADULT AND ELDERLY PATIENTS WITH MODERATE-SEVERE OSAS. PREDICTORS OF ACCEPTANCE

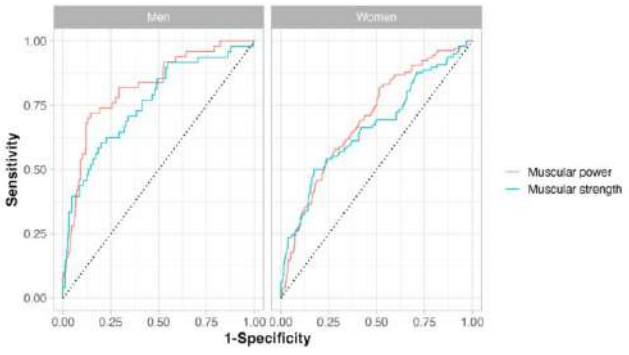
Lo Iacono C.A.M., Mezzadri M., De Angelis C., Gobbi F., Vernucci A., Ettorre E.
Dipartimento di Medicina Interna e Specialità Mediche UOC Geriatria

Introduction: Nocturnal continuous positive upper airway pressure (CPAP) therapy is currently the treatment gold standard for Obstructive Sleep Apnea Syndrome (OSAS). OSAS is a pathology which, if left untreated, can have several and serious negative effects on health, with important cardio-cerebrovascular, neuro-cognitive and metabolic sequelae.
When used appropriately, CPAP treatment is highly effective in normalizing night-time breathing and sleep, improving symptoms and reducing the risk of long-term complications. However, patients often do not accept or effectively adhere to treatment.
Aim of the study: To evaluate whether and which anthropometric parameters, anamnestic data, tests, physical and psychological characteristics and lifestyle habits could be predictive of acceptance of CPAP therapy.
Materials and method: From 2017 to 2021, at the sleep disorders clinic of the UOC of Geriatrics of the Policlinico Umberto I in Rome, 247 patients aged between 19 and 91 years, with moderate-severe OSAS were eligible for CPAP therapy .6 patients due to lack of data were excluded, 108 accepted CPAP therapy and 133 refused it.
An anamnesis was collected for each patient, questionnaires were administered to investigate daytime sleepiness (ESS), insomnia, snoring and sleep quality and anthropometric parameters such as weight, height and body mass index (BMI) were recorded.
Results: The characteristics that were able to approach the adequate statistical weight in predicting acceptance to CPAP were age and history of neurological diseases (TIA, ischemic stroke, Steynert myotonic dystrophy, seronegative myasthenic syndrome, sclerosis lateral amyotrophy, muscular dystrophy). The sample was stratified by age: patients over 65 and under 65 years of age, among young-adult subjects (under 65), those who did not drink alcohol had a greater tendency to accept treatment with CPAP.
In patients over 65, a good inclination to CPAP was observed more in those who were not affected by neurological diseases and in non-smokers,
The test that has been found to be useful in predicting patient predisposition to CPAP is the ESS, but only in patients over 65, indicating that daytime sleepiness is a good predictor of CPAP acceptance.
Conclusions: The results of this study suggest to focus attention on psychological and behavioral factors to increase adherence to CPAP therapy.

379. HAS MUSCLE POWER BETTER DISCRIMINATIVE CAPACITY COMPARED TO MUSCLE STRENGTH IN PREDICTING WORSENING DISABILITY IN OLDER PEOPLE?

Travaglini S.[1], Bonvicini M.[2], Pedone C.[3], Antonelli Incalzi R.[4], Bandinelli S.[5], Ferrucci L.[6]
[1]Training Programme in Internal Medicine, Department of Medicine and Surgery, UniversitàCampusBio-Medico di Roma, Via Alvaro del Portillo 21, 00128 Roma, Italy; [2]raining Programme in Geriatrics, Department of Medicine and Surgery, UniversitàCampus Bio-Medico diRoma, Via Alvaro del Portillo 21, 00128 Roma, Italy; [3]Research Unit of Geriatrics, Department of Medicine and Surgery, UniversitàCampus Bio-Medico di Roma,Via Alvaro del Portillo 21, 00128 Roma, Italy; Operative Research Unit of Geriatrics, Fondazione Policlinico Campus Bio-Medico,Via Alvaro del Portillo 200, 00128 Roma, Italy; [4]Research Unit of Geriatrics, Department of Medicine and Surgery, UniversitàCampus Bio-Medico di Roma,Via Alvaro del Portillo 21, 00128 Roma, Italy; Operative Research Unit of Internal Medicine, Fondazione Policlinico Campus Bio-Medico, Via Alvaro delPortillo 200, 00128 Roma, Italy ; [5]Geriatric Unit, ASF, Florence, Italy; [6]National Institute on Aging, Clinical Research Branch, Longitudinal Studies Section, Baltimore, Maryland

Background: Muscular strength reduction is supposed to be one of the most important age-related changes leading to disability; however, it has been shown to have a poor discriminative capacity in identifying people who will becomedisabled. There is convincing evidence that muscular power is more important than strength as a risk factor for adverseclinical outcomes in older people. Our hypothesis is that muscular power has better discriminative capacity compared to muscular strength in predicting worsening disability. Methods: We used data from the population-based In CHIANTI study and we selected patients in which muscle power and muscle strength were tested. We defined worsening disability the loss of at least one basic or instrumental activity of daily living between baseline and 3-years follow-up visit as our outcome measure. Isometric hip extensor strength and knee extensor strength were measured via a handheld isometric dynamometer. Leg power, hip strength, and knee strength were measured as measures of impairment. Leg power was obtained via a leg power rig as described by Bassey. Subjects sat in a chair and unilaterally depressed a foot lever, in the horizontal plane, attached to a flywheel. Power output was derived from the acceleration of the flywheel and was recorded in Watts. For all strength and power measures, the highest of 2 repetitions was utilized. Both measures were also dichotomized using the sex-specific first quartile (16 kg/s2 and1.46 W/kg for strength and power, respectively, in men and 10.5 kg/s2 and 0.72 W/kg for strength and power, respectively, in women) as cut-off values. Discriminative power was estimated using the area under the receiver operating curves (AUCROC).Sensitivity, specificity and positive/negative predictive values (PPV, NPV) were calculated for people with lower/higher muscle strength/power. All analyses were stratified by sex. Results:We included 923patients (505 women), with a mean age of 73.7 (SD 6.7) in men and 74.5(SD6.8)in women. Mean muscular strength was 19.6 (SD 6) in men and 13.2(SD4.1) in women, corresponding figures for relative muscular power(normalized to body mass) were 2.01 (SD 0.77) and 1.09 (SD0.50). The overall area under the curve for loss of ADL/IADL obtained using muscular strength was 0.76 in men and 0.67 in womenwhile it was 0.82in men and 0.70 in women for muscular power. Considering the categorized values, in men we found that low muscular strength had a sensitivity 0.56, specificity 0.83, PPV0.35, and NPV 0.92 while low muscular power had sensitivity0.72, specificity 0.86, PPV 0.45, and NPV 0.95. In women, low muscular strength had a sensitivity 0.44, specificity 0.84, PPV 0.47, and NPV 0.83 while low muscular power had sensitivity0.42, specificity 0.82, PPV 0.45, and NPV 0.81. Discussion: Overall, wefoundthat in men muscular power hadslightlybetter discriminative capacitycompared to muscularstrength with respect to worseningphysicalfunction with a sizableimprovement in sensitivity. No meaningful difference in overall discriminative capacitynor in individual measures were found in women. Measurement of muscular power does not seem to be warranted in older women, while it may be of clinical relevance in older man in situations where false negativemay be an issue.



380. TREATMENT OF PERICARDITIS IN THE ELDERLY: REPORT OF A CASE SERIES

Massaro M.G.[1], Gerardino L.[2], Verrecchia E.[1], Sicignano L.L.[3], Murace C.A.[1], Gallo A.[1], Montalto M.[2], Manna R.[2]
[1]Department of Geriatric Medicine, Fondazione Policlinico Universitario A. Gemelli, IRCSS, Rome, Italy.; [2]Department of Geriatric Medicine, Fondazione Policlinico Universitario A. Gemelli, IRCSS, Rome, Italy; Università Cattolica del Sacro Cuore, Rome, Italy.; [3] 1Department of Geriatric Medicine, Fondazione Policlinico Universitario A. Gemelli, IRCSS, Rome, Italy.

Background: Current guidelines on the management of pericarditis do not address the topic of management in the elderly **(1).**However the therapeutic approach cannot be the same for younger populations due to the characteristics of frailty and comorbidity typical of the elderly. To date, Anakinra has a recognized role in steroid-dependent recurrent pericarditis resistant to NSAIDs and colchicine and its possible role in the acute phase of pericarditis is little investigated. Some authors manifested a favorable position on the use of anti-IL1 drugs in patients with recurrent or incessant pericarditis, mainly in those patients suffering from comorbidities such as renal insufficiency or atrial fibrillation, often making unreliable the standard therapeutic approach with NSAIDs**(2).**
Aim: We provide our experience about the therapeutic management of pericarditis in the elderly and specifically about the use of Anakinra. To date, although not contraindicated for old patients, there are no available randomized trials concerning the use of Anakinra in the geriatric population, nor for use in recurrent neither other forms.
Methods: In last year,we selected 26 patients with pericarditis, aged over 65 years and over**.** We analyzed patient comorbidities, pericarditis characteristics and therapeutic approach. Median follow-up was three months.
Results: At the time of acute event, most patients (46.2%) had more than three comorbidities concurrently. Idiopathic form of pericarditis was the most common (73%).Anakinra was used in 10 out of 26 patients (38.4%) as reported in **Table 1**. In 2 of 10 patients, aged 71 and 88 years, respectively, anakinra was selected because NSAIDs were not considered safe due to severe renal impairment and the increased risk of bleeding due to concomitant antiplatelet and anticoagulant therapy. In both patients the steroid was also avoided, in the first due to glycemic decompensation and in the second to avoid neuropsychological effects due to major depressive syndrome. In 3 of 10 patients, aged 75, 85, and 87 years, anakinra was used as a "rescue drug" for pre-tamponade pericardial effusion despite NSAID and colchicine therapy with considerable clinical benefit so that the pericardiocentesis was no necessary in all three cases. In 1 of 10 patients aged 85 years, anakinra was used in incessant pericarditis with clinical benefit. Finally, in 4 cases, aged 67, 67, 70, 72 years old, anakinra was used as a third line, as per current guidelines. Regarding safety, there were no particular adverse effects. Regarding efficacy at 3 months, 8 out of 10 patients had no disease recurrence. One patient had a disease recurrence after the patient voluntarily discontinued the biological drug but remission occurred upon restarting anakinra. One patient died of heart failure exacerbation.
Conclusions: In our experience, the most of older patients were not reliable candidates for an adequate dosage of colchicine, steroid therapy or NSAIDs, in view of the relevant comorbidities they suffer from. We favor the use of anakinra in the form of recurrent or incessant pericarditis in patients with relative or absolute contraindication to the use of NSAIDs; moreover, we suggest anakinra in selected elderly patients when the contextual presence of comorbidities, such as renal failure, insulin requiring diabetes or use of anticoagulants, makes unsafe the use of NSAIDs and/or steroids. Another possible scenario emerging from our experience, is the use of anakinra as a "rescue drug". In fact, drug has been shown to be effective, reducing effusion abruptly that would have required pericardiocentesis. Further trials are necessary regarding the use of anti-IL-1, to expand these preliminary data in geriatric patients in comparison to general population.
References: 1. ESC Guidelines for the diagnosis and management of pericardial diseases. *Eur Heart J,***2015; 2.** Recent advances in pericarditis. *Eur J Intern Med,* **2022**

Age (y)	Sex	Etiology	Form	Comorbidities	Clinical outcome	Adverse effects	At 3 months
67	F	Idiopathic	recurrent	HT, HF, AFL, PCI	Remission	No	No recurrence
67	M	Idiopathic	recurrent	n/r	Remission	No	No recurrence
79	M	Idiopathic	recurrent	n/r	Remission	No	No recurrence
71	M	Dressler syndrome	acute	HT, AF, HS, CKD, DM	Remission	No	Relapse after abrupt discontinuation of therapy
72	F	AIDS	recurrent	AF, AH, CKD	Remission	Injection-site reaction	No recurrence
76	M	Idiopathic	acute	HF, AH, CKD, MMS	Pericardiocentesis avoided	No	Death from decompensated acute heart failure
85	M	Idiopathic	acute	HF, AF, AH, DM	Pericardiocentesis avoided	No	No recurrence
85	M	Idiopathic	recurrent	HF, AF, HS, CKD, DM	Remission	Hyperpyrexia	No recurrence
87	M	Bacterial	acute	HF, CKD, COPD	Pericardiocentesis avoided	No	No recurrence
88	M	Idiopathic	acute	HF, AF, HS, CKD, BS	Remission	No	No recurrence

Heart Failure (NYHA I-IV); Chronic obstructive pulmonary disease (COPD); arterial hypertension (AH); ischemic heart disease (HD); Chronic kidney disease stage III or V (CKD); diabetes mellitus (DM); atrial fibrillation or flutter (AF); non-metastatic neoplasm (NMN); Sjögren's disease (SJOGD); depressive syndrome (DS); impaired fasting glycemia (IFG).

381. CHRONIC COUGH IN VERY OLD PATIENTS ON LONG-TERM THERAPY WITH ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND NEW-ONSET CANCER

Massaro M.G. [1], Camilli S.[1], Verrecchia E.[1], Sicignano L.L.[1], Gerardino L.[2], Murace C.A.[1], Macerola N.[1], Gallo A.[1], Montalto M.[3]
[1]Department of Geriatric Medicine, Fondazione Policlinico Universitario A. Gemelli, IRCSS, Rome, Italy.; [2]Department of Geriatric Medicine, Fondazione Policlinico Universitario A. Gemelli, IRCSS, Rome, Italy; Università Cattolica del Sacro Cuore, Rome, Italy; [3]Department of Geriatric Medicine, Fondazione Policlinico Universitario A. Gemelli, IRCSS, Rome, Italy; Università Cattolica del Sacro Cuore, Rome, Italy.

Background: Chronic cough often represents a challenge for Physicians, mainly in older subjects, whose recognition of background disorders may be very complex.Data concerning influence of age on ACEi-induced cough are still not univocally established mainly because very old patients (>80 years) may be often underrepresented in most of studies. Usually, a persistent dry cough appears in the first weeks or months after an ACEi is started **(1).**However, although less investigated, we believe that the possibility that cough may arise several months or even after years of taking an ACEi, cannot be ruled out**.**Here we present the case of a 85-year old patient complaining of a chronic cough who experimented with the most varied but ineffective remedies, finally solving its problem in an apparently, but also unlikely, simple way.
Case report: A 85-year old patient came to our clinic complaining of an incessant cough beginning 8 months earlier and progressively worsening, so much so that it prevented a normal social life. He suffered from chronic heart failure, arterial hypertension, obesity, mild renal insufficiency and recent diagnosis of atrial fibrillation and renal malignancy. He was an ex-smoker (about 20 cigarettes per day for 20 years, up to 30 years before) and his chronic therapy consisted of ramipril, bisoprolol, amlodipine, atorvastatin and enoxaparin. He also started therapy with pazopanib one month before. He underwent many investigations including sputum cultures, routine blood tests, X-rays and a CT-scan of the chest that showed no significant changes except, as collateral finding, a renal mass suspected of malignancy. Subsequently, a total body CT-scan with contrast medium confirmed the right renal neoplasm, also showing renal vein thrombosis that continued in the caval vein to the right atrium. An otolaryngologist ruled out upper airway problems. The patient experimented, ineffectively, with various therapies: antibiotics, steroids, acetylcysteine, antihistamines, and protonic pump inhibitors. As an extreme attempt, even though he had been taking ramipril for about 25 years, we suggested stopping this drug. Over the following 72 hours, the patient showed a progressive improvement of the clinical picture, up to the complete disappearance of the symptom within one week. To obtain a further confirmation of the pathogenetic mechanisms, a repeat trial with ramipril therapy was proposed to the patient who, however, refused.
Discussions: TheACEIs, increasingly used for patients with hypertension, coronary diseases, heart failure, reduce the risk of major cardiovascular events **(1).**Cough is one of the most common not dose-dependent adverse reactions that usually emerge within the first month, mostly within 6 months since the drug initiation **(1).** Nevertheless, our experience leads us to suggest not to rule out ACEi as a possible cause of chronic cough even if the patient is old and comorbid and has been taking them for many years. The mechanism of ACE inhibitor-induced cough is unclear. Possible protussive mediators include bradykinin and substance P, which are degraded by ACE and therefore accumulated in the upper airway or lung where the enzyme is inhibited. This accumulation, which induces sensitization of airway sensory nerves, is likely to be greater in the elderly, due to well-established changes in drug pharmacokinetic and pharmacodynamic through aging **(2)**. We believe that another non-negligible factor in our patient was the new-onset renal cancer. Different studies reported an overexpression of various kallikreins in various types of cancer, mainly in breast and cervical ones. Thus, we can argue that a possible increase in kinins due to the presence of a neoplasm may have determined the onset of cough in such a comorbid subject "already kallikreins-hypersensitized"**(3)**.
Conclusions: Older patients suffering from chronic cough deserve a rigorous careful analysis of background conditions possibly implicated in its etiology, never forgetting that a chronic long-term ACEi therapy, even unlikely, may play a relevant role. It will be interesting to verify in the future the prevalence of cough in ACEi users among oncologic patients, eventual differences among the various type of cancer, influence of age and comorbidities.
References
Eur J Intern Med
2023 *Journal of Hypertension*
2018 *Journal of Hypertension*
2020 *Fundam Clin Pharmacol*
2017 *J Clin Invest*

382. HOSPITAL ACQUIRED FEVER: NOT ALWAYS A MATTER OF INFECTION

Margilio B., Luglio C. V., De Luca A., Belfiore A., Di Ciaula A., Pellegrino M. R., Murri Internal Medicine Group, Portincasa P.
Section of Pathology, Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), University of Bari "Aldo Moro"

A 64 years-old woman presented to the emergency for drowsiness and asthenia since last two days. She is affected by arterial hypertension, Parkinson's disease in pharmacologic treatment with Melevodopa/Carbidopa, Levodopa/carbidopa, Rotigotine, Safinamide, Opicapone and postoperative hypothyroidism and hypoparathyroidism. At the admission, she was asthenic but wakeful and apyretic, she had tremor of upper limb, transient hallucinations; serum investigations revealed hypocalcemia (Calcium corrected for albuminemia 6,4 mg/dL) treated with slow Calcium gluconate infusion. During hospitalization, despite restoration of normal serum calcium values, the patient developed a progressive worsening of the state of consciousness associated with heavy sweating, hypotension alternating with hypertension, fever >38°C, dysphagia that prevented the administration of oral therapy. Blood tests and instrumental examinations were performed in order to identify the pathogen responsible of the fever: CRP was in range, blood culture, urine culture, viral serologies for pneumonia, test for COVID-19 were all negatives. After neurology and infectious consultations, chest x-ray, EEG, CT and MRI scan of the skull were performed to rule out any brain or lung infections. Echocardiography excluded endocarditis. All tests didn't let to identified a specific infections and an empirical antibiotic therapy with tazobactam/Piperacillin intravenous has been set without benefit. At least also chemical-physical examination of the cerebrospinal fluid, viral PCR for HSV, CMV, VZV, EBV, onco-neural antibodies came back negative. In the suspicion of a Neuroleptic Malignant Syndrome (NMS) it was decided to reintroduce oral therapy, including Anti-Parkinsonian drugs, by nasogastric tube and we have seen a quick defervescence and an improvement of the state of consciousness.
NMS is a potentially lethal syndrome linked to exposure to dopamine antagonists or abrupt withdrawal of dopamine agonists [1]. In this patient diagnosis was made more difficult because she had hypocalcaemia which manifests with neurological symptoms too. Particularly she had muscular rigidity and tremor which they are typical symptom of hypocalcemia [2] but they also are present in NMS, along with hyperthermia >38°C, heavy sweating, elevated cpk values, [3] altered level of consciousness, elevate or labile blood pressure [4]. In this case the rapid withdrawal of dopaminergic agents triggered the syndrome. According to the IEC (International Expert Consensus) the possibility of diagnosis is based on priority scores assigned to each clinical main sign. A score ≥ 74 gives the diagnosis of NMS5 with sensibility of 69,6% and a specificity of 90,7% in. In our case we raised 85 points: dopamine agonist withdrawal (20), hyperthermia >38°C (18), rigidity (17) , mental status alteration (13), blood pressure fluctuation (10), negative work-up for infectious, toxic, metabolic, or neurologic causes (7)[6]. NMS always remains a diagnosis of exclusion and if not treated it can result in death or in residual catatonia, renal o cardiopulmonary complications[5].

References

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383. CULF CIRCUMFERENCE IS A PREDICTOR OF DENOSUMAB RESPONSE IN OLDER WOMEN WITH OSTEOPOROSIS

Oliveri C., Di Giovanni A., Iatì V., Lupo E., Bellone F., Morabito N., Squadrito G., Basile G., Corica F., Catalano A.
Dipartimento di Medicina Clinica e Sperimentale, Università degli Studi di Messina

Aging is associated with deterioration of muscle and bone health, resulting in an increased risk of fragility fractures. It is not known whether muscle mass and strength can influence the pharmacological treatment of osteoporosis. The purpose of this study was to analyze the association between muscle mass and strength and response to denosumab treatment in postmenopausal osteoporotic women.
Postmenopausal women referred to the Outpatient Clinic for Bone and Mineral Metabolism Disorders of the Department of Clinical and Experimental Medicine of the University Polyclinic of Messina were clinically evaluated. The likelihood of sarcopenia was estimated by administering the SARC-F questionnaire, which analyzes strength, assistance in walking, getting up from a chair, climbing stairs, and falls. Muscle mass was assessed by measuring calf circumference, and muscle performance was measured by hand grip strength with a Jamar dynamometer. Bone mineral density (BMD) measurements were taken at the lumbar spine and femur, and X-rays of the spine were taken to check for vertebral fractures. A total of 130 women (age 70.2 ± 9.4 years) were recruited. At baseline, mean BMD T-score values were -2.6 ± 1.1 SD and -2.3 ± 0.7 SD at the lumbar spine and femoral neck, respectively, while mean calf circumference and grip strength were 31.9 ± 2.9 cm and 22.7 ± 6.7 kg, respectively. The SARC-F score was associated with the 10-year probability of major osteoporotic fracture ($r=0.21$, $p<0.05$). The calf circumference was positively associated with the T-score values of both lumbar spine ($r=0.262$, $p=0.034$) and femur ($r=0.359$, $p=0.004$). After 42 months of treatment, BMD increased significantly by 9.6% at the lumbar spine level and 7.3% at the femur level. At multiple regression analysis, after adjustment for patient comorbidities, fracture risk and treatment duration, femoral neck circumference ($\beta=1.76$, $SE=0.82$, $p=0.03$) and femoral BMD value at baseline ($\beta=-94.19$, $SE=26.09$, $p=0.0009$) were independently associated with change in femur BMD with denosumab.
In postmenopausal osteoporotic women receiving denosumab, calf circumference was independently and positively associated with treatment response.

384. ATRIAL FIBRILLATION AND IMPAIRED ATTENTIONAL PERFORMANCES IN HOSPITALIZED OLDER ADULTS

Malacarne F.[1], Sardella A.[2], Brischetto D.[1], Ciancio G.[1], Bellone F.[2], Catalano A.[1], Corica F.[1], Squadrito G.[2], Quattropani M.C.[3], Basile G.[4]
[1]Unit and School of Geriatrics, Dpt. of Clinical and Experimental Medicine, University of Messina, Messina, Italy; [2]Dpt. of Clinical and Experimental Medicine, University of Messina, Messina, Italy; [3]Dpt. of Educational Sciences, University of Catania, Catania, Italy; [4]Unit and School of Geriatrics, Dpt of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy

Introduction: Atrial fibrillation (AF) is the most common arrhythmia in older adults, and is associated with increased risk of cognitive impairment even in the absence of clinical stroke [1]. In the presence of AF, several mechanisms may lead to cognitive impairment (e.g. silent cerebral ischemia, cerebral hypoperfusion and cerebral microvascular disease) [2]. The study aimed to investigate the impact of AF on cognitive functioning, particularly on attentional performances, in a sample of hospitalized older adults.
Methods: From February to September 2019, 103 older inpatients (mean age 80.7 ± 6.9 years) were consecutively enrolled; a comprehensive geriatric assessment was undergone on hospital admission. Global cognitive functioning was evaluated using the Mini Mental State Examination (MMSE); selective and sustained attention were evaluated using Visual Search (VS) and Trail Making Test-A (TMT-A), respectively.
Results: In our sample, AF prevalence was of 33%. Compared to inpatients without AF, those with AF showed worse global cognition (MMSE 19.85 ± 3.96 vs 22.1 ± 5.36, $p= 0.042$), and worse attentional performances (VS 22.43 ± 6.76 vs 27.11 ± 9.47, $p= 0.024$; TMT-A 260.96 ± 98.57 vs 209.49 ± 95.56, $p=0.026$). Furthermore, univariate logistic regressions confirmed the association between lower MMSE ($\beta= -0.222$, $p=0.042$), lower VS ($\beta= -0.249$, $p=0.024$), and higher TMT–A ($\beta= 0.246$, $p=0.026$) scores with the occurrence of AF.
Conclusions: The findings confirm the association between AF and global cognitive impairment, including impaired attentional performances, in older adults. Assessing attention appears crucial since this cognitive domain may play a key role in adherence to therapy and in the onset of delirium in hospitalized older adults.

References

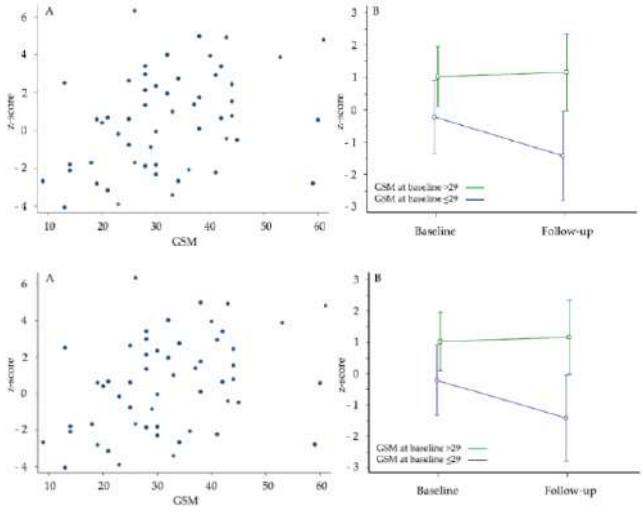
Trends in Cardiovascular Medicine

385. ENHANCED CAROTID PLAQUE ECHOLUCENCY IS ASSOCIATED WITH REDUCED COGNITIVE PERFORMANCE IN ELDERLY PATIENTS WITH ATHEROSCLEROTIC DISEASE INDEPENDENTLY ON METABOLIC PROFILE

Pendenza L.[1], Mastroiacovo D.[2], Mengozzi A.[3], Virdis A.[3], Camerota A.[1], Muselli M.[1], Necozione S.[1], Bocale R.[4], Ferri C.[1], Desideri G.[1]
[1]Department of Life, Health and Environmental Sciences, University of L'Aquila, 67100 L'Aquila, Italy; [2]Angiology Unit, Medical Department, "SS.

Filippo and Nicola" Hospital, Avezzano, 67051 L'Aquila, Italy; [3]Department of Clinical and Experimental Medicine, University of Pisa, 56126 Pisa, Italy; [4]Division of Endocrine Surgery, Agostino Gemelli University Hospital Foundation IRCCS, Catholic University of the Sacred Heart, 00168 Rome, Italy

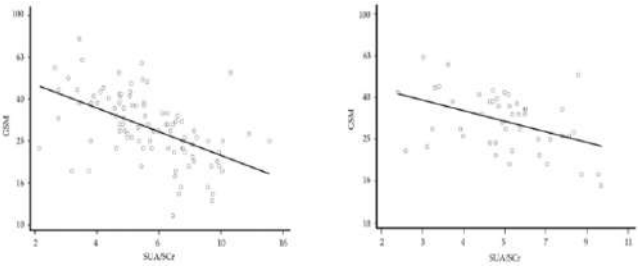
Vulnerable carotid atherosclerotic plaques are related to an increased risk of cognitive impairment and dementia in advanced age.
In this study, we investigated the relationship between the echogenicity of carotid plaques and cognitive performance in patients with asymptomatic carotid atherosclerotic plaques. We enrolled 113 patients aged 65 years or more (72.4 ± 5.9 years) who underwent carotid duplex ultrasound to evaluate plaque echogenicity by grey-scale median (GSM) and neuropsychological tests to assess cognitive function.
The GSM values at baseline were inversely correlated with the number of seconds required to complete Trail Makin Test (TMT) A (rho: -0.442; $p < 0.0001$), TMT B (rho: -0.460; $p < 0.0001$) and TMT B-A (rho: -0.333; $p < 0.0001$) and directly correlated with Mini-Mental State Examination (MMSE) and Verbal Fluency Test (VFT) score (rho: 0.217; $p = 0.021$ and rho: 0.375; $p < 0.0001$, respectively) and the composite cognitive z-score (rho: 0.464; $p < 0.0001$). After a mean period of 3.5 ± 0.5 years, 55 patients were reevaluated according to the same baseline study protocol. Patients with baseline GSM value higher than the median value of 29 did not show any significant variation in the z-score. Instead, those with GSM ≤ 29 showed a significant worsening of z-score (-1.2; $p = 0.0258$).
In conclusion, this study demonstrates the existence of an inverse relationship between the echolucency of carotid plaques and cognitive function in elderly patients with atherosclerotic carotid disease. These data suggest that the assessment of plaque echogenicity, if used appropriately, might aid in identifying subjects at increased risk for cognitive dysfunction.



386. SERUM URIC ACID LEVELS ARE ASSOCIATED WITH THE ECHOGENIC FEATURES OF CAROTID PLAQUE VULNERABILITY IN ELDERLY PATIENTS WITH ATHEROSCLEROTIC DISEASE

Di Tommaso F.[1], Mastroiacovo D.[2], Ettorre E.[3], Mengozzi A.[4], Virdis A.[4], Camerota A.[1], Muselli M.[1], Necozione S.[1], Bocale R.[5], Ferri C.[1], Desideri G.[1]
[1]Department of Life, Health and Environmental Sciences, University of L'Aquila, 67100 L'Aquila, Italy;; [2]Angiology Unit, Medical Department, "SS. Filippo and Nicola" Hospital, 67051 L'Aquila, Italy;; [3]Department of Clinical, Internal Medicine, Anesthesiologic and Cardiovascular Sciences, Sapienza University of Rome, 00161 Rome, Italy; ; [4]Department of Clinical and Experimental Medicine, University of Pisa, 56126 Pisa, Italy;; [5]Division of Endocrine Surgery, Agostino Gemelli University Hospital Foundation Scientific Institute for Research, Hospitalization and Healthcare (IRCCS), Catholic University of the Sacred Heart, 00168 Rome, Italy

Uric acid is a marker of inflammation and a risk factor for atherosclerosis that has been suggested to play a role in carotid plaque instability. Reduced atherosclerotic plaque echogenicity at ultrasound examination is associated with alarming histopathological features and inflammation.
In this study, we investigated the relationship between serum uric acid (SUA) levels and echogenic patterns of plaque instability in elderly subjects with carotid atherosclerosis. Since uric acid metabolism largely depends on renal function, SUA levels were indexed for serum creatinine levels (SUA/SCr).
We enrolled 108 patients aged 65 years or more (72.7 ± 5.9 years; 50 females and 58 males) who underwent carotid duplex ultrasound to evaluate plaque echogenicity by greyscale median (GSM). The regression analysis demonstrated a significant inverse association between the GSM and the SUA/SCr ratio (β: −0.567; 95% CI −0.751 to −0.384 and $p < 0.0001$). Stepwise multivariate regression showed that the SUA/SCr ratio explained 30.3% of GSM variability (β: −0.600; 95% CI −0.777/−0.424, $p < 0.0001$, and semi-partial correlation 0.303). After a mean period of 3.5 ± 0.5 years, 48 patients were reevaluated according to the same baseline study protocol. The regression analysis demonstrated a still significant inverse association between the GSM and the SUA/SCr ratio (β: −0.462; 95% CI −0.745 to −0.178 and $p = 0.002$). Stepwise multivariate regression showed that the SUA/SCr ratio explained 28.0% of GSM variability (coefficient −0.584, 95% CI −0.848/−0.319, $p < 0.0001$, and semi-partial R2 0.280). In conclusion, this study demonstrates that SUA levels indexed for serum creatinine are associated with the echogenic features of carotid plaque vulnerability in elderly patients with atherosclerotic disease. These data could suggest an influential role for uric acid metabolism in carotid plaque biology.



387. FUNCTIONAL AND NUTRITIONAL PATIENT MANAGEMENT AS THE MISSING PIECE FOR IMPROVED HOSPITALIZATION OUTCOMES IN PATIENTS ACCESSING INTERNAL MEDICINE DEPARTMENTS: PRELIMINARY EXPERIENCE FROM A SINGLE-CENTER TERTIARY CARE HOSPITAL

Lucini A.[1], Castellani J.[1], De Lorenzo R.[2], Merolla A.[2], Montagna M.[2], Pontara A.[1], Tresoldi M.[1], Rovere Querini P.[3]
[1]San Raffaele Hospital, Milan, Italy; [2]Vita-Salute San Raffaele University, Milan, Italy; [3]Vita-Salute San Raffaele University, Milan, Italy; San Raffaele Hospital, Milan, Italy

Introduction: Patients accessing Internal Medicine departments are highly heterogeneous in terms of clinical phenotypes and care needs. Although the degree of clinical stability may vary, patients share a global status of fragility and the coexistence of multiple comorbidities that affect hospitalization outcomes. We previously reported that patients admitted to an Internal Medicine department of a tertiary care hospital in Milan, Italy, were mostly elderly, pluricomorbid, and with a high dependency ratio. Also, patient age and functional and nutritional status significantly influenced length of stay and in-hospital mortality, pointing to the importance of accurate patient profiling beyond mere disease characterization to tailor medical decisions and timely adopt preventative measures aimed at reducing the risk of adverse outcomes. Following our observations, starting from February 2023, we implemented physiotherapy and nutritional support to patients admitted to our Internal Medicine department and established a discharge support group to ensure patients safe and appropriate post-discharge conditions and assistance. On the heels of our first report, here we provide our preliminary experience of how our strategy of patient management implementation has affected patient outcomes.
Methods: We compared patients admitted before the introduction of the aforementioned implementations (*pre-implementation group*) and those admitted after (*post-implementation group*) in terms of demographics, length of stay, in-hospital mortality, and functional status at both admission and discharge.
Results: Ninety-three patients enrolled between June and August 2022 were included in the pre-implementation group, while 32 patients enrolled since February 2023 were included in the post-implementation group. Half patients in the first group and 10% in the second group were males, with a me-

dian age of 77 years (IQR 66-85) in the first and 75 years (IQR 65-85) in the second group. In the pre-implementation group 91% of admission were elective while in the second group all patients were hospitalized the department following access to the Emergency department. On admission, the pre-implementation group had an overall worse functional status than the post-implementation group (Glasgow Come Scale 13-15 in 82% vs. 97% of patients, Malnutrition Universal Screening Tool <2 in 72% vs. 21%, total dependence in activities of daily life in 37% vs. 16%, decubitus skin ulcers in 13% vs. 3% of patients, respectively). A similar proportion of patients were on at least 5 chronic medications (54% in the pre-implementation group vs. 46.9% in the post-implementation group). Patients requiring intravenous therapy were 89.2% in the pre-implementation group and 75% in the post-implementation group, while oxygen therapy was administered to 46.2% and 34.4% of patients, respectively. Median length of stay in the first group was 15, while in the second group 14. In the first group, 20% of patients died, while in the second group only one patient died. Of patients discharged alive, 29% vs. 47% in the pre- and post-implementation groups respectively were prescribed at least one medical assistance device at discharge. The proportions of patients who were independent in the activities of daily life at discharge were similar in the two groups (36.6% vs. 37.5%). The discharge settings of patients in the pre- and post-implementation groups were respectively distributed as follows: 57% vs. 78% home; 12% vs. 6% in low-intensity care facilities; 8% vs. 12% in hospice or home with palliative care.

Conclusion: Accurate and timely assessment and management of functional and nutritional status of patients accessing Internal Medicine departments is key to maximize hospitalization benefits and tailor post-discharge destination based on patient needs. Standardized, yet flexible, management strategies for different patient categories might be useful to ensure delivery of appropriate care to all patients and guarantee continuity of care beyond discharge. In a preliminary effort towards the identification and validation of shareable management workflows, we are advancing in the prospective collection of data of patients hospitalized in Internal Medicine departments at our institution and wish to contribute to improve in-hospital patient management by sharing our experience.

388. HYPOGLYCEMIA IN NON-ISLET CELL TUMOR

Turco A.L.[1], Fasciani L.[1], Shehu A.[1], Mancinelli V.[1], Simeone P.[1], D'Ardes D.[1], Bucci M.[1], Santilli F.[1], Guagnano M.T.[1], Cipollone F.[1], Sante D.P.[2]
[1]Clinica Medica" Institute, Department of "Medicine and Science of Aging", University "G. d'Annunzio"; Chieti, Italy; [2]Department of Innovative Technologies in Medicine & Dentistry, University "Gabriele d'Annunzio", Chieti-Pescara, Chieti, Italy.

Work's Objective: Clinical presentation and management of hypoglycemia occurring in a patient with non-islet cell tumor

Materials and Methods: The 65-year-old patient was hospitalized for a transient loss of consciousness at home with consequent head and back trauma. He reported, probably accidental fall at home with right hip and chest trauma. Also reported, confusion lasting a few minutes in the presence of other people, which occurred two weeks earlier. This is a patient with a positive history of hyperthyroidism under thyrostatic treatment and solitary fibrous tumor of the pelvic-obturator excavation (diagnosed in 2015), followed up at the Rome Biomedical Campus where he was treated with Eribulin according to the "Erasing" clinical study protocol and previously chemotherapy with Doxorubicin and Dacarbazine (removed two formations of the pelvic excavation of 11 and 10 cm). Home therapy: Omeprazole, Tapazole, Deltacortene (never started), Retacrit, Eribulin. On admission, the patient presented skin and mucous membranes with macular lesions, like ecchymotic lesions on the arms and ankles; bilateral trochanteric bruising; bilateral periorbital ecchymosis. Normally transmitted MV in the absence of added noise. Valid heart tones, tachycardia, apparently free pauses. No sloping oedemas. Neurological examination normal. Blood tests revealed severe hypoglycemia (30 mg/dl), mild normocytic-normochromic anemia (Hb 9.9 g/dl), mild hypokalemia (K 3.2 mmol/L), CRP 71 mg/L; Normal Hemogasanalysis. ECG: sinus rhythm with HR 92 bpm, without further alterations of the tracing. In addition, x-rays were performed on the ribs, spine, pelvis and hips (in the absence of infractions); brain CT (negative); ECD TSA (negative); Complete contrast abdomen CT with detection of solid lesions in the hypochondrium/left flank and in the pelvic cavity bilaterally (the greater than 15 cm) and pancreas with hyperechoic structure as for fibroadipose involution, already known in the anamnesis. The values of thyroid function (within the norm), martial balance (normal), C-Peptide (0.04 ng/ml from a range between 0.69 and 2.45 ng/ml), Insulinemia (<5 mU/ml for a range between 0 and 25) and IGF-I (22.4 ng/ml for a range between 54.6 and 185.7).

Results: Infusion therapy with 5% glucose solutions was set up and the patient was invited to consume frequent meals. Excluding the diabetic causes provoking such a clinical picture and excluding other etiological factors (exogenous hypoglycaemic drugs, alcohol intake, Addison's disease, neuroendocrine tumor...), together with the laboratory values and analogous cases described in the literature, the diagnosis of Non -Islet Cell Tumor Hypoglycemia (NICTH). Due to the impossibility of dosing IGF-II in our PO, the blood sample was sent to the laboratory center of the University of Tor Vergata in Rome. On discharge, therapy with glucagon and corticosteroids (as indicated in the treatment of soft tissue sarcomas) was set up and the patient was invited to follow up on diabetes/oncology.

Discussion: Non-islet cell tumor hypoglycemia (NICTH) is a rare but serious complication of the tumor. The most common cause of this type of hypoglycemia is tumor overproduction of incompletely processed insulin-like growth factor-II (IGF-II), which results in stimulation of insulin receptors and increased glucose utilization . Other potential but less common causes include the production of autoantibodies against insulin or its receptor and large tumor burden resulting in destruction of the liver or adrenal glands. NICTH occurs most commonly in patients with mesenchymal tumors, fibroids, carcinoids, myelomas, lymphomas, hepatocellular and colorectal carcinomas. In this case, Solitary Fibrous Tumor, it is a mesenchymal neoplasm: it represents 3.7% of all soft tissue sarcomas with an estimated annual incidence of 0.35 cases for 100,000 individuals. No single pathogenic mechanism explains all cases of non-islet cell tumor hypoglycemia (NICTH). However, the major cause appears to be increased glucose utilization (particularly in skeletal muscle) and inhibition of glucose release from the liver due to tumor secretion of incompletely processed insulin-like growth factor, termed " large" IGF-II; rarely can IGF-I be secreted. There are three components of therapy in patients with non-islet cell tumor hypoglycemia (NICTH): immediate correction of the hypoglycemia, direct treatment of the underlying malignancy, and prevention of recurrent hypoglycemia if the tumor cannot be controlled with hyperglycemic drugs.

389. BLOOD LEVELS OF VITAMIN D, VITAMIN B12 AND FOLATE IN ELDERLY PATIENTS.

Marchesi C.[1], Andreoletti M.[1], Galbiati G.[1], Nigro M.[1], Piemonti C.[1], Polvara D. [2], Antivalle M.[1]
[1]UOC Medicina Generale, Casa di Cura Talamoni, Lecco; [2]Laboratorio Analisi, Casa di Cura Talamoni, Lecco

Background and Aims: While low blood vitamin levels are frequently observed in elderly patients, the actual prognostic impact of low vitamin levels and the usefulness of supplementation are still controversial issues (1,2). The aim of the present study was to evaluate blood levels of three vitamins, and their correlation with demographic and clinical variables, in elderly patients admitted to a general medicine unit.

Methods: The study population consisted of consecutive patients admitted to our department. In all patients Vitamin D (25-OH-cholecalciferol, VitD), Vitamin B12 (Vit B12), and Folate blood levels were measured n all patients. Insufficient (I) and deficient (D) blood levels were defined according to international consensus and local laboratory ranges: VitD (I) < 30 ng/mL and (D) < 20 ng/mL; VitB12 (I) < 300 pg/mL and (D) <200 pg/mL; Folate (I) < 5.38 ng//mL, and (D) < 3.39 ng/mL. eGFR was calculated with EPI-CKD equation. All statistical analyses were performed with IBM SPSS software, using parametric and nonparametric methods as appropriate.

Results: 310 patients were studied. Mean age was 82.03 ± 7.12 yrs (range 66-97), 134 (43.2%), males and 176 (56.8%) females. Mean BMI was 24.90 ± 4,85 (range 11.89 – 46.97); 47.4 % of patients were treated with PPIs, and 10.3% with metformin.

Mean blood levels of Vitamin D, Vitamin B12 and folate were 23,80 ± 23,04 ng/mL, 306.76 ± 236,74 pg/mL, and 8.17 ± 6,96 ng/mL respectively. Men showed significantly lower levels of Vitamin D (19.59 ± 15.96 vs 27.00 ± 26.82, p = 0.005) and Vitamin B12 (274.96 ± 210.27 vs 330.98 ± 252.97, p= 0.039), and slightly lower folate levels (7.83 ± 7.16 vs 8.43 ± 6.81, p =0.452) as compared to females.

Normal blood values of all the vitamins tested were recorded in only 31 (10%) patients. Insufficient or deficient levels were observed in 72.9 % of patients for VitD, 62.9 % of patients for VitB12, and 50.4% of patients for folate. The percentages of patients with normal, insufficient, and deficient vitamin levels are shown in Fig. 1.

Vitamin levels were not correlated age, BMI, or eGFR (Pearson r coefficients ranging from -0.22 to 0.091). Patiens treated with PPIs showed higher levels

of VitD (26.44± 23.68 vs 20.72± 16.07, p=0.028), VitB12 (332.71 ± 272.80 vs 274.73 ± 191.65, p=0.056) and folate (9.07 ± 7,39 vs 7.40 ± 6.73, p=0.061).

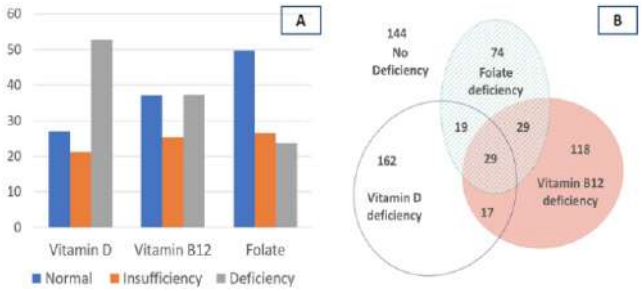


Fig. 1 - Percentages of patients with normal, insufficient, and deficient blood levels (Panel A), and Venn diagram (Panel B) of the deficiencies in vitamin B12, folate, and vitamin D.

Conclusions: Our study confirms that low levels of multiple vitamins are frequently observed in patients >65 years of age. Further studies are needed to fully clarify its clinical impact and appropriate management.

References

Giustina A, et al. Endocrine. 2023 Jan;79(1):31-44.
Herrmann W, Herrmann M. Nutrients. 2022 Mar 28;14(7):1412.

MALATTIE CARDIOVASCOLARI

390. INFERIOR CAVAL VEIN ANOMALIES: CASES REPORT

Di Castri C., Ciammaichella M.M., De Paola G., Ulissi A., Marzano M.A., Pignata D., Fanfarillo F.
UOC Medicina Interna ad Alta Intensità di Cure, Dipartimento di Medicina Interna, A.O. S. Giovanni-Addolorata, Roma

Introduction: A broad spectrum of congenital anomalies and pathologic conditions can affect the inferior vena cava (IVC). Most congenital anomalies are asymptomatic; consequently, an awareness of their existence and imaging appearances is necessary to avoid misinterpretation. Imaging also plays a central role in the diagnosis of Budd-Chiari syndrome secondary to membranous obstruction of the intrahepatic IVC.
Case Report: A basic knowledge of IVC embryogenesis is essential for understanding the anomalies of the IVC. A detailed review of IVC formation is beyond the scope of this article, but the interested reader can refer to an excellent review by Phillips. Briefly, during the 4th week of fetal life, paired posterior cardinal veins drain the caudal portion of the embryo. These veins are progressively replaced, first by the subcardinal veins and later by the supracardinal veins, which together form the subhepatic IVC.
CASE 1: Left IVC has a prevalence of 0.2%–0.5% and represents a persistent left supracardinal vein. The right supracardinal vein regresses in these cases, resulting in a mirror image variant. A leftsided IVC typically joins the left renal vein, and together they course anterior to the aorta to join
the normal (right-sided) IVC. A left-sided IVC per se is of no clinical importance. However, it may be mistaken for left paraaortic adenopathy, complicate surgical repair of an aortic neurysm, and cause difficulty in placing an infrarenal IVC filter with a transjugular approach.
CASE 2: Double (right and left) IVC has a prevalence of 1%–3% and results from persistence of both the right and left supracardinal veins. Typically, the left IVC drains into the left renal vein, which then joins the right IVC. There may be significant discrepancy in the size of the two veins.
CASE 3: Retrocaval ureter is one of the few congenital anomalies of the IVC that can be symptomatic. Unlike other congenital ureteral obstructions, this embryologic defect lies in the developing vena cava rather than the ureter.
CASE 4: Complete absence of the infrarenal IVC with preservation of the suprarenal segment is an extremely rare anomaly. This condition may be a sequela of intrauterine or perinatal thrombosis of the IVC and not truly embryologic in origin. Affected patients are prone to develop deep venous thrombosis and chronic venous insufficiency.
CASE 5: Anomalies of the renal segment of the IVC include variants of the left renal vein. Normally, the left renal vein is derived from the intersubcardinal anastomoses, which course anterior to the aorta. The left renal vein is retroaortic in 1.7%–3.4% of individuals and occurs when the vein derives from the intersupracardinal veins, which lie posterior to the aorta.
CASE 6: Interruption of the IVC with azygous or hemiazygous continuation results from failed formation of the right subcardinal-hepatic anastomosis, with consequent atrophy of the subcardinal vein (suprarenal IVC).
CASE 7: Congenital extrahepatic portocaval shunt is a rare anomaly. Two types have been descrive: Type I shunt is a complete end-to-side shunt between the portal vein and the IVC, with the main portal vein distal to the shunt being absent; type II shunt is a partial side-to-side shunt between the portal vein and the IVC.
CASE 8: Membranous obstruction of the intrahepatic IVC accounts for most cases of primary BCS in India, Nepal, South Africa, Japan, China, and Korea. It is typically a disease of adulthood with an insidious onset and a chronic course that eventually leads to congestive cirrhosis. In contrast, in most Western nations, BCS results from hepatic venous thrombosis due to an nderlying prothrombotic state, has an acute onset, and is often fatal.
CASE 9: Bland thrombus, which is the leading cause of IVC obstruction, typically originates in the lower extremities or the pelvis. Affected patients often have an underlying predisposing condition such as dehydration, sepsis, localized inflammation, pelvic inflammatory disease, coagulopathy, congestive heart failure, immobility, or trauma.
CASES 10-11: In blunt trauma patients, a flattened IVC at multiple levels is a strong indicator of hypovolemia or hypotension and may signify impending cardiovascular collapse. A flat IVC together with *(a)* a decreased caliber of the aorta, *(b)* marked diffuse bowel distention, *(c)* moderate to extensive hemoperitoneum, and *(d)* hyperenhancement of the bowel wall, kidneys, and pancreas constitutes the "hypoperfusion complex" seen at abdominal CT in blunt trauma patients.
CASE 12: Early enhancement of the IVC with dense undiluted contrast material can be due to reflux from the right atrium, aortocaval fistula, superior vena cava obstruction, or arteriovenous shunting in hypervascular liver tumors.
Discussion: The IVC is host to a wide array of congenital anomalies and pathologic conditions. Imaging allows precise diagnosis of congenital variants and membranous obstruction of the intrahepatic IVC and is accurate in depicting the presence and extent of thrombus.
Conclusions: The Authors have explained cases report of patients with inferior vena cava anomalies.

391. SUBCLAVIAN STEAL SYNDROME: CASE REPORT

Fanfarillo F., Pignata D., Ciammaichella M.M., Marzano M.A., Ulissi A., Di Castri C., De Paola G.
UOC Medicina Interna ad Alta Intensità di Cure, Dipartimento di Medicina Interna, A.O. S. Giovanni-Addolorata, Roma

Introduction: We describe the case of a 67-year-old man who was referred to us for a presyncopal episode after effort withthe left upper limb (lifting a weight) and paresthesiathat configured a clinical picture ofsubclavian steal syndrome.
Case Report: On physical examination,a coarse murmur was detected at the left base of the neck. The skin temperature of the upper left limb was maintained. The patient was afebrile. The right PAO was 140/90 mmHg, the left PAO was 110/50 mmHg, the heart rate was 80/m and rhythmic. The following was carried out during hospitalisation: repeated ECG showing sinus rhythm; blood tests that were within the limits; markers for primary and secondary thrombophilia: within limits; chest x-ray: absence of ongoing pleuralparenchymal alterations; TT echocardiogram: normal kinesis, (FE 60%), right sections within limits, absence of pericardial effusion; venous doppler ultrasound on upper and lower limbs: patency of the superficial and deep venous axes; arterial doppler ultrasound of the lower limbs: flussimetric control was within the limits; Doppler ultrasound of the supra-aortic vessels: inversion of the flow of theleft vertebral with occlusion of the prevertebral left subclavian artery; cranian ct scan: absence of tomodensitometric alternations in the acute phase; angio MRI of the left upper limb: arteries correctly viewed; angio MRI of the aortic trunk and supra-aortic vessels: evidence of subclavian steal. The patient is treated withPTA and stent implantation on the left subclavian artery as demonstrated by the angiographic check of the supra-aortic vessels performed after the procedure. The patient was treated with LMWH and clopidogrel for 1 month, salicylates and clopidogrel for 1 year, and salicylates for life. A check with arterial Doppler ultrasound of the supra-aortic vessels was carried out under protected discharge after approximately 20 days, which showed correct positioning of the stent and flussimetric control on the subclavian artery in the limits without inversion onto the left vertebral artery. After discharge, the patient no longer had paresthesias of the upper limb and no longer had pre-syncopes after effort of the upper left limb.

Discussion: The subclavian steal syndrome is a particular hemodynamic situationin which there is a, not uncommon, epiaortic circulation of a pre vertebral subclavian artery. The cause is usually atherosclerosis. The connecting circulation between the large supra-aortic vessels (subclavian, vertebral, external and internal carotid arteries) is abundantly represented; for example, cases of occlusion of the common carotid artery with circulation of the internal and external in an inverted direction are frequently found: this is partly due to the communication between two communicating anteriors and partly due to the interpolation anastomosis between the carotid arteries. However, the most important thing is that the afferent anterior cerebral circulation (carotid arteries) communicates with the posterior circulation through the circle of Willis. In this condition, the presence of subclavian stenosis, placed between its origin and the origin of the vertebral, involves not only the drop in pressure in the same subclavian, but also in the vertebral from which it originated. Since the blood stream flows by pressure gradients, at the circle, in particular at the basilar, the flow inverts and moves back towards the vertebral at low pressure, and, from here, to the next section beyond the stenosis. This creates a circuit for which the subclavian "steals" the blood from the ipsilateral vertebral and the circle of Willis. The debt of the robbed subclavian is paid by the anterior circulation and the contralateralvertebral. It seems pretty obvious that the symptoms relating to this theft can be triggered by a muscular effort of the limb affected by the stenosis (this results in a greater volume of theft to overcome the hyperaemic efforts of the subclavian that must supply the arm muscles) and that this will be characteristic of the area predominantly robbed (anterior in the case of carotid-vertebral compensation and posterior in the case of vertebro-vertebral compensation). Therefore, TIA, vertigo, lipotimia and visual disturbances may be presented at each prolonged effort of the robbed limb, as is the case of our patient.
Conclusions: The authors presented a case report of subclavian steal syndrome in a 67-year-old man, which became evident withpresyncope after effort of the upper left.

392. COELIAC ARTERY DISSECTING: CASE REPORT

Conti M., Ciammaichella M.M., Pignata D., Fanfarillo F., Marzano M.A., Ulissi A., Di Castri C., De Paola
UOC Medicina Interna ad Alta Intensità di Cure, Dipartimento di Medicina Interna, A.O. S. Giovanni-Addolorata, Roma

Introduction: Abdominal pain is one of the most common presenting chief complaints of patients in the emergency department. It is a general chief complaint that represents a wide breadth of diagnoses, ranging from benign to life-threatening, and it is critical that emergency physicians be able to differentiate the two. For this reason, abdominal pain can be a challenging chief complaint, as there is often overlap in symptoms and localization of intra-abdominal pathology can be unreliable on physical exam. A combination of labs, imaging, and physical exam is often needed to determine the diagnosis. The management of abdominal pain has changed over time, and recent trends show an increase in computed tomography (CT) being done to aid in the diagnosis. While increased use of CT carries the risk of radiation exposure, potential of contrast-induced nephropathy, and higher hospital costs, it has led to more reports of diseases that previously could only be identified in the operating room or on autopsy. One such potentially life-threatening diagnosis is spontaneous visceral artery dissection. We describe a case of a 55-year-old woman who presented to the ED with a chief complaint of abdominal pain and was found to have a spontaneous isolated celiac artery dissection (SICAD) and was successfully treated with anticoagulation, antihypertensives, and observation.
Case Report: A 55-year-old female with a past medical history of hypertension presented to our ED for evaluation of abdominal pain. She reported that just prior to arrival he had sudden onset pain in her midepigastric region. It was sharp, severe, radiating to his back and was associated with nausea and dyspnea. He was hypertensive with otherwise normal vital signs. On examination she was tender to light palpation in his epigastric region without rebound, guarding, or tenderness elsewhere. She had a normal electrocardiogram without any signs of ischemia. Her labs were significant for a white blood cell count of 19 thousands (K) per microliter (mcL) (range 3.6-10.6 K/mcL), with a normal lipase, normal liver function tests, and negative troponin. Given the history and exam, a CT angiogram of the chest, abdomen, and pelvis was ordered, which revealed SICAD with extension into the common hepatic artery.
Discussion: SICAD is a rare but potentially life-threatening diagnosis. It is the second leading type of visceral artery dissection after spontaneous isolated superior mesenteric artery dissection. Visceral artery dissections were first described in 1947 and initially thought to be a fatal injury as all cases reported before 1975 were diagnosed at autopsy. However, the implementation of CT angiography has improved the ability to make the diagnosis. Symptoms can range from asymptomatic incidental findings to severe abdominal pain with bowel ischemia resulting in peritonitis; therefore, the diagnosis requires a high level of clinical suspicion. The most common profile of patients presenting with SICAD are male smokers with hypertension, although it will also present in those without these comorbidities. Conservative management is considered the initial treatment for most SICAD patients as long as they do not have bowel ischemia, although there is not a standardized consensus on the best medical therapy. Most medical treatments performed include a combination of fasting, parenteral nutrition support, pain control, and treatment of hypertension. Two large cohort studies to date have shown no benefit with antithrombotic therapy vs observation in clinical outcomes. Our patient was started on an esmolol infusion to control his hypertension along with a heparin infusion at the recommendation of the vascular surgery service. She was admitted and transitioned to oral anticoagulation and antihypertensive medications after her abdominal pain resolved. She did not require intervention and was discharged in good condition several days later.
Conclusions: Abdominal pain as a chief complaint can vary from benign to catastrophic. Spontaneous isolated celiac artery dissection is relatively rare, and can present from asymptomatic incidental finding to severe pain with bowel ischemia and peritonitis. Early diagnosis is critical to reduce morbidity and mortality and is typically detected on a contrast-enhanced CT. SICAD has a wide presentation range, but often resolves with conservative management. It is important for emergency physicians to keep this potentially life-threatening condition on their differential, and to know the appropriate first steps to take once identified.

393. RETROSPECTIVE ANALYSIS ON 12 CASE OF CARDIORESPIRATORY ARREST IN PATIENTS WITH MASSIVE PULMONARY EMBOLISM. "CASTEV" STUDY

Celi F., Ciammaichella M.M., Pignata D., Fanfarillo F., Marzano M.A., Ulissi A., Di Castri C., De Paola G.
UOC Medicina Interna ad Alta Intensità di Cure, Dipartimento di Medicina Interna, A.O. S. Giovanni-Addolorata, Roma

Introduction: The "CASTEV" study, an acrostic deriving from "CArdiac arreST in patiEnts with massive pulmonary embolism", enrolled in the period between January 2016 and December 2022 12 patients with massive pulmonary embolism complicated, in the pre-lysis period, by cardiorespiratory arrest. The initial clinical picture was characterized in all patients by dyspnea (arterial blood gas value of pO2 <60 mmHg) associated with chest pain, hemodynamic stability (SBP <90 mmHg) according to the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. All patients underwent: thoraco-abdomino-pelvic CT with contrast medium; echocardiography with measurement of systolic pulmonary arterial pressures; venous color Doppler of the lower limbs and possible elastic compression; search for thrombophilic and neoplastic markers. Presenting electrocardiographic rhythms at the time of cardiorespiratory arrest were examined in all patients. Therefore, a database with Microsoft Access© named "CASTEV" was created. The database contained the following fields: 1) patient number, 2) shockable rhythm, 3) non-shockable rhythm (PEA or asystole). All patients were analysed, during recruitment, according to the aforementioned 3 fields, collected from time to time in masks created in "structure view" and "data sheet view" mode as allowed by the database program. A comparative analysis was performed for continuous variables with Cochgran's Q parametric test to verify if there is a significant relationship between the cardiorespiratory arrest situation (independent variable A) and the presenting rhythm (variable And employee).
Purpose of the Work: The "CASTEV" study has the following objectives: 1) verify any existing relationships between the cardiorespiratory arrest situation and the presenting electrocardiographic rhythm in the 120 patients enrolled in the "CASTEV" study during the decade January 2016 - December 2022; 2) verify the statistical significance found by applying Cochran's Q parametric test as a comparative analysis test for continuous variables to establish whether the relationships of the variables considered are due to chance.
Materials and Methods: A comparative analysis for continuous variables was performed with Cochran's Q parametric test to verify if there is a significant relationship between the variables considered: cardiorespiratory arrest in the course of massive pulmonary embolism and presentation electrocardiographic rhythm. The "Subjects" column shows the number of patients who participated in the study. The central column shows the variables "ND-

A", "ND-P", "D" which correspond to the clinical classes they belong to: ND-A (Non-Shockable-Asystole), ND-P (Non-Shockable-Asystole), D (Shockable). In column "Y" the number of clinical situations. In the column "Y2" the square of the values of "Y". The total of the conditions is indicated in the "Totals" row. The square of the totals of the clinical conditions is indicated in the "Totals2" row. The abbreviation "Y=12" indicates the total of clinical conditions. The abbreviation "Z=12" indicates the square of the total of clinical conditions. The abbreviation "Y2=144" indicates the square of the total of clinical conditions. The sum of the squared totals is indicated with the following formula: X=xND-A2+xND-P2+xD2=144+0+0=144.
Analysis of Results: Cochran's Q test applied to the 12 patients involved in the retrospective analysis, shows how the clinical situation "ND-A" (Non-Shockable-Asystole) highlighted in all patients is not attributable to chance but assumes statistical significance high because the relative value (VR) of $\chi 2$ obtained is 144 with Degrees of Freedom (GL)=2 and the critical value (VC) of $\chi 2$ for p=0.001 is 13.816. The differences in choice are, therefore, highly significant with p<0.001.
Discussion: The data obtained in the 12 patients enrolled in the "CASTEV" study demonstrate how the electrocardiographic presentation rhythm is in the course of cardiorespiratory arrest, a non-shockable bile rhythm and in particular an asystole. This is due to the severe hypoxaemia and hypovolemia caused by massive pulmonary embolism.
Conclusions: The "CASTEV" study demonstrated that in the group of 12 patients with massive pulmonary embolism complicated by cardiorespiratory arrest, the presenting electrocardiographic rhythm was a non-shockable rhythm and in particular an asystole.

394. VENOUS THROMBOEMBOLISM AND FEMORAL EPIPHYSIS RECONSTRUCTION FOR CEPHALIC NECROSIS: CASE REPORT.

Puglisi L.[1], Ciammaichella M.M.[2], Pignata D.[2], Fanfarillo F.[2], Marzano M.A.[2], Di Castri C.[2], De Paola G. [2], Ulissi A.[2]
[1]UOC Geriatria, Dipartimento di Medicina Interna, A.O. S. Giovanni-Addolorata, Roma; [2]UOC Medicina Interna ad Alta Intensità di Cure, Dipartimento di Medicina Interna, A.O. S. Giovanni-Addolorata, Roma

Introduction: We present a case of a 30 year-old man suffering from dyspnea and chest pain, with a turgid limb since a few days, turgidity in the left inferior limb since 20 days. The results obtained from the case history showed bilateral necrosis of femoral epyphysis. That is why he had an operation approximately one month before for cephalic necrosis stadium III-IV with autolog engineering cartilage, bioceramic cylinders, freeze-dried bone chips in association with piastrinic gel and a concentration of medullary cells.
Purpose of the Experiment: We have the following goals: to show a case report concerning the reconstruction of femoral epyphysis for cephalic necrosis, in order to check the relationship between the operation and venous thromboembolism. Moreover, to report any similar cases in literature.
Case Report: At the beginning the anamnesis showed breathing difficulty (arterial blood gas analysis value pO2<60 mmHg) associated with chest pain, confused state of mind, hemodynamic instability (PAS<90 mmHg) according to American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (2019).
The patient was submitted to: chest, abdomen and pelvic TC with mcm; pulmonary angiography with loco-regional fibrinolysis in association with sodic heparin, in peripheral vein; a pre discharge from hospital echocardiography with pulmonary arterial pressure measurement; implant of removal caval filter OPTEASE; flebography of the left inferior limb with loco-regional fibrinolysis; venous and lower limb echo color Doppler and elastic compression bandage; negative identification of thrombophilic and neoplastic markers; pelvic RM carried out before the operation and 6 months after the operation.
Discussion: This case of venous thromboembolism is chronologically correlated with the operation the patient was submitted to, despite the anticoagulant prophylaxis monitored carefully after the operation. Anyway the research for primary and secondary thrombophilia was negative. The patient belongs to a very restricted group of people enrolled with the same pathology (Stadium III-IV with cephalic necrosis), who were recruited in order to find the reconstruction of femoral epyphysis with autolog engineering cartilage, bioceramic cylinders, freeze-dried bone chips in association with piastrinic gel and a concentration of medullary cells. This was the only patient suffering from thromboembolism among the 20 patients enrolled. We report the experiences of Karatoprak, Hattori, Doi, Wang, Chang, Liang. There are no other case reports correlated with venous thromboembolism.
Conclusions: We showed a case report concerning the necrosis of the femoral head, according to a research project enrolling 20 patients with cephalic femoral necrosis (Stadium III-IV), with the reconstruction of femoral epyphysis with autolog engineering cartilage, bioceramic cylinders, freeze-dried bone chips in association with piastrinic gel and a concentration of medullary cells, complicated by venous thromboembolism.

395. AIR PULMONARY EMBOLISM DEVELOPED AS A RESULT OF OPENING THE CENTRAL CATHETER: CASE REPORT

Riga C.[1], Ciammaichella M.M.[2], Pignata D.[2], Fanfarillo F.[2], Ulissi A.[2], Marzano M.A.[2], Di Castri C.[2], De Paola G.[2]
[1]UOC Medicina Interna, Dipartimento di Medicina Interna, A.O. S. Giovanni-Addolorata, Roma; [2]UOC Medicina Interna ad Alta Intensità di Cure, Dipartimento di Medicina Interna, A.O. S. Giovanni-Addolorata, Roma

Introduction: Central venous catheterization (CVC) is a common medical procedure applied to critically ill patients in the intensive care unit (ICU) for purposes such as dialysis, nutrition, or hemodynamic monitoring. The most common complications of CVC are mechanical complications (haemothorax, pneumothorax, arterial puncture, hematoma), catheter infection, bleeding, and thrombosis during the placement. Air entry into the circulation resulting in air embolism is a very rare but potentially lethal complication of central catheterization. If CVC is no longer necessary in patients discharged from the ICU, it should be removed to avoid those complications. Herein, we report a patient who developed air embolism following discharge from the ICU due to patent CVC in the service.
Case Presentation: A 66-year-old male patient with no known comorbidities underwent laparoscopic total colectomy and protective loop ileostomy due to colon cancer. No complications or problems were reported during the operation. He was taken to the general surgery intensive care unit (ICU) for a close hemodynamic follow-up in the postoperative period. On arrival, he was conscious, oriented, and cooperative, with a Glasgow coma score (GCS) 15/15, blood pressure (BP):120/60 mmHg, SpO2:95% (in room air), heart rate:89 beats/min, respiratory rate (RR) 20 breaths/min. No abnormality was detected in laboratory findings and arterial blood gas analysis. White blood cell (WBC) was elevated due to recent surgery. In the arterial blood gas analysis in room air, the pH was 7.41, PaO2 103 mmHg, PaCO2 30.7, lactate 1.7 mmol/L, HCO3 21.4 mmol/L, base excess -4,3. For venous thromboembolism prophylaxis, enoxaparin 0.6 cc subcutaneous treatment every 24 hours was started in the patient who weighed 75 kg. Prophylactic Cefazolin 1 gram IV every 12 hours started to prevent surgical site infection. The patient was mobilized 6 hours postoperatively. Since the patient was cachectic and could not reach the target of oral nutrition within 1 week, a central catheter was inserted in the right internal jugular vein with ultrasonographic imaging and total parenteral nutrition (TPN) started. No complications were encountered in the chest X-ray following the insertion of central catheter. The patient, who had no hemodynamic and clinical problems in the follow-up, was transferred to the general surgery service on the post-operative 4th day. The patient became unconscious (GCS:5) and had an extensor posture 3.5 hours after the transfer to the ward. On physical examination, there was no nuchal rigidity. Emergency cranial computed tomography (CT) was performed and the patient was taken back to the ICU. On arrival, he was unconscious, eyes were spontaneously open and fixed to the left lateral. Vital findings were blood pressure:193/120 mmHg, heart rate:143 beats/min, SpO2:96% (with 8 L/min oxygen support), RR: 22 breaths/min. Under 10 L/min oxygen therapy, in arterial blood gas analysis pH was 7.41, PaO2 46.1, PaCO2 40.8, lactate 5.4 mmol/L, SpO2 78.4%, HCO3 20.8 mmol/L, base excess -4,5. The patient was hypoxic, and had high D-dimer levels (2.48 µg/ml), with increased high-sensitive troponin T (Hs trop-T) compared to the basal value of 6.68 ng/L (1 ng/L). There was no finding in favor of bleeding in cranial CT. NT pro-brain natriuretic peptide (NT-proBNP) was measured as 4884 ng/L, higher than the reference range (normal range 0-450 ng/L). On transthoracic echocardiography, left ventricular ejection fraction was 60%, and no pathology was found in the right heart chambers. The patient was intubated to protect the airway, as he was having generalized tonic-clonic seizures during his follow-up. Lumbar puncture was performed once to exclude central nervous system infection due to fever of 38.5°C, however, no signs of infection were found. In cerebral spinal fluid (CSF), glucose was 74 mg/dL, chlorine was 128 mEq/L, potassium was 2.21 mEq/L, protein was 84.6 mg/dL. No bacteria or leukocytes were seen on the Gram stain of CSF; and in the cell count, no leukocytes or erythrocytes

were seen per mm3. Before echocardiographic assessment patient underwent multidetector thorax CT angiography at the 24th hour of clinical deterioration and air bubbles were detected in the right atrium, and the patient was placed on his upper right lateral side. Air was not observed in transthoracic echocardiography, and transoesophageal echocardiography could not be performed for technical reasons. The patient underwent hyperbaric therapy and new control with thorax CT angiography.
Discussion: Air embolism is a preventable, relatively rare but catastrophic hospital-acquired complication of CVC. Air can be introduced to the vascular system iatrogenically at the time of catheter insertion, removal, or during accidental or unawaredisconnection of the catheter. In our patient, a central catheter was not removed for the continuation of TPN treatment due to cachexia during the postoperative period.
Conclusions: The Authors presented case report of a patient with air pulmonary embolism developed as a result of opening the central catheter

396. SEX-SPECIFIC IMPACT OF ARTERIAL STIFFNESS ON THE OUTCOME AFTER ISCHEMIC STROKE

Acampa M.[1], Lazzerini P.E.[2], Cartocci A.[3], Domenichelli C.[1], Guideri F.[1], Tassi R.[1], Martini G.[1]
[1]Stroke Unit, Department of Emergency-Urgency and Transplants, Siena, Italy,; [2]Department of Medical Sciences, Surgery and Neurosciences, Siena, Italy; [3]Department of Medical Biotechnology, Siena, Italy

Background and aims: Arterial stiffness (AS) is an independent predictor of cardiovascular events and associated with a poor prognosis. While AS may represent a novel therapeutic target, recent evidence showed that it is sexually dimorphic. Aim of this study was to evaluate sex differences in AS prevalence and their possible impact on the outcome of acute ischemic stroke. Methods: We retrospectively evaluated a cohort of 334 patients (176 males, 158 females) with acute ischemic stroke who underwent 24-h blood pressure in-hospital monitoring. The following parameters were evaluated: systolic blood pressure, diastolic blood pressure, mean blood pressure, pulse pressure and arterial stiffness index (ASI). Results: ASI was similar in women and men but there was a significant sexdependent impact of ASI on 90-day unfavourable Rankin score as only men had a reduced likelihood of favourable outcome with increasing arterial stiffness (OR:1.54, 95%CI:1.06–2.23; P-interaction=0.023). Conclusions: The influence of ASI on 3-month functional outcome after acute ischemic stroke is mediated by sex, suggesting that only in males higher ASI values are correlated with a worse outcome.

397. ATRIAL FIBRILLATION, ANEMIA AND ANTICOAGULATION: ALGORITHM PROPOSED FOR UNCOFORTABLE COMPANY

De Luca P.[1], Benvenuto A.[1], Sollazzo V.[1], De Luca A.[2]
[1]Dipartimento Internistico Multidisciplinare, Ospedale "T. Masselli-Mascia" San Severo ASL Foggia; [2]Dipartimento Internistico Mutidisciplinare, Ospedale "T. Masselli-Mascia" San Severo ASL Foggia

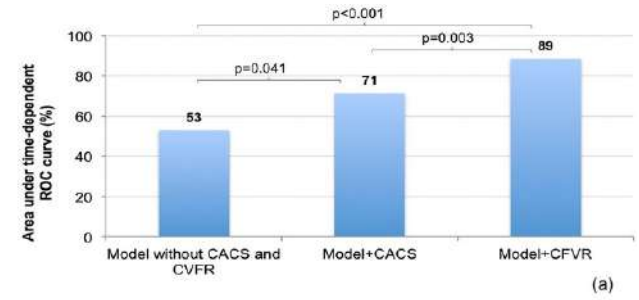
Background: Atrial fibrillation is the most common sustained arrhythmia and frequent cause of emergency room visits with a risk of ischemic stroke 5 times higher than in the general population; the prevention of cardioembolism therefore represents a condition that cannot be postponed right from the first evaluation. Bleeding events represent a common clinical problem in the elderly, and pose difficult decision-making issues in patients indicated for oral anticoagulant therapy. The decision on whether or not to continue anticoagulant therapy in patients who have bled cannot be based on a standardized approach but on a careful individual assessment of the expectation and quality of life, functional status and comorbidities, estimation of the embolic and haemorrhagic risk, and of the clinical impact of any bleeding recurrence. If one opts to resume oral anticoagulant therapy, optimization of therapies aimed at reducing the risk of rebleeding is essential, including the choice of new oral anticoagulants with the best safety profile, and close periodic monitoring of the patient.
Clinical Case: A ninety-year-old man suffering from hypertensive heart disease and chronic atrial fibrillation (on beta-blocker therapy and new oral anticoagulant), arrives in the emergency room for dyspnoea. Discrete vital signs. ECG: atrial fibrillation with medium ventricular rate. Finding of hemoglobin 7.2 g/dl with mild renal insufficiency from dehydration. The patient is hospitalized in Internal Medicine, where he performs blood transfusion and pro tempore suspension of the oral anticoagulant.
Discussion and Conclusions: With aging, the risk of bleeding increases; however, after the age of 75-80 the further increase in the risk of bleeding seems quite modest. Most bleedings in patients treated with vitamin K antagonists occur in patients with optimal INR; it therefore seems to be possible to infer that oral anticoagulant therapy makes bleeding due to lesions more frequently present in old age visible and clinically manifest, rather than being the cause of the bleeding. For this reason the scales for bleeding risk usually used have poor discriminatory capacity, especially in the elderly. Several studies suggest that the resumption of oral anticoagulant therapy after a bleeding event (gastrointestinal or other site) is associated with better clinical outcomes (less mortality and thromboembolic events), with a possible increased risk of general and/or gastrointestinal bleeding recurrences. However, these are observational registers, mostly retrospective, completely devoid of global evaluations of the patient, not always corrected with adequate statistical methodologies and as such burdened by a high risk of selection-bias, to be therefore considered with extreme caution in the absence more robust scientific evidence. In patients with atrial fibrillation, anemia is a predictor of major bleeding during therapy with anticoagulants and for this reason it has been included in various scores for determining the bleeding risk. In such patients there are still several gray areas regarding the available data on the association between anemia and stroke risk. With this review we aimed to reevaluate the efficacy and safety of anticoagulant therapy, in particular of the new oral anticoagulants, in patients with non-valvular atrial fibrillation and chronic anemia. Also in the light of the most recent literature, the conclusions can be summarized as follows: 1) the progressive decrease in hemoglobin is constantly associated with an increased incidence of major haemorrhages, already evident in mild anemia and much more marked in the more severe one (approximately with hemoglobin levels < 10 g/dl), up to > 10% per year; the association between anemia and stroke risk is instead inconstant; 2) warfarin seems to reduce the incidence of stroke in patients with mild anemia at the expense of a modest increase in bleeding events, while in those with more severe anemia it appears ineffective as well as being responsible for a high incidence of bleeding; 3) the new oral anticoagulants, in particular apixaban, seem to induce a lower incidence of major bleeding than warfarin in patients with anemia of varying severity. However, in the presence of hemoglobin levels < ~ 10 g/dl the incidence of major bleeding remains high even with the new anticoagulants. These data suggest that in patients with atrial fibrillation and mild anemia the anticoagulant treatment appears effective, although it requires some attention during the follow-up, while in those with more severe anemia the choice whether to prescribe or not Treatment should be made on a case-by-case basis considering the thromboembolic risk, the aetiology of the anemia, the history and general conditions of the patient. The new oral anticoagulants appear ultimately safer and therefore preferable to warfarin.

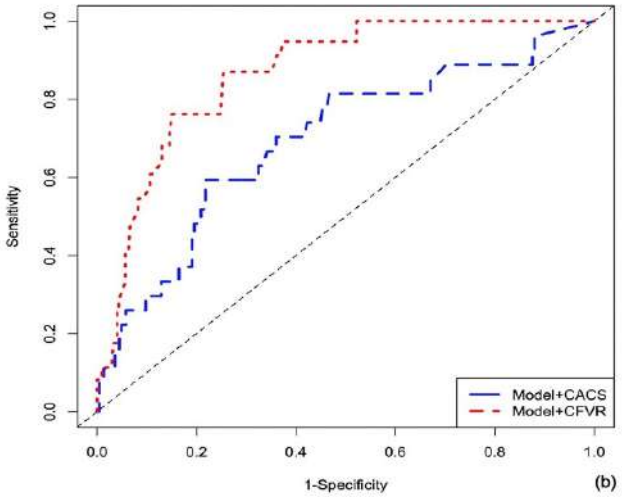
398. COMPARISON BETWEEN CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY AND STRESS-ECHOCARDIOGRAPHY PREDICTIVE VALUES IN LONG-TERM CARDIAC OUTCOME.

Tuttolomondo D., Gaibazzi N.
Cardiology Department, Parma University Hospital, Parma, Italy.

Aims: The study aims to assess which variables on coronary computed tomography angiography (CTA) and vasodilator stress-echocardiography (SE) are best associated with long-term cardiac outcome in patients presenting for suspected chronic coronary syndrome (CCS) who performed both tests.
Methods: We identified 397 patients with suspected CCS who, between 2007 and 2019, underwent both SE and CTA within 30 days. Coronary artery calcium score (CACS) and the number of coronary arteries with diameter stenosis >50% were assessed on CTA. The presence of reversible regional wall motion abnormalities (RWMA) and reduced Doppler coronary flow velocity reserve in the left anterior descending coronary artery (CFVR) were assessed on SE. The association of SE and CTA variables with cardiac outcome (cardiac death or myocardial infarction) was assessed using Fine and Gray competing risk models.
Results: During a median follow-up of 10 years, 38 (9.6%) patients experienced a non-fatal myocardial infarction and 19 (4.8%) died from a cardiac cause. RWMA (HR 7.189, p<0.001) and a lower CFVR (HR 0.034, p<0.001) on SE, CACS (HR 1.004, p<0.001) and the number of >50% stenosed coronary vessels (HR 1.975, p<0.001) on CTA were each associated with cardiac events. After adjusting for covariates, only CACS and CFVR remained associated (both p<0.001) with cardiac outcome.
Conclusion: Our data suggest that only CFVR on SE and CACS on CTA are

independently and strongly associated with long-term cardiac outcome, unlike RWMA or the number of stenosed coronary arteries, usually considered the hallmarks of coronary artery disease on each test.

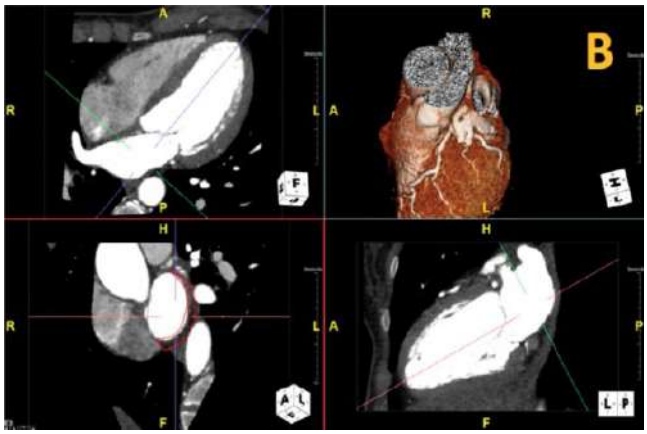




399. THE ROLE OF CARDIAC INFLAMMATION MEASURED THROUGH ADIPOSE TISSUE ATTENUATION ON CARDIAC COMPUTED TOMOGRAPHY IN ATRIAL FIBRILLATION

Tuttolomondo D., Gaibazzi N.
Cardiology Unit, Azienda Ospedaliero-Universitaria di Parma, Via Antonio Gramsci 14, 43126 Parma, Italy.

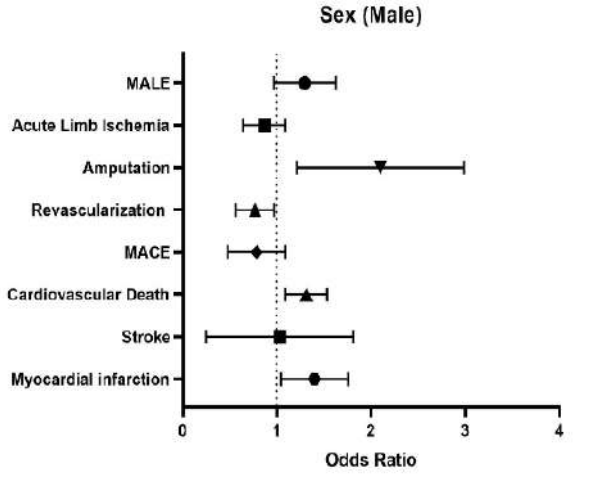
Background: Inflammation plays a key role in atrial fibrillation (AF). Epicardial adipose tissue around the atrial wall can influence atrial morpho-functional properties. The aim of this study was to assess whether an increased quantity and/or density of adipose tissue located around the left atrium (Fat-LA) are related to AF, independently from atrial size.
Methods: eighty patients who underwent AF ablation and 80 patients without history of AF were selected. The Fat-LA mass was quantified as tissue within -190 to -30 Hounsfield Units (HU) on cardiac computed tomography angiograms (CCTA), and the mean adipose tissue attenuation was assessed.
Results: Adipose tissue mass was higher in patients with AF (5.42 ± 2.94 mL) versus non-AF (4.16 ± 2.55 mL, $p = 0.007$), but relative fat quantity did not differ after adjusting for atrial size. Mean fat density was significantly higher in AF (-69.15 HU) versus non-AF (-76.82 HU, $p < 0.0001$) participants. In the logistic regression models, only the addition of mean Fat-LA attenuation led to a significant improvement of the model's chi-square (from 22.89 of the clinical model to 31.69 of the clinical and adipose tissue attenuation model, $p < 0.01$) and discrimination (AUC from 0.775 to 0.829).
Conclusions: Fat-LA volume is significantly greater only in absolute terms in patients with AF, but this difference does not hold after adjusting for the larger LA of AF subjects. On the contrary, a higher Fat-LA density was associated with AF, independently from LA size, providing incremental value over other variables that are associated with AF.



400. SEX-BASED DIFFERENCES IN CLINICAL CHARACTERISTICS AND OUTCOMES AMONG PATIENTS WITH PERIPHERAL ARTERY DISEASE: A RETROSPECTIVE ANALYSIS

De Matteis G.[1], Biscetti F.[2], Della Polla D.A.[3], Serra A.[1], Burzo M.L.[4], Fuorlo M.[3], Nicolazzi M.A.[2], Novelli A.[3], Santoliquido A.[5], Gambassi G.[5], Gasbarrini A.[5], Flex A.[5], Franceschi F.[5], Covino M.[3]
[1]Department of Internal Medicine, Fondazione Policlinico Universitario A.Gemelli IRCCS, Rome, Italy; [2]Cardiovascular Internal Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; [3]Emergency Department, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; [4]Department of Internal Medicine, Ospedale Santo Spirito in Sassia, Rome, Italy; [5]Università Cattolica del Sacro Cuore, Rome, Italy

Peripheral arterial disease (PAD) is a prevalent medical condition associated with high mortality and morbidity rates. Despite the high clinical burden, sex-based differences among PAD patients are not well defined yet, in contrast to other atherosclerotic diseases.
This study aimed to describe sex-based differences in clinical characteristics and outcomes among hospitalized patients affected by PAD. This was a retrospective study evaluating all patients with a diagnosis of PAD admitted to the Emergency Department. The primary endpoint of the study was the difference between male and female PAD patients in cumulative occurrence of a Major Acute Cardiovascular Event (MACE) and of a Major Acute Limb Events (MALE).
A total of 1640 patients were enrolled. Among them, 1103 (67,3%) were males while females were significantly older (median age of 75 years vs 71 years). Females underwent more angioplasty treatments for revascularization than men (29.8% vs 25.6%); males were treated mostly with amputations (19.9 % vs 15.3%). Although MALE and MACE events were more commonly reported in the male group, there was not a statistically significant gender related difference (OR 1.27 [0.99 – 1.64]; p=0.059) (OR 0.75 [0.50 – 1.11] p=0.153). However, despite lower extremity PAD severity seeming similar between the two sexes, among these patients males had a higher probability of undergoing lower limb amputations, of cardiovascular death and of myocardial infarction.
Among hospitalized patients affected by PAD, even if there was not a sex-based significant difference in the incidence of MALE and MACE, adverse clinical outcomes were more common in males.



Abbreviations: MALE, Major Adverse Limb Events; MACE, Major Adverse Cardiovascular Events

Figure 1.

401. A CURIOUS CASE OF LONG-STANDING FEVER

Florenzi C., Reali L., Santagati C., Quartarolo E., Donati M.
Medicina d'Urgenza, Ospedale San Jacopo (Pistoia), Azienda USL Toscana Centro

A 63 year-old Maldivian man with arterial hypertension, dyslipidemia, chronic kidney disease, coronary artery disease, heart failure and previous implantation of ICD due to ventricular arrhythmia, came to the attention of our Emergency Department with fever (up to 40°C) lasting one week associated with shivering, asthenia and vomiting, with no other symptoms. In the last six months he had already presented fever and had been treated with antibiotics.
In the ED he had fever (40°C), arterial hypotension (85/55 mmHg), tachycardia (155 bpm), oxygen saturation 94%. Arterial blood gas test revealed compensated lactic metabolic acidosis. Electrocardiogram showed sinus tachycardia. SARS-CoV-2 antigen test resulted negative. Blood exam showed normal white blood cell count, high levels of C-reactive protein, procalcitonin and creatinine, slight troponin increase without delta. Urinalylis and chest radiograph were normal. Blood cultures were sent. Echocardiogram revealed the presence of a mobile hyperechoic image (greater than 1 cm) adhering to the ICD lead, as well as left ventricular dilatation with areas of akinesia and reduced ejection fraction (28%). We diagnosed septic shock in ICD lead endoplastitis. Chest CT scan (performed without contrast because of decreased renal function) ruled out the presence of peripheral embolization or lung consolidation. The case was discussed with the infectious disease specialist, the cardiologist of our hospital and the cardiac surgeon of the referral centre, who did not give indication for patient centralization. We administered paracetamol, crystalloids, oxygen and we undertook antibiotic therapy with meropenem and vancomycin. The patient was hospitalized in cardiological sub-intensive care.
Transesophageal echocardiogram confirmed the presence of a voluminous vegetation (1,5 x 1,45 cm) involving both the tricuspid valve and the lead. Blood cultures taken in the Emergency Department tested positive for multisensitive Streptococcus gordonii. Antibiotic therapy with meropenem and vancomycin was continued, first empirical, then targeted on the basis of the antibiogram, obtaining a good clinical response, with reduction of fever and inflammation indexes. After a week, new blood cultures were taken which were negative. After another ten days, a further transesophageal echocardiogram was performed which still revealed the presence of the vegetation (2 x 1,6 cm) adhering to the valve flaps and to the lead. There was a new increase in fever and inflammation indexes. After consultation with an infectious disease specialist, the dosage of antibiotic therapy was increased. The case was discussed again with the referral center cardiac surgeon, who indicated cardiac surgery.
The patient was therefore transferred to the referral center, where he underwent tricuspid annuloplasty, removal of the infected leads and of the ICD, implantation of epicardial electrodes and subsequent implantation of a new subcutaneous ICD.
He was then transferred to a nursing home for rehabilitation. He continued antibiotic therapy for about one month and took anticoagulation with warfarin for three months following surgery. At subsequent cardiological checks, he was stable, with no clinical signs of heart failure, despite the persistence of reduced ejection fraction.

402. A COMPARISON STUDY ON VALIDITY OF INTERNAL JUGULAR VEIN AND INFERIOR VENA CAVA ULTRASOUND IN PREDICTING CONGESTION IN ACUTE HEART FAILURE

Parenti N.[1], Bellanti F.[2], Staffieri C.[2], Bastiani L.[3], Silingardi M.[1], Vendemmiale G.[2], Iannone P.[1]
[1]Medicina Interna Ospedale Maggiore Bologna; [2]Università Foggia; [3]Statistica CNR Pisa

Background and aim: Inferior Vena Cava (IVC) ultrasound measures have been suggested to predict congestion in patients with Acute Heart Failure, AHF (1-2). Greater IVC diameters in expirium (IVC-max) , inspirium (IVC-min) and lower IVC collapsibility index, IVC-c (percentage of IVC's diameters variaton during respiratory cicle) seem to suggest hypervolemia and congestion. But this technique has many limitations . Recent reports have hence proposed Internal Jugular Vein (IJV) Ultrasound as alternative test (3). In fact, greater antero-posterior diameters of IJV in expirium (AP-IJV-max) , larger cross sectional IJV area in expirium (CSA-IJV max) and minor variation of AP-IJV max and CSA-IJV max after valsalva could predict hypervolemia and congestion (3).
We test the efficacy for predicting congestion in Acute Heart Failure of IJV Ultrasound . Finally we analyze the correlation of these Ultrasound measures with the IVC ultrasound measures .
Methods: This observational study, conducted in Medicine ward of the Hospital Maggiore in Bologna, from 1st January to 30th november 2022 , included adult patients with a diagnosis of Acute Heart Failure (suggestive symptoms and signs, with BNP >100 pg/ml). We enrolled consecutive patients and health volunteers who underwent transthoracic echocardiography , Inferior Vena Cava and Internal Jugular Vein ultrasound exam. We measured Tricuspid anular plane systolic excursion (TAPSE); Left Ventriculare Ejection Fraction (LVEF); the max and min IVC diameter during the respiratory cycle and IVC collapsibility index; the antero-posterior diameter of IJV , AP-IJV-max and the cross sectional IJV area, CSA-IJV max before and after Valsalva . The Pearson or Spearman's rank tests were used to assess the correlations. ROC curves were plotted for comparing specificity and sensitivity . We considered "congested" patients and healthy volunteers with IVC-max > 21mm and IVC-c < 50%.
Results: Forty-four patients and forty-one healthy volunteers were included. The IVC-max and AP-IJV -max diameter were greater in Acute Heart Failure patients compared to healthy volunteers: mean 19 mm versus 14 mm; 10 mm vs 5 mm (all p values < 0.001) . Between the same groups the CSA-IJV max was larger and IVC-c lower: 1.2 (cm2) vs 0.2 (cm2) ; 30% vs 50% respectively. A significant positive correlation was found between AP-IJV-max and IVC max: r=0.6 (p < 0.001) and CSA-IJV max and IVC max: r=0.6, p< 0.001. The AUROC curve for detecting congestion was 0.86 (95% CI 0.7-0.9) for AP-IJV-max; 0.82 (95%CI 0.8-0.9) for CSA-IJV max , respectively; the best cut-off were 10 mm for AP-IJV-max; 0.8 cm2 for CSA-IJV max.
Discussion: Our results suggest that an AP-IJV max > 10 mm and/or a CSA-IJV max > 0.8 cm2 and minor variation of AP-IJV max and CSA-IJV max after Valsalva could predict congestion among patients admitted for Acute Heart Failure in Medicine wards. According with the previous literature (3), the Internal Jugular Vein ultrasound could be a valid tool to detect congestion and hypervolemia. Because IJV ultrasound is very easy and fast to perform and has not the Inferior Vena Cava pathophysiological limits (e.g. it is influenced by abdominal pressure and diaphragm motion) , if further study wiil confirm its ability in predict hypervolemia and inter-rater reliability, it could be an useful test to guide diuretic therapy.
Limits: many patients were not able to perform Valsalva (so we have few data on the performance of IJV Ultrasound to predict outcome using Valsalva); recent reports speculate that IVC ultrasound could not be a valid reference standard to detect volemia status (4).
Conclusions: In this study the Internal Jugular Vein ultrasound seems a satisfactory tools for predicting congestion, this technique could be suggested as alternative test in guiding diuretic therapy in AHF patients with congestion.

403. EFFECTS OF SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITORS ON CLINICAL, ECHOCARDIOGRAPHIC AND POLYGRAPHIC DATA IN HEART FAILURE PATIENTS AND CENTRAL SLEEP APNOEA ACROSS THE SPECTRUM OF EJECTION FRACTION.

Armentaro G.[1], Condoleo V.[1], Cassano V.[1], Francica M.[1], De Marco M.[1], Severini G.[1], Volpentesta M.[1], Divino M.[1], Miceli S.[1], Maio R.[1], Perticone M.[1], Succurro E.[1], Andreozzi F.[1], Sesti G.[2], Sciacqua A.[1]
[1]Department of Medical and Surgical Sciences, University Magna Græcia of Catanzaro, 88100 Catanzaro, Italy.; [2]Department of Clinical and Molecular Medicine, University Rome-Sapienza, viale Regina Elena n. 324, 00161, Rome, Italy.

Background: Heart failure (HF) is often associated with sleep-disordered breathing (SDB), and this have a negative prognostic impact in this patients; moreover there is no consensus regarding the optimal treatment of Central sleep apnoea (CSA) in patients with HF. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) treatment can potentially attenuate SA development via several pathophysiologic mechanisms, including improvement of global hemodynamics, reduction of extracellular fluid overload, and decrease of sympathetic neural activity.
Purpose: The aim of this study is to evaluate the short term effects of the addition of SGLT2i on the optimal of medical treatment on echocardiographic and polygraphic parameters in diabetic patients with HF and CSA.
Methods: We enrolled 514 diabetic patients with HF, 182 with HF with reduced ejection fraction (HFrEF), of which 92 started SGLT2i at baseline, and 332 with HF with mildly reduced and preserved ejection fraction (HFmrEF-HFpEF), of which 194 started SGLT2i at baseline. Physical examination, echocardiography, nocturnal cardio-respiratory monitoring, and laboratory tests were performed in each patient at baseline and after a 3-month of follow-up. The two different phenotype HF groups differed by a higher prevalence of ischemic heart disease (IHD), hypertension, chronic kidney disease, use of beta-blockers, diuretics, and Sacubitril-Valsartan in patients with HFrEF, instead by a higher use of ACEi/ARBs in patients with HFpEF. In addition, the two groups differed in NT-proBNP, Cardiac Index, GLS and tricuspid annular plane excursion (TAPSE) values that were higher in the HFpEF group and a worse values of Systolic pulmonary arterial pressure, apnea-hypopnea index (AHI) and SpO2 in the HFrEF group.
Results: After 3 months, in all population we observed statistically significant changes in clinical, hemodynamic, biohumoral and echocardiographic parameters. In particular, cardiac index, both atrial and ventricular volumes and TAPSE improved. Moreover, polysomnography, revealed a significant reduction in central AHI value, oxygen desaturation index (ODI) and percentage time of saturation below 90% (p <0.0001). The endpoint of the study was to consider at least a 50% reduction in central AHI, and patients were considered responders if they achieved at least a 50% reduction in central AHI. In a logistic regression model, variables directly correlated with response were: increase in respiratory rate and potassium levels, SGLT2i therapy, reduction in BMI, increase in age and diastolic blood pressure values; while those inversely correlated with response were: IHD, female sex, reduction in TAPSE and increase in inferior vena cava diameter.
Conclusions: Our results suggest that treatment with SGLT2i is able to significantly improve the cardiorespiratory performance of patients with HF and CSA, and contribute to lower the risks of both cardiac and pulmonary complications in HF patients with CSA.

404. PROGNOSTIC ROLE OF ALBUMIN IN PATIENTS WITH HEART FAILURE

Armentaro G.[1], Pastura C.A.[1], Marincola L.[1], Frasca A.[1], Martire D.[1], Crescibene D.[1], Cassano V.[1], Condoleo V.[1], Miceli S.[1], Maio R.[1], Perticone M.[1], Sesti G.[2], Sciacqua A.[1]
[1]Department of Medical and Surgical Sciences, University Magna Græcia of Catanzaro, 88100 Catanzaro, Italy.; [2]Department of Clinical and Molecular Medicine, University Rome-Sapienza, viale Regina Elena n. 324, 00161, Rome, Italy

Background: Heart failure (HF) is a complex clinical syndrome characterized by typical signs and symptoms, recognizing different causes with different clinical phenotypes. Its prevalence is expected to increase due to both better survival and aging of patients. Hypoalbuminemia is a very common condition in HF especially with increasing age and comorbidities, and recognizes inflammation, malnutrition, and cachexia as causes. There is growing evidence that hypoalbuminemia may play a key role in worsening HF, however, we have no evidence on the possible prognostic role in the population with HF and several comorbidities. The main purpose of our work was to assess circulating albumin levels in HF patients, as well as to evaluate the potential prognostic impact on the development of major cardiovascular adverse events (MACE) during follow-up.
Matherials and method: A single-c enter observational study was conducted at Geriatrics Department of "Magna Graecia" University of Catanzaro. We enrolled a number of 378 outpatients affected by chronic HF with a mean age of 67.2 +-11.2 years undergoing clinical and laboratory evaluation for a follow-up of 6.1 (3.1-9.9) years. In addition, all patients underwent echocardiographic examination for subclinical myocardial damage, assessed with speckle tracking echocardiography (STE), and evaluation of carotid-femoral pulse wave velocity (PWV) by Sphygmocor. We stratified the population according to albumin median value into 2 groups < 3.5 g/dl or ≥ 3.5 g/dl. Data were expressed as mean and standard deviation or as median and interquartile range when appropriate. Mann-Whitney test, Student's t-test for unpaired data and chi-square test were performed to compare the variables under study between the two groups when appropriate. In addition, a ROC Curve was performed to assess the diagnostic accuracy of different albumin values as continuous and binary numerical variables in predicting MACE, and then a univariate Cox regression model on the incidence of MACE. The variables that correlated significantly with the occurrence of MACE were included in a multivariate Cox regression model to calculate the hazard ratio (HR) for the incidence of MACE.
Results: A total of 378 patients with HF were enrolled, 220 with mildly reduced ejection fraction HF (HFmrEF) and preserved HF (HFpEF), and 156 with HF with reduced ejection fraction (HFrEF). Considering median value of albumin, 152 had an albumin value < 3.5 g/dl (below median; first group), while the remaining 226 had an albumin value ≥ 3.5 g/dl (above median; second group). The two groups were comparable in gender age, major comorbidities and therapies, laboratory and instrumental variables. In patients with albumin ≥3.5 g/dl, incidence of MACE was 2.3 events/100 patient-years, while in the group with lower albumin levels was 6.3 events/100 patient-years (p < 0.0001). Abuminemia as a continuous variable had greater discriminating power in predicting the development of MACE (AUC 0.708; standard error 0.030; 95% CI 0.650-0.766; p<0.0001), compared with albumina as a dichotomous value (AUC 0.663; standard error 0.032; 95% CI 0.600-0.727; p<0.0001). A multivariate analysis model showed that statin therapy (HR 0.274, p <0.0001), right ventricular diameter reduction of 1 mm (HR 0.458, p=0.010), Pulse wave reduction of 1 m/s velocity (HR 0.550, p=0.030) and reduction of 1 mm of inferior vena cava (HR 0.814, p<0.0001) were protective factors for the onset of MACE, while albumin levels <3.5 g/dl (3.114, p<0.0001), ischemic heart disease (HR 2.264, p=0.003), uric acid levels ≥ 6.0 mg/dl (HR 2.183, p=0.004), chronic kidney disease (HR 2.050, p=0.004), 1 percentage point reduction in Myocardial work (HR 1.542, p=0.007), 1 percentage point increase in Global longitudinal strain (HR 1.402 , p=0.011), 10-year increase in age (HR 1.336, p=0.016), and 1 ml/m2 increase in indexed left atrial volume (HR 1.030, p=0.001) increased the risk of MACE in patients with HF.
Conclusions: The results of this study demonstrated that in HF patients there is an association between lower serum albumin values and a higher incidence of MACE during follow-up.

405. SHORT TERM EFFECT OF SODIUM GLUCOSE COTRANSPORTER 2 INHIBITORS AND SACUBITRIL/VALSARTAN ON COMPREHENSIVE GERIATRIC ASSESSMENT AND OXIDATIVE STRESS IN ELDERLY WITH CHRONIC HEART FAILURE (FROM MAGIC-HF)

Armentaro G.[1], Magurno M.[1], Divino M.[1], Panza A.[1], Panza M.[1], Riillo F.[1], Toscani A.F.[1], Greco A.P.P.[1], Marino D.M.[1], Cassano V.[1], Condoleo V.[1], Miceli S.[1], Maio R.[1], Perticone M.[1], Arturi F.[1], Sesti G.[2], Sciacqua A.[1]
[1]Department of Medical and Surgical Sciences, University Magna Græcia of Catanzaro, 88100 Catanzaro, Italy.; [2]Department of Clinical and Molecular Medicine, University Rome-Sapienza, viale Regina Elena n. 324, 00161, Rome, Italy

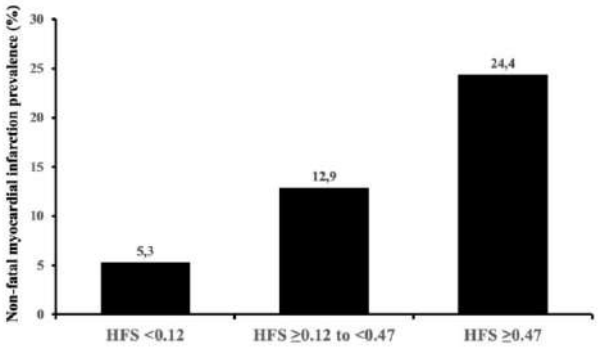
Background: Sodium Glucose Cotransporter 2 inhibitors (SGLT2i) and Sacubitril/Valsartan (Sac/Val) have improved clinical prognosis in patients affected by heart failure (HF) with reduced ejection fraction (HFrEF). Cognitive impairment, depression, and poor physical functional performance are a very common comorbidity in patients with HF and result in a worse prognosis.
Purpose: The aim of this study was to evaluate the potential effects of SGLT2i on functional, humoral, and cognitive aspects, assessed by performing a com-

prehensive geriatric assessment (CGA), and on oxidative stress and platelets activation biomarkers, in a cohort of HFrEF elderly, and any differences between men and women.
Methods: We enrolled 91 HFrEF patients (63 men and 28 women, mean age 73.7±4.7 years) in the "MAgna GraecIa evaluation of Comorbidities in patients with Heart Failure STUDY (MAGIC-HF STUDY). Men and women differed for use of glucagon-like-peptide 1 receptor agonists, antiplatelet drugs, and circulating levels of NADPH Oxidase 2 (Nox-2). SGLT2i therapy was introduced in patients already treated with Sac/Val for at least 12 months who were taking an average dose of 273.6±102.0 mg/die.
Results: After 3 months follow-up, we observed a significant improvement in cognitive, humoral and functional parameters of CGA, NTpro-BNP levels and echocardiographic parameters. Changes (Δ) in Montreal Cognitive Assessment (MoCA) (p=0.015) and Cardiac Index (CI) which were greater in men (p<0.0001) and Geriatric Depression Scale (GDS) which were greater in women (p=0.029). In the whole population, multivariate analysis shows that Δ of CI, Homeostatic model assessment (HOMA), Sp-Selectina, Nox-2 and 8-Isoprostane contributed for 19.7% (p<0.0001), 9.4% (p=0.001), 6.4% (p=0.002), 3.8% (p=0.013) and 2.9% (p=0.024) to Mini mental state examination (MMSE) variability, respectively, and the whole model accounted for a 42.2% of MMSE variation; moreover Δ of HOMA, Sp-Selectina and highly sensitive c-reactive protein (hs-CRP) contributed for 21.6% (p<0.0001), 5.7% (p=0.002) and 4.0% (p=0.014) to MoCA variability, respectively, and the whole model accounted for a 33.3% of MoCA variation. In addition, Δ of Sp-Selectina, Nox-2, CI and HOMA globally contributed for 37.5% of GDS variation (p<0.05); and Δ of HOMA and Sp-Selectina contributed for 30.9% of Short performance physical battery variation (p<0.0001).
Conclusions: This represents the first real-world study carried out in an elderly population suffering from chronic HFrEF with several comorbidities, in which the addition of SGLT2i, in patients already treated with the best medical therapy including Sac/Val, after three months induced important improvements in clinical, humoral, hemodynamic, functional outcomes and cognitive performance. This study shows that echocardiographic and cognitive improvements are greater in men than in women, instead metabolic and humoral improvements are greater in women.

