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apresenta

REUMARIO

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A Few Words From The President

Selma Merenlender

Then, as a blink of an eye, it happened! It went by so fast, that all those three years it took to fulfill a dream, were like a nanosecond. And it came by in great style, in a most pleasant scenario, with most amiable people, awesome sunny days, and all the rest in perfect harmony.

We, Brazilians, had the opportunity to get to know Hopkins' professors, all of them so helpful and caring, from such a small distance, that we could almost take them as old school mates. That helped us a lot to feel confident in asking those "silly but bothering" questions, and everybody could participate. A Sunday morning, the claim of the beach outside, we