406. LIVER FIBROSIS IS ASSOCIATED WITH AN INCREASED RISK OF NON-FATAL MYOCARDIAL INFARCTION

Riccio A. [1], Mazzanti C.[1], Vero L.[1], Fiorentino T.V.[2], Succurro E.[2], Rubino M.[2], Massimino M.[2], Mannino G. C.[2], Sciacqua A.[2], Andreozzi F.[2], Cefalo C.M.A.[1], Sesti. G.[1]
[1]Dipartimento di Medicina Clinica e Molecolare, Università di Roma - La Sapienza; [2]Dipartimento di Scienze Mediche e Chirurgiche, Università Magna Graecia di Catanzaro

Introduction: Liver fibrosis is a risk factor for liver-related adverse outcomes and cardiovascular disease (CVD). Recently, the non-invasive Hepamet fibrosis score (HFS) has been validated as a tool capable to identify with good diagnostic accuracy subjects with advanced liver fibrosis. It is unsettled whether HFS is capable to identify individuals at higher risk of CVD.
Aim: To investigate whether individuals with liver fibrosis measured with HFS have higher risk of myocardial infarction (MI) in adults participating in the CATAnzaro MEtabolic RIsk factors (CATAMERI) study.
Methods: Participants (n=2948) were divided into three groups according to HFS: low risk of fibrosis (<0.12); intermediate risk of fibrosis (≥ 0.12 to <0.47); high risk of fibrosis (≥0.47). The association between the liver fibrosis risk and MI was analysed by a logistic regression analysis.
Results: As compared with those having the lowest risk (5.3 %), a higher proportion of subjects with moderate or high risk of liver fibrosis had MI (12.9% and 24.4%, respectively; P<0.001). In a logistic regression analysis, individuals at increased risk of liver fibrosis exhibited a 3-fold increased risk of having MI as compared with those with low risk (OR 3.18; 95% CI 1.31-7.70) independently of confounders including smoking, cholesterol, triglycerides, anti-hypertensive, lipid-lowering and glucose-lowering therapies.
Conclusion: In this cross-sectional study, individuals with higher values of HFS show a higher risk of MI, suggesting that HFS may be a useful tool to identify not only individuals with liver fibrosis but also those at the increased risk of CVD.
Keywords: cardiovascular disease, hepatic fibrosis, Hepamet fibrosis score, NAFLD.

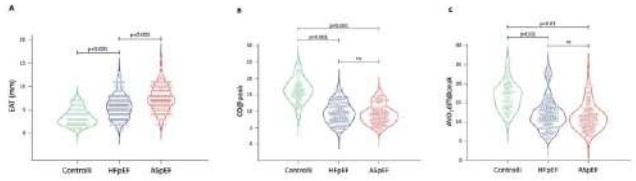


Prevalence of non-fatal myocardial infarction among the enrolled subjects.

407. AORTIC STENOSIS WITH NORMAL LEFT VENTRICULAR SYSTOLIC FUNCTION: A SEPARATE PHENOTYPE OF HEART FAILURE WITH PRESERVED EJECTION FRACTION?

De Biase N.[1], Mazzola M.[2], Del Punta L.[1], Di Fiore V.[1], De Carlo M.[3], Paneni F.[4], Mengozzi A.[1], Masi S.[1], Pugliese N.R.[1]
[1]Dipartimento di Medicina Clinica e Sperimentale, Azienda Ospedaliero-Universitaria Pisana, Pisa; [2]Dipartimento di Patologia, Azienda Ospedaliero-Universitaria Pisana, Pisa; [3]Dipartimento Cardio-Toraco-Vascolare, Azienda Ospedaliero-Universitaria Pisana, Pisa; [4]University Heart Centre, Zurigo, Svizzera

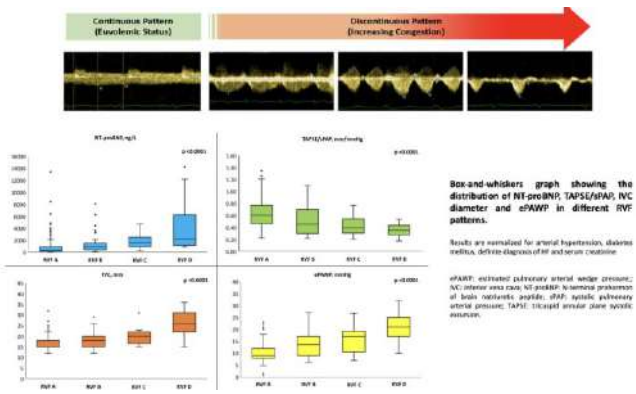
Introduction: Aortic stenosis (AS) is the most prevalent valvular heart disease in Western Countries, and is strongly associated with age and with multiple cardiovascular risk factors (arterial hypertension, dyslipidaemia, visceral obesity, diabetes mellitus). The same risk factors are involved in the development of heart failure with preserved ejection fraction (HFpEF). Notwithstanding these and other similarities, patients with AS and normal ejection fraction (ASpEF) are not usually considered to actually have HFpEF. This study was designed to provide a haemodynamic and metabolic characterization of patients with ASpEF both at rest and during physical effort, in order to highlight similarities and differences with HFpEF.
Methods: We enrolled 148 patients with HFpEF and 150 patients with ASpEF and moderate-to-severe aortic transvalvular gradient, together with 80 age- and sex-matched healthy controls. All patients received a comprehensive laboratory evaluation and a resting echocardiographic examination. Then, they underwent a combined cardiopulmonary-echocardiographic stress test. A subset of patients eligible for transcatheter aortic valve replacement (n=125) also underwent cardiac CT with measurements of aortic valve calcium score and volume.
Results: NT-proBNP values were similar between HFpEF and ASpEF patients after excluding subjects with atrial fibrillation, who were more prevalent in the HFpEF subgroup. Epicardial adipose tissue (EAT) thickness, which is directly related to heightened inflammation at both the local (myocardial) and systemic level, was significantly greater in ASpEF than HFpEF and controls (Figure A), and was inversely related to peak oxygen consumption in all subgroups. Both subgroups of patients showed a significant impairment in peak oxygen consumption and in its central (cardiac output) and peripheral (arteriovenous oxygen difference) components (Figures B and C). Patients with HFpEF showed increased arterial stiffness, worse left ventricular-arterial coupling and worse left atrial function. On the other hand, patients with ASpEF showed worse right ventricular-arterial coupling. Finally, in ASpEF, EAT thickness was directly related to disease severity (as evaluated by aortic transvalvular peak velocity and mean gradient both at rest and peak exercise), and to aortic valve calcium score and volume.
Conclusions: ASpEF displays substantial epidemiological, bio-humoural and haemodynamic similarities to HFpEF. The hypothesis that ASpEF could represent a separate phenotype in the ill-defined spectrum of HFpEF could be evaluated in further and larger studies, in order to refine our understanding of the pathophysiology of ASpEF.



408. HAEMODYNAMIC AND BIO-HUMORAL CORRELATES OF RENAL CONGESTION: EVALUATION OF RENAL VENOUS FLOW ACROSS THE HEART FAILURE SPECTRUM

Del Punta L.[1], De Biase N.[1], Mazzola M.[2], Filidei F.[3], Balletti A.[1], Armenia S.[1], Di Fiore V.[1], Buralli S.[1], Masi S. [1], Pugliese N.R.[1]
[1]Dipartimento di Medicina Clinica e Sperimentale, Azienda Ospedaliero-Universitaria Pisana, Pisa; [2]Dipartimento di Patologia, Azienda Ospedaliero-Universitaria Pisana, Pisa; [3]Reparto di Medicina Interna, Ospedale Versilia, Camaiore, Lucca

Background and objectives: Increased central venous pressure is a key factor in the development of systemic congestion in patients with heart failure (HF); increases in systemic congestion exert a particularly detrimental role in the renal circulation. In this vascular district, congestion can be evaluated by Doppler-derived analysis of the renal venous flow (RVF), which is continuous in healthy subjects and becomes discontinuous with worsening congestion. Analysing RVF abnormalities may allow for a refined physiopathologic characterization of patients with HF. Therefore, this study was designed to evaluate the relationship between different RVF patterns, echocardiographic-derived haemodynamics and bio-humoural indices of congestion and renal function in a population of patients at risk of with overt HF.
Methods: We enrolled 304 patients; 67 patients were at risk of developing HF and 241 had definite HF (61 patients with preserved and 241 with reduced left ventricular ejection fraction). All patients received a comprehensive evaluation including complete blood and urine tests, a resting echocardiogram, lung ultrasound, and Doppler-derived RVF evaluation.
Results: 230 patients (76%) showed a continuous RVF, while 74 (24%) patients showed a discontinuous RVF (dRVF). Among the latter, 39 patients displayed a pulsatile RVF, 18 patients a biphasic RVF (i.e. two separate flow phases in systole and diastole) and 17 patients a monophasic RVF (i.e. flow restricted to diastole). Monophasic RVF was associated with worse haemodynamic profile and with worse renal function in terms of glomerular filtration rate and urinary albumine-to-creatinine ratio. After standardizing for arterial hypertension, diabetes mellitus, definite diagnosis of HF and serum creatinine, progressively worsening RVF was associated with increased levels of N-terminal prohormon of brain natriuretic peptide, worse right ventricular arterial coupling, greater inferior vena cava diameter (i.e. increased central venous pressure) and higher echocardiography-derived pulmonary arterial wedge pressure. A sensitivity analysis confirmed these observations in the subgroup of patients with definite HF, even after standardizing for left ventricular ejection fraction.
Conclusions: Doppler-derived evaluation of the RVF may help characterize patients with HF. In particular, the pathophysiologic meaning of RVF seems to be independent of common cardiovascular risk factors and left ventricular systolic function, which may allow for early identification of patients at higher risk of developing HF or progressing to more advanced stages of the disease.



409. STATINS UNDER-TREATMENT AND MORTALITY IN PATIENTS WITH ATRIAL FIBRILLATION. INSIGHTS FROM THE NATIONWIDE START REGISTRY.

Menichelli D.[1], Antonucci E.[2], Pignatelli P.[3], Violi F.[3], Palareti G.[2], Pastori D.[3]
[1]Department of General Surgery and Surgical Speciality, Sapienza University of Rome; [2]Fondazione Arianna Anticoagulazione – Bologna; [3]Department of Clinical Internal, Anesthesiological and Cardiovascular Sciences, Sapienza University of Rome

Background and Aims: Statins are mainstream drugs for cardiovascular (CV) prevention, but under-prescription is an important clinical challenge. Data on the use of single statins as the rate of under-prescription in atrial fibrillation (AF) are lacking. To evaluate the association of statin underuse with mortality risk in a large AF cohort.
Methods and Results: 5,477 patients from the nationwide START registry were included. The prevalence of different statins was reported and the association with all-cause and CV mortality investigated. Mortality risk of patients with an indication to but not taking statins was also analysed.
Mean age was 80.2 years, 46.4% were women. Among 2,899 patients with a clinical indication to statin, only 1,578 (54.4%) were on treatment. In a mean follow-up of 22.5±17.1 months, 491 (4.7%/year) deaths occurred (106 CV deaths, 1.0%/year). Atorvastatin and Simvastatin inversely associated with all-cause (HR 0.692, 95%CI 0.519-0.923, p=0.012 and HR 0.598, 95%CI 0.428-0.836, p=0.003, respectively). and CV death (HR 0.372, 95%CI 0.178-0.776, p=0.008 and HR 0.306, 95%CI 0.123-0.758, p=0.010, respectively).
The 1,321 untreated patients were older, more frequently women and with a higher prevalence of diabetes, previous cerebrovascular disease, peripheral artery disease compared to those on treatment. Statin undertreatment was associated with higher risk of all-cause (HR 1.565, 95%CI 1.235-1.983, p<0.001) and CV death (HR 2.057, 95%CI 1.188-3.561, p=0.010).
Conclusions: AF patients with an indication to statins but left untreated disclose a high risk of all-cause and CV mortality. Implementation of statin prescription in the AF population can help reducing the residual CV risk.

410. THE ROLE OF KLOTHO AND FGF23 IN CARDIOVASCULAR OUTCOMES OF DIABETIC PATIENTS WITH CHRONIC LIMB THREATENING ISCHEMIA: A PROSPECTIVE STUDY

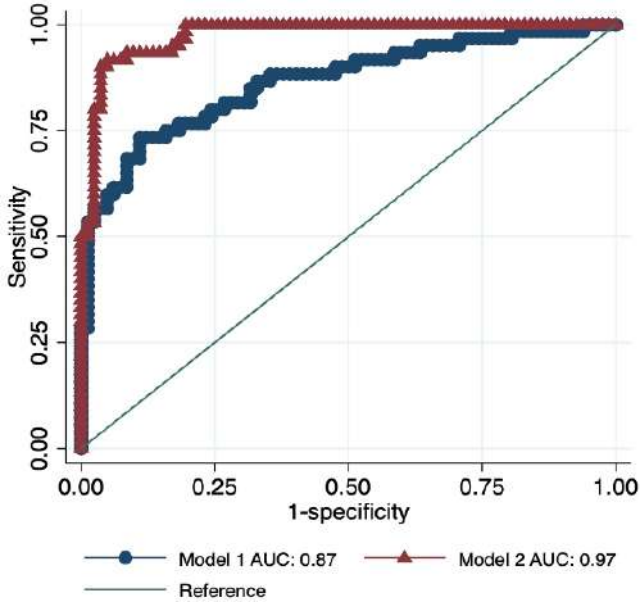
Biscetti F.[1], Rando M.M.[1], Cecchini A.L.[1], Nicolazzi M.A.[1], Rossini E.[1], Nardella E.[1], Santoro M.[2], Eraso L.H.[3], Dimuzio P.J.[3], Pitocco D.[4], Massetti M[5]., Gasbarrini A.[6], Flex A.[1]
[1]Cardiovascular Internal Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy ; [2]Università Cattolica del Sacro Cuore, Largo Francesco Vito 1, 00168 Roma, Italy; [3]Division of Vascular and Endovascular Surgery, Thomas Jefferson University, Philadelphia, Pa, USA; [4]Diabetology Unit, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Roma, Italy; [5]Department of Cardiovascular Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy; [6]Department of Medical and Surgical sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy

Background: Diabetic patients with Peripheral arterial disease (PAD) have poorer quality of life and life expectancy than patients without PAD. One of the most common complications of PAD is chronic limb threatening ischemia (CLTI), which necessitates endovascular revascularization and often results in lower extremity gangrene requiring amputation. Patients with CLTI may also experience major adverse cardiovascular events (MACE) and major adverse limb events (MALE) in the period following revascularization procedure. In fact, cardiovascular complications after lower extremity revascularization (LER) are common in diabetic patients with PAD and CLTI. The Klotho-fibroblast growth factor 23 (FGF23) axis is associated with endothelial injury and cardiovascular risk.
Aims: We aimed to analyze the relationship between Klotho and FGF23 serum levels and the incidence of major adverse cardiovascular events (MACE) and major adverse limb events (MALE) after LER in diabetic patients with PAD and CLTI.
Methods: Baseline levels of Klotho and FGF23, and their association with subsequent incidence of MACE and MALE were analyzed in a prospective, non-randomized study in a population of diabetic patients with PAD and CLTI requiring LER.
Results: A total of 220 patients were followed for 12 months after LER. Sixty-

three MACE and 122 MALE were recorded during the follow-up period. Baseline lower Klotho serum levels (295.3 ± 151.3 pg/mL vs 446.4 ± 171.7 pg/mL, p<0.01), whereas increased serum levels FGF23 (75.0 ± 11.8 pg/mL vs 53.2 ± 15.4 pg/mL, p<0.01) were significantly associated with the development of MACE. Two ROC curves were constructed to predict the incidence of MACE based on Klotho and FGF23 baseline levels and the areas under the curve (AUC) were 0.24 [95% confidence interval (CI) 0.17, 0.32] and 0.87 (95% CI 0.82, 0.92), respectively. To test the efficacy of knowing protein levels at baseline, we compared the predictive power of traditional risk factors and risk factors plus Klotho and FGF23 levels at the moment of the revascularization. Including serum protein levels significantly improved the prediction of incident MACE after LER (**Figure**). A multivariate analysis was performed including all the variables and we found that male sex (p<0.01), BMI (p<0.05), hypertension (p<0.05) and smoking status (current or former, p<0.01) were independent determinants of MACE. Notably, after adjustment for all traditional risk factors, Klotho (p<0.01) and FGF23 (p<0.01) levels were still independent determinants of MACE (Table 3). Furthermore, decreased Klotho levels were associated with the occurrence of MALE after LER (329.1 ± 136.8 pg/mL vs 495.4 ± 183.9 pg/mL, p<0.01). We also constructed ROC curves on Klotho and FGF23 baseline levels to predict the incidence of MALE after LER intervention. The two AUC were 0.24 (95% CI 0.17, 0.31) and 0.61 (95% CI 0.53, 0.68) respectively. We compared ROCs with traditional risk factors alone and with risk factors plus Klotho and FGF23 in predicting MALE. Likewise, addition of baseline protein levels significantly improved the predictive power of MALE after LER.

Conclusions: We have demonstrated that altered Klohto and FGF23 baseline serum levels are associated with the development of MACE after LER and that reduced Klotho baseline levels predict MALE after revascularization. These data were obtained in a relatively small but particularly selected population and need to be confirmed in a larger scenario.

Taken together, these data could improve cardiovascular risk stratification in diabetic patients with PAD and help physicians identify personalized treatments.



411. CEREBRAL VASOMOTOR REACTIVITY IMPAIRMENT IN RESISTANT AND NON-RESISTANT HYPERTENSION: THE ROLE OF THE AUTONOMIC NERVOUS SYSTEM.

Miceli G., Velardo M., Casuccio A., Basso M., Rizzo G., Pintus C., Tuttolomondo A.
Department of Health promotion, Mother and Child Care, Internal Medicine and Medical specialties (ProMISE)

Purpose: Hypertension reduces the ability of the vessel wall to constrict or dilate in response to one of many possible stimuli. Cardiovascular autonomic impairment contributes to the development of hypertension and it can influence cerebral vasomotor reactivity. Little is known about the effect of resistant hypertension. Aim of this study is to analyze the role of sympathovagal imbalance in a cohort of patients with resistant (RH) and non-resistant hypertension (NRH) and its influence on cerebral vasomotor reactivity.

Methods: Forty consecutive hypertension patients, 20 with NRH and 20 with RH, underwent time-domain heart rate variability analysis and transcranial color-coded Doppler at rest and during breath-holding maneuver for evaluation of cerebral vasomotor reactivity.

Results: Hypertensive individuals presented statistically significant reduction of Breath Holding Index (BHI) and time-domain parameters (SDNN and SDANN) in comparison to the control group (BHI control group 1.32 ± 0.41 vs hypertensive patients 0.92 ± 0.65; p=0,018; SDNN control group 137.87± 27.5 vs hypertensive 108.44± 26.48; p <0.0001; SDANN control group 125.76± 24.96 vs hypertensive 87.65± 20.63; p<0.0001). RH patients presented a significant reduction in BHI (NRH group BHI 1.15 ± 0.65 vs RH group BHI 0.70 ± 0.58; p=0.027) and HRV parameters (SDNN in NRH group 118.48 ± 26.01 vs RH group 96.41 ± 23.47; p=0.015; SDANN in NRH group 95.09 ± 22.12 vs RH 80.21 ± 16.36; p=0.021).

Conclusions: Our results show that RH is associated with impairment of sympathovagal balance and cerebral vasomotor reactivity impairment. Autonomic dysfunction could be a concurrent cause for cerebral vasomotor reactivity impairment.

412. SUBTLE CHANGES IN CORTISOL SECRETION ARE ASSOCIATED WITH IMPAIRED GLUCOSE TOLERANCE IN UNCOMPLICATED NONDIABETIC PATIENTS WITH HYPERTENSION

Vacca A.[1], Brosolo G. [1], Da Porto A.[2], Bulfone L.[1], Bertin N.[3], Catena C.[1], Sechi L.A.[1]
[1]Internal Medicine and European Hypertension Excellence Center, Department of Medicine, University of Udine, Udine, Italy; [2]Diabetes and Metabolism Unit, Department of Medicine, University of Udine, Udine, Italy; [3]Thrombosis and Hemostasis Unit, Department of Medicine, University of Udine, Udine, Italy

Background: Glucometabolic abnormalities are associated with clinical and subclinical Cushing syndrome. Because impaired glucose tolerance (IGT) and insulin resistance are frequently detected in patients with essential hypertension, we hypothesized that glucometabolic changes might be related to minor changes in regulation of cortisol secretion.

Methods : In a cross-sectional study, we included 155 nondiabetic, essential hypertensive patients who were recruited at a university clinic and were free of cardiovascular and renal complications. Fasting plasma glucose, insulin, and C-peptide, homeostasis model assessment (HOMA) index, the area under the curve of plasma glucose (AUC-glucose) and insulin (AUC-insulin) concentration following a standard oral glucose load were measured after drug wash-out together with daily plasma cortisol (8 AM, 3 PM, and 12 AM) and 8 AM cortisol after overnight suppression with 1 mg dexamethasone (DST).

Results : IGT was present in 27% of patients who were older and had higher body mass index (BMI), plasma triglycerides and uric acid levels, daily cortisol profile (AUC-cortisol) and DST cortisol, and lower HDL-cholesterol levels. Frequency of IGT increased progressively across tertiles of DST cortisol, together with levels of glycated hemoglobin, fasting insulin and C-peptide, HOMA-index, AUC-glucose, and AUC-insulin. AUC-cortisol and DST cortisol were directly correlated with fasting insulin and C-peptide, HOMA-index, AUC-glucose, and AUC-insulin. Multivariate regression analysis showed that AUC-cortisol was independently correlated with HOMA-index and DST cortisol with HOMA index, AUC-glucose, and AUC-insulin. Logistic regression indicated that IGT was significantly and independently predicted by both AUC-cortisol and DST cortisol.

Conclusions : Daily plasma cortisol and cortisol response to dexamethasone suppression are independent determinants of IGT and insulin resistance in nondiabetic patients with hypertension, suggesting that even minor changes in regulation of cortisol secretion might impair glucose metabolism in these patients.

413. A SINGLE NUCLEOTIDE POLYMORPHISM IN THE ADRB1 GENE INFLUENCES AUTONOMIC NERVOUS SYSTEM ACTIVITY OF HEALTHY VOLUNTEERS AS REFLECTED BY SPECTRAL ANALYSIS OF HEART RATE VARIABILITY

Coratza G., Greco A., De Zanet D., Apostolo D., Minisini R., Grossini E., Pirisi M.
Dipartimento di Medicina Translazionale

Rationale and aim: b-adrenergic receptors are responsible for signaling in the sympathetic nervous system, and single nucleotide polymorphisms (SNPs) in their genes have demonstrated functional effects both *in vitro* and *in vivo*, including response to drugs. Spectral analysis of heart rate variability (HRV) is a non-invasive and sensitive method to study the status of the autonomic nervous system (ANS). To what extent parameters evaluated at spectral analysis of healthy individuals are affected by genetic variability of b-adrenergic receptors is unknown. With this paper, we aimed to fill this gap.
Methods: The study population included N.=241 healthy volunteers (82 males; median age 54 years, interquartile range, IQR, 48-58) not taking any drugs for acute or chronic conditions. All participants were genotyped for two SNPs in the *ADRB2* gene coding for the β2 surface receptor (rs1042713 and rs1042714), as well as for two SNPs in the *ADRB1* gene coding for the β1 surface receptor (rs1801252 and rs1801253). Moreover, all subjects underwent a 6-minute electrocardiographic recording in a resting and supine state using the ECG600G digital electrocardiograph (Contec Medical Systems Co., Ltd, Qinhuangdao, China). ECG recordings were analyzed by the Kubios HRV 3.1.0 software. Heart rate components were extrapolated using time domain analysis and frequency domain analysis. The measures related to the variability of RR intervals in the time domain were: SDNN (standard deviation of NN intervals), RMSSD (mean square root of successive NN intervals), and RR triangular index. Frequency domain analysis of HRV, conducted using various spectral methods of tacogram evaluation, yielded instead the following variables: very low frequency (VLF), low frequency (LF), and high frequency (HF) components.
Results: Concerning the four SNPs, subjects were distributed as follows: β1 rs1801252 reference allele (A) frequency (N 448 - 93%), alternative allele (a) frequency (N 34 - 7%), genotype analysis AA = 209, Aa = 30, aa = 2; β1 rs1801253 A frequency (N 183 - 38%), a frequency (N 299 - 62%), genotype analysis AA = 36, Aa = 111, aa = 94; β2 rs1042713 A frequency (N 316 - 66%), a frequency (N 166 - 34%), genotype analysis AA = 103, Aa = 110, aa = 28; β2 rs1042714 A frequency (N 181 - 38%), a frequency (N 301 - 62%), genotype analysis AA = 37, Aa = 107, aa = 97. Allelic frequencies did not depart significantly from what was expected based on the Hardy-Weinberg equilibrium. The table presents the p-value indicating the strength of the association with spectral analysis variables, analyzed according to either a dominant model (rs1801253, rs1042713, and rs1042714) or a recessive model (rs1801252).

		Time domain			Frequency domain		
Receptor	SNP	SDNN	RMSSD	RR triangular index	VLF	LF	HF
β1	rs1801252	0.001	0.000	0.150	0.001	0.000	0.048
	rs1801253	0.340	0.412	0.436	0.812	0.999	0.810
β2	rs1042713	0.852	0.506	0.259	0.428	0.292	0.260
	rs1042714	0.285	0.469	0.536	0.619	0.258	0.229

Bold characters indicate statistical significance.
Median (IQR) LF components (frequencies between 0.04 and 0.15 Hz; this variable mainly expresses the activity of the sympathetic ANS and, to some extent, the baroreceptor system) was 58 (44-72) normalized units (NU) among rs1801253 A* carriers and 67 (54-76) in aa carriers. Conversely, median (IQR) HF components (frequencies between 0.15 and 0.40 Hz; this variable expresses parasympathetic ANS activity) were 41 (28-56) NU among rs1801253 A* carriers and 33 (25-46) in aa carriers.
Conclusions: A SNP in the *ADRB1* gene (rs1801253; Arg389Gly), previously found to be associated with the variability of response to beta-blockers (Parvez BJ et al. Am Coll Cardiol. 2012), may also influence frequency domain HRV, a proxy measure of ANS activity, under physiological conditions. These findings point to a possible link between b-adrenergic receptor gene variability and increased risk of pathological states characterized by ANS dysfunction.

414. INVESTIGATION OF SPONTANEOUS CORONARY ARTERY DISSECTION: A CASE ILLUSTRATION

Gallo R.[1], Bertolino L.[1], Patauner F.[1], Pinto D.[2], Mattucci I.[3], Amarelli I.[3], Durante-Mangoni E.[4]
[1]Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli", Piazza Luigi Miraglia, 2 80138 Napoli (Italy); [2]Unit of Infectious & Transplant Medicine, A.O.R.N. Ospedali dei Colli - Ospedale Monaldi, Piazzale Ettore Ruggieri, 80131 Napoli (Italy); [3]Unit of Cardiac Surgery and Transplants, AORN Ospedali dei Colli-Monaldi Hospital, 80131- Naples, Italy; [4]Department of Precision Medicine, University of Campania "Luigi Vanvitelli", Via de Crecchio, 7 80138 Napoli (Italy)

A 42-year-old Caucasian woman, who underwent cardiac transplantation on February 2022, was admitted to our Unit for reactivation of cytomegalovirus (CMV) infection ('CMV syndrome'). Her past medical history was significant for prior hearing deficiency and acute myocardial infarction due to spontaneous coronary artery dissection complicated by refractory cardiogenic shock (after PTCA-stenting) treated with the implantation of Impella and arterio-venous Extra Corporeal Membrane Oxygenation, and ultimately requiring heart transplantation. Histopathological findings on the explanted heart showed polymorphous inflammatory infiltrate and numerous eosinophils in the coronary artery adventitia and media. She had no family history or past medical history of cardiovascular diseases, stroke, malignant hypertension or other CV conditions. She denied smoking or taking any type of medication including hormone therapy. She used to be a professional athlete performing high intensity physical activity. One week before admission, she developed fever. At admission, physical examination was significant for a body temperature of 39°C, hypoacusia and hirsutism. Blood tests showed lymphopenia and elevated C-reactive protein (4 mg/dL).
Investigations: CMV-DNA assay showed a viremia of 3,665,760 gEq/mL. Ultrasound of the abdomen and chest x-ray showed no signs of end-organ CMV disease. CT angiography of carotid and cerebral arteries and thoracic and abdominal aorta with their main branches, performed to rule out other dissections, was significant for a tubular stenosis of the right common iliac artery and a focal stenosis of the left renal artery. Audiometric examination showed bilateral sensory-neural deafness.
Management and treatment: the patient underwent intravenous antiviral therapy with Ganciclovir 10 mg/kg/day combined with Foscarnet 60 mg/kg/day in light of the extremely high viral load. Renal function, electrolytes and corrected QT interval were monitored on a daily basis. In addition, immunoglobulins enriched with CMV-specific IgG were administered. After two weeks, intravenous antiviral therapy was switched to oral valganciclovir. CMV-DNA levels were monitored weekly, until clearance of viremia. Therapy with immune suppressants, low dose aspirin, atorvastatin and bisoprolol was continued.
Discussion: while treating CMV reactivation in this heart transplant recipient, we decided to further investigate the etiology of spontaneous coronary artery dissection. Considering the patient's medical history and examinations performed, and after contact with a EU referral center, a diagnosis of suspected fibromuscular dysplasia (FMD) arose. Spontaneous coronary artery dissection (SCAD) is a non-traumatic and non-iatrogenic separation of the coronary arterial wall and is a rare cause of acute myocardial infarction. It is more common in young adults and women [1]. In most cases, a predisposing arterial disease may be identified. Potential predisposing factors include FMD in about 60% of cases [2]. There are identifiable cardiocirculatory stressors that may increase the risk of acute SCAD events in the presence of preexisting arteriopathy such as FMD. These stressors include intense exercise with heavy isometric activities in half of cases, emotional stress, recreational drug use, and high-dose hormonal therapy [1]. A conservative approach is recommended unless there is ongoing ischemia, hemodynamic instability, or left main dissection [3]. FMD is a non-inflammatory, non-atherosclerotic disorder leading to arterial stenosis, occlusion, aneurysm, dissection, and arterial tortuosity. The most frequently involved arteries are the renal and internal carotid arteries, followed by vertebral, visceral, and external iliac arteries. FMD etiology remains unknown, however, given the predominance in females of childbearing age, hormonal influences are thought to play a key role in its pathogenesis [4].
[1] Saw J et al. Spontaneous coronary artery dissection: association with predisposing arteriopathies and precipitating stressors and cardiovascular outcomes. Circ Cardiovasc Interv. 2014 Oct;7(5):645-55. doi: 10.1161/CIRCINTERVENTIONS.114.001760. Epub 2014 Oct 7. PMID: 25294399.
[2] Saw J et al. . Spontaneous Coronary Artery Dissection: Clinical Outcomes and Risk of Recurrence. J Am Coll Cardiol. 2017 Aug 29;70(9):1148-1158. doi: 10.1016/j.jacc.2017.06.053. PMID: 28838364.
[3] Hayes SN et al. ; American Heart Association Council on Peripheral Vascular Disease; Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Genomic and Precision Medicine; and Stroke Council. Spontaneous Coronary Artery Dissection: Current State of the Science: A Scientific Statement From the American Heart Association. Circulation. 2018 May 8;137(19):e523-e557. doi: 10.1161/CIR.0000000000000564. Epub 2018 Feb 22. PMID: 29472380.
[4] Gornik HL et al. First International Consensus on the diagnosis and management of fibromuscular dysplasia. Vasc Med. 2019 Apr;24(2):164-189. doi: 10.1177/1358863X18821816. Epub 2019 Jan 16. Erratum in: Vasc Med. 2019 Oct;24(5):475. Erratum in: Vasc Med. 2021 Aug;26(4):NP1. PMID: 30648921.

415. SERUM PARATHORMONE, VITAMIN D AND CARDIOVASCULAR RISK FACTORS AND MARKERS

Mancusi C., Fucile I., De Luca N., Iaccarino G.
Università Federico II di Napoli

Background: The aim of this study is to evaluate the associations of serum vitamin D and parathormone (PTH) concentrations with blood pressure and hypertension-related target organ damage (HTOD), including left ventricular (LV) hypertrophy and increased carotid intima-media thickness (IMT). **Methods**: We enrolled consecutive patients admitted to the Hypertension Center of Federico II University Hospital in Naples, Italy. All patients underwent carotid doppler ultrasound and echocardiography, measurement of vitamin D and PTH levels and main clinical and laboratory parameters.
Results: A total of 98 patients (mean age 53 years, 69% males) were enrolled. Pearson's correlation analysis indicated that PTH levels directly correlated with age, diabetes, dyslipidemia, hypertension, fasting glucose, and LV mass, and inversely with glomerular filtration rate, LDL cholesterol, and vitamin D. Vitamin D levels correlated inversely with PTH, diabetes and carotid plaques. Multivariate regression models indicated that an increased LV mass was associated with the presence of hypertension (β=0.193; P=0.049) and obesity (β=0.342; P=0.001). Maximal intima-media thickness was significantly associated with an older age (β=0.303; P=0.033) and presence of dyslipidemia (β=0.280; P=0.042). Combined presence of low vitamin D/high PTH level was associated with 3-fold increased risk of having carotid plaque in both univariate (OR 3.78, 95% CI 1.45-9.88, p=0.007) and multivariate regression analysis (OR 3.75, 95% CI 1.01-14.64, p=0.044).
Conclusion: In a population at high cardiovascular risk, vitamin D and PTH levels were not directly associated with hypertension and HTOD. Secondary hyperparathyroidism due to vitamin D deficiency is associate with carotid atherosclerosis independently of other common cardiovascular risk factors.

416. "I OPEN AT THE CLOSE", AN UMBRELLA FOR TRANSIENT ISCHEMIC ATTACK?

Nasta C.[1], Facciuto A.I.[1], Di Sisto A.[2], Fischetti S.[2], Giordano M.[1]
[1]Università degli studi della Campania "Luigi Vanvitelli"; [2]U.O.C. Medicina Interna e P.S. Ospedale "A. Guerriero" Marcianise

Case report: A 60 years woman access to our emergency department transported by ambulance for acute neurological syndrome characterized by loss of consciousness and tonic clonic seizure with residual paraesthesia of the left hemisome. Triage code 3 (blue). In her past medical history she had hypothyroidism in replacement therapy. In October 2022 hospitalization in the resuscitation unit at the Ragusa hospital for septic shock. Chronic diarrhea (probably secondary, post-surgical) already carried out tests such as celiac disease, culture tests, parasitological stools with negative results, clostridium negative. Malabsorption syndrome in nutritional therapy, tonsillectomy. Previous anal fissure surgery 2016. Biliopancreatic derivation in 2006 due to severe obesity (body weight 130 kg). Tummy tuck for pendulous abdomen in 2009. Intestinal loop lengthening surgery about 10 years ago due to severe malabsorption. Two surgeries for retinal detachment, two surgeries for bilateral cataract and laser therapy for retinopathy. Her vital signs were BP100/60mmHg HR 78bpm SpO2 96%, EKG exhibited sinus rhythm with normal intervals and waves. Inspection revealed paleness of skin and mucosae, whereas lungs, abdomen and cardiac examination resulted regular. Neurological evaluation showed mainly a physiological picture: no abnormalities of cranial nerves, preserved muscle strength and stretch reflexes, negative cerebellar tests, intact somatosensory system. We started a screening for cerebrovascular accident. First, we excluded two main subtypes of stroke (large artery atherosclerosis and cardio embolism) through a basic cardiovascular workup based on carotid US, transthoracic echocardiography and Holter monitor – no evidence of significant stenosis of a major brain artery, no potential cardiac source of embolism, absence of supraventricular arrhythmias. Brain CT scan excluded ischemic or hemorrhagic lesions. Moreover, normal values of thrombophilia panel (antithrombin III deficiency, protein C and protein S deficiency, factor V Leiden mutation, activated protein C resistance, prothrombin mutation, antiphospholipid Ab) and ANCAs led us to rule out less common causes of stroke such as both acquired and inherited thrombophilia or vasculitis. The transthoracic echocardiogram showed a left ventricle of normal intracavitary dimensions and preserved wall thicknesses (IVSd 1 cm; LVIDd 4.29 cm, LVPWd 1.7 cm), preserved global and segmental systolic function. Aortic root and ascending aorta of normal caliber (35 mm), tricuspid aortic valve with normal systolic opening. Grade I diastolic dysfunction. Left atrium not dilated. Mild insufficiency. Right sections normal in size and contractility. Mild IT with PAPs within limits. Evidence of atrial septal aneurysm, movable in both directions, without evidence of atrial shunt. Useful TEE evaluation in the context of the diagnostic procedure. The TEE showed a PFO with severe shunt from the right atrium to the left one. We also subjected the patient to brain magnetic resonance which excluded focal lesions. Finally, the patient was discharged with a diagnosis of "Transient ischemic attack with consequent seizure in PFO patient with moderate-severe shunt. History of post-surgical malabsorption syndrome.", with direction for starting antiplatelet therapy (Clopidogrel 75mg OD) and for subsequent percutaneous closure of PFO.
Discussion: Stroke is a major cause of death and disability. Determining the cause of stroke is essential for proper management, however the identification of the etiology may result challenging. In our case stroke presented with atypical clinical features without leaving any results, it was classified as a transient ischemic attack for this reason. Probably the biliopancreatic diversion surgery and the consequent chronic malabsorption made even light efforts a stress test for the patient, favoring the shunt between the two atria and the consequent malaise. The clinical picture is very varied both for the symptomatology and for the severity, up to coma. PFO is a communication between the atria at the level of the fossa ovalis, that usually closes after birth but can remain pervious in about 25% of cases. PFO may allow the passage of emboli from the venous system to the cerebral arteries (paradoxical embolism), for this reason it should be looked for in adults with cryptogenic stroke. In case of suspicion of PFO it is necessary to perform a contrast echocardiography that shows right-to-left shunt and its severity. TEE is the gold standard to define the anatomy of PFO. In adults until 60 years at high-risk (severe shunt and/or interatrial septal aneurysm) transcatheter PFO closure is indicated, to be associated with antiplatelet therapy.

417. CAN GOOD PRESSURE CONTROL IN THE OVERWEIGHT POPULATION BE SUFFICIENT?

Canu P., Brattoli M., Clerici L., Dionisi L., Cecco A., Savioli G., Mugellini A., Di Sabatino A.
IRCCS Policlinico San Matteo - Medicina Interna

Among cardiovascular risk factors in clinical practice, particular attention is paid to obesity, but often that leads to underestimating the population of overweight patients. In this sense, echocardiographic examination could play a role in regulating therapeutic aggression in hypertensive patients, even with a good blood pressure control, in the absence of overt organ damage. Evaluate whether overweight subjects have early echocardiographic signs of left ventricular remodeling compared to normal-weight subjects with equal pressure control and in the absence of comorbidity. We considered patients treated in our hypertension center in 2021 who underwent an echocardiography evaluation at our dedicated clinic. Inclusion criteria were: absence of comorbidity and outpatient blood pressure monitoring that showed good blood pressure control during the 24 hours (< 130/80 mmHg), for a total of 29 patients. We then further layered them for day (< 135/85 mmHg) and night (<120/70 mmHg) pressure control. The patients were then divided according to BMI in normal weight (18.5-24.9) and overweight (24.9-29.9) and were evaluated their respective echocardiographic parameters. The study found that the overweight population (n 16) vs normal weight population (n 13) had significantly higher values of interventricular septal thickness (IVST), left ventricular posterior wall (LVPW), and left atrial diameter (LAD). This finding was confirmed even after dividing the patients according to day and night pressure control. In our work, we highlighted how overweight patients, with equal pressure control, present early signs of cardiac organ damage induced by hypertension, specifically identified in the parameters of IVST, LVPW, and LAD. Despite the limitations of the small number, this study highlights the need to pay more attention to this population, even in the absence of other comorbidities, whose cardiovascular risk is often underestimated.

418. IMMUNE-INFLAMMATORY AND GENETIC PROFILE IN PATIENTS WITH PERMANENT ATRIAL FIBRILLATION AND CORRELATION WITH STRUCTURAL DATA: A CROSS-SECTIONAL STUDY

Daidone M.[1], Pacinella G.[2], Scaglione S.[1], Todaro F.[1], Pipitone R.M.[3], Agnello, L.[4], Ciaccio, M.[4], Di Chiara, T.[1], Di Raimondo, D.[1], Casuccio, A.[3], Tuttolomondo, A.[1]
[1]U.O.C. di Medicina interna con Stroke Care. Dipartimento di Promozione della Salute, Materno-Infantile, di Medicina Interna e Specialistica di Eccellenza "G. D'Alessandro"; [2]U.O.C. di Medicina interna con Stroke Care. Dipartimento di Promozione della Salute, Materno-Infantile, di Medicina Interna e Specialistica di Eccellenza "G. D'Alessandro"Dipartimento di Promozione della Salute, Materno-Infantile, di Medicina Interna e Specialistica di Eccellenza "G. D'Alessandro"; [3]Dipartimento di Promozione della Salute, Materno-Infantile, di Medicina Interna e Specialistica di Eccellenza "G. D'Alessandro"; [4]Sezione di Biochimica Clinica, Medicina Molecolare Clinica e Medicina di Laboratorio, Dipartimento BIND

Background : In recent years, a growing body of evidence supported the role of inflammation in the initiation, maintenance and outcome of atrial fibrillation (AF). Nevertheless, despite a large amount of information, whether AF or the underlying structural heart disease (SHD) is the cause of the inflammatory process is still under debate. We, therefore, sought to determine if the inflammatory process reflects an underlying disease or the arrhythmia 'per se'. Indeed, the current evidence in the literature suggests that the 'inflammatory milieu' of the AF patient is responsible for the recruitment and migration of inflammatory cells to the atrial myocardial tissue, the activation of which, together with the endothelial damage induced by oxidative stress and the hemodynamic alterations that AF presupposes, would cause the prothrombotic state that characterizes the arrhythmia, thus allowing us to infer the existence of a link between inflammation and thrombosis in AF patients. Many questions concerning the complex link between inflammation – genetic – structural damage remains controversial, as it has not been established with certainty whether inflammation is a cause or a consequence of AF.
Aim: our group set out to conduct a study with the aim of assessing whether in a court of patients with permanent AF compared to healthy controls
- upregulation or downregulation of specific mi-RNAs, correlates with serum levels of inflammatory cytokines to suggest pathways that may link inflammation to atrial fibrosis in patients with permanent AF.
- There were documented associations between serum levels of inflammatory cytokines and echocardiographic variables as indices of fibrotic/structural damage.
- Significant correlations exist between fibrotic/structural and metabolic variables.
Materials and Methods: We enrolled 82 consecutive patients with permanent AF admitted to the Internal Medicine with Stroke Care ward of AOUP "P. Giaccone" of Palermo and 82 healthy controls from January 2020 to May 2022. We evaluated plasma levels of inflammatory cytokines (sIL-2Rα, TNF-α, IL-18, MCP-1, IL6, IL8), serum levels of MiRNA involved in electric and structural remodelling (MiR1, MiR21, MiR26), and we performed a TTE for evaluation of the structural damaging and the left atrial strain.
Results : Compared to controls with sinus rhythm, patients with atrial fibrillation showed a higher frequency of hypertension (84% vs 66.6%; $p < 0.001$) and diabetes mellitus (54% vs 30.25%; $p < 0.001$), higher mean blood levels of HbA1c (6.28 ± 1.15 vs 5.31± 1.44; $p < 0.001$), higher mean values of microalbuminuria (162.53 ± 39.72 vs 61.94 ± 31.73; $p < 0.005$).
With regard to echocardiographic parameters, subjects with atrial fibrillation showed, higher mean values of LAVI (51.549 ± 18.36 vs 38.47 ± 7.57; $p<0.005$), lower FE (47.208 ± 10.295 vs 55.58 ± 9.40; $p<0.005$), lower LA strain (20.75 ± 9.83 vs 29.64 ± 2.23). Relative to markers of inflammation, AF patients showed significantly higher mean serum levels of all the investigated cytokines (CRP, sIL-2Rα, TNF-α, IL-18, MCP-1, IL6, IL8). In Spearman's analysis, which correlated echocardiographic variables with structural variables, AF patients showed a statistically significant positive correlation between LAVI and RWT (r 0.264), E/e' (r 0.414), presence of segmental hypokinesia (r 0. 261) and negative correlation with ejection fraction (r 0.283); a positive correlation between left atrial strain and presence of segmental hypokinesia (r 0.411); a positive correlation between LVMI and E/e' (r 0.512) and segmental hypokinesia (r 0.352) and negative correlation with RWT (r 0.282) and FE (r 0.262). By correlating echocardiographic variables with metabolic variables, a negative correlation was shown between ejection fraction and triglyceride levels (r 0.334), the presence of diabetes (r 0.232) and NT-proBNP values (r 0.322), a positive correlation between LVMI and basal blood glucose values (r 0.253) and HbA1c (r 0.235) and a positive correlation between LAVI and basal blood glucose (r 0.272).
With regard to MiRNA analysis, no significant differences were documented between the group of fibrillating patients. and healthy controls.
Discussion: Our study provides further evidence of the central role of inflammation in AF patients. It suggests that the inflammatory process is due to the arrhythmia itself and not to the underlying structural heart disease. We hypothesize that these findings depend on the fact that AF, by virtue of its peculiar characteristics, is able to induce multiple structural changes, especially in forms with high mean ventricular response, consistent with a substantial cellular insult dependent on excessively rapid activation. These include oxidative stress on the myofibrillar proteins of atrial cardiomyocytes, cellular myolysis, cardiomyocyte apoptosis and local myocardial inflammation followed by structural and electrophysiological remodelling that incentivizes AF persistence. Our study offers concrete suggestions to emphasize the 'metabolic' nature of AF.

419. COFFEE CONSUMPTION RELATES TO A REDUCTION OF AORTIC STIFFNESS IN WELL-CONTROLLED HYPERTENSIVES

Marozzi M. S.[1], Rignani F.[2], Gramegna D.[2], Amodio G.[2], Santoro G.[2], De Benedittis L.[2], Schirosi G.[2], Cicco S.[1], Nazzaro P.[2]
[1]UOC Medicina Interna "G. Baccelli" and Unit of Hypertension "A.M. Pirrelli", Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), University of Bari Aldo Moro, AUOC Policlinico di Bari, Italy; [2]Unit of Hypertension "A.M. Pirrelli", Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), University of Bari Aldo Moro, AUOC Policlinico di Bari, Italy

Introduction: Nutritional interventions potentially preventing hypertension-related organ damage are far to be fully defined. Coffee is one of the most used beverages all over the world. Many studies tried to define the optimal amount of coffee in order to understand whether coffee has a role in cardiovascular prevention.
Aim: we evaluated vascular stiffness in well controlled hypertensives according to coffee consumption.
Methods: We evaluated 449 essential hypertensives (225F, 224M, 62.56±11.49 y.) screened for organ damage screening. The median coffee consumption was 2 cups per day. Patients were subdivided into three groups according to tertiles of cups consumed: Group 1, 0-1 cups (87F, 61M; 63.66±12.94 y), Group 2, 2 cups, (77F; 82M; 64.75±10.09 y), Group 3, >2 cups, (60F; 82M; 58.96±10.54 y).
Results: No differences highlighted in body mass index (BMI), in systolic/diastolic blood pressure (SBP/DBP) clinical observation, in carotid-femoral pulse wave velocity (cfPWV) and in ankle-brachial Index (ABI). An overlapping rate (~50%) of smokers/formers was present in all groups. On the contrary, aortic stiffness evaluated as Augmentation Index (AI) was significantly decreased in Group 3 compared to other groups (ANOVA $p<0.0001$): Group 3, 9.54±15.48 vs Group 1, 17.49 ± 19.56 ($p<0.05$); and vs Group 2, 15.88 ± 16.57 ($p<0.05$). To evaluate microcirculation, amydriatic retinography was performed. Arteriolar-to-Venular diameter Ratio (AVR) was higher in Group 1, 0.91 ± 0.10 vs Group 3, 0.87 ± 0.11 ($p<0.05$), but no difference resulted between Group 2 and 3 or Group 1 and 2. AVR did not correlate to Augmentation Index in any group. Results were no influenced according to sex distribution and smoking habits.
Conclusions: Coffee consumption may have a role in prevention of aortic remodelling and stiffness. Consumption of at least 3 cups of coffee per day reduces vascular stiffness and increase central vascular compliance, despite this effect is reduced in distal vascular circulation. Our findings need further analysis, mainly to the effects in distal/central hemodynamics due to different drug treatment.

420. AMBULATORY BLOOD PRESSURE MONITORING AS AN EARLY INDICATOR OF CARDIOVASCULAR DAMAGE: BEYOND AASI AND PULSE PRESSURE.

Brattoli M., Cecco A., Dionisi D., Canu P., Clerici L., Savioli G., Mugellini A., Di Sabatino A.
IRCCS Policlinico San Matteo, UOC Medicina Interna

Introduction: In clinical practice, parameters of ambulatory blood pressure monitoring (ABPM) are frequently used as an estimate of cardiovascular damage. The most common are pulse pressure (PP) and ambulatory arterial stiffness index (AASI), which however become significant only in overt organ

damage. The relationship between reduced nocturnal dipping and increased risk of cardiovascular events is also well known.
Aim: Check for a possible correlation between reduced nocturnal diastolic blood pressure dipping and early echocardiographic changes in patients with normal PP and AASI values.
Methods: This is a retrospective observational study on patients referred to our hypertension center between 2021 and 2022. Inclusion criteria are: age ≥ 18 years, having performed an echocardiogram at our reference echocardiographer and at least one ABPM. We subsequently excluded patients with effective ABPM measurements < 70%, PP values ≥ 65 mmHg and AASI ≥ 0.6. We divided the patients into non-dippers (nocturnal decline <10%) and dippers (nocturnal decline ≥10%) obtaining groups of 24 and 33 patients, respectively. Continuous variables were studied with T-test assuming different variances and categorical variables with Fisher's test.
Results: Two groups were homogeneous for general characteristics such as: age (64±12.9 vs 62±12.3; p=0.3), sex (M 50% vs M 42%; P=0.9), BMI (26.94±3.3 vs 26.6±3.5; p=0.35), and previous comorbidities (table 1); as well as for 24-hour systolic and diastolic blood pressure values. Among the echocardiographic parameters, a significant difference was shown by the left atrial area (21.55±4.89 vs 18.92±4.70; p=0.025), the E/A ratio (0.88±0.25 vs 1.03±0.34; p=0.031) and TAPSE (23.34±5.27 vs 25.75±4.75; p=0.04).
Conclusions: We have shown that a reduced nocturnal diastolic dipping correlates with a significant increase in the size of the left atrium and a reduced E/A ratio and, therefore, is correlated with LV diastolic dysfunction in absence of other organ damage's index. TAPSE also showed a significant difference, however remaining within the normal range in both groups

	All (n=57)		Non dipper (n=24)		Dipper (n=33)		
	mean/N	SD/%	mean/N	SD/%	mean/N	SD/%	p value
Age (years)	63	12,50	64	12,95	62	12,31	0,316
M/F	26/31	46/54	12/12	50/50	14/19	42/58	0,912
BMI	26,74	3,39	26,94	3,30	26,60	3,50	0,351
HR (bpm)	71,49	10,80	70,58	6,70	72,15	13,06	0,279
DBP (mmHg)	80,05	10,76	80,54	9,72	79,70	11,60	0,383
SBP (mmHg)	136,96	16,03	137,54	15,13	136,55	16,87	0,408
Smoke	17	29,82	6	25,00	11	33,33	0,404
Cardiomyopathy	8	14,04	2	8,33	6	18,18	0,095
Diabetes	11	19,30	4	16,67	7	21,21	0,674
CA	16	28,07	5	20,83	11	33,33	0,480
CCD	7	12,28	3	12,50	4	12,12	0,905
OSAS	9	15,79	5	20,83	4	12,12	0,209
CKD	5	8,77	2	8,33	3	9,09	0,058
Hepatopathy	3,00	5,26	1	4,17	2	6,06	0,397

Table 1: general population characteristic. DBP=diastolic blood pressure, SBP= sistolic blood pressure, CA= Carotid artery disease, CCD = chronic cerebral vascular disease, CKD= chronic kidney disease.

421. LONGER HOSPITALIZATION IN HEART FAILURE IS RELATED TO HYSTORY OF HYPERTENSION BUT NOT TO EJECTION FRACTION: A PILOT STUDY

Marozzi M.S.[1], Corvasce F.[1], Albanese F.[2], Desantis V.[3], Solimando A.G.[2], Lauletta G.[2], Pappagallo F.[2], Vacca A.[2], Cicco S.[1]
[1]Unit of Internal Medicine "Guido Baccelli" and Unit of Hypertension "A.M. Pirrelli", Department of Precision and Regenerative Medicine and Ionian Area, University of Bari, Bari, Italy; [2]Unit of Internal Medicine "Guido Baccelli", Department of Precision and Regenerative Medicine and Ionian Area, University of Bari, Bari, Italy; [3]Unit of Internal Medicine "Guido Baccelli" and Unit of Pharmacology, Department of Precision and Regenerative Medicine and Ionian Area, University of Bari, Bari, Italy

Introduction: Hypertension increases the risk of Heart Failure (HF), a leading cause of hospitalization among adults and aged subjects. The HF is classified by Guidelines based on the ejection fraction (EF).
Aim: The study aimed to evaluate differences of EF in HF patients hospitalized in the Internal Medicine Unit "Guido Baccelli", and of the associated comorbidities influencing the hospitalization time (HoTi).
Methods: We evaluated 49 worsening patients with chronic HF: 32 females, aged 79.82±10.26, with no obesity, acute coronary syndromes (ACS) and any pulmonary chronic disease. Patients who underwent bedside echocardiography were divided according to EF into: patients with EF ≥ 40% (preserved, 36 patients, 25 females, aged 78.55±11.34) and those with EF<40% (reduced, 13 patients, 7 females, aged 79.11±7.80).
Results: No significant differences in age, body weight, body surface area (BSA), heart rate, systolic (SBP) and diastolic blood pressure (DBP) Hb, serum creatinine, sodium, potassium and total cholesterol, HoTi between the groups were recorded. Hypertensives presented increased HoTi compared to normotensives (11.5 vs 7 days, p=0.049) and a trend for the HoTi itself and SBP to be associated (r=0.19; p=0.07). The HoTi was directly correlated to the body weight (r=0.35, p=0.04), but inversely correlated to the Hb at admission (r= -0.27; p=0.01). The EF was not related to HoTi, while a significant correlation between HoTi and the NYHA class ad admission (r=0.37; p=0.005) occurred.
Conclusions: lower EF is not closely related with longer HoTi. Comorbidities play a role in HF: specifically, higher body weight leads to a lower control of hypertension, which in turn is associated to a worse HF and NYHA classes. These results are a major challenge for the physician in primary and secondary cardiovascular prevention.

422. ELEVATED PULSE-WAVE VELOCITY AS ADDITIONAL RISK IN PATIENTS WITH ARTERIAL HYPERTENSION

Cicco S.[1], Rignani F.[2], Gramegna D.[2], Marozzi M.S.[1], Corvasce F.[1], Amodio G.[2], Santoro G.[2], Fanelli M.[3], Vacca A.[4], Nazzaro P.[2]
[1]Unit of Internal Medicine "Guido Baccelli" and Unit of Hypertension "A.M. Pirrelli", Department of Precision and Regenerative Medicine and Ionian Area - (DiMePRe-J), University of Bari Aldo Moro, Bari, Italy; [2]Unit of Hypertension "A.M. Pirrelli", Department of Precision and Regenerative Medicine and Ionian Area - (DiMePRe-J), University of Bari Aldo Moro, Bari, Italy; [3]Unit of Anatomical Pathology, Interdisciplinary Department of Medicine, University of Bari, AUOC Policlinico di Bari, I-70124 Bari, Italy; [4]Unit of Internal Medicine "Guido Baccelli", Department of Precision and Regenerative Medicine and Ionian Area - (DiMePRe-J), University of Bari Aldo Moro, Bari, Italy

Background: Vascular stiffness is a well-known parameter to evaluate hypertension mediated organ damage (HMOD) although few doctors are currently using it in their practice. Aim of this study was to evaluate how vascular stiffness by itself may change the evaluation in hypertensives.
Methods: We evaluated 324 hypertensives (147 males, 62.80±11.56 years) under treatment since 1 year. All patients were free by kidney disease, and underwent 2-D echocardiography to calculate left ventricle mass indexed (per height2.7). Patients were divided into those with heart hypertrophy (Group 1, 172 patients 91 males, 66.38 ± 9.80 years) and those without it (Group 2, 152 patients 56 males, 58.75 ± 12.09 years). Then we subdivided Group 2 into those with pulse wave velocity (PWV) ≥ 10 m/s (Group 2A, 46 patients 14 males, 63.41 ± 9.52 years) and those with < 10m/s (Group 2B, 106 patients 37 males, 55.79 ± 12.44 years). Cardiovascular risk score (CVRS) was evaluated using the ESC chart SCORE2/SCORE2-OP.
Results: Group 1 presented an increase in systolic blood pressure (SBP), body weight, BMI and waist circumference compared to Group 2 and Group 2B (p<0.05 each) but not to Group 2A while no difference was found in diastolic blood pressure (DBP) and heart rate (HR). No differences were found in total Cholesterol, HDL and LDL-C. On the contrary, Triglycerides and blood glucose were higher in Group 1 (p<0.05, both) despite the risk of NAFLD (evaluated as TyG score) overlapped between the groups. Moreover, only blood glucose was increased in Group 2A compared to 2B (p<0.05). CVRS was higher in group 1 and group 2A compared to Group 2 and 2B (p<0.05).
Conclusions: PWV allowed to identify a 15% more patients who present a HMOD, and consequently, with a cardiovascular risk and metabolic profile comparable to patients with heart hypertrophy. PWV should be routinely employed to evaluate hypertensives since the early stages of the disease.

423. WHOLE BLOOD VISCOSITY IS ASSOCIATED WITH REDUCED MYOCARDIAL MECHANO-ENERGETIC EFFICIENCY IN NON-DIABETIC INDIVIDUALS

Riccio A.[1], Mazzanti C.[1], Vero L.[1], Fiorentino T.V.[2], Succurro E. [2], Miceli S.[2], Perticone M. [2], Sciacqua A.[2], Andreozzi F.[2], Cefalo C.M.A[1], Sesti G.[1]
[1]Department of Clinical and Molecular Medicine, University of Rome-Sapienza Rome Italy; [2]Department of Medical and Surgical Sciences, University Magna Graecia of Catanzaro, Catanzaro, Italy

Increased evidence suggests that abnormalities in myocardial energetics characterized by reduced left ventricular (LV) mechanical efficiency and elevated oxygen consumption are involved in the development of cardiovascular (CV) disease**.** Pathophysiological mechanisms causing impaired myocardial MEE have not been elucidated so far. Amongst the other ones, whole blood viscosity may be a plausible candidate.
Whole blood viscosity is a measure of the intrinsic resistance of blood to flow and is generated by the frictional interactions between the main blood components, such as plasma, plasma proteins and red blood cells. An increased

whole blood viscosity may result in increase in blood pressure, cardiac postload and myocardial oxygen consumption (MVO2).
To address this issue, we investigated the association between myocardial MEE and whole blood viscosity in 1166 nondiabetic adults participating in the CATAnzaro MEtabolic RIsk factors (CATAMERI) study. All participants underwent physical examination with measurements of body mass index (BMI), waist circumference, and assessment of SBP, diastolic blood pressure (DBP), and heart rate. An OGTT was performed with sampling of plasma glucose. All participants underwent echocardiographic investigation performed by a single skilled examiner. Myocardial MEE was calculated by a simple non-invasive, ultrasound-based method by computing the ratio between left ventricular (LV) stroke work, assessed as stroke volume (SV) × systolic blood pressure (SBP), and MVO2 estimated by the double product, i.e., SBP x heart rate (HR).
Correlations between variables were determined by Pearson's correlation coefficient or Spearman's correlation coefficient for categorical variables. The independent association between myocardial MEE and whole blood viscosity was tested by multiple regression analysis, including the variables significantly associated with myocardial MEE in the univariate analysis.In the univariate analysis, myocardial MEEi was significantly associated with male sex, age, smoking status, BMI, waist circumference, total cholesterol, HDL-cholesterol, triglycerides, glucose tolerance status, HOMA-IR, hsCRP, haematocrit, haemoglobin, albumin, and total plasma protein. Moreover, a significant association was observed between whole blood viscosity and stroke work (r=0.255; P<0.001), MVO2 (r=0.201; P<0.001), and myocardial MEEi (r= -0.197; P<0.001). To estimate the independent contribution of whole blood viscosity to myocardial MEE, we built a multivariable regression model including sex, age, smoking status, BMI, total and HDL cholesterol, triglycerides, hsCRP, glucose tolerance status, HOMA-IR, antihypertensive therapy, and lipid-lowering therapy. We found that whole blood viscosity was independently associated with myocardial MEE (β = -0.124, p<0.001), along with HOMA-IR (β =-0.156, p<0.001), age (β =-0.098, p=0.005) and antihypertensive therapy (β =-0.091, p=0.006).
These data suggest that whole blood viscosity by increasing stroke work and myocardial oxygen consumption may contribute to decreased myocardial MEEi independently of several CV risk factors.

Table 3. Correlation between myocardial MEEi, whole blood viscosity and anthropometric and metabolic variables.

	Myocardial MEEi		White blood viscosity	
Variables	r	P	r	P
Sex	-0.155	<0.001	0.502	<0.001
Age (years)	0.109	<0.001	0.061	0.035
Smoking status	0.065	0.025	0.211	<0.001
BMI (kg/m²)	0.137	<0.001	0.058	0.325
Total cholesterol (mg/dL)	0.067	0.003	0.158	<0.001
HDL-C (mg/dL)	0.101	<0.001	-0.249	<0.001
Triglycerides (mg/dL)	0.114	<0.001	0.254	<0.001
HOMA-IR	0.218	<0.001	0.152	<0.001
Glucose tolerance status	0.132	<0.001	0.108	<0.001
hsCRP (mg/L)	0.162	<0.001	-0.046	0.121
Fibrinogen (mg/dl)	0.119	<0.001	-0.028	0.332
Haematocrit (%)	0.182	<0.001	----	----
Haemoglobin (g/dL)	0.222	<0.001	0.043	<0.001
Albumin (g/dL)	0.004	0.455	0.306	<0.001
Total Plasma Proteins (g/dL)	0.128	<0.001	----	----
Whole blood viscosity	0.199	<0.001	----	----
Systolic blood pressure	----	----	0.226	<0.001
Diastolic blood pressure	----	----	0.206	<0.001
Stroke work (mmHg*ml)	----	----	0.247	<0.001
Myocardial oxygen consumption (mmHg x bpm)	----	----	0.197	<0.001

Triglycerides, HOMA-IR and hsCRP were natural log transformed for statistical analyses, but values in the table represent back transformation to the original scale.
BMI= body mass index; HDL-C= high-density lipoprotein cholesterol; HOMA-IR= homeostasis model assessment index of insulin resistance; hsCRP= high-sensitivity c-reactive protein; IFG= impaired fasting glucose; IGT= impaired glucose tolerance; NGT= normal glucose tolerance.

424. IBRUTINIB RELATED CARDIOTOXICITY: THE ROLE OF ECHOCARDIOGRAPHIC EVALUATION

Gammaldi V., Pucci M., Mocerino L., Iadevaia V., Iervolino A., Capece L. M., Iacono M., Paoletta D., Esposito R.
Department of Clinical Medicine and Surgery, Federico II University Hospital, Naples, Italy

Background: Ibrutinib is a Bruton tyrosine kinase inhibitor, approved in the last few years for treatment as primary option for all subsets of chronic lymphocytic leukemia (CLL). Its use is associated with increased incidence of atrial fibrillation (AF), and other cardiotoxicities.**Objectives:** Aim of the study is to determine whether there are echocardiographic parameters that could identify patients at major risk of developing ibrutinib-related atrial fibrillation (IRAF), and if there are any changes of those parameters at follow-up evaluation at six months.
Methods: We performed a retrospective review of 33 patients (mean age 70,59 ± 11,82; 31% females), admitted at our EchoLab in the last year, who underwent echocardiogram prior to Ibrutinib treatment. Then, we performed a prospective review of eighteen patients out of the thirthy-three evaluated at baseline, admitted at our EchoLab six-months after starting therapy with Ibrutinib. Echo-Doppler assessment was realized according to the standards of the European Association of Cardiovascular Imaging (EACVI) standardization of the echo report. Left atrial (LA) strain was measured with EchoPAC, obtaining peak atrial longitudinal strain (PALS) and peak atrial contraction strain (PACS) on 4-chambers and 2-chambers views. Continuous normally distributed variables were compared by using the Student t-test. A probability value <0,05 was considered statistically significant. Analyses were performed with SPSS version 25 (IBM Corporation, Somers, New York).
Results: Last year we evaluated thirthy-three patients with echocardiogram prior Ibrutinib treatment. We found that six of these developed atrial fibrillation (AF). Those patients had peculiar echocardiographic characteristics compared to the control group: they had lower ejection fraction (EF) (54,71 ± 1,79 vs 60,07 ± 4,30, p-value: 0,000), higher left atrium volume index (49,81 ± 15,06 vs 34,01 ± 9,29, p-value: 0,032), higher pulmonary arterial pressure values (PAPs) (43,00 ± 10,73 vs 32,11 ± 8,32, p-value: 0,037). It was noticed also that peak atrial longitudinal strain (PALS) and peak atrial contraction strain (PACS) were reduced in patients who developed IRAF (PALS 4Ch: 16,90 ± 7,45 vs 29,17 ± 11,14, p-value 0,015; PACS 4Ch: 9,10 ± 5,90 vs 14,37 ± 5,56, p-value: 0,120; PALS 2Ch: 20,15 ± 8,39 vs 29,58 ± 15,40, p-value: 0,83; PACS 2Ch: 11,54 ± 8,45 vs 16,45 ± 9,01, p-value: 0,28). Furthermore, it was noticed that PALS4 was statistically significant (p value: 0,015). Out of those thirthy-three patients, eighteen came back to our EchoLab for follow-up after six months. We noticed that they did not have any worsening of the echocardiographic variables studied at basal evaluation. In fact, there was no statistical significance of ejection fraction (EF) (59,94 ± 5,92 vs 58,05 ± 6,32, p-value: 0,077), left atrial volume (LAVi) (35,20 ± 8,84 vs 37,12 ± 12,91; p-value: 0,317), and pulmonary arterial pressure (PAPs) (32,09 ± 5,59 vs 31,64 ± 5,64; p-value: 0,807). It was noticed that also the peak atrial longitudinal strain (PALS) and peak atrial contraction strain (PACS) didn't reduce between follow-up and basal measurement: (PALS 4Ch: 21,42 ± 10,23 vs 27,41 ± 13,55, p-value: 0,339; PACS 4Ch: 10,15 ± 5,81 vs 13,81 ± 5,71, p-value: 0,202; PALS 2Ch: 21,82 ± 7,64 vs 33,50 ± 20,33; p-value: 0,096; PACS 2Ch: 11,66 ± 4,62 vs 17,88 ± 10,28, p-value: 0,111).
Conclusions: In the first analysis we made a stratification of the patients who had major predisposition to develop ibrutinib-related atrial fibrillation (IRAF). Now, we have the first results on echocardiogram at six months follow-up. We noticed that none of the echocardiographic parameters studied before worsened or were statistically significant. This underlies what we already stated in the first study. We need to emphasize one more time the importance of baseline evaluation by echocardiogram including measurement of atrial strain of patients before starting treatment with Ibrutinib. Pharmacological intervention tailored on each patient could allow the preservation of cardiac function and improve patient outcomes in the long term.

425. RESTING AND EXERCISE RIGHT HEART FUNCTION AND HEMODYNAMICS IN SUBJECTS WITH RISK FACTORS BUT WITHOUT OVERT CARDIOVASCULAR DISEASE: A REPORT FROM THE RIGHT HEART INTERNATIONAL NETWORK (RIGHT-NET)

De Luca M.[1], D'assante R.[1], Crisci G.[1], Gargani L.[2], Giardino F.[1], Ferrara F.[3], Ranieri B.[4], Cittadini A.[5], Marra A.M.[5], Bossone E.[6]
[1]Department of Translational Medical Sciences, University of Naples "Federico II", Naples, Italy; [2]Department of Surgical, Medical and Molecular Pathology and Critical Care Medicine, University of Pisa, Italy.; [3]Cardio-Thoracic-Vascular Department, University Hospital "San Giovanni Di Dio E Ruggi D'Aragona", Salerno, Italy; [4]IRCCS Synlab SDN, Naples, Italy; [5]Department of Translational Medical Sciences, University of Naples "Federico II", Naples, Italy.; [6]Department of Public Health, University of Naples "Federico II", Naples, Italy

Background: Although Stress echocardiography is increasingly being used for the assessment of the right heart – pulmonary circulation unit (RH-PCU), the effects of traditional cardiovascular risk factors (CVRF) on right heart function and pulmonary circulation hemodynamics during exercise in patients without overt CV disease remain not fully explored.
Materials and methods: A total of 375 healthy subjects and 381 patients with CVRF (namely systemic arterial hypertension and/or dyslipidemia and/or type 2 diabetes) but without overt CV disease were enrolled. Among them, 167 had only one CVRF (mean age 58.7±12.6, female 38%) and 214 had two or more CVRF (mean age 65.1±9.9, female 35%). All subjects underwent

transthoracic Doppler echocardiography (TTE) at rest and during exercise on a semi-recumbent cycle ergometer, according to standardized protocols. Key indices reflecting RH-PCU were the tricuspid annular plane systolic excursion to systolic PAP ratio (TAPSE/sPAPs) and mean Pulmonary Arterial Pressure /Cardiac Output (mPAP/CO) slope.
Results: At peak exercise patients with CVRF reached lower workload and HR. The TAPSE/sPAP decreased in CVRF patients, with the lowest value in patients with ³2 CVRF (Figure 1)). The percentage of patients with value of mPAP/CO>3 mmHg/L/min (upper normal limits) was highest in patients with ³2 CVRF (41.3%), dropped to 33% in patients with 1 CVRF and to 18% in controls (Figure 1).
Conclusion: In patients without overt CV disease, right heart function and pulmonary circulation hemodynamics, as assessed by standard exercise TTE, progressively worsens as the number of CVRF increases. Further studies are needed to clarify mechanistic reasons underlying such finding.

TAPSE/sPAP values and percentage of patients with mPAP/CO slope>3 mmHg/L/min among healthy subjects and different CVRF cohorts.

Groups	TAPSE/sPAP (mm/mmHg) At rest	TAPSE/sPAP (mm/mmHg) At peak	mPAP/COslope>3 mmHg/L/min
Healthy subjects	1.04 [0.9-1.3]	0.79 [0.61-1]	18.0%
1 CV risk factors patients	0.90 [0.8-1.1]	0.64 [0.54-0.80]	32.2%
≥2 CV risk factors patients	0.95 [0.8-1.2]	0.61 [0.50-0.89]	41.3%
Only Hypertensives	0.9 [0.8-1.1]	0.65 [0.53-0.83]	33%
Non-Hypertensives	0.85 [0.83-0.86]	0.60 [0.54-0.72]	29%

Abbreviations: CO, cardiac output; mPAP, mean pulmonary arterial pressure; TAPSE/sPAP: tricuspid annular plane systolic excursion to systolic PAP ratio.

426. SLEEP DEPRIVATION AND CARDIOVASCULAR RISK: ARE THERE SEX DIFFERENCES?

Ciampa C.[1], Stefanucci M.[2], Spugnardi V.[2], Fabozzi G.[2], Ferrara F.[3], Bossone E.[4], Salvatore V.[5], Stranges S.[6]
[1]Scuola di Specializzazione in Medicina Interna, UNISA. ; [2]Scuola di Specializzazione in Medicina Interna, UNISA; [3]Cardiologia P.O. Cava AOU S. Giovanni Di Dio e Ruggi D'Aragona-Salerno; [4]Dipartimento di Sanità Pubblica, Università Federico II, Naples; [5]Medicina Interna P.O. Cava AOU S.Giovanni Di Dio e Ruggi D'Aragona- Salerno; [6]Department of Epidemiology and Biostatistics, Schulich School of Medicine and Dentistry, Western University London (ON, Canada)

Background and aims: Sleep deprivation should be considered a modifiable cardiovascular risk factor, in addition to the traditional ones, in risk stratification assessment. Several observational studies worldwide suggest that reduced sleep duration and poor sleep quality are associated with an increased risk of mortality, hypertension, coronary heart disease (CHD), type 2 diabetes, cognitive decline, depression and anxiety, among others. The American Heart Association has recently added healthy sleep as essential for optimal cardiovascular health in adults along with traditional health and lifestyles factors. Recent studies highlight as well that the increased cardiovascular risk driven by sleep deprivation may be particularly relevant among women. Critical life transitions such as menopause are likely to play an important role in these sex differences.
Methods and Material: We performed a literature review using PUBMED. Words like sleep deprivation, cardiovascular risk and sex difference were used in the search engine. We appraised the evidence from observational epidemiological studies assessing both prevalence and incidence of hypertension and cardiovascular events related to sleep deprivation in adult populations, with particular focus on sex differences as well as on age-related differences in the sleep-cardiovascular health association among women.
Results: In the US National Health and Nutrition Examination Survey (NHANES-I), sleeping less than 5 hours was associated with 60% higher risk of hypertension with no sex differences; this data was further supported by findings from the CARDIA study. However, findings from the Whitehall II study in the UK showed that sleeping < 5 hours per night was associated with an increased hypertension risk only in women (OR 1.72; 95% CI 1.07-2.75) compared to the group sleeping 7 hours, while no significant differences were detected in men (OR 0.88; 95% CI 0.63-1.23); these results are in line with findings from the Heinz Nixford Study in Germany, where there was an increased risk of CHD among women reporting short sleep duration (OR 1.24; 95% CI 1.04-1.46) and the MONICA study (HR 2.98; 95% CI 1.46-6.03). Additionally, findings from the Western New York Health Study (WNYHS) supported the notion that sleep deprivation (< 6 hours per night) may be associated with a higher risk of hypertension only among women (OR 1.66; 95% CI 1:09-2:53); in addition, after stratifying the data by menopausal status, the relationship between sleep deprivation and hypertension was stronger among premenopausal women (OR 3.25; 95% CI 1.37-7-76) compared to postmenopausal women (OR 1.49; 95% CI 0.92-2.41). Finally, a meta-analysis of observational studies (including 6 cross-sectional and 7 prospective studies) examined the relationship between sleep duration and hypertension risk. Findings corroborated the evidence of sex differences, with a stronger association among women than men (sleep time ≤ 5 h vs. 7 h, OR = 1.68, 95% CI: 1.39-2.03 in women; OR = 1.30, 95% CI:0.93-1.83 in men).
Conclusions: Sleep deprivation may produce detrimental effects on cardiovascular health via an increased risk of hypertension, especially among women. The mechanisms that can explain this effect are yet unclear. Hormonal influences, psychosocial factor (related mainly to the reproductive stage) and consequently a major activity of sympathetic and ACE system induced by a longer awake exposure may explain the observed associations. Menopausal transition is likely to play a critical role among women. During the premenopausal age, vasomotor symptoms such as flushing and sweating can be responsible for insomnia; in addition, the common occurrence of depression and the increased number of drugs related to this age group can interfere with a good sleep quality. Our literature review suggests the importance to include sleep duration and sleep quality assessment in cardiovascular risk evaluation in the European context as well, as recently implemented by the American Heart Association, due to the growing scientific evidence linking sleep deprivation and poor sleep quality with higher cardiovascular risk. This opens new scenarios such as including sleep duration and quality in cardiovascular risk scores as well as the administration of questionnaires, not only for the detection and diagnosis of clinical disorders such as sleep apnea, but also for the overall assessment of sleep health.

427. MEAN PLATELET VOLUME (MPV) AS NEW MARKER OF CARDIOVASCULAR RISK IN NEWLY DIAGNOSED HYPERTENSIVE PATIENTS WITH DIFFERENT GLUCOSE HOMEOSTASIS.

Cassano V.[1], Armentaro G.[1], Iembo D.[1], Dallimonti Perini D.[2], Condoleo V.[1], Miceli S.[1], Maio R.[1], Fiorentino T.V.[1], Perticone M.[1], Succurro E.[1], Hribal M.L.[1], Andreozzi F.[1], Sesti G.[3], Sciacqua A.[1]
[1]Department of Medical and Surgical Sciences, University Magna Græcia of Catanzaro, 88100 Catanzaro, Italy.; [2]Department of Experimental and Clinical Medicine, University Magna Græcia of Catanzaro, Catanzaro, Italy; [3]Department of Clinical and Molecular Medicine, Sapienza University of Rome, Rome, Italy

The mean platelet volume (MPV) is a measurement of the platelet activity and is considerate a prognostic marker in patients with cardiovascular diseases (CVD). Increased MPV is associated with an increased risk of atherosclerosis and myocardial infarction and can be considered and independent risk factor of death in patients after acute ischemic cardiac incident. It is known that glucose homeostasis alterations are associated with subclinical vascular damage; and the mechanisms of vascular complications of type 2 diabetes (T2DM) already act in the prediabetes phase. Previous studies demonstrated an increase in MPV in patients with T2DM, however it is still unclear whether higher MPV is present in the early phase of diabetes. The aim of the present study was to evaluate MPV values and its possible correlation with arterial stiffness and subclinical myocardial damage, in normal glucose tolerance patients (NGT), in T2DM and in prediabetes patients. We enrolled 400 newly diagnosed hypertensive patients (mean age 60.1±11.9, 251 male and 149 female) referring to Catanzaro Metabolic Risk Factors (CATAMERI) Study. Main exclusion criteria were secondary hypertension, clinical evidence of CV complications, endocrinological and malignant disease, alcohol or smoking abuse. All patients underwent to Oral Glucose Tolerance test (OGTT). Plasma glucose was measured by the glucose oxidation

method and plasma insulin concentration was determined by a chemiluminescence-based assay. Insulin sensitivity was evaluated using the Matsuda index (Matsuda/ISI). Renal function was tested by measurement of estimated glomerular filtration rate (e-GFR) with CKD-Epi formula. Arterial stiffness (AS) was evaluated with the measurement of carotid-femoral pulse wave velocity (PWV), augmentation pressure (AP) and augmentation index (AI). Echocardiographic recordings were perfomed using an E-95 Pro ultrasound system. ANOVA test was used to test the differences between groups. A linear correlation analysis was performed to compare values of MPV, PWV and global longitudinal strain (GLS) with different covariates. Variables reaching statistical significance were inserted in a stepwise multivariate linear regression model. We divided the patients into three groups: normoglycemic patients (NGT) (n=179), prediabetes patients (n=137) and newly diagnosed T2DM (n=84). There were no significant differences among groups regarding age, gender, systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), HDL and LDL cholesterol. By contrast, there was an increase in fasting plasma glucose (FPG) (p<0.0001), 2h-glucose (p<0.0001), fasting plasma insulin (FPI) (p<0.0001), 2-h insulin (p<0.0001), HbA1c (p<0.0001), high sensitivity c reactive protein (hs-CRP) (p<0.0001) and a decrease in renal function as demonstrated by e-GFR values (p<0.0001). Interestingly, from normoglycemic group to T2DM group there was a raise in MPV value (p<0.0001). In particular, higher MPV was found in prediabetes (p<0.0001) and T2DM patients (p<0.0001) compared to normoglycemic subjects. From linear regression analysis, MPV was significantly and directly correlated with HbA1c (r=0.251,p<0.0001), hs-CRP (r= 0.120,p=0.009), platelets (PLT) (r=0.187,p<0.0001), age (r=0.107, p=0.018) and inversely correlated with Matsuda/ISI (r=-0.446, p<0.0001), BMI (r=-0.165,p=0.001) and e-GFR (r=-0.397,p<0.0001). Subsequently, stepwise multivariate linear regression model showed that Matsuda/ISI was the major predictor of MPV justifying 19.7% (p<0.0001) of its variation, e-GFR added another 7.7% and HbA1c and e-GFR added, respectively, 1.7% and 1.1% respectively. In the evaluation of arterial stiffness, from linear regression analysis pulse wave velocity (PWV) resulted significantly and inversely correlated with MPV (r=-0.222, p<0.0001), e-GFR (r=-0.142, p=0.003), hs-CRP (r=-0.102, p=0.023), HDL cholesterol (r=-0.119, p=0.010) and directly correlated with SBP (r=0.102,p=0.022) and LDL cholesterol (r=0.131, p=0.005). Stepwise multivariate linear regression model highlighted that MPV was the main predictor of PWV justifying 7.0% (p<0.0001) of its variation. Regarding to echocardiographic evaluation, GLS was directly and significant correlated with MPV (r=0.334,p<0.0001), E/è (r=0.359,p<0.0001), left ventricular mass index (LVMI) (r=0.329, p<0.0001), SBP (r=0.194,p<0.0001), DBP (r=0.124, p=0.007), hs-CRP (r=0.100, p=0.038) and inversely correlated with Matsuda/ISI (r=-0.245,p<0.0001) and e-GFR (r=-0.116, p=0.011). Stepwise multivariate linear regression model demonstrated that E/è was the main predictor of GLS justifying 12.7% of its variation, MPV added another 6.6%, LVMI and SBP added respectively 2.8% and 1.3%. In conclusion, we highlighted that MPV is significantly increase in newly diagnosed T2DM patients and in early stages of diabetes, indicating that subjects with prediabetes present increased platelets reactivity. Moreover, our results suggest that MPV is associated with increased arterial stiffness and subclinical myocardial damage, indicating MPV as a new marker of CV risk.

428. FROM AORTITIS TO PERI-AORTITIS: EXAMPLE OF A SILENT EMERGENCY

Cipollone A. [1], Ricciardi R. M.[1], D'Ardes D.[1], Rossi I.[1], Serafini F.[2], Guagnano MT .[1], Bucci M.[1], Santilli F.[1], Cipollone F.[1]
[1]"Clinica Medica" Institute, Department of Medicine and Aging Science, "G. D'Annunzio" University of Chieti-Pescara; [2]Department of Neuroscience Imaging and Clinical Sciences, Gabriele D'Annunzio University of Chieti-Pescara

The term"peri-aortitis"refers to an inflammatory state of the wall of this vessel with extension to the periaortic space,differing from"aortitis"which only involves the vessel.Among the possible causes,an initial distinction can be made between"infectious"and"non-infectious",the latter prevalent above all with regard to the possible rheumatic etiology.The infectious causes are mostly of bacterial aetiology.In most cases,the infection develops in conditions of pre-existing vascular damage.72yo patient undergoing EVAR for exclusion of infrarenal abdominal aortic aneurysm at the beginning of April 2023.1 week after the operation,a new hospitalization was necessary due to the appearance of septic state with probable onset from the aorta;some aerial density images on the CT scan inside the aneurysm sac was found.the patient was treated with empiric antibiotic therapy with benefit.a month later he was admitted to our Department due to anemia,hyperpyrexia and increased inflammation indexes.The blood tests documented positivity to 1/4 blood cultures for E. coli(with indication to repeat the blood cultures).A CT scan of the abdomen with contrast medium was performed and the following was highlighted:*excluding aneurysmal sac,in the infrarenal site it shows a reduced axial diameter and the small aerial density images appear less evident in the context;the walls of the aneurysm sac currently appear finely irregular,thickened and characterized by contrastographic impregnation.No evident signs of appreciable endoleak.patency of the endoprosthesis"*.in the absence of surgical emergencies and awaiting further blood culture reports,empirical antibiotic therapy was set up with Ceftriaxone 2g/day and Vancomycin 500mg x 4/day.The patient afebrile reported asthenia and nausea in the absence of angor or other specific symptoms.laboratory research was performed for other possible infectious sources of aortitis and also the autoantibodies attributable to vasculitis of the great vessels;both were negative.The blood and urine cultures found positivity for E. coli so the antibiotic therapy was switched to Meropenem 1gx4/day.Although the patient's symptoms remained stable,in the light of a sudden laboratory worsening the patient was transfused and reevaluated.The new abdomen CT,performed 9days after the previous one,showed a significant worsening of the clinical picture:*slight caudal migration and proximal undocking of the endoprosthesis with signs of evident reperfusion in the cranial portion of the aneurysm sac treated with type IA endoleak.The abdominal aneurysm sac downstream of the aforementioned leak appears slightly increased; he aerial density images persist in the context of the pocket.More evident are the aortic and peri-aortic inflammatory phenomena with radiological indissociability and compression of the inferior vena cava;there is coexisting inflammatory-cranial abscess involvement of the right diaphragmatic pillar and loss of cleavage planes with the horizontal portion of the duodenum.*we proceeded with transfer to the Vascular Surgery Unit of our OP toperform emergency surgery.Axillofemoral bypass procedure was performed with stent graft explantation and aortic stump.the presence of numerous adhesions was highlighted as well as diffuse retroperitoneal fibrosis .Once the detachment was performed,an aorto-enteric fistulous lesion was highlighted.At its end the surgical procedure was burdened by copious bleeding and hemodynamic instability,linked to the finding of hemoperitoneum.Once the emergency had been managed he was transfered to the resuscitation room stabilization.DISCUSSIONThe development of aortitis and/or periaortitis is a rare but serious complication of vascular surgery procedures.The symptomatology is often non-specific;the main symptoms include fever,asthenia,abdominal and/or chest pain.More rare are the signs related to intestinal involvement:hematemesis, caffeine vomiting and/or melena.Despite the presence of an aorto-enteric fistula,the patient never had clinical manifestations but only positivity to 2SOF samples.given the precarious clinical conditions,the negativity of tumor markers,negative EGDS report and the absence of findings at the first CT scan,it was preferred to postpone the execution of a colonoscopy.the laboratory findings are nonspecific,with increased inflammation indices and leukocyte count.The radiological study by CT with contrast is irreplaceabl which allows to characterize the inflammatory state thanks to the thickening, irregularity and contrastographic impregnation of the vessel walls.The infectious nature can be deduced from the presence of aerial findings in the context.thanks to the contrast medium,it is possible to highlight any blood leakage.The radiological study also makes it possible to monitor the development of abdominal fibrotic adhesions.In the early stage,infectious aortitis must be treated by antibiotic therapy targeted;the optimal duration of this therapy is still debated,for the moment settled in a period between 6 and 12 weeks.Given the non-specific clinical-laboratory picture,it can often be misdiagnosed and lead to the evolution with an aggravation such as to constitute surgical emergency.

429. CHRONIC MESENTERIC ISCHEMIA: LOSING WEIGHT BY EATING

Piccirillo S.[1], Spugnardi V.[1], Iovino L.[2], Vigliotti G.[3], Messalli G.[2], Stefanucci M.[1], Cannavaro G.[1], Triggiani M.[1], Adiletta G. [2]
[1]Università degli studi di Salerno; [2]P.O. Martiri di Villa Malta Sarno; [3]Ospedale del Mare Napoli

Background: Chronic mesenteric ischaemia (CMI) is an uncommon and underdiagnosed clinical condition, that includes stenosis or chronic occlusion of the celiac trunk, superior mesenteric artery (MSA) and inferior mesenteric artery. It is characterised by postprandial abdominal pain and weight loss with preserved appetite. The most common cause is atherosclerosis, followed by vasculitis and fibromuscular dysplasia.
Clinical case: 64 years-old male with an involuntary weight loss of 10 kg in three months. Risk factors: arterial hypertension. Performed oncological markers, EGDS and colonoscopy, autoimmunity, thyroid and dyslipidaemic profile with negative results; heterozygosity of the MTHFR gene. The suspicion of HCM was raised and abdominal AngioTC was performed, finding stenosis of more than 90% of the celiac trunk and 75% of the MSA, followed by abdominal aortography with stent insertion in the MSA and subsequent

body weight gain. Subsequently Cardio-CT and coronarography were performed, with finding of total occlusion of the distal part of the right coronary artery and 70% of the MSA treated with PTCA+stent.
Conclusions: Symptomatic HCM is rare, while the asymptomatic form affects 14% of adults with possible even fatal repercussions. The present clinical case demonstrates how this pathological entity, although serious, is underdiagnosed and how fundamental is the clinical assessment of the internist from whose critical eye the suspicion of HCM arose, confirmed by the appropriate therapeutic and diagnostic procedure immediately activated.

430. THE ROLE OF ALB-R2CHA2DS2-VASC SCORE FOR PREDICTING MORTALITY IN HIGH CARDIOVASCULAR RISK POPULATION

Piscitelli P.[1], D'Errico M.M.[1], Pacilli G.[2], Santoliquido M.T.[3], Notarangelo E.[2], Cappucci G.[2], Vigna C.[4], Marchese N.[4], Lamacchia O.[5], Fontana A.[6], Copetti M.[6], Vendemiale G.[7], Pontremoli R.[8], De Cosmo S.[1], Mirijello A.[1]
[1]Unit of Internal Medicine, Fondazione IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, FG, Italy; [2]Internal Medicine Residency School, University of Foggia, FG, Italy; [3]Geriatrics Residency School, University of Foggia, FG, Italy; [4]Unit of Cardiology, Fondazione IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, FG, Italy.; [5]Unit of Endocrinology, University of Foggia, Foggia, Italy; [6]Biostatistics Unit, Fondazione IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, FG, Italy; [7]Chief of the Internal Medicine Residency School, University of Foggia, FG, Italy; [8]Dipartimento di Medicina Interna e Specialità Mediche, Università degli Studi di Genova, Italy

The CHA2DS2-VASc score has been originally developed for the risk prediction of patients with atrial fibrillation (AF). It attributes 1 point to chronic heart failure (CHF), hypertension, age 65-74 years, diabetes mellitus (T2DM), vascular disease and female gender and 2 points for age ≥75 years and prior stroke or transient ischemic attack (TIA). Despite it was originally developed and used to predict the risk of cerebral infarction in patients with AF, it also turned out to be a useful predictor of outcome in different cardiovascular (CV) conditions, independently from the presence of AF. Accumulating evidence suggests that CHA2DS2-VASc score is an independent predictor of major CV events in patients with acute coronary syndrome (ACS), and a predictor of survival, death and cardiovascular hospitalization in patients with heart failure. Moreover, it is a prognostic factor for mortality and major stroke in patients undergoing carotid artery stenting, and an independent predictor of ischemic stroke, coronary events and overall mortality in diabetic patients.
Our research group has recently shown, in a large population of subjects at high CV risk undergoing coronary angiography (CA), that CHA2DS2-VASc as well as R2CHA2DS2-VASc scores are useful predictors also of all-cause mortality. In addition, R2CHA2DS2-VASc score appeared to have a better discriminatory performance in predicting of all-cause mortality as compared to CHA2DS2-VASc score, probably due to the weight of kidney dysfunction on coronary artery disease.
The present study aimed to assess whether the addition of albuminuria to R2CHA2DS2-VASc score further improves its discrimination ability in predicting all-cause mortality in a large sample of high cardiovascular risk population.
Methods: Prospective, monocentric, observational study, evaluating a subset of 737 subjects consecutively undergoing to coronary angiography at Coronary Unit of Scientific Institute "Casa Sollievo della Sofferenza" from June 2016 to December 2018.
Results: The presence of albuminuria was significantly associated with all-cause mortality (p<0.0001). Any one-point increase of Alb-R2CHA2DS2-VASc score increased mortality of about 1.5-fold (adjusted HR 1.49; 95%CI: 1.37-1.63; p<0.0001). Considering tertiles of Alb-R2CHA2DS2-VASc, the third tertile showed a 9.5-fold increased risk of mortality (HR 9.52; 95% CI: 5.15-17.60, p<0.001). Comparing the two scores, the Alb-R2CHA2DS2-VASc score (C-statistic=0.751; 95%CI: 0.69-0.81) outperformed the R2-CHA2DS2-VASc score (C-statistic=0.736; 95%CI: 0.68-0.961) in predicting mortality (delta C-statistic=0.015; 95%CI: 0.001-0.029). The better prediction ability of the Alb-R2CHA2DS2-VASc score was also proven by an IDI of 0.024 (p<0.0001) and a relative IDI of 24.11% (p<0.0001), with an NRI=0.608 (p<0.00001).
Conclusions: The addition of albuminuria to R2CHA2DS2-VASc significantly and independently predicts the risk of all-cause mortality in a sample of high CV risk patients. Moreover, Alb-R2CHA2DS2-VASc outperforms R2CHA2DS2-VASc.

431. DECREASE IN HEMOGLOBIN LEVELS IN ACUTE IDIOPATHIC PERICARDITIS: A MODEL OF ANEMIA OF ACUTE DISEASES?

Casarin F.[1], Mascolo R.[2], Motta I.[3], Cappellini M.D.[3], Brucato A.[4]
[1]Dipartimento di Medicina Interna, Ospedale Fatebenefratelli, Milano ; [2]Dipartimento di Medicina Interna, Ospedale Fatebenefratelli, Milano; [3]Dipartimento di Scienze Cliniche e di Comunità, Università degli Studi di Milano, Milano; Fondazione IRCSS Ca' Granda Policlinico di Milano ; [4]Dipartimento di Scienze Cliniche e Biomediche, Ospedale Fatebenefratelli, Università degli Studi di Milano, Milano

Background: Anemia is a condition defined by hemoglobin (Hb) concentration <120 g/l for women and <130 g/l for men. In chronically ill patients affected by conditions that cause prolonged inflammation, anemia is common and it is defined as anemia of chronic diseases (ACD). ACD usually presents with normocytic anemia, reduced circulating iron concentrations, reduced transferrin saturation, normal or increased ferritin levels. To date, it is well known that anemia is associated to chronic diseases, but to the best of our knowledge we do not know whether there is a form of anemia related to acute inflammation. In our clinic of pericardial disease, we observed some patients with a striking decrease of Hb during the acute attack, followed by a quick return to basal values in a few days. On this basis, we wondered whether Hb values could fall in acute pericarditis, and we tried to study the underlying mechanism.
Materials and Methods: This is an observational prospective study with retrospectively collected data on a cohort of adult patients with idiopathic recurrent pericarditis followed at Fatebenefratelli Hospital in Milan and Papa Giovanni XXIII Hospital in Bergamo from January 2010 to April 2023. As primary endpoint, we analyzed the trend in Hb values and Hb difference between the acute attack of pericarditis and the subsequent remission phase, while, as secondary endpoints, we searched for a correlation between Hb and other clinical variables such as indices of inflammation (C-reactive protein – CRP, neutrophils, and the neutrophil-to-lymphocyte ratio – NLR, which represents the ratio between the absolute value of neutrophils and the absolute value of lymphocytes), and serosal involvements, using uni- and multivariate analysis.
Results: We enrolled 62 patients (female/male 30:32), with a median age at index attack of 39 (26–60) years. For all patients enrolled, Hb levels during attack were lower than those during remission [median (IQR): 12 (11.2 – 13.4) g/dl vs. 13.65 (13.1 – 14) g/dl; p < 0.001]. This reduction of Hb was associated with an elevation of CRP [= 0.391, 95% IC: 0.149 – 0.589, p = 0.002], leukocytosis [= 0.304, 95% IC: 0.051 – 0.520, p = 0.016], mainly neutrophilic [= 0.426, 95% IC: 0.190 – 0.615, p < 0.001], and a high NLR during attack [: 0.278, 95% IC: 0.022 – 0.499, p = 0.029]; instead the reduction of Hb at the attack was not correlated with presence of pericardial [median (IQR): 1.38 (0.97 – 2.06) g/dl vs. 1.75 (0.49 – 1.94) g/dl, p = 0.846], pleural [median (IQR): 1.68 (1.02 – 2.56) g/dl vs. 1.35 (0.90 – 1.80) g/dl, p = 0.145] and peritoneal [median (IQR): 1.65 (0.77 – 2.39) g/dl vs. 1.40 (0.94 – 1.90) g/dl, p = 0.629] involvements. In multivariate analysis, only CRP elevation was associated with variation of Hb [R2 (es) = 0.212 (1.156), p=0.005; β = 0.336, p = 0.007].
Discussion: In this study we found that during the acute attack of pericarditis there is a statistically significant decrease in Hb levels, when compared to the quiescent phase ("anemia of acute diseases"). The reason for this could be related to the high IL-1 production by the inflammasome, which is hyperactivated in the context of acute pericarditis. IL-1 is capable of stimulating the production of other cytokines, such as IL-6 and TNF, which, by the same pleiotropic mechanisms observed in chronic disease, can induce anemia (reduction in ferroportin activity, decrease in bone marrow response to erythropoietin, reduction in Hb production). We also found that in acute pericarditis the decrease of Hb levels significantly correlates with neutrophilia, elevated NLR, and CRP values. This could be explained by the fact that IL-1 has pleiotropic effects on acute inflammation, inducing recruitment of neutrophils and their activation in damaged organs, with inflammatory response and increase in CRP values. In certain patients enrolled in the study, we observed a temporal relationship between Hb and CRP values: first there is a high increase in CRP values, followed by a progressive decrease in Hb; in this way, CRP values rise and 'anticipate' the subsequent fall in Hb, which inversely correlates with CRP and has a slower kinetics. Similarly, once the acute inflammation has resolved, CRP values progressively fall within limits, while Hb remains low for a few more days and later on there is a slower but progressive recovery of Hb values.
Conclusions: Our study showed that Hb values decrease during the acute attack of pericarditis as compared to the remission phase. Acute pericarditis, like other acute inflammatory conditions, could therefore be a risk factor for the onset of acute anemia, representing a pathogenetic model of anemia of acute diseases. This could have some clinical implications, particularly the

anemic state of the acute attack of pericarditis could influence the prognosis and the treatment of the condition, allowing therapy to be modulated for each individual patient. The next step should be to study in detail the possible pathways involved (hepcidin, IL-1, erythropoietin, others) in quick variations of Hb levels during the acute attack of pericarditis.

432. D-DIMER AND PROCALCITONIN IN PATIENTS WITH ACUTE RECURRENT PERICARDITIS

Chirico C.[1], Mauro A.[2], Mascolo R.[1], Marinaro G.[3], Negro E.[3], Serati L.[1], Brucato A.[4]
[1]Department of Internal Medicine, ASST Fatebenefratelli-Sacco, Milan, Italy; [2]Department of Pediatrics, ASST Fatebenefratelli-Sacco, Milan, Italy; [3]Department of Internal Medicine, ASST Fatebenefratelli-Sacco, Milan, Italy; [4]Department of Biomedical and Clinical Sciences, University of Milan, ASST Fatebenefratelli-Sacco, Milan, Italy

Introduction: Recurrent pericarditis is an inflammatory syndrome, whose pathogenesis is not completely understood and that sometimes poses difficult differential diagnoses.
Objective: The aim of this study is to evaluate the correlation of elevated levels of D-Dimer (D-D) and procalcitonin (PCT) with clinical, laboratory and imaging features in patients with recurrent idiopathic pericarditis.
Patients and Methods: We enrolled and analyzed 412 patients with idiopathic recurrent pericarditis in a prospectively maintained registry in our referral center in the period between 2019 and 2023, excluding those associated with neoplasms, bacterial infections, tuberculosis and autoimmune diseases. We usually do not test these patients for D-D and PCT, but in our referral centers we see outpatients coming from all over Italy and we recorded D-D and PCT values as eventually tested in emergency room and hospital admissions in other hospitals.
Results: D-D was measured in 48 of 412 patients (11.6%), where high values, defined as a concentration greater than 500 ng/ml or tenfold patient's age when it crossed 50 years, occurred in 33 of them (68.8%), with a median (IQR) of 1096 (273 - 3654) ng/ml. PCT was tested in 50 of 412 patients (12.1%), getting elevated but marginal amounts in only 4 (8.0%). Regarding clinical aspects, none of these patients had venous thromboembolism and increased D-D was associated with presence of pleural effusion [OR = 16.8; 95% CI: 1.97 - 142.98; p = 0.002] and with fever equal to or greater than 37.5°C [OR = 37.3; 95% CI: 4.27 - 326.51; p < 0.001]. Regarding laboratory parameters, in univariate analysis, patients with elevated D-D values showed higher CRP levels [median (IQR): 120 (20.5 - 204.5) mg/L vs. 3 (0 - 40) mg/L, p < 0. 001], higher white blood cell [median (IQR): 11432 (9350 - 13005)/mm3 vs. 8160 (6049 - 9800)/mm3, p = 0. 005] and neutrophil counts, both absolute [median (IQR): 8954 (6412 - 10400)/mm3 vs. 5712 (4080 - 6720)/mm3, p = 0.007] and relative [median (IQR): 78.7 (70 - 80)% vs. 70 (67.3 - 73)%, p = 0. 036]. Furthermore, relative lymphocyte counts were reduced in these patients [median (IQR): 16 (13 - 20)% vs. 20.4 (20 - 21)%, p = 0.013]. Using multivariate analysis, only presence of fever, regardless of other variables, was correlated with D-D elevation [OR = 19.24; 95% CI: 2.05 - 180.27; p = 0.01]. PCT elevation, that was rare and marginal, did not correlate with any variables.
Conclusions: In idiopathic recurrent pericarditis, in absence of other specific conditions (e.g., venous thromboembolism, aortic dissection or neoplasms), we observed high D-D values, aspecifically related with the intensity of inflammation (CRP and neutrophil leukocytosis). PCT was normal or rarely mildly elevated, underlying the fact that elevated CRP and neutrophil leukocytosis is not sustained by bacterial infections in this context, but probably by activation of IL-1 (escalation of antibiotic therapy is not warranted).

433. METHOTREXATE MIMICRY FOR MTHFR C677T DEFECT INDUCING INCREASED SERUM HOMOCYSTEINE LEVELS AND ENDOTHELIAL PROGENITOR CELL (EPCS) DYSFUNCTION IN ATRIAL FIBRILLATION PATIENTS

Desantis V.[1], Scaringella A.[1], Sgarra L.[2], Potenza M.A.[1], Nacci C.[1], Caradonna I.C.[1], Solimando A.[3], Cicco S.[3], Panebianco T.[3], Vacca A.[3], Montagnani M.[1]
[1]Section of Pharmacology, Department of Precision and Regenerative Medicine and Ionian Area (DiMePReJ), University of Bari "Aldo Moro" Medical School, Bari, Italy. ; [2]General Hospital "F. Miulli" Acquaviva delle Fonti, 70021 Bari, Italy.; [3]Unit of Internal Medicine "Guido Baccelli", Department of Precision and Regenerative Medicine and Ionian Area (DiMePReJ), University of Bari "Aldo Moro" Medical School, Bari, Italy.

Background: Methotrexate (MTX), a folate derivative that inhibits several enzymes responsible for nucleotide synthesis, improved serum homocysteine levels in different diseases [1-3]. Specifically, hyperhomocysteinemia have been associated with an increased risk of stroke and coronary artery disease [4]. Folate cycle disorders are a yet underrated dysmetabolism only partly explained by methylene tetrahydrofolate reductase (MTHFR) defects and involved in the hinderance of circulating endothelial progenitor cell (EPCs) functioning [5], therefore providing one-shot explanation to both atrial stasis (increasing atrial fibrosis and generating atrial fibrillation -AF) and endothelial dysfunction. If such cardiac-bone marrow networking would be verified, a fundamental pathogenic mechanism of AF would be unraveled.
Purpose: This study aims to investigate if: i) atrial fibrosis (AFib) would relate to folate cycle disorders inducing bone-marrow function disorders and increased homocysteine levels associated to MTHFR C677T mutation; ii) AF patients would show dysfunctional EPCs.
Methods: We analyzed 65 patients (General Hospital "F.Miulli"), with preserved EF and subjected to AF ablation, and 30 hypertensive patients as controls (University of Bari Medical School). AFib was quantified by bipolar peak-to-peak voltage at each acquired point, measured and defined through the relative percentage of low-voltage areas (<0,5 mV) with respect to the wholeness of the picked voltage points. Blood count cell was evaluated at the admission. MTHFR C677T genotypes were elucidated by real-time PCR. Serum homocysteine levels were measured by a commercial laboratory test. EPCs isolation and functional analysis in vitro (wound healing assay) and in vivo (Chick Chorioallantoic Membrane Assay - CAM) were performed in the presence/absence of different MTX dosages.
Results: Baseline characteristics did not differ between the FA patients and control groups. The percentage of Afib differs significantly between C677T MTHFR homozygous patients (n=18) versus non-C677T MTHFR homozygous patients (n=47). Once the univariate analysis is performed, the subsequent multivariate analysis shows the reduction of RBC and RDW and the increase of homocysteine in patients with C677T MTHFR homozygosity compared to non-homozygosis ones. The in vitro EPCs migration capacity and the in vivo ability to induce angiogenesis were significantly reduced in FA patients respect to controls.
The treatment with MTX in control samples suggest the same results obtained in C677T MTHFR homozygous patients in vitro and in vivo.
Conclusions: Our findings support the hypothesis that folates dysmetabolism promotes atrial cardiomyopathy/fibrillation identifying C677T MTHFR homozygous as a condition of increased risk in FA patients and focusing on hyperhomocysteinemia and EPCs diversion as new potential pharmacological targets.
References: 1. Yélamos, O.; Puig, L. Systemic methotrexate for the treatment of psoriasis. Expert Rev. Clin. Immunol. 2015, 11, 553–563.
2. van Ede, A.E.; Laan, R.F.; Blom, H.J.; Boers, G.H.; Haagsma, C.J.; Thomas, C.M.; de Boo, T.M.; van de Putte, L.B.A. Homocysteine and folate status in methotrexate-treated patients with rheumatoid arthritis. Rheumatol. (Oxf.) 2002, 41, 658–665.
3. Broxson, E.H., Jr.; Stork, L.C.; Allen, R.H.; Stabler, S.P.; Kolhouse, J.F. Changes in plasma methionine and total homocysteine levels in patients receiving methotrexate infusions. Cancer Res. 1989, 49, 5879–5883.
4. Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke: A meta-analysis. JAMA 2002, 288, 2015–2022.
5. Sgarra L et al., Biomolecules. 2020. doi: 10.3390/biom10060861.

434. RESISTANT HYPERTENSION AND RELATED OUTCOMES IN A COHORT OF PATIENTS WITH CARDIORENAL SYNDROME

Gigante A., Cianci R., Lai S., Brigato C., Melena M., Testa M., Sorato G., Cusumano G., Muscaritoli M.
Dipartimento di Medicina Traslazionale e di Precisione

Background: Resistant hypertension (RH) is a clinical condition characterized by the failure to reach a goal blood pressure despite the administration of three medications with complementary mechanisms at maximally tolerated doses, one of which being a diuretic. Resistant hypertension can be observed in a variety of clinical conditions, such as heart failure and reduced renal function and may confer high cardiovascular risk.
Aim of this observational study was to evaluate the prevalence of RH and its association with clinical outcome (in-hospital mortality and morbidity/mortality outcome) in a cohort of patients with cardiorenal syndrome hospitalized in an internal medicine ward.
Methods: We conducted a retrospective analysis of consecutive hypertensive

patients with cardiorenal syndrome admitted to the Department of Internal Medicine, Sapienza University of Rome, Italy, in 3 consecutively years before COVID-19 pandemia. The prevalence of RH was estimated considering patients who had been consecutively treated with at least three antihypertensive medications, including a diuretic after excluding pseudo-resistant hypertension. The composite outcome was of all-cause of in hospital mortality and occurrence of sepsis, pulmonary embolism/ acute coronary syndrome/acute stroke and the renal replacement therapy.
Results: We collected data in 141 inpatients with a mean age of 77 years ±10 (males 65.9 %), estimated glomerular filtration rate of 34±18.6 ml/min with length of stay of 17±12 days. The prevalence RH was 52.4%. In-hospital mortality was observed in 24 patients (17%) and the composite outcome occurred in 87 patients (61,7%) and among these 74 (52,5%) were patients with RH. No significant differences were observed in the hospital mortality and gender, diabetes, RH, and other comorbidity (p>0.05). Although not statistically significant, there was a trend in the association between age and in the hospital mortality [HR 1.044(C.I. 0.998-1.0092, p=0.059)]. In the composite outcome age did not show a statistically significant association [HR 1.008(C.I. 0,988-1.029, p=0,425)] as well as gender [HR 1.917(C.I. 0,589-1.427, p=0,701)] and diabetes [HR 0.889(C.I. 0,578-1,366, p=0.590)]. Free survival was significantly higher in patients without RH than patients with RH (log rank 7.52, p=0.006). Resistant hypertension was a risk factor for composite outcome [HR 1.857(C.I. 1.170-2.946, p=0,009)].
Conclusion: In patients with cardiorenal syndrome there is a high proportion of RH that represents a risk factor for composite outcome but not for in-hospital mortality. Although the prevalence of RH largely depends on the setting explored, this condition is of clinical importance, because it is associated with an impaired prognosis.

435. USE OF LIPID-LOWERING TREATMENT FOR PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE: THE EXPERIENCE OF THE CARDIOMETABOLIC PREVENTION CLINIC OF THE TRANSFUSION CENTER, OSPEDALE MAGGIORE POLICLINICO (MILAN)

Bianco C.[1], Pelusi S.[1], Periti G.[1], Margarita S.[1], Rondena J.[1], Petrillo E.[2], Sala M.L.[2], Carpani R.[1], Prati D.[1], Valenti L.[1]
[1]Precision Medicine Lab, Biological Resource Center and Transfusion Medicine, Department of Transfusion Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [2]Transfusion Medicine, Department of Transfusion Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

Background and aim: Cardiovascular disease (CVD) are the leading cause of morbidity and mortality, leading to over 17 million deaths worldwide in 2017. [1] Thanks also to primary prevention, that is interventions aimed to prevent the onset of a disease before there is any evidence of the condition, there has been a decline of more than 60% ischemic heart disease in Western countries. [2] The most effective way to prevent CVD is the promotion of healthy lifestyle; in addition, effective and safe drug treatments have been developed. It has been calculated that the decreases in total cholesterol concentration prevented more than 80,000 deaths in the U.S. between 1980 and 2000. [3] Clinical guidelines recommend risk assessment in apparently healthy people to identify individuals at higher risk of CVD and to guide the type and the intensity of intervention. European Society of Cardiology (ESC) proposes the use of the "Systemic Coronary Risk Estimation 2" (SCORE2), a model for the prediction of 10-years risk of fatal CVD including clinical parameters (age, sex, systolic blood pressure, non-HDL cholesterol level, smoking status) which provides three different risk levels (low-moderate, high and very high risk) that define prevention goals and treatment targets. [4]. Aim of the study was to evaluate the adequacy of lipid lowering drug treatment in primary prevention in a cohort of blood donors with metabolic dysfunction.
Methods: We considered 1390 consecutive blood donors (Liver-Bible-cohort up to December 2022) aged 40-65 years with at least 3 features of metabolic dysfunction (overweight/obesity, hyperglycemia, hypertension, low HDL/high triglycerides), who were enrolled in a primary prevention program from June 2019 to December 2022 at the Transfusion Center of Ospedale Maggiore Policlinico in Milan, Italy. For each participant information about lifestyle habits and ongoing therapies, blood pressure at the time of blood donation and lipid levels were collected, and 10-years CVD risk using SCORE2 was calculated. In the definition of target LDL cholesterol levels, the most stringent cut-off suggested by ESC Guidelines were considered (LDL<100 in low-moderate risk, <70 in high risk and <55 in very high risk group). Data were compared using chi-square test.
Results: Among participants, mean age was 53.8±6.3 yrs, 239 (17.2%) were females, 455 (32.7%) were obese and 129 (9.3%) were active smokers. A total of 1207 (86.8%) individuals had arterial blood pressure consistent with a diagnosis of hypertension (n=1099, 79.1%) or were taking anti-hypertensive drugs (n=415, 29.9%). According to SCORE2 classification, 396 (28.5%) individuals were at low-moderate CVD risk, 895 (64.4%) at high risk and 99 (7.1%) at very high risk. Only 148 (10.6%) participants were taking lipid-lowering drugs and specifically 35/396 (8.8%) in low-moderate risk group, 91/895 (10.2%) in high-risk group and 22/99 (22.2%) in very high risk group (p=0.0004). Target LDL levels were reached in 135 (9.7%) individuals, and specifically in 109/396 (27.5%) in low-moderate risk group, 26/895 (2.9%) in high-risk group and 0/99 in the very high risk group (p<0.0001).
Conclusions: Among apparently healthy middle-aged individuals with metabolic dysfunction, only a minority was taking lipid-lowering drugs, almost invariably without meeting the therapeutic target. Implementation of clinical guidelines aimed at the correction of dyslipidemia by pharmacological approaches is a major barrier to the CVD prevention in Italy.
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References:
[1] GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018 Nov 10;392(10159):1736-1788.
[2] Gupta R, Wood DA. Primary prevention of ischaemic heart disease: populations, individuals, and health professionals. Lancet. 2019 Aug 24;394(10199):685-696.
[3] Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. N Engl J Med. 2007 Jun 7;356(23):2388-98.
[4] Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021 Sep 7;42(34):3227-3337.

436. EXPLORING PHYSIOLOGIC VARIATIONS AND RELATED DETERMINANTS OF LEFT VENTRICULAR DIASTOLIC FUNCTION AMONG 381 HEALTHY CAUCASIAN ADULTS BY 2016 AMERICAN SOCIETY OF ECHOCARDIOGRAPHY - EUROPEAN ASSOCIATION OF CARDIOVASCULAR IMAGING GUIDELINES

Crisci G.[1], D'Assante R.[1], De Luca M.[1], Gargani L.[2], Giardino F.[1], Ferrara F.[3], Ranieri B.[4], Marra A.M.[1], Cittadini A.[1], Bossone E.[5]
[1]Department of Translational Medical Sciences, University of Naples "Federico II", Naples, Italy; [2]Department of Surgical, Medical and Molecular Pathology and Critical Care Medicine, University of Pisa, Italy; [3]Cardio-Thoracic-Vascular Department, University Hospital "San Giovanni Di Dio E Ruggi D'Aragona", Salerno, Italy; [4]IRCCS Synlab SDN, Naples, Italy; [5]Department of Public Health, University of Naples "Federico II", Naples, Italy

Current American Society of Echocardiography (ASE)/European Association of Cardiovascular Imaging (EACVI) guidelines (2016) suggest that diastolic function should be assessed, in the absence of myocardial disease, by four echocardiographic indices, including early diastolic velocity at septal and latera mitral annulus sides (e'), ratio of mitral E to the average e' velocities (E/e'), peak tricuspid velocity (TRV), biplane left atrial maximum volume index by BSA. If more than two indexes are within the normal range, diastolic function is classified as normal, whereas if more than 2 values are in the abnormal range, LV diastolic dysfunction is diagnosed. Herein, the aim of present report was to explore the physiologic variations of left ventricular diastolic function by 2016 ASE/EACVI guidelines. Clinical and echocardiographic correlates were also investigated. The study population consisted of 381 consecutive healthy Caucasian adults (volunteers and/or subjects evaluated for work ability; 44±14 years, IQR 32-54 years, 64% women) referred to the echocardiographic laboratory of the Cardiology Division, "Cava de'Tirreni-Amalfi Coast", Heart Department, University Hospital of Salerno, Italy. All subjects underwent standardized comprehensive clinical assessment [including ECG and transthoracic color Doppler echocardiographic exam (TTE)] undertaken by trained and certified staff. The normality of the variables was assessed with the Kolmogorov-Smirnov test. If the distribution was normal, the range of normality was expressed as mean ± 2 SD, whereas if the distribution was not normal, the range of normality was expressed as to be between the 2.5th (lower limit of normal, LLN) and the 97.5th percentile (upper limit of normal, ULN) and median was reported alongside. Multiple linear regression including age, sex, systolic and diastolic blood pressure

(BP), heart rate, LV ejection fraction and mass, was used to identify the variables that most contribute to each index used in the algorithm. Significant results were reported as adjusted beta coefficients with 95% confidence intervals (CI). All variables, beside TRV, were not normally distributed. Septal e' (median 11, range 6-17 cm/s) or lateral e' (median 15, range 7-24 cm/s) were below the normal range in 15% of subjects (Figure 1, upper panel). TRV (mean 2.0, range 0.8-3.2 m/s) was above the normal range in only 0.5 % of normal subjects. On the other hand, no one had LAVI (median 17, range 11-26 ml/m2) and an average E/e' (median 6, range 4-11) above the normal limits. The ASE/EACVI algorithm correctly identified normal LV diastolic function in 99,7% of healthy subjects (Figure 1, upper panel). Multivariable regression analysis showed that age was a significant predictor of all indexes except for LAVI and in particular negatively impacts septal and lateral e' while it positively affects E/e' and TRV (Table 1). Furthermore female sex had a significant increase in E/e' and LAVI as compared with male sex. In conclusion, the present report delineates, among a large cohort of healthy Caucasian adults, the full physiologic range of key TTE LV diastolic indices and related determinants and it confirms the validity of 2016 ASE/EACVI guidelines algorithm to define normal LV diastolic function irrespective of age and gender. Information provided may serve as a reference standard to detect diastolic dysfunction and trigger further large prospective studies to fully explore potential race - sex differences.

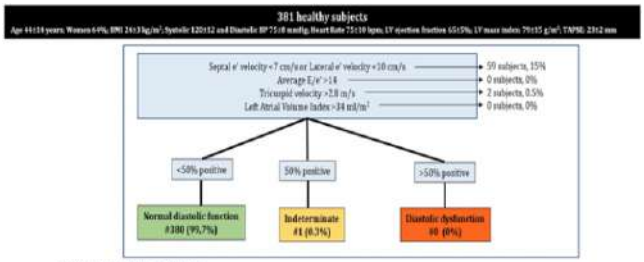


Table 1. Determinants of diastolic indexes.

	Septal e' (cm/s) Adjusted Beta (95%CI)	Lateral e' (cm/s) Adjusted Beta (95%CI)	E/e' Adjusted Beta (95%CI)	TRV (m/s) Adjusted Beta (95%CI)	LAVI (ml/m2) Adjusted Beta (95%CI)
Age (years)	-0.145*(-0.175- -0.139)*	-0.237 (-0.280- -0.193)*	0.052(0.042, 0.062)*	0.003 (0.001,0.005)*	NS
Female sex	NS	NS	0.415 (0.083, 0.747)*	NS	1.548 (0.434,2.662)*
BMI (kg/m²)	NS	NS	0.088 (0.026- 0.150)*	NS	NS
Systolic BP (mmHg)	NS	NS	NS	NS	NS
Diastolic BP(mmHg)	NS	NS	NS	NS	NS
HR (bpm)	NS	NS	NS	NS	-0.047 (-0.086- -0.007)*
LV Ejection Fraction (%)	NS	NS	NS	NS	NS
LV Mass Index (g/m²)	-0.023 (-0.043; -0.004)*	NS	NS	NS	0.037 (0.007,0.068)*

*p<0.05; BMI=Body Mass Index; BP= Blood Pressure; CI= Confidence interval; LAVI= Left Atrial Volume Index; LV=left ventricular; NS=Not Significant; TAPSE:tricuspid annular plane systolic excursion; TRV: Tricuspid Velocity

437. CARDIOEMBOLISM AND ANTICOAGULATION THERAPY IN A RARE DISEASE: A CASE OF NON-COMPACTION LEFT VENTRICULAR CARDIOMYOPATHY

Mattioli M., Ghattas L., Eusebi G., Romani L., Patti A., Giampaolo L., Salemi A., Poli L., Montanari P., Grassi A.
UO Medicina Interna Ospedale "Cervesi" Cattolica, AUSL Romagna

Patients requiring anticoagulants for the prevention of cardioembolic events are mostly affected by atrial fibrillation; but other conditions, such as prosthetic valvular disease or cardiomyopathies, are at high risk for these complications too. So, internists should be able to manage correctly these patients, tailoring therapies according to the most recent scientific evidence.
We report the case of a 73-year-old female that was admitted to our ward for the development of right brachio-crural hypostenia; symptoms started 12 hours before. History was significant for HFrEF secondary to non-compaction left ventricular cardiomyopathy (LVNC) at NYHA class II on best medical therapy (pantoprazole, aspirin, metoprolol, sacubritil/valsartan, canrenon, simvastatin), with implantable ICD for primary prevention (EF 35%).
A first CT scan detected a subacute ischemic lesion involving the right insulo-parietal region (brain CT-angiography wewasre not performed according to the stroke algorithm) and a neurologic consultation excluded therapeutic indications other than optimization of medical therapy and further causal investigations.
No pathological findings were detected after epiaortic ultrasound or arrhythmic events after ICD interrogation. Transthoracic echocardiogram was negative for the presence of ventricular thrombus. She had a good functional outcome at discharge ion (mRS=1).
This ischemic event was highly suspected for embolic etiology, so we were faced with a significant clinical key question: does antiaggregant therapy was enough for secondary prevention of our patient?
After a literature revision, we found the answer. In the recent Heart Rhythm Society expert consensus statement on arrythmogenic cardiomiopathys (2019) was reported that LVNC has an increased risk of thromboembolism when associated with atrial fibrillation or in individuals with prior embolism. Thrombus formation may occur in the intertrabecular recesses of the LV, leading to the possibility of ejection to the coronary arteries, causing ischemia, or to the brain, resulting in a stroke. They recommend anticoagulant therapy (Class I, Level of Evidence B). In the end, after cardiologic consultation and patient education, she started dicumarol.

438. THERAPEUTIC INERTIA: REAL WORLD DATA IN PATIENTS WITH DYSLIPIDAEMIAS.

Merolla A.[1], De Lorenzo R.[1], Bellino C.[1], Manganaro G.[1], Morocutti G.[1], Castellani J.[2], D'Aliberti T.[2], Pontara A.[2], Setola E.[2], Martinenghi S.[2], Rovere-Querini P.[1]
[1]Vita-Salute San Raffaele University, Milan, Italy; [2]San Raffaele Hospital, Milan, Italy

Introduction: Elevated plasma low-density-lipoprotein (LDL) cholesterol plays a major role in the pathogenesis of cardiovascular disease. Despite clear clinical guidelines, adequate management of dyslipidaemias is still an unmet need in clinical practice. Since the atherosclerotic process starts long before clinical complications appear, growing evidence strongly recommends lowering LDL cholesterol as early and as much as possible. Efficient cardiovascular prevention through appropriate lifestyle measures and proper use of lipid-lowering drugs is crucial. Here we describe our preliminary experience in a newly set-up Dyslipidaemias Outpatient Clinic at San Raffaele Hospital, Milan, Italy.
Methods: All patients who were referred for the first time to our Clinic were included in this report. Demographics, lifestyle habits, family and medical history (previous cardiovascular events, history of hypertension, diabetes mellitus, obesity, steatosis, peripheral obliterative arteriopathy, atherosclerotic cardiovascular disease, chronic kidney disease, active cancer, chronic inflammatory disease, HIV infection), lipid panel and data on current lipid-lowering therapy (type, dosage, self-reported intolerance) were collected. Cardiovascular risk categories, lipid goals and potency of lipid-lowering medications were defined according to 2019 ESC/EAS Guidelines for the management of dyslipidaemias and to 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Between-group differences were analysed using the Mann Whitney U test for continuous variables or the Chi square test for categorical variables. Logistic regression models were used for predictive analytics of binary outcomes. Data were expressed as median (interquartile range) or count (percentage). Statistical significance was set at p <0.05.
Results: A total of 163 patients, evaluated from October 2022 to April 2023, with an overall median age of 65 years (56;70), were included. At the baseline visit, 13% of patients were not on lipid-lowering treatment. These naïve patients were significantly younger than on-treatment patients [median age 61.2 (48.9;67) vs 65.7 (57;70.8) years; p 0.002], while no difference was observed in terms of sex, ethnicity, smoking, comorbidities, or statin intolerance. Among naïve patients, no one was found to be on their LDL target, despite a relevant proportion was at very-high (38.1% of patients) and at high (28.6%) cardiovascular risk. Among patients on lipid-lowering therapy, 60% belonged to the very-high cardiovascular risk category, 24% was at high risk and 16% had moderate-to-low risk. Lipid goals were met in only 10%, 9%, and 48% of these three risk groups, respectively. Patients out of target more frequently belonged to the very-high risk group (63% vs. 39%, p 0.00003) and were less frequently on statin therapy (60% vs 91%, p 0.009), as compared with patients on target. However, there was no difference in terms of statin intolerance. Overall, patients who did not met LDL goals emerged as being significantly under-treated compared to those on target. Specifically, 85% (vs. 43% of on-target patients) was taking a low-potency statin and/or ezetimibe/fibrates/nutraceuticals (p <0.0001), while a higher proportion of patients on target was taking high-potency statin (39% vs. 8%, p <0.0001) or PCSK9-I or Inclisiran (17% vs. 7%, p <0.0001). Inappropriate prescription was confirmed within each cardiovascular risk group. Furthermore, we investigated the dispersion of LDL levels from target (difference between LDL concentration in mg/dl and the LDL target for each patient based on the risk group) and found a median dispersion of 48 (21;84), ranging from a minimum of 1 mg/dl to a maximum of 259 mg/dl. At multivariable linear regression analysis, statin therapy was a significant independent predictor of a lower dispersion when adjusting for age and sex (estimate -32.08, Std error 7.79, p <0.0001). In addition, at multivariate logistic regression analysis, the

potency of the lipid-lowering therapy emerged as an independent predictor of missing LDL goals when adjusted for age and sex (odds ratio 0.34, 95% CI 0.18-0.63, p 0.0007). Specifically, high-potency therapy conferred a lower risk of missing LDL target compared to low-potency therapy.
Conclusions: Cardiovascular risk assessment is frequently underestimated, possibly due to physicians' misperception of patient's risk factors. High potency statins are underprescribed and only a minority of patients, especially at high or very-high CV risk, is on LDL target. Our findings reflect the current unsuccessful management of dyslipidaemias in real world. A well-structured outpatient lipid clinic may overcome these pitfalls in clinical practice, so as to improve the proportion of patients on target. Further goals are intercepting specific frail populations (i.e. HIV, haematological, autoimmune patients, ...) to whom tailored interventions may be reserved, and providing study cohorts for future clinical trials on emerging pharmacological treatments.

439. EFFECT OF INCLISIRAN ON IMPROVING METABOLIC PARAMETERS AND SUBCLINICAL CARDIAC ORGAN DAMAGE IN PATIENTS AT HIGH CARDIOVASCULAR RISK: AN OBSERVATIONAL STUDY

Armentaro G.[1], Clausi E.[1], Cassano V.[1], Pastura C.A.[1], Francica M.[1], Maruca F.[1], Rosa M.[1], Condoleo V.[1], Miceli S.[1], Maio R.[1], Perticone M.[1], Sesti G.[2], Sciacqua A.[1]
[1]Department of Medical and Surgical Sciences, University Magna Græcia of Catanzaro, Italy; [2]Department of Clinical and Molecular Medicine, University Rome-Sapienza, viale Regina Elena n. 324, 00161, Rome, Italy

Introduction: Low-density lipoprotein cholesterol (LDL-c) circulating levels represents the main determinant of atherosclerotic cardiovascular (CV) disease, and its reduction is the primary target of hypolipidemic therapies to improve clinical prognosis. Of interest, higher TG/HDL ratio has recently emerged as a marker of increased atherosclerotic burden and it may identify subjects with higher CV risk profile. Inclisiran, is a first-in-class small interfering RNA that acts by preventing translation of proprotein convertase subtilisin/kexin type 9 (PCSK9) in hepatocytes, increasing LDL receptor (LDLR) function and thereby lowering LDL-c. ORION-9, ORION-10 and ORION-11 have demonstrated a significant reduction in LDL-c levels of about 50% percent compared with placebo following inclisiran use for 18 months. However, the effects of this drug in routine clinical practice are not yet known, but more importantly, its effects on biomarkers of oxidative stress and subclinical myocardial damage are unknown.
Purpose: The aim of our study was to investigate, at baseline and after 3-months follow-up, Inclisiran' effects in patients with established coronary artery disease (80% already revascularized) who were statin-intolerant and/or not reaching the target of LDL-C <55 mg/dl using the maximum tolerated drugs' dosage, on glyco-metabolic parameters, oxidative stress validated markers (NOX-2, 8-Isoprostane), and subclinical myocardial damage evaluated by measurement of deformation and efficiency parameters, obtained by speckle tracking echocardiography (STE).
Results: We enrolled 24 patients who completed three-month follow-up (18 male and 6 female, mean age 64.4+8.7 years), 88% showed hypertension, 21% chronic kidney disease, 67% polidistrectual atherosclerosis, 42% type 2 diabetes mellitus (T2DM), 20% COPD, 15% atrial fibrillation and 50% chronic heart failure NYHA class II-III. All subjects underwent main anthropometric and hemodynamic parameters evaluation, blood chemistry analysis, oxidative stress markers assessment, and advanced echocardiogram at baseline and after three months of treatment. The serum values of oxidative stress markers (NOX-2, 8-Isoprostane) were assessed with ELISA sandwich. Echocardiographic recordings with STE were performed, using an E-95 Pro ultrasound system (GE Technologies), to assess subclinical myocardial damage by measurement of deformation and efficiency parameters. For all continuous variables, comparisons between baseline (T0) and post-treatment values (T3) were performed using paired Student's t test. A linear correlation analysis was performed to compare variations (Δ) of Global longitudinal strain (GLS), global myocardial work efficiency (GWE) and E/e' ratio as dependente variables, with (Δ) of different covariates. There were no significant differences among the population regarding systolic blood pressure, heart rate and glycemia after three months of therapy. As expected, lipid profile was greatly improved in all the subjects; infact we obtained a statistically significant reduction of total-cholesterol (160.5±46.1 vs 106.4±29.8, p<0.0001), LDL-c (95.3±42.8 vs 46.1 vs 27.5, p<0.0001), Triglycerides (104.9±25.9 vs 98.1±25.1, p=0.019), TG/HDL ratio (2.3±0.9 vs 2.0±0.7, p=0.034); in addiction an increase of HDL-C (48.5±9.4 vs 49.0±7.4, p<0.0001) were observed. Moreover an improvement of high sensitivity C-reactive protein (hs-CRP) (from 4.0±1.2 vs 3.4±1.1, p<0.0001) and NOX-2 (0.8±0.2 vs 0.6±0.1, p=0.021) were observed. Concerning echocardiographic parameters, we obtained a statistically significant increase of GWE (91.1±5.0 vs 94.2±2.9, p<0.0001), GLS (from -14.4±2.9 to -18.1±1.4, p<0.0001) and E/e' ratio (13.1±4.1 vs 11.5±2.9, p<0.0001) respectively. The linear correlation analysis showed that ΔGWE was significantly and inversely correlated with ΔTG/HDL (r=-0.387, p=0.021), ΔNOX-2 (r= -0.354, p=0.034), ΔLDL-c (r= -0.291, p=0.039) and Δ8-Isoprostane (r= -0.243, p=0.046); ΔGLS was significantly and directely correlated with TG/HDL (r= 0.421, p=0.007) and ΔNOX-2 (r=0.385, p=0.016), ΔLDL-c (r= 0.242, p=0.041) and Δ8-Isoprostane (r=0.221, p=0.032); ΔE/e' was significantly and directly correlated with ΔTG/HDL (r=0.412, p<0.0001), ΔNOX-2 (r=0.385, p=0.019) and Δ8-Isoprostane (r= -0.312, p=0.027);.
Conclusions: Our study showed for the first time that Inclisiran is safe and effective already after 3 months in a population at high CV risk. It has also been shown to reduce left ventricular filling pressure and increase overall cardiac performance. Changes in markers of oxidative stress and inflammation could partially explain the observed improvements. In addition, we observed a reduction in TG/HDL ratio correlated with an improvement in cardiometabolic and lipid profile. Further studies are needed to better analyze the systemic benefits in a larger population with longer follow-up.

440. SEX DIFFERENCES IN RESTING AND EXERCISE RIGHT HEART-PULMONARY CIRCULATION UNIT AMONG SCLERODERMA PATIENTS: INSIGHTS FROM THE RIGHT-NET

Giardino F.[1], D'Assante R.[1], De Luca M.[1], Crisci G.[1], Gargani L.[2], Valente V.[1], Ferrara F.[3], Ranieri B.[4], Marra A.M.[1], Cittadini A.[1], Bossone E.[5]
[1]Department of Translational Medical Sciences, University of Naples "Federico II", Naples, Italy; [2]Department of Surgical, Medical and Molecular Pathology and Critical Care Medicine, University of Pisa, Italy; [3]Cardio-Thoracic-Vascular Department, University Hospital "San Giovanni Di Dio e Ruggi D'Aragona", Salerno, Italy; [4]IRCCS Synlab SDN, Naples, Italy; [5]Department of Public Health, University of Naples "Federico II", Naples, Italy

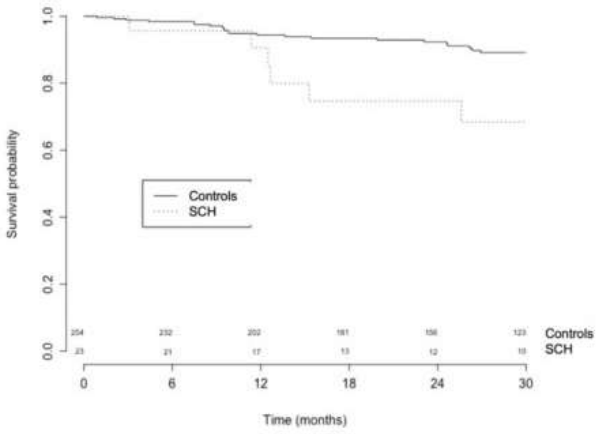
Aims: Systemic sclerosis, also defined as scleroderma, represents a rare autoimmune disease, more frequent in women, characterised by extended tissue fibrosis, involved in the development of pulmonary hypertension, resulting in high morbidity and mortality. Exercise Doppler echocardiography is an effective tool to identify early-stage pulmonary vascular disease. The aim of this study was to investigate sex differences in resting and exercise right heart-pulmonary circulation unit in scleroderma patients enrolled in the Right Heart International Network (RIGHT-NET).
Methods: The RIGHT-NET is a large, multicentre, international, observational study that prospectively recruits subjects at risk or with overt pulmonary hypertension. Healthy subjects were compared with the group of scleroderma patients, with the aim of analysing sex differences in resting and exercise right heart-pulmonary circulation unit as assessed by transthoracic color Doppler echocardiography. Considered indices were: the tricuspid annular plane systolic excursion (TAPSE) to systolic pulmonary arterial pressure (sPAP) ratio [TAPSE/sPAP] and the mean pulmonary arterial pressure (mPAP) to cardiac output (CO) ratio [mPAP/CO].
Results: Among 375 healthy subjects (aged 46 ± 15 years; 53% women) TAPSE/sPAP ratio at peak exercise was significantly higher in the female group [women vs men: 0.9 ± 0.3 vs 0.81 ± 0.3, p 0.03] with sPAP peak significantly higher in the male group [men vs women: 42.2 ± 16.1 vs 38.5 ± 14.0, p 0.03]. The mPAP/CO ratio in healthy subjects had shown no differences according to sex, while in the group of scleroderma patients (aged 57 ± 13 years; 86% women) there was a significant sex difference at peak exercise [men vs women: 10.1 ± 7.7 vs 7.3 ± 4.5, p <0.05] (*Table 1*).
Conclusions: Among scleroderma patients, a significantly different response according to sex in mPAP/CO ratio at peak exercise was detected. Further studies are needed to explore the pathophysiologic underpinnings of such findings and their potential prognostic role.

	Healty Subjects			Scleroderma patients		
Variables	Men (n=177)	Women (n=198)	p	Men (n=124)	Women (n=765)	p
TAPSE base	24.8 ± 3.5	23.8 ± 3.7	0.01	22.7 ± 4.1	22.7 ± 3.7	1.0
TAPSE peak	30.9 ± 5.0	30.4 ± 4.3	0.3	26.4 ± 5.2	26.6 ± 4.0	0.7
TAPSE/sPAP base	1.2 ± 0.4	1.1 ± 0.4	0.1	0.9 ± 0.4	0.9 ± 0.3	1.0
TAPSE/sPAP peak	0.81 ± 0.3	0.9 ± 0.3	0.03	0.7 ± 0.4	0.7 ± 0.5	0.6
mPAP/CO base	3.3 ± 1.5	3.5 ± 1.1	0.2	4.5 ± 2.7	4.6 ± 2.2	0.6
mPAP/CO peak	3.1 ± 1.7	3.2 ± 1.6	0.8	10.1 ± 7.7	7.3 ± 4.5	<0.05
sPAP base	22.6 ± 5.9	23.1 ± 5.4	0.4	31.2 ± 15.3	29.2 ± 12.0	0.1
sPAP peak	42.2 ± 16.1	38.5 ± 14.0	0.03	50.7 ± 21.1	46.8 ± 19.6	0.06

441. SUBCLINICAL HYPOTHYROIDISM IS ASSOCIATED WITH ADVERSE OUTCOMES IN PATIENTS WITH HEART FAILURE: RESULTS FROM THE T.O.S.CA ITALIAN REGISTRY

D'Assante R.[1], De Luca M.[1], Iacoviello M.[2], Triggiani V.[3], Limongelli G.[4], Perrone Filardi P.[5], Mancini A.[6], Volterrani M.[7], Vriz O.[8], Castello R.[9], Passantino A.[10], Campo M.[11], Modesti P.A.[12], Manfredini R.[13], Sciacqua A.[14], Marra A.M.[15], Salzano A.[15], Arcopinto M.[15], Bossone E.[16], Cittadini A.[15]
[1]Department of Translational Medical Sciences, Federico II University, Via Sergio Pansini, 5, 80131 Naples, Italy.; [2]Cardiology Unit, Department of Medical and Surgical Sciences, University of Foggia, 71122 Foggia, Italy; [3]Interdisciplinary Department of Medicine, Section of Internal Medicine, Geriatrics, Endocrinology and Rare Diseases, University of Bari 'A Moro', Bari, Italy; [4]Division of Cardiology, Monaldi Hospital, Azienda Ospedaliera dei Colli, University of Campania Luigi Vanvitelli, Caserta, Italy; [5]Department of Advanced Biomedical Sciences, Federico II University, Naples, Italy; [6]Operative Unit of Endocrinology, Catholic University of the Sacred Heart, Rome, Italy.; [7]Department of Medical Sciences, IRCCS San Raffaele Pisana, Rome, Italy; [8]Heart Center Department, King Faisal Hospital & Research Center, Riyadh, Kingdom of Saudi Arabia; [9]Division of General Medicine, Azienda Ospedaliera Universitaria Integrata, Verona, Italy; [10]Scientific Clinical Institutes Maugeri, IRCCS, Pavia, Italy; [11]Department of Medical and Surgical Sciences, Unit of Endocrinology and Metabolic Diseases, University of Foggia, Foggia, Italy; [12]Dipartimento di Medicina Sperimentale e Clinica, Università degli Studi di Firenze, Florence, Italy; [13]Azienda Ospedaliera-Universitaria S. Anna, Ferrara, Italy; [14]University Magna Graecia of Catanzaro, Catanzaro, Italy; [15]Department of Translational Medical Sciences, Federico II University, Via Sergio Pansini, 5, 80131 Naples, Italy; [16]Department of Public Health, University of Naples "Federico II", Naples, Italy

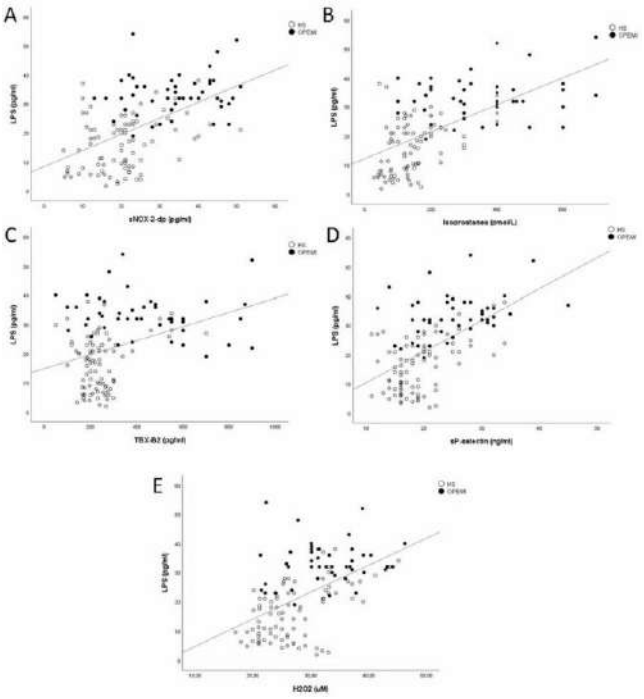
Background: Subclinical hypothyroidism (SCH), defined as increased serum thyroid-stimulating hormone (TSH) level with a normal free T4 level (fT4), is frequently observed in the general population. Reported prevalences range from 0.6% to 1.8% in the adult population, depending on age, sex, and iodine intake. Several studies reported a worse prognosis in patients with heart failure with reduced ejection fraction (HFrEF) and SCH, but they considered heterogeneous populations suffering mainly from severe subclinical hypothyroidism. Aim of the study was to evaluate if SCH was independently associated with the occurrence of cardiovascular death considering 30 months of follow up.
Materials and methods: 277 HFrEF patients enrolled in the prospective, multicentre, observational T.O.S.CA. (Terapia Ormonale Scompenso CArdiaco) Registry, were included in this analysis. Patients were divided according to the presence of subclinical hypothyroidism, which was defined as serum TSH levels higher than 4.5 mIU/L with normal fT4 levels. Data regarding clinical status, echocardiography, and survival were analysed.
Results: Twenty-three patients displayed subclinical hypothyroidism (87% mild vs 13% severe) while 254 had no alterations in TSH levels. No differences were found between the two groups in terms of age, sex, heart failure aetiology and left ventricular ejection fraction. When compared with group 2, subclinical hypothyroid patients showed higher TSH levels (7.7 ± 4.1 vs 1.6 ± 0.9, p<0.001), as expected, accompanied by comparable levels of fT4 (1.3 ± 0.3 vs 1.3 ± 0.3, p=NS). When corrected for established predictors of poor outcome in heart failure employed as covariates in a multivariable Cox regression model (i.e. age, sex, body mass index, aetiology, New York Heart Association (NYHA) class, left ventricular ejection fraction (LVEF)), the presence of subclinical hypothyroidism resulted to be an independent predictor of cardiovascular mortality (HR: 3.0; 5-95% CI: 1.14-7.74; p=0.03) (Figure 1).
Conclusions: Subclinical hypothiroidism impacts remarkably on cardiovascular mortality in patients with HFrEF.



442. INCREASED OXIDATIVE STRESS AND LOW GRADE ENDOTOXEMIA IN OFFSPRING OF PATIENTS WITH EARLY MYOCARDIAL INFARCTION.

Magna A.[1], Cinicola B.L.[2], Palumbo I.M.[3], Pannunzio A.[3], Carnevale R.[4], Bartimoccia S.[3], Cammisotto V.[3], Totè C.M.[1], Capponi M.[2], Brindisi G.[2], Salvatori F.[2], Barillà F.[5], Martino F.[6], D'Amico A.[7], Spalice A.[2], Zicari A.M.[2], Violi F.[6], Loffredo L.[3]
[1]Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy; [2]Department of Maternal Infantile and Urological Sciences, Division of Pediatric Allergology and Immunology, Sapienza University of Rome, Rome, Italy; [3]Department of Clinical Internal, Anesthesiology and Cardiovascular Sciences, Sapienza University of Rome, Rome, Italy; [4]Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy; [5]Unit of Cardiology, University Hospital "Tor Vergata", 00133 Rome, Italy; [6]Department of Pediatrics and Pediatric Neuropsychiatry, Sapienza University of Rome, Piazzale Aldo Moro, 5, 00185 Rome, Italy; [7]Department of Movement, Human and Health Sciences, University of Rome "Foro Italico", Piazza Lauro De Bosis, 15, 00135 Rome, Italy

Background and aims: Offspring of patients with early myocardial infarction are at higher cardiovascular risk, but the underlying physio-pathological mechanism is unclear. NADPH oxidase-type 2 (NOX-2) plays a pivotal role as mediator of oxidative stress and could be involved in activating platelets in these patients. Furthermore, altered intestinal permeability and serum lipopolysaccharide (LPS) could be a trigger to promote NOX-2 activation and platelet aggregation. This study aims to evaluate the behavior of low grade endotoxemia, oxidative stress and platelet activation in offspring of patients with early myocardial infarction.
Methods: We enrolled, in a cross-sectional study, 46 offspring of patients with early myocardial infarction and 86 healthy subjects (HS). LPS levels and gut permeability (assessed by zonulin), oxidative stress (assessed by serum NOX-2-derived peptide (sNOX2-dp) release, hydrogen peroxide (H2O2) production and isoprostanes), serum nitric oxide (NO) bioavailability and platelet activation (by serum thromboxane B2 (TXB2) and soluble P-Selectin (sP-Selectin)) were analyzed.
Results: Compared to HS, offspring of patients with early myocardial infarction had higher values of LPS (16.43 ± 9.09 vs 33.33 ± 7.24 pg/mL, p<0.001), zonulin (1.56 ± 0.66 vs 2.15 ± 0.81 ng/ml, p<0.001), serum isoprostanes (144.84 ± 83.65 vs 352.46 ± 163.58 pg/ml, p<0.001), sNOX2-dp (20.35 ± 9.17 vs 33.83 ± 10.37 pg/ml, p<0.001), H2O2 (26.09 ± 5.17 vs 34.33 ± 6.06 mM, p<0.001), TXB2 (243.01 ± 102.71 vs 429.35 ± 222.86 pg/ml, p<0.001), p-selectin (18.50±4.30 vs 26.13 ± 6.45 ng/ml, p<0.001) and lower NO bioavailability (47.28± 16.54 vs 28.72 ± 7.24 mM, p<0.001). Bivariate analysis in the overall population showed that serum LPS was significantly associated with zonulin (Rs = 0.241; p = 0.005), sNOX-2-dp levels (Rs = 0.546; p < 0.001) (A), serum isoprostanes (Rs = 0.607; p < 0.001) (B), serum TXB2 (Rs = 0.368; p < 0.001) (C), plasma sP-selectin (Rs = 0.575; p < 0.001) (D), serum H2O2 (Rs = 0.561; p < 0.001) (E), age (Rs = 0.228; p = 0.009) and total cholesterol (Rs = 0.230; p = 0.021).



A multiple linear regression analysis, including the variables linearly associated with the dependent variable, was performed to define the independent predictors of serum LPS and sNOX-2-dp. Serum sNOX-2-dp (SE: 0.76; standardized coefficient β: 0.176; p = 0.02), isoprostanes (SE: 0.006; standardized coefficient β: 0.308; p < 0.001), p-selectin (SE: 1.28; standardized coefficient β: 0.263; p < 0.001) and H2O2 (SE: 0.115; standardized coefficient β: 0.264; p < 0.001) were significantly associated with LPS (R2: 0.58). Serum LPS (SE: 0.82; standardized coefficient β: 0.227; p = 0.007), isoprostanes (SE: 0.06; standardized coefficient β: 0.392; p < 0.001) and TXB2 levels (SE: 0.05; standardized coefficient β: 0.219; p = 0.003) were significantly associated with sNOX-2-dp (R2: 0.47).
Conclusions: Offspring of patients with early myocardial infarction have a low grade endotoxemia that could generate oxidative stress and platelet activation increasing their cardiovascular risk. Future studies are needed to understand the role of dysbiosis in this population.

443. BY TRADITIONAL THERAPEUTIC STRATEGIES TO EVINACUMB IN FAMILIAL HOMOZYGOUS HYPERCHOLESTEROLEMIA (HOFH): FROM TRIAL TO REAL WORLD EXPERIENCE

Stanzione C., de Ruberto F., Iannuzzo G., Calcaterra I., Gentile M., Di Minno M.
Department of Clinical Medicine and Surgery, Federico II University, 80131 Naples

Background Evinacumab, a human monoclonal antibody inhibitor of angiopoietin-like protein 3 (ANGPTL3), has been shown to significantly reduce low-density lipoprotein cholesterol (LDL-C) in patients with homozygous familial hypercholesterolemia (HoFH). Familial Hypercholesterolemia (HoFH) is a genetic disorder, characterized by absent (null-null) or impaired (non-null) LDL-receptor activity, resulting in a rimarkable increase of low-density lipoprotein cholesterol (LDL-C). This desease is characterized by cutaneous xanthoma development from infancy, precocious and accelerated atherosclerosis with clinical signs of ischemic heart disease and frequent involvement of left heart valves resulting in stenosis and/or incompetence. Traditional therapeutic strategies, such as lifestyle modifications, invasive treatment, as apheresis and drugs to reduce LDL cholesterol, are insufficient to achieve the objectives of ESC 2019 guidelines in these patients. Evinacumab is the latest lipid-lowering drug, which received FDA approval in February 2021(exclusively in patients with HoFH) in addition to other lipid-lowering therapies, after a phase III trial, ELIPSE HoFH. Material e Methods Seven of our patients (3 males and 4 women) with HoFH, who participated in the ELIPSE trial, continued intravenous infusion of evinacumab (with compassionate use) at 15 mg / kg of body weight over at 60 minutes once monthly from October 2021 to date. Results In line with the data of the trial, after 12 months of treatment, our real word experience confirms a stable reduction of LDL-C (from 277 mg/dl to 92 mg/dl , p 0.002) , triglycerides((from 80 mg/dl to 34 mg/dl , p 0.18) and HDL (from 43.2 mg/dl to 34.1 mg/dl , p 0.001) and at the same time the absence of adverse events. Conclusions The significant reduction of LDL-C and the almost absence of negative adverse effects means that traditional lipid-lowering therapeutic strategies can be abandoned to look towards a new molecule, although high costs and intravenous administration still limit its use and approval by AIFA.

444. RELATIONSHIP BETWEEN HEART RATE AND CENTRAL-TO-PERIPHERAL PULSE PRESSURE AMPLIFICATION MEASURED INVASIVELY

Curcio R.[1], Arrivi A.[2], D'Abbondanza M.[1], Dominici M.[2], Vaudo G.[1], Pucci G.[1]
[1]Department of Medicine and Surgery, University of Perugia – Unit of Internal Medicine, "Santa Maria" University Hospital, Terni, Italy; [2]Unit of Cardiology, "Santa Maria" UniversityHospital, Terni, Italy.

Introduction: Central-to-peripheral pulse pressure amplification (PPA) is a measure of vascular aging, it reflects the extent of the arterial stiffness gradient between the center and the periphery, and it is inversely related to cardiovascular prognosis. Some authors described heart rate (HR) as a direct determinant of PPA.
Aim: The objective of the study is to evaluate whether such relationship exists for measures of arterial pressure (BP) and HR determined invasively during cardiac catheterization.
Methods: 111 subjects undergoing diagnostic coronary angiography and enrolled in a pilot study were evaluated at the end of the invasive examination. Invasive aortic BP (aSBP/aDBP) was determined at the level of the aortic bulb. The brachial invasive BP (bSBP/bDBP) was determined at the medial point of the brachial artery with a sequential pull-back technique. Patients in whom the time interval between the 2 measurements exceeded 30 seconds (n=13) and patients in whom the HR difference between the two sites was greater than 5 bpm (n=20) were excluded.
Results: 78 patients, 87% gender M, age 73±9 years. aSBP/aDBP 137±27/64±12 mmHg, bSBP/bDBP 148±25/63±11 mmHg. Average heart rate 71±12 bpm. aSBP and bSBP showed no significant relationship with HR, while aDBP and bDBP showed positive correlation with HR (R=0.35 and R=0.36 respectively, both p<0.001). Slope=3.6 mmHg/10 bpm for aDBP and 3.4 mmHg/10 bpm for bDBP (difference between slope =ns). In a multivariate model including age, gender, and HR as predictors of PPA (expressed as the bPP/aPP ratio), adding the difference between bSBP and aSBP eliminated the dependence of HR on PPA.
Conclusions: the dependency of PPA from HR is observable only if PPA is expressed as a bPP/aPP ratio. It is determined both by the dependency of DBP from heart rate and by the extent of central-peripheral pressure amplification. It is therefore not necessary to normalize the degree of PPA for FC but simply to represent this latter measure in absolute terms, as the difference between bPP and aPP, rather than as the ratio.

445. QUALITATIVE AND QUANTITATIVE ULTRASAOUND BASED CHARACTERIZATION OF CAROTID ATHEROSCLEROSIS: AN ANALYSIS OF CLINICAL AND LABORATORY PREDICTORS

Curcio R. [1], Martina M. R.[2], Chiatti L.[1], D'Abbondanza M.[1], Campanella T.[1], Bianchini E.[2], Gemignani V.[2], Vaudo G.[1], Pucci G.[1]
[1]Department of Medicine and Surgery, University of Perugia – Unit of Internal Medicine, "Santa Maria" University Hospital, Terni, Italy; [2]Institute of Clinical Physiology, Italian National Research Council, Pisa, Italy

Background: The prevalence of carotid atherosclerosis is underestimated in the general population. Its diagnosis is essential to re-classify the cardiovascular risk (CV) of affected patients. The degree of linear stenosis (SL) is traditionally accounted as the most clinically relevant morphological criterion. The clinical significance of other quantitative and qualitative parameters has not yet been fully elucidated.
Methods: In patients with known carotid atherosclerosis, we conducted a qualitative and quantitative plaque non-invasive analysis with ultrasound imaging equipped with a semi-automatic analyzer (QUIPU) at the level of the common carotid artery, bifurcation, internal carotid artery and external

carotid artery bilaterally. SL, total plaque area (TPA), median gray scale value (GSM), skewness and kurtosis were correlated to the main CV risk factors.
Results: 50 patients (age 74±10 years, 52% male, 80% hypertensive) were analyzed. Total number of plaques n=180, location: internal carotid artery (39%, n=71), carotid bifurcation (26%, n=47), external carotid artery (22%, n=38), common carotid artery (13%, n=24). Plaques at the common carotid contributed more to TPA, whereas a higher degree of SL was observed for external carotid plaques. TPA was positively correlated with age, male sex, and previous CV event, and negatively with statin use and HDL cholesterol (Table). SL correlated only with history of hypertension and previous CV event. A phenotype characterized by low GSM and high skewness and kurtosis was associated with male gender, total calcium values, and no statin use.

N=180	SL, %	TPA	GSM	Skewness	Curtosi
Age, years	0,05	0,38**	0,03	-0,08	-0,08
Male sex, %	-0,02	0,21**	-0,23**	0,15*	0,11
BMI, Kg/m^2	0,05	-0,05	0,03	0,02	0,05
HTN, %	0,20**	0,12	0,08	0,02	-0,05
DM, %	0,06	0,06	0,08	-0,03	0,02
eGFR, mL/min/1,73 m^2	-0,12	-0,11	0,04	-0,09	-0,09
Serum calcium, mg/dL	-0,15	-0,04	-0,31**	0,21**	0,10
HDL-cholesterol, mg/dL	-0,06	-0,21*	-0,09	0,05	-0,01
Statins, %	0,05	-0,15*	0,06	-0,15	-0,16*
Previous CV event, %	0,32**	0,37**	0,02	0,08	0,13

*Spearman's Rho correlation coefficent, *p<0.05, **p<0.01*

Conclusions: we observed that TPA, GSM, skewness and kurtosis have significant and plausible associations with the main CV risk factors and could have a clinical importance in identifying subjects at CV risk regardless of the extent of SL, the only current clinically relevant. A non-invasive ultrasound-based study of the carotid plaques could be useful in the early identification of some plaque phenotypes potentially at high risk of complications.

446. CARDIOVASCULAR RISK IN PATIENT WITH POLYDERMATOMIOSITIS: A CLINICAL CASE

Capece L.M.[1], Paoletta D.[1], Iervolino A.[1], Iacono M.[1], Pucci M.[1], Gammaldi V.[1], Iadevaia V.[1], Bertolini N.[2], Esposito R.[1]
[1]Dipartimento di Medicina Interna, Università "Federico II", Napoli, Italia; [2]Unità di Reumatologia, Dipartimento di Medicina Interna, , Università "Federico II", Napoli, Italia

Background: Polydermatomiositis is an autoimmune systemic disease characterized by chronic muscle weakness and inflammatory cell infiltrates in skeletal muscle and involvement of skin. The most common comorbidities are arterial hypertension, dyslipidemia, abnormalities of cardiac electric conduction, heart failure.
Case: a 43 years-old woman occurs to our cardiological department because of the occurrence of dyspnea and tachycardia.
Her past medical history reports: polydermatomyositis with important involvement of skeletal muscle and skin with no clinical improvement during the immunosuppression therapy; calcification of tendons; arterial hypertension; dyslipidemia; antiphospholipid syndrome (discovered due to three episodes of abortions during the first trimester) in presence of heterozygosis mutation of factor V Leiden and a homozygous mutation of MTHFR; COPD. Regarding the cardiological aspect the patient medical history reports coronary artery disease previously treated with PTCA and CABG.
On physicial examination: venous ulcers in both legs and amputation of the fifth finger of both hand, muffled heart sounds, wheezing, chest telangiectasias, gait impairment due to a femur necrosis.
Management: Blood test reveal a dyslipidemia (LDL = 148 mg/dl), ECG is performed to rule out the tachycardia and show a sinus rhythm with a frequency 105 bpm, previous lower necrosis**.**
Also, an echocardiographic exam is performed and reveals a segmental hypokinesis, pulmonary hypertension, Left ventricular diastolic dysfunction, calcification of the aortic cusps, mild mitral valve insufficiency, reduced ejection fraction.
Treatment: beta-blocker therapy is added to manage the cardiac frequency and the combination of rosuvastatin plus ezetimibe, instead of atorvastatin only, to reduce the LDL level.
Conclusion: Cardiac involvement is frequent in patient with polydermatomyositis, so it's important to be careful to cardiovascular risk factors, such as dyslipidemia and arterial hypertensions. Multidisciplinary approach to manage the different comorbidity is fundamental to prevent cardiovascular injury and hospitalization.

447. THE ASSOCIATION BETWEEN AMBULATORY ARTERIAL STIFFNESS INDEX AND LVMI: A NEW ROLE FOR NOCTURNAL BLOOD PRESSURE DIPPING

Dionisi D., Brattoli M., Cecco A., Canu P., Clerici L., Savioli G., Mugellini A., Di Sabatino A.
UOC Medicina Interna - IRCCS Policlinico San Matteo, Pavia (PV)

Introduction: The association between ambulatory arterial stiffness index (AASI), cardiovascular mortality and cerebrovascular events is well documented. Left ventricular mass index (LVMI) is a well-established marker of cardiac remodelling in hypertensive patient. Nevertheless, previous studies investigated the relationship between AASI and hypertension mediated cardiac damage index as LVMI with controversial results. Furthermore, to our knowledge only one study evaluated the association of AASI with different classes of nocturnal blood pressure dipping specifically.
Aim: We aimed to investigate the relationship between left ventricular mass index and AASI stratifying the population for different classes of nocturnal systolic blood pressure dipping.
Methods: Every patient referring to our hypertension center in 2021 was evaluated for enrolment. Every patient who had diagnosis of primary hypertension and at least one transthoracic echocardiogram in our echocardiography center during this period was included in our database. Finally, only adults who underwent ambulatory blood pressure monitoring were included. Systolic blood pressure nocturnal dipping and AASI were computed for each patient. The enrolled population was divided into four classes: reverse dippers (≤0% dip), non-dippers (> 0% and ≤ 10% dip), dippers (>10% and < 20% dip), extreme dippers (≥20% dip).
Results: A total of 87 patients were enrolled (mean age 66 ± 13 years; men 42%); 14 (16%) were inverted dippers; 46 (53%) were non dippers; 20 (23%) were dippers; 7 (8%) were extreme dippers. AASI and LVMI variables resulted normally distributed. The linear regression analysis showed a positive correlation between AASI and LVMI for the whole population without blood pressure dipping class differentiation (p = 0,0004; r = 0,13). Nevertheless, AASI showed a significant association with LVMI for dippers (p = 0,01; r = 0,31) and inverse dippers (p = 0,003; r = 0,53); missing the significance for non-dippers (p = 0,08; r = 0,06) and extreme dippers (p = 0,872; r = 0,006).
Conclusions: Our findings suggest that blood pressure dipping class could be an important determinant in the relationship between left ventricular mass index (LVMI) as cardiac remodelling marker and AASI in hypertensive patients.

448. THE RELATIONSHIP BETWEEN OVERWEIGHT AND BLOOD PRESSURE CONTROL: A SINGLE-CENTER EXPERIENCE

Cecco A., Brattoli M., Canu P., Dionisi D., Savioli G., Mugellini A., Di Sabatino A.
UOC Medicina Interna - IRCCS Policlinico San Matteo, Pavia (PV)

Introduction: Obesity is one of the most significant cardiovascular risk factors. Scientific literature documented both the relationship between obesity and hypertension and the response to antihypertensive treatment. Despite the emergent problem in general population, no equal attention has been paid for overweight.
Purpose: To evaluate the number of antihypertensive agents required to reach blood pressure target in different BMI classes.
Methods: We considered for enrollment every patient who arrived at our Hypertension Center for a first visit during 2021. Inclusion criteria were: presence of a second visit within 12 months with an ambulatory blood pressure monitoring of 24 hours showing a good pressure control (mean blood pressure values < 130/80 mmHg with 70% of valid measurements). For every patient we collected antihypertensive therapy at first and second visit. We stratified population for BMI: obese (BMI ≥30), overweight (25≤BMI<30) and normal weight (18.5≤BMI<25). Data with a normal distribution are reported as mean ± standard deviation and compared with t-Test.
Results: We enrolled a total of 54 patients: 24 (45%) with normal weight, 19 (35%) overweight and 11 (20%) obese. These groups were homogeneous for general characteristics. The mean number of antihypertensive drugs at first visit was 1.88 ± 1.15 drugs in normal weight, 2.62 ± 1.29 drugs in overweight and 2.63 ± 1.20 drugs in obese. The difference between the number of drugs taken by normal weight and the number of drugs taken by overweight patients reached statistical significance (p=0.03); there was no significant difference between overweight and obese.

Conclusions: According to our experience, the number of antihypertensive drugs which is required to reach pressure control depends on BMI. In particular, overweight patients have to take an higher amount of drugs compared to normal weight patients to reach the same pressure target; on the other hand, the amount of drugs needed is equivalent to obese patients. This result suggests that pressure control in overweight could be as challenging as for obese: the resistance to antihypertensive treatment, which is strictly connected to obesity according to scientific literature, should be taken into consideration also for overweight patients.

449. USE OF TILT TABLE TEST AND AUTONOMIC MANEUVERS TO DETECT EARLY ALTERATION OF CARDIOVASCULAR AUTONOMIC CONTROL IN PATIENTS WITH NEURODEGENERATIVE DISORDERS

Rocco L., Carandina A., Montano N., Tobaldini E.
Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy.

Background and Aims: Tilt table test (TTT) holds significant importance in the evaluation of syncope with unknown cause or in patients with suspected dysautonomia, such as in some neurodegenerative disorders and Postural Orthostatic Tachycardia Syndrome. TTT evaluates dynamic response of autonomic nervous system (ANS) to orthostatic position and it can be implemented with physical autonomic maneuvers that elicit a sympatho-vagal reaction. In particular, the deep breathing test evaluates the respiratory sinus arrhythmia (RSA) and the cardio-respiratory coupling, while the Valsalva maneuver assesses the preservation of the physiological baroreflex response to a forced expiration. Both of them can be used to add information about autonomic integrated control of the cardio-circulatory system, helping in the differential diagnosis between autonomic disorders. The aim of our study was to analyze the prevalence of orthostatic hypotension (OH) at TTT and the autonomic responses to maneuvers according to the different specific pathologies.
Methods: We conducted a retrospective study in the Dysautonomic Disorders outpatient clinic at Policlinico Hospital in Milan, between September 2020 and March 2023. We included the data analysis from all the consecutive patients who underwent TTT, deep breathing test and Valsalva maneuver for the assessment of possible dysautonomia.
Each exam involved the continuous monitoring of heart rate and blood pressure throughout several phases: a baseline supine position mantained for 5 minutes, the Valsalva maneuver and deep breathing test, followed by a passive orthostatic phase of 15 minutes at 70°. The Valsalva maneuver was performed instructing the patient to exhale forcefully (40 mmHg pressure for 7-10 seconds) against a closed glottis after a normal inspiratory effort. A controlled deep breathing test was performed with the subject breathing at 6 breaths per minute for 90 seconds. OH was defined as a fall in BP during TTT >20 mmHg (systolic) or >10 mmHg (diastolic). Alteration of Valsalva maneuver was assessed as the absence of physiological compensatory BP overshoot above baseline after the cessation of expiratory effort. The RSA was evaluated through sinus arrhythmia ratio (SA ratio), calculated by dividing the highest heart rate during inspiration to the lowest heart rate during expiration; this inspiratory/expiratory ratio was defined altered if <1.2.
Patients' data were divided by referral diagnosis, presence of OH during TTT, alteration of the response to Valsalva maneuvers (absence of overshoot), SA ratio < 1.2, final diagnosis. Patients who did not perform the Valsalva maneuver or the respiratory exercise correctly were subsequently excluded from the study.

Results: Data were collected from 96 patients, 51 males and 45 females. 18 patients were excluded because they did not perform all maneuvers due to reduced compliance. Among the 78 patients included in the study, 26 (33%) developed OH during TTT and 52 did not (67%). In the OH group, 15 patients (58%) had altered response to both the autonomic maneuvers, 2 patients (8%) had alteration only in Valsalva maneuvers and 6 (23%) had only impaired SA ratio. The responses to autonomic maneuvers were preserved in 3 patients with OH (11%). In the no-OH group, 11 patients (21%) presented alterations in both response to the Valsalva maneuver and deep breathing, 11 patients (21%) were characterized by the absence of Valsalva overshoot but preserved SA ratio and 10 patients (19%) had a SA ratio <1.2. The responses to autonomic maneuvers were preserved in 20 patients (39%) of the no-OH group.
Among patients with OH and alteration of both Valsalva and SA ratio, the majority (10/15, 66%) had a diagnosis or were undergoing investigations for neurodegenerative diseases (in particular synucleinopathies such as Parkinson's Disease), then confirmed by the neuroimaging. We found similar prevalence of neurodegenerative diseases among patients without OH and both SA ratio and Valsalva alterations (OH group: 67% with neurodegenerative diseases, no-OH group: 73% neurodegenerative diseases; p=0.543). Conversely, most of the patients without any alteration of TTT and maneuvers had internal medicine pathologies or performed the tests for a syncopal episode.
Conclusions: Our data showed that impairment of autonomic maneuvers is more frequent than orthostatic hypotension at TTT. While the tilt table test has always been important in defining the presence of OH and in the differential diagnosis of syncope, the use of Valsalva maneuver and respiratory sinus arrhythmia seem to be more sensitive in detecting forms of dysautonomia when they are at their onset, as it is known that in neurodegenerative disorders the autonomic nervous system can be involved early but determine orthostatic hypotension only in more advanced stages.

450. DIAGNOSIS AND MANAGEMENT OF AN INSIDIOUS INFECTIVE ENDOCARDITIS: THE ROLE OF INTERNAL MEDICINE – BASED MULTIDISCIPLINARY APPROACH

Lobascio D., Luglio C. V., De Luca A., Belfiore A., "A. Murri" Internal Medicine Group, Portincasa P.
Section of Pathology, Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), University of Bari "Aldo Moro"

S.T., a 72-year-old man, was admitted to the emergency room (ER) with dyspnoea and fever symptoms since a week. Medical history included hypertension, De Bakey type I aortic dissection, dyslipidaemia, previous left adrenalectomy 2 years before, and BPH. The aortic dissection was treated nine years earlier with Bentall procedure1: the aortic valve, aortic root, and ascending aorta were replaced with #23 ATS valved tube. Medications included warfarin, rosuvastatin, amlodipine, and bisoprolol. On admission to the ER, the patient underwent systemic arterial blood gas analysis and laboratory tests, which showed reduction of glomerular filtration and augmented CRP; three blood culture samples were also requested, taken during hyperpyrexia. A computed tomography (CT) scan of chest and abdomen was performed, highlighting parenchymal thickening of the right lower lobe as well as the already known residual dissection of the thoraco-abdominal aortic branches. Intravenous therapy with antibiotics (Piperacillin/Tazobactam and Clarithromycin) was initiated in case of a community-acquired pneumonia. After two days in the ER the patient was transferred to Internal Medicine Unit. At arrival, blood pressure and pulse parameters were regular, the patient was apyretic and not hypoxemic on ambient air; a bedside transthoracic echocardiography was also performed, found negative. Following an evening episode of hyperpyrexia, and the finding of positivity for S. Aureus (MSSA) in the all the blood cultures taken in the ER, in the suspicion of infective endocarditis on the prosthetic valve, a multidisciplinary team (MT) composed of an internist, an infectious disease specialist, a cardiologist, and a heart surgeon was set up. Therefore, in consideration of the comorbidities and the high general risk of the patient, intravenous antibiotic therapy was started with Ceftaroline 600 mg x 2/day and Daptomycin 700 mg/day, ending the previous empiric therapy, and a transoesophageal echocardiogram was performed, confirming no vegetations. Nonetheless, considering the positivity for MSSA on two other blood culture samples taken in the ward, a new transthoracic echocardiogram was performed, again not being able to clarify a definitive diagnosis. Therefore, an 18F-FDG PET was requested, as recommended by current guidelines2, which highlighted an uptake area in correspondence of the aortic valve prosthesis (SUV 11.3), compatible with an infectious inflammatory process, as well as another area of hyperaccumulation at the wall of the ascending aorta (SUV 13.3) of similar significance (Figure 1). According to Duke criteria3, the diagnosis of infective endocarditis was confirmed. Interestingly, the Nuclear Medicine Department reanalysed the images captured during the transoesophageal echocardiogram that, while still not clarifying the diagnosis in the first place, could highlight signs of aortic dissection compatible with an abscess (Figure 2). The MT indicated to continue the intravenous antibiotic therapy until the twenty-first day and, considering the antibiogram profile, at discharge opted for a switch to amoxicillin/clavulanate 1g orally three times per day until further evaluation. This conservative approach, aimed at the chronic suppression of the infection, was necessary due to the significant risk of potential surgery, for which the patient was classified as not suitable at first evaluation considering his comorbidities. On the twenty-first day, following three negative blood cultures, the patient was discharged home. At the outpatient follow-up that occurred twenty days later, considering the good clinical response and the absence of adverse reactions, therapy with amoxicillin/clavulanate was confirmed. Two months later, a new evaluation was assessed, without mention

of fever-like symptoms or adverse reaction to therapy, and overall good conditions. Our case highlights the importance of a multidisciplinary approach, as well as conducting a sufficient number of diagnostic procedures in conditions in which traditionally helpful exams (i.e. transthoracic and/or transoesophageal echocardiogram) are still doubtful or not diagnostic, in accordance with current guidelines.

References

1. Mookhoek, A. *et al.* Bentall Procedure: A Systematic Review and Meta-Analysis. *Ann Thorac Surg* **101**, 1684-1689, doi:10.1016/j.athoracsur.2015.10.090 (2016).
2. Habib, G. *et al.* 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J* **36**, 3075-3128, doi:10.1093/eurheartj/ehv319 (2015).
3. Li, J. S. *et al.* Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* **30**, 633-638, doi:10.1086/313753 (2000).

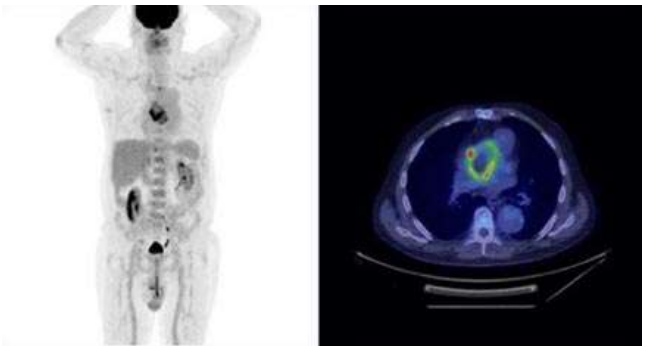


Figure 1.

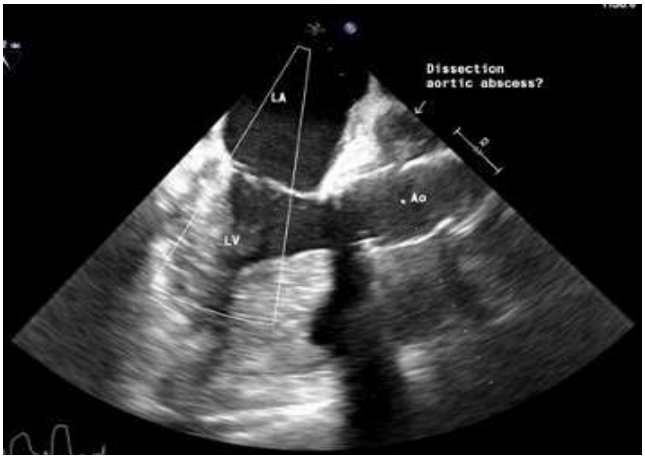


Figure 2 .

451. HEART FAILURE… OR MAYBE NOT?

Carta F.[1], Pasqualucci D.[2], Sanna N.[2], Prof. Manetti R.[1]
[1]Università degli Studi di Sassari; [2]Azienda Ospedaliera Brotzu, Cagliari

Introduction: The amyloidoses are disorders of protein conformation and metabolism in which insoluble fibrils are deposited in body organs, causing organ dysfunction and eventually death. The unifying feature of these proteins is their tendency to form β-pleated sheets aligned in an antiparallel fashion. These sheets then form rigid, nonbranching fibrils that resist proteolysis and cause mechanical disruption and local oxidative stress in affected organs such as the heart, liver, kidneys, and gastrointestinal tract. Moreover, they can be identified on biopsy samples for both their characteristic appearance under electron microscopy and their ability to bind Congo red. The AL amyloidosis is a rare systemic disease that may present with a variety of signs and symptoms, including heavy proteinuria (usually in the nephrotic range), edema, hepatosplenomegaly, and heart failure.
Case description: a 78-years-old male patient accessed the Emergency Room for initial cardiac failure associated with bilateral pleural effusion. He was also suffering from hypertrophic heart disease, arterial hypertension and diverticulosis of the colon. Th patient was taking Furosemide 100 mg/day, Spironolactone 25 mg/day, Olmesartan/Amlodipine 20/5 mg/day and Silodosine 8 mg/day. He was recently hospitalized from the Department of Cardiology, and a heart failure was diagnosed. After discharge, under the advice of the primary care physician, he underwent a 24-hours Holter ECG, and night episodes of 2nd degree atrioventricular block (Mobitz 2 type) were identified. He was visited by our team for the appearance of dyspnea and declivious edema not responsive to the increase in diuretic therapy. A transthoracic echocardiogram was performed, highlighting: a small markedly hypertrophic left ventricle with granular myocardial appearance, a normal overall systolic function with inter-ventricular septum hypokinesia, an ejection fraction of 63%, severely dilated atria, right ventricle dilated and hypertrophic. The ECG showed a low voltage QRS, which is more frequent in forms of amyloidosis AL. The severe biventricular hypertrophy directed the diagnosis towards an accumulation disease. Thus the patient was hospitalized to continue the diagnostic-therapeutic process and for the placement of a bicameral Boston Pace-maker. Blood chemistry tests were performed, such as the analysis of the ratio kappa/lambda free light chains in serum with increased free kappa chains in serum (806.72 mg/L) and kappa/lambda ratio (35.11) immunofixation of serum proteins and immunofixation of urinary proteins. There was also an increase in troponin (290 ng/L) and creatinine. The abdominal ultrasound showed hepatomegaly, that is a condition frequently associated with AL amyloidosis. After that, a bone Scintigraphy was performed; however no areas of accumulation of the radiopharmaceutical at the level of the heart muscle were found: score 0 of the Perugini scale. On the other hand, the heart magnetic resonance with gadolinium showed the left ventricle with slightly reduced indexed volumes, hypertrophic appearance with preserved ejection fraction and radiologica criteria compatible with the suspicion of amyloidosis AL.
Results: In order to make a diagnosis of certainty it was necessary to perform a biopsy of the periumbilical fat, which however was negative. For this reason it was decided to perform an osteomedullary biopsy that resulted fragmented with blood clots: cellularity equal to about 50%, with mature plasma cells with interstitial and perivasal distribution equal to 15% of the total medullary cellularity, monotypic against kappa light chains of immunoglobulins, present and maturing patrimonial series, observed deposits of amyloid (Red Congo +) in the wall of an arterial vessel. The above picture is compatible with diagnosis of multiple myeloma.
Conclusions: All the criteria for diagnosing AL amyloidosis are present: amyloid-related systemic syndrome (in this case heart disease), red congo positivity to bone marrow biopsy, evidence of proliferative disorder of monoclonal plasma cells (in this case multiple myeloma). Heart failure in this case can be defined as a secondary manifestation of the heart accumulation pathology.

452. DIURNAL AND NOCTURNAL HYDROSALINE BALANCE, BLOOD PRESSURE VARIABILITY IN PARKINSON'S DISEASE PATIENTS WITH ORTHOSTATIC HYPOTENSION AND SUPINE HYPERTENSION: EFFECTS OF ANTIHYPERTENSIVE DRUG THERAPY

Calvi A.[1], Tedeschi S.[1], Verzicco I. [2], Bissolotti I.[2], Palladini B.[2], Busi G.[2], Mossini G.[2], Macedoni T.[2], Simoni R.[2], Fischetti I.[2], Vicini V.[2], Coghi P.[2], Montanari A.[2], Musiari L.[2], Cabassi A.[2]
[1]Centro Ipertensione, Clinica e Terapia Medica DIMEC, University of Parma, Parma, Italy ; [2]Centro Ipertensione, Clinica e Terapia Medica DIMEC, University of Parma, Parma, Italy

Disautonomia represents an early concern in Parkinson's disease (PD) patients contributing to altered day-night blood pressure (BP) profile. Orthostatic hypotension (OH), eventually associated to Supine Hypertension (SH-OH), is often observed in PD, because of a sympathetic dysfunction, and represents a challenging clinical issue. Also altered autonomic control of salt and water balance could affect BP profile but data in PD are poor. The aims of the study were to investigate: 1) circadian sodium and water balance changes in PD with SH-OH or with OH alone and 2) the effects of antihypertensive treatment on BP and hydro-saline balance.
PD patients addressed to Hypertension Unit of University of Parma for both hypertensive and hypotensive problems, included in the SHY OR SHAKY study (Supine HYpertension and ORthoStatic Hypotension: A KeY challenge

in Parkinson's Disease, a 20-years monocentric observational study on blood BP variability in these patients with disautonomia) were divided on the basis of the circadian pressure profile (detected with ambulatory BP monitoring for 24 hours, ABPM) into 2 groups: Group 1 (SH-OH, n = 11) and Group 2 (OH alone, n = 6). Patients followed a fixed sodium (165 mEq/day) and potassium (60 mEq/day) diet, and after urine collection, separate day-night natriuresis, kaliuresis and urine aquaporin2(AQP2)/creatinine were determined. Group 1 patients were treated with Eprosartan, an Angiotensin-II AT1-receptor antagonist (200-600 mg/day at night, n=7) or Nicardipine, a short acting calcium-channel blocker (10-20 mg at night, n=4). These patients repeated ABPM and urine analysis after 3 weeks treatment period. ABPM showed higher systolic and diastolic BP during the night in SH-OH compared to OH (p<.001). In SH-OH group, after treatment, daytime systolic BP increased (p<.05), and night-time systolic and diastolic BP decreased (p<.05), leading to better BP control. Eprosartan was more effective (p<.05) than Nicardipine. SH-OH had lower day/night natriuresis ratio versus OH (p<.01), meaning that a consistent night sodium elimination is exerted in response to higher BP values (according to Guyton's model). SH-OH group had also an increase in day/night AQP2/creatinine ratio, consistent with a reduced sensitivity to ADH during night-time. Night-time AQP2/creatinine decreased after treatment in SH-OH group. Eprosartan restored sodium day/night urinary excretion and determined an equal sensitivity to ADH during day and night-time. Nicardipine instead failed to normalize sodium day/night profile excretion (maybe due to its slight natriuretic effect), but reduced day/night AQP2/creatinine; the latter observation is mainly driven by decreased day-time AQP2 excretion.
In conclusion, altered day-night salt excretion can affect BP profile in PD patients, with low diurnal natriuresis potentially affecting BP levels at night; so, it is important to consider also water and salt balance when choosing an antihypertensive class of drug. In this study, Eprosartan positively affect BP profile and salt balance in supine hypertensive PD patients.

453. PULMONARY HYPERTENSION: A NOT SO RARE CAUSE OF DYSPNEA IN BETA-THALASSEMIC PATIENT

Paolozzi G.[1], Di Mauro A.[2], Scaramellini N.[3], Cassinerio E.[2], Curioni M.[2], Currà J.[2], Tafuri F.[1], Peyvandi F.[4], Vicenzi M.[5]
[1]Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico di Milano, UOC Medicina Interna-Emostasi e Trombosi, 20122 Milan, Italy; [2]Unit of Internal Medicine and Metabolic Disease, Fondazione IRCCS Ca` Granda Ospedale Maggiore Policlinico, Milan, Italy; [3]Department of Clinical Sciences and Community Health, Universita` degli Studi di Milano, Milan, Italy; [4]Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Milan, Italy; Department of Pathophysiology and Department of Transplantation, Università degli Studi di Milano, Milan 20122, Italy; [5]Department of Cardio-Thoracic-Vascular Diseases, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, 20122 Milan, Italy; Department of Clinical Sciences and Community Health, University of Milan, 20122 Milan, Italy

Introduction: Betathalassemias are a group of inherited hemoglobinopathies characterized by ineffective erythropoiesis, due to imbalance in alpha and beta chains ratio, leading to hemolytic anemia and iron overload.Usually, heart failure is characterized by myocardial iron overload leading to left ventricle hypokinetic-dilatative cardiomyopathy with subsequent pulmonary and right ventricle chronic stress. Different forms of pulmonary hypertension (PH), included form of pre-capillary PH, can be associated with hemoglobinopathies.
Case Report: G.N., a 49-years-old man, was admitted to the emergency department of the IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico presenting with an acute worsening of exertional dyspnea and desaturation. His medical history included transfusion-dependent β-thalassemia, with need for 2 units of packed red blood cells every 21 days. The patient underwent a splenectomy several years before to reduce the need for transfusions and hypersplenism and was on chronic iron chelation with Deferasirox without MRI signs of cardiac nor liver iron overload. Moreover, he was on treatment with Luspatercept, an erythroid maturating agent. At presentation, cardiac fast echoscopy was performed, showing dilated right ventricle, hence the patient underwent CT scan with contrast medium that excluded pulmonary embolism and parenchymal lung diseases but showed indirect signs of PH. At admission to the ward, the patient was anemic (Hb 9 g/dl) we performed echocardiography which demonstrated the presence of chronic right cardiomyopathy and PH: interventricular septum systolic and diastolic D-shape, PASP 60 mmHg, shortened right ventricle outflow tract acceleration time of 70ms with notched shape, TAPSE <16mm. The hemodynamic clinical picture identified numerous causes of reduction in delivery O2; modifiable elements were treated. (a) During the hospitalization the patient was transfused with a total of 4 blood cells concentrates to reach stable levels of Hb 11 g/dl. (b) Oxygen therapy with low flow nasal cannula was administrated with good response in SpO2 levels. (c) Significant intracardiac shunt was excluded with contrast echocardiography, that showed late passage of microbubbles, with clinical significance of extracardiac shunt in the context of PH. To confirm the diagnosis the patient underwent right cardiac catheterization which established the presence of precapillary PH and normal cardiac output (PAPs 63 mmHg, PAPm 38, right atrium pressure 2 mmHg, PAWP 3 mmHg, cardiac output 5.2 L/min, cardiac index 2.9 L/min/m2, pulmonary vascular resistance 6.7 WU, SvO2 55%, Hb 11 g/dL). The clinical scenario was suggestive for pulmonary hypertension group 5 (WHO), secondary to chronic hemolysis and splenectomy. Despite, the diagnosis did not indicate specific treatment, G.N. was put on chronic treatment with Riociguat.
Discussion: PH is classified into five groups based upon etiology and mechanism. Patients with hematologic disorders belong to group 5 and are not usually treated with specific drugs. A recent study shows that the prevalence of PH in β-thalassemia patients is 2.1% and it is quite deadly. [Derchi G, et al., 2014]. PH in β-thalassemia major correlates with the time of exposure to hemolysis, it represents a subtle and smoldering disease that is not prevented by the iron chelation unlike the iron cardiomyopathy. Moreover, to date the therapeutic possibilities for group 5 PH are limited and, in our case, mainly anecdotal, given the lack of large studies in literature. Erythrocyte dysfunction and chronic hemolysis contribute to impair nitric oxide (NO) bioavailability. Free hemoglobin inactivates NO and its vasodilatory properties within the pulmonary circulation. Also splenectomy has been claimed to be a risk factor in the development of PH, since the spleen functions as a filter for damaged erythrocytes and debris. The loss of this function is thought to enhance erythrocyte breakdown in the systemic and lung circulation. Each of these factors may cause changes within the pulmonary vasculature leading to pre-capillary PH that is clinically comparable to the pulmonary arterial hypertension (group 1 PH) or to the chronic thromboembolic pulmonary hypertension (CTEPH). In the present case report, G.N. received specific treatment through Riociguat to treat the hemodynamic instability and reduce right ventricle overload. Riociguat allows to stabilize patients and to discharge from hospital, keeping good cardiocirculatory balance. Riociguat is a stimulator of soluble guanylate cyclase (sGC) and increases the sensitivity to NO. Its main effect is to antagonize vasoconstriction regardless of NO availability, so far riociguat is thought to act on the leading pathogenic culprit of hemolysis related PH but its use still off-label since the lack of studies in this population [Blasi FBM, et al., 2021].
Conclusions: Pre-capillary PH in patients with hemoglobinopathies, although frequently overlooked, represents a significant entity with potential severe prognostic implications and a complex pathophysiology, that requires a particular management with disease-specific measures.

454. NIGHT-TIME BLOOD PRESSURE AND BLOOD PRESSURE VARIABILITY IN HYPERTENSIVE PATIENTS WITH OR WITHOUT INSOMNIA. A PILOT STUDY

Dal Pont C., Sartorio A., Benedetti E., Bonafini S., Ferrante L., Dalbeni A., Minuz P., Fava C.
Dipartimento di Medicina, Università di Verona, Italia

Objective: Recent studies found that insomnia is an independent risk factor for cardiovascular diseases, particularly arterial hypertension. Among the hypertensive population, insomnia could contribute to a worse blood pressure (BP) profile. In a sample of hypertensive patients, we compared those with and without insomnia with the aim of evaluating possible differences in BP, its variability, and breathing pattern.
Design and method: We conducted a case-control study on patients with and without insomnia, based on the "Insomnia Severity Index" (ISI) questionnaire. Patients were recruited from the general practitioner's registry and were sent an invitation e-mail. All of them had long-lasting hypertension. One-hundred-and-fifty patients replied to the ISI questionnaire. Among them, twenty people with insomnia were selected (ISI ≥15) and matched, based on their gender and age (±3 years), to 20 controls (with ISI <15). All participants underwent night-time cardiorespiratory and 24-hour blood pressure monitoring by using a new cuff-less device that can estimate beat-to-beat BP (SomnoTouch-NIBP).
Results: Comparing the two groups (insomnia vs. non-insomnia), no diffe-

rences were observed in BP profile and all the respiratory indices, including the apnea-hypopnea index(AHI), the number of desaturations, and peripheral oxygen saturation (SpO2) values. Even the average BP and the indices of BP variability, such as the standard deviation (SD), the pressure coefficient of variation (CV), the BP dipping, and the nocturnal BP fluctuations (NBPF), were similar between the groups. Interestingly, to obtain the same average BP control, the insomnia group required a greater number of antihypertensive drugs (2,85 ± 0,88 vs. 1,95 ± 1,00 in the non-insomnia group; p<0.01).
Conclusions: Patients with insomnia may need more antihypertensive medications to achieve the same average BP as patients without insomnia. Anyhow, they did not show, as expected, higher BP variability. How much beat-to-beat BP estimations are reliable compared to BP measurements by standard cuff-based devices is still under debate.

455. SEVERE ATHEROSCLEROTIC PATIENTS TREATED WITH RIVAROXABAN: AN ECHOCARDIOGRAFIC STUDY

Iadevaia V., Pucci M. , Iervolino A. , Gammaldi V. , Paoletta D., Capece L.M., Cuomo V., Sciascia D., Iacono M. , Esposito R.
Department of Clinical Medicine and Surgery, Federico II University Hospital, Naples, Italy

Background: The COMPASS Trial has demonstrated a reduction of the risk of myocardial infarction, stroke, or cardiovascular death in subjects with coronary artery disease (CAD) or peripheral artery disease (PAD) in patients treated with rivaroxaban 2.5 mg twice daily (bid) + aspirin 100 mg once daily (od) compared with aspirin 100 mg od. Little is known about the change in ventricular function using noninvasive imaging in patients taking asa and rivaroxaban 2.5 bid
Objectives: Our study performed an echocardiographic evaluation of patients affected by CAD and PAD in therapy with rivaroxaban 2.5 mg twice daily (bid) + aspirin 100 mg once daily (od) at baseline and after three months.
Methods: We performed a prospective review of 10 patients out of the 17 evaluated at baseline, admitted at our EchoLab in the last year, who underwent echocardiogram prior starting therapy with rivaroxaban 2.5 mg twice daily (bid) + aspirin 100 mg once daily (od). Echo-Doppler assessment was realized according to the standards of the European Association of Cardiovascular Imaging (EACVI) standardization of the echo report. Continuous normally distributed variables were compared by using the Student t-test. A probability value < 0,05 was considered statistically significant. Analyses were performed with SPSS version 25 (IBM Corporation, Somers, New York).
Results: We observed an improvement of echocardiographic variables at three months compared to baseline: higher ejection fraction (EF) (56,80 ± 4,04 vs 54,80 ± 2,25, p-value: 0,044) and higher Global Longitudinal Strain (GLS) (19,55 ± 3,34 vs 17,91 ± 3,48, p-value: 0,026); those two variables were statistically significant. There is no worsening of diastolic function:E/E' ratio (10,24 ±3.58 vs 10.65 ± 2.89, p-value 0.372) , polmonary artery systolic pressure (PAPS) (27.6 ± 7.46 vs 26.4 ± 7.19, p-value 0.736) and tricuspid annular plane systolic exursion (TAPSE) (21.4 ± 3.59 vs 22.4 ± 3.41, p-value 0.311).

Conclusions: COMPASS trial has demonstrated a lower rate in adverse events through the addition of rivaroxaban 2.5 mg twice daily to ASA, particularly stroke and cardiovascular mortality, whereas severe bleeding events were less frequent and had less impact. Our study add new informations on the data already present in literature. Despite the small number of patients enrolled, the reported data indicate a clinical and echocardiographic improvement of patients affected by CAD and PAD treated with the COMPASS protocol.
This is the first analysis based on echocardiography and this It also underlies the importance of echocardiographic evaluation.

456. MICROCIRCULATION ALTERATIONS IN A COHORT OF PATIENTS WITH ERECTILE DYSFUNCTION

Nardin M.[1], Malerba P.[2], Delbarba A.[3], Agabiti-Rosei C.[2], Rossini C.[2], Facondo P.[4], Chiarini G.[2], Baresi M.[2], Laera N.[2], Leidi F.[2], Sinaimeri G.[2], Porteri E.[2], Rizzoni D.[2], Ferlin A.[5], De Ciuceis C.[2]
[1]Third Medicine Division, ASST Spedali Civili di Brescia, Brescia, Italy; [2]Internal Medicine, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy; [3]SSD of Endocrinology and Metabolism, ASST Spedali Civili di Brescia, Brescia, Italy; [4]Endocrinology, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy; [5]Andrology and Reproductive Medicine Unit, Department of Medicine, University of Padua, Padua, Italy

Introduction: The presence of erectile dysfunction (ED) is correlated with the subsequent occurrence of cardiovascular (CV) disease, in ED forms with a predominantly vascular component. The presence of penile arterial damage, assessed by dynamic penile echo color doppler, doubles the risk of a subsequent CV event. Alterations of the microcirculation, and in particular an increase in the media tunica/lumen ratio (M/L) of subcutaneous small arteries or in the wall-to-lumen ratio (WLR) of retinal arterioles, are present in several clinical conditions, including hypertension, and are predictors of CV events. The aim of this study is to evaluate the possible presence of structural alterations of the retinal microcirculation in patients with vascular ED assessed through dynamic penile echo color doppler.
Methods: Patients attending the Endocrinology outpatient clinics of the ASST Spedali Civili in Brescia undergoing dynamic penile echo color doppler to determine the vascular or non-vascular etiology of ED were included in the study. The patients underwent a capillaroscopic evaluation of the capillary density at the dorsum of the IV finger and an evaluation of the retinal microcirculation through adaptive optics to assess the WLR and the wall cross-sectional area (WCSA) of the retinal arterioles.
Results: A total of 33 patients were included, of whom 10 (30.3%) had vascular ED and 23 (69.7%) did not. The main characteristics of the enrolled patients are shown in the **Table**. A higher prevalence of the main cardiovascular risk factors was observed in patients with vascular ED, although none reached statistical significance. No difference in basal or total (after venous congestion) dorsal capillary density was observed. Evaluation of the retinal microcirculation showed a significantly increased WLR in patients with vascular-based ED compared to patients without (0.29 vs. 0.26, p=0.031) with no difference in WCSA, an index of eutrophic remodeling.
Conclusions: Our preliminary data highlight a potential correlation between arterial vascular changes present in the penile circulation and retinal microcirculation, suggesting the possibility of common damage mechanisms and new potential elements of population risk stratification.

Table. Main characteristics of the population

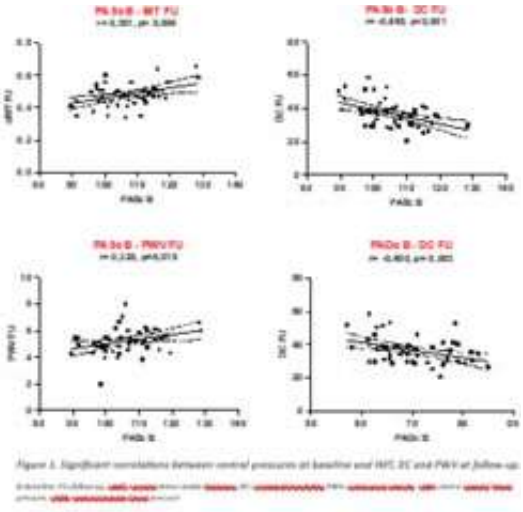
VARIABLE		ED NOT ON A VASCULAR BASIS (N=23)	ED ON A VASCULAR BASIS (N=10)	P-VALUE
Age, years (±SD)		53.3 (±13.2)	60.9 (±7.8)	0.102
BMI, kg/m^2 (±SD)		27.4 (± 6.6)	27.0 (±3.0)	0.845
SBP, mmHg (±SD)		126 (±19)	140 (±15)	0.074
DBP, mmHg (±SD)		80 (±11)	83 (±7)	0.439
HR, bpm (±SD)		84 (±14)	78 (±8)	0.170
Smoke, %				0.648
	Active	18.2	30.0	
	Former	36.4	40.0	
Hypertension, %		50.00	70.0	0.446
Diabetes mellitus, %		14.3	50.0	0.074
Dyslipidemia, %		47.3	70.0	0.280
Peripheral arteriopathy, %		4.8	0.0	1.000
COPD, %		5.0	10.0	1.000
CKD, %		23.8	0.0	0.147
Familiarity for ischemic heart disease, %		42.9	30.0	0.697
Previous myocardial infarction, %		9.5	30.0	0.296
Previous TIA, %		4.8	10.0	1.000
Early stroke, %		9.5	0.0	1.000
Previous malignancy, %		4.8	0.0	1.000
Dorsal basal capillaries, n (±SD)		80 (±14)	90 (±27)	0.213
Dorsal capillaries after venous congestion, n (±SD)		87 (±13)	94 (±29)	0.505
WCSA, µm^2 (±SD)		4517 (±963)	4697 (±576)	0.650
WLR, absolute (±SD)		0.26 (±0.04)	0.29 (±0.03)	0.031

ED= erectile dysfunction; DS= standard deviation; BMI= body mass index ; SBP= systolic blood pressure; DBP= diastolic blood pressure; HR= heart rate; COPD= chronic obstructive pulmonary disease; CKD = chronic kidney disease; WCSA= wall cross-sectional area; WLR= wall-to-lumen ratio

457. SUBCLINICAL TARGET ORGAN DAMAGE IN PATIENTS WITH TYPE 1 DIABETES MELLITUS. A PROSPECTIVE PRELIMINARY STUDY.

Rosin E.[1], Franzin A.[1], Burrei G.[1], Sabbà G. E.[1], Biasotto A.[1], Morellini S.[1], Giontella A.[1], Tagetti A.[1], Cattazzo F.[1], Marcon D.[1], Piona C.[2], Maffeis C.[2], Bortolotti S.[1], Dalbeni A.[1], Minuz P.[1], Fava C.[1]
[1]Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy; [2]Department of Surgery, Dentistry, Pediatrics and Gynecology, Section of Pediatric Diabetes and Metabolism, University and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy

Introduction: Early atherosclerosis is the main cause of cardiovascular damage and death in patients with type 1 diabetes mellitus (T1DM). Some vascular indexes can help to identify and stratify patients before clinical events. This study aims to evaluate the trend over time of some markers of subclinical vascular damage to identify possible associations with anthropometric parameters, blood pressure (BP) and metabolic variables.
Methods: Fifty-six patients with T1DM (mean age: 17.5±2.5 years; mean duration of diabetes: 8.9± 4.0years) were assessed in two occasions (mean follow-up time: 2.7±0.9 years). Peripheral BP (pBP), central BP (cBP) and Pulse Wave Velocity (PWV) were measured by the SphygmoCorXCEL. Carotid Intima-Media Thickness (cIMT) and the carotid Distensibility Coefficient (cCD) were assessed by ultrasound connected with an image acquisition and analysis system (CardiovascularSuite). Biochemical and anthropometric data were also recorded.
Results: At follow-up, PWV and BP values increased significantly while cDC further decreased with the 80.4% of patients that presented a pathological cDC (lower than 40x10-3KPa or the 5th percentile). BP values at baseline correlated with all vascular indices at follow-up: in particular, cSBP was associated with cDC (r=-0.46, p<0.001), cIMT (r=0.39, p=0.004) and PWV (r=0.32, p=0.01). These associations remained significant even after adjustment for metabolic (including glycated hemoglobin) and anthropometric parameters. Moreover, baseline arterial stiffness significantly correlated with BP values at follow-up: particularly cDC and PWV were associated with cDBP (r=-0.354, p=0.009 and r=0.40, p=0.002; respecitvely) even after multiple adjustments. Regarding metabolic parameters, non-HDL-to-HDL-cholesterol ratio correlated with both cDC (r=-0.36, p=0.007) and PWV (r=0.30, p=0.03).
Conclusion: The most important finding of this study is the strict and independent association between BP parameters, especially cSBP at baseline, and indices of vascular damage at follow-up, even after multiple adjustments. Indeed, cDC at baseline is also associated with increased cDBP at follow-up. Our data support the hypothesis of a vicious cycle between BP and arterial stiffness, which may worsen both parameters over time.



458. URINARY HYALURONIDASE ACTIVITY IN NORMOTENSIVE AND HYPERTENSIVE SUBJECTS FROM WEST AFRICA: RELATIONSHIP WITH ESSENTIAL HYPERTENSION PREDISPOSITION

Bongrani A.[1], Verzicco I.[1], Tedeschi S.[1], Graiani G.[2], Cavazzini S.[2], Figus G.[1], Vicini V.[1], Calvi A.[1], Montanari A.[1], Perlini S.[2], Cabassi A.[1]
[1]Clinica e Terapia Medica, Dipartimento di Medicina e Chirurgia, Università di Parma; [2]Medicina Interna, Malattie Vascolari e Metaboliche c/o Policlinico San Matteo - Clinica Medica II Università di Pavia, Italia

Introduction:
It has long been known that African populations have a higher prevalence of essential hypertension, with an earlier age of onset and greater severity. African subjects also show low levels of plasma renin activity, even in the absence of hyperaldosteronism, higher mean levels of antidiuretic hormone (ADH or vasopressin), increased urinary osmolarity and a lower ability to dilute urine in response to water loading. Considering that alterations in the water-sodium balance are a crucial factor in the development of essential hypertension and that hyaluronic acid metabolism appears to play a key role in the regulation of water reabsorption in the collecting duct, our aim was to study hyaluronidase activity in the urine of normotensive and hypertensive subjects from West Africa, compared to Caucasian subjects.
Material and Methods: The study cohort included 50 adult men from West Africa, of whom 21 were normotensive and 29 hypertensive, and 50 adult Caucasian men, of whom 29 were normotensive and 21 hypertensive. The recruitment took place between December 2013 and October 2016 in the context of a multicentre observational study promoted by the Italian Society of Hypertension (Società Italiana dell'Ipertensione Arteriosa, SIIA, Project I Demand). All subjects underwent a water load consisting of oral administration of 15-20 ml water/kg body weight for 40-45 minutes. Urinary hyaluronidase activity was measured by turbidimetric assay every 60 minutes for 4 hours and values were corrected for urinary creatinine concentration.
Results: Urinary hyaluronidase activity decreased in response to water loading in all study groups, reaching its lowest levels between 60 and 120 minutes, and then gradually returned to baseline values. This decrease, however, was significantly less relevant in West African subjects in both the normotensive (p<0.01 at 60 minutes and p<0.001 at 120 minutes) and the hypertensive subgroups (p<0.05 at 60 minutes and p<0.0001 at 120 and 180 minutes).
Conclusions: Urinary hyaluronidase activity was inversely correlated to hydration status, as observed in all study groups in response to oral water loading. However, while no difference was found in baseline levels, the decrease in hyaluronidase activity resulting from water intake was significantly less in West African subjects. Since hyaluronic acid metabolism is influenced by several hormones involved in water-sodium homeostasis, including ADH, our results confirm the existence of a close relationship between hyaluronidase activity in the renal interstitial medullary and the vasopressinergic system, and suggest, as already proposed by other authors, that subjects from West Africa have an increased renal sensitivity to vasopressin action, resulting in alterations in water metabolism that could contribute to and even precede hypertension development.

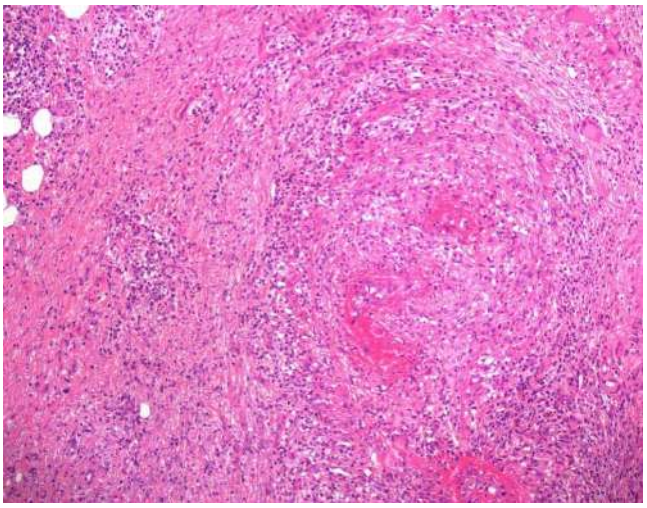
MALATTIE INFETTIVE

459. A RARE CASE OF PANNICULITIS

Caldarelli M.[1], Cianci R.[2], D'addio S.[2], Di Stefani A.[3], Gambassi G.[2]
[1]Department of Translational Medicine and Surgery, Catholic University of the Sacred Heart, 00168 Rome, Italy; [2]Department of Translational Medicine and Surgery, Fondazione Policlinico Universitario A. Gemelli IRCCS, 00168 Rome, Italy; [3]Department of Translational Medicine and Surgery, UOC Dermatology, Fondazione Policlinico Universitario A. Gemelli IRCCS, 00168 Rome, Italy

An 86-year-old woman came to the emergency room due to fever and appearance of purulent exudate at the level of the adipose tissue of the right thigh.History: type 2 diabetes, permanent atrial fibrillation on oral anticoagulant therapy with acenocoumarol and previous right saphenectomy.In the emergency room, ceftriaxone therapy was started, with little benefit.CT of the leg was therefore performed, which showed thickening of the cutaneous and subcutaneous tissue, without the presence of air bubbles. An ultrasound

of the lower limb excluded signs of deep vein thrombosis.On physical examination, appearance of a swelling of increased consistency, taut - elastic, at the level of the middle third of the right thigh.Empiric antibiotic therapy with vancomycin and meropenem was set up in our department of Internal Medicine, which was followed by a significant improvement in the clinic and inflammation indexes.A monoclonal component of IgG K was observed in blood and urine tests.Other microbiological serological tests were negative: HIV, HBV, HCV. A CT scan of the thigh was performed which confirmed the thickening of the subcutaneous adipose cell on the medial side of the distal part of the right thigh, extending superficially to the skin plane and deeply to the muscular fascial plane, in the context of which some ecstatic vessels ran. Not collected or aerial density images.A skin biopsy was performed which revealed a picture of lobular and septal panniculitis, with the presence of inflammatory granulomatous infiltrate associated with necrotizing vasculitis of the venous septa.Panniculitis is an inflammation of the subcutaneous fat layer.The etiology is varied: infectious, iatrogenic, associated with systemic inflammatory diseases or autoimmune disorders.The clinical presentation is usually characterized by erythema, swelling and tender subcutaneous nodules.Panniculitis is classified according to histopathological criteria, depending on the location of the inflammatory infiltrate and the presence or absence of vasculitis.The most common type of panniculitis is erythema nodosum which is the prototype of septal panniculitis.The initial lesions are usually characterized by the presence of neutrophils, the increase of which is also detectable in peripheral blood, the increase of which is associated with the production of reactive oxygen products which cause tissue damage.Erythema nodosum is typical of young women and is characteristically localized in the pretibial regions.It is caused by various antigens (infectious agents, IBD, Behcet's disease).Clinically, ulceration and suppuration are rare manifestations. Another pathology that can present with skin involvement is sarcoidosis; it is an example of systemic inflammatory granulomatous disease, which usually presents with lobular panniculitis.A CT scan of the chest and abdomen was then performed which documented bilateral thickening of the interlobular and interlobular subpleural septa, in relation to a picture of initial fibrosis, and the presence of a solid non-calcified nodule (5 mm) at the level of the lung left and finally the presence of other non-specific nodules bilaterally. Furthermore, the Quantiferon test was indicative of latent tuberculosis status.Erythema induratum of Bazin is a form of granulomatous lobular panniculitis caused by infectious agents such as tuberculosis.



460. ATYPICAL VARICELLA-ZOSTER VIRUS REACTIVATION: A CASE REPORT

Salvotti F., Chiarini G., Trapletti S., Castellano M., Muiesan M.L.
Internal Medicine, Department of Clinical and Experimental Sciences, University of Brescia

Background: Varicella-Zoster Virus (VZV) is a double-stranded DNA alphaherpesvirus. VZV infection commonly causes benign skin manifestation in children, known as chickenpox. Then the virus establishes a latent infection, by retrograde migration to the sensory neuron body of the ganglion; it may reactivate and cause herpes zoster by reaching the skin via anterograde axon transport. The most common zoster complication is postherpetic neuralgia, but complications can also occur without rash and might lead to ocular, visceral and gastrointestinal disorders. VZV infection may cause neurological manifestations including encephalitis, meningitis and Ramsay Hunt syndrome. Even vasculopathy may occur both in primary and reactivated VZV infection: clinical presentation includes stroke, temporal artery involvement, arterial dissection and cerebral venous sinus thrombosis (CVST). Thrombotic complications are mainly described in children, while few case reports have described CVST, deep veins of the lower limbs thrombosis and pulmonary embolism in adults.
Case presentation: A 37-year-old woman was referred to Spedali Civili's Emergency Room (ER) for the onset of fever, psychomotor impairment and refusal to eat or drink for few days. She had a history of bipolar disorder; her home therapies were lithium and estro-progestin vaginal ring. At ER admission an increase of C-reactive protein, abnormal liver function, hemoconcentration and a pre-renal acute kidney injury were detected. A Computed Tomography (CT) with contrast agent of the abdomen, performed because of a mild abdominal pain,showed inferior vena cava thrombosis, occlusive thrombosis of the left lower limb venous system and right common femoral vein thrombosis. At the chest CT scan pulmonary embolism was identified. Psychomotor impairment was further investigated by electroencephalogram, which described slow central-anterior waves, and by a magnetic resonance imaging (MRI) which revealed CVST involving the superior sagittal sinus, right lateral sinus, and right internal jugular vein. In summary, our patient was affected by acute hepatitis, neurological manifestations suggesting encephalitis, multiple deep venous thrombosis and persistent fever (with multiple negative blood cultures). The suspected unifying diagnosis of a viral infection was confirmed by the elevated anti-VZV IgG antibodies and slight increase in IgM titer. When serology was repeated during the hospitalization IgG level remained elevated and IgM titer progressively became negative, as described in literature during VZV reactivation.
Differential diagnosis of multiple deep venous thrombosis: Thrombophilia tests resulted negative for factor V Leiden or prothrombin mutation; levels of protein C, protein S and homocysteine were normal. Antiphospholipid syndrome was ruled out and levels of anti-nuclear antibodies were normal. Myeloproliferative disorders were excluded, jak2 mutation was absent and paroxysmal nocturnal hemoglobinuria was absent. CT imaging excluded neoplasm and a positron emission tomography resulted negative for vasculitis. Among the risk factors associated with venous thromboembolism, only the estro-progestin therapy (promptly removed at admission) was present in our patient.
Treatment and Outcome: Antithrombotic therapy with enoxaparin 6000 UI bid (the patient's weight was 60 Kg) was immediately started. When the viral aetiology was confirmed by laboratory findings, intravenous acyclovir was started. The patient gradually showed neurological improvement, and fever disappeared. Biochemical exams (including liver function) started normalizing and a brain MRI described a partial CVST recanalization. Acyclovir was administered over a three-weeks period and antithrombotic treatment was shifted from enoxaparin to direct oral anticoagulant (apixaban 5 mg bid). The patient was discharged after about 35 days of hospitalization, and she gradually recovered in the following months. A venous echocolordoppler performed after three months from the discharge revealed a partial recanalization of venous lower limbs thrombosis. Long-term anticoagulant therapy was maintained.
Conclusions: Only few isolated cases of VZV-related CVST and other deep veins thrombosis have been reported in adults. The first case report of pulmonary embolism associated with Zoster Sine Herpete was described by Sahra *et al.* in 2021. The exact pathogenetic mechanism is not completely known; the postulated theories are vasculitis, direct endothelial damage and acquired protein S deficiency secondary to molecular mimicry. Our patient was extensively studied for possible prothrombotic diseases, but all the diagnostic workup resulted negative. This underlines the importance of further studies on pathogenetic mechanisms still unclear in many cases. This case report would like to raise awareness on rare VZV manifestations and to underline the central role of clinical multidimensional evaluation in order to recognize and promptly treat the disease.

461. RITIRATO

462. DERIVATION AND VALIDATION OF A PREDICTIVE MORTALITY MODEL OF IN-HOSPITAL PATIENTS WITH ACINETOBACTER BAUMANNII NOSOCOMIAL INFECTION

Gagliardo C.M.[1], Cimino M.C.[1], Giammanco A.[1], Catanzaro A.[2], Averna M.[1], Baldassare A.[1], Tuttolomondo A.[1], Noto D.[1]
[1]Department of Health Promotion, Maternal and Child Health, Internal and Specialized Medicine of Excellence "G. D. Alessandro" (PROMISE), University of Palermo, Italy; [2]Department of Engineering, University of Palermo, Italy

Background: Acinetobacter baumannii (Ab) is a Gram-negative opportunistic bacterium responsible for nosocomial infections or colonization. Mortality rate ranges from 34 to 44,5%. of hospitalized patients. It is considered one of the most alarming pathogens due to its multi-drug resistance.
Objective and Methods: Aim: to create a predictive mortality model for hospitalized patient with Ab infection or colonization. A cohort of 140 patients were randomized into a training cohort (TC) (100 patients) and a validation cohort (VC) (40 patients). In the TC, statistical bivariate analysis was performed to discriminate significant differences between dead and alive patients, both at admission time (T0) both at detection time of Ab in microbiological samples (T1). Variables with a p <0,1 entered into a logistic regression model, that was validated in the VC and compared with models obtained from the "Status" alone variable (Ab colonization or infection), SAPS II and APACHE II scores. ROC curves were constructed to identify the best cut-off for each model.
Results: Ab infection ("Status"), use of penicillin within 90 days prior to ward admission, acidosis, GCS, blood pressure, hemoglobin and use of NIV entered the logistic regression model. Our model was confirmed to have a better sensitivity (63%), specificity (85%) and accuracy (80%) then the other models. Comorbidity burden did not influence mortality.
Conclusion: Our predictive mortality model has been demonstrated to be a reliable and feasible model to identify hospitalized patient with Ab infection or colonization with higher mortality risk at time of Ab detection.

463. DISSEMINATED NOCARDIOSIS IN A KIDNEY TRANSPLANT RECIPIENT: A CASE REPORT

Laffranchi M.[1], Catarinella D. [2], Gremizzi C.[2], Tentori S. [2], Paloschi V.[2], Caldara R.[2], Piemonti L.[1]
[1]Università Vita-Salute San Raffaele; [2]IRCCS Ospedale San Raffaele

Solid organ transplantation, such as kidney transplantation, is associated with an increased risk of Nocardia infection, most likely due to the immunosuppressive medications used to prevent rejection. Lung is the primary site of infection (approximately 80% of cases in immunocompromised individuals) and the most common site of dissemination is brain. Antibiotic therapy and its duration is based on the severity and the extent of disease, the isolated Nocardia species and the clinical and radiographic response to treatment.
Objective: to underline the importance of considering Nocardia infection as one of the differential diagnosis in immunocompromised patients who present with brain abscesses and pulmonary infiltrates, and of monitoring the response and toxicity of the therapy.
Case report: we report a case of disseminated nocardiosis (lung, brain and 28^ tooth) occuring in a 51 years-old Peruvian woman, after deceased-donor kidney transplantation in March 2022. She was on dyalisis since 2012 for end stage kidney disease caused by microscopic polyangiitis (MPA) associated with Myeloperoxidase-Antineutrophil Cytoplasmic Autoantibody (MPO-ANCA). The induction immunosoppressive therapy consisted of a combination of immunosuppressive agents (Anti-thymocyte globulin (ATG), tacrolimus, mycophenolate mofetil (MMF) and corticosteroid (CS)); then, it was switched to the maintenance one, consisting of tacrolimus, MMF and CS. Intravenous immune globulin (IVIG) therapy was associated to the induction therapy, since she is an hyperimmunized patient. She was admitted to our hospital in December 2022 following severe seizures and persistent cough, with infiammatory markers increased in the blood tests. The brain magnetic resonance imaging (MRI) scans showed two lesions and the chest computed tomography (CT) scans a polmonary infiltrate. Empiric, broad spectrum antibiotics and antifungineal therapy were started. In addition, dreinage of brain abscesses and bronchoalveolar lavage (BAL) for microscopic examination and culture were performed. Nocardia Farcinica/Barduliensis was isolated from both sites. The antimicrobial therapy was therefore modified according to the antibiogram, using trimethoprim-sulfamethoxazole (TMP-SMX) and linezolid, and immunosoppressive therapy with MMF and tacrolimus was gradually reduced up to interruption. A close clinical, laboratory and instrumental monitoring was carried out. Because of the onset of severe symptomatic myelotoxicity (600/uL white blood cells (WBC) with respectively 100 neutrophils and 0 lymphocytes, 7.6 g/dl hemoglobin (HB), 7.000/uL platelet (PLT)), after excluding deficiency state and infectious causes (e.g. CMV), given its probable iatrogenic nature, it was decided to replace the above mentioned antibiotics with imipenem, aware of the risk of seizures related to carbapenem antibiotics. Follow-up imaging studies (e.g. chest radiographs and CT scans for polmonary disease, and brain CT and MRI scans for CNS disease) were obtained, showing a gradual improvement of lesions, especially the brain ones. According to the literature, since our patient has CNS involvement and immunodecifiency, the treatment should be continued for at least one year or longer, depending on clinical and imaging response.
Discussion: a review of the literature identified other similar cases of disseminated nocardiosis in kindey transplanted patients, with pneumonia as the most frequent presentation. Studies show that the incidence of Nocardia infection in kidney transplant recipients is approximately 0.4-1.3% and the first year after transplantation is the period of greatest risk. Traditionally, TMP-SMX is used as first-line therapy.
Conclusion: Nocardia infection is an uncommon but important cause of morbidity and mortality in kidney transplant recipients. Early diagnosis with identification of the Nocardia species and drug susceptibility testing are essential in guiding the management and increasing the chances of survival.

464. BACTERIEMIA FROM STREPTOCOCCUS CONSTELLATUS REVEALING A GASTROINTESTINAL STROMAL TUMOR

Chessa S., Belfiori E. , Mandis G. , Manconi G. , Scuteri A.
SC Medicina Interna - Policlinico Universitario Monserrato - Cagliari

Streptococcus constellatus, member of *Streptococcus anginosus* group, is usually part of the normal flora of mouth and gastro-intestinal tract, but isolates can be found in association with abscesses formation. This generally occurs in several gastrointestinal pathologies such as infection, perforation, and malignancy.
We here describe a case of bacteriemia from *S. constellatus* revealing the presence of pyogenic liver abscesses and, above all, ileal cancer.
An 80-year-old Caucasian woman with a medical history of hypertensive heart disease and psoriasis presented with three-days fever occurring after dental treatment and no other relevant symptoms. She reported one hospitalization for bowel sub-occlusion over the previous year. During this admission an abdominal CT scan was performed, detecting the presence of a jejunal mass, described as a heterogeneous roundish lesion (54x 48 mm). According to the surgeon and the patient's relatives, it was not judged necessary to make any other investigation nor treatment for it.
At the access to the emergency department, the patient was febrile (38.5°C) in the absence of a remarkable physical examination, while laboratory investigations were significant for leucocytosis (23.6 x 109/L) with 84.4% neutrophils and increase of CRP (88.2 mg/L) and procalcitonin (41.2 ng/mL). After obtaining blood cultures, she started a broad-spectrum antibiotic treatment with piperacillin-tazobactam. Then she was admitted to our Internal Medicine Department.
In the early days after admission blood cultures grew *S. constellatus*. Intravenous teicoplanine was added to therapy with clinical and laboratory benefit.
An abdominal US was performed, revealing the presence of multiple hepatic roundish lesions (the greatest at SVIII [55x42 mm]), heterogeneous in echogenicity. Subsequent contrast-enhanced CT scan described three gross multiloculated cystic lesions surrounded by pseudocapsules consistent primarily for pyogenic liver abscesses. Paradoxically, the jejunal mass found at the previous hospitalization was undetectable, leaving place to an eccentric thickening (20 x 10 mm) of the same loop with some inner cystic areas. We also performed CT scan of facial bones, echocardiography and colonoscopy, which were negative.
Both Interventional Radiology and General Surgery were consulted. As the abscesses appeared to have a multilocular aspect, they were not immediately drained but first treated with antibiotics, obtaining just a slightly reduction of their size.
Then a liver resection was practised together with the excision of the jejunal mass.
The pathological examination of jejunal mass showed a Gastrointestinal Stromal Tumor (GIST) which, due to its location, size (30 mm) and mitotic index (25/20 HPF), was considered as high-risk, so she also started treatment with imatinib, according with current guidelines.
Our patient was found to have *S. constellatus* bacteriemia with liver abscesses. Potential causes include bile duct perforation, portal bacteriemia, septicemia, direct extension from intraperitoneal infection, direct trauma to the liver, and secondary infection of metastatic cancer.
In association with liver abscesses, we found a primary small bowel GIST.
GISTs may present with vague symptoms such as abdominal pain, gastrointestinal bleeding, perforation, and obstruction. Clinical aggressiveness mainly manifests itself in the form of peritoneal dissemination and/or hepatic metastasis. Surgery is the first-choice treatment. There is consensus to per-

form a complete resection with free margins. Our patient started therapy with imatinib, a selective inhibitor of a family of tyrosine-kinase enzymes used both for inoperable GISTs and in a neo-adjuvant or adjuvant setting. In fact, adjuvant therapy with imatinib for three years is considered conventional in patients at high risk of recurrence, as it has been shown to improve recurrence free survival. Regarding the hepatic abscesses, treatment usually involves drainage and intravenous antibiotics, but, if multiple or loculated (that is the case of our patient), they are in general not amenable to nonsurgical drainage.
A literature review showed only a few case reports about the relationship between bacteriemia, liver abscesses by a member of *S. anginosus* group and gastro-intestinal cancer.
This association is likely not causative: it is thought that neoplastic growth can disrupt the integrity of gastro-intestinal mucosa creating a pathway for the systemic spreading of this bacterium.
In conclusion, our case further validates the relationship between *S. constellatus* systemic infection and the presence of a gastro-intestinal malignancy (similar to the well-described association between *Streptococcus bovis* and colorectal malignancies). This should prompt physicians to screen for upper and lower gastro-intestinal lesions in patients presenting with systemic infections caused by *S. constellatus*, in order to facilitate an appropriate and timely treatment.

465. A RARE CASE OF LUNG CAVITATION AND MENINGITIS FOLLOWING ACHROMOBACTER XYLOSOXYDANS INFECTION IN AN IMMUNOCOMPROMISED PATIENT

Marcanio S.[1], Colangeli L.[1], Arnò V.[1], Burelli G.[1], Sunseri S.[1], Nguena M.S.P.[1], Mosti A.L.[1], Starnino D.[1], Ruscitti C.[1], Zupo F.[1], Musumeci F.[1], Zamparelli C.[1], D'Adamo[2], Sbraccia[3]
[1]Dipartimento di Scienze Mediche, Università degli Studi di Roma Tor Vergata; [2]Monica; [3]Paolo

Introduction: Achromobacter xylosoxidans is a gram-negative, motile, flagellated, non-fermenting bacillus, positive for oxidase and catalase. Infections in humans typically occur asymptomatically, but in immunocompromised patients, they can cause pneumonia, urinary tract infections, gastrointestinal infections, device-related infections, otitis, and meningitis. (1) The first isolation of the bacterium was in a case of middle ear infection dating back to 1971. (2)
Case Description: A 41-year-old woman presented to the Emergency Department with asthenia, general malaise, vomiting, and diarrhea that had been occurring for about a month. In her medical history, she had undergone a kidney transplant in 2021 and was on triple immunosuppressive therapy (tacrolimus, mycophenolate mofetil, prednisone) with residual chronic renal insufficiency (under conservative treatment). She also had a nodular pulmonary lesion with partially cavitary appearance on radiological follow-up (noted since 2021), and a recent paucisymptomatic SARS-CoV-2 infection. Additionally, in the past month, she had been hospitalized for transplant rejection treated with high-dose steroid therapy and complicated by cytomegalovirus (CMV) reactivation, for which she received antiviral therapy and continued with a prophylactic regimen at home. Upon admission, her blood tests revealed acute renal failure, likely caused by dehydration induced by diarrhea, requiring urgent hemodialysis sessions with progressive improvement of her clinical condition. As the diarrhea persisted, stool culture was performed, including an extended search for Clostridium difficile toxin and CMV testing in plasma, urine, and feces, with only CMV PCR positivity detected in plasma (1345 IU/mL). Consequently, mycophenolate mofetil was discontinued, and the CMV therapy was modified. To investigate the nature of the previously known cavitary lesion, the patient underwent a Quantiferon test (negative result), sputum examination, and whole-body PET-CT, which did not reveal areas of tracer hypercaptation. During hospitalization, the patient experienced a worsening of her neurological condition with signs of meningeal irritation: worsening headache, nausea, vomiting, dizziness, nuchal rigidity, and low-grade fever, accompanied by increased inflammatory markers. In suspicion of meningitis, a lumbar puncture was performed, yielding opalescent cerebrospinal fluid characterized by marked neutrophilic pleocytosis, low glucose level, and elevated protein level. Empirical therapy with vancomycin, meropenem, and ambisome was immediately initiated. Achromobacter xylosoxidans was isolated from the cerebrospinal fluid sample, and the same bacterium was also found in the sputum culture. Based on the microbiological results, targeted antibiotic therapy was initiated, leading to a progressive resolution of the neurological symptoms. As her overall condition improved, the patient reported the onset of unilateral left-sided hearing loss in the days preceding the neurological symptoms. In light of this new symptom, further investigation was conducted using facial CT, which revealed a picture of left-sided otomastoiditis with endotympanic effusion. This additional diagnostic examination was crucial in identifying the infectious focus.
Conclusions: Although rare, literature reports cases of meningitis originating from middle ear infections caused by A. xylosoxidans in immunocompromised individuals, as well as cavitary lung lesions that need to be differentially diagnosed from tuberculosis and lung tumors (3). In the presented case, the patient exhibited both clinical pictures, presumably linked by a cause-effect relationship, which presents scenarios not yet described in the literature. Despite the emerging multidrug resistance of Achromobacter xylosoxidans, prompt antibiotic therapy based on aminoglycosides, sulfonamides, tetracyclines, or carbapenems is mandatory (4).
Bibliography
1. JMM Profile: Achromobacter xylosoxidans: the cloak-and-dagger opportunist This article is part of the JMM Profiles collection.
2. Schoch PE, Cunha BA. Nosocomial Achromobacter xylosoxidans infections. Infect Control Hosp Epidemiol. 1988 Feb;9(2):84-7. doi: 10.1086/645791. PMID: 3278052.
3. Yabuuchi E, Ohyama A. Achromobacter xylosoxidans n. sp. from human ear discharge. Jpn J Microbiol 1971; 15:477–481 [View Article]
4. Chan Hee Hwang, Woo Jin Kim, Sung Heon Song. Community-acquired acromobacter xylosoxidans infection presenting as a cavitary lung disease in an immunocompetent patient.
5. M.A.Kish, B.P. Buggy, B. A Forbes. Bacteremia caused by Achromobacter species in an immunocompromised host. 1984 jun 19 (6): 947-948

466. INTRA ARTICULAR INFECTION AND GENERALIZED SEPSIS FOLLOWING AN INTRAMUSCULAR INJECTION IN AN IMMUNOCOMPETENT HEALTHY INDIVIDUAL: A CASE REPORT

Bruggi F.
Dipartimento di Medicina Traslazionale, Scuola di Specializzazione in Medicina Interna presso Università degli Studi del Piemonte Orientale "Amedeo Avogadro"

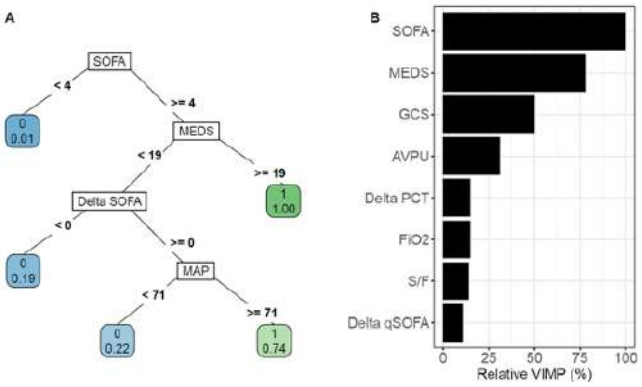
Introduction: Intramuscular injections can provoke local infectious complications, such as skin necrosis, abscesses, and intra-articular infections; these conditions can rarely progress to generalized sepsis, eventually leading to multi-organ failure.
These severe kinds of infections are more likely to occur in immunocompromised patients but have also been reported in immunocompetent people. The most common microorganism associated with IM-related infections is Staphylococcus aureus, and it usually requires appropriate medical and surgical treatment. In the literature, there are only a few cases of life-threatening generalized sepsis due to complications of IM injection, requiring aggressive treatment at the Intensive Care Unit (ICU).
Aim: In this report, we present a rare case of an immunocompetent patient who came to us in a critically ill condition, with multiple chambered abscesses and generalized sepsis caused by S. aureus, after an intramuscular injection in an uncommon site of puncture. We believe that prompt targeted antibiotic treatment, associated with surgical drainage, are both key elements to achieve optimal patient outcome.
Presentation: A 60-year-old Caucasian male in apparent good health was admitted to the Emergency Room (ER) with high fever for the last three days and a worsening dull pain in the left lower limb for about two weeks. Two months earlier, he had suffered from a low back acute pain, treated with intramuscular NSAIDs, with complete recovery.
He had no significant chronic conditions, did not take any medication on regular basis, and did not report having food or drug allergies. He had been fully vaccinated for SARS-CoV2.
Physical examination revealed that the patient's left lower limb was warmer than the contralateral, without skin discoloration, ecchymosis, or superficial hematomas and thigh palpation provoked severe local pain. Peripheral pulses were present and synchronous. Blood chemistry tests showed the presence of neutrophilic leukocytosis and increasing levels of inflammatory indexes. In addition, there was a pathological elevation of the D-dimer value. SARS-CoV2 test was negative for current infection.
Chest x-ray showed minor findings, while bone x-ray of lumbosacral spine, pelvis and left hip showed a left coxo-femoral joint space reduction, with left femur proximal epiphysis deformation. Based on these findings, the patient was subjected to contrast enhanced computed tomography (CECT) of the

chest, which excluded pulmonary embolism, and CT of the lower limbs, which did not show evident osteoarticular morpho-structural alterations. Finally, a left lower limb venous echo-color Doppler excluded deep vein thrombosis.
Outcame: Based on our soft-tissue-infection initial hypothesis, we focused on the patient's left lower limb and performed a targeted joint ultrasound examination, which showed subcutaneous adipose lobules' interstitial edema, with little epicondylar effusion in the left knee. We thus collected blood cultures and started empiric intravenous antibiotic therapy. After detection of methicillin-sensitive S. aureus on blood cultures, we switched to intravenous targeted antibiotic therapy.
By the middle of the fourteen-day of his antibiotic course, the inflammatory indexes were still high, and the clinical response had not been as brilliant as we would have expected, with resurgence of the fever and persistent pain in the patient left thigh. Having repeated multiple negative blood cultures, we requested an MRI of the hip and left thigh, which showed us the presence of multiple chambered abscesses around the coxo-femoral joint, with diffuse spongy bone edema and involvement of all the abductor compartment muscles. Based on these radiological findings, we enhanced antibiotic therapy and requested trans-thoracic and trans-esophageal echocardiography, which ruled out the endocarditis hypothesis.
Considering the difficulties, reported by our Interventional Radiologist consultant, in draining the numerous chambered abscesses with a single percutaneous maneuver, we contacted the Infectious Diseases Department of the S. Andrea Hospital in Vercelli, at the forefront in bone infections management and treatment, to propose the patient for surgical remediation, which was quickly organized and was carried out without any issue. Subsequently, we continued the antibiotic therapy until the inflammation indexes normalized (i.e., for three weeks after surgery) and then the patient was transferred to an affiliated Rehabilitation facility, aiming for adequate motor recovery.
Conclusions: Even minor medical interventions, such as intramuscular injections, can trigger aggressive and complicated infections that in some cases can be life-threatening. When a patient contracts a serious infection, it is extremely helpful to isolate the offending pathogen to devise the most appropriate antibiotic therapy quickly. Well-timed surgical intervention, with abscess drainage, is crucial to achieve the most effective healing process. In some cases, as ours, the rapid administration of the targeted antibiotic therapy can prevent the patient from clinical deterioration and helps reduce further complications risk.

467. COMPARING DIFFERENT STATISTICAL MODELS AND MACHINE-LEARNING ALGORITHMS TO IDENTIFY THE PREDICTORS ASSOCIATED WITH RISK OF DEATH OR ADMISSION TO INTENSIVE CARE UNIT IN INTERNAL MEDICINE PATIENTS WITH SEPSIS

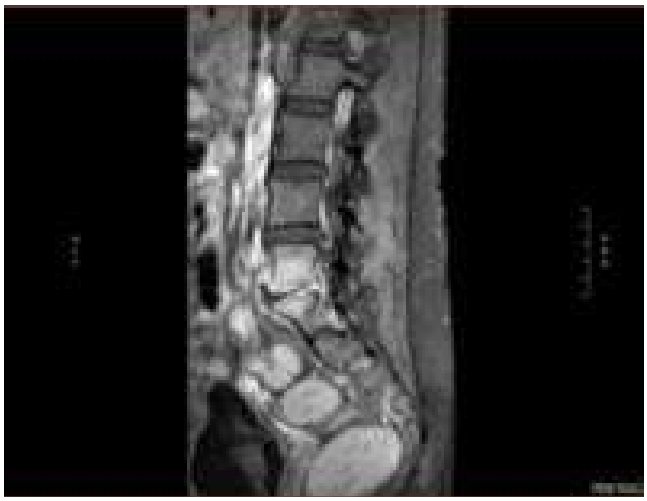
Mirijello A.[1], Fontana A.[2], Greco A.P.[1], Tosoni A. [3], D'Agruma A.[1], Pacilli G.[1], Labonia M.[4], Copetti M.[2], D'Errico M.M.[1], Piscitelli P.[1], De Cosmo S.[1], The Internal Medicine Sepsis Study Group[1]
[1]Department of Medical Sciences, Fondazione IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, FG, Italy; [2]Unit of Biostatistics, Fondazione IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, FG, Italy; [3]Department of Internal Medicine and Gastroenterology, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Rome, Italy; [4]Unit of Microbiology, Fondazione IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, FG, Italy

Background: According to Sepsis-3 Consensus, sepsis is "a life-threatening organ dysfunction caused by a dysregulated host response to infection, and septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to increase mortality". Despite a global decline in its incidence and mortality, sepsis still represents one of the main causes of health loss worldwide. Sepsis is a time-dependent disease: the early recognition of patients at risk for poor outcome is mandatory.
Aim: To identify prognostic predictors of the risk of death or admission to Intensive Care Unit in a consecutive sample of septic patients, comparing different statistical models and machine-learning algorithms.
Methods: Retrospective study including 148 patients discharged from an Italian Internal Medicine Unit with a diagnosis of sepsis/septic shock and microbiological identification.
Results: Thirty-seven (25.0%) patients reached the composite outcome. The Sequential Organ Failure Assessment (SOFA) score at admission (Odds Ratio (OR): 1.83; 95% Confidence Interval (CI): 1.41-2.39; p<0.001), delta-SOFA (OR: 1.64; 95%CI: 1.28-2.10; p<0.001) and the Alert, Verbal, Pain, Unresponsive (AVPU) status (OR: 5.96; 95%CI: 2.13-16.67; p<0.001) were identified through the multivariable logistic model as independent predictors of the composite outcome. The Area Under the receiver operating characteristic Curve (AUC) was 0.894; 95%CI: 0.840-0.948.
In addition, different statistical models and machine-learning algorithms identified further predictive variables: delta-quick-SOFA, delta-Procalcitonin, Mortality in Emergency Department Sepsis, mean arterial pressure and Glasgow Coma Scale. The Cross-validated multivariable logistic model with the Least Absolute Shrinkage and Selection Operator (LASSO) penalty identified 5 predictors; and Recursive PArtitioning and Regression Tree (RPART) identified 4 predictors with higher AUC (0.915 and 0.917, respectively); the Random Forest (RF) approach including all evaluated variables obtained the highest AUC (0.978). All models resulted well-calibrated.
Conclusions: Although structurally different, each model identified similar predictive covariates. The classical multivariable logistic regression model was the most parsimonious and calibrated one, while RPART was the easiest to interpret clinically. Finally, LASSO and RF were the most costly in terms of number of variables identified.



468. A 44 YEAR OLD WOMEN WITH SPONDYLODISCITIS, HIGH LODE EXCERCISE AND INFECTION OF COVID 19

Cabrera J.S.[1], Castro D.[1], Poddighe A.[1], Fadda V.[2], Flore G.[1], Pileri P.[1], G. Mula[1], A. Monni[1], A. Delitala[1]
[1]Patologia Medica, AOU Sassari; [2]Radiologia, AOU Sassari



A 44 year old women with spondylodiscitis, high lode excercise and infection of COVID 19.
A 44 year old women was evaluated in our Hospital because of fever and lower back pain. Approximately one year before the admission, the patient lost 17 kg of body weight through extreme physical activity and dieting. She therefore complained severe acne. Two weeks before the admission, the patient had a SARs COV2 infection, treated with steroids. Fourteen days after negativized nasal swab, the patient had fever and progressive lower back pain. At the admission the CT scan revealed the presence of multiple septic emboli in the lungs. The patient denied using intravenous drugs. Echocardiogram

was negative for endocarditis. The MR of the column was suggestive for spondylodiscitis and has revealed the presence of an abscess in the psoas muscle. Blood culture as well colture of specimen of the abcess were positive for Methicillin Sensitive *Staphylococcus Aureus*, and specific antibiotic was started. The psoas muscle abscess has been drained. A CT scan performed 20 days after the beginning of the treatment revealed the reduction of lung abscesses. In this patient spontaneous spondylodiscitis occurred as a complication of vertebral alteration caused by sport overload, immunosuppression caused by infection by COVID 19, and its treatment. This scenario created a susceptibility to infection by *Staphylococus Aureus* which probably spread into the blood by the sever acne of the skin, which was secondary to hormonal change of weight loss.

469. ERDHEIM-CHESTER DISEASE AND MACROPHAGE ACTIVATION SYNDROME CAUSED BY LEISHMANIASIS IN THE SAME PATIENT: WHEN IT RAINS, IT POURS!

Pacinella, G.[1], Miceli, S.[1], Daidone, M.[1], Del Cuore, A.[1], Puleo, M.G.[1], Norrito, R.L.[1], Cataldi, M.[1], Todaro, F.[1], Riolo, R.[1], Napolitano,C.[2], Scaglione, S.[1], Di Chiara, T.[1], Florena, A.M.[2], Tuttolomondo, A.[1]
[1]U.O.C. di Medicina Interna con Stroke Care, Dipartimento di Promozione della Salute, Materno Infantile, Medicina Interna e Specialistica di Eccellenza "G. D'Alessandro" (PROMISE), University of Palermo, Piazza delle Cliniche n.2, 90127 Palermo, Italy; [2]Dipartimento di Patologia Umana, University of Palermo, Palermo, Italy

This clinical case represents an element of both scientific and clinical interest as it addresses the problem of differential diagnosis between diseases with similar aspects against the background of a rare syndrome, Erdheim-Chester disease (ECD): there are no cases in the literature of macrophage activation syndrome (MAS) triggered by visceral leishmaniasis in patients with the above-mentioned disease, and it was complex to recognise the infectious cause of MAS as the more probable hypothesis of a progression of the underlying pathology loomed in the background. Erdheim-Chester disease is a rare form of non-Langerhans histiocytosis with systemic clinical manifestations: skeletal involvement, with bilateral osteosclerotic lesions of the long bones, and cardiovascular involvement, with a thickening of the aorta or a right atrial pseudotumour, which is one of the most iconic features of ECD. In addition, characteristic clinical features are retroperitoneal manifestations (with perirenal fat infiltration or retroperitoneal fibrosis in many cases complicated by bilateral hydronephrosis), skin lesions (xanthelasma-like lesions occurring in 25-30% of patients), neurological disorders (seizures, headaches, cognitive impairment) and endocrinological diseases (such as diabetes insipidus). The patient in question, a 67-year-old man living in a rural area, went to the Emergency Department of the Policlinico di Palermo for fever, pancytopenia, altered liver enzymes and increased indices of inflammation; on the echocardiogram, he also presented a mass in the right atrium and at the atrioventricular junction suspected, at least initially, of endocarditis. At the Cardiology Department, where the patient was admitted immediately after admission to the hospital, serial blood cultures were requested, and empirical antibiotic therapy was introduced for infective endocarditis; due to the negativity of the culture tests, the persistence of the above-mentioned symptoms and the absence of benefit despite the antibiotic therapy administered, the patient was transferred to our U. O. C. where, for the first time, he was treated with antibiotics. O.C. where, due to the findings of hypertriglyceridaemia, hypofibrinogenemia, peripheral cytopenia, splenomegaly and persistence of fever for more than two weeks, a diagnosis of macrophage activation syndrome was made. Although, at first, it seemed obvious to consider MAS an extrinsic manifestation of the basic disease, a more thorough evaluation revealed a detail that reopened the differential diagnostic reasoning, making it possible to go beyond the most plausible hypothesis, thus refuting it: serum protein electrophoresis revealed hypogammaglobulinemia, which, together with the anamnestic data of residence.

470. DIFFERENTIAL PROFILES OF BACTEREMIA IN EMERGENCY AND MEDICINE DEPARTMENTS: PRELIMINARY DATA FROM A MULTIPURPOSE HOSPITAL REGISTRY

Manganaro G.[1], Soggetti C.[1], Cavallo L.[1], Carletti S.[2], Damanti S.[3], Scotti R.[4], Zaccagnini G.[4], Donatoni M.[1], Peracino R.[1], Ciocca L.[1], Secci M.[4], Bozzolo E.P.[4], Ramirez G.A.[5], Rovere- Querini P.[6], Tresoldi M.[7]
[1]Unit of General Medicine and Advanced Care,IRCSS Ospedale San Raffaele, Milan, Italy. Università Vita-salute San Raffaele, Milan, Italy; [2]Unit of Microbiology, IRCSS Ospedala San Raffaele, Milan, Italy; [3]Unit of General Medicine and Advanced Care,IRCSS Ospedale San Raffaele, Milan, Italy. Università Vita-salute San Raffaele, Milan, Italy. Unit of Specialities and Healthcare Continuity IRCCS Ospedale San Raffaele, Milan, Italy. ; [4]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy; [5]Unit of General Medicine and Advanced. Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS Ospedale San Raffaele, Milan, Italy Care, IRCCS Ospedale San Raffaele, Milan, Italy. Università Vita-Salute San Raffaele, Milan, Italy. ; [6]Università Vita-Salute San Raffaele, Milan, Italy. Unit of Medical Specialties and Healthcare Continuity IRCCS Ospedale San Raffaele, Milan, Italy .; [7]of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy

Background: obtaining blood cultures in patients with suspected bloodstream infection is crucial, since bacteremia is associated with higher 30-day mortality and early start of appropriate antibiotic treatment is essential to reduce mortality. Emergency (ED) and Medicine Departments (MED) differ in logistical and practice features. Therefore, we aimed to investigate whether blood cultures may have different results and management in these two settings.
Material and methods: we recorded demographics and clinical features of patients admitted to ED and MED of our Institution from November 2022 to April 2023 and recruited in a prospective observational registry (MedCli protocol).This evidence was integrated with the results of blood cultures collected during hospitalization and subsequent antibiotic treatments. The primary aim was to compare pathogens isolated in ED and in MED. Secondary aims were to evaluate potential differential rates of nosocomial infections, antibiotic susceptibility and therapeutic strategies among patients being tested in the two clinical settings. We classified antibiotics in three categories (first, second and third line) according to the ordinary clinical practice of our hospital (Table 1). Here, we present preliminary data extracted from the registry, expressed as median (interquartile range) unless otherwise specified.
Results. We analyzed 45 positive blood cultures collected from 39 patients. Nineteen blood cultures were obtained in ED from 16 different patients and 26 in MED from 23 patients. Clinical and demographic characteristics of the patients on admission were similar in the two groups, except for gender (38% male in ED vs 78% in MED; p=0.010). There were no significant differences between ED and MED in terms of age (76 (69–81) years in ED vs 76 (70–81) years in MED), vital signs on admission and comorbidity burden as per the Charlson's Comorbidity Index [CCI= 7 (6–8) in ED vs 6 (4–8) in MED; p=0.464]. Escherichia coli (E.coli) was the most frequently isolated microorganism in ED. By contrast, a significantly lower prevalence of E. Coli was found in MED (23% vs 7%; p=0.038). Conversely, Staphylococcus species were the most common in MED and were significantly less represented in ED (44% vs 15%; p=0.011), with Staphylococcus aureus representing 50% of all Staphylococci. Hospital-acquired infections accounted for 50% of positive blood cultures in MED vs 12% of ED cases (p=0.018). Multi-drug resistance (MDR) was numerically more frequent in MED than in ED (52% vs 31%; p=0.119). More than one microorganism was isolated in 6/19 blood cultures from ED vs 1/26 from MED (p=0.011). Antimicrobial strategies were similar in the two groups. 9/19 ED cases and 16/26 MED cases received multidrug treatments (p=0.345). Microbiological data were not associated with differential survival curves.
Conclusions. Preliminary data from a prospective registry show a higher prevalence of Staphylococcal and MDR isolates from blood cultures drawn in MED, suggesting a prominent role of devices and other factors related to hospitalization in this setting. Indications to blood cultures in ED were more frequent in women and microbiological isolates in ED showed a higher prevalence of E. coli and polymicrobial flora, possibly suggesting earlier presentation of signs of community-acquired infections in women, maybe due sex-based imbalances in intensity of the inflammatory response. Detecting distinct microbiological profiles among distinct clinical settings might inform empiric antimicrobial treatments. However, microbiological divergence between isolates in ED and MED did not correspond to different

antimicrobial strategies, possibly suggesting similar clinical severity between infected ED and MED patients, independent on the etiological agent. Although similarity in CCI scores between the groups corroborate this hypothesis, further studies are needed to confirm our results and exclude potential biases due to diverging practice standards between distinct clinical environments.

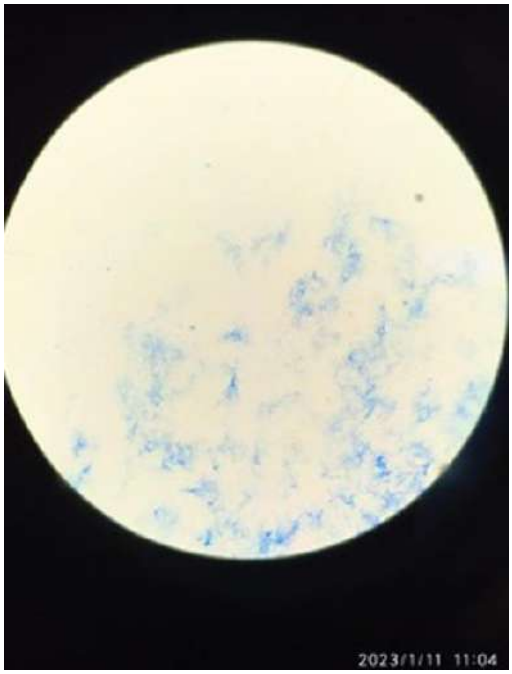
Table 1

First Line	Second Line	Third Line
Amoxicillin	Piperacillin-tazobactam	Ceftazidime-avibactam
Oxacillin	Daptomycin	Meropenem
Ceftriaxone	Linezolid	Cefiderocol
Azithromycin	Teicoplanin	Fidaxomicin
Clarithromycin	Ganciclovir	Tigecyclin
Ciprofloxacin	Voriconazole	Anidulafungin
Levofloxacin		Caspofungin
Trimethoprim-sulphamethoxazole		
Fosfomycin		
Nitrofurantoin		
Doxycyclin		
Vancomycin		
Clindamycin		
Fluconazole		
Aciclovir		

471. TB OR NOT TB: A STRANGE CASE OF ARTHRITIS IN A SLE PATIENT

Filippini E.[1], Santangeli R.[1], Gamba L.[1], Montozzi G.[1], Cocco C.[1], Manfredi L.[2], Festa A.[2], Prof. Moroncini G.[3]
[1]Scuola di Specializzazione in Medicina Interna, Università Politecnica delle Marche, Ancona, Italia; [2]Clinica Medica, Dipartimento di Medicina Interna, Azienda Ospedaliero Universitaria delle Marche, Ancona, Italia; [3]Clinica Medica, Dipartimento di Medicina Interna, Azienda Ospedaliero Universitaria delle Marche, Ancona, Italia; Scuola di Specializzazione in Medicina Interna, Università Politecnica delle Marche, Ancona, Italia

Background: Tuberculosis (TB) is a serious multiorgan infectious disease caused by the bacterium Mycobacterium tuberculosis.
TB arthritis, also known as osteoarticular tuberculosis, is a rare (less than 1% of all TB cases) form of extrapulmonary TB that affects joints, bones, and surrounding tissues, presenting with non-specific symptoms such as joint pain, swelling, and stiffness, which can mimic other rheumatologic conditions. It can cause significant morbidity and disability if not promptly diagnosed and treated. We present a clinical case of a 48-year-old Caribbean female affected by Systemic Lupus Erythematosus (SLE) with a TB arthritis involving the ankle joint.
Case presentation: We describe the clinical case of a 48-year-old Caribbean female with complaints of left ankle pain, swelling and difficulty to walk from one month. Patient is affected from three years by systemic lupus erythematosus with cutaneous, hematologic, serositis, and renal involvement, treated with hydroxychloroquine and corticosteroid before with high dose an actually with a low dose for a better disease control.
On physical examination, patient referred tenderness over the left ankle joint with limited range of motion and signs of synovitis. Laboratory investigations revealed slight increase of C-reactive protein (CRP), without leukocytosis and other inflammatory markers elevation.
For the arthritis, she performed a magnetic resonance of the ankle with evidence of erosive synovitis with areas of synovial thickening and marked regional bone edema.
According to the rheumatological condition of the patient, the first hypothesis was an arthritis related to the systemic lupus but we also performed an infectious diagnostic workup for the monoarthritis, with positivity of interferon gamma release assay. We decided to perform an ankle joint biopsy with coltural samples with evidence of Mycobacterium tuberculosis, so we confirmed a diagnosis of TB arthritis. No evidence of pulmonary TB was revealed after chest CT scan.
An anti-tubercular therapy with isoniazid, rifampicin, pyrazinamide was started in association to SLE treatment with low-dose prednisone and hydroxychloroquine.
Patient presented a significant clinical improvement and she was able to walk without assistance after six weeks of treatment without evidence of relapse.
Conclusion: This clinical case highlights the diagnostic and therapeutic challenges of TB arthritis, a rare form of extrapulmonary TB that can affect the joints, bones, and surrounding tissues.
TB arthritis should be considered in the differential diagnosis of articular involvement, particularly in patients with a history of TB exposure or systemic diseases such as SLE in prolonged immunosuppressive treatment.
Early diagnosis and prompt initiation of specific treatment are crucial to prevent morbidity and disability. This case report emphasizes the importance of a high degree of suspicion for TB arthritis in patients with compatible symptoms and clinical history and the need for multidisciplinary collaboration among clinicians and laboratory to achieve a successful outcome.



472. REZAFUNGIN TREATMENT OF CANDIDEMIA AND INVASIVE CANDIDIASIS: OUTCOMES STRATIFIED BY BASELINE RENAL FUNCTION – ANALYSIS OF THE PHASE 2 + PHASE 3 TRIALS

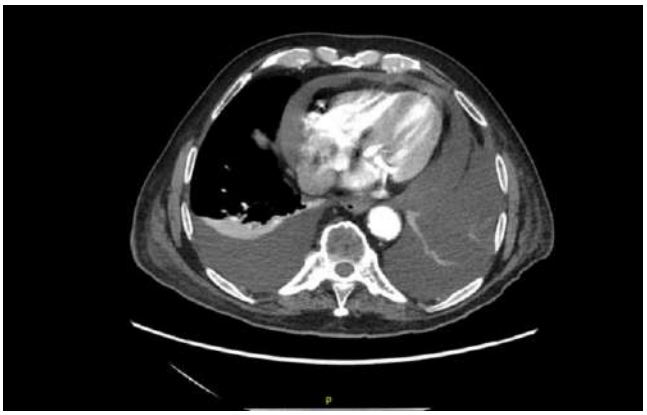
Sandison T.[1], Vazquez J.A.[2], Honore P.M.[3], Soriano A.[4], Horcajada J.P.[5], Slavin M.[6], Merelli M.[7]
[1]Cidara Therapeutics, Inc., San Diego, CA, USA; [2]Augusta Univ, Augusta, GA, USA; [3]Brugman Univ Hospital, Brussels, Belgium; [4]Hospital Clínic, CIBERINFEC, Univ. of Barcelona; Barcelona, Spain; [5]Hospital Del Mar-IMIM, CIBERINFEC, Barcelona, Spain; [6]Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, Australia; [7]Clinica di Malattie Infettive, Udine

Background: Rezafungin (RZF) once weekly (QWk) is a next-generation echinocandin in development for treatment of candidemia and invasive candidiasis (IC) and prevention of invasive fungal disease caused by *Candida*, *Aspergillus*, and *Pneumocystis* spp. in BMT. RZF QWk was compared to caspofungin (CAS) QD in two double-blind, randomized, controlled trials of treatment of candidemia and/or IC: STRIVE (Phase 2, NCT02734862) and ReSTORE (NCT03667690).
Aim: Trial data (Phase 2+Phase 3) were analyzed to evaluate outcomes stratified by renal function at baseline: CrCl ≥60 mL/min (normal/mild impairment [Norm/Mild]) and <60 mL/min (moderate/severe impairment [Mod/Sev]).
Methods: Outcomes were evaluated for differences between CrCl categories and between treatment groups: RZF QWk 400mg on Wk 1 then 200 mg vs CAS QD 70 mg on Day (D)1 then 50mg, for ≥14 days (≤4 Wks) w/optional oral fluconazole stepdown for CAS.
Conclusions: RZF efficacy was comparable across CrCl categories, with higher ME and lower D30 ACM in Mod/Sev group. Further analyses are needed to evaluate the observed differences between treatment groups.

473. HEMATURIA AND RECURRENT PLEURAL-PERICARDIAL EFFUSIONS: WHERE IS THE LINK?

Passaro G., Giorgi A. , Celi M. , Caporuscio S. , Lovello M.C., Imperoli G.
UOC Medicina Interna - P.O. "San Filippo Neri"

A 79-year-old male suffering from hypertension, glaucoma and benign prostatic hypertrophy was admitted because of fatigue with pericardial and pleural effusions. Seven months before, after paucisymptomatic SARS-CoV-2 infection, he was hospitalized for macroscopic hematuria and evidence of pleuropericardial effusion. During hospitalization it was carried out evacuative thoracentesis bud no etiological diagnosis was made and empirical therapy with colchicine was started. It was performed transurethral resection of bullous/papilliform areas of the bladder neck (histological examination "nephrogenic adenoma"). The patient was discharged with an indication of periodic echocardiographic controls. Despite the ongoing therapy, after a few months, because of fatigue and worsening of dyspnea, he was sent to the emergency department. At admission baseline investigations revealed plentiful bilateral pleural effusion with atelectasis of the lower lobes and large pericardial effusion (3 cm) (image 1). PCR and NT-proBNP were normal. A new evacuative thoracentesis was performed with drainage of 1500 cc citrine liquid. It was a transudative effusion, neoplastic cells and acid-fast bacilli were not identified, aerobic and PCR for Mycobacterium tuberculosis, bacterioscopic examination and Mycobacterial culture resulted negative.
Total-body CT scan, upper and lower gastrointestinal tract endoscopy, autoimmunity panel and tumors markers were negative.
For anemia with recurrent macroscopic hematuria cystoclysis was started and the patients' needs for blood transfusion and intravenous iron therapy. No urological abnormalities were detected by ultrasound and computed tomography (CT) imaging of the urinary tract.
He denied any previous exposure to Tuberculosis but the Quantiferon TB-Gold test was positive.
Before performing a new cystoscopic evaluation, a search for mycobacterium was carried out in urine. Bacterioscopic examination of urine, in 3 out of 4 samples, revealed the presence mycobacteria.
Patient was sent to further investigation at National Institute for Infectious Diseases and a specific antimycobacterial therapy was started with improvement of symptoms.
High clinical suspicion is necessary to identify extrapulmonary forms of Tuberculosis because the diagnosis can be elusive.
Bibliography: Golden, M. P., & Vikram, H. R. (2005). Extrapulmonary tuberculosis: an overview. *American family physician*, *72*(9), 1761-1768.



474. A CASE OF LIFE-THREATENING SEPSIS CAUSED BY CAPNOCYTOPHAGA CANIMORSUS, THE "DOG BITE BACTERIUM"

Vai F.[1], Bertolino G.[2], Giangreco A.[1], Lo Bello A.[1], Rifaldi F. [1], Malomo G.[3], Asperges E.[4], Capra Marzani F.[5], Di Sabatino A.[2]
[1]Dipartimento di Medicina Interna e Terapia Medica, Università di Pavia, Pavia; [2]UOC Medicina Generale 1, Fondazione IRCCS Policlinico San Matteo, Pavia; [3]Dipartimento di Scienze del Sistema Nervoso e del Comportamento, Università di Pavia, Pavia; [4]UOC Malattie Infettive, Fondazione IRCCS Policlinico San Matteo, Pavia; [5]UOC Anestesia e Rianimazione 1, Fondazione IRCCS Policlinico San Matteo, Pavia

Introduction: *Capnocytophaga canimorsus* is a Gram-negative bacillus commonly isolated as a commensal bacterium in the normal oral flora of domestic animals such as dogs and cats. As a consequence of the animal biting, scratching or licking it could be responsible for adverse events like sepsis and septic shock, in some cases with an extremely rapid and potentially fatal evolution. A small number of cases have been described worldwide and the majority was about immunocompromised patients. The main predisposing factors include hyposplenism, a previous splenectomy, alcoholism and the use of corticosteroids. However, in 40% of cases the infection occurs in subjects without clear risk factors and it has sometimes been fatal.
Case Report: A 54-year-old man accessed the Emergency Room following the onset of fever with chills, hypotension, vomiting, diarrhoea and syncopation. These signs and symptoms emerged about 10 days after being scratched on the right ear by his own dog. Patient's medical history was unremarkable, except for a significant smoking habit, and he wasn't taking any medications. Vital signs and blood tests (*see Fig.1*) were suggestive of septic shock complicated by multi-organ failure (MOF) and disseminated intravascular coagulation (DIC). In fact, the clinical examination allowed to identify some petechial lesions attributable to the severe thrombocytopenia and a purpuric lesion with a necrotic evolution on the right side of the nose (*see Fig. 2*). The patient was immediately transferred to the Intensive Care Unit (ICU) where oxygen therapy, broad-spectrum empiric antibiotic therapy (Piperacillin/Tazobactam and Azithromycin), intravenous hydration, amine infusion and steroid therapy were started. Moreover, due to the concomitant bleeding diathesis, a unit of fresh frozen plasma (FFP) and a pool of platelets were transfused. Blood cultures were positive for *C. canimorsus*, while urine culture was negative. Following the clinical improvement and the stabilization of the haemodynamic parameters, the patient was transferred to the Internal Medicine Department. During hospitalization the most important causes of acquired immunodeficiency and major comorbidities were excluded; in detail, infectious causes (for example HIV-1 and 2) and main neoplastic causes have been ruled out. In addition, a condition of hyposplenism/asplenism was excluded by abdomen US and by studying the percentage of circulating Pitted Red Cells (PRC). Furthermore, other prominent causes of primary immunodeficiency were excluded (i.e. IgA deficiency and CVID – Common Variable Immunodeficiency). The gradual improvement of the clinical conditions allowed the suspension of the parenteral therapies and the de-escalation of the antibiotic therapy by starting Amoxicillin/Clavulanic Acid after an appropriate consultation with the infectious disease specialist. In conclusion, it seems possible to state that the bacterium *C. canimorsus* can lead to extremely serious septic events even in healthy adults. Based on the results of published case reports, these events can cause death within hours of symptoms onset and purpura may have a primary role in causing death. In fact, in the described case, it's possible that the favorable prognosis is partly linked to the presence of a non-fulminant purpura. Furthermore, it's also possible that smoking plays a negative role as an altering factor of a normal and balanced immune function. Finally, it emerges the effectiveness of the use of Piperacillin/Tazobactam as a first-line antibiotic therapy in order to obtain a significant clinical and biohumoral improvement.

Haemoglobin (g/dl)	12,5	INR	2,44
WBC (10^3/uL)	24,1	BNP (pg/ml)	1246
Neutrophils (%)	94	Albumin (g/dl)	2,9
PLT (10^3/uL)	14	Amylase (U/L)	360
RCP (mg/dl)	34,54	Lipase (U/L)	453
Procalcitonin (ng/ml)	67	Creatinine (mg/dl)	3,43
Total bilirubin (mg/dl)	2,2	ALT (U/L)	149

Fig. 1

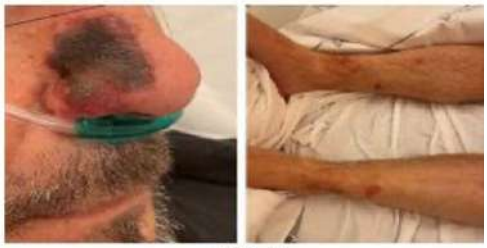


Fig. 2

475. RITIRATO

476. TIME IS LIFE: CARBAPENEM-RESISTANT ENTEROBACREALES OR CLOSTRIDIUM DIFFICILE OR BOTH?

Solaro E., Verrillo D., Schettino M., Schiavo L., , Tibullo L.
Internal Medicine Ward, Sant' Anna and San Sebastiano Hospital, Caserta

Background: Sepsis is a constantly increasing health emergency, with a fatal outcome if not diagnosed early and treated promptly. An emergency is closely linked to two other problems of great importance: multi-resistance and hospital infections.
In December 2022, Mr B. A., 52 years old, came to our observation, going to the Emergency Room for profuse diarrhoea that had arisen a few days ago. In recent history, colorectal cancer surgery was subsequently treated with chemotherapy (last cycle on December 20), complicated by metastases of the right ileo-psoas muscle and right ureteral stenosis for which nephrostomy had been positioned. Upon entering the ward patient was soporous, awake unable with a painful stimulus (GCS 9), pale, and suffering. Dry skin and mucous membranes. Hypo-tachysphygmic peripheral wrists. Blood pressure 90/60 mmHg, heart rate 105 bpm, rhythmic, peripheral oxygen saturation in ambient air 97% in aa. Apyretic.
Total diuresis, from nephrostomy and bladder catheter placed in the emergency room, about 100 ccs of hyperchromic urine. Objectively treatable abdomen diffusely painful on deep palpation in the absence of signs of peritonism, valid peristalsis, tympanic. At heart, rhythmic tachycardia tones. To the chest, nothing relevant. Blood chemistry revealed pancytopenia with severe neutropenia (450 neutrophils/mm3), consistent with recent chemotherapy, renal impairment and electrolyte changes consistent with profuse diarrhoea (creatinine 5 mg/dl, urea 101 mg/dl; Na 159 mEq/L; K 5.9 mEq/L), high inflammation indices, at the ECG sinus tachycardia. Blood gas analysis showed a mixed disorder (metabolic alkalosis and metabolic acidosis with a high anion gap). The patient was isolated and promptly initiated medical therapy with growth factors (filgrastim and epoetin zeta) and intravenous hydration. Samples were collected and sent to the laboratory for blood cultures, urine cultures, detection of Clostridium difficile in the faeces, chemical-physical, cultural and parasitological examination of faeces, Vidal-Wright test, and viral panel. The microbiology laboratory communicated the positivity of the Clostridium Difficile search in the stool and, after a few hours, the positivity of the screening for carbapenemase. Therapy with oral vancomycin (125 mg 4 times daily) and intravenous ceftazidime/avibactam (0.75 g/0.1875 g every 12 hours, GFR-corrected dosage) were initiated simultaneously and empirically. The subsequent results of blood culture and urine (Klebsiella pneumoniae KPC) and related antibiograms confirmed the goodness of the therapeutic choice. In the following days, there was a progressive improvement of the clinical picture, with a resolution of diarrhoea, a clear improvement of the sensory, resumption of an adequate volume of daily diuresis and progressive improvement of renal function and hydroelectrolyte alterations.
Conclusions: Carbapenem-resistant enterobacreales are bacteria that can cause serious infections in humans due to high levels of resistance to antibiotics, particularly carbapenems, a class of broad-spectrum antibiotics considered last-line therapy. Risk factors associated with these infections include antibiotic use in the previous three months, malignancies, immunodepression, indwelling urinary or venous catheters, poor functional status, severe illness, and residence in a long-term care facility.

477. SURVEILLANCE AND CONTROL OF CARBAPENEM-RESISTANT ENTEROBACTERIA (CRE) INFECTIONS IN THE INTERNAL MEDICINE DEPARTMENT

Tibullo L.[1], Solaro E.[1], Coscia Ma.[1], Fazio V.[1], Sommese A.[1], Verrillo D.[1], Italiano G.[1], Schettino M.[1], Schiavo L.[1], Vinciguerra A.[1], Greco R.[2]
[1]Internal Medicine Ward, Sant' Anna and San Sebastiano Hospital, Caserta;
[2]Microbiology unit, Sant' Anna and San Sebastiano Hospital, Caserta

Background: The excessive and often inappropriate use of antibiotics in both human and veterinary settings has led to the spread of strains of antibiotic-resistant bacteria, reducing the effectiveness of these drugs over time. Many bacteria have developed resistance to different antibiotics over time, sometimes becoming resistant to multiple antibiotics simultaneously (multi-drug resistant or MDR). Treatment options for MDR bacteria are limited, and consequently, the risk of serious complications or deaths from previously treatable infections is increased. Therefore, AMR represents a serious global public health problem with a strong clinical and economic impact and has been defined by the World Health Organization (WHO) as one of the priority challenges for health systems. One of the most impactful problems in terms of AMR in our country is represented by the emergence of carbapenem-resistant Enterobacteria (CRE). Enterobacteria, such as E. coli and K. pneumoniae, are Gram-negative bacteria normally found in the human gut microbiota. However, in particular conditions, they can cause infections, mainly of the respiratory system (pneumonia), the urinary system, intra-abdominal infections, the surgical wound and the bloodstream, especially in hospitals. The emergence of CRE strains is a relevant clinical problem since carbapenems are currently the antibiotics of first choice for treating invasive Gram-negative Enterobacteria infections already resistant to other antibiotics. CRE epidemiology appears highest in Greece, Italy, Romania, Cyprus, Bulgaria and Malta.
Materials and Methods: Hospitalized in our Unit of Internal Medicine, patients at risk for colonization or infection by CRE (such as older adults from assisted healthcare facilities, dialysis patients, patients with frequent contacts with healthcare facilities, such as those undergoing dialysis or anti-cancer chemotherapy in the previous 12 months, or in any case immunosuppressed) we carried out active surveillance of CRE colonization with rectal swabs for CRE between September 2022 and April 2023 at the UOC of Internal Medicine. Surveillance swabs were carried out at the entrance to the ward and every seven days during the entire hospital stay.
Results: A total of 251 rectal swabs for CRE Enterobacteria were performed from October to December 2022 with a total of 24 positive swabs (equal to 9.6%); from January to April 2023, we carried out 341 rectal swabs with 54 positivity for CRE (equal to 15.8%). A possible positivity on CRE microbiological samples was also sought, with only one positive sample found in the four months of January-April 2023, while, in 2022, 20 positive microbiological samples were found. In the case of positivity, the prevention and control measures for CRE infections were envisaged at the company, and the ministerial level was activated, with contact isolation.
Discussion: Active surveillance of CRE colonization in hospitals is of fundamental importance; it is an essential tool in controlling CRE infections, not only during epidemic outbreaks but also as a routine measure. CRE surveillance is cost-effective, even in healthcare settings such as internal medicine, and makes healthcare safer. Indeed, it is useful to define the local epidemiology of these pathogens and implement the appropriate isolation of infected and colonized patients, contact precautions and other necessary measures.
Conclusions: The positivity of CRE infections is high in the internal medicine ward. The correct surveillance reduces the lenght of stay, mortality rate incidence and legal costs in case of quarrels. Furthermore, this kind of surveillance has a high cost.

478. LEISHMANIA: AN EARLY DIAGNOSIS

Tibullo L. [1], Fazio V. [1], Sommese A.[1], Verrillo D.[1], Coscia Ma[1], Solaro E.[1], Dormiente I.[2], Franzese M.[2], Giugliano Mp[2], Petrazzuolo D.[2], Ricciardi D.[2]
[1]Internal Medicine Ward, Sant' Anna and San Sebastiano Hospital, Caserta;
[2]Geriatric ward, Luigi Vanvitelli University of Campania, Caserta

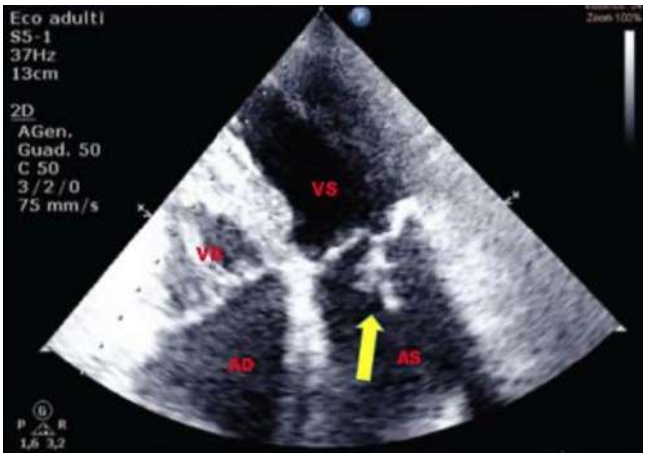
Introduction: Leishmania is an infectious disease of parasitological origin due to the protozoans of Leishmania generis, a parasitological agent intracellular of the reticuloendothelial system in men and domestic animals. It is a zoonotic infectious disease, very diffused and, in some cases, may represent a real-world emergency. The government provided a national surveillance plan in Italy to check and monitor dog leishmania. There is a specific surveillance plan in some Italian regions such as Emilia Romagna, Marche, Lazio, Campania and Calabria.
Background: A male patient, 50 years old, went to the emergency room for weakness, poor endurance and intermittent fever. He referred a tick bite two months before. The physicians performed routine laboratory exames, infectious disease consultations, chest X-rays and abdomen ultrasounds with evidence of the increased liver and spleen size. The patient's laboratory exames showed anti-toxoplasma Immunoglobulin G and cytomegalovirus antibodies. The patient was admitted to the internal medicine ward.
Case Report: During the ward admission, the patient presented intermittent fever and weakness. The physicians performed cultural exames, quantizer tests, HIV tests, Widal Wright, and chest tomography, and all these exames resulted negative.

The procalcitonin was increased, as well as C reactive Protein and VES. Pancytopenia (WBC: 3400, RBC 3.950.000, PLT 123.000) and hypergammaglobulinemia. The laboratory exames also evidenced a monoclonal component IG G Kappa with increased Beta 2 microglobulin(3.6 mg/dl). Positivity for Rickettia antibodies Ig G and Ig M. The physicians made a possible diagnosis of Leishmania disease, and a screening test for the antibodies of Leishmania was performed. The bone marrow biopsy showed macrophagic elements with cytoplasm stuffed with Leishmania. Treatment with amphotericin B was begun.
Conclusions: Leishmania is a rare disease that may also present after two months of tick bite. Correct anamnesis should always be done about tick bites, especially in some Italian regions where the government provides surveillance. The diagnosis of Leishmania provided a specific therapy.

479. THE MILK PITFALL: ENDOCARDITIS BY EQUI STREPTOCOCCUS

Antonini C.[1], Pellone M.[1], Cicconi F.[1], Bassino E.M.[1], Ferretti M.[1], Luzi E.[1], Andreoni R.[1], Caltabiano L.[1], Alfonsi A.[1], Di Donato C.[1], Delle Monache F.[2]
[1]Università degli Studi dell'Aquila, UOC Medicina Interna, PO Teramo;
[2]UOC Medicina Interna, PO Teramo

Infective endocarditis (IE) is a disease of high clinical and social impact, with approximately 43,000 cases per year in the United States and with significant in-hospital mortality of 15 to 20 percent. Endocarditis is inflammation of the endocardium and heart valves. In most cases, this condition is caused by infection: the most common etiologic agents are: Staphylococcus aureus; viridans group streptococci, coagulase-negative staphylococci and group C streptococci, to the latter group belongs Streptococcus equi sub. Zooepidemicus pathogen frequently found in veterinary settings while rarely causing infection in humans. Risk factors for infective endocarditis include: dental procedures, skin lesions, intravenous drug use, contaminated needle use, artificial and/or damaged heart valves.
Objectives: Description of a single case of Streptococcus equi endocarditis in a patient with recent dairy intake.
Clinical Case: A 60-year-old patient comes to our observation for hyperpyrexia associated with shaking chills. On admission patient was eupnoic in room air, vital parameters normal, MV normotransmitted, finding of systolic murmur on mitral focus. Remote pathological history: hypertension, thalassemic trait, anxiety- depressive disorder, gallbladder lithiasis, hypovisus. Proximate pathological history: no reported risk factors for endocarditis. Blood tests showed, only, neutrophilic leukocytosis increased indices of inflammation (C-reactive protein and Procalcitonin). Empiric antibiotic therapy was started with meropenem and linezolid. Later Linezolid was suspended for thrombocytopenia. The blood cultures was positive for Streptococcus Equi. A review of the literature revealed the transmissibility of the bacterium through ingestion of raw milkor contact with infected horses or pigs; in addition, The SIESP (Servizio di igiene, Epidemiologia e sanità Pubblica) in Pescara with the Istituto Zooprofilattico di Teramo decribed, to December 2021 from May 2022, 36 cases of human infection with S. Equi, in the suburbs of the Pescara city, sampling raw milk cheese farms. At a second interview, the patient reported that she was a habitual consumer of raw milk foodsproduced by the farm accused. She underwent to cardiac echocolordopplergraphy that showed: moderate left ventricular hypertrophy with ejection fraction 60%, moderate mitral insufficiency with gross calcification of the posterior mitralic flap, also confirmed by a transesophageal echocardiotomy. During her hospitalization, she underwent to ophthalmologic examination which placed an indication for left retinal detachment surgery for ocular embolization, likely septic emboli. Vitreal cultures was positive for Streptococcus Equi. After about 6 weeks of antibiotic therapy, there was a clinical and laboratory improvement so the patient was discharged, with oral antibiotic therapy for an additional 30 days with a follow-up transesophageal echocardiogram.
Conclusions: Streptococcus Equi sub. Zooepidemicus is a bacterium belonging to the group C betahemolytic streptococci. It is a commensal and opportunistic pathogen that infects various animals while it has rarely been isolated in humans. In literature there are anecdotal cases of infection with meningeal involvement, pneumonia, pericarditis, rheumatic fever, and local infections such as arthritis and local abscess. Infective endocarditis is suspected in the presence of prolonged fever of an indeterminate nature with the detection of heart murmurs, not caused by prior valvular defects. These signs coupled with increased indices of inflammation: PCR, procalcitonin, and leukocytosis may raise the suspicion of infective endocarditis. The most useful elements for diagnosis are blood culture collection and cardiac echocolordopplergraphy.



480. VISCERAL LEISHMANIASIS: AN ENDEMIC AND POTENTIALLY LIFE-THREATENING DISEASE OF THE MEDITERRANEAN REGION

Calzavara E.[1], Lombardi R.[2], Muti Shuenemann G.E.U.[3], Marsicano R.M.[4], Serafino S.[4], Bandera A.[5], Fracanzani A.L.[6]
[1]SC Medicina ad Indirizzo Metabolico, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy; [2]1. SC Medicina ad Indirizzo Metabolico, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy; Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Milan, Italy; [3]SC Medicina ad Indirizzo Metabolico, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy; 2. Department of Health research methods, Evidence and Impact, McMaster University, Hamilton ON Canada; [4]SC Medicina ad Indirizzo Metabolico, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy; [5]SC Malattie Infettive, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy; 2. Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Milan, Italy; [6]SC Medicina ad Indirizzo Metabolico, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy; Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Milan, Italy

Case Report: A 41-year-old woman was admitted to the Emergency department (ER) because of fever up to 41°C lasting for 2 weeks. She denied cough, dysuria, diarrhea, or abdominal pain, as well as travels abroad, risky food intake, promiscuous sexual intercourse or recent contact with animals.
In her past medical history, she had skin lupus erythematous and morphea (ANA positive).
At the ER, her vitals and physical examination were normal except for rhythmic tachycardia (102 bpm) and presence of petechiae on legs, neck and back of the hands without mucocutaneous bleeding.
Blood tests showed pancytopenia (Hb 10,4 g/dL; GB 2120/microL; PLT 43.000/microL), increased CRP (13.4 mg/dL), elevated liver enzymes (AST 86 U/L; ALT 53 U/L) and LDH (658 U/L). Coagulation tests were normal. A chest-X Ray was negative, as well as antigenic test for Sars-Cov2, influenza virus and respiratory syncytial virus. The patient was then admitted to our ward of Internal Medicine.
During hospitalization she remained hemodynamically stable but persistently pyretic (with fever up to 40°C). Microbiological investigations resulted all negative, including serial blood and urinary cultures, HIV1/2, HCV, HBV, Mycoplasma pneumoniae and Borrelia burgdorferi serology, molecular research for EBV, CMV, VZV and Parvovirus. Interferon-gamma release was undetermined.
The autoimmune screening showed only the known ANA positivity (speckled pattern, titre 1/160) and positivity of IgM anticardiolipin antibodies (Ab). Conversely, IgG anticardiolipin Ab, IgG and IgM anti-beta2 glycoprotein I Ab, anti-dsDNA Ab, ENA and ANCA were negative. Therefore, antithrombotic prophylaxis with subcutaneous fondaparinux 2,5 mg/die was initiated.
Since the patient had persistent fever with worsening of peripheral blood cytopenia (Hb 8,5 g/dL, PLT 44.000/microL, absolute neutrophil count 770/mi-

croL), along with slightly elevated triglycerides (239 mg/dL) and elevated serum levels of ferritin (5968 mcg/dL), performed as routinary assessment during hospitalization, the suspicion of hemophagocytic lymphohistiocytosis (HLH) arouse. Thus, the patient underwent a bone marrow biopsy, which confirmed the diagnosis of HLH and, in agreement with the immunologist, a high-dose intravenous steroid therapy with methylprednisolone 1 g/die was started. A total body CT scan revealed only hepatosplenomegaly without evidence of lymphadenopathies.
As for the aetiology of the HLH, an autoimmune or neoplastic genesis of the syndrome became unlikely, as well as the most common infections. The suspect of an involvement of uncommon pathogens became prominent and was then confirmed by a positive PCR testing for Leishmania donovani/infantum, firstly on the bone marrow tissue and secondly on peripheral blood. After a re-investigation of the patient's history, we discovered that she used to spend her summers in Romagna, an Italian region in which Leishmania is currently endemic.
After the diagnosis, a 5-days initial induction therapy with liposomal amphotericin B was administered and the infusion of the drug was repeated on the tenth, seventeenth and twenty-third day. Contextually, steroidal therapy was then tapered, and a 4-days intravenous infusion of high-dose Immunoglobulin added.
However, as no sign of improvement, neither clinical nor biochemical, was observed over the days, off-label intravenous Anakinra was also introduced with consequent apyrexia and resolution of cytopenia. Negativity of the PCR test for Leishmania donovani/infantum on peripheral blood was also observed, as well as of the antiphospholipid antibody tests, so antithrombotic prophylaxis was stopped.
As the clinical scenario improved, the immunomodulatory therapy was gradually de-escalated.
The patient was, then, discharged with a close infectivologist follow-up and a therapy with oral prednisone 50 mg/die, subcutaneous anakinra 100 mg 1 fl/die and liposomal amphotericin B intravenous infusion on day 30th and 37th from the diagnosis of VL as outpatient.
Discussion: Visceral leishmaniasis is a potentially fatal disease, caused by Leishmania donovani and L. infantum, transmitted by phlebotomine sandflies which reservoir are often dogs. Commonly the infection presents with malaise, fever, weight loss, hepatosplenomegaly, pancytopenia and elevated liver enzymes, but rarely it associates with potentially fatal diseases as disseminated intravascular coagulation (DIC) and hemophagocytic lymphohistiocytosis (HLH), as in our case. Indeed, since it is currently endemic in the Mediterranean area, it should be considered in many diagnostic pathways, especially in case of fever from unknown origin, mainly if associated to blood cytopenia and/or elevated liver enzymes or in the presence of HLH or CID. Diagnosis should be confirmed by direct demonstration of Leishmania or PCR tests in tissue specimens or cultures, or by serologic testing. First-line therapy is constituted by liposomal amphotericin B.

481. RETROPERITONEAL FIBROSIS AS MANIFESTATION OF EXTRAPULMONARY TUBERCULOSIS: A CASE REPORT

Gamba L.[1], Paladini A.[2], Sordillo R.[2], Cocco C.[2], Cozzi M.F.[2], Manfredi L.[3], Moroncini G. [3]
[1]Scuola di specializzazione in Medicina Interna, Università Politecnica delle Marche, Ancona; [2]Scuola di specializzazione in Medicina Interna, Università Politecnica delle Marche, Ancona, Italy ; [3]Clinica Medica, Dipartimento di Medicina Interna, AOUM, Ancona, Italy

Background: Retroperitoneal fibrosis (RPF) is an uncommon disease, characterized by the replacement of normal retroperitoneal tissue with fibrosis and/or chronic inflammation. Sometimes retroperitoneal fibrosis occurs in the context of a "chronic periaortitis", characterized by inflammation and formation of fibrotic tissue surrounding the aorta and iliac arteries. The presenting signs and symptoms are non-specific; systemic manifestations, often associated with local symptoms, such as lumbar and/or abdominal pain, are usually found to be related to the entrapment of retroperitoneal structures. In two thirds of the cases retroperitoneal fibrosis is idiopathic (IRF), whereas in the remaining ones it is secondary/associated to cancer, infections, drugs, autoimmune disease and vasculitis. Differential diagnoses play a central role as the different causes require specific interventions and because an apparently idiopathic case of RPF may hide underlying infections or neoplasms with potential a rapid evolution and a poor prognosis in the short term.
Objectives: We wanted to describe a case of extrapulmonary tuberculosis manifested with periaortitis associated with retroperitoneal fibrosis.
Methods: A 54-year-old man of African ethnicity presented to the emergency department due to right lumbar pain, asthenia and pain in the pelvic girdle. No pathology in his past medical history.
On physical examination, abdomen was soft and non-tender with no palpable lymph nodes. Laboratory tests revealed slight increase of inflammation markers (VES 21 mm/h, PCR 2.4 mg/dl) and a polyclonal hypergammaglobulinaemia. Blood count and liver and renal function test were in range.
An abdomen ultrasound showed right grade II hydroureteronephrosis which was investigated by contrast-enhanced abdominal CT scan that revealed the presence of solid amorphous tissue around the infrarenal aorta, some abdominal lymphadenopathy and dilatation of the right urinary tract with thickening of the ureter's walls. Considering the ureteral thickening, a negative urinary cytological examination was performed for the presence of atypical cells.
In order to evaluate large vessel vasculitis, we required autoimmune serology that was negative and a contrast-enhanced chest CT scan which showed thickening of the ascending aortic wall and pericoronary cuff hyperdensity. A CT-PET confirmed a hypermetabolism of the periaortic retroperitoneal tissue. Therefore, the clinical and radiological picture were suggestive for periaortitis associated with retroperitoneal fibrosis.
The immunoglobulin G4-related disease was ruled out by normal serum IgG subclasses and for an infectious etiology we did the infectious disease screening including syphilis' serological tests (TPHA and VDRL) with negative results and a positive Quantiferon test. Given the thickening of the ureteral wall, we performed a microscopic examination of and PCR urine test that resulted negative for mycobacteria. At the time of patient hospital discharge, the urine culture for mycobacteria was awaiting reporting. Given the difficulty in taking a biopsy of retroperitoneal tissue due to deep location and proximity to the great abdominal vessels, the clinical picture was interpreted as RPF and intravenous steroid therapy with methylprednisolone 0.5 mg/kg was started, after initiating prophylaxis for tuberculosis with isoniazid (300 mg/day).There was therefore an improvement in the pain symptoms and we discharged the patient in therapy with prednisone 25 mg/die introducing methotrexate (15 mg/day) as a steroid-sparing therapy.
Results: A mouth after hospital discharge, we got urine culture result that was positive for Mycobacterium avium.
So in the light of the final diagnosis of retroperitoneal fibrosis secondary to tuberculous infection we immediately suspended the methotrexate and rapidly reduced the steroid therapy, entrusting the continuation of treatment to infectious disease specialist.
Conclusion: We report a case of RPF expression of extrapulmonary tuberculosis with clinical presentation and typical CT scan findings that could be suggestive for idiopathic retroperitoneal fibrosis.
RPF as a complication of tuberculosis has rarely been reported in scientific literature. However, the patient's ethnicity and the finding of ureteral wall thickening led to suspicion of a possible underlying tuberculosis infection without pulmonary manifestations. The correct etiological classification of the retroperitoneal fibrosis made it possible to avoid immunosuppressive therapy which could have exacerbated the tuberculous infection.
So with this case report we want to highlight the importance of a careful search for potential causes of RPF, even when it is apparently idiopathic, and a tuberculous infection should come to mind whenever dealing with an unknown mass or unusual pathology in the developing world.

482. ENCRUSTED UROPATHY BY CORYNEBACTERIUM UREALYTICUM, AN UNDERDIAGNOSED DISEASE

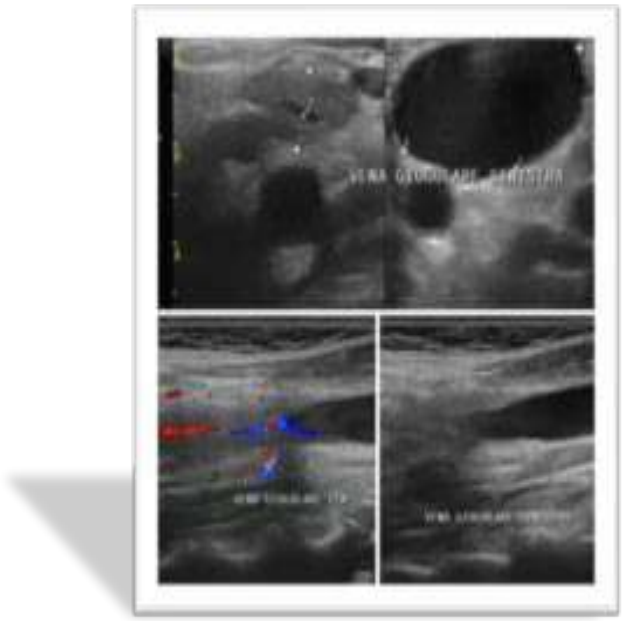
Santomenna F[1], Lombardi R.[2], Muti Schuenemann G.[3], Maira D.[4], Fracanzani A.L[5]
[1]SC Medicina -Indirizzo Metabolico, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy. Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Milan, italy ; [2]SC Medicina -Indirizzo Metabolico, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy. Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Milan, italy ; [3]SC Medicina -Indirizzo Metabolico, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy. 3. Department of Health Reasearch Methods, Evidence and Impact, McMaster università, Hamilton ON Canada; [4]1. SC Medicina -Indirizzo Metabolico, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy; [5]SC Medicina -Indirizzo Metabolico, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy . Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Milan, Italy

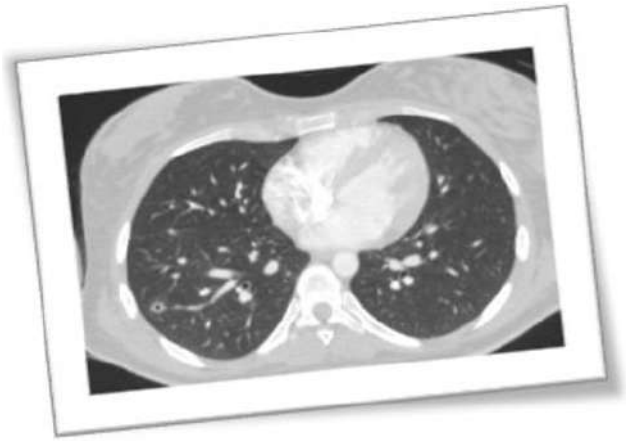
Case report: A 73-year-old male was admitted to our ward of Internal Medicine for persistent haematuria and dysuria (three episode) in the past 12 months, requiring periodic catheterizations. In his past medical history, he had atrial fibrillation in therapy with direct oral anticoagulants (DOACs) and chronic kidney disease (CKD, creatinine 1.5 mg/dL) with a solitary functioning kidney and a double-J stent in the right kidney for ureteral stenosis. At the emergency department physical examination was unremarkable and blood tests were all normal except for a normocytic anemia (Hb 10 g/dL), an increase in creatinine up to 5 mg/dl, an increase in CRP (2.34 mg/dL) and in white blood cell count (11.83 10e9/L). A strip test detected urinary leukocytes, nitrites and blood, thus being suggestive for urinary infection, not confirmed by a urine culture. Nevertheless, also because of the rise in inflammatory markers, antibiotic therapy with ceftriaxone was empirically started. In addition, a urinary catheter was placed without continuous bladder lavage due to minimum haematuria and anticoagulation was preventively stopped.
The patient was then admitted to our ward of Internal Medicine where a progressive worsening of the haematuria was noticed over the days, so continuous bladder lavages were introduced. An abdominal non-enhanced CT scan demonstrated grade 2 hydronephrosis in the right kidney with calcium deposits in the renal pelvis, possibly causing an obstruction of the stent. Therefore, the right ureteral stent was substituted and coltures of urine samples retrieved during the procedure resulted positive for Corynebacterium urealyticum. In addition, the urinary sediment revealed struvite crystals with a urine pH of 8. According to the infectivologist consultation, antibiotic therapy was then shifted from ceftriaxone to teicoplanin and acidification of urine, in order to prevent the formation of struvite crystals, was obtained with methionine and cranberry supplements. After the procedure, a control CT scan demonstrated a reduction in the hydronephrosis despite persistent parietal calcifications in the right pyelocaliceal cavities and a reduction in serum creatinine levels back to the basal values was observed. In addition, during the hospitalization, also the hematuria resolved so anticoagulation was reintroduced. Long-term antibiotic therapy was continued in a subacute facility as the patient was discharged after 30 days of hospitalization.
Conclusion: We present a case of encrusted uropathy, a rare subacute to chronic inflammatory disorder caused by the infection with urease-producing bacteria, mainly Corynebacterium urealyticum. The disorder is characterized by urothelial deposition of struvite and carbonated apatite, resulting in encrustations and ulcerating necrotic inflammation of the urothelium and surrounding tissues, possibily causing haematuria. Conventional urine cultures are usually negative as these bacteria require selective culture media and prolonged cultural incubation period, so that the disease remains often underdiagnosed. Nevertheless, a high urinary pH and presence of urine struvite crystals should raise suspicion, especially in subjects with risk factors, as previous hospitalizations and antibiotic treatments, as well as urologic procedures associated with mucosal breach or frequent ureteral catheterizations. Non-enhanced CT-scan is the gold standard diagnostic tool and prognosis is dependent on timely diagnosis and correct treatment, which comprises urological removal of encrustations, if possible, in combination with urinary acidification and long-term antibiotic treatment, as in our patient.

483. ONCE IN A BLUE MOON

Pellone M.[1], Antonini C.[1], Bassino E. M.[1], Cicconi F.[1], Alfonsi A.[1], Andreoni R. [1], Caltabiano L.[1], Ferretti M.[1], Luzi E.[1], Di Donato C.[1], Delle Monache F. [2], Vertolli P. [2]
[1]Università degli studi dell'Aquila; [2]UOC Medicina Interna PO Teramo

Lemierre's syndrome has been shown to be increasing in incidence in the past 20 years with one popular suggesting that said rise occurred from less aggressive antibacterial coverage. Lemierre's syndrome is characterized by pharyngotonsillitis or peritonsillar abscess and developed neck swelling and tenderness secondary to septic thrombophlebitis of the internal jugular vein, metastatic abscesses (mainly to the brain and lungs, but also to the kindneys or jonts) and anaerobic septicemia. Most cases involve young healthy patient. Lemierre's syndrome can be life threatening if it is not promptly recognized and treated adequately. Bacteraemia in Lemierre's can be polymicrobial, with Fusobacterium necrophorum reported in 90% of the cases.
Case Report: A 25-year-old female presented to ED with a 15 days history of severe sore throat, odynophagia and flu-like symptoms, myalgias, weakness, and fever. She denied any recent dental procedures, sick contacts, recent travel, or IV drug use. Her physical exam at hospital admission revealed tachycardic patient, pale skin, normal blood pression and temperature 39,5° C, erythematous posterior pharynx with no exudates, dry mucous membranes, and positive lymphadenopathy of lateral cervical lymph nodes. Her chest was clear to auscultation and percussion bilaterally with no tenderness of the chest wall. Exam of her skin did not show any Janeway lesions, Osler nodes or splinter hemorrhages. A complete blood count showed significant leukocytosis with WBC 12.600, hemoglobin 10.3 g/dL, and platelets 880,000. She was found to have normal kidney function, liver function was found to be abnormal with ALT 296 IU/L, AST 309 IU/L and CPR was 450 mg/L and PCT 7,87 ng/mL. She was found to have Ab-EBV IgM > 160 U/mL so it was made diagnosis of infectious mononucleosis. Chest x-ray which showed no acute cardiopulmonary process. The blood culture was positive for fusobacterium necrophorum. Echocardiogram showed normal left ventricular ejection fraction at approximately 70%, no clots, masses or vegetations were visualized. After a week of antibiotic therapy, she developed pain with tenderness in the left side of the neck so a doppler ultrasonography of the neck was performed and showed thrombophlebitis of internal left jugular vein and normal vertebral flow bilaterally. A CT-angiogram of the chest with and without contrast showed multiple small cavitary lung masses, suggestive of septic emboli and thrombophlebitis of internal left jugular vein. She was placed on IV metronidazole and IV meropenem for 3 weeks. Also was practiced anticoagulant therapy with fondaparinux for 3 months. Our patient did meet the usual diagnostic criteria for Lemierre's syndrome, which includes positive blood cultures, radiological evidence of internal jugular venous thrombophlebitis and an oropharyngeal infection which progressed to sepsis and developed septic emboli growing fusobacterium necrophorum, a microbe that is part of normal oropharyngeal flora and closely associated with past cases of Lemierre's. After 3 months a doppler ultrasonography of the neck showed a complete resolution of thrombophlebitis.





484. WATER AND SOIL: RECIPE FOR AN ATYPICAL ENDOCARDITIS

Tricarico E.[1], Bertolino L. [1], Gallo R. [1], Scarpulla N.[1], Patauner F. [1], Durante Mangoni E. [2]
[1]Dipartimento di Scienze Mediche e Chirugiche Avanzate; [2]Dipartimento di Medicina di Precisione

Past medical history: We describe the case of a 49-year-old man, who was admitted to the ER due to a hypertensive crisis and underwent transthoracic echocardiography showing native mitral valve vegetation and valve regurgitation.He was a Chief Engineer in a ship company, with possible exposure to contaminated water. He also did gardening with bare hands. Past medical history was significant for recent onset arterial hypertension, mitral valve regurgitation (with posterior leaflet prolapse) and bicuspid aortic valve (type 1) with regurgitation, known for ten years and under regular follow-up. It also included benign prostate hyperplasia, high-risk sexual behaviors, frequent balanitis and prostatitis treated at home with antibiotics, GERD and anxiety. The patient was afebrile, but reported episodes of night sweats. C-reactive protein and blood counts were normal at the time of admission. However, he had taken cotrimoxazole at home for a few days after urology consultation for acute prostatitis.
Diagnostic and therapeutic approach: During hospitalization, several blood cultures were performed, also during fever, resulting all negative, after appropriate antibiotic wash-out. Transesophageal echocardiography confirmed the presence of a vegetation (16x7 mm) on the mitral valve ring, severe mitral regurgitation due to valve prolapse, aortic valve stenosis and severe regurgitation. Screening for blood culture negative infective endocarditis (IE) ruled out atypical etiologies, such as Bartonella, Coxiella, Brucella. Considering both the possible diagnosis of IE (echocardiographic evidence + predisposing heart condition) and the indication for urgent cardiac surgery, empirical antimicrobial therapy with Ampicillin/Sulbactam 3gr QID and Gentamicin 240 mg/die was started and aortic and mitral valve replacement with mechanical prostheses was performed. Valve culture grew *Sphingomonas paucimobilis*, confirming the diagnosis of infective endocarditis (according to ESC 2015 criteria - positive valve culture implies a diagnosis of definite IE). The post-surgical echocardiography showed mild aortic and mild to moderate mitral regurgitation due periprosthetic leak. The patient underwent four weeks of targeted antibiotic intravenous therapy with Piperacillin/Tazobactam 4.5 gr QID and Fosfomycin 4 gr QID.He was then discharged home on partial oral treatment with Cefixime 400 mg BID for two more weeks and appropriate anticoagulant therapy.
Follow-up: the patient was discharged home in good clinical conditions. He remained asymptomatic during follow-up with normal inflammatory biomarkers and stable echocardiographic findings.
Discussion: *S. paucimobilis* is an aerobic, glucose non-fermenting, Gram-negative bacillus widely distributed in the natural environment, such as soil and water. It forms biofilm in water piping, and it has been identified in ultrapure water in industrial and laboratory systems too. It is not considered to be a major pathogen and its virulence is thought to be low.[1] Many infections caused by this bacterium are nosocomial and are associated with indwelling medical devices, such as catheters and central venous lines, usually in patients with significant comorbidities.[2] *S. paucimobilis* infections are not common, but the number of cases reported is increasing. A recent Australian retrospective study collected a large number of infections caused by this bacterium (involving soft tissue, abdomen, urinary tract, lung), of which 77% were community acquired and mostly involved young male adults with few comorbidities. [3]However, in literature, only four cases of *S. paucimobilis* endocarditis have been reported. One of these, described in an American case report, is a 47-year-old male patient with no comorbidities, supervisor for a refrigeration plant, affected by *S. paucimobilis* endocarditis with a large vegetation [2] that required valve replacement, similar to our patient. In cases with an atypical clinical presentation, echocardiography and valve cultures remain of utmost importance for diagnosis and management of patients with IE and in our case these findings led to the identification and correct treatment of this atypical microorganism. Whether the work exposure to possible contaminated water, the contact with soil during gardening or the high-risk sexual behaviors and frequent balanitis may have played a role remains unclear.
Bibliography
[1] M.P. Ryan; C.C.Adley. *Sphingomonas paucimobilis: a persistent Gram-negative nosocomial infectious organism, 2010*[2] Rognrud K.; Diaz A.; Hill C.; Kershaw M. *Bacterial Endocarditis Caused by Sphingomonas paucimobilis: A Case Report and Literature Review. Case Reports in Infectious Diseases, 2020.*[3] Laupland K.B., Paterson D.L., Stewart A.G, Edwards F., Harris P.N.A *Sphingomonas paucimobilis bloodstream infection is a predominantly community-onset disease with significant lethality, 2022*[4] Jiun-Nong Lin et al. *Sphingomonas paucimobilis Bacteremia in Humans: 16 Case Reports and a Literature Review, 2010*

485. AN ATYPICAL DIAGNOSIS FOR ABDOMINAL PAIN

Galliano R., Dupuis A., Ruocco I., Sasia G., Posillico F., Bracco C., Magnino C., Brignone C., Raviolo A., Fenoglio L. M.
Division of Internal Medicine, Department of Medicine, Santa Croce e Carle Hospital, Cuneo, Italy

A 55-year-old patient was admitted to the Emergency Room of "Santa Croce e Carle" general teaching Hospital for diarrhea, intense abdominal pain and fever. There was nothing to report in his past medical history. At the first evaluation, the patient had fever, while the other vital signs were normal. Physical examination revealed abdominal tenderness, with no signs of peritonism. Lung examination showed crackles in the right mid-basal area. Initial laboratory tests showed normal blood count, with markedly increased C-reactive protein (CRP, 163 mg/L), procalcitonin (PCT, 64 ng/mL), alanine-aminotransferase (ALT, 1654 UI/L) and aspartate-aminotransferase (AST, 4294 UI/L). Blood gas analysis revealed mild type 1 respiratory failure. Chest X-ray showed a right mid-basal interstitial thickening, while the abdominal ultrasound was normal. The patient was then admitted to our Internal Medicine department. After carrying out blood and stool culture, antibiotic therapy with Piperacillin/Tazobactam was started. A high-resolution chest CT scan was then requested, which confirmed the extensive thickening with a ground-glass appearance of the right lung. Given the negativity of the culture tests and the slow clinical improvement, the patient underwent a Bronchoalveolar Lavage (BAL), which made it possible to identify the etiological agent responsible for the clinical picture in Chlamydia Psittaci. The patient, questioned again, informed us that he had had four parrots for less than a month, two of which died a few days before hospitalization. The antibiotic therapy with Piperacillin/Tazobactam was therefore replaced with Doxycycline, with a rapid clinical improvement; there was a total regression of diarrhea and abdominal pain and an improvement of laboratory tests, with a clear decrease in inflammation indices and almost normalization of hepatic cytolysis indices. The patient was then discharged home in excellent general condition, asymptomatic and with normal vital signs.
Psittacosis is a disease caused by Chlamydia Psittaci and it is usually spread by inhaling dust from dried droppings from birdcages or by handling infected birds in slaughterhouses. Clinically, the disease presents with the sudden onset of fever, myalgias and headache. 80% of patients present with respiratory symptoms, such as dry cough, dyspnea and more rarely chest pain and hemoptysis. Diarrhea is present in about 25% of patients and it may be the main symptom. Hemolytic anemia, icteric hepatitis, encephalitis and endocarditis are the least frequent symptoms. On physical examination splenomegaly and hepatomegaly can be detected in about 10% of cases. Laboratory tests rarely show neutrophilic leukocytosis, while C-reactive protein and procalcitonin are often greatly increased. In half of patients requiring hospitalization, cytolysis indices are increased, especially AST. Other laboratory findings are hyponatremia and an increase in creatinine. Currently, serology is the most used diagnostic tool, as the culture test is performed only in specialized laboratories. Polymerase chain reaction for the detection of bacterial DNA is a very sensitive tool; the best material to search for is bronchoalveolar lavage, which appears to be better than blood and sputum. The treatment of choice for psittacosis involves the use of tetracyclines (e.g. Doxycycline 100 mg orally twice daily) or macrolides.
We have reported this clinical case to underline how some rare infectious diseases to which we attribute only respiratory symptoms may have an atypical presentation. We also want to highlight how the search for the DNA of the pathogen through bronchoalveolar lavage has been decisive in our clinical case, but at the same time how a thorough medical history could have already helped us in the differential diagnosis.

486. ESOPHAGEAL PERFORATION AS UNUSUAL PRESENTATION OF DISSEMINATED TUBERCULOSIS

Ruocco I.[1], Bracco C. [2], Magnino C.[2], Brignone C.[2], Silvestri A.[2], Fenoglio L.[2]
[1]Dipartimento di Medicina, Università degli studi di Torino; [2]Dipartimento di Medicina Interna, Ospedale S.Croce e Carle, Cuneo

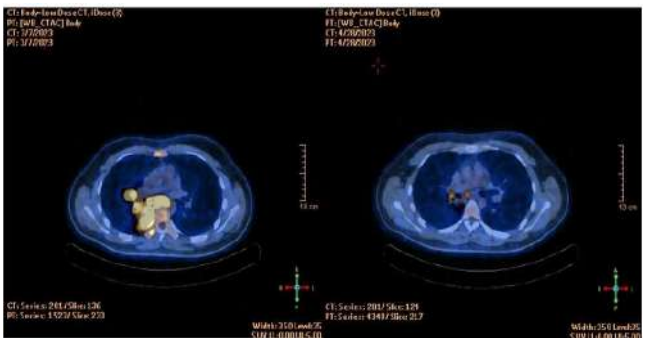
Background: Tuberculosis (TB) affects 10.6 million people worldwide. The WHO Global Tuberculosis Report estimates 4.1 million deaths in 2021 [1].

TB was the leading cause of death from a single infectious agent worldwide, until the Covid-19 pandemic. Italy is a low-prevalence country with about 4000 new infections per year and an incidence rate of 3.8/100.000 inhabitants in 2020; about 66% of cases are diagnosed in immigrant people. TB is a multisystemic disease, but gastrointestinal tract is an uncommon extrapulmonary site. Esophageal TB is rare, even in endemic countries, accounting for 0.2-0.1% of tuberculosis cases of the gastrointestinal tract [2]. We present a rare case of esophageal perforation due to wall erosion from contiguous mediastinal adenopathies, in disseminated tuberculosis.

Case presentation: A 21-year-old man of Ecuadorian origin presented at the Emergency Department for intense retrosternal pain accompanied by hematemesis. He reported a weight loss of 10 Kg in the last 3 months with malaise, cough and nocturnal fever. Laboratory findings showed normal white blood and platelet count, mild anemia, normal renal and hepatic function and elevated C-reactive protein (152.2 mg/L). A nasogastric tube was placed, which revealed about 50 mL of bright red hematic fluid in the gastric cavity, then an urgent endoscopy was performed. He had a laceration and perforation of distal oesophagus, closed with six metallic clips. A thoracic and abdominal CT scan noted pneumonia of the inferior right lobe in addition to perigastric, peritracheal and mediastinal adenopathies. Sputum polymerase-chain reaction (PCR) analysis was positive for Mycobacterium tuberculosis complex, while the acid-fast bacilli (AFB) smear was negative. The Quantiferon-TB positive result confirmed these findings. Additional testing was negative for Human Immunodeficiency Virus infection. An FDG PET scan revealed disseminated tuberculosis, with thoracic and abdominal adenopathies and involvement of vertebrae, pelvis and skull base. Culture of sputum specimens isolated drug-sensitive M. tuberculosis. The patient remained hemodynamically stable through his hospital course. We administered initial quadruple anti-tubercular regimen with rifampicin, isoniazid, ethambutol and levofloxacine. Endovenous amikacin was added for the first 3 weeks of therapy. Repeated sputum specimen were negative for AFB smear and culture. At the 2-months follow-up PET scan and clinical monitoring revealed good response to antitubercular therapy (Fig.1), therefore we gave indication to continue only isoniazid and rifampicin for 4 months.

Discussion: We present a case of tubercular esophageal perforation successfully treated with conservative management. Esophageal involvement of TB usually results from direct spread from mediastinal or pulmonary localization. On the contrary, primary esophageal infection is rare due to several protective factors such as stratified squamosum epithelium, mucus, saliva and gravity. Endoscopic findings are eterogeneal: esophagitis, ulcerations, strictures, fistulas and perforation. Scarring and retraction associated with mediastinal tuberculosis can manifest as traction diverticula [2]. The middle third of esophagus is the segment most frequently involved, probably due to proximity to the lymph-rich subcarinal region. Reported symptoms of esophageal TB are dysphagia, odynophagia, retrosternal pain as well as the systemic manifestations of TB (weight loss, malaise and productive cough). True perforation can be a life-threatening condition due to complications such as mediastinitis or tracheoesophageal fistula. Diagnosis of tuberculous involvement of esophagus is established by PCR or observation of AFB on endoscopic biopsies; histology can show caseous granulomas of the submucosa [2]. The treatment of esophageal TB is usually medical, according to the standard 6-months protocol (rifampicin, isoniazid, ethambutol, and pyrazinamide for 2 months, followed by only rifampicin and isoniazid for 4 months). However, optimal duration is not established. The outcome is generally favourable [3]. In our case, positive results of PCR assay and sputum smear microscopy in a disseminated disease was diagnostic and an antitubercular therapy was immediately given with success.

Conclusion: In summary, esophageal perforation caused by tuberculosis is rare. It results from contiguous mediastinal disease, usually in multisystemic TB. It requires prompt initiation of antitubercular medications, but it can be treated nonoperatively.



487. THE CAVERN OF PANDORA: SOMETIMES EVEN THE EVIDENCE CAN BE QUESTIONED

Scuderi P.[1], Agrelli L.[1], Di Giacomo I.[1], Vitale P.[1], Sottolano A.[1], Caturano M.[2], Guida A.[2], Triggiani M.[2]
[1]Università degli Studi di Salerno; [2]A.O.U. San Giovanni e Ruggi D'Aragona

Polyneuropathy is a clinical manifestation of different neurological, metebolic, hematological, infectious disorders; investigating them completely unexpected causes and concomitant factors can emerge.

A young moroccan woman, aged 35, living in Italy for 3 years, presented to the ER with confusional state, progressive walking disorder and malnutrion. She was previously hospitalized in a long-term care facility to recover after pneumonia complicated by myocarditis. She was currently on therapy with: acetylsalicylic acid, bisoprolol and duloxetine. In her medical history she referred alcoholic abuse. Physical examination showed generalized muscles hypotrophy and hyporeflexia, with no sensitive deficiencies, mild distal oedema and swallen of the lower limbs. A brain CT scan was initially performed and tested negative; blood tests showed microcytic hypochromic anaemia (Hb 10mg/dl, MCV 79.7 fL, MCHC 30 pg), normal white blood cells, elevated platelet count 737.000 µL, hypopotassaemia (3.1 mEq/l), hypoalbuminemia (2.2g/dl) and elevated inflammatory markers (PCR 20.48 mg/dl). The patient was then admitted to the Internal Medicine Department to investigate the neurological picture. During the hospitalization the patient presented low grade fever, for which serial blood cultures were executed, all resulted negative. Chest X-Ray showed consolidation in the left superior upper lobe, so empirical antibiotic therapy was introduced, with no response. For the persistence of fever and neurological signs, the patient underwent a lumbar puncture in the suspect of a septic neurological involvement: cerebrospinal fluid was clear, with normal pressure and no protein or glucose increase. Neurology consultant suggested a metabolic cause for the neuropathy, recommending the execution of an electromyography, that revealed signs of axonal sensorimotor polyneuropathy in all the four limbs, especially in the lower ones. Tiamine, cyanocobalamin and pregabalin were administered. Brain and spinal cord MRI scan were performed, also tested negative. In the suspect of a paraneoplastic aetiology, whole body contrast-enhanced CT scan was performed, showing: multiple cavitation to the left superior lobe with thick walls and full of fluid material, connected to segmental bronchus suggestive of an acute tuberculosis, and concomitant consolidation areas in the right and left superior lobes with hilar and mediastinal lymphadenopathy. In the suspect of an active tuberculosis, sputum and Quantiferon tests were required, but unexpectedly resulted negative. Immunodeficiency disorders were ruled out through HIV negative test and normal lymphocyte subpopulations count. In addition, a bronchoscophy was executed with brocho-alveolar lavage (BAL) researching for Koch's bacillus (BK), culture test for BAAR and pneumonia filmarray. While waiting for the results, triple anti tubercular therapy with isoniazide, rifampicin and pyrazinamide was started with partial benefit, fever resolution and inflammatory markers reduction. The results from the BAL showed a positive Ziehl Neelsen stain for acid-fast bacilli (AFB) associated with negative BK and colture BAAR tests. Nucleic acid amplification testing (NAAT) for tuberculous mycobacteria tested negative, indicating nontuberculous mycobacteria (NTM) pulmonary disease. Due to these results and a markedly transaminases increase, treatment was continued with azithromycin, rifampicin, and pyrazinamide with good clinical response. NTM pulmonary disease preferentially impacts patients with impaired host defence of the lung, such as HIV, cystic fibrosis or chronic obstructive pulmonary disease; other minor risk factors are malnutrion, tobacco and alcohol abuse. Peripheral neuropathy is commonly seen in patients with tuberculosis and other co-morbid conditions as HIV, diabetes and malnutrition. The patient's history of alcohol abuse and malnutrition probably exposed her to a major risk of developing NTM pulmonary disease and a severe polyneuropathy.

MALATTIE RARE

488. A STRANGE INVOLVING POEM(S)

Di Stefano C.[1], Bizzarri L.[2], Levrero G.[3], Agostinelli D.[4]
[1]Dipartimento di Scienze Mediche e Chirurgiche (DIMEC), Università Alma Mater Studiorum Bologna; IRCCS Azienda Ospedaliero-Universitaria of Bologna; U.O. Semeiotica Medica; [2]Dipartimento di Scienze Mediche e Chirurgiche (DIMEC), Università Alma Mater Studiorum Bologna; IRCCS Azienda Ospedaliero-Universitaria of Bologna;U.O. Medicina Interna, malattie neurovascolari ed epatometaboliche; [3]Dipartimento di Scienze Mediche e Chirurgiche (DIMEC), Università Alma Mater Studiorum Bologna, IRCCS Azienda Ospedaliero-Universitaria of Bologna; U.O. Medicina Interna, malattie neurovascolari ed epatometaboliche; [4]IRCCS Azienda Ospedaliero-Universitaria of Bologna; U.O. Medicina Interna, malattie neurovascolari ed epatometaboliche

Background: POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes) is a rare paraneoplastic disorder. Polyneuropathy and monoclonal protein are usually considered essential for diagnosis.
Case report: A 68-year-old man was admitted in our department because of subacute progressive bilateral inferior limbs weakness which was affecting his ability to walk. The symptoms started 4 months before admission but in the previous weeks they had become disabling. His past medical history was unremarkable.
Physical evaluation showed normal vital sign, inferior limbs muscle weakness (proximal worse than distal), hyporeflexia in superior limbs and areflexia in the distal limbs.
Blood tests were normal.
Total body CT scan was performed, it showed a solitary sclerotic bone lesion involving L4 vertebra. MRI and FDG-PET confirmed a solitary lesion in L4 vertebra characterized by a high uptake of FDG and involving less than 30% of the vertebra canal.
An infective etiology was ruled out and microbiological tests excluded active infection by T. Pallidum, T. Gondii, B. Burgdorferi, HCV, HBV, HIV, CMV, EBV and Mycobacterium tuberculosis.
In the first week of hospitalization the patient complained worsening of the neurologic symptoms with severe weakness affecting his ability to walk or firmly grip objects, tetraparesis was observed. An electromyography was performed and demyelinating polyneuropathy with disomogeneous distribution was diagnosed.
The clinical presentation was suspicious for either a paraneoplastic syndrome and a chronic inflammatory demyelinating polyneuropathy; as first line therapy we started high dose methylprednisolone, without any response and subsequentially intravenous immunoglobulin with minimal improvement.
We decided not to perform a lumbar puncture because the sclerotic lesion was in the classical site of the procedure and there would have been a high risk of complications.
In the meanwhile, a CT-guided biopsy of the lesion was obtained, the histologic exam revealed a plasmacytoma with lambda monoclonal restriction.
A bone marrow biopsy was then performed, it showed a normal population of hematopoietic cells with minimal plasma cells component without any pathological significance.
We diagnosed a non-secretory solitary plasmacytoma, in fact there were no classical sign neither of myeloma nor of monoclonal protein in the laboratory tests (normal complete blood count, kidney function, serum electrolytics, liver function, serum immunoglobulin, kappa/lambda light chain, serum and urinary immunofixation, urine test and urine protein).
As the diagnosis of POEMS syndrome seemed probable, we performed additional test and on one hand we found out a very high level of serum VEGF 1349.60 pg/mL (n.v. 62-707 pg/mL), testosterone deficiency and a tendency to erythrocytosis (JAK-2 mutation resulted negative), on the other hand we didn't find any skin changes, papilledema and organomegaly (except for normal spleen with multiple splenic infarction).
POEMS syndrome was diagnosed in our patient based on the fulfillment of three major criteria, namely demyelinating polyradiculoneuropathy, plasmacytoma, elevated VEGF and two minor criteria: endocrinopathy and erythrocytosis.
The patient was treated with 22 radiotherapy sessions directed at plasmacytoma and intensive rehabilitation. During the following months he slowly improved neurological symptoms and nowadays he can walk again with a walker.
Conclusion: The diagnosis of POEMS syndrome demands a high index of suspicion and often one or more criteria are missing, in our case serum monoclonal protein which is commonly thought to be essential for diagnosis. Since the syndrome can be fatal, early diagnosis is pivotal for patients' survival and quality of life.

489. GIVOSIRAN AS NEW FRONTIER IN THE TREATMENT OF ACUTE HEPATIC PORPHYRIA: OUR EXPERIENCE

Tumminia C., Gagliardo C.M., Giammanco A., Baio C., Belfiore A., Furnari L., Averna M., Baldassare Cefalù A., Noto D.
Department of Health Promotion, Maternal and Child Health, Internal and Specialized Medicine of Excellence "G. D. Alessandro" (PROMISE), University of Palermo, Italy

Introduction and aims: "Acute Hepatic Porphyria (AHP)" describes a group of rare inherited metabolic disorders caused by dysfunctions of enzymes involved in the hepatic pathway of heme biosynthesis.
Up-regulation of hepatic delta-aminolevulinic acid synthase 1 (ALAS1), with resultant accumulation of delta-aminolevulinic acid (ALA) and porphobilinogen, is central to the pathogenesis of acute attacks characterized mainly by neuro-psychiatric and/or gastrointestinal symptoms in AHP. Hematin and dextrose administration are usually administered to manage these crises. Givosiran is a newer small interfering RNA (siRNA) which inhibits ALAS1 expression and decreases accumulation of neurotoxic porphyrin precursors in patients with AHPs thus reducing acute attacks frequency and improving symptoms. In this study we report the management of two patients with AHP treated with Givosiran in a Metabolic Unit in Palermo.
Cases presentation: Two patients, a 57-year-old woman (patient n.1) and a 29-year-old man (patient n.2) with AHP and recurrent porphyria attacks were administered Givosiran therapy, 189 mg/monthly, subcutaneously. Liver and kidney function tests, urinary aminolevulinate acid (ALA) and porphobilinogen were evaluated every month. Furthermore, the frequency of composite porphyria attacks expressed as attacks requiring hospitalization, urgent healthcare visit or intravenous hemin administration were monitored over the follow-up period.
Results: Over the treatment with Givosiran, urinary ALA and porphobilinogen levels were within the normal range. No elevations in serum aminotransferase levels and/or changes in kidney function tests were reported as well as any injection-site reactions. In both patients the rate of attacks decreases and they stopped hemin use.
Conclusion: Givosiran is effective and safe in the management of AHP by decreasing attack frequency, hemin use and severity of symptoms. Quality of life improved and no adverse events were reported.

490. ERDHEIM-CHESTER DISEASE: A CASE REPORT

Sartori F., Tosi F., Girelli D.
UOC Medicina d'Urgenza, Azienda Ospedaliera Universitaria Integrata di Verona

Erdheim–Chester disease (ECD) is a rare non-Langerhans' cell histiocytosis characterized by the abnormal proliferation, overproduction, and infiltration of foamy histiocytes within various tissues and organs, accompanied by fibrosis. It can be detected incidentally in asymptomatic individuals or manifest as severe multiorgan involvement. Since its initial identification in 1930, only approximately 1500 cases have been reported. The majority of ECD patients (over 80%) harbor mutations activating the MAPK pathway, with the BRAFV600E mutation being the most common (57% to 70% of cases), followed by MAP2K1 mutations (approximately 20% of patients).
ECD presents with several notable clinical manifestations, including involvement of long bones (80%-95%), a distinctive appearance of the kidneys on computed tomography (CT) scans referred to as "hairy kidney" (63%), a "coated" aorta (40%), and neurological signs such as cerebellar and pyramidal syndromes (41% and 45% respectively). Another characteristic feature is pseudo-tumoral infiltration of the right atrium (36%). In symptomatic patients, bone pain is the most common initial symptom, occurring in 50% of cases.
Diagnosis of ECD relies on a combination of clinical presentations, imaging features, and histopathological findings. Histologically, foamy histiocytes lacking Birbeck granules (intracellular organelles found in Langerhans' cells) are observed, and immunohistochemical staining shows positivity for CD68 and negativity for CD1a.
In this case report, we present a 79-year-old Caucasian male with ECD who

visited the emergency room after experiencing hematemesis and anemia. The patient had a history of hematologic disorder (Polycythemia Vera JAK2-V617F -) treated with periodic phlebotomy, as well as recurring pleural effusion with a small ground-glass area in the apical region of the left lung observed on multiple CT scans over the past 7 years (initially in 2016). Additionally, he had a history of hypopituitarism secondary to a macroadenoma, which was managed with surgery and gamma-knife treatment. The patient was also undergoing neurological evaluation due to hesitant speech and ataxia and had taken NSAIDs for right leg pain in the five days prior to recovery.
An X-ray performed in the emergency room revealed an irregular sclerotic area measuring 7 cm in the diaphysis of the right femur. Subsequent investigations included esophagogastroduodenoscopy (EGDS), which identified a Forrest III gastric ulcer, and a thoracic and abdominal CT scan that showed thoracic aorta ectasia with markedly irregular walls. The scan also revealed hypodense, slightly enhanced tissue surrounding the aorta in both the thoracic and abdominal regions, as well as displaying a characteristic "hairy" pattern around both kidneys. Initially, the periaortic tissue findings were misleading, but further evaluation with additional CT scans ruled out vascular involvement such as aortic dissection. The examination did, however, show enhanced tissue in the apical region of the left lung and the presence of pericardial effusion.
Based on the combination of radiological findings and the patient's suggestive medical history involving bone, perivascular, neurological, and pericardial manifestations, a diagnostic hypothesis of Erdheim-Chester disease was formulated. Subsequent perirenal-tissue biopsy confirmed the diagnosis, demonstrating the typical presence of CD1a-CD68+ foamy histiocytes.
Currently, the patient is undergoing immunologic screening prior to the initiation of immunosuppressive therapy.
In this case, the two main genetic mutations associated with Erdheim-Chester disease (ECD), *BRAFV600E* and *MAP2K1*, were excluded in the patient. Consequently, targeted inhibitors specific to these mutations were not applicable as a treatment option.
This case serves as an example of the diagnostic challenges associated with ECD, primarily due to its involvement of multiple systems and its initial asymptomatic nature in many instances. It underscores the significance of conducting a comprehensive evaluation of patients, considering the diverse clinical manifestations that may be present.
Furthermore, the case emphasizes the importance of recognizing the characteristic radiological findings associated with ECD, which aid in guiding the diagnostic process.
Additionally, the case reinforces the established association between ECD and myeloproliferative neoplasms and/or myelodysplastic syndromes, which are known to be present in approximately 10% of ECD cases.

491. DIAGNOSTIC DELAY IN RARE DISEASES: THE DRAMA OF A SILENT KILLER

Coppola C., Rizzi L., Hbaidi Y., Cocco V., Morea F., Suppressa P.
Department of Internal Medicine and Rare Diseases Centre "C. Frugoni", Lipigen Centre, University of Bari "Aldo Moro"

A forty-five years old man has come to our attention for an outpatient internist evaluation.
He was a former smoker of 20 cigarettes/day, working in a sole factory with reported occupational exposure to solvents. Salient events in his pathological anamnesis were a previous bariatric surgery in 2011 and surgical correction of vertebral herniated discs.
The clinical history of our interest began in 2016: due to the onset of dyspnea for moderate efforts, the patient performed tests of respiratory function, which were altered. Since that time, a diagnostic process made of laboratory and instrumental investigations began, which led to a new finding of anaemia and leukopenia. Therefore, in 2017 the patient underwent bone marrow biopsy, which highlighted an infiltrate of numerous non-necrotizing granulomas. Unfortunately, this histological picture was not translated into a specific clinical diagnosis by the reference haematologist, although the patient was suffering from a type of anaemia that required periodic intravenous iron infusions.
In addition, due to the increase in transaminases and cholestasis indices, an abdominal ultrasound was performed which detected evolved chronic liver disease and splenomegaly. Impaired liver function was accompanied by an increase of beta-2-microglobulin values and hypergammaglobulinemia. Therefore, a chest-abdomen CT scan was performed, which detected the presence of multiple lung and liver micronodules, hepatomegaly, splenomegaly with related hypodense lesions and abdominal confluent lymph nodes. In September 2017, the patient was admitted to the Thoracic Surgery Department, where he underwent to an atypical pulmonary resection, whose histological examination showed a chronic, inflammatory, non caseous granulomatous disease with giant epithelioid cells. Based on the histological examination and the imaging evaluation of the previous CT, a diagnosis of systemic sarcoidosis with multiorgan involvement was done.
After a few years, the patient was admitted to the General Surgery Department, where he underwent a hepatic segment resection: the histological examination showed micronodular cirrhosis. The clinical picture, complicated by esophageal varices, was not immediately attributed to sarcoidosis by the reference gastroenterologist, so a diagnosis of cryptogenic cirrhosis was done, for which there were no therapeutic indications other than non-selective beta blockers for the prevention of digestive bleeding.
In May 2022, the patient was referred to our Sarcoidosis Centre for a clinical revaluation. During the hospitalization, the patient performed further instrumental examinations that confirmed the presence of advanced chronic liver disease with macronodular appearance, complicated by portal vein thrombosis, splenomegaly and esophageal varices, these last treated by elastic ligature during endoscopic examination; laboratory tests confirmed anaemia and leukopenia already known since 2017, in addition to a lately emerging thrombocytopenia, also determined by evolved liver disease; spirometry showed a moderate restrictive deficit; microbiological investigations for mycobacteria and hepatic viral and neoplastic markers were carried out, with negative result. PET-CT detected pathological radiotracer accumulation in thorax and abdominal compartment, with SUV not indicative of cancer and compatible with chronic inflammatory disease with low metabolic activity.
In consideration to the patient's liver impairment in the context of multiorgan sarcoidosis and his young age, he was placed on the waiting list for liver transplantation. The surgery was performed in June 2022 without complications and the patient regularly continues the outpatient follow-up at our Sarcoidosis Centre.
This clinical case is an example of how sarcoidosis, which generally has a benign clinical course, can sometimes lead to an organ involvement so deleterious that it can be considered a life-threatening condition. In this case, the patient underwent an organ transplant to avoid an unfortunate outcome. Moreover, sarcoidosis determined an unusual organ involvement, that is, the bone marrow one, responsible for pancytopenia, that also contributed to the diagnostic delay. A holistic vision of the patient is often crucial to put together the pieces of a puzzle apparently disconnected from each other and to make a timely diagnosis, which is often the most effective tool to face diseases that can act as a silent killer.

492. "THE LOWER IS BETTER": GENETIC PITFALLS OF A PARADIGMATIC APPROACH FOR DYSLIPIDEMIA

Coppola C., Cocco V. , Rizzi L. , Russo R. , Suppressa P.
Department of Internal Medicine and Rare Diseases Centre "C. Frugoni", Lipigen Centre, University of Bari "Aldo Moro"

Several clinical trials stressed the importance of an aggressive approach in LDL cholesterol (LDL-c) reducing for primary and secondary cardiovascular prevention. The concept of "Lower is Better" is based on the evidence of how cholesterol reduction induces a proportional decrease in the probability of incurring in the clinical complications of atherosclerotic disease. If, on the one hand, it is necessary to use all the pharmacological tools currently available for the massive abatement of atherogenic cholesterol, on the other hand we must not always remain worry-free in front of very low values of cholesterol, because they could be a sign of complex and life-threatening clinical events, as well as vascular events caused by hypercholesterolemia.
Very low (<30 mg/dL) LDL-c can be found in patients with genetic conditions characterized by hypocholesterolaemia: for example, loss-of-function mutations in Proprotein Convertase Subtilisin/Kexin 9 gene (PCSK9), familial hypobetalipoproteinemia, abetalipoproteinemia, chylomicron retention disease and Smith-Lemli-Opitz syndrome are genetic conditions characterized by congenital, lifelong, very low LDL-c values.
Among these, abetalipoproteinemia (ABL) is a rare autosomal recessive genetic disease caused by mutation of the triglyceride microsomial transfer protein (MTP), involved in ApoB lipoproteins assembling. This disease is characterized by the absence of lipoproteins containing ApoB, undetectable LDL and lack of fat-soluble vitamins (A, D, E, K). Affected individuals may have severe neurological manifestations (retinal degeneration, spinocerebellar ataxia, peripheral neuropathy), steatorrhea, hepatic steatosis, haemorrhagic diathesis, osteoporosis, myositis, and acanthocytic anemia. The clinical manifestations related to ABL are induced by vitamin deficiency and chole-

sterol reduction and the currently approved therapy involves vitamin supplementation, in particular A and E, to stop ocular and neurological degeneration. Among the possible complications of ABL, there is hepatic steatosis, due to the accumulation of triglycerides in the liver. In these patients, steatosis can evolve into cirrhosis, that sometimes could require liver transplantation. A late or missed diagnosis can lead to a fatal outcome even by the third decade of life.
Our Rare Disease Centre takes care of patients with lipid metabolism disorders, even during the transition from childhood to adulthood. In April 2023, a 23-years-old patient, diagnosed with ABL in a Paediatric Centre during the first year of life, came to our attention. Since the first months of life, due to persistent diarrhea and growth delay, the patient performed several laboratory and instrumental tests to exclude most common pathologies, such as celiac disease. Given the negativity of the laboratory tests and jejunal biopsy, further investigations were done. Acanthocytic anemia, elevation of transaminases and appearance of widespread skin haemorrhagic manifestations were found. Lipid profile showed: TOTc 61 mg/dl, LDLc not dosable, HDLc 57 mg/dl, triglycerides 56 mg/dl, ApoB 23.4 mg/dl, ApoA1 69 mg/dl. According to the tests performed and the familiarity for ABL, a diagnostic hypothesis about abetalipoproteinemia was done and the young patient was treated with fat-soluble vitamin supplementation (E, A and K) and a specific hypo-lipidic diet, with considerable clinical benefit. Subsequently, diagnosis has been confirmed in 2019 with genetic analysis, showing mutations of the MTP gene and the apoB gene. The patient performed periodic eye check for initial rods dystrophy, regressed with early vitamin supplementation. In our Centre, the patient underwent to a clinical, laboratory and instrumental re-evaluation that led to dosage adjustment of the therapy with vitamin E (deficient in recent laboratory tests); because of the persistent elevated transaminase values, he also underwent to an abdominal ultrasound, showing mild-to-moderate hepatic steatosis that should be periodically checked, in the light of the young age and the possibility of evolution into liver cirrhosis.
This clinical case is an example of how low LDL cholesterol does not necessarily associate with a favourable clinical prognosis. The so rightly exalted concept of "Lower is Better" should not lead us to underestimate the meaning of hypocholesterolemia. In fact, even if it plays a cardioprotective role, on the other hand it can become part of some clinical conditions characterized by a particularly important impairment of quality-of-life and life expectancy. In this context, the importance of knowledge of Rare Diseases is emphasised, especially when the "time" factor plays a crucial role: recognizing rare pathologies can often make the difference between life and death.

493. THE PORTRAIT OF "MRS GREYSH": AN UNUSUAL PRESENTATION OF ALKAPTONURIA

Battaglia S.[1], Doronzo R.[1], Susca N.[2], Casieri G.[1], Di Buduo E.[1], Calabrese G.[1], Casamassima A.M.[1], D'Andrea M.[1], Suppressa P.[1], Moschetta A.[1], Sabbà C.[1]
[1]Department of Interdisciplinary Medicine, University of Bari "Aldo Moro", 70124 Bari, Italy; [2]AOU Policlinico Consorziale di Bari – Ospedale Giovanni XXIII, Emergency Medicine and Surgery Unit, 70124 Bari, Italy

Alkaptonuria (or Ochronosis) is a rare autosomal recessive genetic disorder of the tyrosine metabolism, characterized by the lack of homogentisate 1,2 dioxygenase (HGD), whose role is to convert homogentisic acid (HGA) into 4-maleylacetoacetate. This causes an impaired catabolism and abnormal accumulation of HGA in the liver, where it is oxidized in the typical ochronotic polymers. These melanin-like pigments show high affinity for connective tissues and eventually bring to arthropathy, vascular calcification and cardiac valve disfunction. The worldwide prevalence of alkaptonuria is 1 case in 250000 – 1000000 inhabitants.
Here we report the case of a 75-year-old Caucasian woman admitted to our Internal Medicine Unit for a significant bleeding from tracheostomy that she received three months before during Intensive Care Unit hospitalization. In February 2023 she suffered from diffuse subarachnoid hemorrhage following internal carotid artery giant aneurysm rupture, treated with embolization procedure and stent placement. After this critical event, the patient presented left hemiparesis with permanent disability, requiring enteral nutrition via Percutaneous endoscopic gastrostomy tube. Her past medical history reported hypertension and surgical treatment of lumbar spinal stenosis. Thoracic computed thomography (CT) scan revealed a tracheoesophageal fistula as probable cause of bleeding, confirmed by endoscopy. After general optimization, a surgical fistula repair procedure was indicated.
Dermatological examination showed inky black spots in the sclerae and greyish auricles cartilage and skin, worsening during acute conditions or a transient systemic dehydration.Also, the urine turned to brown and grey color when collected and left exposed to open air.These clinical findings along with history of carotid aneurysm led us to our diagnostic hypothesis of alkaptonuria.Thus, we performed laboratory investigations on blood and urine, showing an increase of urinary organic acids, urinary amino acids, phenylalanine, and acyl-carnitine. In addition, we performed genetic tests for definitive confirmation.
In the described case, connective weakening is likely to have favored fistolization of the posterior tracheal wall. Moreover, tunica intima of vessels is a less common site of pathological accumulation, that might have contributed to cerebrovascular disease. Indeed, our report depicts an extremely rare manifestation of alkaptonuria, so far undescribed in literature.

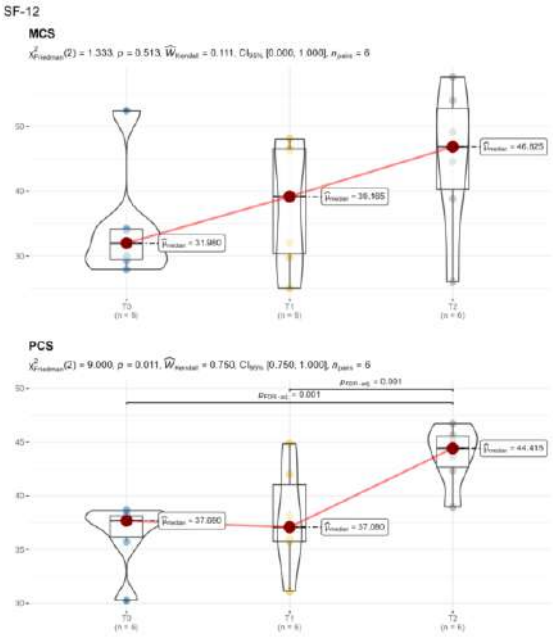
494. HEALTH-RELATED QUALITY OF LIFE IN HOME CARE PATIENT SUPPORT PROGRAM (PSP) FOR PATIENTS AFFECTED BY ACUTE HEPATIC PORPHYRIA

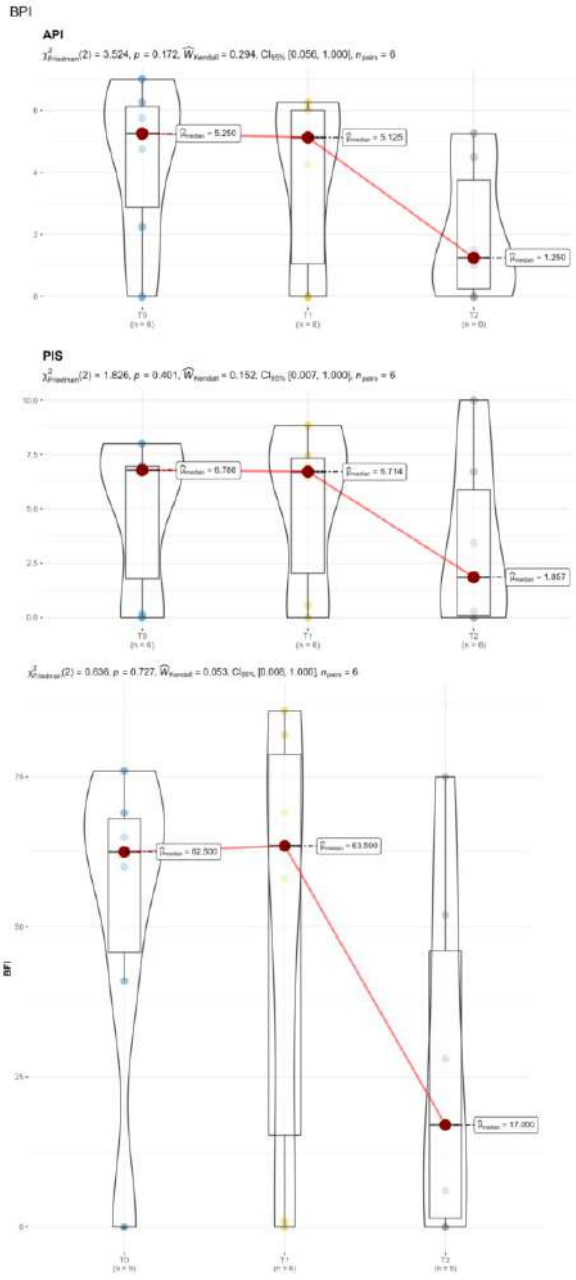
Brambillasca F.[1], Porreca A.[2], Balena N.[1]
[1]Healthcare Network Partners (HNP), Italy; [2] Department of Medical, Oral and Biotechnological Sciences, Laboratory of Biostatistics, D'Annunzio University of Chieti-Pescara, Italy

Background: Acute hepatic porphyria (AHP) is a family of four rare genetic diseases characterised by potentially life-threatening acute attacks and, for some patients, chronic manifestations impacting daily functioning and health-related quality of life (HRQoL). AHP is a group of genetic disorders resulting from deficiencies in specific enzymes in the heme biosynthetic pathway, which can cause life-threatening acute neurovisceral symptoms. Comprehensive clinical guidelines for initial evaluation, follow-up, and long-term management are needed to ensure optimal outcomes, particularly because no guidelines exist for monitoring disease progression or response to treatment. The Porphyrias Consortium of the National Institutes of Health's Rare Diseases Clinical Research Network has developed recommendations for the diagnosis, management, and monitoring of these disorders, which include diagnostic confirmation by biochemical testing, subsequent genetic testing, a complete medical history and physical examination, counselling about avoiding known precipitating factors, and regular follow-up and monitoring for long-term complications. The frequency of follow-up depends on the clinical subgroup, with close monitoring of patients with recurrent attacks who may require treatment modifications and those with clinical complications. Comprehensive care should include subspecialist referrals when needed. In a phase 3 study called ENVISION, a randomised, placebo-controlled trial involving 94 patients with AHP and recurrent attacks, givosiran treatment for six months during the double-blind period resulted in significant reductions in the daily worst pain compared to placebo. Patients receiving givosiran treatment reported improved quality of life and other patient-reported outcomes. Here we report interim data of the patients with acute hepatic porphyria enrolled in the Patient Support Program (PSP) provided by Healthcare Network Partners (HNP) who completed 6 to 12 months of follow-up to assess HRQoL and health status.
Material and Methods: SF-12v1 Italian version questionnaire was used to measure the perception of health-related quality of life. SF-12 is a self-administered questionnaire developed and validated as a shorter alternative to SF-36, the gold standard among the generic measures for evaluating the perception of HRQoL. The SF-12 has two dimensions: the physical composite (PCS) and the mental composite (MCS) scores. PCS and MCS scores range from 0 to 100, with higher scores indicating better functioning. The Brief Pain Inventory (BPI) questionnaire was used to measure both the intensity of the pain (sensory dimension-PIS) and the interference of pain in the patient's life (reactive dimension-API). For both, 0=no interference/pain and 10=interferes completely/pain is as bad as you can imagine. Indeed, the brief fatigue inventory (BFI) questionnaire was also used to quickly assess the severity of fatigue experienced by patients, it ranges from 0 to 90, and higher scores correspond to more severe fatigue. The Shapiro–Wilk test was performed to evaluate the normal distribution of the data. Median, 1st, and 3rd quartiles were reported as summary and variability measures, respectively, and the violin plot was used as a visualisation method. The Friedman test evaluated differences over time, and the post-hoc False discovery rate corrected the Wilcoxon test. As the Friedman test does not handle missing data, missing values were removed for the analysis. All statistical tests were 2-sided, with a significance level set at $p < 0.05$. Statistical analysis was performed using R software environment for statistical computing and graphics version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results: Referring to clinical variables, at baseline, patients in the study were 13, at 1st follow-up at six months (T1) n=11 and after 12 months follow-up (T2) n=5. Of 13 patients, 12 (92.3%) were female and one male (7.7%). The sample has a median age of 47.8 years [q1=34.7; q3=54.3]. The clinical variables considered for the study are Max and Min Blood pressure (BP), Heart Rate (HR), Respiratory Rate (RR), Oxygen saturation (SpO2), Body temperature (BT), and Dose (mg). Figure 1 shows any statistically significant change over time in clinical parameters. Figure 2 shows SF-12 dimensions (MCS and PCS) over time, revealing an improvement in both PCS and MCS but only in PCS statistically significant. Figure 3 shows trends over time in the pain dimensions of the BPI. The two dimensions (API and PIS) report similar trends revealing a decrease in the median value after six months. Figure 4 shows the 12-month trend in BFI, demonstrating, although not statistically significant, a dramatic reduction in the median value between 6 and 12 months of follow-up.
Conclusions: In conclusion, although not in a statistically significant manner due to the presence of missing values and thus the small sample size, the clinical parameters were under control with a stable trend at 12 months, while HRQoL, fatigue, and pain scales improved.

Variables	T0	T1	T2	Friedman test
	n=13	*n=11*	*n=5*	p-value
Max BP (mmHg)	115.0 [105.0;120.0]	105.0 [100.0;120.0]	115.0 [110.0;120.0]	0.873
Min BP (mmHg)	70.0 [65.0;75.0]	65.0 [60.0;70.0]	70.0 [70.0;75.0]	0.602
HR (bpm)	71.0 [67.0;78.0]	75.0 [64.0;83.5]	67.0 [62.0;74.0]	0.551
RR (bpm)	18.0 [16.0;18.0]	20.0 [18.0;22.0]	19.0 [18.0;20.0]	0.074
SpO2 (%)	98.0 [98.0;99.0]	98.0 [97.0;99.0]	98.0 [98.0;99.0]	0.769
BT (Celsius degree)	36.0 [36.0;36.5]	36.0 [36.0;36.3]	36.0 [36.0;36.0]	0.669
Dose (mg)	151.0 [132.0;152.0]	132.0 [132.0;151.0]	146.0 [146.0;151.0]	0.607





495. SEVERE REFRACTORY THROMBOCYTOPENIA IN A PATIENT WITH ANGIOSARCOMA: A CASE OF KASABACH-MERRITT SYNDROME

Caputo C.[1], Bregani E. R. [2], Pandolfi A. [3], Peyvandi F.[1]
[1]University of Milan, Department of Pathophysiology and Transplantation, Milan, Italy; [2]Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Internal Medicine - Hemostasis and Thrombosis, Milan, Italy; [3]Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Cardiology Division, Milan, Italy

Background: Kasabach-Merritt syndrome (KMS) is a rare phenomenon associated with vascular tumors, characterized by thrombocytopenia and consumptive coagulopathy, due to intra-tumoral platelet (PLT) trapping and activation. First described in children affected by hemangiomas, it is now recognized to occur also in adults suffering from other types of cancer.
Case report: We present the case of a 79-year-old Italian-French man, first diagnosed with angiosarcoma, located on the right side of his neck, in France in 2022. His past medical history was relevant for atrial fibrillation and SARS-CoV-2-related pneumonia in 2021 complicated by heparin-induced throm-

bocytopenia (HIT) and ischemic stroke. Follow-up blood tests showed normalization of the PLT count (218.000/mmc in April 2021), therefore Apixaban at full dose was reintroduced a few months after HIT.
When a firm mass on the right side of the neck appeared in March 2022, the patient was first followed in France. A full battery of tests was performed: an ultrasound and a whole-body contrast-enhanced CT confirmed the presence of a mass on the right side of the neck (diameters 48 x 33 x 45 mm) and revelead a suspicious lesion of the right iliac bone. A whole-body FDG-PET showed intense radionuclide uptake of the neck lesion (SUV max 7.9) and of the right iliac bone lesion (SUV max 10.5). The patient finally underwent an excision biopsy. The histological result showed epithelioid cells delimiting numerous vascular structures and fissures, consistent with a diagnosis of angiosarcoma, with vascular thrombosis and hemorrhagic suffusions within the tumor.
At this point, he opted to be treated in an Italian cancer reference center in July 2022. His new oncologists ordered another full-body CT, which showed the appearance of new metastatic lesions in the lungs and the head of the pancreas and a spleen of normal size. At a follow-up visit a month later, a new mass was visible and palpable at the previous excision site. Moreover, the patient complained of gingival bleeding and bruising. Blood test revealed severe thrombocytopenia (PLT count 15.000/mmc). For this reason, Apixaban was stopped and the patient was transferred to our hospital. We confirmed the PLT count: blood test showed a PLT count of 10.000/mmc, elevated D-dimer (40.619 mcg/l) and hypofibrinogenemia (69 mg/dl), with normal coagulation times (suggestive of chronic coagulopathy), moderate normocytic anemia (Hb 9.6 g/dl) and no signs of intra-vascular hemolysis. Methylprednisolone was immediately administered, on suspicion of immune-mediated thrombocytopenia (ITP). Fresh frozen plasma was also administered to correct hypofibrinogenemia. Major and minor hepatic viral serology was negative, as was an autoantibody screening (rheumatic factor, ANA, ENA, anti-dsDNA antibodies) and fecal H. pylori antigen. Erythropoietin, thyroid function and vitamin B9 and B12 were within range. Moreover, considering the need to rule out a bone marrow involvement, we performed a bone marrow aspiration and biopsy, after PLT infusion. The results revealed an hypercellular bone marrow, with no lymphocyte infiltration or atypical cells. During the stay, the PTL count did not improve with corticosteroid administration. Therefore, intra-venous immunoglobulins were added to the therapy, but again with no improvement. The case was discussed with hematologist consultants: taking in account all the tests results and the lack of response to therapy, ITP was ruled out. Instead, a diagnosis of consumption thrombocytopenia and coagulopathy in the context of metastatic angiosarcoma was made, consistent with KMS. The patient's conditions deteriorated quickly thereafter, and he became unfit to undergo any further treatment, so he opted for transitioning to palliative care.
Discussion: KMS is a rare syndrome, occurring mostly in children affected by tufted angioma and kaposiform hemangioendothelioma. It is characterized by thrombocytopenia, consumptive coagulopathy and anemia. Fibrinogen consumption is typical, while aPTT and PT are normal or mildly prolonged. Anemia is due to erythrocytes sequestration or more rarely to microangiopathic hemolysis. In more recent years, KSM has been described in patients with angiosarcoma or hepatic hemangioma. In all these cases, the interactions between the endothelium of highly vascular tumors and PLT leads to PLT trapping and consumption. PLT activation also leads to the initiation of the coagulation cascade and hyperfibrinolysis. Treatment include resection of the mass when feasible and sirolimus plus corticosteroids and anti-platelet agents. In KMS the prognosis depends on the severity of hemorrhagic events and its consequences, the underlying tumor and response to therapy.

496. FROM TORSADE DE POINTES TO AUTOIMMUNE POLYGLANDULAR SYNDROME

Carta F., Prof. Manetti R.
Università degli Studi di Sassari

Introduction: Autoimmune polyndocrine syndrome is a rare disease defined as the coexistence of at least two autoimmune endocrinopathies among Graves' disease, Hashimoto's thyroiditis, type 1 diabetes, Addison's disease and premature hypogonadism. Polyndocrine syndrome type I is the juvenile form, while type II, III and IV are the forms of adulthood. The most frequent is type III, that is characterized by the association between type 1 diabetes and autoimmune thyroid disease, which can manifest as hypothyroidism (Hashimoto's thyroiditis) or hyperthyroidism (Graves' disease). The etiology of this syndrome is multifactorial; a predominant role is played by the genes present at the level of chromosome 6. Also the cellular-mediated immune processes are very important: the lymphocyte infiltration of the various glands occurs due to functional loss of epithelial cells in association with an abnormal production of cytokines by T cells.
Case description: a 68-year-old man accessed the emergency room for an episode of loss of consciousness associated with trismus; his relatives referred that the patient had not reported clones or sphincter release and that the episode have resolved immediately. However, from that moment the patient was aphasic. Checking his medical history we found that he had a melanoma of the right foot with lymph node metastases, treated with Nivolumab until June 2022. Moreover, he was suffering from arterial hypertension (in ACE inhibitors), hypothyroidism with negative autoantibodies following chemotherapy (in substitution therapy with Levothyroxine), type 1 GADA + diabetes (in insuline therapy), bilateral kidney cysts and recent evidence of mild left ventricular dysfunction with 45% ejection fraction. In the emergency room he underwent a brain CT angiogram, that tested negative for acute events, but was hospitalized in the department of Neurology. The patient was in severely expired clinical conditions with persistence of aphasia and subsequent ideo-motor slowdown. Blood tests highlighted a severe hyponatremia (119 mEq/L), while the study of the patient's thyroid function revealed high TSH values (10.69 μU/ml), reduced FT3 and FT4 values and positive antibodies to anti-thyroid oxidase (AbTPO) and anti-Tireoglobulin (AbTg), thus allowing to diagnose an autoimmune thyroopathy. Due to the expired conditions and the symptomatology of the patient, a pituitary function study (IGF1 <15 ng/ml, Prolactin 16.7 ng/ml, LH 5.1 mIU/ml, Testosterone 0.97 ng/ml) and an MRI of the brain were also performed. This last examination evidenced a partial empty saddle in the absence of pituitary alterations. The above picture is compatible with a probable panipopituitarism resulting from the recent therapy with Nivolumab. It was also performed an electroencephalogram that adressed towards a diagnosis of metabolic-type encephalopathy. Furthermore, a study of the adrenal function was performed, although at the Total Body CT Scan there was no evidence of adrenal alterations. The exam showed: Dosage of plasma renin activity 0.05 ng/ml/h, Aldosterone 19.49 pg/ml, ACTH 4.99 pg/ml, Cortisol h 8 1.1 μg/dl, Cortisol h 12 1.4 μg/dl, Cortisol h 24 1.0 μg/dl. Consequentely, in the suspicion of hypoadrenalism a therapy with Cortone Acetate was set, with subsequent partial benefit and reduction of asthenia. During the stay in the department of Neurology the patient presented a syncopal episode associated with torsade de pointes (QT elongation, hypomagnesemia, hyponatremia) so he was transferred to the Cardiology Department. Thus he underwent a coronary angiography with evidence of bivasal coronary artery disease with a critical stenosis of the anterior descending artery, which was treated with angioplasty and implantation of medicated stent.
Results: Given the blood chemistry and instrumental investigations results, the diagnosis of Autoimmune polyendocrine syndrome type III was made because of the association of type 1 GADA+ diabetes, complicated by cardiac and cerebral vasculopathy, pituitary gland with radiological picture of empty saddle and panipopituitarism, and Hashimoto's thyroiditis.
Conclusions: In type III polyndocrine syndrome it is necessary to set up a replacement therapy in the case of glandular insufficiency. In this case the patient responded discreetly to Cortone acetate and Levothyroxine, in association with the therapies of all the other single pathologies involved, such as the insulin therapy for the diabetes.

497. FREE LIGHT CHAINS AND INFLAMMATION MARKERS FOR FAMILIAL MEDITERRANEAN FEVER

Carrabba M.[1], Serafino S.[1], Zarantonello M.[2], Fabio G.[1]
[1]Internal Medicine Dept., RITA-ERN Centre, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico; [2]Università degli Studi, Department of Clinical Sciences and Community Health

Introduction: Familial Mediterranean Fever (FMF) is a systemic autoinflammatory disorder genetically defined by pathogenic mutations of the pyrin protein coded by MEFV gene. The most serious complication is renal amyloidosis as consequences of chronic and uncontrolled inflammation. Long-life main standing treatment effective in preventing amyloidosis and controlling FMF attacks is colchicine. Recently anti-IL1 blocking has been introduced only for the colchicine-resistant patients. Adequate follow up is necessary for monitoring efficacy of therapy and preventing complications. The production of elevated levels of serum free light chains (sFLCs), normally found in the bloodstream in small amounts have been found in inflammatory disorders. This finding could be a biomarker for the presence of chronic subclinical inflammation leading to organ damages.

Objective: This study aims to describe in a monocentric cohort of FMF patients the incidence of high sFLCs and proteinuria and their correlation with the persistency of inflammatory activity.
Patients and Methods: We are enrolling the FMF patients with clinical and genetic diagnosis followed at our reference RITA-ERN centre. All the patients are under treatment (colchicine or colchicine + anti-IL1). They are periodically monitored with urine and blood tests, instrumental follow up (abdominal and heart US, heart MRI or CT-scan when indicated). In February 2023 we started to screen the patients for the presence of monoclonal serum protein, sFLCs and light-chain protein excretion. All the clinical data, genetics, instrumental and laboratory tests will be analysed and compared.
Results: Since February 2023 to present, 25 FMF patients (10F and 15M) have been tested for monoclonal serum protein, sFLCs and light-chain protein excretion. The patients' age at examination ranged from 28 to 63 years, with a mean of 34 years (±11.4). All the 25 patients were in clinical remission under treatment: 21 are under colchicine and 4 are under colchicine + anti-IL1 treatment.
The screening for the presence of monoclonal serum protein, sFLCs, light chain protein excretion, and proteins in 24-hours urine sample showed that 6 patients had slight proteinuria and 8 patients had high sFLC, among these, two had also monoclonal component, all k chains. *Table below shows data.*

	mean	±SD	range	reference range
creatinine	0.85	0.19	0.6-1-22	0.72-1.18 mg/dL
ESR	17	19	2-67	< 20 mm
C-RP	1.4	4.2	0-6.6	< 0.5 mg/dl
LDH	191	47	131-268	135-214 U/L
beta2microglobulin	1.8	0.68	1.1-4.4	0.8-2.2 mg/dL
gammaglobulin%	15.9	2.7	12-23.9	11.1-18.8 %
gammaglobulin g/dL	1.2	0.3	0.8-2.3	0.7-1.4 g/dL
sFLC κ	37.6	79.5	1.9-31.1	3.3-19.4 mg/dL
sFLC λ	14.5	5.3	0.97-24.8	5.71-26.3 mg/dL
sFLC ratio	2.9	6.5	1-1.76	0.26-1.65
U-proteins	12.1	16.5	0-28.2	2-12 mg/dL

Among all the patients, two had monoclonal serum protein, both IgG kappa sFLC. One of both had also urine-positive light chains protein excretion (bence jones, BJ protein) but not 24h proteinuria, while the other one had no bence jones but proteinuria (84 mg/dL 24h). Both patients come from Egypt and they presented with delayed diagnosis and more than one FMF attack per month before starting colchicine therapy. The MEFV genotype of the former patient with positive BJ protein was compound heterozygous for M694V and V726A. The genotype of the latter patient without BJ protein was compound by MEFV gene homozygosity for deletion I692DEL and homozygosity for E148Q mutation. Both patients underwent bone marrow examination. AA amyloidosis related to FMF was excluded by abdominal fat tissue biopsy.
The *Pearson's correlation* showed that sFLC have a positive correlation with beta2microglobulin and inflammation markers (ESR and C-RP), not with proteinuria. Beta2microglobulin correlates with inflammation markers and LDH. *Results are reported in the table below.*

	serum free light chains			
	κ	λ	b2micr.	U-prot.
beta2microglobulin	0.313	0.550	-	0.008
U-proteins	-0.059	-0.090	0.008	-
ESR	0.075	0.359	0.397	-0.145
C-RP	0.342	0.470	0.350	-0.167
LDH	-0.053	0.095	0.325	0.348

C-RP = C-reactive protein; ESR = erythrocyte sedimentation rate;
LDH = lactate dehydrogenase; U-prot. = urine proteins

Conclusions - So far, few case reports and one study on 15 FMF patients reported the findings about light-chain proteins. Some studies concludes that monoclonal light chains protein excretion is not a feature of FMF and AA-type renal amyloidosis. Other studies reported that serum free light chains can be higher if inflammation is present (and correlate with beta2microglobulin and inflammation markers), as we found also in the present study. The findings of serum free light chains in patients with FMF without lymph proliferation is still of unknown significance. Further investigations and data are necessary to understand if this biomarker can be considered in order to highlight subclinical inflammation related to FMF.

498. NEVER TOO OLD

Pedi A., Bua C., Mangiafico M., Stancanelli B.
Department of clinical and experimental medicine, University of Catania
UO Medicina Generale AOU Policlinico "San Marco" Catania

Background: Chronic ulcers of the lower limbs complicated with superinfection is a difficult challenge for the clinician and requires a careful management of the patient. The skin biopsy of the lower limbs is mandatory and answers many clinical questions, allowing the diagnosis of systemic pathologic conditions with cutaneous localization.
Case Report: A 82-year-old female patient was admitted to our department for diarrhea, bloody fecal mucus, abdominal pain, anemia associated with chronic ulcers of the lower limbs. Her clinical history included anemia, chronic constipation and the onset of lower limbs ulcers in the last six months, attributed to chronic venous disease. Initially, the lesions appeared resistant to medications.
On laboratory analysis we found CRP 243.6 mg/ L, procalcitonin 38.57 ng/ml, and more than 800 μ/g of fecal calprotectin, and Hb 7.0 g/dL. The physical examination revealed presence of leg's ulcers with erythematous basis and purple border. Ulcer biopsy showed dense neutrophilic infiltrate, whereas cultures showed infection by P.aeruginosa. The patient was treated with piperacillin-tazobactam and fosfomycin. In addition, the patient underwent abdominal CT, colonoscopy and biopsy allowing the diagnosis of Crohn's disease. The scenario was clear: Pyoderma gangrenosum associated with Crohn's disease. Glucocortocoids treatment was started.
Therapy was effective: given the resolution of sepsis, the improvement of clinical conditions and the disappearance of diarrhea, glucocorticoids' tapering and ustekinumab were initiated.
Discussion and conclusion: This is a rare case of pyoderma gangrenosum in a old patient. The most likely cause was that paraneoplastic. However, this desease has a second peak of age of incidence (although it is more rare) and may be related to Crohn's disease or chronic inflammatory bowel disease. Especially in the elderly, chronic ulcers could often be underestimated and misdiagnosed, but cutaneous biopsy is mandatory because helps making a correct diagnosis.

MEDICINA D'URGENZA

499. MOTTLING SCORE AND SOFA SCORE: "MOSCO" STUDY. CORRELATIVE ANALYSIS BETWEEN NOMINAL VARIABLES IN 30 PATIENTS WITH SEPTIC SHOCK

Ulissi A., Marzano M.A., Ciammaichella M.M., Pignata D., Fanfarillo F., De Paola G., Di Castri C.
UOC Medicina Interna ad Alta Intensità di Cure, Dipartimento di Medicina Interna, A.O. S Giovanni-Addolorata, Roma

Premises and purpose of the study: The Authors present the "MOSCO" study, acrostic deriving "MOttling score and sofa SCOre", which enrolled 30 patients, aged between 44 and 85 years, with septic shock. In all patients the Mottling Score and SOFA Score were evaluated at the entrance to the ward.The "MOSCO" study proposes the following objectives: check if there is a relationship between the Mottling and SOFA score; check if the relation reaches statistical significance according to the Q Cochran Test.
Materials and methods:The SOFA Score and Mottling Score values were compared with Cochran Q testFor the calculation of $\chi 2$ the following formula is applied: $\chi 2 = (k-1)\ [(k\ x)\ -y2]\ /\ (k\ y)\ -z$. With "k" we indicate the 3 variables considered, with "x" we indicate the total of the squares of the 3 variables considered. "Y" indicates the total of clinical conditions. With "y2" we indicate the square of the total climatic conditions. With "z" is indicated the total of the squares of the clinical conditions.
Results: The Cochran Q test shows how the clinical situation "S3-4 / M4-5"

highlighted in all patients is not attributable to the case but assumes a high statistical significance since the relative value (VR) of the obtained is 60 and the critical value (VC) of $\chi 2$ for p = 0.001 is of 13.816. The differences of choice are, therefore, highly significant with p <0.001.
Conclusions: The authors have shown that in the 30 patients enrolled in the "MOSCO" study there is a statistically significant correlation between the values of Mottling Score and those of SOFA Score

500. MOTTLING SCORE AND PESINDEX: "MOPESI" STUDY. COMPARATIVE ANALYSIS FOR CONTINUOUS VARIABLES IN 30 PATIENTS WITH UNSTABLE PULMONARY EMBOLISM

Marzano M.A., Ulissi A., Di Castri C., De Paola G., Fanfarillo F., Pignata D., Ciammaichella M.M.
UOC Medicina Interna ad Alta Intensità di Cure, Dipartimento di Medicina Interna, A.O. S. Giovanni-Addolorata, Roma

Premises and purpouse of the study:: The authors present the "MOPESI" study, an acrostic study that derives from the "MOttling score and Pulmonary Embolism Severity Index", which enrolled 30 patients between the ages of 48 and 85, with pulmonary embolism and haemodynamic instability. In all patients the Mottling Score and PESIndex were evaluated at the entrance in the ward. The study "MOPESI" proposes the following objectives: check if there is a relationship between the Mottling score and PESIndex; check if the relationship reaches statistical significance according to the Parametric Student's T test for comparative analysis of the variables considered.
Materials and Metods: In the 30 patients enrolled in the "MOPESI" study, the Mottling score and PESIndex were evaluated whose values were compared with Student's T Test. The test calculates the relative value (VR) of the index t to be associated with the difference found according to the following formula: t = (M1-M2) / √DS12 / N1 + DS22 / N2.
Results: The Student's "t" test applied to the 30 patients shows a highly significant correlation (p <0.001) of the two variables examined (Mottling Score and PESIndex pre-lysis values) and, therefore, not attributable to the case. In fact, the value of "t" obtained is 15.01 and the VC (critical value) of "t" for p = 0.001 is 3.659 with DF = 29.
Conclusions: The authors have shown that in the 30 patients enrolled in the "MOPESI" study with unstable pulmonary embolism there is a statistically significant correlation between the Mottling Score values and those of PESIndex.

501. INTRACAVITARY ECG VERSUS CHEST RADIOGRAPHY: BIENNAL RETROSPECTIVE ANALYSIS (2021-2022) ON 100 PATIENTS

Ciammaichella M.M., Taflaj B., Gasbarri D.
UOC Medicina Interna ad Alta Intensità di Cure, Dipartimento di Medicina Interna, A.O. S. Giovanni-Addolorata, Roma

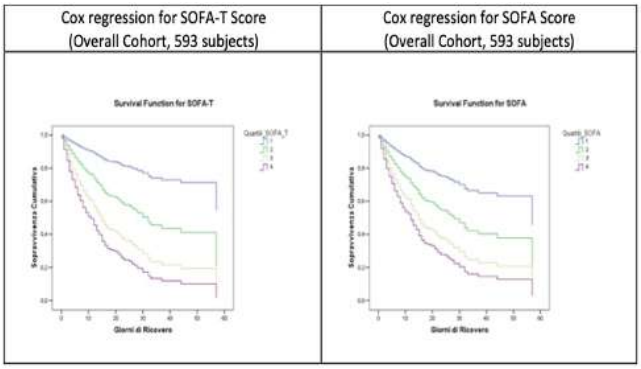
Background: Recently, intracavitary electrocardiogram technology has been applied to peripherally inserted central catheter placement and demonstrates many potential advantages. However, the tip positioning accuracy of intracavitary electrocardiogram technology compared to conventional X-ray method is unknown.
Introduction: The authors present a retrospective analysis that enrolled 100 patients aged between 68 and 94 years during the two-year period 2021-2022. A PICC was implanted in all patients, the correct positioning of which is verified with chest X-ray and intracavitary ECG (Photo 2). Therefore, a database with Microsoft Access© was created. The database contained the following fields: 1) patient number, 2) CRX check, 3) intracavitary ECG check. All patients were analysed, during recruitment, according to the aforementioned 3 fields, collected from time to time in masks created in "structure view" and "data sheet view" mode as allowed by the database program.
Materials and methods: The verification of the correct positioning of the PICC takes place through radiographic control of the chest and intracavitary ECG. To verify the effectiveness of the two methods, the chi-squared test with a 2x2 contingency table is applied.
Purpose of the study: Verify that there are no statistically significant differences between the two methods, with null hypothesis (chi-squared = 0)
Analysis of the results: The chi-square test applied to the 100 enrolled patients demonstrated that there are no statistically significant differences in the control of PICC positioning through chest radiography and intracavitary ECG.
Discussion: PICC placement by IC-ECG guidance is plausible, safe, presents adequate indexes of validity and reliability, and allows reducing the time of catheter placement. However, radiological verification is still necessary, especially in cases of negative or uncertain ECG.
Conclusions: The authors demonstrated that in checking the correct positioning of a PICC, the two methods used in 100 patients are equivalent (null hypothesis: chi squared = 0)

502. HIGH-RESOLUTION TROPONIN ASSAYS FOR THE RISK ASSESSMENT OF ELDERLY PATIENTS ADMITTED IN INTERNAL MEDICINE FOR SEPSIS AND OF SEPTIC SHOCK: AN UPDATE FROM THE SOFA-T GROUP

Lagonigro G.[1], Carletti S.[1], Falsetti L.[2], Zaccone V.[2], Fioranelli A.[3], Viticchi G.[4], Guerrieri E.[1], Santini S.[1], Diblasi I.[1], Moroncini G.[5], Burattini M.[3], Tarquinio N.[3]
[1]Emergency Medicine Residency Program, Università Politecnica delle Marche, Ancona, Italia; [2]Internal and Subintensive Medicine Department, Azienda Ospedaliero Universitaria Delle Marche, Ancona, Italia; [3]UOC Medicina Interna - Presidio Ospedaliero di Osimo (AN), INRCA IRCCS; [4]Clinica di Neurologia, Università Politecnica delle Marche, Ancona, Italia; [5]SOD Clinica Medica, AOU delle Marche, Ancona, Italy

Introduction: Elderly, critically ill patients with sepsis and septic shock may be admitted to Subintensive Internal Medicine (SDU) wards. Risk stratification is necessary to optimise their management and to choose the best setting for these patients. In this work, we aimed to evaluate the accuracy of SOFA score in this setting and to evaluate the performances of the SOFA-T score by adopting different TnI tests.
Methods: We retrospectively evaluated patients aged >65 years admitted to a single SDU in 48 months (INRCA-IRCCS Osimo, Ancona), considering age, sex, days of admission, in-hospital death, SOFA-score, TnI and hsTnI. We considered the TnI cutoff at the upper 99th percentile for both normal and hsTnI. SOFA-T was obtained by adding one point to the SOFA-score when the value of TnI or hsTnI was above the 99th percentile. SOFA and SOFA-T were recoded into quartiles.
Results: 593 patients were enrolled (baseline characteristics are in Table 1); a subgroup (203 patients) was assessed with hsTnI (age:83.6±11.3 years, males:53.2%): the addition of hsTnI to SOFA increased its accuracy (AUC-SOFA:0.670;95%CI:0.594-0.745; AUC-SOFA-hsTnI:0.707;95%CI:0.634-0.779;p<0.001), with a slight performance improvement, not significantly better than in the subgroup of patients evaluated with SOFA-non-hsTnI (p>0.05). Considering the entire cohort, a one-quartile increase in SOFA score was associated with a lower increase in risk (HR:1.395;95%CI:1.141-1.706;p<0.001) than that observed with a one-quartile increase in SOFA-T (HR: 1.622;95%CI:1.302-2.020;p<0.001), as shown in Figure 1. Considering a cutoff >3, SOFA-T showed a better negative predictive value than SOFA (SOFA-T-VPN:86%;95%CI:76-95%; SOFA-VPN:81.0%;95%CI:73-87%)
Conclusions: In elderly patients admitted with sepsis or septic shock, both SOFA and SOFA-T are useful in excluding in-hospital death, allowing a risk stratification and identifying patients that will benefit of an SDU admission.

Table 1.



503. ADMISSION HEART RATE VARIABILITY AND IN-HOSPITAL DEATH IN A COHORT OF ELDERLY PATIENTS ADMITTED FOR SEPSIS AND SEPTIC SHOCK

Carletti S.[1], Lagonigro G.[1], Santini S.[1], Guerrieri E.[1], Diblasi I.[1], Falsetti L.[2], Zaccone V.[2], Fioranelli A.[3], Moroncini G.[4], Burattini M.[3], Tarquinio N.[3]
[1]Emergency Medicine Residency Program, UNIVPM; [2]Internal and Subintensive Medicine Department, Azienda Ospedaliero-Universitaria delle Marche; [3]Medicina Interna, INRCA-IRCCS di Osimo, Ancona; [4]Clinica Medica, UNIVPM

Introduction: an alteration of heart-rate variability (HRV) is a marker of autonomic dysfunction that has been associated to worse outcomes in several critical illnesses, such as in sepsis and septic shock. However, data on this topic do not consider elderly patients, who often show several pre-existing causes of autonomic dysfunction. With this work we aimed to assess whether HRV was associated to worse outcomes in sepsis or septic shock in a cohort of older or oldest-old patients.
Methods: In the timeframe 01/01/2021-01/01/2023 we retrospectively enrolled all the patients admitted to an Internal Medicine Department (INRCA, Osimo) for sepsis or septic shock. In each subject, we assessed age, sex, days of admission, SOFA score, in-hospital death and HRV. HRV was calculated in the admission ECG adopting the SDNN method and treated as a binary variable.
Results: We obtained a cohort of 203 patients (age:83,6±11,3 years, males:53,2%). HRV alteration was present in 129 subjects, and it was associated with in-hospital death in 71 patients (p=0,018, chi-squared test). A HRV alteration was associated to an increased risk of in-hospital death in a Cox Regression model considering days of hospitalization and in-hospital death, but maintained its predictive value even when considering HRV (HR:1.568;95%CI:1,011-2,431;p=0,045), SOFA score (HR:1,126;95%CI:1,048 -1,210;p<0,001) and their intersection.
Conclusions: HRV could be considered as an additive risk factor for in-hospital death also among elderly patients admitted for sepsis or septic shock.

504. ACCURACY OF CHADS2, CHA2DS2-VASC, HAS-BLED AND MACHINE LEARNING MODELS IN PREDICTING THE RISK OF STROKE/TIA AND MAJOR BLEEDING IN CRITICALLY ILL PATIENTS WITH ATRIAL FIBRILLATION: THE AFICILL 2.0 STUDY.

Guerrieri E.[1], Santini S.[1], Giuliani L.[1], Ferrini C.[1], Diblasi I.[1], Pierdomenico G.[1], Zaccone V.[2], Nobili L.[2], Nitti C.[2], Rucco M.[3], Falsetti L.[2], Moroncini G.[4]
[1]Emergency Medicine Residency Program, Università Politecnica delle Marche, Ancona; [2]Internal and Subintensive Medicine, Azienda Ospedaliero-Universitaria delle Marche, Ancona; [3]Biocentis Ltd.; [4]Clinica Medica, Università Politecnica delle Marche, Ancona

Introduction: Non-valvular atrial fibrillation (NVAF) is common among critically ill patients, associated with an increased risk of stroke/TIA (TEE) and major haemorrhage (MB): antithrombotic therapy is difficult, as risk stratification of TEE/MB is performed with unvalidated scores in this setting: CHADS2, CHA2DS2-VASc and HAS-BLED scores were not useful for stratifying TEE/MB in the AFICILL 1 study. 0, and we proposed new methods based on topological data analysis (TDA) and machine learning (ML). With this work, we aimed to validate the ML system on a larger cohort.
Methods: We retrospectively enrolled all consecutive, critically ill patients over a 10-year timeframe, admitted to the our Subintensive Care Medicine Unit, affected by NVAF. CHADS2, CHA2DS2-VASc and HAS-BLED were calculated according the original definitions; we observed therapeutic failure (defined as death or ICU transfer), TEE and MB during admission and calculated accuracy of prediction using ROC curves. AFICILL-ML algorithms generated in the AFICILL 1.0 cohort were validated with this new cohort.
Results: After eliminating trauma and non-critical patients, we obtained 3482 consecutive critical patients (age:78.5±8.82 years; females:52.8%), observing 508 (14.6%) deaths or ICU transfer, 339 (9.70%) TEE and 368 (10.6%) MB. CHADS2 (0.54;95%CI:0.50-0.57;p<0.0001), CHA2DS2-VASc (0.54;95%CI:0.51-0.58;p=0.006) and HAS-BLED 0.51;95%CI:0.48-0.54;p= 0.184) had very low AUCs in predicting TEE/MB. We validated AFICILL-ML with 2870 new patients (1326 already used to generate AFICILL-ML in AFICILL 1.0 group) obtaining ML-TEE AUC:0.96(95% CI:0.94-0-96) and MB-ML AUC:0.97(95%CI:0.95-0.98).
Conclusions: Mortality and ICU transfer, TEE and MB were common. ML algorithms are more accurate than the classical scores in predicting events, and should be considered to guide antithrombotic therapy in this context.

505. DESCRIPTION OF A CASE OF SLEEPING STATE: HOW USEFUL IS THE MORPHOLOGICAL ANALYSIS OF THE ELECTROCARDIOGRAM IN THE DIFFERENTIAL DIAGNOSIS?

De Luca P. [1], Benvenuto A.[1], Sollazzo V.[2], De Luca A.[1]
[1]Dipartimento Internistico Multidisciplinare, Ospedale "T. Masselli-Mascia" San Severo ASL Foggia; [2]Dipartimento Internistico Multidisciplinare, Ospedale "T. Masselli-Mascia" San severo ASL Foggia

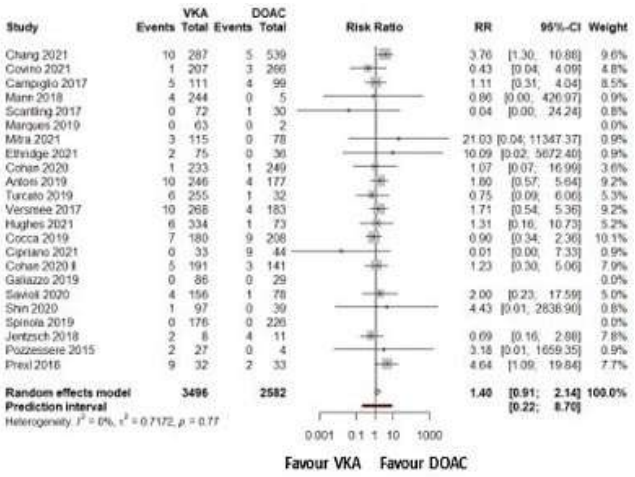
Background: The soporous state is a condition with a multifactorial genesis and the differential diagnosis is often not unambiguous and easy to interpret. In addition to laboratory investigations, which can discern a metabolic factor responsible for this pathological condition, the accurate morphological analysis of the ECG can certainly provide a valid contribution to the identification of the underlying alterations and/or determining the clinical-objective picture.
Clinical Case: A 94-year-old woman, suffering from arterial hypertension, diabetes mellitus, dyslipidemia, osteoporosis, cognitive impairment in vascular dementia, was taken to the emergency room due to sleepiness. Relatives report hyporexia and worsening of the psycho-organic state for a week. The patient is on home therapy with ramipril, furosemide, atorvastatin, metformin, vitamin D, quetiapine and serotonin reuptake inhibitors (citalopram and sertraline). Upon arrival in the emergency room, the patient is sleepy and dehydrated. No chest pain, but mild dyspnea. Blood pressure 130/70 mmHg, heart rate 120/min, oxygen saturation in ambient air 90%, body temperature 36.8°C. High sensitivity Troponin T 150 ng/l. BNP: 620 pg/ml. BUN 108 mg/dl, creatinine 1.80 mg/dl. CPK-MB, sodium and calcium normal. D-dimer 380 ng/ml. Hypokalemia (2.4 mEq/l) and hypomagnesaemia (1.20 mg/dl). At blood gas analysis: metabolic alkalosis (pH 7.58). Toxicological test in urine: negative. ECG: sinus tachycardia 120/min; PR interval at the upper limit of normal (198 ms); QRS within limits (95 ms); ubiquitous pattern of "lambda wave" or "lambda-like" appearance (elevated ST-T complex with rapid descending phase incorporating part or all of the R wave); alternation of ventricular repolarization, characterized by the alternating voltage of the lambda wave. QTc prolonged (510 ms). Echocardiogram: hypertensive heart disease with normal left ventricular kinetics, mild mitro-aortic valve regurgitation with indirect signs of pulmonary hypertension. Chest X-ray: picture of bilateral interstitial disease with basal right pleural effusion layer, but no bronchopneumonic foci. Brain CT: multiinfarct leukoencephalopathy on a chronic vascular basis with notes of cerebral atrophy, no evident signs of ischemia and/or acute haemorrhage.
Discussion Conclusions:
The clinical case described highlights the importance of a correct and targeted methodological approach in the differential diagnosis of a clinical condition that is not easy to interpret, such as sleepiness, for which elderly people are often taken to hospital. In particular, the diagnostic usefulness of a simple and non-invasive examination, such as the electrocardiogram, is highlighted, which can lead to a more precise diagnosis, obviously confirmed after the exclusion of other pathological conditions that can determine or contribute to the appearance of a precise clinical-objective symptomatology.
First of all, hypothermia (Osborn wave), acute cerebrovascular events and acute coronary syndrome were excluded. The ECG appears to be correlated to the synergistic effect of serious disorders and/or drugs. Correction of fluid and electrolyte imbalance and drug washout allowed normalization of the ECG. The lambda wave has been described in cases of ST-segment elevation myocardial infarction ("shark fin" morphology), with negative prognostic significance (see below), in Brugada syndrome and in intracranial hemorrhages (intraparenchymal cerebral hemorrhage and/or subarachnoid). Other causes include: vasospastic angina, Takotsubo cardiomyopathy, hypercalcemic states, propofol infusion, post-electrical cardioversion state, cocaine use, overdose of psychotropic drugs, and severe disorders.
In particular, in the setting of acute ST-segment elevation myocardial infarction (STEMI) the lambda-like pattern is defined as an elevation of the J-point followed by a descending ST-segment that is indistinguishable from the T wave. it is due to profound alterations already present in the earliest stages of ventricular repolarization linked to severe myocardial ischemia. The markedly increased dispersion of ventricular repolarization underlies the high risk of developing ventricular fibrillation/ventricular tachycardia. In fact, it has been shown that this particular ECG sign is related to fatal ventricular arrhythmias, cardiogenic shock and in-hospital mortality.
The overdose of psychotropic drugs (chronic intake and dehydration) and

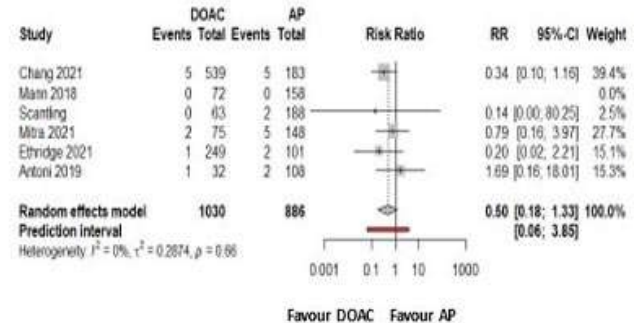
the severe electrolyte alterations can explain both the morphological alterations of the ECG and the lengthening of the QTc. The blockade of the sodium channels and of the voltage-gated calcium and blockade of voltage-gated potassium channels increase transmural voltage gradients resulting in the onset of lambda waves. Systematic exclusion of other causes, the ex juvantibus criterion and biological plausibility validate the diagnosis.

506. RISK OF DELAYED INTRACRANIAL HEMORRHAGE ACCORDING TO ANTITHROMBOTIC TREATMENT IN PATIENTS WITH TRAUMATIC BRAIN INJURY: SYSTEMATIC REVIEW AND META-ANALYSIS

Cimini L.A.[1], Giomi E.[2], Becattini C.[1], Vedovati M.C.[1]
[1]Vascular and Emergency Medicine, University of Perugia; [2]UOC Pronto Soccorso e Medicina d'urgenza, Ospedale Apuane, Massa

Background: Antithrombotic treatment is a risk factor for the development of delayed (DICH) intracranial hemorrhage after head trauma. However, it is not known whether i) the risk of DICH differs according to antithrombotic treatments and ii) the prescription of serial brain CT after a first normal CT scan is indicated.
Aim: The aims of this study are: i) to evaluate the risk of DICH after traumatic brain injury (TBI) according to different antithrombotic treatments (vitamin K antagonist [VKA], direct oral anticoagulants [DOACs], antiplatelets [AP]); ii) to evaluate the usefulness of serial CT scans vs clinical observation to rule out a DICH.
Methods: Medline and Embase databases were searched from inception up to June 2022 to find studies that met the following characteristics: i) enrolling TBI patients admitted to emergency departments within 24 hours since trauma; ii) enrolling patients were receiving VKA, DOACs or APs at the time of TBI; iii) had a normal brain-CT scan at admission. The primary study outcome was DICH, defined as the presence of subdural, epidural, or parenchymal hematoma, subarachnoid hemorrhage, or cerebral contusion.
Results: 3070 records were identified, and 27 observational studies were included. No significant difference in the risk of DICH was observed in patients receiving VKAs or DOACs (23 studies, 6078 patients) at the time of TBI: 2.52% vs 2.01%, risk ratio (RR) 1.40, 95% CI 0.91;2.14, I2: 0% (Fig.1A). Similarly, no difference was observed between patients receiving VKAs or APs (10 studies, 3864 patients): 1.43% vs 1.54%, RR 0.92, CI 95% 0.40;2.14, I2: 0%; and between DOACs or APs (6 studies, 1916 patients): 0.87% vs AP 1.81 %, RR 0.62, 95% CI 0.10-3.71, I2 = 0% (Fig. 1B). No studies comparing serial brain-CT vs clinical observation were found.
Conclusion: Our study shows that the risk of developing DICH after TBI does not differ across the antithrombotic treatments. Further studies should assess the role of serial brain CT in this setting.





507. NEUROGENIC FEVER IN ISOLATED CEREBRAL FAT EMBOLISM

Nurzia C.[1], De Matteis G.[1], De Vito F.[1], Cianci R.[2], Iaquinta A.[3], Gambassi G.[2]
[1]Dipartimento di Medicina Interna, Fondazione Policlinico Universitario A.Gemelli IRCCS, Roma, Italia; [2]Dipartimento di Medicina Interna, Fondazione Policlinico Universitario A.Gemelli IRCCS, Roma, Italia; Università Cattolica del Sacro Cuore; [3]Medicina Interna, Policlinico Casilino, Roma, Italia

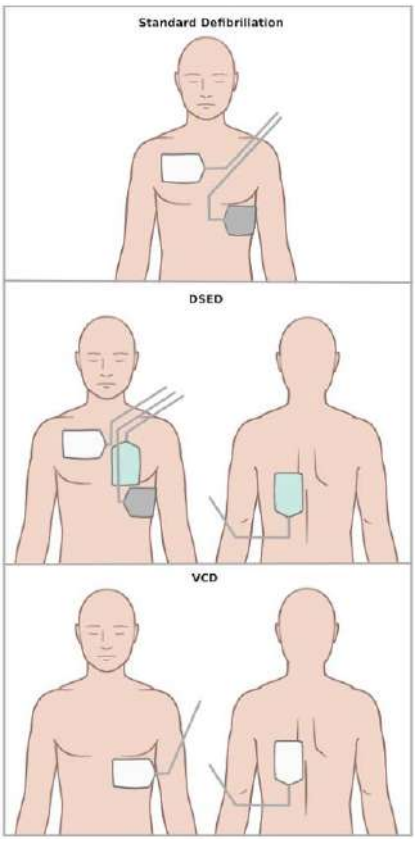
Introduction: Fat embolism syndrome (FES) is a rare complication of long bone fractures. Fat globules generated within the systemic circulation induce pulmonary dysfunction, neurological changes, and dysfunction of several other organs. It occurs 24 to 72 hours after the initial insult and the classic triad includes hypoxaemia, neurologic abnormalities and a petechial rash. Neurogenic fever (NF) is a rare entity that can develop due to autonomic dysregulation in a patient with brain injury, especially hypothalamic injury.
We report a case of neurogenic fever in a patient with isolated cerebral fat embolism (CFE), without pulmonary involvement, after multiple long bone fractures, to provide tips for management and identify critical gaps in knowledge.
Case Report: A previously healthy 20-year-old man was admitted to our hospital because of minimal consciousness in polytrauma, after a motorcycle accident. The patient, after first aid at another hospital, where he presented with a normal state of consciousness (GCS 15), was transferred to our secondary healthcare facility for maxillo-facial competence to treat a left orbital floor fracture. He also sustained several fractures of the left limb.
Upon admission to our Emergency Department, the patient's state of consciousness worsened progressively (GSC 9). A head CT scan with contrast enhancement showed no alterations. Because of further deterioration of the patient's neurologic state (GCS 5), he was intubated and transferred to the Intensive Care Unit (ICU). A brain MRI showed a random distribution of bilateral multiple hyperintensities "starfield-like", suggestive of fat embolism. On day one after admission to the ICU, the fractures were reduced. A transesophageal echocardiography revealed a "tunnel-like" patent foramen ovale (PFO) with significant right-to-left shunt. During the ICU stay, the patient developed hyperthermia, which would abate neither with antibiotic therapy

nor with first-line antipyretic therapy, with a need for diclofenac continuous intravenous infusion and active cooling of the body with a cooling machine (CritiCool).
On day 30, the patient was discharged from the ICU and transferred to the General Medicine department. At admission he appeared alert, in a minimally conscious state with no verbal response to stimulus, in a decerebrate posture (GCS 7), diaphoretic, with a body temperature of 39.6°C, blood pressure of 127/70 mmHg and heart rate of 130 bpm. Empiric antibiotic therapy with vancomycin was started and then upgraded, adding meropenem and ceftazidime/avibactam, after Kl. pneumoniae and a multi-drug-resistant Ps. aeruginosa were isolated in blood cultures.
Blood tests showed rapid improvement of inflammatory markers, but the patient was still hyperpyretic, requiring opioids, clonidine, propranolol, and baclofen in addition to the diclofenac continuous intravenous infusion and the active cooling of the body.
He was slowly weaned off active cooling with the CritiCool, still presenting a mild fever (37.6°C). Chlorpromazine was started and the temperature abated. The patient transitioned to a decorticate posture and a new brain MRI showed resolution of most DWI-restricted diffusion areas.
The patient was transferred to the High-Intensity Neurorehabilitation ward and discharged 8 months after the accident, with minimal self-organization and executive function impairment and complete spontaneous movement in all four arms.
Discussion: CFE without pulmonary involvement is rare. Patients with CFE typically present with a wide range of neurologic dysfunctions, mostly 24-72 hours after trauma or surgery.
Typically, after a long bone fracture, fat particles enter the systemic circulation, possibly causing CFE. In the described case, the patient presented with long bone fractures.
Afterwards he developed isolated neurologic symptoms, with no respiratory involvement. The extended and exclusive brain injury was likely caused by fat embolism shifted mainly to the brain across the patient's patent foramen ovale. In CFE brain damage is caused by micro-embolism, vasogenic edema, and microhaemorrhages. Symptoms in CFE vary widely from diffuse encephalopathy to focal deficits and can be transient.
Our patient presented with a constant hyperpyretic state, and the body temperature was only entirely controlled with active cooling, propranolol and chlorpromazine added to therapy, suggesting a central neurogenic etiology of the patient's fever. Indeed, reports suggest that neurogenic fevers are resistant to traditional pharmacologic therapies. In the described case, CFE may have triggered a dysregulated thermoregulation: we hypothesize that any inflammatory trigger was not counter-regulated, maintaining the high temperature even when the infectious etiology ceased, causing what we can define a neurogenic fever. To date, our case appears to be the first in literature to describe neurogenic fever as a complication of extensive CFE.
Early identification of CFE and of neurogenic fever requires a high index of clinical suspicion and knowledge of the diagnostic workup and is critical for successful treatment and to avoid permanent disability.

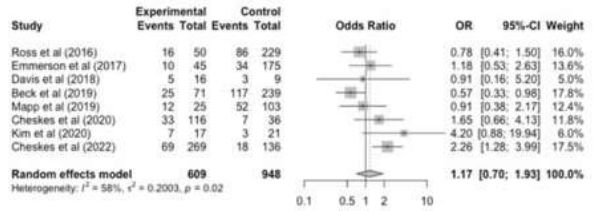
508. ALTERNATIVE DEFIBRILLATION STRATEGIES FOR REFRACTORY VENTRICULAR FIBRILLATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

Perna B.[1], Guarino M.[1], de Fazio R.[1], Esposito L.[1], Portoraro A.[1], Rossin F.[2], Remelli F.[3], Trevisan C.[3], Volpato S.[3], Raparelli V.[1], Marasco G.[4], Barbara G.[4], Stanghellini V.[4], Petrini S.[2], Vason M.[2], De Giorgio R.[1]
[1]Department of Translational Medicine, St. Anna University Hospital of Ferrara, University of Ferrara, Italy; [2]Emergency Department, S. Anna University Hospital of Ferrara, Italy; [3]Department of Medical Sciences, St. Anna University Hospital of Ferrara; [4]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

Background: Out-of-hospital cardiac arrest (CA) with refractory ventricular fibrillation (rVF) represents a dramatic medical emergency. Despite recent advances, its treatment is challenging and still poorly defined. This systematic review and meta-analysis aimed at assessing whether alternative defibrillation strategies (ADS), including double sequential external defibrillation (DSED) and vector-change defibrillation (VCD), improve post-CA survival among individuals with rVF as compared to standard care (SC).



Methods: Randomized clinical trials (RCTs) and observational studies, both prospective and retrospective, were included if: (1) they compared ADS versus SC in rVF; (2) they enrolled individuals older than 18 years; (3) data onsurvival post-CA were available. English-language papers were retrieved from MEDLINE, Google Scholar, Cochrane Library, MeSH, World Health Organization, EMBASE and CINAHL, published from inception to December 2022. The risk of bias was assessed following the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies and the revised Cochrane risk of bias tool for randomized trials, as appropriate. A random-effects meta-analysis was performed to estimate the pooled Odds Ratio (pOR) with 95% Confidence Interval (95%CI) of ADS and survival at hospital admission. Furthermore, a sensitivity analysis was performed to compare SC with each type of ADS. The protocol was registered on PROSPERO (CRD42022379049).
Results: Eight studies (2 RCTs, 5 retrospective and 1 case-control study) were retrieved for qualitative and quantitative analyses. The study population included 1557 individuals (ADS = 609 vs. SC = 948) with a pooled mean age of 62.2 ± 1.8 years; among those, only 296 (19.0%) were female. The random-effect meta-analysis did not show differences in survival at hospital admission among ADS vs. SC (pOR = 1.17, 95%CI: 0.70-1.93). The sensitivity analysis confirmed that neither DSED (pOR = 1.27, 95%CI: 0.67-2.43) nor VCD (pOR = 1.57, 95%CI: 0.83-2.98) were associated with improved survival at hospital admission.



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Conclusion: The present metanalysis did not show any difference on survival at hospital admission post-CA between current available strategies for rVF. However, the small sample size of the prior studies and the female underrepresentation do not allow drawing final conclusions. Therefore, future well-powered trials are very much needed to clarify the more beneficial approach in those individuals post-CA.

509. HYPERTENSIVE EMERGENCIES AND URGENCIES IN EMERGENCY DEPARTMENT: A SIX MONTHS REGISTRY FROM THIRD LEVEL EMERGENCY DEPARTMENT

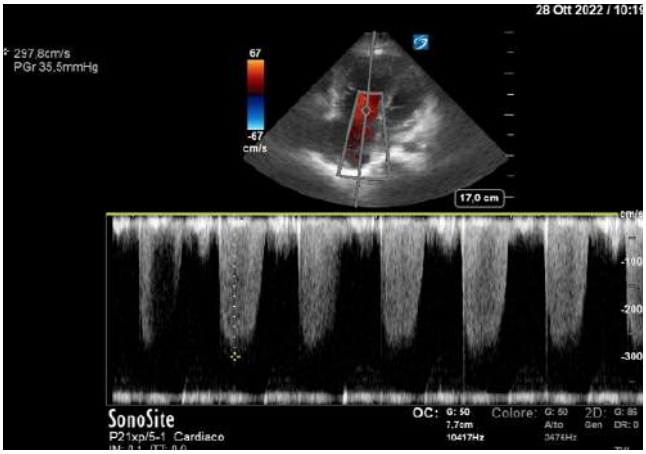
Mancusi C., Fucile I., Paladino F., De Luca N.
Università Federico II di Napoli

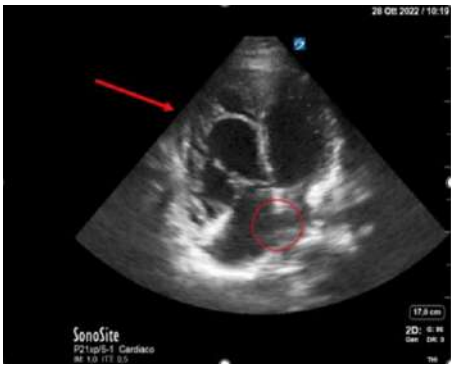
Introduction: Hypertensive emergencies (HE) and urgencies (HU) represent a frequent challenge for physicians in Emergency Department (ED). Rapid and careful assessment of the clinical presentation is crucial in order to allow prompt recognition of HE that require appropriate treatment targeted to the affected organ(s).
Aim: The aim of our study was to evaluate the prevalence, clinical presentation and treatment of patients admitted for HE or HU in ED.
Methods: Medical records of consecutive patients aged at least 18 years, admitted to the ED of "Antonio Cardarelli" hospital in Naples (Italy) over a six month period and presenting with SBP at least 180 mmHg and/or DBP at least 110 mmHg were prospectively analyzed.
Results: We screened 23678 patients and analyzed 224. The mean age of the participants was 65 ± 13 and 55% were men. 76% of the patients had treated hypertension. Overall, 82 had HE and 142 had HU. Among HE, the different forms of organ damage were: acute coronary syndrome (33%), abdominal aorta fissure (2%), acute heart failure (20%), hemorrhagic stroke (16%) and ischemic stroke (22%).
BP values were higher in patients with HE than in those with HU (BP 191 ± 21/104 ± 17 vs 169 ± 23/93 ± 17 mmHg, both p<0.01). Neurological deficit (27%) and dyspnea (28%) were more common among patients with HE than HU (p<0.01).
Total mortality was 4%, higher in the group of patients with HE (90%) (p<0.05);
Conclusion: This 6 months single-center registry demonstrates a reasonable prevalence of HU and HE contributing to the high volume of visits to the ED. Neurological symptoms and dyspnea were the most common presenting symptoms in patients with HE. Acute stroke, acute coronary syndrome and acute heart failure were the most frequent clinical pictures.

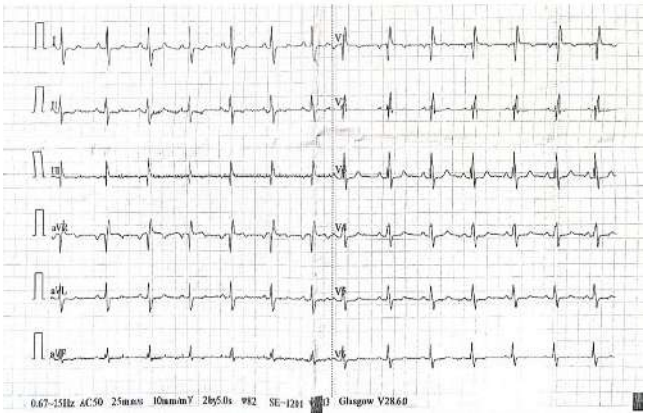
510. FOCUS ON POCUS: ABDOMINAL PAIN IN EMERGENCY DEPARTMENT

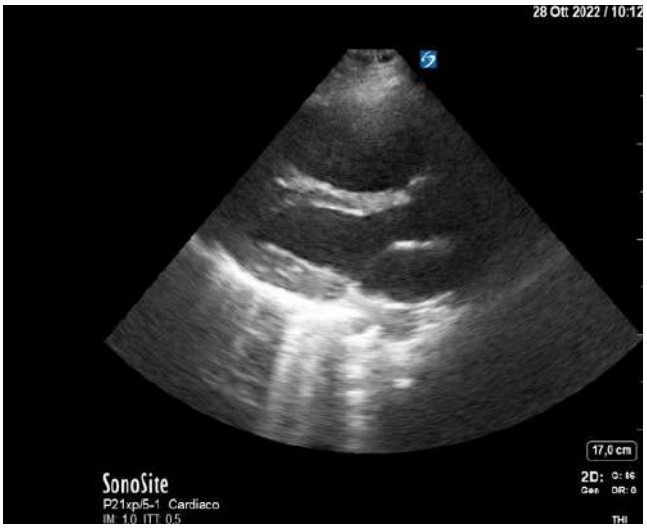
Leggio S.[1], Maiorca D.[2], Scilletta S.[1], Musmeci M.[1], Di Marco M.[1], Miano N.[1], Grasso S.[2], Antic T.[2], Ciampi G.[2], Piro S.[1], Scicali R.[1], Purrello F.[1], Di Pino A.[1]
[1]Dipartimento di Medicina Clinica e Molecolare, Universita di Catania;
[2]U.O.C. di Medicina e Chirurgia d'Accettazione e d'Urgenza, ARNAS Garibaldi, Catania

In emergency department, abdominal pain is a common presentation and a diagnostic challenge for the physician. As demonstrated by Jang *et al* (1), in patient presenting with nonspecific abdominal pain (NSAP), Point of Care Ultrasonography (POCUS) may impact positively on decision making and diagnostic workup in the contest of an Emergency Department (ED). In this case, the use of POCUS associated to clinical examination and diagnostic evaluation, allowed us to make diagnosis of uncommon cause of abdominal pain. A 20-year-old woman went to ED complaining intermittent, non-specific and generalized abdominal pain that had been present since several hours. The patient reported that her symptoms were not triggered by food intake or fasting. Furthermore, she referred intermittent headache since the age of fifteen years old. She had no significant medical history nor previous abdominal surgery. In her family, an uncle died for sudden cardiac death and two cousins of her were affected by non-specified congenital heart disease.At arrival at ED, the patient was well appearing, her clinical signs were stable with blood pressure 120/70 mmHg, heart rate of 60 bpm, O2 saturation 98% on room air. On physical examination her abdomen was flat, soft, and non-distended without palpable mass and gurgling and normoactive bowel sound. Laboratory tests, including blood count and liver, kidney, and pancreatic function, were normal. The serum β-human chorionic gonadotropin level was negative. Coagulation test showed a slightly elevated D-dimer, and we noticed a right branch block (RBB) on EKG. So, we decided to perform POCUS to evaluate any potential causes of her abdominal pain. Following a systematic approach, we began from lower quadrant of abdomen, and we rule out appendicitis, bladder stones and gonadal pathology. Then, we focalized our attention on upper quadrant and rule-out acute cholecystitis, cholelithiasis and choledocholithiasis. We also excluded, with renal POCUS, hydronephrosis and nephrolithiasis. Considering that the patient complained generalized abdominal pain we focused our attention, first, on bowel in order to exclude small bowel obstruction and intussusception and then on large vessel. Aorta was normal in dimension without signs of aneurysm or dissection and inferior vena cava not present thrombus or signs of pathology. Considering RBB on EKG, slight elevated D-dimer, we performed CUS (compression ultrasonography) in bilateral femoral and popliteal vein that resulted negative. Then, considering family history, we decided to perform subxiphoid approach, and we noticed a dilatated right ventricle. So, we passed on POCUS of the heart. We observed, on parasternal long axis and apical 4-chamber, a severe dilatation of right ventricle and interatrial defect. Arterial pulmonary pressure (PAPs) was elevated (40 mmHg). Then, to exclude acute pulmonary embolism, we performed TC scan that showed signs of chronic pulmonary hypertension with dilatated pulmonary artery. So, the patient was recovered in cardiology unit and was diagnosed interatrial defect as ostium secundum. Ostium secundum is the most common type of Atrial septal defects (ASDs). Secundum ASDs are typically located within the fossa ovalis (remnant of the foramen ovale in the right atrium). Unrepaired ASDs may be associated with right heart volume overload, atrial arrhythmia or pulmonary arterial hypertension. In the last years, POCUS is gaining interesting by many clinicians because help them to initial evaluation and management of the patient (2). Indeed, POCUS ensures a rapid and systematic evaluation to different clinical situations, and, for this reason, several protocols have been developed: acute respiratory failure, shock state, severe trauma and cardiac arrest. (3). It can add diagnostic information to clinical examination ad laboratory test and, furthermore, can give essential information to monitor the patient during follow up. Compared to other diagnostic tools such as Rx or Computed Tomography, POCUS allows us to obtain essential information in a short period of time. For these reasons, Emergency ultrasound application, performed by skilled physicians, represent a clinical bedside skill that can be of great advantage in a variety of emergency settings. (4). According to Torres-Macho et al (5), patient presenting to ED with abdominal localized pain, POCUS is useful in can guide the examination with ultrasound. In our case, Abdominal POCUS was useful to rule-out, rapidly, any cause of the symptoms and to focus our attention on the heart as cause of her abdominal pain. Indeed, chronic right heart failure can impair gastrointestinal tract function as a consequence of increased central venous pressure and reduced cardiac output, leading to reduced absorption and malnutrition (6). This case was interesting because if we limited to clinical and laboratory evaluation probably, we didn't make a diagnosis. Otherwise, a POCUS approach can allow us to obtain rapid information on abdomen and thorax and directed us to external causes of abdominal pain.









511. TOO MUCH SALT OR TOO LITTLE WATER: FINDING A BALANCE

Morelli R., Baccaro S., Di Sisto A., Franzese A., Giordano M.
Università degli studi della Campania - L. Vanvitelli

A 66-year-old caucasian woman arrives in the emergency departmen due to a comatose state, history of an unspecified rapidly evolving dementia since 4 years, left femur fracture 6 months earlier with subsequent complete bed rest and difficulty swallowing with progressive inability to eat. On physical examination: Glasgow Coma Scale of 3, markedly reduced vesicular murmur throughout, peripheral oxygen saturation 96% in venti-mask (60% FiO2), skin appears anelastic and dehydrated with dry tongue. Arterial blood gas shows metabolic acidosis with increased anion gap and finding of severe hypernatremia (180 mEq/L) and hyperglycemia (448 mg/dL). We immediately begin correction of the hypernatremia with free water infusion via nasogastric tube (80 mL/hr), 0.2 normal saline (110 ml/hr) and intravenous insulin administration. Chest CT is performed, which identifies bilateral basal foci as from ab ingestis pneumonia and cerebral CT which identifies severe cortical atrophy and cerebral vasculopathy. Laboratory tests shows evidence of thrombocytopenia, acute renal failure (creatinine 2.67 mg/dL), CRP 5 mg/dL and procalcitonin 3.30 ng/mL. We take two sets of peripheral vein blood cultures and begin empiric antibiotic therapy with meropenem and, after 48 hr, she is admitted to the Medicine department. Here, hypernatremia (160 mEq/L), metabolic acidosis and hyperglycemia persist, bedside ultrasound shows the presence of filiform IVC, therefore we continued infusion of hypotonic solution, with buffered glucose and bicarbonates and continuous enteral nutrition via NGT. Our main focus was the controlled reduction of serum sodium: we calculated the free water deficit, of which we administered 2/3 as glucose solution 5% and the remaining 1/3 as free water through NGT. The target, in a symptomatic patient with hypernatremia, is to reduce the serum levels of 1.0 mEq/l/h (maximum 10-12 mEq/24h), with the aim of bringing the Na levels to target within about 72 hours. It is of utmost importance the monitoring of the neurologic state as an extremely fast correction can potentially lead to cerebral edema and central pontine myelinolysis. The following day the patient's clinical conditions worsen, with evidence of anuria with hypotension unresponsive to fluids; we make diagnosis of hypovolemic shock so we begin norepinephrine infusion and continue O2 therapy. At fourth day from admission, there is a gradually restoration of blood pressure and blood volume, a slight improvement in the pulmonary condition, with a reduction in the need for O2, normalization of sodium and glucose values, the dosage of the inotrope is progressively reduced until it is completely discontinued. Previously sent culture samples come negative. The state of consciousness improves with spontaneous opening of the eyes and reactivity to verbal stimuli, pulmonary imaging is repeated, and meanwhile we assist to a reduction of the inflammatory process and contextually inflammatory indices and procalcitonin negativization. Transfusion of two units of GRC is required for evidence of multifactorial normochromic normocytic anemia in the absence of obvious blood loss. Once hemodynamic stability has been reached in the absence of the use of inotropes, the patient moves to another facility for continuity of care.
Conclusions: the development of hypernatremia, especially in a non-autonomous patient affected by dementia in advanced state, can easily go overlooked. Its management requires precise and tailored fluid intervention, with fluid administration and continuous monitoring through ABGs, in specific time windows.Furthermore, the management of the hemodynamic conditions related to the fluid-electrolyte unbalances is paramount in the acute setting in order to reduce patient morbidity and mortality.

512. THE DARK SIDE OF THE SGLT2: A STRANGE CASE OF KETOACIDOSIS IN A PATIENT WITH DIABETES MELLITUS ON METFORMIN AND EMPAGLIFLOZIN

Petralia M.[1], Sberna F.[1], Vinciguerra G.[1], Carpinteri G. [2], Campagna D.[3]
[1]Scuola di specializzazione MEU - Università di Catania; [2]U.O.C. MCAU P. O. "G. Rodolico" - A.O.U. Policlinico "G. Rodolico - San Marco" di Catania; [3]Dip. di Medicina Clinica e Sperimentale - Università di Catania

S.J.M. an Argentinian man (47 y.o.) affected by type 2 diabetes mellitus (T2DM) for 5 years presented the Emergency Department of the Policlinico teaching Hospital of Catania for nausea, vomit, abdominal pain and general discomfort. He was in treatment with sitagliptin/metformin (50 mg + 1000 mg) with a very recent add of empagliflozin (25 mg) because of the glycaemic decompensation (HbA1c 14%).
At the first medical visit, the patient was hemodynamically stable, with no abnormalities at physical examination. However, the Arterial Blood Gases (ABG) showed a severe metabolic acidosis (pH 6.9, pCO2 46 mmHg, HCO3- 4.6 mmol/L, Lac 2.4 mmol/L, Na+ 137 mmol/L, K+ 4.28 mmol/L, Cl- 104 mmol/L, Glu 226 mmol/L, BE -46 mmol/L). Other blood test showed signs of dehydration as increased value of Hb (17.7 g/dL), HT 51.2 %, PLT 434.000, WBC 17.49*103, NEUT 14.47*103/µL; furthermore CRP (8.33 mg/L), Glucose (238 mg/dL), (Creatinine 1.2 mg/dL) and fibrinogen (414 mg/dL) were slightly altered.
Because of the suspect of metabolic acidosis due the use of metformin, the patient was immediately treated with sodium bicarbonate infusion and fluids. A close monitoring of HGT and potassium values was performed by serial checks of ABG.
Despite the therapy, patient's clinical conditions worsened with a persistence of metabolic acidosis (PH 7, K+ 4.26 mmol/L, Lac 3.9 mmol/L, HCO3- 4.6 mmol/L, Hb 16 g/dL, Glu 310 mmol/L). So 10 units of rapid insulin were added to the therapy with an improvement of the acidosis (pH 7.31, HCO3 6.4 mmol/L, lac 1.5 mmol/L, Na+ 133 mmol/L, K+ 2.85 mmol/l).
Given this kind of clinical and blood chemistry presentation, a hypothesis of euglycemic ketoacidosis as an adverse drug reaction empaglifozin was supposed. After clinical stabilization, the patient was admitted to the Internal Medicine Ward.
During the stay in this ward, a diabetological consult suspected the presence of a Latent Autoimmune Diabetes of Adults (L.A.D.A.). Proper antibodies were requested for diagnosis. In the general ward an infusion of sodium bicarbonate, insulin and potassium iv continued, but the patient started to feel sick, tired and somnolent. A new ABG check showed severe metabolic acidosis: pH 7.03, pCO2 10 mmHg, pO2 140 mmHg, HCO3- not detectable. Due to the worsening of the patient's clinical conditions a transfer to a semi-intensive ward was arranged with the diagnosis of "Metabolic acidosis and diarrhoea as empagliflozin adverse event".
In the meantime, LADA's antiboides resulted one negative (anti-MAG) and one slightly positive (islet cell antibodies 1/80 - normal values > 1/20).
During the stay in semi-intensive ward, basal-bolus insulin subcutaneous

therapy was fixed, infusion of sodium bicarbonate, lactated Ringer's solution and KCl until stabilization of the clinical status and the normalization of ABG values. After discharge, patient continued his follow up visits at the Department of Endocrinology with a good response to insulin therapy. Finally, he was fine. Of course, he did not resume previous oral metformin and empagliflozin therapy. This case report let us to properly think to T2DM diagnosis in a young patient. All types of DM have to be taken into account and excluded when possible. So clinicians have to be more careful and prescribe the appropriate treatment before giving a SGLT2 inhibitor without a specific indication as history of heart failure or chronic renal disease.
SGLT2 inhibitors are new drugs with a lot of benefits for renal and cardiac function. They were assessed to reduce mortality and hospitalisation with an excellent safety profile. However, we have to remember recent clinical studies that showed these drugs could provoke metabolic acidosis in some rare cases. The new challenge for clinicians is to early recognize signs and symptoms of this rare condition and stop these drugs as soon as possible switching to intravenous insulin and support therapy.
In addition, clinical studies show that this side effect to SGLT2 inhibitors is more common in type 1 diabetes mellitus (T1DM) than in type 2, indeed these drugs are not indicated in T1DM. Therefore, this particular case of severe metabolic and euglicemic chetoacidosys as side effect of empaglifozin in addition to the clinical history and the glycaemic decompensation let us suspect L.A.D.A. as real diagnosis, even if the dosage of specific antibodies was not conclusive.
The take home message of this case report is that a wrong diagnosis with a consequent inappropriate treatment could be very dangerous.

513. IT'S ALL ABOUT THE BRAIN

Galiero G.[1], Puoti M.[1], A. Di Sisto[1], Fischetti S.[1], Giordano M.[1], Paolisso G.[2]
[1]Dipartimento di Medicina ed emergenze, P.O. Marcianise Prof. Mauro Giordano - Università degli studi della Campania Luigi Vanvitelli;
[2]Dipartimento di Medicina Interna, Università degli studi della Campania Luigi Vanvitelli

In this abstract we discuss the clinical case a 72 years old man who was taken to the hospital for a sudden coma. He arrived in a critical condition: he was soporous and not responsive to painful, tactile or verbal stimuli (Glasgow coma scale: 3/15). He presented with a blood pressure of 100/70 mmHg, an irregular pulse of 80 beats per minute due to his atrial fibrillation, a peripheral oxygen saturation of 98% on air and, additionally he was pyretic (Tc 38,5 °C). According to his presentation, he was assigned a blue code. His daughter provided his past medical history. He was a smoker who suffered from diabetic mellitus with micro and macroangiopathy (he had his left toe amputated), ischemic heart disease and hypertensive disease in permanent atrial fibrillation, chronic kidney disease and COPD with frequent bronchial inflammatory flare-ups. Blood tests showed abnormal values: severe hyperglycemia (Glucose: 500 mg/dL), severe hypernatremia (Na 160 mmol/L, corrected for glycemia), acute renal failure with an estimated glomerular filtrate of 8 ml/min/1.73 m2 (CKD-EPI) and raised inflammatory markers suggesting of sepsis. An urgent head CT scan was done, that excluded a stroke and only showed signs of chronic cerebral vasculopathy. He had done an abdominal and chest CT scan, that showed kidney stones with inflammation of the perirenal tissue suggesting a sepsis secondary to a urine tract infection. A continuous intravenous hypotonic sodium chloride solution with rapid acting insulin was given to treat both the glycemic and electrolyte desorders. An empiric antibiotic therapy was started to avoid delays in treatment, then adjusted once microbiology results were available; the blood culture showed a staphilococcous haemolyticus systemic infection. Finally, fluids were administered to restore water balance with focus on kidney function. After a few days there was an improvement of some of the clinical presentations described: blood glucose returned within normal range, electrolyte improved with consecutive improvement of renal function and a partial resolution of the septic state with slight reduction of inflammatory markers. However, the patient still had fever and remained in a soporous state (Glasgow coma scale: 5/15), showing only a very slight overall improvement. Therefore, a neurological cause of his altered state was highly suspected. As per his fever, a possible encephalitis was suspected and a rachicentesis with cerebrospinal CSF sampling and filmarray was performed: the negative results excluded a bacterial or viral infection. Subsequentially, an MRI scan was done: the exam showed an encephalitis pattern called ADEM: acute disseminated encephalomyelitis. This is an is an inflammatory demyelinating disorder which most often occurs in children following an infection, and it is characterized by encephalopathy and multifocal neurological deficits. The presumed cause is an autoimmune response against myelin-associated peptides triggered by infectious agents with similar epitopes. When occurring in adults, ADEM reports a worse outcome with higher mortality (> 10%) and high rate of residual neurological deficits in patients who survive (47.5%). First line treatment for ADEM was quickly administrated: IV methylprednisolone 30 mg/Kg/day. However, the expected result was not achieved and sadly he passed away a few days after starting the corticosteroid treatment. Despite the unwanted result, this remains a very interesting case which shows the value of observing the patient and making an overall clinical assessment in order to reach a diagnosis in a timely manner. It is paramount to observe, to reason and not exclude even the least likely hypotheses from the differential diagnosis. Fascinatingly ADEM is a rare disorder with an incidence of about 0.26 per 100,000 persons in adults and yet a case presented to our hospital. Observing and analysing the clinical data was key to reach the diagnosis. It was all about the brain.

514. PAIN MANAGEMENT AT THE END OF LIFE IN THE EMERGENCY DEPARTMENT. A NARRATIVE REVIEW.

Spampinato M.D.[1], Serra S.[2], Riccardi A.[3], Guarino M.[4], Fabbri A.[5], Orsi L.[6], De Iaco F.[7]
[1]Department of Translational Medicine and for Romagna, University of Ferrara, 44124, Ferrara, Italy ; [2]Emergency Department, Maurizio Bufalini Hospital, Cesena, 47521, Italy; [3]Pronto Soccorso Ospedale di Imperia, 18100, Imperia, Italy; [4]UOC MEU Ospedale CTO- AORN dei Colli Napoli, 80131, Napoli, Italy; [5]Emergency Department, AUSL Romagna, Presidio Ospedaliero Morgagni-Pierantoni, 47121 Forlì, Italy; [6]Palliative care physician and Scientific Director of "Rivista Italiane di Cure Palliative" , Crema (CR), 26013; [7]Struttura complessa di Medicina di Emergenza Urgenza Ospedale Maria Vittoria, ASL Città di Torino, 10144 Torino, Italy

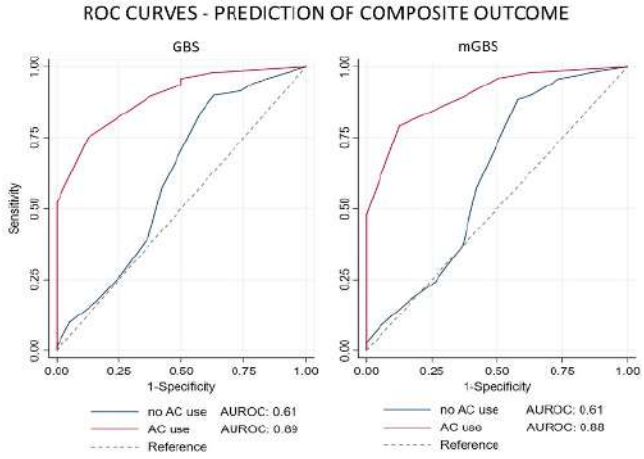
Access to pain management is a fundamental human right for all people, including those who are at the end of life (EOL). For end-stage patients, severe and uncontrolled pain is a common cause of admission to the emergency department (ED) and its treatment is challenging due to its complex, often multifactorial genesis. This systematic review (SR) was conducted on MEDLINE, SCOPUS EMBASE and CENTRAL up to 1 April 2023 and included randomised controlled trials, observational studies, systemic or narrative reviews, case reports and guidelines on the management of end-of-life pain in the ED. A total of 589 articles were identified (136 in MEDLINE, 11 in SCOPUS, 374 in EMBASE and 68 in CENTRAL), and 9 articles were finally included. In this SR, i) the available literature on the management of severe EOL pain in ED was reviewed; ii) knowledge gaps were identified; and iii) the available medications for the management of EOL pain were reviewed. We provide elements for a multidimensional, patient-centred pain assessment and multidisciplinary approach to end-of-life pain management in ED, including non-pharmacological and pharmacological techniques and palliative sedation.

515. UPPER GASTROINTESTINAL BLEEDING RISK SCORES: EFFECTS OF ANTICOAGULANT THERAPY

Di Gioia G.[1], Paglia A.[2], Parente F.[3], Cornacchia M.G.[1], Cavallone F.[1], Villani R. [1], Romano A.D.[1], Serviddio G.[1], Sangineto M.[1]
[1]University Center for Liver Disease Research and Treatment (C.U.R.E, Liver Unit, Department of Medical and Surgical Sciences, University of Foggia; [2]U.O.C. Medicina Interna, P.O. "S.C.Novella" di Galatina, ASL Lecce; [3]U.O.C. Medicina Interna Ospedale "V. Fazzi", Lecce

The upper gastrointestinal bleeding (UGIBs) is a leading cause of hospital admission worldwide with an annual incidence of 50-150/100.000 cases depending on risk factors such as advanced age, prior UGIB, and the use of anticoagulants (AC). Individuals with severe UGIB often present hemodynamic failure requiring advanced medical support and hospitalization. This entails high mortality and morbidity rate, and high health-care costs. Despite their proven benefits in preventing and treating thrombo-embolism, AC drugs are associated with an increased risk of bleeding from the gastrointestinal (GI) tract. Among AC medications, differences in terms of GI bleeding rates between direct-acting anticoagulant (DOACs) and vitamin K antagonists (AVK) are still debated. In order to predict relevant outcomes including in-hospital mortality, severity of GI bleeding, rebleeding and length of hospital stay, several risk scores have been developed. Moreover, scores have been suggested to be useful tools for UGIB patient stratification: "low-risk" UGIB candidates for outpatient management, while "high-risk" patients are hospi-

talised as they may require urgent endoscopy or intensive care. Demographic, biochemical, clinical and endoscopic data - but not anticoagulant medications use – are considered in some of the most recommended scores for UGIB assessment such as Aims65, Rockall and Clinical Rockall (C-Rockall), Glasgow-Blatchford Bleeding (GBS) and its modified version (mGBS). In this study we explored the effects of AC medications use on these scores in predicting a composite endpoint (transfusion, bleeding lesion findings, endoscopic treatment and rebleeding) and in-hospital mortality. We recruited 145 patients admitted for acute UGIB to the Internal Medicine Unit, "Vito Fazzi" Hospital, Lecce and to the Liver Unit, University Hospital of Foggia between November 2021 and May 2022. All participants underwent esophagogastroduodenoscopy. Given the aim of our study we excluded patients with severe haematological disorders, inflammatory bowel disease, simultaneous bleeding from a non-gastrointestinal source and lack of laboratory findings for the risk scores assessment. Patients' data about sociodemographics, clinical signs, medical history, medication usage and laboratory tests were collected. Additionally, information about vital status, endoscopic findings, need for packed red blood cells transfusion, management of bleeding with need for haemostatic procedures and the need for repeated endoscopies due to rebleeding were gathered. We compared Aims65, Rockall, C-Rockall, GBS and mGBS scores' ability to predict the predetermined outcomes separately, using logistic regression, area under the receiver operating characteristic curves (AUROCs) and 95% confidence intervals (CI). Following, we repeated the analyses taking into account AC medication use and compared the AUROCs. Finally, we stratified the analyses for composite outcome by specific AC category (DOACs and AVK; no sufficient data for EBPM).Aims65 (OR=4.99, AUROC= 0.77, 95% CI 0.63-0.91) was the only risk score associated with mortality rate, but no significant differences were found in AUROCs when considering AC therapy. GBS (OR=1.35, AUROC= 0.70, 95% CI 0.59-0.82) and mGBS (OR=1.40, AUROC= 0.70, 95% CI 0.58-0.85) were positively associated with the composite outcome. Significant differences were found when accounting for AC therapy; in particular, GBS showed higher AUROC when considering AC users compared to those not taking AC (AUROC= 0.89, 95% CI 0.79-0.95 vs. AUROC= 0.61, 95% CI 0.44-0.77; p-value=0.001) as well as mGBS (AUROC= 0.88, 95% CI 0.80-0.97 vs. AUROC= 0.61, 95% CI 0.44-0.78; p-value=0.004). The results of analyses of specific AC medications indicated a statistically significant association between GBS (OR=1.24, AUROC= 0.68, 95% CI 0.55-0.81) and mGBS (OR=1.28, AUROC= 0.69, 95% CI 0.55-0.82) with composite outcome in DOACs users. AUROCs showed significant differences when comparing participants taking DOACs to those not taking AC for GBS (AUROC= 0.89, 95% CI 0.70-0.99 vs. AUROC= 0.61, 95% CI 0.44-0.77; p-value=0.02) and mGBS (AUROC= 0.90, 95% CI 0.73-0.98 vs. AUROC= 0.61, 95% CI 0.44-0.78; p-value=0.01). Similarly, in participants taking AVK, GBS (OR=1.23, AUROC=0.64, 95% CI 0.50–0.78) and mGBS (OR=1.27, AUROC=0.64, 95% CI 0.48–0.78) were associated with the composite endpoint but not significant differences were found after stratification for AVK users. UGIBs remain a major concern and developing valuable tools able to detect UGIBs severity represents a crucial challenge. AC use is a key factor to be considered in bleeding risk assessment. According to our results, Glasgow-Blatchford Bleeding (GBS) and its modified version (mGBS) may be biased by not considering anticoagulant therapy, especially DOACs, in assessing UGIB severity. Taking into account anticoagulant use may improve UGIB risk scores performance.



516. CORRELATION BETWEEN MILD TRAUMATIC BRAIN INJURY AND D-DIMER: A PROSPECTIVE STUDY

Balsamo I.[1], Candelli M.[2], Gemma S.[3], Pignataro G.[4], Pala M.[5], Lumare M.[6], Tullo G.[7], Novelli M.[8], Spaziani G.[9], Sacco Fernandez M.[10], Rozzi G.[11], Piccioni A.[12], Ojetti V.[13], Franceschi F.[14]

[1]Department of Emergency Medicine, University Cattolica del Sacro Cuore, Facoltà di Medicina, Rome, RM, IT; [2]Department of Emergency Medicine, Fondazione Policlinico Universitario A. Gemelli – IRCCS of Rome, RM, IT. ; [3]Department of Emergency Medicine, University Cattolica del Sacro Cuore, Facoltà di Medicina, Rome, RM, IT.; [4]Department of Emergency Medicine, Fondazione Policlinico Universitario A. Gemelli – IRCCS of Rome, RM, IT; [5]Department of Emergency Medicine, University Cattolica del Sacro Cuore, Facoltà di Medicina, Rome, RM, IT; [6]Department of Emergency Medicine, University Cattolica del Sacro Cuore, Facoltà di Medicina, Rome, RM, IT; [7]Department of Emergency Medicine, University Cattolica del Sacro Cuore, Facoltà di Medicina, Rome, RM, IT. ; [8]8. Department of Emergency Medicine, University Cattolica del Sacro Cuore, Facoltà di Medicina, Rome, RM, IT; [9]Department of Emergency Medicine, University Cattolica del Sacro Cuore, Facoltà di Medicina, Rome, RM, IT.; [10]Department of Emergency Medicine, University Cattolica del Sacro Cuore, Facoltà di Medicina, Rome, RM, IT; [11]Department of Emergency Medicine, University Cattolica del Sacro Cuore, Facoltà di Medicina, Rome, RM, IT. ; [12]Department of Emergency Medicine, Fondazione Policlinico Universitario A. Gemelli – IRCCS of Rome, RM, IT; [13]Department of Emergency Medicine, University Cattolica del Sacro Cuore, Facoltà di Medicina, Rome, RM, IT; [14]Department of Emergency Medicine, Fondazione Policlinico Universitario A. Gemelli –IRCCS of Rome, RM, IT

The aim of this study was to investigate the prognostic role of D-dimer in predicting cerebral hemorrhage in patients with mild traumatic brain injuryBackgroundTraumatic brain injury is the most common cause of death and disability among all trauma-related injuries. Mild traumatic brain injury accounts for 80% of all trauma and is characterized by a GCS score of 14-15. Acquired coagulopathy is known to be associated with posttraumatic hemorrhage and correlates with in-hospital mortality rates of up to 50% and poor outcomes. Acute traumatic coagulopathy is the result of an imbalance between anticoagulant and procoagulant factors, endothelial function, and fibrinolysis due to tissue damage and hypoperfusion in trauma, which can lead to progressive hemorrhagic injury.The relationship between coagulation and fibrinolysis parameters and treatment outcome is a focus of research. D-dimer is an end product of both coagulation and fibrinolysis (it is a breakdown product of fibrin), and its elevated plasma levels at the time of admission are thought to reflect the overall upregulation of hemostasis after trauma.Materials and methodsFrom April 1 to September 30, 2022, we collected data on all patients admitted to the emergency department of the Fondazione Policlinico Gemelli with a mild head injury. For the entire study population, we analyzed demographic characteristics (eg, age, sex), preexisting risk factors (eg, alcohol and drug use, anticoagulant therapy), trauma-related factors (eg, diffuse worsening headache, loss of consciousness), and determined D-dimer levels. We then divided patients into low, intermediate, and high risk, as suggested by current Italian guidelines.We divided patients into two groups: those with and those without CT scans indicating cerebral hemorrhage. We examined all known risk factors to determine which of them were actually associated with cerebral hemorrhage, both in univariate and multivariate analysis after adjustment for confounding factors. We compared D-dimer concentrations between patients with and without posttraumatic cerebral hemorrhage. Finally, we examined D-dimer concentrations in different subgroups of patients (patients with fractures, patients not taking anticoagulants, and patients with fractures not taking anticoagulants)ResultsWe enrolled 370 patients, 178 (48.1%) men, with a mean age of 63.2 ± 23.8 years; 57.8% were older than 65 years.The major trauma dynamic (21.4%) was the most frequent risk factor due to trauma.82 patients were taking antiplatelet agents and 61 anticoagulants. Based on the risk factors, we found a high risk in 15.4% of the patients examined, a moderate risk in 52.2%, and a low risk in 32.4%.At the first CT examination, we found 51 hemorrhages, of which 18 were subdural, 20 subarachnoid, 2 epidural, and 11 intraparenchymal.Of the patients who underwent follow-up head CT scan within 6-48 hours (31.6%), only 4 patients had cerebral hemorrhage. In addition, only one patient underwent neurosurgery, and 4 patients died within 30 days.In univariate analysis, gender (p=0.013), headache (p=0.012), loss of consciousness (p=0.022), retrograde amnesia (p< 0.001), and major trauma dynamics (p=0.012) were found to be risk factors for hemorrhage; In multivariate analysis, only male sex proved to be an independent risk factor for hemorrhage (OR =2.101, p=0.030), while younger age was a protective factor (OR =0.973, p=0.002).We investigated the correlation between D-dimer

levels and the presence or absence of bleeding, but it was not possible to determine a cut-off value with good sensitivity, specificity, or accuracy. D-dimer levels did not correlate with the presence of cerebral hemorrhage in patients with (3523±6723 vs. 2354±5439, p=0.13) and without fractures (2392±4814 vs. 1992±3654, p=0.48); D-dimer levels did not differ between patients with and without hemorrhage, even in patients not treated with anticoagulants (2672±5497 vs. 1861±2306, p=0.1). Only in patients without fracture and without anticoagulant treatment we found a significant difference in Didmer values between patients with and without cerebral hemorrhage (2235±4488 vs. 1373±1936, p=0.05). However, diagnostic accuracy, as measured by the area under the ROC curve, was also low in this case (< 0.6). D-dimers were not useful for distinguishing cerebral hemorrhage in patients with mild traumatic brain injury.ConclusionsD-dimer was not useful for discriminating between patients with and without cerebral hemorrhage. Its usefulness in a specific subgroup of patients (not taking anticoagulants and not having fractures) should be further investigated in larger prospective studies

METABOLISMO E OBESITÀ

517. ANALYSIS OF STEATOSIS BIOMARKERS AND INFLAMMATORY PROFILE AFTER ADDING ON PCSK9 INHIBITOR TREATMENT IN FAMILIAL HYPERCHOLESTEROLEMIA SUBJECTS WITH NONALCOHOLIC FATTY LIVER DISEASE

Bosco G., Di Pino A., Urbano F., Ferrara V., Marchisello S., Di Mauro S., Scamporrino A., Filippello A., Rabuazzo A.M., Purrello F., Piro S., Scicali R.
Dipartimento di Medicina Clinica e Sperimentale, Università degli Studi di Catania

Non alcoholic fatty liver disease (NAFLD) may be crucial in subjects with familiar hypercholesterolemia (FH). We aimed to evaluate the effect of the proprotein convertase subtilisin/kexin type 9 (PCSK9-i) on steatosis biomarkers such as triglyceride-glucose index (TyG) and hepatic steatosis index (HSI) and analyse the role of TG/ HDL in this population before and after adding-on PCSK9-i.
In this observational study, we evaluated 26 genetically confirmed FH patients with NAFLD and an LDL-C off-target despite high-intensity statins plus ezetimibe. All patients added PCSK9-i treatment and obtained biochemical analysis and TyG and HSI evaluation at baseline and after six months of PCSK9-i.
No difference of steatosis biomarkers was found after adding-on PCSK9-i therapy. In a secondary analysis, we divided the study population in two groups according to TG/HDL median value: high TG/HDL group (H-TG/HDL) and low TG/HDL group (L-TG/HDL). TyG and HSI were significantly lower in the L-TG/HDL than H-TG/HDL group (for TyG 9.05 ± 0.34 vs 9.51 ± 0.32; for HSI 38.43 ± 1.35 vs 41.35 ± 1.83, p value for both < 0.05). After six months of PCSK9-i therapy, TyG and HSI were significantly reduced in the L-TG/HDL group after PCSK9-i therapy (7.5% and 8.4% respectively, p value for both < 0.05) and these biomarkers were lower compared to H-TG/HDL group (for TyG 8.37 ± 0.14 vs 9.19 ± 0.12; for HSI 35.19 ± 1.32 vs 39.48 ± 1.33, p value for both < 0.05).
PCSK9-i therapy significantly ameliorate steatosis biomarkers in FH patients with low TG/HDL; results may be consistent with a beneficial role of PCSK9-i on steatosis biomarkers in FH subjects with NAFLD.

518. EVALUATION OF HDL-BOUND LONG NON-CODING RNAS IN SUBJECTS WITH FAMILIAL HYPERCHOLESTEROLEMIA

Di Giacomo Barbagallo F.
Dipartimento di Medicina Clinica e Sperimentale Università degli Studi di Catania

Aims: Long non-coding RNAs (IncRNAs) could be attractive circulating biomarkers for cardiovascular risk stratification in subjects at high ASCVD risk such as familial hypercholesterolemia (FH). Our aim was to investigate the presence of IncRNAs carried by HDL in FH subjects and to evaluate the associations of HDL-IncRNAs with lipoproteins and mechanical vascular impairment assessed by pulse wave velocity (PWV).
Methods: This was a retrospective observational study involving 94 FH subjects on statin treatment. Biochemical assays, HDL purification, IncRNA and PWV analyses were performed in all subiects.
Results: LncRNA HIF1A-AS2, LASER and LEXIS were expressed in HDL; moreover, HDL- IncRNA LEXIS was associated with Lp(a) plasma levels ($p < 0.01$). In a secondary analysis, the study population was stratified into two groups based on the Lp(a) median value. The High-Lp(a) group exhibited a significant increase of PWV compared to the Low-Lp(a) group (9.23 ± 0.61 vs 7.67 ± 0.56, $p < 0.01$). While similar expressions of HDL-IncRNA HIFIA-AS2 and LASER were found in the two groups, the High-Lp(a) group exhibited a significant downregulation of HDL-IncRNA LEXIS compared to the Low-Lp(a) group (fold change -4.4, $p < 0.0001$).
Finally, Lp(a) and HDL-IncRNA LEXIS were associated with PWV (for Lp(a) p < 0.01; for HDL-IncRNA LEXIS $p < 0.05$).
Conclusions: LncRNA HIFIA-AS2, LASER and LEXIS were expressed in HDL; moreover, significant relationships of HDL-lncRNA LEXIS with Lp(a) levels and PWV were found. Our study suggests that HDL-IncRNA LEXIS may be useful to better identify FH subjects with more pronounced vascular damage.

519. IMPACT OF MALNUTRITION-ASSOCIATED HEPATIC STEATOSIS, MYOSTEATOSIS AND CONUT SCORE ON IN-HOSPITAL OUTCOMES IN AN INTERNAL MEDICINE DEPARTMENT

Miano N., Todaro G., Di Marco M., Scilletta S., Leggio S., Capuccio S., Scicali R., Piro R., Purrello F., Di Pino A.
Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy

Background and aims: Malnutrition is considered a prognostic indicator of worse in-hospital outcomes and many studies have identified both fatty liver disease and myoteatosis as markers of malnutrition in different clinical settings. There is currently no standardized non-invasive diagnostic approach for identifying patients with malnutrition, fatty liver disease and myosteatosis, however, computed tomography (CT) and Magnetic Resonance Imaging (MRI) have been increasingly used. There is currently no gold standard method for diagnosing malnutrition and the available methods are not useful for daily clinical practice primarily because of their effectiveness/cost ratio. Recently, a new score has emerged, the COntrolling NUTritional status score (CONUT score), which appears to have a promising prognostic impact in many clinical settings. It is based on the serum albumin concentration, total cholesterol (TC) serum levels and total peripheral lymphocyte count. In view of the importance of an early identification of patients with malnutrition, an appropriate nutritional assessment tool should be highly recommended in Internal Medicine Departments. Given the CONUT score includes the nutrition and immune response, it was hypothesized that it could predict in-hospital prognosis. Thus, the aim of this study was to investigate a possible correlation between the presence of malnutrition, estimated by the presence of liver steatosis and/myosteatosis evalued by CT images, and CONUT score. Moreover, we evaluated the impact of malnutrition on in-hospital outcomes such as all cause death, sepsis and length of in-hospital stay.
Methods: This is a retrospective study analyzing clinical, pathological and radiological data from 127 patients, hospitalized in the Internal Medicine Department of Garibaldi-Nesima-Hospital in Catania, Italy. We collected data on liver radiodensity and skeletal muscle radiodensity by evaluating X-ray attenuation in the peripheral areas of the liver parenchyma and on the right multifidus muscle trough abdomen CT without contrast medium. The CONUT score was calculated, according to the original study, from the serum albumin concentration, total peripheral lymphocyte count, and TC concentration. Our population was stratified into three groups based on the values of hepatic radiodensity: absence of steatosis (≥60 HU), mild steatosis (between 50 and 59.99 HU), moderate-severe steatosis (≤48 HU).
Then, we further, stratified patients into 2 groups: those with a CONUT score 5-12 (high CONUT) and those with a CONUT score 0–4 (low CONUT). The primary outcome measure of the present study was to evaluate a possible correlation between CONUT score, hepatic steatosis and myosteatosis . The secondary outcome was to estimate the prognostic impact of malnutrition on in-hospital outcomes such as all cause of death, sepsis and length of stay. We used a multivariable logistic regression model, subsequently adjusted for possible confounders.
Results: Baseline characteristics of our population are reported on Table 1. The CONUT score was significantly higher among patients with moderate-severe hepatic steatosis and mild steatosis compared to those without steatosis (6.4±2.9 vs 3.4±2.6, p< 0,005) (6.4±2.9 vs 5.8±2.5, p<0,005). Liver

density values were significantly lower in the group with high CONUT score (50.8±8.2 vs 55.7±7.4; p 0.001). Skeletal muscle density (SMD) values were also statistically significantly lower in the high CONUT group (-11.9±23 v 26.1±30; p < 0.0001).
All cause death and risk of sepsis were significantly higher among patients with a high CONUT score (17.6% vs 2.3%; p<0,001) (38.4% vs 16.2%; p<0,01).
We, therefore, used multivariate logistic regression to investigate the effects of high CONUT, fatty liver disease, and myosteatosis on outcomes such as mortality and risk of sepsis. Our results showed that higher liver density and skeletal muscle density are related to worse in-hospital outcomes [all cause death vs liver density (coef.0.018; p 0.68; 95% CI 0.93-1.10); all cause death vs muscle density (Coef.-0.40; p 0.07; 95% CI 0.92–1.00). Sepsis vs CONUT (Coef. 0.29; p 0.02; 95% CI 1.03–1.74); sepsis vs liver density (coef. 0.06; p 0.07; 95% CI 0.99-1.13); sepsis vs skeletal muscle density (Coef.-0.01; p 0.94; 95% CI 0.97–1.02)]. Then, we used simple regression to investigate a possible correlation between CONUT score and liver density: a strong correlation emerged between these variables (R -0.34; p < 0.0001). Equally significant was the correlation between CONUT score and skeletal muscle density (R -0.55; p < 0.0001).
Conclusion: high CONUT score is associated with greater lipid infiltration in the liver and muscles corresponding to a poor nutritional state; these radiological findings have shown an association with in-hospital outcomes such as mortality and risk of sepsis. Thus, the CONUT score can be used as a prognostic tool to identify patients affected from malnutrition that are at higher risk of morbidity and complications.

	Low CONUT score (0– 4) n = 42	High CONUT score (5- 12) n = 85	P-value
Age (years)	55.6±21.9	72.3±11.5	< 0.0001
Sex (M%)	54%	61%	0.48
Systolic Pressure (mmHg)	124.7±17.7	126.4±21.3	0.65
eGFR (ml/min/1.74 m²)	87.6±36.6	68.9±29.9	0.002
HDL Cholesterol (mg/dL)	38.4±14	27.6±12.2	<0.0001
GOT (U/L) ≥35 (%)	30.9%	28.5%	0.78
GPT (U/L) ≥56 (%)	19.0%	15.4%	0.61
Hs-PCR (mg/dL)	3.1 (6.9 – 1.1)	6.6 (12.7 – 2.8)	0.05
WBC (10^3/ µL)	8.3 (10.2 – 6)	7.5 (10.4 – 5.8)	0.9
Haemoglobin (g/dL)	11.9±2.1	10.4±1.7	< 0.0001
Liver density (HU)	55.7±7.4	50.8±8.2	0.001
Skeletal muscle density (HU)	32.4 (48.3 – 16.5)	-9.4 (6.1 - -28.0)	< 0.0001
Arterial Hypertension (%)	50.0%	57.8%	0.40

520. INCREASED DUODENAL LEVELS OF THE FRUCTOSE CARRIER GLUT-5 IN SUBJECTS WITH NONALCOHOLIC FATTY LIVER DISEASE

Fiorentino T.V.[1], De Vito F.[1], Celia A.[1], Suraci E.[1], Marasco R.[1], Arturi F.[1], Luzza F.[1], Andreozzi F.[1], Sesti G.[2]
[1]Department of Medical and Surgical Sciences, University Magna Graecia of Catanzaro; [2]Department of Clinical and Molecular Medicine, University of Rome-Sapienza, Rome

Dietary fructose consumption has risen dramatically in the last decades, thus contributing to the growing diffusion of obesity and its related disorders, including nonalcoholic fatty liver disease (NAFLD). Preclinical studies have demonstrated that fructose may directly stimulate hepatic lipogenesis, and promote NAFLD development. In the proximal intestine, dietary fructose is absorbed by its specific carrier glucose transporter 5 (GLUT-5), located on the brush border of the enterocytes. Increased duodenal levels of GLUT-5, resulting in a higher dietary fructose absorption, have been reported in subjects with obesity and type 2 diabetes. However, whether subjects with NAFLD have an augmented duodenal abundance of GLUT-5 has not been investigated. In this study we evaluated the link between duodenal GLUT-5 protein abundance, assessed by western blot, and ultrasound defined presence of NAFLD in a cohort of 31 non-diabetic subjects, who underwent a complete anthropometrical and biochemical characterization, including OGTT, and an upper gastrointestinal endoscopy with duodenal mucosa biopsies. Study participants were subdivided into two groups on the basis of presence or absence of ultrasonography defined NAFLD: 12 without NAFLD (5 males and 7 females, aged 45±11 years) and 19 with NAFLD (11 males and 8 females, aged 45±10 years). As compared to the group without NAFLD, subjects with NAFLD were significantly heavier. After adjusting for BMI, subjects with NAFLD displayed significantly higher levels of triglycerides, uric acid, fasting and 2h-post load insulin levels, hepatic insulin resistance degree assessed by HOMA-IR and lower values of HDL and Matsuda index, a proxy of peripheral insulin sensitivity. Conversely, no difference in fasting and post-load glucose levels was detected between the two study groups. Interestingly, we found that subjects with NAFLD had significantly 1.32-fold increased duodenal GLUT-5 protein levels as compared to the group without NAFLD, even after adjusting for age, gender and BMI (*P*=0.02). By performing univariate analyses, we found that duodenal GLUT-5 protein levels were positively correlated with BMI, waist circumference, fasting and 2h post-load insulin levels, insulin resistance degree assessed by HOMA-IR (r=0,44; *P*=0.02) and inversely associated with peripheral insulin sensitivity estimated by Matsuda index (r=-0,43; *P*=0.05). In addition, we observed a positive correlation between duodenal abundance of GLUT-5 and serum concentrations of uric acid (r=0.40; *P*=0.05), which is a product of fructose metabolism, widely known to play a pathogenic role in development and progression of NAFLD. In conclusion, our findings demonstrate that increased duodenal levels of the fructose carrier GLUT-5 are associated to NAFLD and its related metabolic disarrangements, suggesting that a higher dietary fructose uptake mediated by GLUT-5 may play a pathogenic role in NAFLD development and represent a potential target for prevention and treatment of NAFLD.

521. THE IMPACT OF THE MEDITERRANEAN DIET WITH HIGH-POLYPHENOL CONTENT EXTRA-VIRGIN OLIVE OIL INTAKE ON MAFLD: PRELIMINARY RESULTS FROM A 3-YEARS DOUBLE-BLIND CLINICAL TRIAL

Seidita A.[1], Giannitrapani L.[2], Citarrella R.[2], Licata A.[2], Cusimano A.[3], Cusimano A.[3], Chianetta R.[2], Muratori I.[2], Terranova A.[2], Jovanna J.L.[4], Carroccio A.[1], Soresi M.[2]
[1]Unit of Internal Medicine, "V. Cervello" Hospital Ospedali Riuniti "Villa Sofia-Cervello", Palermo, Italy. Department of Health Promotion Sciences, Maternal and Infant Care, Internal Medicine and Medical Sp ecialties (PROMISE), University of Palermo, Palermo, Italy; [2]Unit of Internal Medicine, Department of Health Promotion Sciences, Maternal and Infant Care, Internal Medicine and Medical Sp ecialties (PROMISE), University of Palermo, Palermo, Italy; [3]Institute for Biomedical Research and Innovation (IRIB), National Research Council, Palermo, Italy; [4]Cancer Research Center of Marseille, Aix Marseille University, CNRS, INSERM, Institut Paoli Calmettes , CRCM, Marseille, France

Introduction: Metabolic Syndrome (MS) is a global health problem resulting in a significant risk of cardiovascular events and mortality. In addition, liver steatosis is recognized as a stigma of these patients, so that the new term metabolic-associated fatty liver disease (MAFLD) has been recently introduced. In this context, the only effective, preventive treatment is lifestyle modification, with the increase of physical activity and the consumption of a balanced diet: the Mediterranean Diet (MD). Extra Virgin Olive Oil (EVOO), rich in monounsaturated fatty acids and polyphenols, is the real added value of MD. Aims: we evaluated the efficacy of the intake of high-polyphenol content EVOO (high polyphenols EVOO, HPPE) on clinical and laboratory parameters related to cardiovascular risk, metabolism, and liver function in two groups of MS/MAFLD patients. Here, we present the preliminary results of the 1st-year of a 3-year study co-financed by the European Union - PON Research and Innovation 2014-2020 - DM1062/2021.
Methods: thirty consecutive MS/MAFLD patients were enrolled at Internal Medicine Department of University Hospital of Palermo and randomized, in a single-center double-blind prospective study, to add HPPE or standard EVOO (SE) (40 ml/daily for 6 months) to the MD. Anthropometric/demographic measures, liver function, metabolic and inflammatory status, flow mediated dilatation (FMD), liver ultrasound and abdominal fat features, were analyzed at baseline (T0) and after 6 months (T6). We further analyzed the gene expression pattern of some of the major metabolic pathways involved in systemic inflammation, oxidative stress, lipidic and glucose metabolism and development of hepatic steatosis, by extraction and subsequent amplifi-

cation, via RT-PCR, of the RNA from peripheral blood mononuclear cells.
Results: to correctly identify the EVOO with the best chemical features to be used in our study, a preliminary analysis was performed on the oils of three native cultivars (Biancolilla, Nocellara and Cerasuolo) coming from the same area of Western Sicily (Val di Mazara, Valle del Belice, Valli trapanesi), milled with 4 different methods (discs, hammers, opposing wheels and stoner). A Cerasuolo EVOO milled by opposing wheels was selected as HPPE.
The dietary intervention was well accepted by patients who showed high compliance (mean Perceived Dietary Adherence Questionnaire = 45, in both groups). No differences were found in all analyzed parameters at T0 between groups. From T0 to T6, waist circumference (WC), glycated hemoglobinemia (HbA1C), visceral fat thickness and FMD significantly improved ($p<0.05$) in both HPPE and SE group. On the contrary body mass index (BMI), insulinemia, HOMA-IR, AST and subcutaneous fat thickness improved ($p<0.05$) only in HPPE group. However, when comparing the two groups at T6, no significative differences were observed, even though a major reduction was shown in the HPPE group for BMI, WC, ALT, HbA1C, triglycerides, total and LDL-cholesterol, subcutaneous and visceral fat thickness.
In both HPPE and SE group we proved a significant improvement of FMD ($p<0.002$) which rises of 1.1% (from 7.8% to 8.9% in SE group and from 8.0% to 9.1% in HPPE group), thus proving a consisting reduction of endothelial disfunction.
Looking at the gene expression patterns, both groups showed a consistent reduction ($p<0.05$) of TRIB3 (known to be upregulated in insulin resistance mechanisms, specifically in adipose tissue) and SREBP expression (involved in the pathogenesis of MAFLD and insulin resistance) from T0 to T6.
Finally, we analyzed PNPLA3 (rs738409), TM6SF2(rs58542926), PCSK9 (LOF) (rs1159114), PCSK9 (GOF) (rs505151) and GCKR (rs1260326) polymorphisms, proving that the minor allele frequency (MAF) in both HPPE and SE group are equivalent to those of the general population.
Conclusion: this preliminary analysis shows that the MD plus EVOO intake for 6 months can improve metabolic and cardiovascular parameters in MS/MAFLD subjects, reducing both anthropometric and insulin resistance indexes, and improving endothelial disfunction. However, no differences at T6 were found between HPPE and SE groups, even though HPPE seems to potentially have more extended efficacy. No effect was proved regarding liver steatosis, even if we showed a consistent reduction of SREBP expression. This last evidence might suggest that MD *plus* EVOO intake might influence the pathways involved in liver steatosis development and that probably a longer duration (> 6 months) of this dietary intervention might reduce the degree of liver steatosis. Our preliminary data were most likely affected by the low number of patients, and we hope to prove significance while completing the study.

522. REAL-WORLD EFFICACY AND SAFETY OF INCLISIRAN: A PROSPECTIVE COHORT STUDY

Cocco V. , Coppola C. , Rizzi L. , My M. , Suppressa P.
Department of Internal Medicine and Rare Diseases Centre "C. Frugoni", Lipigen Centre, University of Bari "Aldo Moro"

Background: Inclisiran is a small interfering RNA (siRNA) therapeutic agent that reduces hepatic synthesis of PCSK9. In Phase III clinical trials, Inclisiran has shown the ability to reduce LDL cholesterol levels by about 50% with a good safety profile, and with the advantage of infrequent administration, which could promote therapeutic adherence. Inclisiran received reimbursement from Italian Drug Agency (AIFA) only in October 2022; but our dyslipidemia Centre, relating to the LIPIGEN NETWORK, had the opportunity to give it early to patients as early as the summer of 2022. We therefore carried out a prospective cohort study to evaluate the efficacy and safety of Inclisiran in real life.
Methods: The inclusion criteria were essentially those provided by AIFA for the prescribability of the drug. Enrollment began in July 2022 and preliminary analysis was conducted in April 2023. For all patients included in the study, Inclisiran was administered at time 0, after 90 days and every 180 days thereafter, according to drug administration protocol. The main parameter examined to verify the drug effectiveness was the average percentage reduction of LDL cholesterol at the same time intervals. Secondly, we also evaluated the average percentage changes of the other components of the lipid profile (total cholesterol, HDL cholesterol and triglycerides). The safety profile assessment was performed by comparing the liver (AST, ALT, GGT) and renal (creatinine, uricemia) function values recorded at baseline with those observed during therapy (both at days 90 and 270). In addition, injection site reactions were verified by monitoring patients within 15 minutes following subcutaneous administration of Inclisiran.
Results: 14 patients were enrolled from July 2022 to April 2023 (5 females and 9 males) with a mean age at the start of therapy of 57.35 years. All patients had a high or very high cardiovascular risk, defined according to the latest ESC/EAS guidelines (2021). The mean percentage reduction in LDL-C values was 29.3% at 90 days and 38% at 270 days (-41.43mg/dl and -73.7 mg/dl respectively). Using the T-test for paired samples, these variations were statistically significant between T0 and T1 and between T0 and T2 (p value 0.013 and 0.028, respectively). The reduction, on the other hand, was not statistically significant between T1 and T2 (p value = 0.699). This last data, although it may be the result of the sample smallness, is in accordance with the mechanism of action of the drug, which immediately determines a reduction in LDL-C levels, subsequently undergoing a plateau phase with stabilization of its effectiveness.
Total cholesterol values showed an average percentage reduction of about 20% at 90 days and about 26.1% at 270 days (-46 mg/dl and -69.67 mg/dl respectively). Also in this case the variations were statistically significant between T0 and T1 and between T0 and T2 (p value respectively 0.018 and 0.027), while they were not statistically significant between T1 and T2.
As for HDL cholesterol values, there was an average percentage increase of 6.14% after 90 days and 2.6% after 270 days. These variations were not statistically significant between T0 and T1 or between T0 and T2, but between T1 and T2 (p value 0.032). This indicates the existence of a tendency to increase over time the HDL cholesterol levels, which will be interesting to analyze again when the sample will be more numerous and the follow-up longer.
About the average values of triglycerides, there was an average percentage reduction of 28.56% at 90 days and 2.6% at 270 days. In any case, these changes were not statistically significant, although in our population there were no patients suffering from hypertriglyceridemia.
Regarding the safety profile, almost all patients showed a reaction at the injection site, when the drug was administered at the deltoid level, characterized by painless muscle fasciculations, lasting about two minutes, which subsequently resolved without sequelae.
In all phases of treatment, there was no change in liver or kidney function indices, indicating a good safety profile of Inclisiran, according to what has been reported in the literature.
Moreover, since the drug was administered in an intra-hospital environment and by medical staff, it was easy to evaluate the adherence to the therapy which turned out to be 100%, favoured by infrequent administration.
Conclusions: Our data represent a first analysis of the efficacy and safety of Inclisiran in real life. According to the literature, even in our sample of patients, the therapy with Inclisiran was effective in reducing LDL-C and TOT-C levels, with a good safety profile and an optimal patient adherence. Further studies are needed to evaluate the impact of therapy on HDL-C and triglyceride values.

523. INFLUENCE OF GENETICS AND METABOLIC FACTORS ON NEUTROPHIL-TO-HIGH DENSITY LIPOPROTEIN CHOLESTEROL RATIO: A PERSPECTIVE OBSERVATIONAL STUDY

Coppola C., Rizzi L., Cocco V., Russo R., Morea F., My M., Suppressa P.
Department of Internal Medicine and Rare Diseases Centre "C. Frugoni", Lipigen Centre, University of Bari "Aldo Moro"

It is well known that prolonged exposure to high LDL values and inflammation play a key role in atherosclerosis. The function of HDL cholesterol (HDLc), however, is controversial: several studies define HDLc as a cardioprotective factor; others, instead, suggest that high values could be paradoxically associated with an increased cardiovascular risk. Based on the different role played by inflammation and HDLc in atherosclerotic disease, the possibility of using a new, non-invasive and easily obtainable instrument, namely Neutrophil to High-density Lipoprotein Cholesterol Ratio (NHR), has recently been studied for cardiovascular risk stratification. NHR has been related to the degree of coronary stenosis: in detail, a higher NHR was shown to be indicative of moderate or severe coronary disease, documented at myocardial perfusion imaging. In addition, high NHR plays an important negative prognostic role in patients with cardiovascular events undergoing angioplasty, facing a greater risk of complications. Also in primary prevention, NHR can act as an independent cardiovascular risk factor, unbound from other factors such as BMI, smoking, diabetes, hypertension, LDLc, kidney function, reactive C protein or pharmacological therapy taken.
The aim of our perspective observational study was to examine NHR behavior in a cohort of dyslipidemic subjects (defined "cases") and in a cohort of

healthy subjects (defined "controls"): in detail, the goal was to assess NHR trend in different forms of hypercholesterolemia (homozygous familiar hypercholesterolemia, HoFH; heterozygous familiar hypercholesterolemia, HeFH; polygenic hypercholesterolemia), in order to understand how the genetic component could affect its value. In addition, the study aimed to highlight the possible influence of metabolic features of the patient on NHR, to define a possible role played by dysmetabolism in causing an increase of this ratio.
A total of 100 subjects were enrolled (63 cases afferent to our Lipigen Center and 37 healthy controls), ruling out patients with pathologies or ongoing therapies that could cause blood count abnormalities. Cases were divided into 3 groups: patients suffering from HoFH (2), HeFH (21) and polygenic hypercholesterolemia (40). At the time of enrolment, medical, clinical-anthropometric and recent laboratory data were collected; NHR, surrogates of steatosis (Fatty Liver Index and Hepatic Steatosis Index - FLI and HSI), indices related to metabolic syndrome and insulin resistance (triglyceride-glucose index - TyG index; triglyceride-glucose-body mass index - TyG BMI) and the Framingham score were calculated. Intra-abdominal fat thickness (IFT) was measured using a standardised ultrasound method. Student t-test for the comparison of means, Pearson test for correlation studies and receiver operating characteristics (ROC) curve were used for statistical analysis; a p-value less than 0.05 was considered statistically significant.
Results revealed a significative difference in NHR between HoFH and HeFH patients (124.21±14.50 vs 72.39±36.86, p=0.038) and a difference at the limits of statistical significance between HoFH and polygenic patients (124.21±14.50 vs 69.39±38.82, p=0.052), while no significative differences were found between HeFH and polygenic patients (p=0,768). NHR was higher in patients with metabolic syndrome than in non-metabolic ones (89.08±32.76 vs 57.40±29.83, p=0.000). Moreover, analysis showed a correlation between NHR and FLI (r= 0,445; p=0,000), HSI (r=0,297; p=0,003), TyG index (r= 0,367; p=0,000), TyG BMI (r= 0,404; p=0,000), waist circumference (r= 0,279; p=0,005), glycemia (r=0,306; p=0,002) and IFT (r= 0,341; p=0,045).
Finally, ROC curve analysis was used to deepen the role of TyG index/TyG BMI and FLI/HSI in predicting a NHR value greater than 103.2 (associated with moderate/severe coronary artery disease, according to the literature). A TyG index cut-off value of 7.58 (95% sensitivity, 94% specificity) with an area under the curve (AUC) of 68% (95% CI 55-81) and a TyG BMI cut-off value of 186.83 (95% sensitivity, 73% specificity) with an AUC of 70% (95% CI 59-83) were found; a FLI 10.5 cut-off value (94% sensitivity, 76% specificity) with an AUC of 72% (95% CI, 60-85) was also found, while ROC curve analysis about HSI didn't find statistically significant results.
Concluding, our study shows that NHR could be affected by genetic component of dyslipidemia, while it seems to be strongly influenced by metabolic assessment: at our knowledge, in fact, this is the first study that highlights a positive correlation of NHR with hepatic steatosis and visceral abdominal obesity. Thus, our results emphasize the importance of a holistic approach to dyslipidemia which must consider metabolic features of the patient because of their remarkable influences on cardiovascular risk. NHR can be considered an additional tool for prognostic stratification of dyslipidemic patients, identifying which of them deserve a closer follow-up and a more aggressive treatment of risk factors.

524. RISK OF ATHEROSCLEROTIC DISEASES IN HYPERTENSIVE PATIENTS WITH NAFLD AND SLEEPING DISORDERS

Cicco S.[1], Gramegna D.[2], Marozzi M.S.[1], Rignani F.[2], Amodio G.[2], Santoro G.[2], Lauletta G.[3], Nazzaro P.[2], Vacca A.[3]
[1]Unit of Internal Medicine "Guido Baccelli", and Unit of Hypertension "A.M. Pirrelli", Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), University of Bari Aldo Moro, AUOC Policlinico di Bari, Italy; [2]Unit of Hypertension "A.M. Pirrelli", Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), University of Bari Aldo Moro, AUOC Policlinico di Bari, Italy; [3]Unit of Internal Medicine "Guido Baccelli", Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), University of Bari Aldo Moro, AUOC Policlinico di Bari, Italy

Introduction: Nonalcoholic Fatty Liver Disease (NAFLD) defines liver conditions caused by cell fat infiltration in subjects with no history of alcohol addiction. Triglyceridexglucose (TYG) index is a risk score for NAFLD that along with sleep apnoea might relate to an increased risk of atherosclerotic cardiovascular disease (ASCVD).
Aim: we wondered whether OSAS and NAFLD might be associated to induce the ASCVD.
Methods: We studied 121 caucasian hypertensives with a negative Alcohol Use Disorders Identification test (AUDIT) score for alcohol addiction. Patients were evaluated by physical examination (BMI, waist circumference) and routine lab tests. Lausanne Neck circumference, Obesity, Snoring, Age, Sex (NoSAS) Score, ASCVD Risk Score and TYG index were calculated. Patients were divided respectively into high risk of OSAS (Group H, NoSAS Score ≥8; 82 patients, 47 males, 66.72±8.67 y) and low risk of OSAS (Group L, NoSAS Score <8; 48 patients, 14 males, 60.72±13.43 y).
Results: Group H presented an increased BMI and waist circumference (p<0.0001 both). An increased rate of diabetes was seen as well (Group H 21.95% vs Group L 2.56%, p=0.006). HDL was significantly decreased in Group H (p=0.027). No differences were found in blood glucose, triglycerides, total and LDL cholesterol and, in particular, TYG score, systolic (SBP) and diastolic (DBP) blood pressure and heart rate (HR) overlapped. On the contrary, the ASCVD risk significantly increased in Group H (Group H 15.65±10.49% vs Group L 9.04±10.70%; p=0.008). A significant direct correlation highlighted between the ASCVD Risk Score and both TYG (r= 0.274; P<0.005) and NoSAS (r=0.403; p<0.005).
Conclusions: All patients with an increased OSAS risk have a tight correlation with a high risk of NAFLD and particularly with enhanced ASCVD Risk Score. This result shows the close correlation between sleeping disorders and NAFLD that might be involved to the onset of ASCVD. Further studies will enhance, then, the primary and secondary prevention of cardiovascular events, including factors still considered as extracardiovascular.

525. EVALUATION OF A NEW ALGORITHM FOR CLINICAL ASSESSMENT OF SARCOPENIA IN HIGHLY COMPLEX HOSPITALISED PATIENTS: ASSOCIATION WITH KEY CLINICAL LABORATORY VALUES.

Di Raimondo D., Rubino E., Pirera E., Daidone M., Barile A.M., Buscemi S., Tuttolomondo A.
Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (ProMISE) "G. D'Alessandro", University of Palermo.

The definition of sarcopenia has been fundamentally revised over the years, most recently in the second consensus document of the European Working Group on Sarcopenia in Older People (EWGSOP2), which recognises it as a true "muscle disease" with an increased risk of adverse events such as falls, disability and mortality.
Sarcopenia complicates all major chronic diseases and hospitalisation is a risk factor in itself. All diagnostic algorithms require instrumental confirmation (CT, MRI), which is often difficult to perform in a highly complex internal medicine setting. There is an urgent need for a more streamlined clinical algorithm. Given the major clinical and prognostic importance of sarcopenia, the difficulty in accessing instrumental methods to assess its severity, and the lack of validated clinical criteria to identify and quantify sarcopenia in the elderly hospitalised patient, the aims of this study are to
- To determine the percentage of sarcopenic patients by evaluating the applicability of an original clinical algorithm derived from that proposed by EWGSOP2.
- To identify the main anthropometric, laboratory and anamnestic elements associated with sarcopenia.
- To verify the existence of a correlation between sarcopenia and the result of a battery of reproducible multidimensional tests capable of capturing crucial aspects of the predisposition to sarcopenia, such as: level of habitual physical activity (IPAQ test), degree of disability, nutritional status (Mini Nutritional Assessment-short form - MNA-SF) and quality of life.
The observational cohort study included 100 patients aged > 65 years admitted to the U.O.C. of Internal Medicine with Stroke Care of the University of Palermo for acute pathology.
Exclusion criteria:
Presence of acute or chronic, neurological or orthopaedic pathologies leading to a functional deficit.
Patients with amputations, diabetic foot and other conditions affecting mobility.
Patients with respiratory failure requiring continuous oxygen therapy and/or NIV.
Life expectancy of less than 6 months.
We defined "probable sarcopenic" as patients with SARC-F test scores ≥4/10 total points and muscle strength assessed by handgrip test < 27 kg in men and < 16 kg in women.

We defined "most likely sarcopenic" as patients with SARCF ≥4/10 total points and hand grip strength < 27 kg in males and < 16 kg in females + Short Physical Performance Battery (SPPB): ≤ 8/12 total points.
Results: - Using our diagnostic algorithm, 45% (45/100) of the patients were most likely to be sarcopenic. It should be noted that all 'probable sarcopenic' patients also had reduced physical performance on the SPBB, confirming the associated severe functional impairment.
Comparing the anthropometric, anamnestic and laboratory data between the most likely sarcopenic patients and all other patients (Student's t-test for unpaired data, Chi-square test, Fischer's exact test), the most likely sarcopenic state is associated with: higher age (78. 7 vs. 74.3 years, p: 0.001); a lower frequency of males (p: 0.038); a worse renal function (47.8 vs. 59.8 ml/min, p: 0.001); a lower haemoglobin value (10.4 vs. 11.6 g/dl, p<0.01). However, there was no difference in BMI or body weight (either increase or decrease).
- The SARC-F test is an excellent screening test. Pearson's correlation shows a high degree of correlation between SARC-F and all the tests performed. (grip strength, SPPB, MNA, average arm and calf muscle circumference, IPAQ);
- The linear regression analysis (independent variable: "sarcopenia very likely", dependent variable: the main tests performed) showed a negative linear relationship between sarcopenia status and the level of physical activity assessed by the IPAQ test (β: - 0.278; p: < 0.001); physical performance assessed by the SPPB (β: - 0.493; p: < 0.001) and nutritional status assessed by the MNA (β: - 0.167; p: 0.016).
- The multiple logistic regression model with a SARC-F score ≥ 4 as dependent variable and the main indices and tests predictive of sarcopenia as independent variables shows that only the SPPB score (p>0.001) and arm circumference (p: 0.033) retained statistical significance.
Conclusions: A clinical diagnostic algorithm including multidimensional screening (SARC-F, SPPB, handgrip, MNA, IPAQ) and clinical-anthropometric assessments seems to be able to identify patients at high risk of sarcopenia and to quantify its severity, even in the absence of instrumental confirmation. This approach seems to be able to identify a population of frail patients with comorbidities and nutritional impairment who deserve targeted support and treatment already during their hospital stay.

526. METEORIN-LIKE PROTEIN IS ASSOCIATED WITH NON-ALCOHOLIC FATTY LIVER DISEASE IN SUBJECTS WITH DIFFERENT GLUCOSE TOLERANCE

Monea G.[1], Massimino M.[1], Rubino M.[1], Averta C.[1], Palummo A.[1], Mancuso E.[2], Mannino G.C.[1], Andreozzi F.[1]
[1]Medical and Surgical Sciences, University of Magna Graecia, Catanzaro, Italy; [2]Sciences of Health, University of Magna Graecia, Catanzaro, Italy

Background and aims: Meteorin-like protein (METRNL) is an adipomyokine highly expressed in white adipose tissue during exposure to cold and in skeletal muscle upon exercise. METRNL serum levels are significantly reduced in subjects with type 2 diabetes (T2DM) with mechanisms not completely elucidated. Preclinical evidences suggest that METRNL increases glucose uptake via the calcium-dependent AMPKa2 pathway in skeletal myocytes. Furthermore, adipocyte-KO of METRNL exacerbates insulin resistance, whereas METRNL overexpression reduces the onset of insulin resistance, suggesting that adipocyte METRNL ameliorates overall insulin resistance by acting on local adipose tissue in an autocrine/paracrine fashion. T2DM patients have 2fold increased risk to develop Non-Alcoholic Fat Liver Disease (NAFLD) and vice versa, a complex association supported and mediated by insulin resistance. Herein, we examined the existence of an interaction connection between NAFLD and METRNL levels in subjects with different glucose tolerance.
Materials and methods: The study population includes 72 individuals stratified on the basis of their glucose tolerance in: normal glucose tolerance (NGT) (n=33), prediabetes (n=20) and T2DM (n=19). A 75 g oral glucose tolerance test (OGTT) was performed with 0, 30, 60, 90, and 120 min samplings for circulating plasma glucose and insulin measurements. Serum levels of METRNL were measured by a commercial ELISA kit. Liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) were measured by transient elastography (FibroScan touch 502) to assess the presence of NAFLD.
Results: Serum levels of METRNL were progressively reduced in individuals with prediabetes and T2DM as compared to those with NGT (P<0.001). To assess the independent contribution of METRNL to the risk of developing T2DM, we performed a multiple logistic regression analysis. The results confirmed that METRNL increase was associated with reduced risk to develop T2DM (OR=0.907; P=002) independently from several confounding factors. CAP values were higher in subjects with prediabetes and T2DM compared with NGT (P<0.001); similarly significant differences were observed for LSM values (P=0.012). A partial correlation analysis corrected for age, sex and body mass index (BMI), showed that METRNL levels were negatively correlated with CAP (*r*=-0.395; P<0.001) and fasting plasma glucose (*r*=-0.312; P<0.01); whereas no correlation was revealed between METRNL and LSM values. To estimate the contribution of METRNL to the risk of NAFLD we performed a multiple logistic regression analysis including age, sex, BMI and degree of glucose tolerance as covariates: METRNL resulted significantly associated with reduced odds of NAFLD (OR=0.966; P=0.047) independently from the other factors included in the model.
Conclusion: Our findings support the hypothesis that METRNL may have a protective role against dysglycaemic conditions. Furthermore we report that a reduction in the expression of METRNL occurs also in subjects with elevated CAP values, independentlyfrom their glucose tolerance status. This first report on the matter should be considered hypothesis-generating and requiring confirmation by additional prospective studies assessing the impact of METRNL in predicting the development of NAFLD.

527. REDUCTION IN MYOCARDIAL GLUCOSE METABOLISM IS ASSOCIATED WITH WHOLE BLOOD VISCOSITY

Succurro E.[1], Giofrè F.[1], D'Agostino A.[1], Monea G.[1], Rubino M.[1], Fiorentino T.V.[1], Sciacqua A.[1], Veltri P.[2], Cascini G.L.[3], Andreozzi F.[1], Sesti G.[4]
[1]Dipartimento di Scienze Mediche e Chirurgiche, Università "Magna Graecia", Catanzaro; [2]Dipartimento di Ingegneria Informatica, Modellistica, Elettronica e Sistemistica, Università della Calabria, Cosenza; [3]Dipartimento di Medicina Sperimentale e Clinica, Università "Magna Graecia", Catanzaro; [4]Dipartimento di Medicina Clinica e Molecolare, Università Sapienza, Roma

An increased blood viscosity is associated with type 2 diabetes and cardiovascular disease (CVD). An impaired insulin-stimulated myocardial glucose metabolism has been shown to be a risk factor for the development of CVD in patients with type 2 diabetes. However, whether blood viscosity is associated with myocardial insulin resistance is unsettled. To elucidate this issue, we evaluated the association between whole blood viscosity and insulin-stimulated myocardial glucose metabolic rate (MRGlu) in 57 subjects without coronary heart disease exhibiting different glucose tolerance status. Myocardial MRGlu was assessed using dynamic cardiac 18F-FDG PET combined with euglycemic hyperinsulinemic clamp. Whole blood viscosity was calculated using a validated equation including hematocrit and plasma proteins: whole blood viscosity (WBV) = [0.12 x *h*] + [0.17 x (*p*-2.07)], where *h* is the hematocrit (%) and *p* the plasma proteins (g/dl). The 57 subjects in study were stratified into tertiles according to their myocardial MrGlu values. As compared with subjects in the highest myocardial MrGlu tertile, those in the lowest tertile showed an age-adjusted increase in whole blood viscosity (5.54 ± 0.3 cP vs 6.13 ± 0.4 cP respectively; P=0.001), hematocrit (39.1 ± 3.1% vs 43.2 ± 3.7% respectively; P=0.004), total proteins 7.06 ± 0.3 g/l vs 7.60 ± 0.3 g/l respectively; P<0.0001) and white blood cells (WBC) count (6123 ± 917 x109/l vs 7468 ± 1817 x109/l respectively; P=0.006). Blood viscosity was significantly negatively correlated with myocardial MRGlu (r= -0.416, P=0.001), whole-body insulin-stimulated glucose disposal (MFFM) (r= -0.378, P=0.006) and positively correlated with fasting plasma glucose (r= 0.302, P=0.02) waist circumference (r= 0.414, P=0.001), systolic (r= 0.406, P=0.002), and diastolic blood pressure (r= 0.333, P=0.01). In a stepwise multivariate regression analysis, including several cardiovascular risk factors, the only variables significantly associated with myocardial MrGlu were erythrocyte sedimentation rate (ESR) (b -0.503; P<0.0001), whole blood viscosity (b -0.347; P=0.006) and MFFM (b 0.278; P=0.002) explaining the 72.4% of its variation. In conclusion, our data represents the first evidence of a significant correlation between whole blood viscosity and an impairment of myocardial glucose metabolism. Whole blood viscosity may represent a conceivable link with the increased risk of CVD observed in subjects with myocardial insulin resistance.

528. IDENTIFICATION AND VALIDATION OF THE CHRONO MED DIET SCORE: A SURVEY IN 9200 SUBJECTS

De Matteis C.[1], Crudele L.[1], Battaglia S., Gadaleta R.M., Piazzolla G., Suppressa P., Carlo Sabbà C., Marica Cariello M., Moschetta A.
Department of Interdisciplinary Medicine, University of Bari "Aldo Moro", 70124 Bari, Italy

Introduction and Aims: The Mediterranean Diet (MedDiet) is associated with reduced mortality from all causes, especially cardiovascular disease, and obesity. To study adherence to the MedDiet there are at least two previously validated MedDiet adherence scores, such as MEDI-LITE and Mediterranean Diet Score (MDS). These scores, however, define as high adherent to the Med Diet also patients with abdominal obesity. Therefore, we designed a new, easy-to-use adherence questionnaire to the MedDiet, called the Chrono Med Diet Score (CMDS), to select patients that are adherent to the MedDiet but are not affected by abdominal obesity, measured with waist circumference (WC). Indeed, CMDS considers the timing of the day in which farinaceous products are consumed, as well as the time dedicated to physical activity (see Figure). Here, we propose the data from validation of the CMDS as a reliable questionnaire to the MedDiet both in a cohort of metabolic patients, as well as the results of the online questionnaire of more than 9000 subjects.
Methods: First, we enrolled 300 patients from our outpatients' clinic to assess Metabolic Syndrome, fatty liver disease, and NAFLD. At first evaluation, CMDS, MEDI-LITE and MDS were calculated for each patient. We validated the CMDS using MDS as gold standard. ROC curves were performed to identify the capability of each score of detecting visceral adiposity. The correlation between continuous variables was analyzed using Spearman's Correlation Coefficient (r). T-test comparisons for comparison of continuous variables. P-values lower than 0.05 were considered significant. Second, the CMDS questionnaire was made available (since April 2023) at www.chronomeddiet.org for external compilation. The online survey was translated in English and Italian, and requested each participant to insert age, height, weight, and waist circumference. Each participant was given a unique ID to avoid multiple inputs from the same subject. The software was then able to calculate Body Mass Index (BMI) from each input. Only data from subjects that inserted all requested parameters from the online survey were collected and processed. Among the 9208 subjects that participated in the online survey, a total of 7550 inserted all the required data, therefore reaching the overall number of subjects of this external cohort for second validation.
Results: In our first cohort, CMDS showed a significant correlation (r= 0.68, p<0.001) with MDS, with a robust discriminative power (AUC 0.7468, optimal cut-off 13) to detect adherence to the MedDiet (76% sensitivity, 82% specificity). ROC curves for MDS and MEDI-LITE for visceral adiposity highlighted no significance, meanwhile the same procedure for CMDS showed a significant power for increased WC (AUC= 0.7018, optimal cut-off 14). Subjects with CMDS ≤14 presented altered metabolic markers, such as BMI, total and HDL cholesterol (HDL-c), triglycerides (TG), and fasting glucose (FG). At the variance of MDS and MEDI-LITE, CMDS negatively correlates with WC (*r*= -0.6, p<0.001), TG (*r*= -0.5, p<0.001), and cardiovascular risk (*r*= -0.61, p<0.001). Interestingly, results from the online survey confirmed that subjects with CMDS ≤14 had increased WC in both genders, whereas BMI was not able to capture this difference. We then analyzed the same cohort according to four different age ranges (18-30, 31-50, 51-65, 65+). In all ranges, subjects with CMDS ≤14 exhibited pathologic, statistically higher WC, especially in patients aged 31-50 years old (p<0.0005) compared to more adherent subjects, while BMI was not significantly altered in subjects of more than 50 years of age.
Conclusions: CMDS is a reliable, easy-to-use adherence questionnaire to the MedDiet that considers information on food and lifestyle habits, creating a comprehensive score to detect adherence to the MedDiet and an inverse association with WC and metabolic derangement biomarkers. Results of both the first cohort and the online group highlight the role of MedDiet to protect against abdominal obesity and cardiovascular disease.
*These authors contributed equally to this work.

FRUIT *1 portion= 150g* *(examples: 1 apple, pear, orange; 3 prunes, tangerines)*	<1 portion/d **0**	1-1.5 portions/d **1**	>1.5 portions/d **2**	
VEGETABLES *1 portion= 100g* *(examples: 1 salad plate, 3 cherry tomatoes; ½ portion of cooked vegetable)*	<1 portion/d **0**	1-2 portions/d **1**	>2 portions/d **2**	
LEGUMES *1 portion= 70g* *(examples: ½ can of beans, chickpea, lentils or peas)*	<1 portion/w **0**	1-2 portions/w **1**	>2 portions/w **2**	
FARINACEOUS PRODUCTS *(bread, pasta, cookies...)* *1 portion= 130g* *(examples: 1 portion of pasta= 80g; 4 cookies= 50g)*	<1 portion/d **0**	1 portion/d **2**	1-1.5 portions/d **1**	>1.5 portions/d **−1**
TIME OF INTAKE OF FARINACEOUS PRODUCTS	by 3PM **1**	by 7PM **−1**	After 7PM **−2**	Lunch + Dinner **−4**
CEREALS *(barley, oat, spelt ...)* *1 portion= 130 g* *(examples: 1 portion of rise= 70g; 1 portion of spelt= 80g)*	<1 portion/d **0**	1-1.5 portions/d **1**		
FISH *(except shellfish and crustaceans)* *1 portion= 100g*	<1 portion/w **0**	1-2 portions/w **1**	>2 portions/w **2**	
MEAT AND MEAT PRODUCTS *1 portion= 80g (examples: 1 portion of meat :100g)* *1 portion of meat products= 50g (1/2 bowl of ham)*	<1 portion/d **2**	1-1,5 portions/d **1**	>1.5 portions/d **0**	
MILK AND DAIRY PRODUCTS *1 portion= 180g* *(examples: 1 cup of milk=150g; 1 yogurt= 125g)*	<1 portion/d **2**	1-1.5 portions/d **1**	>1.5 portions/d **0**	
EXTRA VIRGIN OLIVE OIL	Occasional use **−1**	Frequent use **1**	Regular use **2**	
BUTTER, MARGARINE, LARD	Occasional use **1**	Frequent use **−1**	Regular use **−2**	
ALCOHOL *1 A.U.= 1 glass of wine; 12g of alcohol*	<1 A.U./d **3**	1-2 A.U./d **1**	2-3 A.U./d **−1**	>3 A.U./d **−2**
PHYSICAL ACTIVITY *30 min/d x5 days x week*	Rare **−3**	Occasional **−1**	Frequent **1**	Regular **3**

529. THYROID NODULES MALIGNANCY IS ASSOCIATED WITH INCREASED NON-INVASIVE HEPATIC FIBROSIS SCORES IN METABOLIC SUBJECTS.

Crudele L.[1], Novielli F.[1], De Matteis C.[1], Petruzzelli S.[1], Suppressa P.[1], Berardi E.[1], Antonica G.[1], Piazzolla G.[1], Sabbà C.[1], Graziano G.[2], Moschetta A.[1]
[1]Department of Interdisciplinary Medicine, University of Bari "Aldo Moro", 70124 Bari, Italy; [2]Center for Outcomes Research and Clinical Epidemiology (CORESEARCH), 65124 Pescara, Italy

Background and aims: Besides familiarity and exposure to ionizing radiation, lifestyle changes and dietary habits play a significant role in the development of thyroid malignancy. Indeed, obesity and its associated diseases, such as diabetes and fatty liver, are known to create a cellular microenvironment predisposing or promoting genetic instability, which underlies neoplastic transformation and proliferation and, consequently, leads to an increased risk of cancer. In this study, we aimed to detect any anthropometric, bio humoral and clinical features that might be associated with thyroid nodules malignancy, potentially representing a novel noninvasive predictor of malignancy.
Material and methods: The study was conducted in a group of 142 consecutive out-patients (47 males, 95 females) who underwent Fine Needle Aspiration Biopsy/Cytology (FNAB/C) in the suspicion of malignancy from January 2018 to September 2022. We compared lipid and glycemic blood profile as well as non-invasive liver fibrosis indexes such as AST to ALT ratio (AAR), AST to Platelet Ratio Index (APRI), Fibrosis Index Based on 4 factors (FIB-4), between patients with benign and malignant newly diagnosed nodules. Then, we performed ROC analysis to assess the best cut-offs in malignancy prediction. To understand whether and to what degree dysmetabolic conditions increased the risk of thyroid nodules malignancy, we calculated the Odds Ratio (OR) of main biomarkers.
Results: After FNAB/C, 121 (85%) patients were diagnosed with benign thyroid nodules, while 21 (15%) individuals were diagnosed with thyroid cancer. Comparing groups of patients with benign and malignant nodules, we found

that patients with thyroid cancer exhibited increased BMI (p=0.048), as well as increased fasting glycemia levels (p=0.046). Lipid profile, 25-OH Vitamin D, and thyroid function markers did not statistically differ between these two groups. Intriguingly, considering non-invasive scores for liver fibrosis, subjects with thyroid cancer presented increased AAR (p<0.001) and APRI score (p=0.007). then, we performed ROC curve analyses of AAR, APRI score, BMI, and FPG to define cut-off values for the prediction of thyroid nodules malignancy. AAR was characterized by the largest AUC (p<0.01) as well as the highest Youden's Index (Sensitivity=52%, Specificity=87%) in malignancy prediction, with a cut-off value of 1.12. APRI score presented intermediate sensitivity and high specificity (48% and 85%, respectively), with an AUC higher than 0.5, and a cut-off value of 0.45 (p<0.01), while the ROC curves of BMI and FPG levels were not significant. To understand whether and to what degree dysmetabolic conditions increased the risk of thyroid nodules malignancy, we calculated Odds Ratio (OR) of these biomarkers, stratifying our population according to both internationally validated cut-offs and cut-offs that had been calculated through the analysis of our ROC curves. AAR values above the ROC cut-off of 1.12 showed the highest OR (7.1, 95% CI: 2.4-18.5), with a significant p-value (p<0.001). Considering APRI score, values above the international cut-off of 0.5 and the ROC cut-off of 0.45 were both associated to risk of malignancy, with an OR of 6.6 (95% CI: 2.0-20.0) and 5 (95% CI: 1.9-12.6), respectively.
Discussion: To the best of our knowledge, this is the first study pointing to the possible association between thyroid cancer and liver fibrosis, which represents the manifestation of chronic hepatic injury associated with metabolic diseases such as obesity and diabetes. In our study, AAR and APRI scores are associated with increased risk for malignancy, with cut-off values consistent with those described in scientific literature, confirming the usefulness of these scores in predicting a wide range of conditions, beyond liver fibrosis. It has been hypothesized that, as soon as hepatic steatosis progresses, leptin release may cause death of macrophages and hepatocytes through CD8+ T lymphocytes, which could in turn promote the proliferation and invasiveness of tumors such as thyroid cancer. Furthermore, the evidence that patients with thyroid malignancy, especially papillary histological variants, display elevated serum leptin levels, and the association between a high concentration of its receptors on thyroid cancer cells and tumor aggressiveness increase may support these pathogenetic hypothesis.
Our study also shows that increased glycemia is associated with a higher risk for malignant nodules. Indeed, chronic hyperglycemia has been observed to directly influence cancer cell growth through promotion of oxidative stress. Thereby, on the one hand, in the future exploring this association might lead to elaborate new scores to predict thyroid malignancy and to speed up the diagnostic process. On the other hand, future studies are needed to prove that reducing obesity and counteracting fatty liver-associated diseases and metabolic derangements could probably prevent also thyroid cancer onset at least in specific groups of patients.

530. TOTAL SERUM FGF-21 LEVELS POSITIVELY RELATE TO VISCERAL ADIPOSITY DIFFERENTLY FROM ITS FUNCTIONAL INTACT FORM.

Crudele L.[1], Garcia-Irigoyen O.[1], Cariello M., Piglionica M., Scialpi N., Florio M., Piazzolla G., Suppressa P., Sabbà C., Gadaleta R.M., Moschetta A. Department of Interdisciplinary Medicine, University of Bari "Aldo Moro", Piazza Giulio Cesare 11, 70124 Bari, Italy

Background and aims: The Fibroblast Growth Factor-21 (FGF-21) is produced by the liver and through its binding to the receptor complex FGFR1c-KLB, selectively expressed in metabolic tissues, exploits several functions aimed to counteract metabolic derangement, metaflammation and stress damage. The FGF-21 paradox lays its foundation on the finding that, although counteracting metabolic derangement and being postulated as therapeutic actor in obesity and diabetes, high levels of this hormone in the serum are observed in obese and dysmetabolic subjects. Nevertheless, the functional FGF-21 hormone is its intact form. Indeed, circulating FGF-21 is inactivated by Fibroblast activation protein (FAP), a member of dipeptidyl peptidase-IV (DPP-IV) family, which by the way it is increased in obese subjects. Therefore, one can postulated that the increased level of FGF-21 in obese subjects may be represented from its cleaved not functional form.
In this observational study, we assessed intact and total (both cleaved and intact forms) FGF-21 levels in two cohorts of subjects with putative risk for Metabolic Syndrome and obesity-related diseases with the goal of identifying the relationships between FGF-21 serum levels and visceral obesity, as well as with its related complications.
Material and Methods: Total and intact serum FGF-21 concentrations were measured with an ELISA assay respectively in 51 and 46 subjects, comparing FGF-21 levels in dysmetabolic subjects and performing correlations between FGF-21 serum levels and biochemical and clinical metabolic parameters.
Results: Total FGF-21 mean serum level was 189.9±38.1 pg/mL, while intact FGF-21 level was 147.4±42.2 pg/mL. Both total and intact forms of FGF-21 were not significantly increased in high-risk conditions such as visceral obesity, Metabolic Syndrome, diabetes, smoking, and atherosclerosis. Waist Circumference (WC), but not BMI, positively correlated with total FGF-21 levels (r=0.31, p <0.05), while HDL-cholesterol (r=-0.29, p <0.05) and 25-OH Vitamin D (r=-0.32, p <0.05) showed a significant negative correlation with total FGF-21. Conversely, serum intact FGF-21 levels did not correlate with WC, HDL-c and Vitamin D levels. ROC analysis (AUC=0.63, p-value <0.05) of total FGF-21 in prediction of increased WC, showed that patients with total FGF-21 level over cut-off value of 161.47 pg/mL presented with impaired FPG. Conversely, ROC analysis for prediction of visceral adiposity by intact FGF-21 serum level finding a not-significant (AUC of 0.58, p-value=0.18).
Discussion: First, circulating total FGF-21 levels are directly linked to WC, but not BMI and body weight, thus underscoring the role of visceral obesity *versus* systemic obesity in driving meta-inflammatory diseases. Second, no significant association was found between serum levels of the intact functional form of FGF-21 either with WC or with BMI, suggesting that the eventual increased circulating form of FGF-21 measured in obese subjects might not be the functional one. This supports the hypothesis that obese and dysmetabolic subjects might have circulating increased FAP levels. Thus, measurement of intact functional serum form of FGF-21 will help clinicians to identify those patients who could eventually benefit from therapies aiming to increase the functional hormone level in serum as well as treatments increasing endogenous not-cleaved FGF-21, using DPP-IV or FAP inhibitors. In conclusions, our newly calculated cut-off of total FGF-21 according to visceral adiposity identified subjects with fasting hyperglycemia, and visceral adiposity appears to be responsible for increased levels of total FGF-21, although this does not necessarily translate into an increased hormonal biological activity.
*equally contribution

531. THE LIVER-GUT AXIS IN COLORECTAL CANCER DEVELOPMENT: A SINGLE CENTER 8 YEARS PROSPECTIVE STUDY IN 1145 METABOLIC SUBJECTS

Crudele L.[1], De Matteis C.[1], Novielli F.[1], Petruzzelli S.[1], Cariello M.[1], Piccinin E.[2], Gadaleta R.M.[1], Moschetta A.[1]
[1]Department of Interdisciplinary Medicine, University of Bari "Aldo Moro", 70124 Bari, Italy; [2]Department of Translational Biomedicine and Neuroscience (DiBraiN), University of Bari "Aldo Moro", Bari, Italy

Introduction: Liver steatosis represents the hepatic manifestation of increased adiposopathy, whose pathogenetic features have been proposed as tumorigenic triggers, specifically in colorectal cancer (CRC). Fatty liver diagnosis challenges clinicians since it is clinically silent and may be complicated with liver fibrosis. Since liver biopsy is not feasible in all patients, non-invasive and point-of-care indexes have been proposed to detect liver steatosis and fibrosis. We performed a prospective analysis among 1145 metabolic subjects to reveal any condition that may predict and concur to CRC development during a 8-years period.
Material and methods: Anthropometric and bio humoral parameters were recorded at time zero. Non-invasive liver fibrosis scores were calculated as follows: AAR= AST/ALT; FIB-4= (age x AST)/(platelet count x √ALT); mFIB-4=(10 x age x AST)/(platelet count x ALT); Forns=7.811-3.131 x ln(platelet count) +0.781 x ln(GGT) +3.467 x ln(age) - 0.014 x(total cholesterol); APRI= AST/Upper limit of normal values x 100/platelet count; AARPRI= AST/ALT/platelet count x 150. Comparisons were carried out by Student-T test (p-value <0.05 was considered significant) and ROC analysis was performed to assess cut-off values. Chi-square test was used to calculate the associated Odds Ratio (OR) with 95% confidence interval (CI).
Results: During a 8 years period, 28 patients (2.4%) developed CRC. No association between CRC development and visceral and general obesity was detected, while fasting plasma glucose was significantly higher and Vitamin D was significantly lower in patients who later were diagnosed with CRC, compared to those who did not develop cancer. We found that all non-invasive liver fibrosis scores significantly identified CRC-developer at time 0 (see Table). In ROC analysis, these scores also showed good sensitivity and specificity in predicting colon cancer (AAR AUC= 0.59, sensitivity 44% and specificity 78%; FIB-4 AUC= 0.74, sensitivity 84% and specificity 57%; mFIB-4

AUC=0.69, sensitivity 80% and specificity 53%; Forns AUC= 0.67, sensitivity 73% and specificity 54%; APRI AUC= 0.63, sensitivity 57% and specificity 75%; AARPRI AUC =0.64, sensitivity 44% and specificity 83%). We then calculated ORs for values above the ROC cut-offs finding that higher FIB-4 was associated with a 6-fold increased risk of developing CRC (95% CI=2.2-16.5), while mFIB-4 showed a OR=3.6 (95% CI=1.4-8.7), Forns OR was 3.1 (95% CI=1.3-7.9), APRI OR was 3.2 (95% CI=1.4-6.9) and AARPRI OR was 3 (95% CI=1.3-6.4).

Conclusions: These findings support the hypothesis that liver steatosis and fibrosis may play a role in the clinical background of CRC and bring to light the fascinating possibility of a reversed gut-liver axis communication in the pathogenesis of CRC. Thus, the use of non-invasive scores of liver fibrosis may be helpful to predict the risk of CRC and serve as novel prognostic factors for prevention and therapeutic strategies.

532. EFFECT OF DARK CHOCOLATE ON LOW GRADE ENDOTOXAEMIA IN PATIENTS WITH NON-ALCOHOLIC STEATOHEPATITIS: IS THERE A ROLE FOR "CHOCOBIOTA"?

Pannunzio A.[1], Loffredo L.[2], Palumbo I.M.[1], Baratta F.[2], Magna A.[1], Totè C.M.[1], Carnevale R.[3], Bartimoccia S.[2], Cammisotto V.[2], Nocella C.[2], Angelico F.[4], Del Ben M.[1], Violi F.[4]

[1]Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy; [2]Department of Clinical Internal, Anesthesiology and Cardiovascular Sciences, Sapienza University of Rome, Rome, Italy; [3]Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy. 00185 Rome, Italy; [4]Sapienza University of Rome, Rome, Italy

Background and Aims: It is known that cocoa beans mimics the effect of prebiotics and probiotics and exerts this effect on gut microbiota. Lipopolysaccharide (LPS) is an endotoxin derived from the membrane of gram-negative bacteria which binds to Toll-like receptor 4 (TLR4), activates intracellular transcription of several inflammatory mediators and increses oxidative stress. Oxidative stress plays a pivotal role in liver diseases and can induce the progression of Non-Alcoholic Fatty Liver Disease (NAFLD) to NASH (Non-Alcoholic Steato-Hepatitis). The aim of this study was to assess the effect of chocolate on endotoxaemia in a population affected by NASH compared to healty subjects.

Methods: In a cross-sectional study we analyzed endotoxaemia by circulating LPS, gut permeability assessed by serum zonulin, endothelial function, as assessed by flow mediated dilation (FMD), oxidative stress, with by Nox2 activation, serum isoprostanes and nitric oxide bioavailability (NOx), in patients with NASH (n=19) and controls (n=19). Then, we performed a randomized, cross-over study in 19 subjects with NASH comparing the effect of 14-days administration of 40g of chocolate at high (dark chocolate, cocoa >85%) versus low content (milk chocolate, cocoa <35%) of polyphenols on FMD, oxidative stress and endotoxaemia.

Results: Compared to controls, NASH patients had higher Nox2 activity, isoprostanes, LPS and zonulin levels and lower FMD, NOx (see Table 1). A significant difference for treatments was found in subjects with respect to LPS (p=0.04) and zonulin (p=0.02) from the ANOVA performed on crossover study data. The pairwise comparisons showed that, compared to baseline, after 14 days of dark chocolate intake, LPS and zonulin decreased from 22±4 to 19±4 pg/dl and from 3.2±0.9 to 2.5±0.8 pg/ml (Figure 1 and 2).

Conclusions:

Dark chocolate, and not milk chocolate, reduces LPS and zonulin in NASH patients. Dark chocolate could improve endothelial function and gut permeability via Nox2 down-regulation. Nevertheless, the effect of chocolate on dysbiosis deserves further studies.

Table 1 Clinical characteristics

Figure 1.

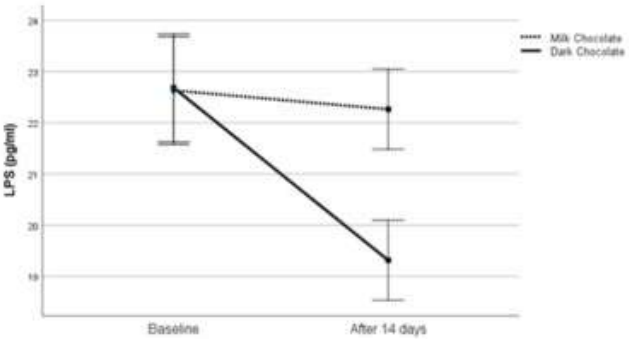
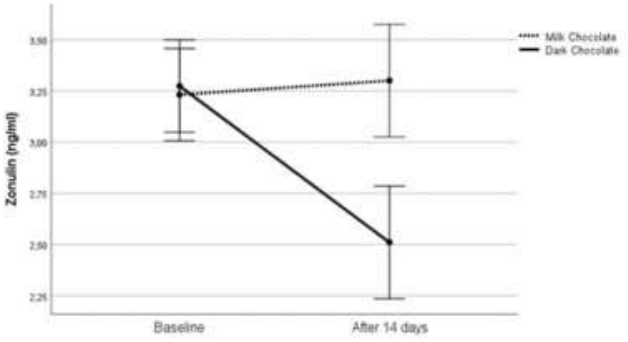


Figure 2



533. LEAN NAFLD, ACROSS BODY MASS INDEX

Pecani M.[1], Mallamace M.[2], Angeloni G.[2], Cenciarelli Ch.[2], Barbitta A.[2], Iannone I.[2], Miglionico M.[1], Andreozzi P.[2], Basili S.[3]

[1]Dipartimento di Medicina Sperimentale, Sapienza Università di Roma, Roma.; [2]Medicina Predittiva, genere specifica e cronicità. Azienda Ospedaliero-Universitaria Policlinico Umberto I. Roma.; [3]Dipartimento di Medicina Traslazionale e di Precisione, Sapienza Università di Roma, Roma

Background and aim: The association between obesity and non-alcoholic fatty liver disease (NAFLD) has been well-established, with both conditions experiencing a simultaneous rise in prevalence. In recent years, researchers have shown a growing interest in studying NAFLD in nonobese individuals. This study aims to explore the differences between lean NAFLD patients and their overweight or obese counterparts, as well as lean individuals without NAFLD.

Methods: Subjects medical history, demographic, laboratory findings were collected. The diagnosis of non-alcoholic fatty liver disease (NAFLD) entailed identifying hepatic steatosis through liver ultrasound, with careful exclusion of other liver diseases or secondary causes. To assess the presence of metabolic syndrome (MetS) in participants, modified criteria outlined by the NCEP Adult Treatment Panel III were used. Data analysis was conducted using SPSS 27 software, and statistical significance was determined by considering p-values below 0.05, indicating significant associations or differences between variables. To categorize the subjects effectively, we employed a comprehensive classification system, segregating individuals into four distinct groups based on their body mass index (BMI) and non-alcoholic fatty liver disease (NAFLD) status. These groups encompassed lean individuals with NAFLD (BMI < 25 kg/m^2), overweight individuals with NAFLD (BMI 25-29.9 kg/m^2), obese individuals with NAFLD (BMI > 30 kg/m^2), and lean individuals without NAFLD (BMI < 25 kg/m^2).

Results: In this study, we recruited a total of 156 subjects. Among them, 135 patients had non-alcoholic fatty liver disease (NAFLD) and were further divided into three distinct groups: 25 (18.5%) lean individuals with NAFLD, 41 (30.4%) overweight individuals with NAFLD, and 69 (51.1%) obese individuals with NAFLD. Additionally, the study included 21 patients without NAFLD who were classified as lean. The study population had an average age of 52.9 years and comprised of 67 males and 89 females. Significant differences were observed when comparing the lean NAFLD group with the over-

weight and obese NAFLD groups in terms of BMI, waist circumference, and metabolic syndrome (p = 0.00001, p = 0.0003, and p < 0.00001, respectively). The lean NAFLD group also showed a significantly lower homeostasis model assessment of insulin resistance (HOMA-IR) compared to the obese NAFLD group (p = 0.022381), along with a lower prevalence of type 2 diabetes mellitus, hypertension, and dyslipidemia (p = 0.028041, p = 0.015141, p = 0.04033, respectively). The overweight NAFLD group exhibited a lower prevalence of type 2 diabetes mellitus and metabolic syndrome compared to the obese NAFLD group (p = 0.031243, p = 0.02969, respectively). However, no statistically significant differences were found in the serum lipid profile among the three BMI categories with NAFLD. When comparing lean individuals without NAFLD to the lean NAFLD group, several notable differences were observed. Despite both groups were lean, the lean non-NAFLD group demonstrated significantly lower BMI and waist circumference (p = 0.000719, p = 0.03266, respectively). Additionally, the prevalence of dyslipidemia was found to be lower in the lean non-NAFLD group (p = 0.021092) and dyslipidemia was the variable with the strongest association with NAFLD in lean individuals (p = 0.0251, odds ratio = 4.25, 95% confidence interval 1.1205-16.1204). On the other hand, the lean NAFLD group exhibited significantly higher levels of HOMA-IR and triglycerides (p = 0.03489, p = 0.047048, respectively) and lower levels of HDL cholesterol (p = 0.045594) when compared to the lean group without NAFLD.
Conclusion: When comparing lean NAFLD patients to overweight and obese NAFLD patients, the first group exhibit a lower prevalence of metabolic syndrome, MetS features and a lower HOMA-IR index. However, in comparison to lean individuals without NAFLD, lean NAFLD patients have higher BMI, waist circumference, HOMA-IR, and triglyceride levels, while having lower HDL cholesterol levels.

534. NAFLD, METABOLIC SYNDROME AND GENDER

Pecani M.[1], Mallamace M.[2], Angeloni G.[2], Cenciarelli Ch.[2], Barbitta A.[2], Iannone I.[2], Miglionico M.[1], Andreozzi P.[2], Basili S.[3]
[1]Dipartimento di Medicina Sperimentale, Sapienza Università di Roma. Roma.; [2]Medicina Predittiva, genere specifica e cronicità. Azienda Ospedaliero-Universitaria Policlinico Umberto I. Roma.; [3]Dipartimento di Medicina Traslazionale e di Precisione, Sapienza Università di Roma, Roma

Background and aims: Non-alcoholic fatty liver disease (NAFLD) is a common liver condition characterised by the accumulation of excess fat in liver cells, not related to excessive alcohol consumption. NAFLD is often associated with Metabolic Syndrome (MetS), which is a cluster condition that includes abdominal obesity, high blood pressure, high blood sugar levels, and abnormal cholesterol or triglyceride levels. Recent studies have shown common underlying mechanisms between these conditions, such as insulin resistance, oxidative stress, inflammation, and dyslipidemia. Furthermore, individuals with MetS are more likely to develop NAFLD, and vice versa. Therefore, this study aims to explore the relationship between MetS and NAFLD, with a particular focus on potential gender differences in these associations.
Methods: Medical history and demographics, lifestyle factors, and laboratory data of the participants were collected. Diagnosis of NAFLD was based on the evidence of hepatic steatosis in liver ultrasound, in the absence of other liver diseases or secondary causes. MetS was defined using the modified criteria outlined by the NCEP Adult Treatment Panel III. Data analysis was conducted using the SPSS 27 software. P values < 0.05 were considered significant.
Results: In this study, we investigated 152 patients with non-alcoholic fatty liver disease (NAFLD) with a mean age of 53.8 years. The study population consisted of 87 females and 65 males, with males comprising 42.8% of the sample. Among the NAFLD patients, 91 individuals (58.6%) met the diagnostic criteria for metabolic syndrome. In this study population the most prevalent feature of metabolic syndrome was waist circumference, observed in 90 patients (59.2%), followed by HDL cholesterol (80 patients), triglycerides (79 patients), fasting plasma glucose (74 patients), and blood pressure (71 patients). We did not observe a significant difference in the prevalence of metabolic syndrome, or the number of metabolic syndrome criteria based on gender (p=0.759, p=0.723, respectively). However, we did find significant gender differences in waist circumference and HDL cholesterol levels, with p-values of 0.029 and 0.041, respectively. Moreover, there was a statistically significant association between the Fibrosis-4 (FIB-4) index and gender, with a p-value of 0.044.
Top of Form
Conclusion: According to literature, our study confirms the high prevalence of metabolic syndrome (MetS) in patients with non-alcoholic fatty liver disease (NAFLD). We found that a substantial proportion of the study population could be diagnosed with MetS, with waist circumference being the most common component, followed by HDL cholesterol. The most interesting result of our study was the observation of significant gender differences in waist circumference, HDL cholesterol, and the FIB-4 index. These findings highlight the importance of screening for MetS in NAFLD patients, especially for those with higher waist circumference measurements or lower HDL cholesterol levels.

535. CORRELATION BETWEEN MAFLD AND REACTIVE HYPOGLYCAEMIA IN NON-DIABETIC OBESE INDIVIDUALS

Trapanese V., Natale M.R., Donato U., Vatalaro C., Cosentino F., Giofrè F., Sergi S., Melina M., Arturi F.
Dipartimento di Scienze Mediche e Chirurgiche, Università degli Studi "Magna Graecia" di Catanzaro, Catanzaro, Italia

Background: Metabolic associated fatty liver disease (MAFLD) is defined as liver steatosis entity in addition to the presence of overweight or obesity, diabetes mellitus or evidence of metabolic dysfunction. Previous studies have indicated that liver cirrhosis is associated with hypoglycemia, but there have been no studies investigating the association between MAFLD and hypoglycemia in noncirrhotic obese populations without type 2 diabetes.
AIM: To explore the association between MAFLD and reactive hypoglycemia among obese patients without type 2 diabetes.
Methods: Fiftyfive obese patients were divided into two groups based on presence or absence of MAFLD evaluated throught ultrasound, before a 75-gram prolonged oral glucose tolerance test (POGTT). Each subject underwent an anthropometric and biochemical assessment and a 7-day diary of alcohol intake. The incidence of reactive hypoglycemia (blood glucose ≤3.1 mmol/L or 55 mg/dL at points of 0–5 hours) was compared among two groups, and blood glucose and insulin levels were monitored simultaneously from POGTT to assess the level of insulin resistance and insulin sensitivity.
Results: Among the two groups, the incidence of hypoglycemia was significantly different after 3 hours (p=<0.05) and the incidence of reactive hypoglycemia in the MAFLD group was approximately 3 times that in the group without MAFLD. Similary, the insulin levels in MAFLD group after 3 hours was slightly higher than in group without MAFLD (18,3 ± 12,8 mU/L vs 16,4 ± 17,3 mU/L, respectively). In addition, the insulin levels in the hypoglycemia subgroup in patients with MAFLD had higher level than in non-hypoglycemia patients (19,0 ± 13,9 mU/L vs 16,0 ± 4,2 mU/L, respectively). The homeostasis model assessment of insulin resistance index was increased in MAFLD group (3,7 ± 1,6 vs 3,2 ± 1,9 mU/L), while the Matsuda index was decreased (3,2 ± 1,6 vs 3,7 ± 1,9). Participants with reactive hypoglycemia had lower mean body mass index (39.8±5.6 vs 39.3±5.1). In addition, metabolic parameters were higher in patients with reactive hypoglycaemia: Waist circumference (119±14 vs 115.6±13.4), Serum triglycerides (133.3±86.3 vs 116.2±68), Systolic blood pressure (131±22 vs 124±10.5) and Diastolic blood pressure (83±11 vs 78±9).
Conclusions: Obese people with MAFLD without type 2 diabetes has higher rate of reactive hypoglycemia. Moreover, metabolic syndrome components may have a probably role on incidence of reactive hypoglycemia.

536. THE IMPACT OF BATRIATIC SURGERY ON CARDIO-METABOLIC PROFILE

Giofrè F.[1], Natale M.R.[1], Melina M.[1], Cosentino F.[1], Vatalaro C.[1], Trapanese V.[1], Cloro C.[2], Sciacqua A.[1], Segura Garcia C.[1], Currò G.[1], Arturi F.[1]
[1]Dipartimento di Scienze Mediche e Chirurgiche, Università degli Studi "Magna Graecia" di Catanzaro, Catanzaro, Italia; [2]Azienda Ospedaliera "S.S. Annunziata", Cosenza, Italia

Background: Obesity is associated with cardiac remodeling resulting in hypertrophy of the left ventricle (LV) with a predominantly concentric pattern. LV remodeling and fibrosis induce mechanical and electrical dysfunction of the myocardial tissue, an increase in cardiac output, an increase of myocardial workload and mean arterial pressure.
Objective: Aim of our study was to evaluate the impact of bariatric surgery, and therefore of anthropometric and cardio-metabolic variations, on cardiac structure and function.

Methods: Twenty-eight obese patients treated with bariatric surgery were enrolled. All the patients at baseline and at 6 and 12 months underwent a complete anthropometrical evaluation, laboratory determinations and echocardiogram evaluation. The IR has been assessed by HOMA-IR. The patients were divided into two groups: the first group (10 patients) carried out a follow-up at 6 months post-surgery; the second group (18 patients) at 12 months post-surgery.
Results: As expected, an improvement in the anthropometric and metabolic profile in patients treated with bariatric surgery was observed. Echocardiographic data showed a significant increase in the Ejection Fraction (P <0.001) and the E / A Ratio (P <0.001) 6 months after bariatric surgery, a significant reduction in the Interventricular Septum thickness at 6 months (P <0.001) and at 12 months (P <0.002) post-surgery and a significant reduction in the Left Ventricular Mass at 6 months (P = 0.02) and at 12 months (P = 0.05) after bariatric surgery. A reduction no significant in the Left Ventricular posterior wall thickness has been observed.
Conclusions: Our data showed an increase of the systolic function, an increase of the left ventricular diastolic compliance and a reduction in subclinical cardiac organ damage. Therefore, significant weight loss obtained with bariatric surgery may lead to reverse cardiac remodeling, associated with beneficial effects on myocardial structure and systo diastolic function.

537. LOW HDL-CHOLESTEROL AND VISCERAL ADIPOSITY PREDICT CARDIOVASCULAR EVENTS: A SINGLE CENTER 4 YEARS FOLLOW-UP STUDY IN 737 PATIENTS

De Matteis C.[1], Petruzzelli S.[1], Crudele L., Novielli F., Di Buduo E., Caggiula V., Gadaleta R.M., Moschetta A.
Department of Interdisciplinary Medicine, University of Bari "Aldo Moro", 70124 Bari, Italy

Introduction and Aims: Cardiovascular events (CVEs) represent the first cause of death worldwide. Dietary and voluptuary habits are modifiable risk factors. Abdominal, more than systemic obesity is linked to dyslipidemia, one of the most significant risk factors for atherosclerosis development. Indeed, low levels of high-density lipoprotein-cholesterol (HDL-c) and high levels of low-density lipoprotein-cholesterol (LDL-c) have been suggested as an indicator for early prevention of CVE, especially in metabolic subjects. To reduce the overall burden of CVEs, it is necessary to further identify novel bio humoral and clinical parameters for both prediction and prognosis. To this end, we prospectively followed-up a cohort of subjects suspected of metabolic derangement, registering CVEs occurring after their first evaluation.
Methods: 737 patients from our outpatient's clinic of Metabolic Diseases at Teaching Hospital Policlinico di Bari, Italy were followed-up every-year from 2014 to 2021. None of these patients reported previous CVEs. Most common CVE's risk factors, such as smoking, diabetes, increased waist circumference (WC), arterial hypertension, and high BMI were explored and recorded. Student-T test comparisons were performed between subjects who did and did not develop CVEs during the follow-up period. P-values <0.05 were considered significant. Chi-square tests were performed to calculate the associated Odds Ratio (OR) with 95% confidence interval (CI).
Results: During the mean observational period of 4.09 years, 133 (18.0%) developed CVEs. 34.7% of them were smokers, 34.9% were diabetics, 60.2% suffered from arterial hypertension, and 78.3% presented visceral obesity (i.e., increased WC according to Metabolic Syndrome diagnosis. At index day, Systolic Blood Pressure (SBP) (p = 0.149), LDL-c (p=0.417), and BMI (p=0.147) were not significantly increased in the subjects who develop CVEs compared to those who did not, WC (95.7 ± 12.7vs 98.3 ± 10.6, p=0.018) was significantly increased in patients who later presented CVEs. Furthermore, baseline HDL-c levels (idem, p=0.015) were significantly reduced in affected patients. When calculating ORs of single metabolic criteria for CVE development in subjects with increased fasting plasma glucose (FPG) or glycosylated hemoglobin (HbA1c), triglycerides (TG), WC, BMI (cut-offs for both overweight and obesity), as well as in those with hypertension and low HDL-c levels, only low HDL-c and high TG levels showed a statistically significant association. Specifically, HDL-c was associated to CVEs with a OR of 1.5 (95% CI: 1.044-2.278, Sensitivity: 39.4% Specificity: 70.4%) and TG showed a OR=of 1.5 (95% CI: 1.006- 2.25, Sensitivity: 33.6% Specificity: 61.4%).
Conclusions: In our cohort, baseline HDL-c level was the most accurate bio humoral parameter to discriminate years in advance patients who presented a CVE, also in the stratification of individual risk assessment. The finding that WC, and not BMI, is increased in patients who develop CVEs underlies the role of visceral adiposity in HDL synthesis and mobilization, strengthening the reverse cholesterol transport (RCT) involvement in CVEs pathogenesis. Besides, pathological conditions such as diabetes or hypertension commonly associated with increased CVR, resulted insufficient, per se, in the prediction of a CVE. Thus, our data points to cholesterol HDL as a predicting parameter of CVE and under emphasize the role of visceral adiposity with subsequently systemic inflammation and pro atherosclerotic scenario in the pathogenesis or development of a CVE.
*These authors contributed equally to this work.
**The abstract mistakenly did not previously contained one of the authors. Therefore, since it was not editable, it has been reuploaded to reflect the correct number and order of authors. i apologize for the inconvenience.

538. VOLANESORSEN TO TREAT SEVERE HYPERTRIGLYCERIDEMIA: A POOLED ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Stanzione C.[1], Calcaterra I.[1], Donnarumma S.[1], Palermo V.[1], Schiano N.[1], Pontoriero M.T.[1], Di Minno A.[2], Lupoli R.[3], Tufano A.[1], Iannuzzo G.[1], Di Minno M.[1]
[1]Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy; [2]Department of Pharmacy, Federico II University, Naples, Italy; [3]Department of Molecular Medicine and Medical Biotechnology, Federico II University, Naples, Italy;

Background: Patient with severe hypertriglyceridemia (sHTG) are often refractory to lipid lowering therapy. Apolipoprotein (Apo) CIII inhibition could be promising to treat subjects with sHTG. The antisense oligonucleotide against APOC3 mRNA volanesorsen was recently introduced to treat sHTG. We performed a systematic review and meta-analysis of RCTs on efficacy and safety of volanesorsen as compared to placebo treatment in patients with severe HTG. Methods: Studies were systematically searched in the PubMed, Web of Science, Scopus databases according to PRISMA guidelines. Last search performed on 07thFeb2022. Results: Four studies showed significant reduction in TG after 3 months of treatment with volanesorsen as compared with placebo (MD: -73.9%; 95%CI: -93.5%, -54.2; P<0.001 I2= 89.05%; P<0.001); VLDL-C level (MD: -71.0%; 95%CI: -76.6%, -65.4%; P<0.001 I2= 94.1 %; P<0.001); Apo-B48 level (MD: -69.03%; 95%CI: -98.59.4%, -39.47%; P<0.001, I2=93,51%; P<0.001); Apo- CIII level (MD: -80.0%; 95%CI: -97.5 %, -62.5; P<0.001 I2= 94.1 %; P<0.001) with an increase HDL-C level (MD: +45.92.5%, 95%CI: +37.24%, +54.60%; P<0.001 I2= 94.34%; P<0.001) and in LDL-C level (MD: +68.6%, 95%CI: +7.0%, +130.1%; P<0.001 I2= 96.18%; P<0.001) without a significant elevation of Apo-B100 level (MD: +4.58%, 95%CI: -5.64%, +14.79%; P=0.380 I2= 95.09%; P<0.001) in 139 volanesorsen patients as compared to 100 placebo-treated controls. Most of adverse events were mild and related to local injection site reactions.
Conclusions: In patients with severe HTG, volanesorsen is associated with a significant reduction in TG, VLDL-C, Apo-B48, non-HDL-C, and increment of HDL-C as compared to placebo. Documented efficacy is accompanied by an acceptable safety profile.

MISCELLANEA

539. LILAC PATH INSIDE THE UOC M.C.A.U. OF THE PAPARDO HOSPITAL

Signoriello.G
UOC M.C.A.U. Ospedale Papardo

5) Would you claim that food dominates your life?

An answer with yes to two or more questions leads to a more complete evaluation. The triage nurse will therefore report the patient with a lilac ALERT on the computerized medical record. The doctor of the UOC M.C.A.U., once he visualized the ALERT among patients awaiting a visit, will therefore direct the patient to a suitable path.

540. A LIFE-THREATENING CASE OF METHOTREXATE INTOXICATION FROM ARBITRARY INTAKE WITHOUT MEDICAL PRESCRIPTION

Miceli G.[1], Corpora F.[1], Daidone M.[1], Torres D.[1], Di Raimondo D[1], Basso G.[1], Pintus C.[1], Rizzo G.[2], Pennacchio A.R.[1], Cocciola E.[1], Vivoli S.[1], Profita M.[1], Cuffaro M.G.[1], La Russa E.[1], Cucina A.[1], Indelicato S.[1], Di Gaudio F.[1], Tuttolomondo A.[1]

[1]Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, Università degli Studi di Palermo, Piazza delle Cliniche 2, 90127 Palermo, Italy; [2]Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, Università degli Studi di Palermo, Piazza delle Cliniche 2, 90127 Palermo, ItalyDepartment of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, Università degli Studi di Palermo, Piazza delle Cliniche 2, 90127 Palermo, Italy

Methotrexate is a drug interfering with the metabolism of folic acid suitable, at different dosages, for treating neoplastic and rheumatic diseases. It is characterized by a narrow therapeutic index and several collateral effects may appear during the administration of this drug, especially when used at high dosage. Methotrexate intoxication represent a medical urgency requiring the prompt administrations of antidotes and accurate management of the frequent complications. We report a particular complex case of a 60-year-old patient with acute methotrexate intoxication. The clinical history revealed arterial hypertension under pharmacological treatment and a thirty-year-lasting diagnosis of psoriasis, just occasionally treated with steroid therapy. In February 2023, the patient referred the appearance of numerous dyskeratotic lesions on the limbs, subsequently extended centripetally and to the face, and symptoms such as dysuria, watery diarrhoea, vomiting and dysphagia for solid and liquid food. For this reason, he accessed the emergency area of the Policlinico P. Giaccone in Palermo, where he performed blood tests that showed increased creatinine levels with hyperkalemia and metabolic acidosis, so he underwent an urgent hemodialysis session and, afterward, admitted to our ward. Upon admission, an objective examination was performed with evidence of erythematous/desquamative lesions extended to the trunk, limbs, scalp and face, and erosions of the genital mucosa and oral cavity, while the thoracic, abdominal, cardiovascular and neurological objectivity was normal. Blood chemistry at the entrance showed increased renal function indices, while blood count and liver function indices were within normal limits. After a careful interview, the patient reported that he had arbitrarily administered, about five days before, therapy with methotrexate subcutaneously at a dosage of 15 mg for four consecutive days, in the absence of a medical prescription. Therefore, considering the reported information and the clinical manifestations characterized by signs of mucositis of the gastrointestinal and genitourinary tracts, skin involvement and acute renal damage suggestive for methotrexate intoxication, after a telephonic consultation with the Poison Control Centre of Pavia, high-dose levopholinic acid therapy was promptly undertaken. In addition, hydration and sodium bicarbonate therapy for the alkalinization of urine in the attempt to promote the renal elimination of the drug was practiced. In the second day of hospitalization, we witnessed the appearance of pancytopenia at blood tests, with "nadir" of blood count with severe neutropenia (0/mcl), severe anaemia and thrombocytopenia (<50000/mcl) on the third day of hospitalization, so granulocyte and erythroid growth factors and antimicrobial prophylactic therapy was administered and the patient placed in spatial isolation considering the high risk of infection. However, despite the undertaken therapy and the further increase of the dosage of levopholinic acid up to the dosage of 1 gram/day, high plasma levels of methotrexate were dosed by our laboratory without improvement in the clinical findings, which were also superimposed on the appearance of ideo-motor slowdown and visual hallucinations attributable to encephalopathy. Therefore, given the worsening of the patient's status burdened by a high risk of mortality and the persistence of severe renal dysfunction that compromised an adequate elimination of methotrexate, the specific antidote (Glucarpidase), not present in our region (Sicily), was shipped in few hours from Northern Italy and administered for compassionate use, although beyond the time limit indicated (more than 48-60 hours from the administration of the methotrexate) for its optimal effectiveness. Following the administration of Glucarpidase, the patient's condition gradually improved. Unfortunately, hemodialytic treatment continuation was necessary considering the persistence of the renal damage secondary to acute tubular necrosis by methotrexate. Although the doses of methotrexate taken by the patient were lower than those defined as "High dose methotrexate" (>500mg/m2), possible concomitant factors such as the lack of folic acid supplementation, the use of other drugs or the probable not-known pre-existing renal impairment may have predisposed the development of systemic toxicity even at low doses of the drug. Thus, individual assessment of patients is necessary for the prediction of the risk of methotrexate intoxication. Hence, at the stabilization of the clinical status, the patient was discharged at home with the strong advice not to take medication without previous specialistic consultation. The case was reported to the Police considering the dispensation of a potentially-lethal drug without medical prescription.

In conclusion, this case shows the increasing tendency of people to self-medication and the importance of an accurate anamnesis and the multidisciplinary coordination for the early recognition and management of complexes life-threatening conditions such as methotrexate intoxication.

541. HOW CAN WE IMPROVE THE QUALITY OF LIFE OF PATIENTS WITH SYSTEMIC IMMUNE-MEDIATED DISEASES?

Filippini E.[1], Salvucci S.[1], Gazzoli F.[1], Lucarelli L.[1], Santangeli S.[1], Festa A.[2], Manfredi L. [2], Prof. Moroncini G[3]

[1]Scuola di Specializzazione in Medicina Interna, Università Politecnica delle Marche, Ancona, Italia; [2]Clinica Medica, Dipartimento di Medicina Interna, Azienda Ospedaliero Universitaria delle Marche, Ancona, Italia; [3]Scuola di Specializzazione in Medicina Interna, Università Politecnica delle Marche, Ancona, Italia. Clinica Medica, Dipartimento di Medicina Interna, Azienda Ospedaliero Universitaria delle Marche, Ancona, Italia

Background: Our objective is to assess whether a multidisciplinary integrative approach, based on yoga, mindfulness, counseling, and Tuina or Shiatsu massage, can enhance the quality of life of patients with chronic immune-mediated diseases (IMDs). Pain and fatigue are frequently reported by patients with IMDs, and can significantly impact their quality of life, even when the disease is in remission according to validated assessment methods. Therefore, the management of these symptoms is a real challenge in the treatment of patients with IMDs.

Research has shown that complementary and alternative medicine (CAM) approaches, such as yoga, mindfulness, and massage therapy, may be effective in managing chronic pain and fatigue in patients with various medical conditions, including IMDs. These interventions can help patients develop self-awareness, cope with stress, and improve their physical and mental well-being.

By evaluating the impact of an integrative approach that combines CAM therapies with standard pharmacological treatment, we aim to provide evidence-based recommendations for the management of pain and fatigue in patients with IMDs. Ultimately, our goal is to improve the quality of life of these patients and enhance their overall well-being.

Methods: Our study involved the evaluation of patients affected by immune-mediated diseases (IMDs) through an uncontrolled observational approach. All outpatients consecutively followed by our Clinic, who reported physical or psychological distress despite receiving standard-of-care treatment, were included in the study.

Our integrative approach was comprised of small group sessions of either yoga or mindfulness, held for 60 minutes once a week for a duration of 6 months. Additionally, patients were provided with 8 sessions of either Tuina or Shiatsu massage, or counselling treatment, with each session lasting for 60 minutes. Each patient participated in at least one of these activities.

To measure the quality of life (QoL) of the patients, we utilized the validated Italian version of the Medical Outcome Study Short Form 36 (SF-36) questionnaire at baseline and after the treatment. The Wilcoxon signed-rank test was employed to analyse the difference between pre- and post-treatment values. The data analysis was carried out using the R software.

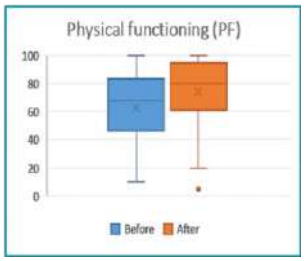
Results: Commencing in June 2019, 49 patients were recruited for our study, with 28 individuals (11 SSc, 7 SLE, 2 UCTD, 1 RA, 5 PsA, 1 SS, 1 GPA; sex: 27 F, 1 M) completing the entire study. The median age of these patients was 57.5 years (IQR 40.75-62.25). It was observed that 3 out of 28 patients (10.7%) fulfilled the diagnostic criteria for fibromyalgia1.

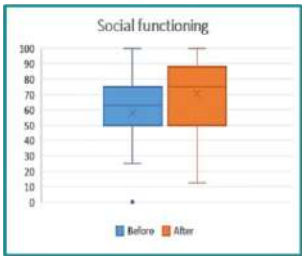
Upon conducting data analysis, statistically significant differences (p-values<0.05) between pre- and post-treatment values were observed in 5 out of 8 SF-36 scales (Physical functioning, Role physical, Social functioning, Role emotional and Mental health) and in the PCS and MCS summary scales. It was noted that all patients exhibited a positive inclination towards the new approach.

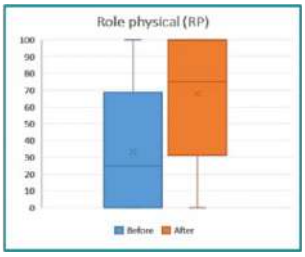
The logistics and the distance from the hospital were identified as the primary reasons for the study's rejection by certain patients.

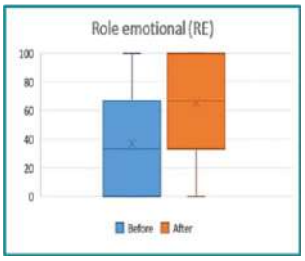
Conclusion: While a larger cohort is needed to validate these preliminary findings, our study indicates that the integrative approach recommended for

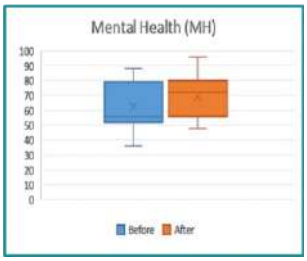
patients suffering from IMDs has the potential to enhance their quality of life.

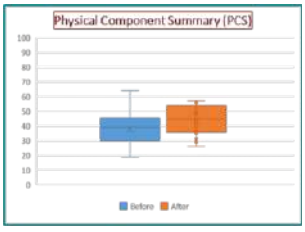


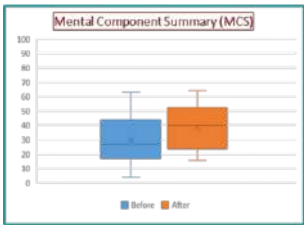












542. ASSESSING COMPLEXITY IN INTERNAL MEDICINE THROUGH A MULTIPURPOSE DIGITAL PLATFORM: THE MED-CLI REGISTRY

Rovere-Querini P.[1], De Lorenzo R.[2], Ramirez G.A.[3], The Internal Medicine residents team[2], Sala C.F.[4], The CGP team[4], Tresoldi M.[5]
[1]Unit of Medical Specialties and Healthcare Continuity IRCCS Ospedale San Raffaele, Milan, Italy; [2]Università Vita-Salute San Raffaele; [3]Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS Ospedale San Raffaele, Milan, Italy; [4]Center for omics science (COSR), IRCCS Ospedale San Raffaele, Milan, Italy; [5]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy

Background: Decision making in healthcare should always be based on evidence-based knowledge. The acquisition and progression of such knowledge, in turn, is based on research, which is contingent on the accurate collection of trustworthy data to maximize the reliability and generalizability of findings. The expanding availability of innovative informatic strategies to safely store large amounts of data has revolutionized quantitative research processes involving data collection and analysis, and has paved the way for critical advances in our understanding of diseases. Key to such strategies is to guarantee the quality of the data collected while protecting the dignity, confidentiality, and privacy of research subjects. Specialized governance procedures (i.e. approval by an Ethics Committee, written informed consent, privacy protection by design and by default, etc.) are vital to safeguard donors' rights while securing stakeholders' interests. Different types of registries exist depending on their scope. While disease-oriented ones address a specific research question, population-based repositories collect data from patients with different clinical phenotypes and thus allow various stratification criteria to be tailored to multiple research purposes, representing a valuable resource also for future, yet undefined goals. This latter approach is particularly relevant to address the multifaceted biological, clinical, and social concerns characterizing patients populating Internal Medicine departments of nowadays hospitals, in the broader context of an aging population with a growing prevalence of multimorbidity. To address this issue, we took advantage of the setting of a large multi-specialty hospital and built up a comprehensive digital registry where clinical data of patients accessing internal medicine departments are systematically and prospectively collected for present and future research purposes. Besides answering patient-related questions, healthcare quality is also part of the general research aims in this project. Here we show some preliminary data on the progresses of the study and on its preliminary outputs.
Methods: Upon approval by our local Ethics Committee, we initiated a prospective project focused on dissecting the multifaceted aspects of clinical complexity in patients of Internal Medicine interest. To this purpose, we designed a multipurpose data collector (Med-Cli protocol) integrating information from the institutional clinical workstation software with systematically collected social and clinical data of adult in- and outpatients referring to internal medicine departments of San Raffaele University Hospital. This collector was integrated within the framework of the Cohort Genomics Platform©, an Electronic Data Capture (EDC) tool developed by the Center for Omics Science (COSR) of the same Institution to assist researchers and clinicians in the collection and management of clinical research data, which conforms to the prescriptions of the General Data Protection Regulation (GDPR) and its interpretations by the Italian Law. The logics behind the digital case report form for the Med-Cli project are founded upon the distinction between static and dynamic data. Static data encompass variables that are time-independent (such as sex) or irreversibly accumulating over time without rapid variations, such as chronic comorbidities. Dynamic data include events and decisions happening during clinical episodes (i.e. longitudinal occurrences of clinical events such as outpatient visits or hospitalisations) or showing potential fluctuations over time with or without coincidence with clinical episodes, such as laboratory tests and treatment changes. In order not to strain the clinical staff with research duties, informed consent administration, data collection, and data entry into the platform are carried out by research nurses and internal medicine residents, who responded with enthusiasm and dedication to this research call.
Results: From the launch of the platform in November 2022 to April 2023, we have collected comprehensive data of 960 patients, of whom 641 referring to outpatient clinics and 319 to internal medicine wards (out of 439 hospitalised). Building on these preliminary data, seven projects focusing on several unmet needs in patient management such as prolonged hospitalisations, deprescribing, hospital-acquired infections, modulation of lipid metabolism for cardiovascular risk, differential hospitalisation courses among patients with and without cancer, and pregnancy morbidity in patients with chronic disorders have been initiated.
Conclusion: A multipurpose prospective registry based on a flexible digital platform for data collection represents a cost- and effort-effective, scalable tool for addressing a multitude of research questions and dissect the various contributors to clinical and management complexity in patients of Internal Medicine interest.

543. LENGTH OF STAY IN INTERNAL MEDICINE: PRELIMINARY DATA FROM A MULTIPURPOSE HOSPITAL REGISTRY

Critelli S.[1], Ciocca L. [1], Fanile M.T.[1], Menchi S.[1], Festorazzi C.[2], Bozzolo E.P.[3], De Sa' Pedroso C.[3], Salmaggi C.[3], D'Angelo E.[1], Bagnati C.[1], Borgonovo E.[1], Deonette G.[3], Damanti S.[4], Ramirez G.A.[5], Rovere-Querini P.[6], Tresoldi M.[3]
[1]Unit of General Medicine and Advanced Care, Università Vita-Salute San Raffaele, Milan, Italy; [2]Unit of Medical Specialties and Healthcare Continuity, Università Vita-Salute San Raffaele, Milan, Italy; [3]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy; [4]Unit of General Medicine and Advanced Care, Unit of Medical Specialties and Healthcare Continuity, IRCCS Ospedale San Raffaele, Università Vita-Salute San Raffaele, Milan, Italy; [5]Unit of General Medicine and Advanced Care, Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS Ospedale San Raffaele, Università Vita-Salute San Raffaele, Milan, Italy; [6]Unit of Medical Specialties and Healthcare Continuity IRCCS Ospedale San Raffaele, Università Vita-Salute San Raffaele, Milan, Italy

Background: Length of stay (LOS) is a proxy of healthcare efficiency, since prolonged LOS represents a risk factor for hospitalization-related complications, besides significant economic effects for public health systems. LOS might also indicate the degree of patient clinical complexity and constitute a measure of the challenge of managing multi-comorbid patients. Nonetheless, little is known about potential differential traits and clinical outcomes among internal medicine patients with distinct LOS.
Aim of the Analysis: to identify clinical, social and healthcare-associated risk factors for prolonged LOS in patients admitted to Internal Medicine Departments and define distinct outcome profiles in patients with different durations of hospitalization.
Methods: We relied on data extraction from a multipurpose prospective registry (Med-Cli) collecting clinical, social and healthcare quality data from patients admitted to the Internal Medicine Departments of San Raffaele Hospital. The protocol was approved by the local Institutional Review Board and patients enrolled upon informed consent. We selected data from patients admitted from November 2022 to April 2023 in the wards involved in the registry and classified patients into three classes according to their LOS: A) short-stay (1-14 days); B) long-stay (15-30 days); C) very-long-stay (more than 31 days). Data are expressed as median (interquartile range), unless otherwise specified.
Results: Of 439 patients hospitalized in the study timeframe, data were available from 315/319 enrolled inpatients (169 men, 146 women) with a median age of 76 (67-83) years. Among them, 129 had a short stay, 108 a long stay and 37 a very long stay. There was no statistical difference in demographics, distribution of comorbidities or intensity of care needed on admission and during the disease course among the three groups. Almost half of the patients needed assistance at home. When this information was stratified by LOS, the fraction of dependent patients was numerically higher in the very long-stay group (24%) than in the long- (15%) or short-stay group (18%). Dependency in Activities Of Daily Life (ADL) was either partial or total in the majority of inpatients (57% of the sample). Total dependency was higher in the very-long-stay group (46%) than in the short-stay (20%; p<0.001) and long-stay group (17%; p<0.001). Almost half of the patients (44%) had at least one hospitalization in the previous 12 months. Nevertheless, admissions in the previous 12 months did not associate with specific LOS groups. Patients in the very-long stay group had a significantly higher prevalence of nosocomial infection (46%) when compared with long-stay (15%; p<0.001) and short-stay patients (9%; p<0.001). Pressure ulcers during hospitalization were also more frequent in the very-long-stay group (30%) than in the long-stay (4%, p<0.001) and short-stay group (6%, p<0.001). There were no differences in mortality rates among the three groups. Patients with very long stay were more frequently discharged to lower intensity of care facilities for further treatment (32%) than patients who were discharged after a short (2%; p<0.001) or long hospitalization (6%; p<0.001).
Conclusions: Preliminary data from a large university hospital suggest that no single pathology has an impact on LOS. Conversely, the level and complexity of home assistance and dependence in ADL might predict a longer stay (more than 30 days) in internal medicine wards and may predict the development of hospitalization-related complications such as nosocomial infections and pressure ulcers. Difficult access to post-acute care facilities after discharge might further complicate the course of hospitalization and further prolong patient LOS. Dedicated management strategies for highly-disabled patients could reduce the human, clinical and economic costs of prolonged LOS and of excessive rates of hospitalization-related adverse events.
References
1. Barba, R et al. Eur J Int Med, 2015
2. Anderson ME et al., J Hosp Med, 2015

544. AN UNTARGETED LIPIDOMIC ANALYSIS REVEALS DEPLETION OF SEVERAL PHOSPHOLIPID CLASSES IN PATIENTS WITH FAMILIAL HYPERCHOLESTEROLEMIA ON TREATMENT WITH EVOLOCUMAB

Donnarumma S.[1], Calcaterra I.[1], Andrea A.[2], Di Minno A. [3], Cavalca V. [4], Porro B.[4], Gabriella I.[1], Tufano A.[1], Cardiero G.[5], Di Taranto M.D.[5], Fortunato G.[5], Di Minno M.N.D.[1]
[1]Dipartimento di Medicina Clinica e Chirurgia, Università degli Studi di Napoli "Federico II", 80131 Napoli, Italy; [2]Fondazione Edmund Mach Research and Innovation Centre, Food Quality and Nutrition Department, Via E. Mach, 1, 38010 S. Michele all' Adige, Italy; [3]Dipartimento di Farmacia, Università degli Studi di Napoli "Federico II", 80131 Napoli, Italy; [4]Centro Cardiologico Monzino, IRCCS, 38010 Milano, Italy; [5]Dipartimento di Medicina Molecolare e Biotecnologie Mediche - Università degli Studi di Napoli "Federico II", Napoli, Italy

Background: Familial hypercholesterolemia (FH) is caused by mutations in genes involved in low-density lipoprotein cholesterol (LDL-C) metabolism, including those for pro-protein convertase subtilisin/kexin type 9 (PCSK-9). The effect of PCSK-9 inhibition on the plasma lipidome has been poorly explored.
Methods: Using an ultra-high-performance liquid chromatography-electrospray ionization-quadrupole-time of flight-mass spectrometry method, the plasma lipidome of FH subjects before and at different time intervals during treatment with the PCSK-9 inhibitor Evolocumab was explored.
Results: In 25 FH subjects, heterozygotes or compound heterozygotes for different LDL receptor mutations, untargeted lipidomic revealed significant reductions in 26 lipid classes belonging to phosphatidylcholine (PC), sphingomyelin (SM), ceramide (CER), cholesteryl ester (CE), triacylglycerol (TG) and phosphatidylinositol (PI). Lipid changes were graded between baseline and 4- and 12-week treatment. At 12-week treatment, five polyunsaturated diacyl PC, accounting for 38.6 to 49.2% of total PC at baseline; two ether/vinyl ether forms; seven SM; five CER and glucosyl/galactosyl-ceramide (HEX-CER) were reduced, as was the unsaturation index of HEX-CER and lactosyl-CER (LAC-CER). Although non quantitative modifications were observed in phosphatidylethanolamine (PE) during treatment with Evolocumab, shorter and more saturated fatty acyl chains were documented.
Conclusions: Depletion of several phospholipid classes occurs in plasma of FH patients during treatment with the PCSK-9 inhibitor Evolocumab. The mechanism underlying these changes likely involves the de novo synthesis of SM and CER through the activation of the key enzyme sphingomyelin synthase by oxidized LDL and argues for a multifaceted system leading to vascular improvement in users of PCSK-9 inhibitors.

545. PERCEPTION OF ASSISTANCE-RELATED BURDEN AMONG CAREGIVERS IN A COHORT OF CHRONICALLY ILL, COMPLEX, AND FRAIL PATIENTS

Bagnati C.[1], Ramirez GA.[2], Lubiati L.[3], Montagna F.[3], Brambilla G.[3], Lonati G.[3], Rizzi B.[3], Soddu D.[4], Guaschino G.[5], Scotti R.[5], Marinosci A.[5], Bozzolo EP.[5], Desapedroso C.[5], Tresoldi M.[5]
[1]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy ; Università Vita-Salute San Raffaele, Milan, Italy; [2]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy ; Università Vita-Salute San Raffaele, Milan, Italy ; Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS Ospedale San Raffaele, Milan, Italy ; [3]VIDAS, Volontari Italiani Domiciliari per l'Assistenza ai Sofferenti; [4]Unit of of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy; [5]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy

Background: Increasing prevalence of chronic diseases has led to a growing number of chronically ill, complex, and frail patients (CCF). These patients often require tailored continuity of care programmes, taking into account their unique health and social needs after hospital discharge. Less is known about the impact of the assistance burden on caregivers of CCF patients.
Materials and Methods: The PRO-CCF cohort study is a monocentric, observational prospective protocol aiming to collect clinical data from CCF patients entering a joint post-hospital care programme involving San Raffaele Hospital, and VIDAS a non-profit organization operating in Lombardy, Italy. Collected data include patient history, clinical events during hospitalization and post-discharge follow-up along with patient quality of life before and after hospitalization, and the caregiver's perception of the assistance burden. Here, we focused on patient status and caregiver perceptions at six months (T6) post-discharge, by measuring patient Karnofsky performance scale (KPS), patient Euro Quality Five Dimensions-Five Levels Score (EuroQol 5D-5L), and the Modified Caregiver Strain Index (MCSI), a tool designed to assess various aspects of caregiver burden, including emotional, physical, and financial strain. Data are expressed as median (interquartile range), unless otherwise specified.
Results: Data were available from 10/37 patients (eight women, two men), with a median age of 79 (73- 83) who were enrolled between May 10, 2021 and April 10, 2022. All patients had a non-oncological primary diagnosis at the time of discharge. Four subjects had a KPS score of 50%, indicating moderate impairment in their functional status, while six subjects had a KPS score of at least 70%, suggesting a relatively better functional status. Additionally, the median perceived EuroQol 5D-5L score was 60 (50-66).
Each patient had a primary caregiver, with 40% being female and 60% being male. Among the caregivers, 70% cohabited with the patients, while in 20% of the cases, the caregiver was only present during daytime. Eight caregivers responded to the MCSI questionnaire: 75% reported that providing assi-

stance to the patient limited their freedom and leaded to changes in their family routine, 63% stated that the burden of care imposes limitations on their personal projects. Seven caregivers (88%) considered giving assistance to the patient mildly stressful, one (13%) reported a moderate level of stress associated with the assistance burden.
Conclusion: Data from a very small sample size suggest that despite limited functional autonomy, CCF patients enrolled in a dedicated continuity of care programme do not experience high-severity grade of perceived illness and report a good perceived health quality. This evidence might indicate that the programme is effective in addressing patient wellbeing. Furthermore, most caregivers were able to manage their caregiving duties without significant strain, although the majority of them reported some degree of limitations to their usual lifestyle. More data are needed to confirm these preliminary trends.

546. TREATMENT WITH PCSK9 INHIBITORS IN PATIENTS WITH FAMILIAL HYPERCHOLESTEROLEMIA LOWERS PLASMA LEVELS OF PLATELET-ACTIVATING FACTOR AND ITS PRECURSORS: A COMBINED METABOLOMIC AND LIPIDOMIC APPROACH

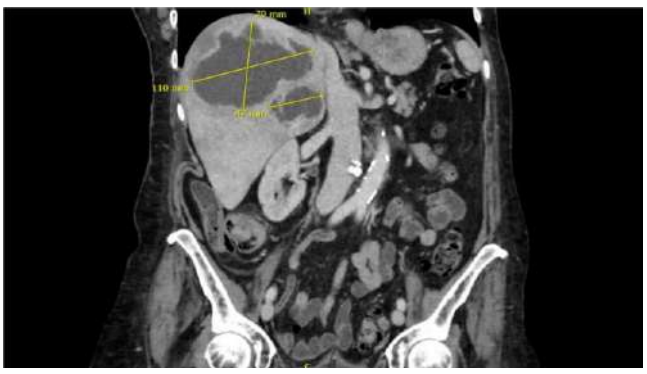
Palermo V.[1], Calcaterra I.[1], Tufano A.[1], Pontoriero M.[1], Di Minno A.[2], Orsini RC.[3], Cavalca V.[4], Chiesa M.[4], Anesi A.[5], Colombo G.[4], Di Taranto M.D.[6], Tremoli E.[4], Fortunato G.[6], Porro B.[4], Di Minno M.[1]
[1]Department of Clinical Medicine and Surgery,Federico II,Naples,Italy; [2]Department of Pharmacy, University of Naples "Federico II", 80131 Naples, Italy; [3]Department of Clinical Medicine and Surgery,Federico II University, Naples,Italy; [4]Centro Cardiologico Monzino, IRCCS, 38010 Milano, Italy; [5]Fondazione Edmund Mach Research and Innovation Centre, Food Quality and Nutrition Department, Via E. Mach, 1, 38010 S. Michele all' Adige, Italy; [6]Department of Molecular Medicine e Medical Biotechnologies, Federico II University, Naples, Italy

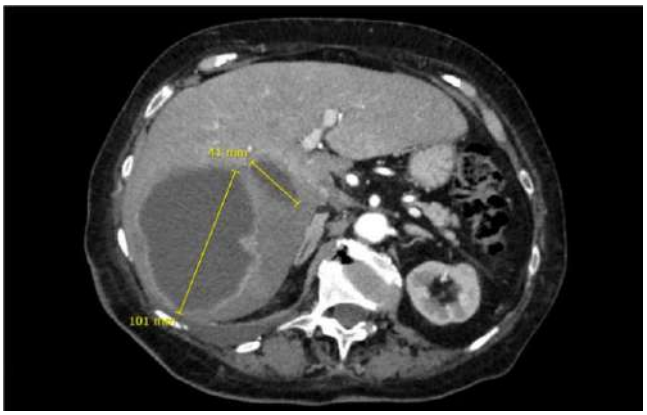
Background: Familial hypercholesterolemia (FH) is characterized by extremely high levels of circulating low-density lipoprotein cholesterol (LDL-C) and is caused by mutations of genes involved in LDL-C metabolism, including LDL receptor (LDLR), apolipoprotein B (APOB), or proprotein convertase subtilisin/Kexin type 9 (PCSK9). Accordingly, PCSK9 inhibitors (PCSK9i) are effective in LDL-C reduction. However, no data are available on the pleiotropic effect of PCSK9i. To this end, we performed an untargeted metabolomics approach to gather a global view on changes in metabolic pathways in patients receiving treatment with PCSK9i.
Methods: FH patients starting treatment with PCSK-9i were evaluated by an untargeted metabolomics approach at baseline (before PCSK9i treatment) and after 12 weeks of treatment.
Results: 25 FH subjects were enrolled on maximal tolerated lipid-lowering therapy prior to study entry. After a 12 week treatment with PCSK9i, we observed an expected significant reduction in LDL-cholesterol levels (from 201.0 ± 69.5 mg/dL to 103.0 ± 58.0 mg/dL, $p < 0.001$). The LDL-C target was achieved in 36% of patients. After peak validation and correction, after 12 weeks of PCSK9i treatment as compared to baseline, we observed increments in creatine (p-value = 0.041), indole (p-value = 0.045), and indoleacrylic acid (p-value= 0.045) concentrations. Conversely, significant decreases in choline (p-value = 0.045) and phosphatidylcholine (p-value < 0.01) together with a reduction in platelet activating factor (p-value = 0.041) were observed.
Conclusions: Taking advantage of untargeted metabolomics, we first provided evidence of concomitant reductions in inflammation and platelet activation metabolites in FH patients receiving a 12 week treatment with PCSK9i.

547. STREPTOCOCCUS ANGINOSUS LIVER ABSCESSES AS FIRST MANIFESTATION OF COLORECTAL CANCER, A CASE REPORT.

Amoruso M.V. , Caprotti F.
Department of Internal Medicine, IRCCS San Gerardo, Monza (Italy)

An 81-years-old woman came to the E. R. for dizziness,shortness of breath and deteriorating of general conditions with weight loss in the last months.She denied fever at home.She had a clinical history of hypertension and osteoporosis,which she was taking chronic medications for.She reported no allergies to any drug during the past.She had undergone previous appendectomy and three shots of Covid-19 vaccine.She did not smoke tobacco and did not drink alcohol nor use illicit drugs.On examination the patient was hemodynamically stable,T.C. was 36°C,B.P. 135/60 mmHg,HR 84 bpm,R.R. 16 bpm and O2 saturation 98% in a.a..She presented bilateral peripheral edema,without any focal neurological deficit,but bilateral hyposthenia of the lower limbs.The remaining physical examination was negative, particularly, the abdomen was soft and nontender,Murphy and Blumberg signs were negative.Laboratory test showed anemia,neutrophilic leukocytosis with inflammatory activation,AKI,elevated levels of liver function and cholestasis. SARS-CoV-2 nucleic acid testing of a nasopharyngeal specimen was negative,as well as testing for Influenza virus types A and B and RSV.Abdomen ultrasound: the liver was characterized at the level of the VII-VIII segment by the presence of voluminous hypo-anechoic formation with a maximum size of about 11 cm,apparently without a significant Doppler vascular signal;further anechoic alteration,irregularly cystic in appearance,of about 55 mm was noticeable in the periportal area of the VII segment.The chest X-ray did not show signs of pneumonia,pulmonary edema nor pleural effusion.She was drawn for emocultures and urinocoltures.I.V fluids and empirical antibiotic therapy with piperacillin/tazobactam was administrated.There was a progressive normalization of the renal and liver function,stable levels of hemoglobin,tendency to hypokalemia which was corrected with the administration of IV supplementation.The patient was evaluated with an abdomen CT (Figure 1 and Figure 2) with endovenous contrast which characterized the liver formations as abscesses,so she was tested for antibodies for Entamoeba histolytica, Echinococcus granulosus, Widal Wright,Brucella and parassitologic/coltural stool analysis:all of the above resulted negative. A percutaneous drainage was performed,with the collection of purulent material of which the cultural examination detected Prevotella spp and Streptococcus anginosus, confirming the initial hypothesis of pyogenic liver abscess (PLA).The drainage remained in place for 20 days, during which the antibiotic therapy was continued,confirmed by the antibiograms.As soon as the general conditions improved,it was possible to perform further investigations in order to search for the source of the culprit infection:she underwent a negative dental evaluation and a CT scan of the facial bones with the exclusion of odontogenic abscesses or other infectious processes affecting the dental arches or the oral cavity.Then, the patient undertook a colonoscopy,with the evidence of a 4 cm- ulcerated polyp at the level of the hepatic flexure,not conditioning enteral stenosis,identified as the lesion responsible for the spread by bacterial translocation and by the portal circulation of the liver infection.The bioptic sample of the polyploid formation showed a histology of intestinal adenocarcinoma G2.Furthermore, a trans-thoracic echocardiography was performed which ruled out concomitant valvular vegetation or other abnormalities suggestive of endocarditis.During the hospitalization the patient showed persistent normocytic anemia.There was no iron deficiency, normal vitamin asset,but increased hemolysis markers (aptoglobin 0.9 mg/dl, lactic dehydrogenase 295 U/L, Coombs test was negative) and reticulocyte compensation (3.95%),referable to a autoimmune hemolytic anemia with hot antibodies,secondary to infection by Streptococcus anginosus,recovered with the reduction of the inflammatory activity with targeted antibiotic therapy.Concurrently there was an improvement in laboratory parameters and asthenia,with reduction of the inflammation levels and progressive normalization of the cytonecrosis and cholestasis markers.Abdomen CT of re-evaluation after 23 days of treatment showed reduction of the abscesses,with an indication of further 6 weeks of antibiotic therapy.The patient was transferred to a long-term stay facility in order to continue the treatment.At the end of the 6 weeks period of therapy she was re-evaluated and underwent surgery of right hemicolectomy,with a good clinical outcome.Histopathological analysis reported signet ring cells mucosecreting adenocarcinoma (pT3N0 R0).The post-surgery CT showed complete regression of the liver abscesses,without any scarring or fibrosis.





548. EFFECTIVE RESPONSE TO TREATMENT IN PATIENT WITH VERISIMILAR ANTIBODY-NEGATIVE PARANEOPLASTIC LIMBIC ENCEPHALITIS : A CASE REPORT

Troiano F.[1], Caporale M.[1], Montagano M.[1], Matarazzo G.[1], Vizzarri P.[1], D'Ardes D.[1], Marchione M.[1], Evangelista G.[2], Bucci M.[1], Cipollone F.[1], Guagnano M.T.[1], Simeone P.[1], Santilli F.[1], Pierdomenico S. D. [3]
[1]"Clinica Medica" Institute, Department of "Medicine and Science of Aging", "G. d'Annunzio"; University, Chieti, Italy.; [2]Department of Neuroscience, Imaging and Clinical Science; [3]Department of Innovative Technolog. In Medicine & Dentistry; "G. D'Annunzio" University, Chieti, Italy

77-year-old man entered PS for soporous state, asthenia and fever, reported by family member and occurred in the last 2 days before hospitalization, with progressive deterioration of general clinical conditions, after infection with Sars-COV2, treated at home with paracetamol 1gr A/B and brufen 1200 mg/day. High values of creatinine (10.2 mg/dl), neutrophil leukocytosis and increased index of inflammation were found at blood tests in PS, as for IRC revived in septic state, for which EGA examination and nephrological evaluation were also practiced, in the absence of indications for dialysis treatment.
With regard to the neurological state, the patient was subjected to CT without MDC, which excluded acuity, neurological evaluation and EEG, which documented the presence of recurrent crises, for which he performed extemporaneous therapy with Midazolam, subsequently setting cover with Levetiracetam.
As a result of the worsening of the clinical conditions, with the appearance of an epileptic state, the patient was subjected to rachicentesis in the suspicion of infectious encephalitis, subsequently starting antiviral therapy with Acyclovir 10 mg/kg x 3/day.
For further aggravation of the state of consciousness, with the appearance of a state of coma, were alerted fellow resuscitators, who transferred the patient to the ICU for treatment. Upon entering the Intensive Care Unit, there was a sudden episode of TV with FC 180 bpm and PA 65/40 mmhg and defibrillation was carried out by Shock 200 J, with the RS restored. NMR was performed with MDC, which showed mild FLAIR and DWI hyperintensity of the hippocampus and left insula.During the hospitalization in Intensive Care, because of the negativity of the molecular tests for herpetic viruses, the antiviral therapy was suspended, while starting research on serum and liquor antibodies for paraneoplastic/autoimmune forms, neoplastic markers and HIV (with subsequent negative result in full and, specifically, also the autoantibody profile consisting of Ab anti-Hu and Ab anti-CV2/ CRMP5).
A total-body CT was performed with MDC, which documented the presence of a solid pseudo lesion of about 3 x 2.5 cm, corresponding to the proximal III of the pancreatic body also evaluated by CEUS examination, which confirmed focal hypo/avascular area at the level of the pancreatic body, about 2.5 cm, immediately downstream of the dilation of the main pancreatic duct, strongly suspected by heteroformative process.
Assuming a pancreatic neuroendocrine tumor, characterized by hypoenhancement for possible subversion of the tissue architecture (with increased values of Cromogranin A), surgical and oncological consultations were performed, with indication to perform Cholangium-NMR and EUS-FNA, however not programmed for severe clinical conditions. In the suspicion of paraneoplastic encephalitis with negative antibodies, plasmapheresis started, for a total of 5 sessions with slight clinical improvement, and, subsequently, was practiced therapy with IgEv 0,4 g/Kg/day for 5 days, with associated steroid therapy using Deltacortene 1 mg/Kg/day, to be modulated according to clinical condition. During the hospitalization in the Intensive Care Unit, the patient was also treated with VMI by tracheostomics, because of a state of severe acute respiratory insufficiency hypoxyemic-hypercapnic and treated with antibiotic therapy with Meropenem and Amikacina because of septic state. After carrying out the treatment set, a good clinical improvement was observed with the patient recovering a state of vigilance, exploring the environment with his gaze, following the examiner and turning to whom he was speaking from time to time, fulfilling simple and complex orders. He practiced new cycle of IgEv, before the transfer to the rehabilitation facility.
The relevance of the reported case lies in the response to treatment with plasmapheresis, Igev and steroid therapy in a framework of limbic encephalitis with probable paraneoplastic etiology, tendentially not responsive to the therapeutic processes currently available.
It is important to report the presence in literature of a single work entitled "Anti-Hu paraneoplastic brainstem encephalitis caused by a pancreatic neuroendocrine tumor presenting with central hypoventilation" by Najjar M. et al, who describes a similar case of a 59-year-old man, hospitalized for hypercapnic respiratory failure with abdominal CT with MDC, documenting heteroformation of the pancreas tail, and positive anti-Hu antibodies in CSF and serum, treated with discrete response by immunosuppressive therapy. In addition, it may also be interesting to focus on carcinoid or Hedinger syndrome. Several cardiac arrhythmias, reported in literature as FA and TV, have been described associated with such condition, as well as development of fibrous-like plaques on the valves, with possible development of related heart failure.

549. FOSTERING THE INTERSECTION BETWEEN PRIMARY CARE AND HOSPITAL: THE PRIME (PRIMARY CARE-HOSPITAL EMBEDDING) PROJECT

Montagna M.[1], Chiabrando F.[1], Vitali G.[2], Canti V.[2], Spano' A.[1], Fait F.[1], Di Resta A.[1], Rovere Querini P.[3]
[1]Internal Medicine Residency, Vita-Salute San Raffaele University, Milan; [2]IRCCS San Raffaele Hospital, Milan; [3]Faculty of Medicine, Vita-Salute San Raffaele University, Milan; IRCCS San Raffaele Hospital, Milan

Background: The challenges faced by primary care, among which its reduced efficacy and lack of workforce turnover are the subject of intense discussions in Italy and in other countries. Some scenarios even posited the "the end of the family doctor". Instead, the World Health Organization defines primary care as "the most equitable, efficacious, and cost-effective way to enhance the health of populations" and supports an integrated and synergic approach between primary care and hospital/secondary care.
During the COVID19 crisis, hospitals represented the main care setting and, soon, the limitation of available resources and the inappropriateness of such strategy became evident. Several stakeholders and policy makers therefore proposed new solutions to reduce the burden on hospitals and shift some of it to primary care settings. Unfortunately, as primary care had been neglected for many years, it turned out to be unprepared to face the challenges of the successive COVID19 waves. In our hospital, we designed a new care pathway for COVID19 patients that was grounded in the synergy between local General Practitioners (GPs) and our hospital.
Based on this experience, we asked ourselves how an enhanced interface and collaboration with hospitals could make primary care more efficient, efficacious, and patient-centered.
Aims: This is the focus of the PRIME project (PRIMary care-hospital Embedding) that we launched as a consortium mixing medical teams of three big Milanese hospitals with the experiences of GPs representing the city's primary care. We are offering to GPs a way to fast-track their patients to hospital resources, but not to the Emergency Room (ER), when such patients require advanced, but not critical, care.
Materials and Methods: For the aim of the project, we set up an outpatient clinic at San Raffaele Turro Hospital, a facility which is embedded inside the north-eastern districts of Milan, easily accessible and easy to navigate for patients. The clinic is led by internists, granting a holistic approach to care. The clinic has a dedicated nurse, allowing for on-site blood drawings, urinary tests and ECGs. Consultants, among which a cardiologist if an echocardiogram is needed, are available for discussion of the cases, also with the aid of telemedicine. Close to the clinic is the radiology unit for any required imaging test. GPs are given a mobile phone number to call the internists to discuss and eventually send patients, who are usually seen in 24-72h time. The main addressed pathologies are the Ambulatory Care Sensitive Conditions, but we are available for any case in which the GP considers the need of further discussion. An ad-hoc prospective observational clinical trial was ap-

proved by our Ethic Committee to capture data about the activity of this innovative service and capture feedback from the involved GPs.
Results: As of May 30th, 2023, we started a collaboration with 30 GPs and we visited 13 patients. As reported in Table 1, median age of patients was 79 years old (IQR: 62-86), 77% of patients were females and median BMI was 24.4 (IQR: 20.5-27.1). Concerning visit data, as shown in Table 2, the median time elapsed from referral to visit was 3 days (IQR: 1-6), in 46% of cases the first visit was enough to solve the case and the patient was discharged from the service while in 46% of cases either a further ambulatory visit or a referral to a specialist was necessary. A summary of vitals and laboratory examinations of patients can be found in Table 3.Notable diagnoses made at the outpatient clinic were: 1. a liver abscess in a patient presenting with long standing fever; 2. primary aldosteronism in a patient presenting with uncontrolled hypertension and hypokalemia; 3. post-infective pleuro-pericarditis in a patient presenting with fever, chest pain and pleural and pericardial effusion. In one case only it was necessary to send the patient to the local ER, as she was presenting with severe anemia, worsening congestive heart failure and decompensated type 2 diabetes mellitus.
Discussion: Albeit little, the experience acquired so far is promising. It shows that GPs can indeed benefit from a direct communication with internists working inside a large hospital. Without our service, some patients we evaluated would have been inappropriately directed to the ER. Instead, we could successfully reach a diagnosis and start a therapy exclusively through outpatient evaluations. Building on the evidence acquired during the pandemic, we think that this approach may represent a turning point in healthcare organization by: 1) Increasing the support received by GPs from local hospitals; 2) Reducing inappropriate admissions to the ER and healthcare costs; 3) Increasing the overall quality of care offered to patients in terms of experience and outcome.

Demography (n=13)

	count or median	%	IQR
Age	79		62-86
Female sex	10	77	
BMI	24,4		20,5-27,1
Obesity	2	18	
Hypertension	11	85	
Diabetes	3	23	
Dyslipidemias	5	38	
COPD	3	23	
CKD	5	38	
CAD	4	31	
Cancer	4	31	
Heart failure	3	23	

Visit data (n=13)

		Count or median	%	IQR
Logistics	Time to visit (d)	3		1-6
	Resolved by phone	2	15	
	Consultation requested	6	46	
Reason	Suspected pneumonia	3	23	
	Urinary infection	0	0	
	Fever with no potential diagnostic clues	2	15	
	COPD exacerbation	1	8	
	Heart failure	1	8	
	Non traumatic leg pain	0	0	
	Hyperglycemia	0	0	
	Uncontrolled hypertension	1	8	
	Angina	0	0	
	Arrythmia	0	0	
	Other	5	38	
			100	
Outcome	Dismissal	6	46	
	Sent to ED	1	8	
	Sent to specialist	3	23	
	Further Ambulatory visit	3	23	

Vitals (n=11)	median	IQR
Systolic BP (mmHg)	135	126-146
Diastolic BP (mmHg)	65	65-78
Heart rate (mmHg)	80	71-88
SpO2 (%)	97,0	94,5-100,0

Laboratory (n=13)	median	IQR
WBC (x10^9/L)	9,6	8,6-12
Hb (g/dL)	11,7	9,3-12
Hct (%)	36	30,5-39
PLT (x10^6/L)	361	260-465
AST (U/mL)	22,5	16,25-30
ALT (U(mL)	17	10-12
Bilirubin (mg/dL)	0,25	0,2-1
Creatinine (mg/dL)	1,05	0,7-2
eGFR (ml/min)	51,1	25,9-68,3
proBNP (pg/mL)	2101	694-6467
Total cholesterol (mg/dL)	176	162-211
LDL-C (mg/dL)	90	59-130
Triglycerides (mg/dL)	149	121-179
HbA1c (mmol/mol)	39	26-52
Albuminuria (mg/dL)	44	44
CRP (mg/dL)	1,45	0,58-3
Glucose (mg/dL)	97	93-175

NEFROLOGIA

550. LIGHT-CHAIN DEPOSITION DISEASE: A SNEAKY AND UNKNOWN ENEMY

Nicotra V.[1], Bosco V.[2], Mauceri F.[2], Piro S.[3], Urso S.[4]
[1]Dipartimento di Medicina Interna, Catania; [2]Dipartimento di Geriatria, Catania; [3]Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy; [4]U.O.C. Nefrologia, Garibaldi-Nesima

Introduction: Light chain deposition disease (LCDD) is a rare condition associated with the excessive production of monoclonal light chain immunoglobulins and their subsequent deposition in various organs and tissues. In LCDD renal involvement is always present (however, sporadic cases of LCDD with exclusive extrarenal involvement are described in the literature) and manifests itself with renal insufficiency, nephrotic syndrome, hematuria and/or proteinuria. In addition to the kidney, the deposition of light chains in the heart and liver is frequent, in order of frequency. The diagnosis of the disease is complex and requires a differential diagnosis with AL amyloidosis and diabetic nephropathy among the most frequent conditions. In most cases, LCDD is associated with a plasma cell neoplasm (particularly multiple myeloma) or other lymphoproliferative disorders (about 60%) even if there is an ever-increasing number of idiopathic cases (according to the most recent series around to 35%).
Clinical Case: 50-year-old woman with diffuse focal proliferative lupus nephropathy, known from a young age. The patient underwent, in the past, pharmacological therapy with mycophenolate, azathioprine and cyclophosphamide and sessions of plasmapheresis and selective immunoadsorption with stable renal function indices. In the light of the finding of a monoclonal lambda peak, the patient underwent a bone marrow biopsy with the diagnosis of "immunophenotypic histological picture of modest increase in the plasmacyte level, compatible with MGUS". Furthermore, during blood chemistry tests, there was a worsening of the renal function indices and the appearance of proteinuria (6.1 g/24h) for which high-dose corticosteroid therapy was started, initially by the intravenous route and then by the oral route but with little benefit. For this reason, the patient underwent a renal biopsy which, by immunofluorescence, demonstrated "widespread and intense positivity for lambda light chains at the level of the tubular basement membranes, the capillary walls and the mesangium (3+) in the face of complete negativity for kappa" for which the picture was compatible with a lambda-type light chain deposition disease (LCDD). For the purpose of a correct

differential diagnosis with amyloidosis, the patient underwent an echocardiogram and a search for amyloid on periumbilical fat, both with negative results. Total body examinations excluded the detection of extra-renal disease. Chemotherapy was then started with 4 cycles of Dara-VTD (Daratumumab in combination with bortezomib, thalidomide and dexamethasone), with suspension of Thalidomide due to patient intolerance and subsequently bone marrow autotransplantation. However, due to the constant worsening of renal function, the patient was started on peritoneal dialysis.
Discussion: Clinically, LCDD usually presents with hypertension, microhematuria and proteinuria and its clinical course is characterized by rapid progression which most often requires renal replacement therapy. In the idiopathic form, if a kidney transplant is performed, the results are generally unsatisfactory, and a recurrence of the disease usually occurs within a few years. The renal glomerular disorders associated with multiple myeloma are mainly primary amyloidosis and LCDD and the differential diagnosis is exclusively histological. Histologically, primary amyloidosis results in glomerular deposition of AL amyloid in mesangial, subepithelial, or subendothelial areas with a typical random orientation of the fibrils (composed of the variable regions of the lambda light chains) while LCDD is characterized by the glomerular deposition of unpolymerized light chains, generally the constant regions of the lambda light chains and to a lesser extent of the lambda chains (as occurred in our case clinical).
Conclusions: Renal biopsy is the diagnostic gold standard for the study of nephropathies. If a history of lymphoproliferative or plasma cell disease is already present, the suspicion of LCDD, as well as AL amyloidosis, must always be suspected. MGUS already known to the patient has evolved into an exclusively renal form, with deposition of lambda light chains in the kidney. However, it is still unclear how to prevent the onset of LCDD and how to decrease the risk of LCDD recurrence, given that both renal and bone marrow transplants are not free from disease recurrence. Given the rarity of LCDD cases in the literature, there are still many questions that need to be answered.
Bibliography
- Popov H, Stoyanov GS, Ghenev P. Light Chain Deposition Disease: A Morphological Case Report. Cureus. 2022 Jun 27;14(6):e26357
- Wang Q, Jiang F, Xu G., The pathogenesis of renal injury and treatment in light chain deposition disease. J Transl Med. 2019;17:387
- Pozzi C, D'Amico M, Fogazzi GB, et al. Light chain deposition disease with renal involvement: clinical characteristics and prognostic factors. Am J Kidney Dis. 2003;42:1154–1163.

551. PARASYMPATHETIC ACTIVITY AND TOTAL FIBROTIC KIDNEY IN AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE PATIENTS: A PILOT STUDY

Gigante A.[1], Lai S.[1], Perrotta A.M.[1], Panebianco V.[2], Mazzaferro S.[1], Menè P.[3], Gammaitoni G.[1], Farroni S.[1], Tinti F.[1], Cianci R.[1], Muscaritoli M.[1]
[1]Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy ; [2]Department of Radiological, Oncological and Anatomo-Pathological Sciences, Sapienza University of Rome, Rome, Italy Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy ; [3]Department of Clinical Sciences, Division of Nephrology, University of Rome La Sapienza, Sant'Andrea University Hospital, Rome, Italy

Background: Autosomal dominant polycystic kidney disease (ADPKD) is an inherited kidney disease which leads to a progressive kidney failure. About 5-10% of patients requiring renal replacement therapy are affected by ADPKD. Cardiovascular diseases are the main cause of morbidity and mortality in these patients and arterial hypertension is the first symptom with a very early onset. Cystic enlargement probably causes parenchymal hypoxia, renin secretion and endothelial dysfunction. Sympathetic and parasympathetic balance is altered in this condition, especially during the night, also affecting blood pressure circadian rhythm. Hyperactivation of the sympathetic system not only leads to an increased basal heart rate, but also promotes myocardial hypertrophy and fibrosis associated with increased risk for sudden cardiac death.
Aim: of this pilot study was to assess in ADPKD patients the sympathetic/parasympathetic balance using heart rate variability (HRV) parameters and correlate it with renal damage progression, as total kidney volume enlargement.
Methods: Sixteen adult ADPKD patients were enrolled in the study. Eleven patients (68.8%) were male, and the median age was 42 years (IQR 36–47.5). Inclusion criteria were rapidly progressive disease (as kidney function loss>5 ml/min/year) with chronic kidney disease ≥stage G3b corresponding to estimated glomerular filtration rate (eGFR) 30–44 ml/min/1.73 m2), absence of cardiovascular events, blood pressure values in normal range with angiotensin converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARBs) and calcium channel blockers (CCB).
HRV parameters were calculated using 24 h-ECG Holter. In the time domain, the standard deviation of normal-to-normal RR intervals (SDNN)(ms) and the square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD), representing global sympathetic and the parasympathetic system, respectively, were evaluated. Total power in the frequency domain range (0–0.40 Hz) was divided into low frequency (LF: 0.04–0.15 Hz, modulated mainly by sympathetic system) and high frequency (HF: 0.15–0.40 Hz, modulated by parasympathetic system). LF/HF rate is sympatho-vagal balance. The power of LF and HF components was considered in normalized units (nu). A kidney magnetic resonance imaging (MRI) scan 3 Tesla was performed to evaluate total kidney volume (TKV) and total fibrotic volume (TFV).
Results: Median serum creatinine was 1.38 mg/dl (IQR 1.2–1.61), and median eGFR was 58.1 ml/min (IQR 52–60). MRI of the kidneys showed a median TKV of 2102 ml (IQR 1372.5–3155.3) and a median TFV of 298.51 cm3 (IQR 177–352.9); median length was 17.97 cm (IQR 16.41–21.39) and median stiffness was 22.13 kPa (IQR 15.8–30). Median heart rate was 75.2 bpm (IQR 67.5–82.25). Moreover, median SDNN was 127.85 ms (IQR 113.9–168.25) and median RMSSD was 41.35 ms (IQR 27.2–50.5). A significant positive linear correlation was observed between length of kidneys and LF nu ($r=0.595$, $p < 0.05$) and LFday nu ($r = 0.587$, $p < 0.05$). Moreover, a significant positive linear correlation exists between HF nu and TFV ($r=0.804$, $p<0.01$) and height adjusted (ha) TFV ($r=0.801$, $p<0.01$). Finally, we found a significant positive linear correlation between HFnight nu and TKV ($r=0.608$, $p<0.05$), ha-TKV ($r=0.685$, $p<0.01$), TFV ($r=0.594$, $p<0.05$) and ha-TFV ($r=0.615$, $p<0.05$).
Conclusion: To the best of our knowledge, this is the first study evaluating TKV and TFV in ADPKD patients in relation to autonomic balance. We hypothesize that the increase in TKV and TFV could lead to a parasympathetic tone hyperactivation, probably in response to hypoxic stress and vasoconstriction due to cystic enlargement.

552. A STRANGE CASE OF "MULTI" DRUGS INTOXICATION: THE IMPORTANCE OF MEDICAL HISTORY

Pettinari P., Cenerelli S., Giacchetta G.M., Sorice M., Tedesco S., Fanciulli E.
Ospedale "Principe di Piemonte" - Senigallia (AN) - Nefrologia e Dialisi

A 46 years old man came to the emergency department (ED) for the presence since 3 days of epigastric and right flank pain with irradiation to right groin. The medical history was positive for alcohol use (more than a liter of wine/day), and obesity.
He reported to the ED doctor that he didn't take any drugs and to feel well the days before. Suspecting a renal colic the ED doctor asked for a routinely blood exam and an abdominal ultrasound. Normal vital sign were normal, only bradycardia (50 bpm).
The routine exam showed kidney failure (creatinine 10,65 mg/dl, blood urea nitrogen 167 mg/dl), acute hepatitis (AST 190 U/l, ALT 1.235 U/l, GGT 538 U/l, normal alkaline phosphatase, normal level of total bilirubin, normal PT and aPTT), CRP 3,36 mg/dl, normal RBC and Hb, normal WBC, PLT 133.000/mmc, normal glucose, normal amylase and lipase, normal electrolyte except calcium 7,8 mg/dl. Arterial blood gas test showed compensated metabolic acidosis (pH 7,37, pCO2 28, pO2 102, HCO3 16,2, BE -9,1, lac 0,8).
Abdominal ultrasound: increased kidney size (12,5 cm right and 12,4 cm left kidney diameter) with globous aspects and cortical iperecogenicity. No urinary tract dilatation. Liver bigger than normal with no detectable lesion, normal gallbladder, absence of biliary tract dilatation. Presence of moderate fluid amount in the pelvic cavities.
A nefrologic evaluation was demanded. Asking again the patient about the medical history and drug assumption he confessed that the week before, while he was abroad (Romania), he suffered from influenza syndrome (headache, fever and throat pain); so he took acetaminophen (paracetamol) 3 g/day for 5 days (tot 15 g) and a non-specified antibiotic for 5 days. Later the flank and epigastric pain appeared and, suspecting himself a biliary colic, for other 3 days he assumed acetaminophen 3 g/day (9 g, 15+9 24 g altogether) and a non precised amount of Anghirol 3,25 mg tablets (a choleretic drug

sold in Romania, containing Cynara Scolymus dry extract, contraindicated in patient with renal failure or hepatic failure) and NoSpa 40 mg tablets (antispasmodic drug containing drotaverine hydrochloride, contraindicated in patient with renal failure or hepatic failure). Eventually, for the persistence of the symptoms, he came to the emergency department.
Medical examination: No confusion or neurological deficit. Abdominal pain evocated with palpation of right flank, murphy sign +/-. Negative Giordano sign bilaterally. No jaundice. No other pathological sign. Diuresis was active.
Finally, with all available data, we suspected a drug-induced liver injury (DILI) and drug-induced AKI with acute tubular necrosis.
After telephonic consultation with "Centro AntiVeleni- Policlinico Gemelli" we started endovenous treatment with N-acetilcistein, antidote of acetaminophen and we performed a continuous renal replacement therapy with continuous veno-venous hemodiafiltration (CVVHDF) for 12 hours in order to remove all the potential damaging metabolites of the assumed drugs and correct metabolic acidosis. Heparin sodium was used for anticoagulation of the dialysis system.
In the following days blood exams showed an important improvement of kidney function without additional dialytic needing (creatinine 3,62 mg/dl) and a transaminase decrease (AST 71 U/l, ALT 654 U/l, GGT 424 U/l), normal CPK. HBV, HCV, HEV, CMV and HIV serology were negative. Urine analysis showed proteinuria (100 mg/dl, 1.428,0 mg/24h) and hemoglobinuria. The urine sediment showed red cells (32.986/mmc), white cells and white cell casts, with other unidentified cast. Negative urine culture.
Only fluid therapy was carried out, arterial hypertension and hyperuricemia was corrected. Control of blood and urine exams after 5 days showed: normal kidney function (, further reduction of aminotransferases, normal CRP, reduced proteinuria (276,0 mg/24h), improvement of urine sediment: red cells (388/mmc), white cells and absence of white cell cast.
Vital sign and diuresis were normal for all the hospitalization. Since kidney function completely recovered, kidney biopsy was spared.
We confirmed the clinical diagnosis of acute tubular necrosis and DILI. The presence of dehydration in a recent virosis, the chronic alcohol use and the abuse of OTC drugs promoted acetaminophen toxicity inspite of a normally tolerated dose. The patient was discharged after ten days and the follow up exams carried out a month later showed no sequelae (normal hepatic and kidney function).
What it seemed to be a classic renal colic (and perhaps with the need of NSAID treatment that could have worsen kidney failure and acute hepatitis) or a biliary colic, with an accurate medical history, showed its real face.

References

1) Drug-induced hepatotoxicity, Lee WM, N Engl J Med. 2003;349(5):474
2) Drug-induced Liver Injury, David S, Hamilton JP, US Gastroenterol Hepatol Rev. 2010 Jan 1; 6: 73–80
3) Acetaminophen hepatotoxicity in alcoholics. A therapeutic misadventure. Seeff LB, Cuccherini BA, Zimmerman HJ, Adler E, Benjamin SB. Ann Intern Med. 1986;104(3):399.

553. RENAL SALT WASTING: AN INAPPROPRIATE URODILATIN SECRETION SYNDROME? A PILOT STUDY

Della Corte V.
U.O. di Medicina Interna con Stroke Care, AOU Policlinico P. Giaccone, Palermo

Renal Salt Wasting Syndrome (RSW) is a clinical syndrome with laboratory characteristics completely overlapping with the syndrome of inappropriate ADH secretion (SIADH). The fundamental difference between the two syndromes lies in the extracellular volume (ECV), reduced in RSW and normal or slightly increased in SIADH. The difficulties in the differential diagnosis of this syndrome and in understanding the precise pathogenetic mechanism have contributed some authors to question the very existence of RSW. Considering the characteristics of RSW, natriuretic peptides were investigated to explain its onset such as ANP and BNP, with unsatisfactory results. However, no studies have yet investigated the possible role of urodilatin, a peptide belonging to the natriuretic peptide family, which seems to have a crucial role in regulating blood sodium and urinary sodium even more than ANP. We performed a retrospective observational study, the patients were divided into 3 groups: a group of patients without hyponatremia and two groups of patients with hyponatremia, one consisting of patients with RSW and the other consisting of patients with hyponatremia from other causes. patients with RSW display significantly higher mean urodilatin levels than both patients with (median 5.46 vs 0.57 ng/mL, p=0.006) or without hyponatremia (median 5.46 vs 0.27 ng/mL, p<0.001) (Figure 1). Statistically significant higher mean levels of urodilatin were also observed when patients with RSW were compared with the other two groups of patients considered together (5.46 vs 0.32 ng/mL, MW test p<0.001). Conversely, proANP levels were not statistically different among the 3 subgroups (overall KS test p=0.266) or between patients with RSW and patients with/without hyponatremia (4.9 vs 9.7 nM, MW test p=0.122). Diagnostics performances of mean urodilatin levels for RSW diagnosis were evaluated by ROC curve (Figure 2). Area under the curve (AUC) was 0.94 (95%CI 0.86-1.00). Best cut-off for mean urodilatin levels, according to Youden's index, was 2.87 ng/mL. At this cut-off sensitivity, specificity, positive predictive value and negative predictive value were, respectively, 1.00, 0.88, 0.60 and 1.00. In conclusion, this pilot study has shown interesting results regarding the dosage of urinary urodilatin in patients with RSW, with potentially clarifying implications and of practical utility both regarding the pathogenesis of this syndrome and regarding its diagnostic criteria and therefore on the clinical management of patients. We hope that further future studies can continue to shed light on this interesting topic.

ONCOLOGIA

554. INCREASED TISSUE FACTOR MRNA EXPRESSION IS ASSOCIATED WITH HIGH PLASMA LEVELS OF ACTIVATED FACTOR VII–ANTITHROMBIN COMPLEX AND PREDICTS MORTALITY IN PRIMARY LIVER CANCER

Moruzzi S.[1], Martinelli N.[1], Udali S.[1], Castagna A.[1], Di Santo L.[1], Ambrosani F.[1], Baroni M. [2], Pattini P.[1], Pizzolo F.[1], Suardi S.[1], Ruzzenente A.[3], Conci S.[3], Campagnaro T.[3], Van Dreden P. [4], Guglielmi A.[3], Bernardi F. [2], Olivieri O.[5], Friso S.[5]
[1]Department of Medicine, University of Verona, Verona, Italy; [2]Department of Life Sciences and Biotechnology, University of Ferrara, Ferrara, Italy; [3]Department of Surgery, University of Verona, Verona, Italy; [4]Clinical Research Department, Diagnostica Stago, Gennevilliers, France; [5]Department of Medicine, University of Verona, Verona

Background: Tissue factor (TF) is the main initiator of the coagulation cascade and has been shown to play a role in cancer physiopathology. Activated factor VII-antithrombin complex (FVIIa-AT) is considered an indirect marker of TF exposure by reflecting TF-FVIIa interaction.
Aims: To assess the potential link between TF gene expression and FVIIa-AT plasma levels in primary liver cancer.
Methods: TF gene expression analysis was performed by Real-Time RT-PCR in 91 patients with primary liver cancer (51 hepatocellular carcinoma and 40 cholangiocarcinoma) undergoing surgical intervention with a curative intent. The analysis was performed by comparing TF gene expression levels in neoplastic *versus* homologous non-neoplastic liver tissues. Data of FVIIa-AT plasma levels were available for all these subjects.
Results: Considering TF gene downregulated when fold change < 1 or upregulated when fold change >1, 49 cancer tissues showed TF downregulation, while 42 cancer tissues had TF upregulation as compared to homologous non-neoplastic liver tissue. Subjects with cancer tissues showing TF upregulation had marginally higher FVIIa-AT plasma levels. Stratifying this subsample according to FVIIa-AT plasma concentration, the proportion of subjects with induced TF gene increased progressively from the lowest to the highest quartile (33.3%→71.4%, P=0.037 by $\chi 2$ for linear trend, Figure 1). Considering overall survival in the study cohort after a 34-month median follow-up, Kaplan-Meier survival curves showed an increased mortality rate in patients with TF upregulation as compared to those with TF downregulation (54.8% versus 36.7%, P=0.036 by log-rank test, Figure 2). TF upregulation in cancer tissue was associated with an about two-fold increased risk of mortality (HR=1.98, 95%CI 1.04-3.77, P=0.038) after adjustment for sex, age, and creatinine levels.
Conclusions: Increased TF gene expression was associated with both high FVIIa-AT plasma levels and an increased risk of mortality in patients with primary liver cancer. The evaluation of FVIIa-AT plasma levels may allow to identify patients with highly TF-expressing cancer.

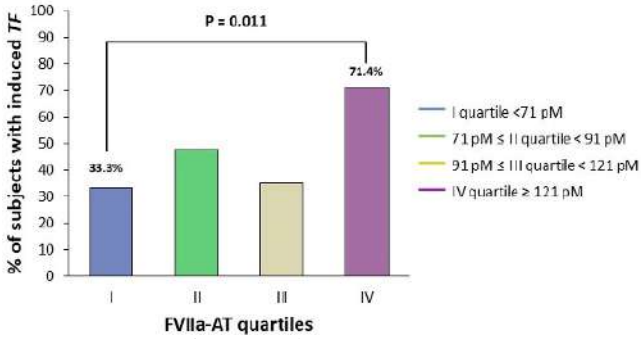


Figure 1. Percentage of patients with TF gene overexpression in cancer tissue according to FVIIa-AT quartiles

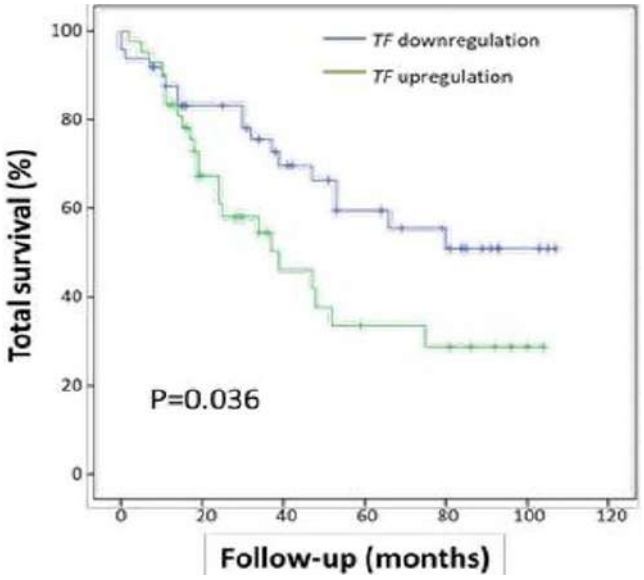


Figure 2. Kaplan-Meier survival rate in cancer patients according to TF expression levels in liver cancer tissues.

555. HOSPITALIZATION COURSE AND OUTCOMES OF CANCER PATIENTS ADMITTED TO INTERNAL MEDICINE UNITS: PRELIMINARY DATA FROM A MULTIPURPOSE HOSPITAL REGISTRY.

Borgonovo E.[1], Di Lucca G.[1], Ramirez G.A.[2], Damanti S.[3], Deonette G.[4], Paolelli F.[1], Xhelali D.[1], Actis P.[1], Santoro S.[1], Angiulli S.[1], Critelli S.[1], Manganaro G.[1], Cattelan F.[4], Rovere-Querini P.[5], Tresoldi M.[4]
[1]Università Vita-Salute San Raffaele, Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy; [2]Università Vita-Salute San Raffaele, Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy, Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS Ospedale San Raffaele, Milan, Italy; [3]Università Vita-Salute San Raffaele, Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy, Unit of Medical Specialties and Healthcare Continuity IRCCS Ospedale San Raffaele, Milan, Italy; [4]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy; [5]Università Vita-Salute San Raffaele, Unit of Medical Specialties and Healthcare Continuity IRCCS Ospedale San Raffaele, Milan, Italy

Background: Cancer is a major cause of morbidity and mortality, with incidence and prevalence reportedly grown in the last years, especially in the elderly population [1]. Increased awareness of cancer as a public health issue has enabled the establishment of dedicated assistance strategies, including palliative care. Nonetheless, cancer patients requiring hospitalization often exceed the capacity of oncology wards, prompting admission to general Internal Medicine units [2] [3]. We seized the chance given by the coexistence of comparable numbers of cancer and non cancer patients within the population of subjects hospitalized in Internal Medicine to perform a case-control study aimed at analyzing the differential profiles of these patients in terms of hospitalization course and outcomes.
Methods: A multipurpose registry (Med-Cli) was instituted to prospectively collect clinical, social and healthcare quality data of patients admitted to the Internal Medicine Departments of San Raffaele Hospital. The protocol was approved by the local Institutional Review Board and patients enrolled upon informed consent. Here, we extracted data from patients admitted from November 2022 to April 2023 in 2/3 wards involved in the registry and focused on patients with solid or hematologic tumors, who were compared to patients without a history or new diagnosis of cancer. We analyzed data regarding demographics, comorbidity burden (assessed through the Charlson's Comorbidity index), quality of life (through the EuroQol-5D-3L questionnaire), dependence for daily activities (with Barthel's scale), previous hospitalization history, reasons for admission, hospitalization-related complications, intensity of care, and hospitalization outcomes. The primary endpoint was to evaluate the duration of stay and the outcomes of cancer patients admitted in Internal Medicine departments. Data are expressed as median (interquartile range) unless otherwise specified.
Results: Four hundred and thirty-nine patients were admitted in six months of which three-hundred-fifteen were included. Of them, 90 (29%) had cancer, including 81 with solid cancer, six with hematological malignancies and three with both types of cancer. Forty-eight patients with cancer were male (53%); the median age was 75 years (42 – 89). Patients with cancer had similar demographics and comorbidity burdens on admission when compared to control subjects. Nevertheless, cancer patients had been more frequently hospitalized within the preceding 12 months (58% vs 44% in controls, p=0.018) and showed a higher number of previous hospitalizations [1 (0 – 1) vs 0 (0 – 1) in controls; p=0.028]. Cancer patients were more often hospitalized for hematological abnormalities compared to controls (5.56% vs 0.89% p=0.011). Patients with cancer had lower disability scores for mobility [1 (1 – 2) vs 2 (1 – 2) in controls; p=0.029] and self-care [1 (1 – 2) vs 2 (1 – 3) in controls; p=0.031] on admission as assessed by the EuroQol-5D-3L questionnaire. However, a higher percentage of cancer patients had worsening EuroQol-5D-3L mobility (22% vs 11% p=0.011) and anxiety or depression (16% vs 8% p=0.031) scores during hospitalization compared to controls. Barthel indices showed a parallel, significant decline from admission to discharge in patients with [Δ=-10 (-35 – 0); p<0.001 by ranked sign test] and without cancer [Δ=-10(-45 – 0), p<0.001], while no intergroup difference was observed. There were no differences in intensity of care, length of hospitalization and in-hospital survival. Nonetheless, a higher fraction of cancer patients was discharged to palliative care (11% vs 3%; p=0.020).
Conclusions: These preliminary data suggest that hospitalization seems to be related to accelerated disability accrual in all patients, regardless of cancer diagnosis. However, cancer patients had more previous admissions than non-cancer patients, suffer worsening of mobility and mood quality at discharge, and are referred to palliative care more often than patients without cancer, potentially indicating that identification of non-cancer patients requiring palliative care is insufficiently developed in the current healthcare context.

556. DNA HYPOMETHYLATION IS PRESENT IN LUNG CANCER-ASSOCIATED ANOREXIA

Molfino A.[1], Imbimbo G.[1], Tambaro F.[1], Ambrosani F.[2], Udali S.[2], Moruzzi S.[2], Pattini P.[2], Castagna A.[2], Muscaritoli M.[1], Friso S.[2]
[1]Department of Translational and Precision Medicine, Sapienza University of Rome, Italy; [2]Department of Medicine, University of Verona School of Medicine, Verona, Italy

Introduction: The pathophysiology of cancer anorexia is multifactorial and we aimed at evaluating the potential role of epigenetic regulation on those gene expression marks by analyzing changes in methylation on PBMCs DNA of lung cancer patients presenting with poor appetite.
Methods: Genome wide DNA methylation analysis was performed in lung cancer patients at their first diagnosis compared to healthy controls. Anorexia was assessed by FAACT questionnaire. Four groups of genes were identified: hypermethylated repressed, hypermethylated induced, hypomethylated repressed and hypomethylated induced.
Results: The analysis was carried out on 24 participants to compare the DNA methylation status of neoplastic anorexic patients (n=8) versus neoplastic non-anorexic patients (n=8) and healthy controls (n=8). In cancer patients, 382 genes were differentially methylated compared to controls. Anorexic cancer patients presented 586 hypomethylated and 174 hypermethylated genes compared to controls. 211 genes were hypomethylated and 90 hypermethylated in anorexic versus non-anorexic cancer patients. When microarray me-

thylation data were merged with RNA sequencing, we observed significant differences in anorexic cancer patients with respect to controls. In this comparison, 42 genes resulted hypomethylated induced, 5 hypermethylated repressed, 10 hypermethylated induced and 15 hypomethylated repressed. The CG sites analyzed by targeted bisulfite sequencing in four genes of interest (*FLNA, PGRMC1, GNL3L* and *FHL1)* that resulted hypomethylated in the anorexic patients compared to healthy controls, allowed to validate the data obtained from DNA methylation analysis. Moreover, the four genes resulted significantly hypomethylated in anorexic patients with respect to non-anorexic patients and to controls (p<0.0001).
Conclusions: Our data support for the first time in humans that epigenetic mechanisms through DNA methylation are implicated in anorexia in lung cancer patients.

557. BODY WEIGHT LOSS AND CACHEXIA: ASSESSMENT OF LIPOLYSIS IN SUBCUTANEOUS ADIPOSE TISSUE OF GASTROINTESTINAL CANCER PATIENTS

Molfino A.[1], Imbimbo G.[1], Tambaro F.[1], Lauteri G.[2], Andreini M.[1], Melena M.[1], Toccini L.[1], Amabile MI.[1], Nigri G.[2], Ferraro E.[3], Muscaritoli M.[1]
[1]Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy; [2]Department of Medical-Surgical Sciences and Translational Medicine, Sapienza University of Rome, Rome, Italy; [3]Department of Biology, University of Pisa, Pisa, Italy

Introduction: Enhanced lipolysis and concomitant inhibition of adipogenesis are implicated in adipose tissue loss during cachexia. However, these mechanisms are not completely clarified in patients with cancer. In this study, we investigated the expression levels of lipolysis-associated genes in subcutaneous adipose tissue (SAT) obtained from newly diagnosed gastrointestinal (GI) cancer patients according to the presence/absence of cachexia.
Methods: We considered gastrointestinal cancer patients (first diagnosis) and controls undergoing surgery for tumor resection and for benign diseases, respectively. Cachexia was defined as involuntary body weight loss > 5% in the prior 6 months. We collected SAT samples during surgery. Total RNA was extracted from SAT and expression levels of ATGL, HSL, PPARα and MCP1 were analyzed by qRT-PCR.
Results: We enrolled 24 GI cancer patients (pancreatic n=9, gastric n=7 and colorectal n=8) and 15 controls. Cancer patients did not differ from controls in terms of BMI (Kg/m2) (27.0 ± 3.3 vs 27.9 ± 4.4). We found significant upregulation of ATGL and HSL in GI cancer patients respect to controls (p=0.008, p= 0.006). We observed a trend of increased mRNA levels of PPARα (p=0.055) in GI compared to controls, whereas no significant difference was observed in MCP1 levels. Compared to controls, we found an upregulation of ATGLin GI cancer patients with cachexia (p= 0.037), and also in the group without cachexia (p=0.021). HSL levels resulted upregulated in GI cancer patients with cachexia (p= 0.020), without cachexia (p= 0.021), compared to controls. Interestingly, we found an upregulation of ATGL in gastric patients compared to controls (p=0.014) and higher HSL levels in gastric cancer and in pancreatic cancer compared to controls (p< 0.04).
Conclusion: In our cohort of gastrointestinal cancer patients, we found a modulation in the expression of genes of lipolysis and significant differences in their levels according to cancer type.

558. ANALYSIS OF AN INTERNATIONAL SURVEY ON NUTRITIONAL ISSUES IN PATIENTS WITH CANCER

Imbimbo G.[2], Molfino A.[2], Wesseling J.[2], Kastrati K.[3], Ventura J-J.[4], Muscaritoli M.[1]
[1]Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy; [2]The European Nutrition for Health Alliance, Amsterdam, Netherlands; [3]Klinik für Innere Medizin II, University Hospital Jena, Jena, Germany; [4]European Cancer Patient Coalition, Brussels, Belgium

Introduction: Nutritional disorders are common in patients with cancer and can lead to poor quality of life and survival. By the present international survey, we aimed at assessing the patients' perspectives on different nutritional aspects during cancer journey
Methods: This survey was developed by Das Lebenshaus with The European Cancer Patient Coalition (ECPC) and The European Nutrition for Health Alliance (ENHA), and designed and analyzed by researchers from Sapienza University of Rome. The majority of the participants were from Germany, Italy, United Kingdom and Hungary. The survey consisted of 46 questions on different nutritional issues. For this analysis, we considered the most relevant questions related to nutritional alterations
Results: The survey reached 1010 patients with cancer. The mean age of the participants was 55 ± 14 y. Based on the answers available, the most represented cancer type was breast (28%) and renal (16%); a recent diagnosis of cancer was performed in 35%, whereas 27% were diagnosed more than 8 years before. About 40% of the participants reported eating problems, such as loss of appetite (116/252) (46%), nausea (119/252) (47%), diarrhea (114/252) (45%). Regarding quality of life, patients answering on impact of nutritional problems reported a score of 3.5 ± 1.1 (from 1= no impact, to 5 = extremely negative impact). 441/672 (66%) reported that "rarely or never a physician or a member of the cancer care team asked about any feeding problems", and 483/670 (72%) believe that "oncology team do not take care of nutritional issues". 176/643 (27%) of the participants reported unvoluntary body weight loss and 138 out of 153 (90%) presented no awareness about the risk of not receiving anticancer treatment for this reason
Conclusion: Patients with cancer largely experienced nutritional alterations with a negative impact on quality of life. Well-structured health-care programs for nutritional intervention are needed.
*equally contributed

559. METABOLIC ADVERSE EVENTS OF MULTITARGET KINASE INHIBITORS: A SYSTEMATIC REVIEW

Maiorca C., Acitelli E., Maranghi M., Grani G.
Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy

Background and Aims: Multitargeted kinase inhibitors (MKI) are increasingly approved and used for multiple solid and hematological malignant neoplasms and target several molecular pathways involved with cellular growth and de-differentiation. Due to their off-target activities and interactions with multiple kinases, several systemic side effects are commonly reported with these drugs (e.g., arterial hypertension, mucositis, and skin lesions) but, during randomized clinical trials, not all adverse events were reported. Furthermore, drug side effects are heterogeneous by nature, being influenced by age, drug interactions, pharmacokinetics and pharmacodynamics. Their underdetection and consequent underreporting may thus lead to an underestimate of the impact on patients' health.While the metabolic adverse effects of MKIs are known, data on their severity and prevalence are scarce. Here, we focused on the alterations of glucose and lipid metabolism in patients treated with some commonly used MKIs (Cabozantinib, Lenvatinib, Sorafenib, and Vandetanib). We chose to focus on drugs approved for thyroid malignancies because these patients have a better overall survival rate and a worse metabolic control may impact life expectancy.
Methods: We searched for articles, published between January 2012 and December 2022, evaluating the effects on lipid and glucose metabolism of four MKIs (Cabozantinib, Lenvatinib, Sorafenib and Vandetanib) in adult patients with cancer. We focused on drugs approved for thyroid malignancies, since a worse metabolic control may potentially impact life expectancy, due to their better overall survival. Adverseevents' grades were classified according to Common Terminology Criteria for Adverse Events [CTCAE]).
Results: As for glucose metabolism, many evidences suggest that MKIs can influence glucose levels through different pathways. Most importantly, MKIs belonging to the same class can determine both hyper- or hypoglycemia. Only a small number of reports (3/68) described glucose- lowering effects associated with MKIs use. On the other hand, a great number of studies (42/68) reported elevation of serum glucose levels in patients treated with MKIs, while neutral effects were reported in a minority of cases (25/68): 18 studies reported only grade 1 or 2 hyperglycemia, while the others reported also CTCAE grades 3 or 4. Interestingly, Sorafenib is frequently associated with all CTCAE grades of hyperglycemia, including death, both as a single agent or in combination with other MKIs. Furthermore, Sorafenib is the only MKI, among those included in our review, known to determinehypoglycemic episodes of different severity, including grade 3 or greater, in patients treated for hepatocellular carcinoma or glioma. Cabozantinib, Lenvatinib and Vandetanib are mostly associated with mild to moderate high blood glucose and no studies showed evidence of grade 5 hyperglycemia or hypoglycemia associated with their use. As regards cholesterol metabolism, worsening or newonset of high serum cholesterol levels has been reported in only 12 studies. Most studies (7/12)reported CTCAE grade 3 and 4 hypercholesterolemia, while grade 5 was not reported. Sorafenib, Cabozantinib and Lenvatinib have all been implicated in new onset of different grades of hypercholesterolemia, either when used as a single agent or in combination with other MKIs. Cho-

lesterol metabolism alterations associated with Vandetanib were not described. Regarding triglycerides metabolism, 19 studies reported on the occurrence of hypertriglyceridemia in patients treated with MKIs. Cabozantinib, Lenvatinib, Sorafenib and Van detanib adversely affect triglycerides metabolism with different degrees of severity, from mild to life-threatening levels.
Conclusions: Despite some inherent limitations, our analysis may cast light upon some of the MKIs metabolic disorders that can impact on patients' health, especially when long-term survival is expected. Future clinical trials should consider routine assessment of glucose and lipid levels, because underdetection and underreporting of alterations can lead to the overlooking of important adverse events.

560. PATIENTS WITH MYELOFIBROSIS: PRELIMINARY RESULTS OF RUXOLITINIB'S METABOLIC AND NUTRITIONAL EFFECTS

Antonini S., Amabile MI., Molfino A., Martellucci O., Melena M., Scalzulli E., Breccia M., Muscaritoli M.
Department of Translational and Precision Medicine, Sapienza University of Rome, Italy

Introduction: Ruxolitinib is the first JAK1/2-inhibitor available for treatment of myelofibrosis (MF), a chronic myeloproliferative neoplasm whose median survival expectation may range from <2 years to >20 years according to several baseline factors, including reduced nutritional intake for massive splenomegaly and metabolic disturbances due to systemic inflammatory state that may lead to cachexia. We aimed to establish modifications of metabolic parameters and nutritional status in MF patients during Ruxolitinib treatment.
Methods: Malnutrition (GLIM criteria), Anorexia (FAACT score), body composition (BIA) were assessed before (T0) and during treatment (3 months, T1; 6 months, T2; 12 months, T3).
Results: From 05/21 to 05/23, 23 MF patients (M:13, F:10, mean age 64.7±12.5) were enrolled. At T0, unintentional weight loss, malnutrition and anorexia were present in 70%, 50% and 22% of them, respectively. Ruxolitinib was associated with benefit in anorexia score for all patients (p= 0.002) and for anorexic ones (T0 26±6.2; T2 41.2±4.2; T3 40±2.4) (p=0.0005), body weight (BW, Kg) (T0 68.6±14.22; T3 74.5±15), fat mass (p=0.03)(FM, Kg) (from T0 15.8±5.8; to T2 21.2±8.1 and to T3 21.7±7.6) (p=0.03, p=0.007 respectively) and with preservation of lean body mass (LBM, Kg) (T0 52.8±12; T2 52.6±11.5; T3 52.7±12.1) (p>0.05), regardless of disease response to treatment according to IWG criteria (clinical improvement:11 patients, stable and progressive disease:7 and 3 respectively, not evaluable for recent enrolment:2).
Conclusion: Preliminary data show that in MF patients Ruxolitinib therapy induces clinically significant improvement in anorexia score and BW. The latter is mainly due to increased FM, and preservation of LBM. This data suggest that Ruxolitinib may be associated with improvements in nutritional status and body composition, irrespective of clinical response in patients with MF.

561. LOSS OF MUSCLE MASS AND TISSUE-SPECIFIC MICRORNAS PROFILING OF PATIENTS WITH GASTROINTESTINAL CANCER

Tambaro F.[1], Imbimbo G.[1], Lauteri G.[2], Amabile MI.[3], Gigante A.[1], Nigri G.[2], Ramaccini C.[1], Gallicchio C.[1], Molfino A.[1], Muscaritoli M.[1]
[1]Department of Translational and Precision Medicine, Sapienza University of Rome, Italy; [2]Department of Medical and Surgical Sciences and Translational Medicine, Sapienza University of Rome, Italy; [3]Department of Surgical Sciences, Sapienza University of Rome, Italy

Introduction: The imbalance between catabolic and anabolic processes is the defining reason for skeletal muscle (SM) atrophy, a key feature of cancer cachexia (CC). microRNAs (miRs) were shown to mediate several signalling pathways associated to muscle wasting. However, their biological roles in CC are still poorly explored. This study aimed at evaluating the expression of muscle-derived miR486-5p and miR15b-5p, which both have been found to have a regulatory effect on inflammatory pathways as well as on modulation of protein synthesis and SM homeostasis, making them attractive as early non-invasive diagnostic tools and potential novel therapeutic targets in CC therapy.
Methods: SM biopsies were obtained from 25 newly diagnosed gastrointestinal (GI) cancer patients (CP) and 10 healthy controls (C), undergoing abdominal surgery for cancer resection or for a non-malignant condition, respectively. Total RNA was extracted from SM specimens and expression levels of miR486-5p and miR15b-5p were analyzed through RT-qPCR.
Results: BMI (Kg/m2) did not differ in GI CP and C (24.57±4.11 vs 24.41±4.00). In GI CP, the expression of miR486-5p was lower, whereas miR15b-5p was overexpressed with respect to C (0.90±0.49 vs 1.90±1.98, p=0.038 and 1.5±0.49 vs 0.53±0.49, p=0.041, respectively). Both miR486-5p and miR15b-5p expression levels were higher in weight-losing (n=11) than in non-weight losing (n=13) CP (1.10±0.63 vs 0.69±0.25, p=0.042 and 1.84±2.14 vs 0.60±0.43, p=0.053, respectively).
Conclusion: These preliminary data suggest that miR486-5p and miR15b-5p are differentially modulated in the SM of GI CP. Moreover, unintentional weight loss, a main feature of CC, is also associated with changes in the expression patterns of these miRs. Further investigations are mandatory in order to better clarify their role in CC-related SM wasting.

562. EVERY CLOUD HAS A SILVER LINING

Pellone M.[1], Antonini C.[2], Cicconi F.[2], Bassino E.M.[2], Alfonsi A.[2], Andreoni R.[2], Ferretti M.[2], Luzi E.[2], Caltabiano L.[2], Di Donato C.[2], Delle Monache M.[2], Vertolli P.[2]
[1]Università degli studi dell'AquilaUniversità degli studi dell'Aquila; [2]Università degli studi dell'Aquila

Gastrointestinal bleeding encompasses a broad array of clinical scenarios. The spectrum is diverse because of the multiple types of lesions that can cause bleeding, and because bleeding can occur from virtually anywhere in the gastrointestinal tract. The etiology of gastrointestinal bleeding is divided into upper gastrointestinal (GI) and lower gastrointestinal bleeding. Mortality remained relatively constant in the last 50 years at approximately 12%. Peptic ulcers remain the most common cause of upper GI bleeding and account approximately 50% of all cases. Next leading causes are esophageal and gastric varices, and gastroduodenal erosions. Mallory Weiss tears, angiodysplasia and gastric antral vascular ectasia (GAVE)-Watermelon stomach are less frequent but important causes of upper GI bleeding that contribute substantially to the overall morbidity and mortality. Recognition of such lesions is crucial to provide effective hemostasis.
Case Report: A 35-year-old woman, caucasian race, came to our observation for a symptomatology characterized by worsening asthenia, dyspnea at rest, pale skin. On admission, the CBC examination recorded severe microcytic hypochromic anemia with Hb of 3.4 g/dL and ferritin 1.64 ng/mL. In history endometrial resectoscopic polypectomy about a year earlier and no other pathology of note. She denies metrorrhagia. Clinically alert, cooperative, hypotensive patient. On physical examination no evidence of any signs of ongoing or recent bleeding, treatable abdomen, no pain from palpation, no auscultatory changes in peristalsis. Rectal exploration was negative. Transfusion therapy with concentrated red blood cells and blood products was started. Therefore, gastrointestinal endoscopy was ordered, which failed to detect any pathologic esophago-gastro-duodenal and colonic lesions to justify the anemia. During the hospitalization we observed a progressive drop in hemoglobin level, so It was performed an urgent CT angiography of the abdomen which revealed an oval-shaped, hypervascular solid formation with central scar of digiunal relevance, compatible in first hypothesis with neuroendocrine intestinal cancer. On diagnostic completion, enteroscopy with oral access was performed, which confirmed the neoformation about 2 m from the pylorus, and multiple biopsies were taken. Locating the site of bleeding and initiating transfusion therapy again, surgical treatment was performed. Tissue specimens were examined and on macroscopic examination the lesion jutted over the serosal surface, ulcerated the mucosa and infiltrated the jejunal wall to the subserosal tonaca, and on cutting showed grayish color with hemorrhagic areas. On microscopic examination, the jejunal neoplasm consisted of spindle cell proliferation with minimal cell pleomorphism, elongated nuclei, and large eosinophilic cytoplasm. Necrosis was absent and marked vascular congestion was observed. Surgical resection margins were unscathed. The immunohistochemistry results showed high expression of proto-oncogene CD117 and vimentin, actin was negative. Mitotic index: 2x10 high-power field. Proliferation index assessed by Ki67 was about 8%. Histopathological framework compatible with low mitotic index digiunal GIST (TNM: pT2-R0). The interest of our clinical case lies in the rarity of the pathology itself, representing GISTs 2-5% of all soft tissue sarcomas and less than 1% of digestive tract cancers. Their estimated incidence is 10 –15 per million. GIST patients have a median age at diagnosis of 65 years, and less than 10% are diagnosed before the age of 40. One of the most common clinical manifestations of GISTs is bleeding in its acute and chronic forms, gastro-intestinal stromal tumors procure low-grade and absolutely non specific symptomatology, but as is well known, in most cases, GISTs remain asymptomatic.

PNEUMOLOGIA

563. SARCOIDOSIS: HYPOTHESIS OF CLINICAL-PATHOLOGICAL CORRELATIONS AND DIAGNOSTIC-THERAPEUTIC STRATEGIES

De Luca P., Benvenuto A., Di Pumpo M. , Conte M., Sollazzo V. , Morlino P. , De Luca A.
Dipartimento Internistico Multidisciplinare - Ospedale "T. Masselli-Mascia" San Severo ASL FG

Background: Sarcoidosis is a multisystem granulomatous disease of unknown etiology characterized by the presence of noncaseating granulomas. It is characterized by nonspecific clinical manifestations commonly affecting the pulmonary system and other organs including the eyes, skin, liver, spleen, lymph nodes, heart, nervous system. Diagnosis can be difficult due to nonspecific symptoms and can be verified only after histopathological examination. Because of its unknown etiology, early diagnosis and detection are difficult; however, the advent of advanced technologies has improved our ability to reliably diagnose this condition and accurately predict its prognosis.
Clinical Case: 44-year-old patient (bricklayer and baker), hospitalized for sneezing, rhinorrhea and lachrymation. HRCT chest: diffuse interstitial thickening with centrilobular micronodules and sparing of peripheral regions, with ground glass appearance. Fibrobronchoscopy: aspiration of scarce mucous secretions; after toilet, evidence of patent bronchial lumens, of regular caliber, with thin mucosa; the selective BAL of the middle lobe sent for study of lymphocyte and cytospin subpopulations showed: macrophages 25%, lymphocytes 60%, neutrophils 14%, eosinophils 1%, CD4/CD8: 2.4; samples were sent for culture and common germs (positive for Klebsiella pneumoniae, treated with targeted antibiotic therapy) and cyto-oncological (negative) tests. Echocardiogram and flow-volume curve: within normal limits. DLCO: apnea not maintained. Walk test: oxyhemoglobin desaturation significant in the second minute (from 95% to 88%). Blood tests: rheumatoid factor 48.9 IU/ml, IgE 74.1, ESR 23, CRP 13.9, TPA 124.2, negative immunological panel. Discharged with diagnosis of "Respiratory failure on exertion, hypersensitivity pneumonitis and superinfection with Klebsiella pneumoniae", recommended steroid and diuretic therapy. After outpatient evaluation, the patient was readmitted for exertional dyspnea and poorly productive cough. Repeat the fibrobronchoscopy: on the right, at the level of the sub-segmental branches of the anterior segment of the upper lobar, blind transbronchial biopsies are performed and samples are sent for histological examination (fragments of lung parenchyma characterized by the presence of multiple foci of chronic epithelioid granulomatous inflammation non-necrotizing giant cell, sometimes confluent). The patient was then discharged with a diagnosis of "Pulmonary sarcoidosis. Latent respiratory insufficiency". Recommended home therapy with corticosteroids and outpatient clinical-instrumental follow-up.
Discussion and Conclusion: Despite extensive research conducted in recent decades, the etiology of sarcoidosis remains unknown. Numerous potential etiological agents have been identified and the most recent hypothesis suggests that host-microbe interaction and genetic factors play an important role in the pathogenesis of this disease when interacting with various environmental factors, which results in the clinical presentation of this disease. Sarcoidosis is usually diagnosed when typical radiologic and clinical findings are reinforced by histologic confirmation of non-necrotic granulomas. New diagnostic strategies for sarcoidosis, including HRCT, PET, TBNA and EBUS, MRI technologies, have strengthened its prognosis. Serological biomarkers should be the focus area for researchers as these are the least invasive and the most accessible. Although the higher ratios of serum angiotensin converting enzyme and BAL lymphocytes are widely debated, their utility is limited as these are not specific to sarcoidosis.
Corticosteroids play an important role in the treatment of sarcoidosis, but cause many side effects when used for a long time. Second-line treatments include azathioprine, methotrexate, cyclosporine, cyclophosphamide, leflunomide, and hydroxychloroquine, but all of these drugs have been shown to be less effective than steroids. Pathogenesis-based therapeutic treatment is the most advanced and targeted approach for the treatment of sarcoidosis. Several cytokines play critical roles in the immunopathogenesis of sarcoidosis. Cytokine monoclonal antibodies are a specific way to modulate cytokine networks, thereby influencing disease progression. These cytokine-directed treatments manifest as third-line therapies. Precision medicine is the new hope in this field and should be monitored closely for progress towards targeted interventions. For a better management of the disease, multifaceted approaches remain the best practice to ensure competent and effective patient care.

564. EFFECT OF CONTINUOUS POSITIVE AIRWAY PRESSURE ON MACE INCIDENCE AND AF RECURRENCE IN ELDERLY WITH OBSTRUCTIVE SLEEP APNEA AND SEVERAL COMORBIDITIES

Severini G.[1], Condoleo V.[1], Armentaro G.[1], Francica M.[1], Maruca F.[1], Ciaccio G.[1], Fuoco C.[1], Monaco V.[1], Barbara K.[1], Cassano V.[1], Miceli S.[1], Maio R.[1], Perticone M.[1], Arturi F.[1], Andreozzi F.[1], Sesti G.[2], Sciacqua A.[1]
[1]Department of Medical and Surgical Sciences, University Magna Græcia of Catanzaro, 88100 Catanzaro, Italy.; [2]Department of Clinical and Molecular Medicine, University Rome-Sapienza, viale Regina Elena n. 324, 00161, Rome, Italy.

Background: Obstructive sleep apnea (OSA) is the most common and clinically significant sleep breathing disorder, its's high prevalent in elderly with cardiovascular disease (CVD). OSA is often under-recognised and undertreated in clinical practice, although guidelines recommend screening for OSA in patients with resistant/poorly controlled hypertension, paroxysmal atrial fibrillation (PAF), independently from spleepiness syntoms. Recurrent apnoic and hypopnoic obstructive events causes episodic hypoxemia, nocturnal sympathetic nervous system activation, chronic inflammations and sleep fragmentation; in addition, large negative swings in intrathoracic pressure produce mechanical stress on the heart and great vessels, which can lead to structural and functional remodelling of the cardiac chambers, mainly the right sections. These events increase the risk of CV and arrhythmic diseases. Despite several clinical studies have shown that the use of Continuous positive airway pressure (CPAP) is associated with lower rates of cardiovascular (CV) events and death, particularly among compliant patients, the topic is still under debate.
Purpose: The aim of this work is to investigate possible differences in major adverse cardiac events (MACE) incidence and AF recurrence between patients receiving CPAP treatment versus no CPAP treatment, in a cohort of elderly OSA patients with several comorbidities and history of PAF.
Material and methods: This is an observational study where we followed 420 patients aged ≥ 65 years, suffering from PAF, with a first diagnosis of moderate/severe OSA recorded during a home nocturnal respiratory polygraphy and indication for CPAP-mode ventilotherapy according to the American Academy of Sleep Medicine (AASM) guidelines. Two groups were defined: CPAP-treated group (n.176) and untreated group (n.244) because they refuse treatment. The study population underwent clinical-instrumental and laboratory evaluation for a follow-up of 24 months, and to detect AF appearance, patients underwent, every 6 months, standard 12 lead electrocardiogram. In the CPAP group, efficacy parameters and therapy compliances were closely monitored, achieving an average time of use >4 hours per night. Mann-Whitney test and Student's t-test were performed for unpaired data, chi-square test when appropriate. In addition, a log rank test was performed to compare the risk function estimates of two groups at each time point of the observed events, followed by a univariate Cox regression model on the incidence of MACE and AF recurrence; and variables that significantly correlated were included in a multivariate stepwise Cox regression model to calculate independent predictors associated with the incidence of MACE and AF recurrence.
Results: The two groups were over comparable for sex, CHA2DS2VASC-score and drugs. Enrolled population had: mean age 75±4.6, estimated glomerular filtration rate (eGFR) 61.8±17.2 ml/min/1.73m2, Hb 13.7±1.7 g/dl, BMI 32.6±6.1 Kg/m2, AHI 36.6±15.9 e/h, ODI 29(21.3-42.2) e/h, SpO2 92±3.2%, TC90% 11.2% (3.2-32.7) and Epworth Sleepiness Scale 11±4.7pt. CPAP's group had a higher prevalence of ischemic heart disease (IHD) (23.3% vs 21.7%; p=0.702), Type 2 diabetes mellitus (T2DM) (62.9% vs 52.9%, p=0.049), chronic obstructive pulmonary disease (COPD) (39.8% vs 34.4%, p=0.261), chronic kidney disease (CKD) (48.3% vs 46.3% p=0.687), nocturnal respiratory insufficiencies (NRI) (40% vs 18.9%, p<0.001) and they were older than without treatment (75.5.4±5.1 vs 74.6±4.3 years; p<0.045). The incidence of MACE in the CPAP group was 8.2 events/100 patient-years, while in the untreated group was 14.3 events/100 patient-years (p<0.003). A multivariate analysis model showed that CPAP treatment (HR 0.31, p<0.001), SGTL2-i (HR 0.23, p<0.001), Loop Diuretics (HR 0.29, p<0.001), ARNI (HR 0.31 p=0.013), ACEi/ARB (HR 0.34 p<0.001), NOAC (HR 0.35, p<0.001), lowering HbA1c by 1% (HR 0.76, p=0,030) and lowering ODI by 10 e/h (HR 0,83; p=0,016) reduced risk of MACE, while female gender (HR 3.77, p<0.001), IHD (HR 2,89, p<0,001), 1-point increase in CHA2DS2VASc-score (HR 2.43, p<0.001) and 5-year increase in Age (HR 1.77, p<0.001), increased the risk of MACE. Concerning recurrence of AF, we observed 5.4 events /100 patient-years in CPAP's group and 9.8 events/100 patient-years (p <0.014) in untreated group. A multivariate analysis model showed that CPAP treat-

ment (HR 0.33, p<0.001), ARNI (HR 0.29 p=0.002), GLP-1RAs (HR 0.34, p<0.001), LABA/LAMA/ICS (HR 0.37, p=0.015) and NOAC (HR 0.43, p=0.002), reduced risk of recurrence of AF, while history of COPD (HR 3.43, p<0.001), 5-year increase in age (HR 1.55, P=0.006) and 1-point increase in CHA2DS2VASc-score (HR 1.36, p<0.001) increased the risk of recurrent AF.
Conclusion: This study support the role of moderate/severe OSA as a risk factor for MACE and recurrent AF. CPAP treatment with optimal compliance, combined with usual medical care for cardio-metabolic comorbidities, is associated with a lower incidence of MACE and recurrent AF in an elderly patients with several comorbidities.

565. TLRS EXPRESSION IN COPD PATIENTS

Perticone M.[1], Russo M.[1], Maruca F.[1], Crudo G.[1], Miceli S.[2], Maio R.[2], Scarcelli M.[1], Greco A.[1], Sciacqua A.[1], Gigliotti S.[3], Perticone F:[1]
[1]Dipartimento di Scienze Mediche e Chirurgiche - Università Magna Graecia di Catanzaro; [2]UO di Geriatria - AOU "Mater Domini" di Catanzaro; [3]Dipartimento di Scienze della Salute - Università Magna Graecia di Catanzaro

Introduction: Chronic obstructive pulmonary disease (COPD) is one of the most prevalent lung disease, characterized by exertional dyspnea, coughing and sputum. The above described symptoms are the expression of inflammation of the small airways (obstructive bronchiolitis) and pulmonary emphysema.
Chronic inflammation is one of the most important features of COPD, triggered by several stimuli, especially cigarette smoking.
This aberrant inflammation of the airways indiscriminately involves immunity cells such as macrophages, T-lymphocytes and neutrophils, mediators of the same such as cytokines and chemokines, and Toll-like Receptors (TLRs). These receptors are able to recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) and selectively induce inflammation, recruitment of inflammatory cells, and release of pro-inflammatory cytokines. In particular, TLR2 and TLR4 are considered the main TLRs responsible for maintaining inflammatory responses in inflammatory diseases. We recently demonstrated an overexpression of both TLR2 and TLR4 in subjects with heart failure, in particular in patients with reduced ejection fraction.
Thus, the aim of this work was to compare the expression of TLR-2 and TLR-4 between COPD patients and HF patients.
Materials and Methods: According to the purpose of the study, we enrolled 25 consecutive Caucasian outpatients with chronic heart failure (21 M and 4 F, mean age 70.2±12.8 years), 10 patients (8 M and 2 F, a mean age 69.1 ± 8. 61 years) with COPD, and 25 control subjects (20 M and 5 F, mean age 71.1±8.3 years), referred to the outpatient clinics dedicated to HF and respiratory diseases of the elderly of the Geriatrics Unit of the University Polyclinic of Catanzaro.
The diagnosis of HF was made according to the recent guidelines of the European Society of Cardiology, considering the presence of symptoms and/or signs as well as echocardiographic parameters. All enrolled patients had chronic HF under treatment.
The diagnosis of COPD was made according to GOLD recommendations, and the severity of flow obstruction was assessed according to GOLD criteria. For the present thesis work, we considered only GOLD stage I-II patients undergoing treatment.
TLRs expression was measured in peripheral blood mononuclear cells (PBMCs), which were isolated from fresh peripheral specimens by Ficoll gradient, labeled with a phycoerythrin (PE)-conjugated anti-CD14 antibody to identify monocytes within the isolated population, and with a fluorescein isothiocyanate (FICT)-conjugated anti-TLR-2 antibody or an allochocyanin (APC)-conjugated anti-TLR-4 antibody. A nonspecific ISO CD 14 (PE) antibody was used as an isotype control to exclude nonspecific binding. The expression of TLRs was considered as the ratio of the mean fluorescence intensity (MFI) of the sample to the MFI of the isotype control.
ANOVA test was used to test the differences between the groups of continuous variables, and Bonferroni's post-hoc test was used for multiple comparisons. For dichotomous variables, the $\chi 2$ test was used. Data are expressed as mean+standard deviation. All analyses were performed with a standard statistical package.
Results: Both COPD and HF patients showed significantly higher values than the control group of the following examined variables: TLR-2 (1617.3±376.4, 1306.1±281.1, 974.4±228.6 MFI, respectively), hs-CRP (4.3±1.7, 4.5±1.6, 3.1±0.1 mg/L, 33 respectively), fibrinogen (358±98, 336±78, 285±57, respectively). Comparison of TLRs expression between HF group and COPD group showed that patients with COPD had significantly higher values of TLR-2 (1617.3±376.4 vs 1306.1±281.1 MFI), while, surprisingly, they showed significantly lower values of TLR-4 (141.4±59.7 vs 440.8±229.9).
Conclusions: The results of this study demonstrate a higher expression in of pro-inflammatory molecules in COPD patients vs HF patients, except for TLR-4. This finding is only apparently inconsistent with the hypothesis of a higher degree of inflammation in COPD rather than in HF. In fact, it has been shown that in COPD subjects a TLR-4 deficiency promotes the development of pulmonary emphysema, as well as in symptoms worsening, even if the exact pathophysiological mechanisms still remain not fully understood. Thus our data, even if obtained in a small cohort of patients, are demonstrate a higher degree of inflammation in COPD rather than in HF patients. These data need to be confirmed in wider studies evaluating TLRs expression also in sputum cells.

566. THE MANAGEMENT OF THE COPD PATIENT: ANALYSIS OF A SURVEY IN GENERAL MEDICINE

Crescenti A.[1], Crescenti F.[1], Garufi L.[2], Crescenti R.[3]
[1]General Medicine - ASP Messina; [2]Oncology - "S. Camillo de Lellis" Hospital Rieti; [3]Internal Medicine - AO Papardo Messina

COPD is one of the top three causes of death worldwide. It has a prevalence of 2.9% in the Italian population (HS 2021 report). The management of COPD patients must aim to improve the quality and expectancy of life, reduce the impact of symptoms and contain the risk of exacerbations. The recent introduction of the Aifa note 99 concerning the prescribability of drugs for COPD has focused the interest on the management of these subjects and the importance of the role of the GP. For this reason it is useful to know the real-life data of patients with COPD. In the light of the aforementioned data, a survey was conducted involving the SIMG research group of Messina. Objective of the research: a) to know the prevalence of subjects with COPD, b) to know the behavior of the GP and evaluate, through some parameters, the correct management of this pathology (registration of smoking data, use of mMRC and CAT questionnaires, spirometry and bronchodilatation tests , exacerbations and access to the ED, drug appropriateness and adherence).
Materials and methods: The survey involved the population belonging to the general medicine studies of 20 doctors for a population of about 25,000 subjects. The survey is structured into ten questions: number assisted and number of COPD subjects, smoking data, use of mMRC and CAT questionnaires, use of spirometry with bronchodilatation tests, pulmonary examination, access to emergency departments and/or hospitalisations, use of antibiotics and systemic cortisone in the last year, given FEV1, use of inhaled drugs.
Results and conclusions: The study found the prevalence of COPD subjects to be 4.3%. Physicians answered for 55% who record smoking data for more than 70% of COPD patients, only 29% administer the questionnaires for more than 50% of subjects, 36% use spirometry with bronchodilation test for diagnosis for more than 70% and of these only 7.2% claim to have performed it in the general medicine practice. 64% of the doctors report that the patients have resorted to the PS at least 1-2 times in the last year and that 57% of the patients have used systemic antibiotics and cortisone for at least 5 consecutive days in the last year. 64% of physicians state that less than 10% of patients have FEV1 < 50%. 43% answered that 50-70% of patients used LAMA or LABA and 64% answered that 10-30% used LAMA/LABA with a single inhaler. 57% of physicians report that 30-50% of these subjects use ICS/LABA. And finally, 90% of doctors responded that patients use LAMA/LABA/ICS with a single inhaler for 10-30% of patients. Pharmacological therapy for 70% of doctors does not exceed 6 months a year. These data underline how smoking data is not always recorded, questionnaires are still rarely used, spirometry with bronchodilation tests for diagnosis and still few GPs carry it out in the clinic. Pharmacological adherence is low, patients mostly use LAMA or LABA, and few doctors prescribe LAMA/LABA in a single inhaler, while there is a good percentage of patients who use LABA/ICS and who resort to the ED for exacerbations at least 1-2 times a year.

567. ANALYSIS OF THE POSTOPERATIVE DIAPHRAGMATIC DYSFUNCTION BY SPIROMETRY-ULTRASONOGRAPHIC CORRELATION: PROSPECTIVE OBSERVATIONAL STUDY

Wu M.A.[1], Travella G.[2], Bartoli A. [1], La Cava L.[1], Salvi E.[1], Signorello J.C.[3], Cogliati C.B. [1], Fossali T. [2], Colombo R. [2]

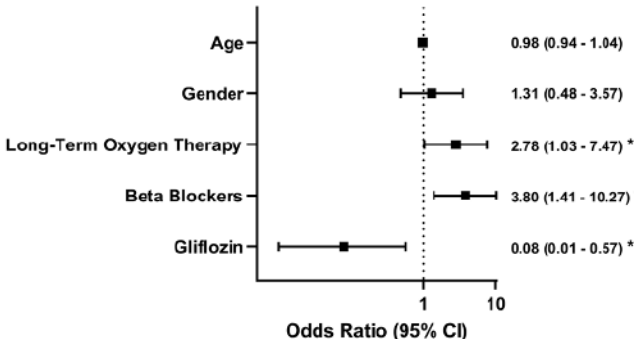
[1]Division of Internal Medicine, ASST Fatebenefratelli Sacco, Luigi Sacco Hospital, Department of Biomedical and Clinical Sciences, University of Milan, Milan Italy; [2]Division of Anesthesiology and Intensive Care, ASST Fatebenefratelli Sacco, Luigi Sacco Hospital – Polo Universitario, University of Milan, Milan, Italy; [3]Division of Pneumology, ASST Fatebenefratelli Sacco, Luigi Sacco Hospital, Department of Biomedical and Clinical Sciences, University of Milan, Milan Italy

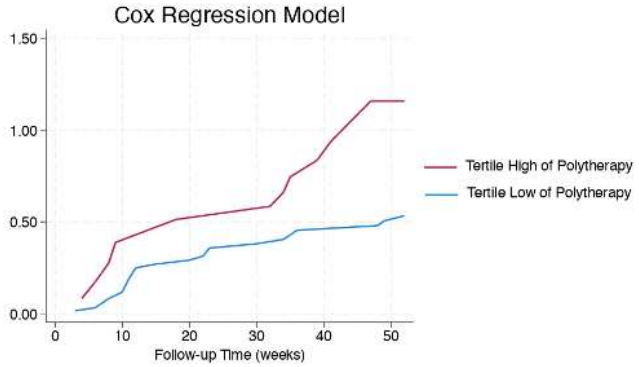
Background: Diaphragm dysfunction can occur as a complication after abdominal surgery, leading to impaired breathing and respiratory difficulties. The diaphragm is a crucial muscle involved in the process of inhalation and exhalation, separating the chest and abdominal cavities. Surgical procedures involving the abdomen can disrupt the normal function of the diaphragm, resulting in weakened or paralyzed movement.
Postoperative diaphragm dysfunction can manifest as reduced lung capacity, shallow breathing, and decreased oxygenation. It can lead to respiratory complications such as atelectasis, pneumonia, and prolonged mechanical ventilation. Factors contributing to diaphragm dysfunction include anesthesia, surgical trauma, pain, and inflammation.
We conducted a prospective observational study aiming to evaluate diaphragm function using spirometry and diaphragm ultrasonography, as well as assess the correlation between spirometry and ultrasonography indices. Additionally, we aimed to explore the relationship between diaphragm function and functional tests alongside dynamic imaging.
Methods: Patient with anesthesiology physical status (ASA) class I-III scheduled for elective abdominal surgery under general anesthesia were enrolled. Spirometry and diaphragm ultrasonography were performed one hour before surgery and after 24 hours while patients were lining supine. Vital capacity (VC), forced vital capacity (FVC), forced expiratory volume within the first second (FEV1), FEV1/FVC ratio, peak expiratory flow (PEF) were considered as spirometry variables, while diaphragm thickening % (DiT), diaphragm distance shift (DiDS), and diaphragm velocity (DiV) during inspiration were considered as ultrasonography variables. Type of surgery (open vs laparoscopic and vs other approach), length of surgery, patient intraoperative position, and postoperative pain assessed by numerical rating scale were considered in the analysis.
Results: forty-two patients were studied with a median (IQR) age of 55.5 (42-69) years and BMI 24.1 (19.8-26.6). 25 (59.5%) were female, 34 (80.9%) were ASA class I-II. Almost all considered indices markedly decrease at 24 hours after surgery (median percentage change [IQR]): VC (-23,7 [-46,9 to -15,4)] p<0.0001, FVC (-16,4 [-40,1 to -10,1)] p<0.0001, FEV1 (-17 [-40,2 to -10,2)] p<0.0001, PEF (-22,9 [-49,4 to -10,1)] p<0.0001, DiT (-11,7 [-20,8 to -6,6)] p<0.0001, DiDS (-39,1 [-49,9 to -22,3)] p<0.0001, DiV (-23,5 [-37,9 to -7)] p<0.0001. Only FEV1/FVC, expression of airway resistance, remained unchanged (-0,8 [-4,2 to 3,9)] p=0.471. There was a weak correlation between DiT and VC (r=0,477, p=0,003), FVC (r=0,474, p=0,003), FEV1 (r=0,464, p=0,004), and PEF (r=0,400, p=0,014). The decrease of FVC (p=0.032), FEV1 (p=0.042) and PEF (p=0.011) was more marked in open vs laparoscopic access; the decrease of DiT (p=0.004) and DiDS (p=0.018) was more marked in open vs other access.
Conclusions: Patients in good physical status, who underwent surgical procedures had significant postoperative diaphragm dysfunction. Postoperative ultrasound assessment of the diaphragm may add insights into the postoperative respiratory assessment in patients at risk for respiratory failure.

568. INFLUENCE OF POLYTHERAPY ON THE RATE OF MODERATE-TO-SEVERE EXACERBATION IN THE PATIENT WITH HIGH-COMPLEXITY COPD: FOCUS ON B-BLOCKERS AND GLIFLOZINS

Pirera E., Di Raimondo D., Pintus P., De Rosa R., Russo G., Rizzo G., Brascì V., Musiari G., Daidone M., Tuttolomondo A.
UOC di Medicina Interna con Stroke Care, Dipartimento di Promozione della Salute, Materno Infantile, Medicina Interna e Specialistica di Eccellenza "G. D'Alessandro" (PROMISE), Università di Palermo; Palermo (Italy)

Background: Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide; it is now well established that concomitant comorbidity with COPD is associated with more severe clinical involvement and poorer outcome: worse quality of life, increased risk of exacerbations, hospitalization and mortality. Therefore, given the potential interactions between polypharmacy and inhaled bronchodilator therapy, the cornerstone of pharmacological management of COPD, the pharmacological approach is not always easy to handle for the highly complex COPD patient. Patients with COPD are often not treated with this class of drugs, even when there is an evidence-based indication for the use of such drugs, because of concerns about possible adverse effects on lung function. This pattern of practice persists despite several observational studies suggesting that beta-blockers benefit patients with COPD and co-existing cardiovascular disease, with results similar to those seen in patients without COPD. Several non-randomized observational studies in patients with COPD have also indicated that beta-blockers reduce the risk of exacerbations and death regardless of the presence of heart disease. However, these observational data are subject to bias, making determination of cause and effect impossible. The aims of the study were to determine whether polytherapy as a surrogate for patient complexity is associated with a higher clinical severity of COPD and/or higher incidence of acute moderate-to-severe exacerbations of COPD.
Materials and Methods: we conducted an observational prospective study involving 86 patients referring to the U.O.C. Internal Medicine and Stroke Care ward in the Policlinico Paolo Giaccone in Palermo from 01/01/2019 to 01/01/2022. Inclusion criteria were: 1) ascertained COPD diagnosis according to GOLD 2023 report; 2) History of ≥2 moderate exacerbations or ≥ 1 leading to hospitalization. A comprehensive medical history collection with specific attention to COPD and evaluation of all comorbidities was performed, as well as a medication history. Each participant enrolled in the study underwent a 12-month follow-up in which information on both moderate to severe acute exacerbations was collected. The primary outcome was a composite of moderate or severe exacerbations within 12 months after the last acute severe exacerbation.
Results. There were no significant differences on COPD-related variables between the tertiles of distribution of polytherapy computes ad continuous variable. The total number of daily drugs taken by the participants showed a significant positive correlation with breathlessness severity assessed by the mMRC scale ($\rho = 0.452$, $p < 0.001$) and a significant negative correlation with the spirometric parameters (FVC as volume, $\rho = -0.227$, $p = 0.03$; FVC as percentage of predicted value, $\rho = -0.308$, $p < 0.01$; FEV1 as volume/second, $\rho = -0.220$, $p = 0.042$; FEV1 as percentage of predicted value, $\rho = -0.276$, $p = 0.01$). The multivariate logistic model (Figure 1) showed a higher rate of moderate to severe exacerbations in participants treated with β-blockers (odds ratio (OR) = 3.8, 95% confidence interval (CI) = 1.41-10.27, $p < 0.01$), under long-term oxygen (OR = 2.78, 95% CI = 1.03-7.47, p=0.04) and a lower risk in those treated with gliflozins (OR: 0.06, 95% CI = 0.006-0.57, p=0.015) over a period of 12-months follow-up. The Cox-regression model (Figure 2) according to the tertiles of distribution of the total number of daily drugs showed a higher rate of moderate to severe exacerbations during the 12-month follow-up (Tertile high: Hazard ratio (HR) = 2.5, 95% CI = 1.22-5.1, $p = 0.01$;Tertile Low, HR = 0.37, 95% CI = 0.17-0.79, $p = 0.01$).
Conclusions. Our analysis raises doubts or putative future indications about the role of drugs commonly used on clinical practice in the determins of acute exacerbations. This poses a potential area for future works as the current prescriptive panorama of β-blockers in COPD subjects has not yet found a unanimous consensus. Among patients with COPD, the risk in moderate to severe exacerbations was higher in those with an increaing number of daily drugs as a surrogate of the complexity of patients and it also correlates with the breathless severity and spirometric features. Our results showed the clinical and prognostic usefulness in this specifically settings.





569. SHORT- AND MEDIUM-TERM PROGNOSIS IN PATIENTS WITH MULTIMORBID COPD SUBJECTS AT HIGH-RISK OF ACUTE EXACERBATION: THE PROGNOSTIC PERFORMANCE OF THE CUMULATIVE ILLNESS RATING SCALE (CIRS)

Edoardo P., Di Raimondo D., Pintus C., De Rosa R., Russo G., Rizzo G., Brascì V., Musiari G., Daidone M., Tuttolomondo A.
UOC di Medicina Interna con Stroke Care, Dipartimento di Promozione della Salute, Materno Infantile, Medicina Interna e Specialistica di Eccellenza "G. D'Alessandro"(PROMISE), Università di Palermo; Palermo (Italy);

Background: Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide; it is now well established that concomitant comorbidity with COPD is associated with more severe clinical involvement and poorer outcome: worse quality of life, increased risk of exacerbations, hospitalization and mortality. The prevalence of multimorbidity in COPD-cohorts is widely reported: a meta-analysis by Putcha et al. showed that approximately 86% to 98% of COPD-patients have at least 1 comorbidity (average number of comorbidities per individual = 1.2 - 4). Although the underlying pathophysiological mechanisms linking COPD and comorbidities are not fully clarified, evidence suggests that a putative trait d'union might be represented by the chronic low-grade systemic inflammatory status frequently observed in these patients. Against this background, a patient-centered approach and holistic and integrated management, instead of a forced expiratory volume in the 1st second (FEV1)/dyspnea-centered approach represents a major paradigm shift. Adherence to guidelines aimed at single disease management may be inappropriate for patients with multimorbidity and, moreover, separate management of multimorbid COPD patients is still strongly emerging. In recent years, several multidimensional indices such as the DOSE index (dyspnea, airflow obstruction, smoking status and exacerbation frequency), the "Charlson Comorbidity Index" (CCI), the "Comorbidity Test" (COTE) and the "Comorbidities in chronic obstructive lung disease" (COMCOLD) have emerged to be predictors of mortality, hospitalization, exacerbation, degree of dyspnea, providing physicians with new tools beyond lung function indices (for example, FEV1). Their prognostic validation in COPD cohort is well established but they are not able to explore the illness severity of comorbidity burden. The Cumulative Illness Rating Scale (CIRS) is a multidimensional instrument commonly used as part of the Comprehensive Geriatric Assessment that examines 14 organ systems based on a rating from 0 to 4. Three indices were derived from the CIRS: the total score or the sum of each of the 14 system scores; the severity index (CIRS-SI) or mean of the scores of the first 13 categories (excluding the psychiatric / behavioral pathologies category); the comorbidity index (CIRS-CI) or the number of categories in which a score greater than or equal to 3 is obtained (excluding the psychiatric / behavioral pathologies category). The main objectives of this study were to determine whether a high severity index, a high comorbidity index are associated with a higher incidence of acute exacerbations of COPD and to conduct a c-statistics analysis with the prognostic COPD indeces already validated.
Materials and Methods: we conducted an observational prospective study involving 86 patients referring to the U.O.C. Internal Medicine and Stroke Care ward in the Policlinico Paolo Giaccone in Palermo from 01/01/2019 to 01/01/2022. Inclusion criteria were: 1) ascertained COPD diagnosis according to GOLD 2023 report; 2) History of ≥2 moderate exacerbations or ≥ 1 leading to hospitalization. A comprehensive medical history collection with specific attention to COPD and evaluation of all comorbidities was performed, as well as a medication history. Each participant enrolled in the study underwent a 12-month follow-up in which information on both moderate to severe acute exacerbations was collected. The primary outcomes were: 1) severe exacerbations at 3 months after the last acute severe exacerbation; 2) severe exacerbations at 12 months after the last acute severe exacerbation; 3) a composite of moderate or severe exacerbations within 12 months after the last acute severe exacerbation.
Results. CIRS-TS, CIRS-SI and CIRS-CI were associated with readmission for severe exacerbation at 3 months (CIRS-TS, Hazard Ratio (HR): 1.10, 95% CI = 1.01 – 1.20, p = 0.02; CIRS-SI, HR 1.14, 95% CI = 1.01 – 1.29, p = 0.02; CIRS-CI, HR 1.34, 95% CI = 1.02 – 1.79, p = 0.03), with readmission for severe exacerbation at 12 months (CIRS-TS, HR: 1.15, 95% CI = 1.08 – 1.22, p < 0.0001; CIRS-SI, HR: 1.24, 95% CI = 1.12 - 1.37, p < 0.0001; CIRS-CI, HR: 1.51, 95% CI = 1.25 – 1.84, p < 0.0001) and with the composity primary outcome (CIRS-TS, HR: 1.17, 95% CI = 1.10 – 1.24, p < 0.0001; CIRS-SI, HR: 1.25, 95% CI = 1.15 - 136, p < 0.0001; CIRS-CI, HR: 1.58, 95% CI = 1.33 – 1.87, p < 0.0001). DOSE, CODEx, CCI and COMCOLD indexes showed similar increased risk in primary outcome. All CIRS c-statistics showed a better predictive performance compared to those of the DOSE, CODEx, CCI and COMCOLD indexes except for the readmission for severe exaacerbations at 3 months.
Conclusions. Our analysis showed that CIRS indexes were a useful predictor of readmission at both 3 and 12 months for severe exacerbations and for a composite of moderate or severe exacerbations at 1 year with a prognostic performance superior to the other indexes previously validated in COPD cohort.

Severe exacerbation at 3 month	*Hazard Ratio*	*p value*	*95% CI*	*AUC*	*95% CI*
CIRS - Total Score	1.10	0.02	1.01-1.20	0.669	0.531-0.806
CIRS - Severity Index	1.14	0.02	1.01-1.29	0.668	0.532-0.804
CIRS - Comorbidity Index	1.34	0.03	1.02-1.79	0.670	0.554-0.786
DOSE	1.52	0.004	1.14-2.04	0.705	0.574-0.835
CODEx Index	1.43	0.008	1.09-1.87	0.716	0.590-0.841
Charlson Comorbidity Index	1.23	0.11	0.95-1.58	0.608	0.482-0.734
COMCOLD	1.13	0.088	0.98-1.32	0.607	0.469-0.745

Severe exacerbation at 12 month	*Hazard Ratio*	*p value*	*95% CI*	*AUC*	*95% CI*
CIRS - Total Score	1.14	< 0.0001	1.07-1.22	0.733	0.619-0.847
CIRS - Severity Index	1.24	< 0.0001	1.12-1.37	0.737	0.623-0.851
CIRS- Comorbidity Index	1.51	< 0.0001	1.25-1.84	0.715	0.604-0.826
DOSE	1.59	< 0.0001	1.26-2.02	0.691	0.575-0.807
CODEx Index	1.53	< 0.0001	1.24-1.88	0.704	0.594-0.814
Charlson Comorbidity Index	1.41	< 0.0001	1.18-1.70	0.652	0.534-0.770
COMCOLD	1.21	< 0.0001	1.09-1.35	0.701	0.596-0.806

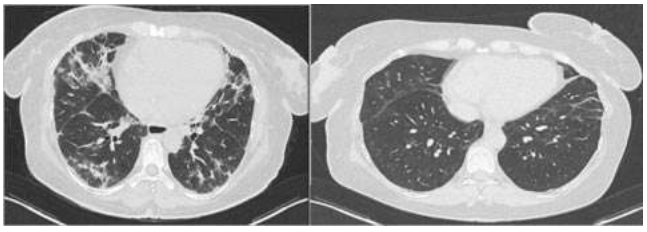
Moderate or Severe exacerbation at 3 month	*Hazard Ratio*	*p value*	*95% CI*	*AUC*	*95% CI*
CIRS - Total Score	1.17	< 0.0001	1.10-1.24	0.809	0.716-0.901
CIRS - Severity Index	1.25	< 0.0001	1.15-1.36	0.813	0.721-0.905
CIRS- Comorbidity Index	1.58	< 0.0001	1.33-1.87	0.815	0.729-0.901
DOSE	1.57	< 0.0001	1.28-1.93	0.713	0.607-0.819
CODEx Index	1.53	< 0.0001	1.27-1.83	0.737	0.635-0.840
Charlson Comorbidity Index	1.21	0.013	1.04-1.42	0.605	0.486-0.723
COMCOLD	1.07	0.122	0.98-1.18	0.599	0.485-0.713

570. INTERSTITIAL PNEUMONIA WITH AUTOIMMUNE FEATURES – A DIAGNOSTIC CHALLENGE

Golgo S.
Scuola di Specializzazione in Medicina Interna, Università degli Studi di Genova. U.O. Medicina Interna a Indirizzo Oncologico

Introduction. Interstitial Pneumonia with Autoimmune Features (IPAF) is a particular clinical entity at the border between Pneumology and Rheumatology. It refers to patients with lung disease who do not fullfill the diagnostic

criteria for a specific connective tissue disease.
Case description. A 48 years old woman was admitted in ER for dyspnea and left arm swelling. Chest TC scan was performed, with evidence of thickenings with pseudonodular morphology, some excavated, on both sides, more numerous in the lower lobes, trending to confluence. Ultrasound examination showed left brachial, axillary and subclavian vein thrombosis and anticoagulant therapy was set. Screening for infectious diseases was negative. The patient was transferred to Internal Medicine for further diagnostic investigation.
Upon admission to Internal Medicine the patient was asthenic, tachycardic, with edema affecting the left upper limb and poor tolerance to effort due to the onset of dyspnoea. Medical history showed fatigue,diffuse arthromyalgias, mild dysphagia, periorbital, wrist and ankle edema occurred in the last 4 months. The clinical picture has been deepened with autoimmune profile. ANA>1:640 with nucleolar pattern, anti-PM/Scl 75 and 100 positivities were detected, along with TSH-receptor antibodies. In order to clarify the pulmonary picture, **lung criobiopsy was performed**. The results clearly showed the presence of an interstitial lung disease with an inflammatory component, organizing pneumonia and little interstitial fibrosis, compatible with a diagnosis of **Interstitial Pneumonia with Autoimmune Features (IPAF)**. The patient met all the requirements for the diagnosis: Interstitial pneumonia proved by the biopsy, clinical presentation (joint pain, oedema), serology (ANA>1:640) and morphological (interstitial pneumonia). In order to rule out the diagnosis of sclerodermia, and safely starting a high-dose steroid therapy, esophageal manometry and videocapillaroscopy were performed, both negative. **Steroid therapy was then started**, with the administration of methylprednisolone 1g/die for 3 consecutive days, with subsequent embrication of Prednisone 75mg/die, with progressive dose reduction, up to the manteinance of a daily dose of 25mg. **The clinical picture underwent a rapid improvement,** with reduction of dyspnoea and marked improvement of exercise tolerance. The patient was then discharged, with the indication of the administration of a monthly bolus of 1g of methylrednisolone in Day Hospital regimen.
Results: After discharge, there were no disease exacerbations, and the patient's quality of life improved, as estabilished at periodic check-ups in Day Hospital. 6 months after discharge, a control with chest TC scan was performed, showing significant dimensional reduction of pulmonary thickenings bilaterally. Blurred areas of increased ground-glass lung density remain, more evident in the lower lobes in the mantle region.



REUMATOLOGIA

571. METABOLIC, CARDIOVASCULAR, AND AUTOIMMUNE COMORBIDITIES IN MEN AND WOMEN WITH PSORIATIC ARTHRITIS SUPPORT SIGNIFICANT GENDER DIFFERENCES.

Barone E.[1], Luciano N.[2], Brunetta E.[2], De Santis M.[3], Ceribelli A.[3], Caprioli M.[2], Guidelli G.M.[2], Lleo De Nalda A.[4], Selmi C.[3]
[1]Department of Biomedical Sciences, Humanitas University, Milano; [2]Rheumatology and Clinical Immunology Division, Istituto Clinico Humanitas, Milano; [3]Department of Biomedical Sciences, Humanitas University, Milano; Rheumatology and Clinical Immunology Division, Istituto Clinico Humanitas, Milano; [4]Department of Biomedical Sciences, Humanitas University, Milano; Internal Medicine and Hepatology Division, Istituto Clinico Humanitas, Milano

Background: Psoriatic arthritis (PsA) is a highly heterogeneous disease characterised by a wide spectrum of articular and extra-articular manifestations, often associated to comorbidities relevant to the internist. There is a growing interest in these gender-related differences as they could impact on PsA management. The male:female ratio of the disease is equal but the clinical course and the prevalence of comorbidities seems to differ in recent studies.
Objectives: To investigate the gender-related clinical differences in a real-world cohort of patients with PsA.
Methods: We retrospectively collected data of consecutive PsA patients ≥ 18 years old attending the Rheumatology outpatients Clinic at Humanitas Research Hospital of Milan between January 1st 2022 and March 30st 2023. All patients fulfilled the 2006 CASPAR classification criteria; demographic, laboratory and clinical data were recorded at the last follow up visit; in particular we focused the analysis on concomitant comorbidities. T-test and chi-square test were used to compare data of males versus females. Logistic regression models analysed the impact of gender on comorbidities, adjusted for confounders.
Results: The study included 361 PsA patients (164 M, 45%) and we considered male and female cohort separately. Variables analysed are summarized in **table 1.** Peripheral arthritis and extrarticular manifestations of the disease (skin and nail PSO, uveitis and IBD) were equally observed in the two groups; females were more frequently affected by enthesitis (p=0.003) than men, while male cohort showed higher prevalence of axial involvement (p=0.055) and dactylitis (p=0.056). The comparative analysis focused on comorbidities, showed that most of cardiovascular and metabolic conditions were more prevalent among males: congestive heart failure (p=0.010), NAFLD (p=0.029), angina (p=0.015), hyperuricemia (p=0.001), metabolic syndrome (MetS, p=0.013) and diabetes (p=0.064). Conversely, PsA in women was more frequently associated with other non-inflammatory musculoskeletal disease (fibromyalgia, p<0.0001; osteoarthritis, p=0.010; osteoporosis, p=0.001 and degenerative disk disease, p=0.015), neurological diseases (p=0.039) or autoimmune thyroiditis (p<0.0001). Multivariate analysis confirmed relations between males, MetS (p=0.005, OR 5.04±2.88 IQ 1.65-15.41) and NAFLD (p=0.024, OR 2.81±1.29 IQ 1.14-6.91) regardless of age. At the same time, correlation between females, fibromyalgia (p<0.001, OR 0.05±0.02 IQ 0.02-0.13) and autoimmune thyroiditis (p<0.0001, OR 0.20± 0.08 IQ 0.09-0.42) was also substantiated.
Conclusions: Men with PsA have an higher prevalence of metabolic and cardiovascular comorbidities compared to women, while musculoskeletal disease, fibromyalgia and autoimmune thyroiditis disorders are more frequent in women. Further prospective studies are needed to confirm these gender related disease and determine the impact of therapeutic choices.

Variable	Men (n=164)	Women (n=197)	p-value
Median Age (years)	55.4±11.44 [IQ 53.6-57.2]	56.2±12.37 [IQ 54.4-57.9]	0.532
Clinical Domains			
AxPsA (n[%])	**75 (46%)**	**71 (36%)**	**0.055**
Psoriasis (n[%])	134 (82%)	147 (75%)	0.106
Dactylitis (n[%])	**54 (33%)**	**47 (24%)**	**0.056**
Enthesitis (n[%])	**88 (54%)**	**136 (69%)**	**0.003**
Nail Disease (n[%])	40 (25%)	45 (23%)	0.746
Peripheral Arthritis (n[%])	158 (96%)	191 (97%)	0.746
Uveitis (n[%])	3 (2%)	2 (1%)	0.505
Ulcerative Colitis (n[%])	1 (1%)	3 (2%)	0.413
Crohn Disease (n[%])	5 (3%)	5 (3%)	0.761
Comorbidities			
Cancer (n[%])	16 (10%)	24 (12%)	0.465
Depression (n[%])	12 (7%)	20 (10%)	0.345
Fibromyalgia (n[%])	**3 (2%)**	**48 (24%)**	**<0.0001**
Myocardial Infarction (n[%])	11 (7%)	6 (3%)	0.102
Congestive Heart Failure (n[%])	**17 (10%)**	**7 (4%)**	**0.010**
Peripheral Vascular Disease (n[%])	10 (6%)	13 (7%)	0.846
Cerebral Vascular Event (n[%])	6 (4%)	11 (6%)	0.390
Dementia (n[%])	3 (2%)	2 (1%)	0.510
Chronic Obstructive Pulmunary Disease (n[%])	6 (4%)	7 (4%)	0.957
Chronic Kidney Disease (n[%])	12 (7%)	7 (4%)	0.111
Non Alchotic Fatty Liver Disease (n[%])	**22 (13%)**	**13 (7%)**	**0.029**
Osteoarthritis (n[%])	**23 (14%)**	**49 (25%)**	**0.010**
Osteoporosis (n[%])	**14 (9%)**	**41 (21%)**	**0.001**
Asthma (n[%])	3 (2%)	8 (4%)	0.219
Angina (n[%])	**12 (7%)**	**4 (2%)**	**0.015**
Neurological Disease (n[%])	**14 (9%)**	**31 (16%)**	**0.039**
Diabetes (n[%])	**19 (12%)**	**12 (6%)**	**0.064**
Upper Gastrointestinal Disease (n[%])	18 (11%)	29 (15%)	0.292
Anxious Syndrome (n[%])	6 (4%)	8 (4%)	0.844
Hearing Impairment (n[%])	3 (2%)	3 (2%)	0.821
Visual Impairment (n[%])	10 (6%)	10 (5%)	0.673
Degenerative Disc Disease (n[%])	**0 (0%)**	**7 (4%)**	**0.015**
Obesity (n[%])	34 (23%)	33 (19%)	0.340
Hypertension (n[%])	58 (36%)	60 (31%)	0.322
Fracture (n[%])	25 (15%)	26 (13%)	0.578
Cancer (n[%])	16 (10%)	24 (12%)	0.465
Autoimmune Thyroiditis (n[%])	**11 (7%)**	**45 (23%)**	**<0.0001**
Dyslipidemia (n[%])	47 (29%)	51 (26%)	0.556
Hyperuricemia (n[%])	**13 (8%)**	**2 (1%)**	**0.001**
Metabolic Syndrome (n[%])	**19 (12%)**	**9 (5%)**	**0.013**

Table 1. Principal Variables Analyzed

572. SUCCESSFUL TREATMENT OF SECONDARY MACROPHAGE ACTIVATION SYNDROME WITH ANAKINRA IN PATIENTS WITH NEWLY DIAGNOSED ADULT-ONSET STILL'S DISEASE: CASE REPORT AND REVIEW OF THE LITERATURE

Piccinni F.[1], Leone P.[1], Susca N.[2], Guastadisegno C.M.[3], Vacca A.[3], Racanelli V.[4], Prete M.[1]
[1]Department of Interdisciplinary Medicine, Section of Internal Medicine, School of Medicine, 'Aldo Moro' University of Bari; [2]Department of Interdisciplinary Medicine, Emergency Department Unit, School of Medicine, 'Aldo Moro' University of Bari; [3]Department of Precision and Regenerative Medicine and Ionian Area, Section of Internal Medicine, School of Medicine, 'Aldo Moro' University of Bari; [4]Department of Cellular, Computational and Integrative Biology - CIBIO, University of Trento, Trento, Italy

Macrophage activation syndrome (MAS) is a severe, potentially fatal condition that may complicate autoimmune diseases, and it belongs to hemophagocytic lymphohistiocytosis (HLH) disorders. In this report, we describe two cases of adult patients with adult-onset Still's disease (AOSD) with their clinical manifestations, laboratory data, and management, who were newly diagnosed in the setting of secondary macrophage activation syndrome (MAS).
1° case-report
We present a case of a 27-year-old male presented to the hospital with high fever, chills, myalgia and splenomegaly. Significant laboratory exams revealed anemia, thrombocytopenia, and elevated serum ferritin (30.068 ng/mL) and LDH (3304 UI/L).
Initial evaluation at the time of presentation suggested sepsis likely due to intermittent fever and increased acute parameters, CRP (179 mg/L) and procalcitonin (4.85 ng/ml). The patient was started on antibiotics and intravenous fluid hydration. However, further workup suggested that his symptoms were non-infectious and were likely due to MAS, a rare systemic juvenile idiopathic arthritis (SJIA) onset. He met the diagnostic criteria of AOSD and MAS, while genetic testing excluded primary causes of MAS. Bone marrow biopsy showed "*numerous CD68 histiocytes filled with hematopoietic cells decomposed as from hemophagycytosis and a modest amount of small and medium-sized T lymphocytic elements dispersed in the interstitial area*". Therapy with corticosteroids 1 mg/kg was started, with only partial remission of fever, but persistent cytopenias and high inflammatory markers.
2° case-report
A 56-year-old patient who went to the Emergency Department for persistent fever preceded by shaking chills and skin erythema on back, abdomen and face. Following hospitalization, he had joint pain in right wrist with blockage and functional limitation. Laboratory tests showed elevated ferritin (44073 ng/mL) and CRP (78 mg/dl), elevated transaminase values. All culture and serology tests for possible infectious etiology were negative. Total body CT scan showed a modest amount of effusion in the endoabdominal site in the submesocolic and pericholecystic compartment with extension in the pericephalopancreatic site; enlarged lymph nodes (aboout 15 mm of diameter) bilaterally axillary, pre- and subcarinal and pulmonary hilar, in the root of the mesentery and in the inguinal site.
Therapy with corticosteroids 0.8 mg/kg were added to the home therapy with levofloxacin with partial regression of the febrile symptoms and improvement of the inflammatory parameters. In suspicion of adult Still's dieseas, a bone marrow biopsy was performed with evidence of a clear picture of *hemophagycytosis*. The introduction of the anti-IL1 (anakinra) to both described patients brought about prompt remission of the symptoms, normalization of the altered parameters within a month, allowing for a rapid withdrawal of the corticosteroid at a dosage of 7.5 mg/day. The literature review revealed 13 cases of MAS complicating AOSD treated with anakinra. All the patients showed a fast and persistent improvement, starting in some cases only 24 hours after the first dose. Some authors suggest that, in more critical cases, i.v. administration is a safe alternative and has a more predictable pharmacokinetic profile than the s.c. route.

573. WHEN YOU HEAR HOOVES, THINK OF A HORSE, NOT A ZEBRA. ARE YOU REALLY SURE?

Facciuto A. I.[1], Nasta C.[1], Pasquale M. D.[2], Rozza G.[2], Giordano M.[3], Paolisso G.[3]
[1]Università degli studi della Campania "Luigi Vanvitelli"; [2]U.O.C. Medicina Interna e P.S. Ospedale "A. Guerriero" Marcianise; [3] Università degli studi della Campania "Luigi Vanvitelli"

Case report: An 80 years old woman access to our Emergency Department due to a fall to the ground caused by lower limbs hyposthenia, without loss of consciousness and inability to get up independently, so she was rescued after several hours. Moreover, the patient reports that she was experiencing lower limbs hyposthenia and walking difficulties for about one month. Triage code 3 (blue). In her past medical history she had type 2 diabetes mellitus on insulin therapy, arterial hypertension and chronic phlebitis in lower limbs. Her vital signs were BP 180/70 mmHg, HR 70 bpm rhythmical, SpO2 96% in aa, BT 36°C, GCS 15. On the examination of chest, heart and abdomen there were no abnormalities. The examination of lower limbs showed a marked hyposthenia, especially for the right one, and skin appeared symmetrically hyperchromic. On breast examination we noticed that the right breast had a retracted nipple and a palpable lump in the outer lower quadrant characterized by solid texture. In order to rule out acute cerebrovascular accident, two brain CT scans were performed, both showing no acute brain injuries. X-ray of right hip, femur, knee and foot and orthopedic evaluation showed no fractures. Blood tests revealed increased levels of CPK (1246 UI/L), myoglobin (469 ng/mL) and C-reactive protein (3.66 mg/dL), with normal serum creatinine levels. Hydration, diuretics, and glucocorticoids therapy were begun. Unfortunately, during the hospitalization a nasopharyngeal swab for Sars-Cov-2 tested positive, so the diagnostic work up focused on the breast lump was temporarily interrupted. Monoclonal antibody therapy was administered and only after approximately one week the nasopharyngeal swab for Sars-Cov- 2 tested negative. After that we restarted the diagnostic work up and the mammography detected on the right breast a 25 mm irregular margin opacity with calcifications (BIRADS B4). This lesion was biopsied. Finally the patient presented a slight improvement in lower limbs hyposthenia, so she was discharged with a diagnosis of "*Post-traumatic rhabdomyolysis in a patient with suspected right breast cancer, type 2 diabetes mellitus undergoing insulin treatment, high blood pressure, chronic phlebitis of lower limbs, solved Sars-Cov-2 infection*".
Follow up: After patient dischargement we received the biopsy's result which identified a "classical invasive lobular carcinoma E-cadherin-negative well-differentiated CK19-positive with fibro-hyaline stromal desmoplasia". Oncologists got in touch with the patient to propose the continuation of treatments, but she refused to start the therapy because of the worsening clinical conditions due to the myopathy.
Discussion: Inflammatory myopathies are a heterogeneous group of autoimmune disorders represented by: polymyositis, dermatomyositis and cancer-associated myositis. The latter represents a paraneoplastic syndrome that can occur before, after or at the same time of the tumor. Regardless, it has been observed that the identification of malignant tumor occurs within 3 years of the diagnosis of myositis. Among the tumors that are most frequently associated with paraneoplastic myositis, breast cancer stands out. The typical clinical manifestations are: proximal muscle weakness, skin manifestations, increased serum CPK levels and inflammatory cells infiltrating the muscle tissue on biopsy. Muscle weakness is generally rapidly progressive and severe, leading to immobility and distal involvement. Dysphagia, oropharyngeal dysfunction, and respiratory muscle involvement are a frequent way of progression, and the following respiratory failure can be fatal. The pathophysiological mechanism is autoimmune cell-mediated in which the response is stimulated by a cross-reactivity between tumor antigens and skin and muscle antigens. Diagnosis is based on erythrocyte sedimentation rate, serum muscle enzyme levels, myogenic signs on electromyography, and clinical manifestations. Pharmacological treatment includes use of glucocorticoids, immunosuppressants and antimetabolites such as Methotrexate and Azathioprine, intravenous immunoglobulins, and Rituximab. In this clinical case, the concomitant positive swab for Sars-cov2 made it necessary to proceed with the isolation of the patient and starting specific therapy for Covid 19, in order to avoid the spread of the infection. This made difficult to continue the diagnostic work-up and to investigate other causes of rhabdomyolysis. Therefore, Covid19 still represents an indirect cause of diagnosis and treatment delay. Moreover, this case showed the difficulties associated with a prompt diagnosis of an unusual case of paraneoplastic polymyositis from breast cancer.

574. ROLE OF SUBTLE SYMPTOMS AND WHOLE-BODY PET-CT SCAN IN THE DIAGNOSTIC WORK-UP OF A WOMAN WITH AORTIC ANEURYSMS

Scarpulla N.[1], Gallo R.[1], Patauner F.[1], Bertolino L.[1], Tricarico E.[1], Durante Mangono E.[2]
[1]Dipartimento di Scienze Mediche e Chirurgiche Avanzate; [2]Dipartimento di Medicina di Precisione

A 73-year-old Caucasian woman was admitted to our unit with a four-week

history of dyspnea, myalgias and polyarthralgias. Her past medical history was significant for bio-prosthetic aortic valve replacement, thoraco-abdominal aneurysm treated with endovascular repair (Valliant endoprosthesis implantation), arterial hypertension, permanent atrial fibrillation, chronic disseminated intravascular coagulopathy and osteoporosis. Presenting complaints included new onset headache, localized in the left region of the face with homolateral flushing, carotidynia and tenderness of the temporal area. On clinical examination, she appeared dyspnoic during mild physical activity, with limbs' movement limitation due to proximal muscle pain, and polyarthralgias of the distal joints. Edema of the lower limbs was also present. At admission, laboratory findings were significant for leukocytosis with neutrophilia, increased C-reactive protein (CRP) (22 mg/L), normal erythrocyte sedimentation rate hyperfibrinolysis and hypofibrinogenemia.
Investigations: as the suspicion of polymyalgia rheumatica (PR) and giant cell arteritis (GCA) was raised, we performed laboratory test for autoimmune vasculitis (p-ANCA, c-ANCA) and for non-vascular inflammatory disease (ANA, ENA, FR), that resulted negative. We dosed interleukin-6 serum levels, that were equal to 8.3 pg/mL (normal values 0-5). Two sets of blood cultures were drawn and remained negative. Doppler ultrasound of temporal artery, supra-aortic trunks, aorto-iliac arteries, and lower limb arteries did not show any inflammatory changes. Whole-body PET-CT scan showed increased tracer uptake in the thoracic aorta especially in distal part with maximum SUV 4.87 (last aortic endoprosthesis implantation 4 years before the evaluation).
Management: considering the age, medical history, and typical clinical presentation, a presumptive diagnosis of long-standing, unrecognized PR with GCA was done. Differential diagnosis included infective arteritis, autoimmune arteritis and non-vascular inflammatory disease that were ruled out in light of clinical presentation and laboratory results. A diagnosis of GCA was plausible according to the 2022 American College of Rheumatology/EULAR GCA classification criteria(1). In details, patients satisfied two clinical criteria (morning stiffness in shoulders/neck and new temporal headache) plus one laboratory and one imaging criteria (CRP ≥10 mg/L and a positive whole-body PET-CT scan, respectively), for a total of 7 points. Considering the history of osteoporosis limiting high dose steroid administration, the patient is currently under evaluation for treatment with tocilizumab.
Discussion: PR is a systemic inflammatory disorder characterized by aching and stiffness of shoulders, neck and pelvic girdles, occurring especially in the morning, and constitutional symptoms.(2) GCA is a systemic vasculitis that involves large and medium-sized arteries, frequently affecting elderly people.(1) It is common for GCA and PR to develop together as they could be different manifestation of a shared disease. It is estimated that just about 50% of patients with GCA will develop PR. GCA can present with a wide range of manifestations, depending on the cranial or extracranial involvement of the arteries, including headache, face swelling, vision loss, jaw or limb claudication, aortic valve disease with extensive aortic aneurysms, constitutional symptoms, fever of unknown origin.(2) Once the suspicion of large vessel vasculitis is made, it is important to exclude mimicking conditions (like infective arteritis, non-vasculitis inflammatory diseases) and to satisfy classification criteria. (1) In this patient, with a major history of aortic disease, careful assessment of subtle symptoms and whole body PET-CT scan played a pivotal role in the diagnostic work-up.
References
1. Ponte, C. et al. 2022 American College of Rheumatology/EULAR classification criteria for giant cell arteritis. Ann Rheum Dis 81, 1647–1653 (2022).
2. Lally, L. & Spiera, R. Management of difficult polymyalgia rheumatica and giant cell arteritis: Updates for clinical practice. Best Pract Res Clin Rheumatol 32, 803–812 (2018).

575. MACROPHAGE ACTIVATION SYNDROME IN EARLY SYSTEMIC LUPUS ERYTHEMATOSUS: A CLINICAL CASE REPORT

Santoro S.[1], Di Terlizzi G.[2], Soddu D. [2], Ramirez G.A.[3], Damanti S.[4], Moroni L. [3], Bozzolo E.P.[5], Scotti R.[1], Tresoldi M.[2]
[1]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan Università Vita-Salute San Raffaele; [2]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy; [3]Università Vita-Salute San Raffaele Unit of Medical Specialties and Healthcare Continuity IRCCS Ospedale San Raffaele, Milan, Italy; [4]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy Università Vita-Salute San Raffaele Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS Ospedale San Raffaele, Milan, Italy; [5]Unit of General Medicine and Advanced Care, IRCCS Ospedale San Raffaele, Milan, Italy Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS Ospedale San Raffaele, Milan, Italy

Background Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease of variable severity and course which can affect various organs and body tissues. It is characterised by a tendency to relapse. Clinical manifestations and the pattern of organ involvement are highly heterogeneous, reflecting the complex mosaic of dysregulated molecular pathways that converge in the clinical phenotype of SLE. Macrophage activation syndrome (MAS) is a life-threatening hyperinflammatory state characterised by uncontrolled cytokine storm and haemophagocytosis that can lead to multiorgan failure and death. MAS in children is most associated with systemic juvenile idiopathic arthritis (JIAA). The association with systemic lupus erythematosus is relatively rare. According to recent literature, MAS may occur in systemic lupus erythematosus (SLE), particularly as an initial manifestation, with an incidence of approximately 0.9-4.6%, increasing to 9.4% in patients with liver dysfunction. The mortality rate of MAS complicating adult SLE has been reported to be between 4.5% and 9.8%.
Objective To describe the clinical characteristics of a case of MAS-SLE and possibly demonstrate the importance of considering MAS as a complication of SLE onset in the setting of multi-organ involvement, recognising characteristic laboratory abnormalities, and initiating appropriate therapy early after adequate exclusion of possible differential diagnoses.
Case summary We report the case of a 20-year-old Caucasian boy with no relevant past medical history who was admitted to hospital with a history of diffuse arthromyalgia, rash on the lower limbs and trunk and high fever for several days and chest pain with chest CT findings consistent with pneumonia and multiple lymphadenopathies, and a transthoracic echocardiogram showing non-haemodynamic effusion. Haematological cancer was ruled out by PET-CT scan and bone marrow biopsy, which showed hyperplasia with mild to moderate dyshaematopoiesis and non-specific haemophagocytosis. Axillary lymph node biopsy showed atypical lymphoproliferation. Blood tests initially showed WBC 14.2 x 109/L (3.5-9.5 x 109/L), Hb 10.5 g/dl (14-18 g/dl), creatinine 0.59 mg/dL (0.8-1.2 mg/dl), C-reactive protein (CRP) 118 mg/dL (0-8 mg/dl), aspartate transaminase (AST) 70 U/L (8-48 U/L), alanine aminotransferase (ALT) 31 U/L (7-55 U/L), ferritin 57288 ng/ml (15-300 ng/ml) and triglycerides 540 mg/dl (less than 150 mg/dl). The patient was initially treated with broad-spectrum antibiotic treatment, which, however, failed to induce any clinical improvement. Consistently, blood cultures and microbiological investigations did not show evidence of viral, bacterial and fungal infection. During hospitalisation the patient worsened with new-onset respiratory failure and seizures. Further diagnostic work up revealed positive antinuclear antibodies (ANA), anti-Ro, anti-La and anti-cardiolipin antibodies, which led to the diagnosis of SLE (21 points by EULAR/ACR 2019 classification criteria, obtained for the presence of fever, seizure, acute pericarditis, joint involvement and anti-cardiolipin antibodies) with secondary MAS. Pleuropulmonary manifestations are frequent in SLE, particularly pleurisy. Although in a few reports, pneumonia has also been described among the parenchymal manifestations. Physicians must be aware of this phenomenon, in which the inflammatory state is unresponsive to antibiotic therapy, and which may require intensive care, as in our case. Combination treatment with high-dose intravenous methylprednisolone, anakinra and cyclophosphamide, was therefore promptly initiated with immediate reduction in inflammatory parameters and fever. The patient remained in clinical remission during the 4-month follow-up period with improved MAS markers (triglycerides 150 mg/dL, ferritin 616 ng/mL). SLE disease activity also improved, with SLE disease activity index 2000 (SLEDAI-2K) score falling from 27 (seizure, psychosis, arthritis, inflammatory-type rash, pleuritic chest pain with plural effusion, pericarditis and fever) during hospitalisation to 4 points at last follow up visit.
Conclusion MAS can be a life-threatening complication of autoimmune disorders such as SLE and occur at disease onset, making it more difficult to differentiate the clinical scenario from infectious or neoplastic disorders. This case also highlights that MAS can also develop on the background of atypical SLE presentations, which makes its recognition even more challenging.

576. MANAGEMENT OF LUPUS NEPHRITIS: EXPERIENCE OF A SINGLE CENTER

Santangeli R.[1], Gamba L.[1], Montozzi G.[1], Salvucci S.[1], Cocco C.[1], Fioretti P.[1], Curina L.[1], Manfredi L.[2], Moroncini G.[1]
[1]Scuola di Specializzazione in Medicina Interna, Università Politecnica delle Marche, Ancona, Italy; [2]Clinica Medica, Dipartimento di Medicina Interna, AOUM, Ancona, Italy

Purpose: Kidney is one of the organ most often involved in Systemic Lupus Erythematosous (SLE) and renal injury is a major cause of morbidity and

mortality(1). In this report we describe our experience in the management of lupus nephritis (LN).
Methods: In our clinical department, we follow one hundred SLE patients, of which approximately one third with LN. We collaborate with the Department of Nephrology to discuss clinical cases, to evaluate indication for renal biopsy and to decide therapeutic strategy. We periodically assess our patients monitoring serum creatinine, urine analysis, sierology and 24h – proteinuria. Renal biopsy is still the diagnostic gold standard to assess renal involvement in SLE patients and during clinical practice it should be done as soon as possible; it could be contraindicated for severe hematological or coagulative disorders. A renal biopsy had been performed in seventy – percent of our patients and the most frequent histopathology reports are LN class III or V, less often class IV, according to the "2003 International Society of Nephrology/Renal Pathology Society Classification"(2). One third of patients have required treatment with cyclophosphamide (CY) combined with high – dose steroid therapy in the past years during the active phase of LN, while nowadays the induction treatment protocol is most often performed with steroid and mycophenolate mofetil/mycophenolate acid (MMF/MPA) because of minor side effects. For subsequent immunosuppressive treatment, we often use MMF, observing a good clinical outcome. In one case we replaced MMF therapy with azathioprine (AZA) because of patient's desire of pregnancy, and after the delivery treatment with AZA was continued without renal flares. Since belimumab has been approved for LN(3), we started to use it in combination treatment with a satisfying disease control.
Results: In our cohort one third of patients is on treatment with MMF and one third with Belimumab: immunosuppressive therapy is established according to features of patient, comorbidities and severity of renal involvement. Six patients are taking both of them because of the difficulty to control LN with a single immunosuppressive drug and to reduce the corticosteroid dosage. Indications for the timing of suspension of immunosuppressive therapy (1) are not available and so we gradually discontinue the treatment after a long period of remission (10 years or more). To date, one third of our patients with previous LN are in good control with hydroxychloroquine and low – dose of steroid, that we continue to reduce slowly until possible suspension.
Conclusions: In our experience a short term clinical and laboratoristic evaluation is required to early detect a disease flare, to collaborate with Nephrologists in order to perform renal biopsy as soon as possible and to start subsequent immunosuppressive therapy to preserve renal function. Anyway more clinical studies are required to improve diagnostic and therapeutic lupus nephritis management.
Fanouriakis A, Kostopoulou M, Cheema K, et al. Ann Rheum Dis 2020;79:713–723
Weening JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. Kidney Int 2004;65:521–30.
Furie R, Rovin BH, Houssiau F et al (2020) Two-year, randomized, controlled trial of belimumab in lupus nephritis. N Engl J Med 383:1117–1128

577. A CASE OF MRSA SPONDYLODISCITIS WITH MULTIPLE SEPTIC EMBOLI

Coscia Ma.[1], Italiano G.[1], Cortese L.[2], Solaro E.[1], Sommese A.[1], Vinciguerra A. [1], Tibullo L.[1]
[1]Internal Medicine Ward, Sant' Anna and San Sebastiano Hospital, Caserta; [2]Rheumatology ward, Luigi Vanvitelli University of Campania, Caserta

Background: patient B.R., 53 years old, female, baker, entered the Emergency Department in August 2022 due to a fever. The patient was hospitalized for diagnostic-therapeutic classification at the UOC of Internal Medicine of the AORN Sant'Anna and San Sebastiano of Caserta, in the history of hypothyroidism under pharmacological treatment and mixed low back pain for about two years, treated spontaneously with cycles of NSAIDs and corticosteroids.
Clinical case: during hospitalization, the patient presented with fever and lumbar pain. Serial and culture tests (blood cultures and urine cultures) were performed. The tests revealed a positive urine culture for Proteus Mirabilis, neutrophilic leukocytosis (GB 28.84 x103/uL, neutrophils 26.24 x103/uL) and a significant increase in inflammation indices (VES 114 PCR 38 mg/dl). Procalcitonin (PCT) had a value of 1.88 ng/ml. Autoimmunity was negative. Antibiotic therapy was started for the urinary tract infection. However, the laboratory and clinical picture did not improve. On the contrary, a picture of respiratory insufficiency requiring oxygen therapy and anaemia (with a multifactorial genesis) requiring blood transfusions took over. On the ECG (which was normal on admission), a type I Brugada pattern was unveiled and subjected to arrhythmological consultancy. For the persistence of low back pain, magnetic resonance imaging (MRI) of the spine with and without contrast medium was performed, which showed the presence of an emphysematous collection along the entire axis of the spine at the left posterior paravertebral level of the dorsolumbar, with "cluster" organization, and right pelvic site. Meanwhile, the patient suddenly presented with skin manifestations and signs of hot joints in the IV and V MCF and IFP of the left hand and the left sternoclavicular joint. The most probable hypothesis was that of septic emboli originating from spondylodiscitis. Therefore, arthrocentesis was performed with drainage of the purulent collection.The most probable hypothesis was that of septic emboli starting from spondylodiscitis. Therefore, arthrocentesis was performed with drainage of the purulent collection. The culture was positive for Methicillin-Resistant Staphylococcus Aureus (MRSA). The blood culture was also positive for the same germ. Thus, targeted antibiotic therapy was undertaken. About a week after the start of the antibiotic therapy, MRI was repeated, which showed a clear reduction of the collection along the vertebral canal but showed numerous suspicious areas for abscess collections in the pelvic area. A CT scan highlighted the presence of fluid collection in the right gluteal region (max diameter 11x18 cm), which was subjected to C.T.-guided drainage. Antibiotic therapy continued, and other infectious events were excluded with the execution of a transesophageal echocardiogram with a negative result for endocarditis and a search for B.K., which gave a negative result. The patient improved clinically, oxygen therapy was no longer necessary, and the pleuro-pericardial effusion previously emerged from the instrumental investigations was in the resolution process; laboratory tests showed an improvement in leukocytosis and inflammation indexes, and repeated culture tests were negative. Functionality was considerably recovered; also, thanks to the help of FKT practised in hospitalization and a CampC35 bust. The patient was discharged with indications to continue antibiotic, anti-inflammatory and pain-relieving therapy. The individual rehabilitation plan was delivered to continue FKT.
Conclusions: our case shows a picture of severe sepsis in a patient with S. Aureus Spondylodiscitis MRSA with multiple septic emboli. In the anamnesis, the patient presented a history of chronic low back pain, self-medicated with NSAIDs and steroids, but never investigated. Therefore, one could also think of an underlying inflammatory condition on which an infectious process has been triggered. The patient is currently in follow-up at our facility and is in current clinical well-being.

578. SEVERE INFECTIONS IN SLE PATIENTS: A DESCRIPTIVE ANALYSIS FROM A SINGLE CENTRE

Montozzi G.[1], Salvucci S.[1], Santangeli R.[1], Gamba L.[1], Cocco C.[1], Fioretti P.[1], Manfredi L.[2], Moroncini G. [2]
[1]Scuola di Specializzazione in Medicina Interna, Università Politecnica delle Marche, Ancona, Italy; [2]Clinica Medica, Dipartimento di Medicina Interna, AOUM, Ancona, Italy

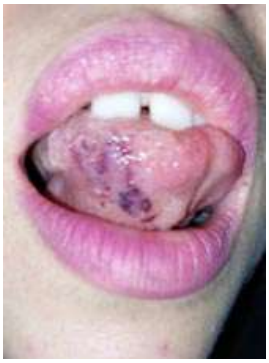
Background: Infectious risk in immunocompromised patients, particularly if affected by Systemic Lupus Erythematosus (SLE), is associated with both disease-related and treatment-related factors; high-dose glucocorticoid therapy, mycophenolate mofetil and rituximab are all associated with an increased risk for infection, meanwhile high disease activity, severe leukopenia and presence of renal involvement also contribute independently.
If a patient presents an infectious event, immunosuppressive treatment has to be discontinued for an increased risk of more severe disease and subsequent risk of hospitalization, even if we can assist to a flare of autoimmune disease. In this work, we analyze the rate of severe infections (an infectious disease is defined severe if immunosuppressive therapy has to be interrupted and/or patient has to be hospitalized for intravenous/oral antibiotic/antiviral therapy) in our cohort of SLE patients. The objective of this descriptive analysis is to identify specific risk factors for the development of infections in immunocompromised SLE patients.
Methods: In our cohort we have enrolled 71 SLE patients (7 M, 64 F), of which 51 (71%; 5 M, 46 F) in actual or past immunosuppressive therapy, with a median age of about 44 years (IQR 31-56 years). Patients who had to interrupt immunosuppressive treatment for severe intercurrent infections were 17 (33.3% of patients on immunosuppressive therapy, 23.9% of the total cohort, 16 F and 1 M), with a median age of 37 years (IQR 28-48) and a median disease duration of 12 years (IQR 5-16).
9/17 (52.9%) patients experienced Herpes Zoster, 7/17 (41.2%) Covid19 infection and 6/17 (35.3%) other types of infections (in particular enteritis, urinary tract infections, extra-pulmonary tuberculosis, pneumonia and cellulitis). Herpes zoster was the most frequent severe infection in our cohort. With regard to patients with severe infections, all of them required im-

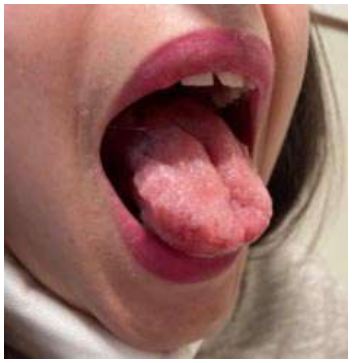
mediate discontinuation of immunosuppressive therapy; 3/17 experienced a disease flare (17.6%), 6/17 (35.3%) required specific therapy (antibiotic/antiviral) to treat the infection, 7/17 (41.2%) required hospitalization and intravenous antibiotic/antiviral therapy. After healing, 14/17 (82.3%) patients resumed immunosuppressive therapy. We have also conducted a comparison with the cohort of patients on immunosuppressive therapy who did not experience severe infections. We analyzed presence of cardiovascular risk factors in the two cohorts, also related to the disease involvement, and also the different types of immunosuppressive treatment (Belimumab, Rituximab, Mycophenolate Mofetil, CYC previous therapy, corticosteroid).
Results: From our data analysis, conducted with statistical tests (t-Test, Fisher exact test, p-value 0.05) with the R-project software, there is no significant difference about specific risk factors that could favour the occurrence of severe infectious disease between patients in immunosuppressive therapy.
Conclusions: In our cohort we did not identify specific risk factors for severe infections in immunosuppressed patients. Analysis of larger cohorts has to be encouraged to identify potential risk factors for severe infections, so that they could be treated or prevented without treatment discontinuation, necessary strategy to prevent flare disease.

579. AN INCOMPLETE FORM OF BEHCET DISEASE

Caporuscio S., Lovello M.C. , Di Cello E., de Tschudy A., Imperoli G.
Dipartimento di Medicina Interna San Filippo Neri Roma

Behcet's disease (BD) is a rare and poorly understood condition that results in inflammation of the blood vessels and tissues. Confirming a diagnosis of Behcet's disease can be difficult because the symptoms are so wide-ranging and general and can be shared with a number of other conditions. We report the case of a 27 -old Albanian woman admitted to our emergency department in September 2021.She presented with swelling of half the tongue associated with aphthous ulcers and geographic aspects (Fig1). She referred several episodes of tongue swelling during adolescence and complained of intermittent arthralgia of the small joints of the hands and feet and abdominal pain episodes associated with diarrhea. Laboratory tests revealed normal value of erythrocyte sedimentation rateand C reactive protein, while antinuclear antibodies, antineutrophil cytoplasmatic antibodies, and rheumatoid factor were negative. At emergency department admission, the patient started treatment with amoxicillin and clavulanic acid and metilprednisolon with poor improvement of the tongue lesions. To better evaluate the tongue aspect, maxillofacial MRI was performed showing the presence of an enlarged tongue with signs of body edema and an uneven surface, and the presence at the lower side of the tongue body of a nodular formation with an irregularly oval morphology of about referable to hemangioma. Due to the high risk of bleeding related to the presence of hemangioma, the otorhinolaryngologist decided not to perform a tongue biopsy. The evaluation of HLA class I polymorphisms was performed, and while results were pending colchicine treatment at a dosage of 1 mg bid was started in the suspicion of BD. The pathergy test resulted negative.To exclude other possible diagnoses, , Clq inhibitor was tested periombelicular fat biopsy was performed but resulted negative. The patient presented a rapid significant clinical improvement in the tongue oedema and aphthous ulcers with colchicine treatment (Fig 2). The HLA class I evaluation revealed the presence of the B51 allele, corroborating the suspicion of BD. In relation to the presence of mouth ulcers with swelling of the tongue, arthralgia of small joints, HLAB5 1 positivity, and the good response to colchicine treatment, a diagnosis of incomplete form of BD was made.





580. TIF1-Γ ASSOCIATED DERMATOMYOSITIS: A CASE REPORT

Piacevole A., Catalini C., Rocco M., Alfano M., Ferrara R.
Medicina Interna, Università della Campania L. Vanvitelli

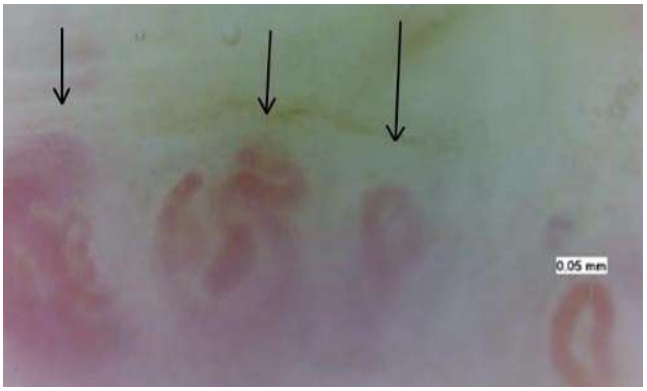
A 64-year-old man, florist, apparently was healthy until May 2022 when erythematous and itchy rash appeared on his upper limbs; this condition was first diagnosed as contact dermatitis. After 3 months, the same lesions spread to the face and there was also presentation of eyelid edema, for this reason he received a diagnosis of "allergic angioedema" and initiated corticosteroid and antihistamine therapy. His clinical conditions worsened in September 2022 since skin lesions were persistently present despite medical therapy but also dysphagia mostly related to solid foods and strong debilitating weakness of upper and lower limbs appeared. The patient was admitted to our Internal Medicine department in October 2022. Only benign prostatic hyperplasia was documented in his past pathological history. During clinical examination, the patient appeared to be in good clinical condition, afebrile, and hemodynamically compensated. Diffuse erythema on the face was detected, expecially on the forehead, nasolabial folds, periorbital regions, as well as considerable bilateral eyelid edema. Additionally, Grotton's papules, erythematous squamous lesions, were found on the dorsal surface of both hands' metacarpophalangeal joints, and no symptoms or signs of arthritis were observed. The neurological clinical examination revealed an active and passive functional limitation of the limbs, associate to hyposthenia and mild/moderate hypotonia of the proximal muscles of the limbs. Cranial nerves and osteotendon reflexes were intact, as well as heart, thorax and abdomen clinical examination did not reveal any pathological alteration. Routine blood tests showed an increase of muscle cytolysis indexes (CPK: 1083 IU/L, AST: 125 IU/L, LDH: 345 IU/L) and a slight increase of pro-inflammatory markers (ferritin 867: ng/mL, PCR: 19.6 mg/L). Normal C1q inhibitor and complement levels allowed us to rule out hereditary angioedema. In case of suspicion of an inflammatory myopathy, electromyography was performed and a characteristic pathological pattern was found, also high blood levels (92, strongly positive >51) of myositis-specific antibodies against TIF1-γ (human transcriptional intermediary factor 1-gamma) were detected. The diagnosis of dermatomyositis was then confirmed by right deltoid muscle biopsy. Dermatomyositis could represent, in some cases, the initial sign of a malignancy. There are several risk factors associated to the presence of an occult cancer, including male gender, advanced age, skin necrosis, and dysphagia; nevertheless, the presence of anti-TIF1-y is the most associated to increased oncogenic risk. Oncological screening was then performed: tumor markers dosage, total body CT scan with contrast media, esophagogastroduodenoscopy, colonoscopy, and PET-CT did not reveal any suspicious lesion. Specific therapy was initiated and was based on administration of 500mg methylprednisolone boluses and 7.5mg/week metrotrexate which was later switched to mycophenolate mofetil due to poor clinical response. The patient received a diagnosis of dermatomyositis associated to antibodies against TIF1-y positivity and at discharge he was at almost complete clinical remission. Conclusions: Dermatomyosites are a group of idiopathic inflammatory diseases defined by muscle inflammation, proximal muscle asthenia, and characteristic skin rush; arthritis and systemic manifestations can sometimes coexist. Several subtypes are identified based on the type of antibodies linked with them, which affect the characteristics and severity of clinical manifestations. In our case, dermatomyositis tested positive for anti-TIF1-y antibodies. TIF1-y is a protein found in several biological processes and can act as a transcription promoter in specific tissues. This kind of DM, in fact, represents a paraneoplastic manifestation up to 85% of patients. Despite this, our patient, while having multiple risk factors for cancer, scored negative on the oncological screening. However, as in literature, these signs can anticipate the evidence of malignant lesion. For this reason, the patient was placed in a cautious follow-up regimen.

581. NAILFOLD VIDEOCAPILLAROSCOPY IN DIAGNOSIS AND FOLLOW-UP OF IDIOPATHIC INFLAMMATORY MYOPATHIES

Cozzi M.F.[1], Auria S.[2], Palmeri D.[2], Mezzanotte C.[1], Moroncini G.[3], Danieli M.G.[4]
[1]Postgraduate School of Internal Medicine, Università Politecnica delle Marche, Ancona, Italy; [2]Postgraduate School of Allergy and Clinical Immunology, Università Politecnica delle Marche, Ancona, Italy; [3]Clinica Medica, Dipartimento di Medicina Interna, AOU delle Marche, Università Politecnica delle Marche, Ancona, Italy; [4]SOS Immunologia delle Malattie Rare e dei Trapianti, AOU delle Marche, Università Politecnica delle Marche, Ancona, Italy

Objective: Nailfold videocapillaroscopy (NVC) is a simple, repeatable, pain-

less and non-invasive procedure to assess characteristic morphological abnormalities in the nailfold capillaries. NVC is frequently used to differentiate between primary and secondary Raynaud's phenomenon due to scleroderma spectrum diseases and employed in the identification of morphological anomalies in nailfold capillaries in rheumatic diseases. NVC has recently been shown to be a promising diagnostic asset in the diagnosis of dermatomyositis (DM) and marker for organ involvement and follow-up. In addition, low capillary density and abnormal shaped capillaries seem to be associated with active disease in DM, while immunosuppressive treatment appears to reduce NVC abnormalities. To date, there are few NVC studies in idiopathic inflammatory myopathies (IIM) patients. We analysed the capillaroscopic features in IIM patients, including dermatomyositis.
Methods: NVC was performed with VideoCap® 3.0 Optical probe videocapillaroscopy high resolution (with a magnification of 200-fold) in diagnostics for imaging of the microcirculation. We analysed the capillaroscopic pattern of patients with DM, diagnosed according to the Bohan and Peter's criteria for definite myositis and later reclassified to meet the new 2017 EULAR/ACR classification criteria for IIM.
Results: Twenty-five patients with DM (F/M: 16/9) were studied. All of them had Raynaud's phenomenon. Capillaroscopic parameters showing microvascular involvement, as abnormal shaped capillaries, dilations and isolated microhaemorrhages have been detected in all the patients with DM. Reduced capillary density (<7 capillaries/mm) was seen in 19 cases. Avascular areas and neoangiogenesis was documented in twelve patients with DM. In some patients, we found a nailfold capillaroscopy pattern featuring mixed microvascular markers of the scleroderma patterns, that is defined "scleroderma-like" pattern (see Fig.A).

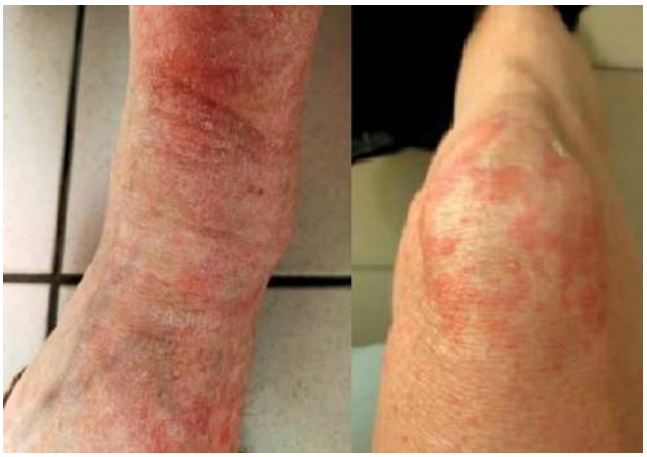


Capillaroscopic characteristics:
4 capillaries in 1 linear mm;
Presence of giant;
Abnormal shaped
capillaries;
None;
Scleroderma-like pattern
The correlation with disease duration, activity and severity was analysed, as the correlation with positivity to myositis specific antibodies and level of creatine kinase or acute phase proteins. We investigated if immunosuppressive treatment could impact on NVC abnormalities.
Conclusion: Nailfold video capillaroscopy confirms to have a promising role in the detection of early and late abnormalities of the microvascular involvement and as additional asset in diagnosis and follow-up in subjects with DM.

582. ADULT-ONSET STILL'S DISEASE (AOSD): A DIAGNOSIS OF EXCLUSION

Sasia G.[1], Bracco C.[2], Ruocco I.[1], Dupuis A.[1], Galliano R.[1], Posillico F.[1], Migliore E.[2], Giraudo A.V.[2], Silvestri A.[2], Fenoglio L.M.[2]
[1]School of Internal Medicine, University of Turin, Turin, Italy; [2]Division of Internal Medicine, Department of Medicine, "Santa Croce e Carle" Hospital, Cuneo, Italy

Background: Adult-Onset Still's disease (AOSD) is a rare autoinflammatory disease characterized by intermittent fever, arthralgia/arthritis, evanescent rash and other systemic presentations and it is typically diagnosed after exclusion of other aetiologies. We report a case of a vet with fever, sore throat and migrating arthralgias in which AOSD was diagnosed making a differential diagnosis ruling out uncommon and common conditions that can mimic the disease.
Case Report: A 63-years old male veterinary surgeon profession, with a medical history of coronary artery disease with normal follow-up, skin melanoma found one year ago, removed with sentinel lymph node and negative follow-up, presented to our Emergency Department for fever, sore throat and migrating arthralgias for the past two weeks. Initially was prescribed amoxicillin -clavulanic acid 1 g x3/day at home, subsequently appearance of salmon-coloured rash from the trunk to the limbs (Fig.1) for which antihistamine and steroids were started. According to him, he had been exposed to ticks in the past. Examination revealed a well built male with fever of 39.0°C. There was no lymphadenopathy or splenomegaly. His throat was mildly congested, however other systems were unremarkable. Hematological investigations showed a neutrophilic leucocytosis, increased erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and serum ferritin, mild liver dysfunction. Renal and coagulation profiles were normal. Blood and urine cultures revealed no evidence of bacterial, fungal or viral infection. Tests for infectious diseases and the autoimmunity panel were negative. Abdominal ultrasonography (US) and transthoracic echocardiogram (TTE) were normal. Empirical antibiotic therapy with clarithromycin (500 mg x2 /day) and steroid i.v. (20 mg/day) were started. Based on his clinical features and review of the laboratory evaluations, he was diagnosed to have AOSD using the Yamaguchi criteria. He was responsive to steroid therapy, but due to recurrence of symptoms on dose reduction, he started therapy with Tocilizumab 162 mg/0.9mL pre-filled syringe weekly and continued steroid therapy, reducing progressively the dosage of methylprednisolone by 4 mg per week until the next check-up.
Discussion: AOSD is a rare clinical entity with unknown etiology. Its clinical manifestations are broad-spectrum, so the diagnosis is often difficult depending on the clinical context and disease. It is an exclusion diagnosis.The Yamaguchi criteria are known as AOSD classification criteria. They demand the exclusion of other diseases, including infections (especially acute viral syndromes, bacterial infection and endocarditis), malignancy (especially lymphoproliferative disorders, paraneoplastic syndromes associated with solid cancer), systemic rheumatic diseases, vasculitis, such as polyarteritis nodosa, auto-inflammatory diseases, drug reactions and neutrophilic dermatoses. Infections represent the most complex issue in differential diagnoses because AOSD therapies can be highly deleterious. In this case it was important to exclude them, considering the occupational risk which is subjected the vet, who work in contact with potentially infected subjects and/or materials. Pathogenesis is quite uncertain. It is suspected to involve aberrant activation of the innate immune system leading to an overproduction of proinflammatory cytokines but the exact mechanism is still unknown [1]. Laboratory tests supporting the diagnosis of AOSD include anemia, leukocytosis, raised LDH, ESR, CRP. Hyperferritinemia is a characteristic feature and has been suggested as a serological marker to monitor response to treatment. Clinically disease course may be monophasic, polycyclic systemic, or chronic articular [2]. Our patient suffered from monophasic type. AOSD treatment choices depend on its clinical course. The pharmacological treatment includes glucocorticoids often in combination with methotrexate (MTX) and ciclosporine (CSA) for reduction of steroids. The interleukin 1 (IL-1) receptor antagonist Anakinra, the IL-1beta antibody Canakinumab or an IL-6 receptor blockage with Tocilizumab are used where there is no response to MTX or CSA. Steroid replacement with Tocilizumab may result in steroid dose reduction and improved long-term prognosis. In this case disease remission was successfully maintained by Tocilizumab.
Conclusions: AOSD is a diagnosis of exclusion. It should be considered a differential in patients with FUO. A careful documentation of symptoms, exclusion of other differentials and use of Yamaguchi criteria can help in diagnosis. A timely diagnosis and treatment along with proper counselling about regular follow-up and disease status can improve the outcome of disease as well as quality of life of the patient.
References
[1] Wang M.Y. et al. Pathogenesis, disease course, and prognosis of adult-onset Still's disease: an update and review. Chin Med J (Engl). 2019, 132:2856-64
[2] Giacomelli R. et al. A comprehensive review on adult onset Still's disease. J Autoimmun. 2018, 93:24-36



583. SPLENIC CALCIFICATIONS: AN UNUSUAL PRESENTATION OF SYSTEMIC LUPUS ERYTHEMATOSUS

Venturelli A.[1], Nardella J.[2], Renna E. [3], Trotta C.[3], De Padova A.[2], Calvani M.[3], Di Stefano R.[3]
[1]U.O.C. Medicina Interna, Ospedale San Paolo, Bari ; [2]Dipartimento di Medicina, U.O.C. C. Frugoni, Policlinico di Bari Paolo, Bari; [3]U.O.C. Medicina Interna, Ospedale San Paolo, Bari

Background: Systemic Lupus Erythematosus (SLE) is a chronic multisystem autoimmune disease that can affect a variety of organs and tissues including skin, musculoskeletal system, kidneys, brain, hematopoietic system, heart, and lungs. The clinical presentation of SLE is heterogeneous, ranging from mild symptoms to significant life-threatening organ impairment. Splenic involvement in SLE is not common and few cases of splenic calcifications have been reported in the literature.
Case Report: We report the case of a 61-year-old man admitted to the Internal Medicine Unit for persistent pain in the left hemithorax and left hypochondrium, fatigue, and fever resistant to antibiotic and anti-inflammatory therapy. The past medical history of the patient reported a recent diagnosis of hypertension and a six-month history of mild xerostomia and xerophthalmia. The vitals upon admission were unremarkable. Physical examination was positive only for the presence of the intense pain at the level of the left hemithorax and hypochondrium and local tenderness upon compression as well as referred pain upon compression of trigger points especially at the level of the neck, shoulder, and pelvic girdle, in absence of peripheral lymphadenopathy. Laboratory data showed an increase of D-dimer level (7158 ug/L normal range <500 ug/L) and erythrocyte sedimentation rate (101 mm/h normal range <10 mm/h) and mild anaemia (10.2 g/dL). Blood, urine, and Bronchoalveolar Lavage (BAL) cultures were negative. Serological tests for BK and other microorganisms (hepatitis B and C viruses, HIV, and Brucella) were negative. An abdominal ultrasound was performed showing an altered echogenicity of the spleen characterized by a non-homogenous ultrasound structure with multiple calcifications. These calcifications were uniformly distributed with splenic capsule sparing and collateral evidence of bilateral pleural effusion. The whole-body CT scan was also performed. It confirmed many sub centimetric and differently sized smooth calcific foci compatible with the radiologic presentation of granulomatous disease without enlarged lymph nodes. Calcification was not observed in the liver, whereas rare and undefined pulmonary micronodules were described. Flow cytometry of peripheral blood and BAL revealed a normal CD4/CD8 ratio. Autoantibody laboratory testing showed a significant positivity for ANA (1:1280, granular pattern), Anti-dsDNA, ANCA, Anti-ENA such as SS-A and B, complement C3 was reduced while C4 was normal. On the fourth day of hospitalization the patient presented with sudden and severe retrosternal pain and dyspnoea with evidence of a pericardial effusion on the echocardiogram. Given the clinical picture and the peculiar presentation of autoantibodies array and organ involvement, we concluded that the most likely diagnosis was Systemic Lupus Erythematosus with a possible association of Sj gren Overlap Syndrome. The treatment was initially based on intravenous methylprednisolone (1mg/kg/day), progressively reduced to orally administered prednisone 75 mg/day and hydroxychloroquine 200 mg twice a day with progressive clinical improvement.
Conclusions: This clinical case opened a complex scenario of differential diagnosis between lymphoproliferative/granulomatosus disorders and infectious/connective tissue diseases. Therefore, a rapid onset of targeted therapy was needed for sudden clinical deterioration. Although, anatomical and physiological changes in the spleen are reported in SLE, calcifications have rarely been described. However, the splenic calcifications have a unique pattern which could be considered distinctive for the diagnosis of SLE. The pattern described in patients with SLE is characterized by widely distributed small, rounded, calcific lesions scattered throughout the spleen. It is unclear why this calcification took place only in the spleen. Further studies will be needed to understand the pathogenetic mechanism underlying this histologic alteration and to establish the possible impact on the evolution of the disease and on the response to therapy.

584. A STRANGE CASE OF PARAVERTEBRAL MASS

Bresolin A., Cosi E., Diogo M., Trepin Kuete Kanah W., Pagin E., Randi M.L.
Department of Medicine-DIMED,University of Padua

Introduction: granulomatosis with polyangiiitis (GPA) is an uncommon systemic autoimmune disorder characterized by small to medium vessel vasculitis, inflammation of lower and upper respiratory tract, renal manifestation and peri- and extravascular granulomatosis [1]. GPA is associated with the presence of antineutrophil cytoplasmic authoantibodies (ANCAs) directed against proteinase 3 (anti-PR3) in approximately 90% of systemic forms and in 50% of localized forms [2]. General symptoms include fever, joint pain, asthenia, muscle weakness, hyphorexia unintentional weight loss. Inflammatory masses are an uncommon manifestation of GPA, mostly described in the upper respiratory tract, lungs or skin, whereas these lesions are rarely reported in other organs or districts.
Clinical case: in April 2023, a 65 years-old man was admitted to our emergency department in Padua in April 2023 for fever, fatigue, symmetrical joint pain, muscle weakness, pharyngodynia and weight loss of 9 kg in the last 3 months. The patient referred a medical history of dyslipidemia, prostatic hypertrophy, a recent right shoulder dislocation, previous kidney stones and right knee arthrosynovitis treated with arthrocentesis. Before the admission, he was taking only red yeast rice supplements. At admission to our department, we observed only mild fever while the vital signs and the physical examination were normal. In particular, we didn't observe any sign of joint inflammation. The laboratory tests revealed only increase inflammatory markers (C-reactive protein of 127 mg/L, erythrocyte sedimentation rate of 112 mm/h and rheumatoid factor of 51 kU/L) and moderate anemia (Hb 9 g/dl). The standard ECG showed a normal sinus rhythm and a chest ray didn't show any abnormality. We performed multiple microbiological tests, but all resulted negative (Salmonella typhi, Borrelia burgdoferi, Brucella, Treponema pallidum, Mycoplasma and Chlamydia pneumoniae, Coxiella, Plasmodium, HBV, HCV, and HIV serology and the tuberculosis Quantiferon test). During hospitalization, the patient had continuous feverish peaks so, to exclude endocarditis, we played heart ultrasound and eyes fundus examination that were normal. Also orthopantomography and joints x-ray didn't reveal any abnormalities. Suspencting polymyalgia, the patient was treated with nonsteroidal anti-inflammatory drugs (indomethacin) and empirical ceftriaxone, but the fever persisted. In the meantime, the patient presented oral aphthae, otitis media and a worsening renal function (the creatinine increased from 95 up to 236 umol/L with moderate proteinuria 1.56 gr/die) but an abdominal ultrasound was negative. We decided to perform a fluorodeoxyglucose PET RM that showed the presence of paravertebral hyperenhancing tissue from T2 to S1 suspiciuos for lymphoma/inflammatory process. The tissue biopsy was negative for lymphomatous pathology: it revealed only the presence of fibrous-inflammatory process; also immunophenotype on bone marrow biopsy was normal. Suspecting a granulomatous disorder, we dosed the PR3-ANCA that were considerably increased (2358 CU) but also the IgG4 were elevated (2.145 g/L). We diagnosed a granulomatosis with polyangitiis ANCA-PR3 positive with a systemic, kidney and ear, nose and throat (ENT) involvement and paravertebral masses; the patient was transferred to the rheumatology department and treated with high doses of glucocorticoids. The research of IgG4 on the paravertebral biopsy is still ongoing.
Conclusion: GPA is an uncommon systemic autoimmune disorder rarely associated with inflammatory masses. In particular paravertebral masses are the second most common site of inflammatory masses of GPA, but frequently asymptomatic, difficult to threat and poor responder to immunosuppressive treatment (less than 20% had a complete resolution, while the 36% resulted refractory to any treatment [3]). According to Padoan et al[3], since 2010 only 11 cases of GPA with paravertebral masses have been reported in literature. The presence of retroperitoneal masses should lead to IgG4 related

disease as differential diagnosis. The histopathological examination allows to differentiate the two disorders. An overlap syndrome between GPA and IgG4 related disease is also described in the literature [4]; it represents a peculiar disease phenotype with a good sensitive to rituximab treatment.

References

1.Holle JU, Laudien M, Gross WL. Clinical manifestations and treatment of Wegener's granulomatosis. Rheum Dis Clin North Am 2010;36:507–26.
2.Xavier Puéchal, Granulomatosis with polyangiitis (Wegener's) Joint Bone Spine. 2020 Dec;87(6):572-578. Epub 2020 Jun 17.
3.Roberto Padoan, Debora Campaniello, Mariele Gatto, Franco Schiavon, Andrea Doria. Current clinical and therapeutic approach to tumour-like mass lesions in granulomatosis with polyangiitis. Autoimmunity Reviews 21 (2022) 103018
4.Danlos F-X, Rossi GM, Blockmans D, Emmi G, Kronbichler A, Durupt S, et al. Antineutrophil cytoplasmic antibody-associated vasculitides and IgG4-related disease: a new overlap syndrome. Autoimmun Rev 2017;16:1036–43.

585. A CASE OF PARANEOPLASTIC DERMATOMYOSITIS

Posillico F., Bracco C., Sasia G., Dupuis A., Ruocco I., Galliano R., Ariaudo M., Gollè G., Canta R., Fenoglio L.
Internal Medicina, Cuneo, Italy

Case Description: In February 2023 a 67-years-old male presented at our ward complaining muscle weakness, joint pain and progressive asthenia. The patient had a past medical history of prostatic cancer, heart attack and MGUS with regular follow-up. On lab tests normocytic severe anaemia (Hb 7.9 g/dL) with iron deficiency was found. The faecal occult blood test was positive on three out of three samples. Before hospital admission he had already received a blood transfusion and an esophagogastroduodenoscopy with normal findings had been performed to investigate the anaemia. During the first days of hospitalization he developed a psoriatic dermatitis with an erythematous eruption on the periorbital skin and on the neck. He was immediately treated with high doses of corticosteroids with a mild clinical response, and myositis-specific autoantibodies were researched. Autoantibodies anti-TIF-1α and anti-Ro52 were found positive and the diagnostic hypothesis of dermatomyositis was then confirmed. Later, the patient also developed progressive dysphagia. To investigate the cause of anaemia a total body CT scan was performed; nodular formations in the lungs as well as an intestinal lesion suggestive of Treitz adenocarcinoma were found. A second esophagogastroduodenoscopy was then performed with multiple biopsies on the duodenal lesion, which confirmed the histological diagnosis of adenocarcinoma. In consideration of the new diagnosis of Treitz adenocarcinoma the patient was transferred to the surgical ward. He underwent surgery and a segmental resection of duodenum was performed. Unfortunately, the postoperative course was complicated by septic shock from *Enterococcus faecalis* and subsequent acute pulmonary oedema which led to the patient's death.

Clinical Hypothesis: Dermatomyositis are immune-mediated myopathies, characterized by the shared features of proximal skeletal muscle weakness, muscle inflammation and a variety of characteristic skin manifestations, such as Gottron papules, heliotrope eruption and psoriasiform changes in skin. A strong association between inflammatory dermatomyositis and cancer was recently found.

Diagnostic Pathways: Differential diagnosis should include other rheumatic diseases, such as systemic sclerosis, systemic lupus erythematosus, polymyalgia rheumatica and mixed connective tissue disease. The skin manifestations may have a key role in the differential diagnosis process, helping the clinical through the diagnostic pathway. In case of specific autoantibodies positivity, such as anti-TIF-1α+, a particular attention to any cancer-related symptoms is requested; in this case report the severe anaemia with positive faecal occult blood was a red flag that needed to be investigated.

Discussion and Learning Points: This clinical report shows clearly the main clinical manifestations and the main symptoms of dermatomyositis. The first symptom reported was weakness, followed by common skin findings, such as heliotrope eruption (an erythematous to violaceus eruption on the periorbital skin) and psoriasic dermatitis. It is also interesting that the diagnosis of carcinoma leads us to the conclusion of paraneoplastic dermatomyositis; it was found that the incidence of cancer for patients with dermatomyositis was increased five to seven-fold compared with the general population; in particular, an increased risk of ovarian, lung, breast, pancreatic and colorectal cancers was demonstrated. Moreover, the patient developed dysphagia, which is the most commonly reported gastrointestinal symptom in dermatomyositis and its prevalence resulted significantly higher in patients with cancer-associated dermatomyositis (1).It is important to underline that in anti-TIF-1α+ patients with dermatomyositis the incidence of cancer is 42-75% (2), with the development of a malignancy within 3 years of the diagnosis of dermatomyositis/myositis. In a recent review is explained that cancer risk factors should be evaluated in patients with dermatomyositis for risk stratification and, even if screening evidence is limited, a CT scanning could be useful in some cases, leading to earlier cancer diagnosis and improved patient outcomes. (3)

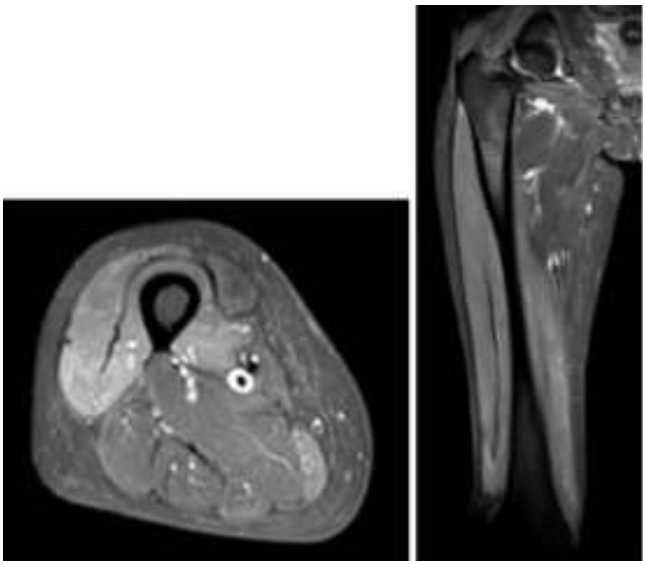
586. HYDROXYCHLOROQUINE-INDUCED MYOPATHY IN A SYSTEMIC LUPUS ERYTHEMATOSUS PATIENT: A CASE REPORT

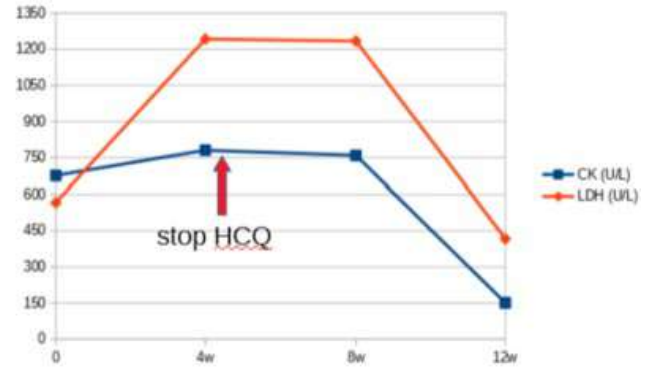
Piffero R., Masera G., Tacchelli C., Bellan M., Pedrazzoli R., Sola D., Pirisi M., Sainaghi PP.
AOU Maggiore della Carità Novara, SCDU Medicina Interna 1

Hydroxychloroquine (HCQ) is an antimalarial drug widely used in the treatment of connective tissue diseases (CTDs) due to its immunomodulatory effects, although the mechanism of action is not completely understood yet. It is generally thought that HCQ has a favorable safety profile, with rare but serious adverse reactions including retinal toxicity, cardiomyopathy and QT prolongation. A less known adverse effect of HCQ treatment, and of antimalarials in general, is a myopathy that in most cases occurs after a long-term treatment. It generally involves proximal muscle in the lower extremities with an insidious onset of proximal muscle weakness associated with elevation of serum muscle enzymes. Over time muscle atrophy can occur. Rarely, it may involve pharyngeal and diaphragmatic muscles causing dysphagia and dyspnea, respectively.

A new onset myopathy in the context of an autoimmune disease represents a diagnostic challenge since the differential diagnosis is broad, including drugs, alcohol, endocrinopathies or inflammatory myositis. It is essential to make the correct diagnosis, since the treatment depends on the etiology: in the case of iatrogenic myopathy the treatment consists in discontinuing the culprit drug, while an inflammatory myositis would require an immunosuppressive treatment.

Here we report a case of a new onset myopathy in a 52-year-old female patient affected by systemic erythematosus lupus (SLE), on treatment with azathioprine, prednisone, hydroxychloroquine and belimumab. During the follow-up, scheduled every three-four months, the patient developed an insidious onset of fatigue and proximal weakness, associated with persistent elevation of serum muscle enzymes. For diagnostic purpose we performed the following tests: (1) the research of myositis-specific and myositis-associated antibodies (a panel including anti-Jo1, PL-7, PL-12, EJ, SRP, MI-2, MDA, TIF-1y, SSA/Ro52, SAE1, SAE2, NXP-2; Scl-70, CENP-A, CENP-B, Pm-Scl100, Pm-Scl75, Ku, U1-RNP) resulted negative; (2) an MRI of right quadricep showed muscle atrophy and edema (figure 1); (3) we then performed a targeted biopsy of the right vastus lateralis, with histological findings of great variability of muscle fibers size, degenerative changes with cytoplasmic vacuoles and absence of inflammatory cell infiltrate; moreover, a histochemical assay demonstrated an increase of phosphatidic acid activity. These findings were consistent with the hypothesis of HCQ-induced myopathy. After discontinuation of HCQ therapy the patient showed a clinical improvement and serum muscle enzyme levels returned to normal values in about eight weeks (as shown in figure 2). In conclusion, HCQ-induced myopathy is a rare but probably underestimated complication of HCQ long term treatment, that we must consider in the differential diagnosis of CTDs patients with clinical onset of proximal muscle weakness with or without elevation of serum muscle enzymes. A biopsy is required for the diagnosis, since it may show specific alterations caused by HCQ treatment. The discontinuation of the drug usually determines a clinical and laboratory improvement, in a variable amount of time (weeks to months).





587. TAKAYASU'S ARTERITIS: THE DIFFERENTIAL DIAGNOSIS WITH A TOO TIGHT WEDDING RING

Cicconi F.[1], Antonini C.[1], Pellone M.[1], Luzi E.[1], Ferretti M.[1], Caltabiano L.[1], Andreoni R.[1], Alfonsi A.[1], Vertolli P.[2], Delle Monache F.[2]
[1]Università degli studi dell'Aquila; [2]UOC Medicina Interna, PO Teramo

Takayasu's arteritis is a rare chronic granulomatous inflammatory disease of unknown origin in which cell-mediated inflammation mainly involves the aorta and its main branches. Its incidence varies between 1.2 and 2.6 cases per million people each year and most cases are women between the ages of 20 and 40 years old.
Clinical manifestations include constitutional symptoms, elevated levels of inflammation markers, arterial stenosis, aneurysms resulting in claudication and absent pulses.
Here we report a case of a 28-year-old female patient who was admitted into the internal medicine complex unit of our hospital because of her left arm paresthesias and cyanosis of her 4th left finger.
Physical examination showed: left radial and ulnar wrists not present; preserved mobility and sensitivity of the entire left upper extremity; her body temperature was 37.2 C; her blood pressure was 135/80 mmHg on the right arm and 110/65 mmHg on the left one with a difference of more than 20-mmHg systolic pressure between two limbs.
The laboratory examination showed a modest increase in c-reactive protein, in normal range CBC, ANA, ENA, ANCA, rheumatoid factor, complement, immunoglobulins, hepatorenal function, coagulation balance, serum electrolytes, thyroid function. The culture tests performed (urine culture and blood cultures) were also negative.
Carotid artery ultrasound showed a severe involvement of left common carotid artery (sleeve stenosis), left subclavian-axillary-humeral arterial axis with preserved radial and ulnar arterial flow, without aneurysmal dilatation of any examined artery.

The results of CT ANGIO showed a circumferential parietal thickening of the aortic arch, max thickness of about 5 mm, homogeneous density, with postcontrastographic enhancement. Circumferential parietal thickening extended to the origin of the epiaortic vessels; in particular, the brachio-cephalic truncus arteriosus presented fair circumferential parietal thickening, with mild degree caliber reduction of the vessel. Significant segmental parietal thickening of the proximal and middle reached of the left common carotid artery, with a maximum thickness of about 3 mm and moderate-grade caliber reduction of the vessel lumen. We noticed a marked circumferential parietal thickening of the subclavian artery and left axillary artery, with pre-occlusive stenosis of the former and occlusive stenosis of the latter.
Treatment options include glucocorticoids, nonglucocorticoid immunosuppressive agents such as methotrexate, tumor necrosis factor inhibitors and azathioprine, and surgical management of vascular abnormalities.
We used aspirin and clopidogrel to antiplatelet therapy, low molecular weight heparin (LMWH) to anti-coagulation, high-dose glucocorticoids with gradual clinical and laboratory improvement. She was discharged with deltacortene 25 mg (one tablet twice a day) and methotrexate 15 mg/2 ml (one injection per week).
Two months later, blood chemistry tests were all normal and positron emission tomography showed weak and diffuse tracer fixation at the level of major vessels of the upper and lower extremities bilaterally. No additional areas of significant tracer hyperfixation were observed at the vascular level, particularly at the sites reported at the past angio-CT examination. The PET picture was not suggestive of definite vasculitis in active phase.
Today the patient is asymptomatic and there's no progression of her previously identified vascular lesions.
Will she have achieved remission?
It is still too early to tell; we are monitoring disease activity through inflammation markers and noninvasive imaging.
What is certain is that, for fear of seeing her cyanotic finger again, the patient no longer wears her wedding ring, despite now knowing that her previous symptomatology was due to another cause.

588. A RARE CAUSE OF PERIPHERAL PITTING EDEMA IN ELDERLY MAN

Giachi A.[1], Rossio R.[2], Semproni E.[1], Bichard C.[1], Peyvandi F.[1]
[1]Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico di Milano, Centro Emofilia e Trombosi Angelo Bianchi Bonomi, S.C. Medicina – Emostasi e Trombosi, Milan, Italy; Department of Pathophysiology and Transplantation, Università degli studi di Milano, Milan, Italy; [2]Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico di Milano, Centro Emofilia e Trombosi Angelo Bianchi Bonomi, S.C. Medicina – Emostasi e Trombosi, Milan, Italy

Background: Among the different causes of peripheral pitting edema in elderly patients, cardiovascular diseases and renal failure are the most frequent ones. However, many other conditions are characterized by a swelling of the extremities, and rheumatic diseases must be considered in the differential diagnosis.
Case report: On 24th of February 2023, a 79 years old male patient presented at the emergency department of our hospital because of deterioration of general conditions, limb pain with joint stiffness and walking problems. His previous medical history showed arterial hypertension, chronic vascular encephalopathy and previous prostate adenocarcinoma treated with radical prostatectomy and radiotherapy. He was recently hospitalized for TAVI and PM implant due respectively to severe aortic stenosis and a third-degree AV block.
On the examination, the patient appeared asthenic, with pitting legs edema and hard symmetric hands edema. The peripheral pulses were normal and symmetric, and there were no signs of redness or heat. During the observation in the ER, the patient referred the presence of numbness and pain in both arms, worsening during the evening. Blood analysis showed: creatinine 0.79 mg/dL (normal values (n.v.) 0.78-1.18), CPK 59 UI/L (n.v. 38-174), C-reactive protein 5.08 mg/dL (n.v. < 0.5), white blood count 10610/mmc (n.v.

4800-10800), hemoglobin 10.2 g/dL (n.v. 13.5 – 17.5). The ECG showed sinus rhythm, while the chest X-ray was substantially normal.
In order to investigate the hand edema, we performed a CT scan of the thorax at admission in our ward which excluded the presence of superior vena cava syndrome, as well as the presence of any thrombotic formation in the explored section. Due to the increase in inflammation markers, empiric antibiotic therapy with ceftriaxone was started, and a transesophageal echocardiogram was done to rule out the presence of endocarditis. Pain medications such as ibuprofen and paracetamol were administrated with partial resolution of the symptom. a transesophageal echocardiogram was done to rule out endocarditis.
Considering the probable rheumatic origin of the condition, we performed a joint echography and a wrist X-ray, which revealed the presence of severe osteoarthritis. A complete autoimmune panel, including antinuclear antibodies (ANA), exctractable nuclear antibodies (ENA), anti-cyclic citrullinated peptide (anti-CCP), rheumatoid factor (RF), anti-double stranded DNA (anti-dsDNA) and erythrosedimentation rate (ESR), was performed, resulting completely negative except for an ESR value of 92 mm/h (n.v. 0 – 19).
Due to the clinical characteristic of the presentation, namely a symmetric synovitis with muscle pain located in the upper limbs, the sex and age of the patient and the absence of RF at blood examination, we started an empiric therapy with prednisone 7.5 mg per day suspecting the presence of remitting seronegative symmetrical synovitis with pitting edema (RS3PE), with great improvement of the symptoms. It was later increased to 15 mg per day in order to reach complete remission and slowly tapered in the following months without new disease outbreaks.
For this reason, during the hospitalization we also performed a complete abdominal ultrasound and a dosage of the prostate specific antigen, in order to rule out the presence of malignancies. Both exams resulted negative.
Currently, the patient is following a therapeutic scheme of prednisone 2.5 mg two times a week with complete clinical and biochemical remission.
Conclusion. RS3PE is a rare rheumatic disease, distinct from rheumatic polymyalgia or rheumatoid arthritis, characterized by symmetrical synovitis of hands and ankles with pitting edema, negative RF and high values of inflammatory markers. The onset is typically in the elderly and occurs more in men than women, while the incidence rate is 0.09%. US and MRI demonstrate tenosynovitis of the extensor tendon of the forearms and hands, with lesser amounts of flexor tenosynovitis and synovitis of the metacarpophalangeal and proximal interphalangeal joints, resulting in the appearance defined as "boxing glove".
This disease is associated with hematologic malignancies, such as non-Hodgkin lymphoma or leukemia, as well as solid tumors involving, among others, the prostate, lung, bladder and gastrointestinal.

589. OSTEONECROSIS OF FEMORAL CONDYLES AND TIBIAL PLATEAUS ASSOCIATED WITH POSITIVE LUPUS ANTICOAGULANT IN A PATIENT WITH UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE: A CASE REPORT

Masera G., Piffero R., Tacchelli C., Bellan M., Pedrazzoli R., Sola D., Pirisi M., Sainaghi P.P.
SCDU Medicina Interna 1, Ospedale Maggiore della Carità di Novara, Università del Piemonte Orientale

Osteonecrosis, also called avascular necrosis of the bone, is a condition often found in patients suffering from immuno-rheumatological conditions, and in particular from connective tissue diseases such as systemic lupus erythematosus, often in association with chronic steroid therapy. Outside of this association, which finds numerous confirmations in scientific literature, it is still debated whether other conditions may play a role in the pathogenesis of bone necrosis. However, it should be considered that the pathogenic process underlying this condition has not yet been fully clarified.
With this case report we present the finding of osteonecrosis of the femorotibial joints bilaterally in a patient affected by undifferentiated connective tissue disease with lupus anticoagulant (LAC) positivity.
Therefore, we present the case of a 48-year-old woman sent by the general practitioner to the immuno-rheumatological clinic of the Maggiore University Hospital of Charity of Novara.
The patient had so far been in good health in the absence of relevant comorbidities, except for anaphylactic shock after taking acetylsalicylic acid. She had one full-term pregnancy and no miscarriages. She didn't take chronic medications.
She complained of the onset, several months before, of symmetrical arthralgias in the hands and wrists, more present at night and upon awakening in the morning, improving during the day even in the absence of frank swellings. She also reported morning stiffness lasting about an hour. However, there was also bilateral knee pain of a more nuanced nature for about three years which had never been investigated with specific tests.
He did not report recurrent oral or genital aphthosis, photosensitivity, rash on the face or other sites, xerostomia, xerophthalmia, dyspnea, chest pain or Raynaud phenomenon.
She had already performed a rheumatological evaluation two months earlier at another center in which they had interpreted the arthralgias as inflammatory and had started treatment with hydroxychloroquine and prednisone with a dosage of 25 mg/day and a tapering schedule. Initially she had witnessed a clear response in terms of joint symptoms both at the level of the upper limbs and at the level of the knees. However, with reduction of the prednisone dose, a recrudescence of these pain manifestations was observed.
Blood tests performed a few weeks earlier showed positivity of antinuclear antibodies (1/360 with homogeneous pattern) with negativity of ENA screening, positivity of LAC with negativity of anticardiolipin antibodies and beta-2-glycoprotein I. Blood counts, renal function and electrolytes, liver biochemistry were normal as well as rheumatoid factor and anti-cyclic peptide antibodies. Other blood tests performed a few months earlier, at the first manifestations of symptoms, already showed the positivity of ANA and LAC with negativity of ENA screening and other antiphospholipid antibodies.
He brought to view a report of a bilateral knee resonance, performed a few months earlier, which highlighted hyperintense pseudonodular areas with sharp edges and sclerotic edges with a lacunar appearance affecting both femoral condyles and the medial tibial plateau attributable to previous alteration of bone trophism (bone infarcts).
Therefore, we concluded that the patient was affected by undifferentiated connective tissue disease supported by positivity of antinuclear antibodies and LAC with associated peripheral arthralgias of inflammatory nature with concomitant finding of a previous bone infarction in the absence of chronic steroid therapy or other obvious triggering factors. Therapy with hydroxychloroquine and low doses of prednisone was confirmed and antiplatelet therapy was started in primary prophylaxis with ticlodipine (in consideration of the history of allergy to acetylsalicylic acid). For the bone picture, we were inclined to start an infusion therapy based on neridronic acid.
This case report has been presented to show the possible association between LAC positivity in the context of a connective tissue disease and ostenecrosis in a patient without another clear triggering factor such as previous steroid therapy or a history of trauma. Further studies are needed to clarify if the peculiar characteristics of LAC, which appears to be anticoagulant *in vitro* but in fact prothrombotic *in vivo*, may be another factor contributing to the process of bone necrosis.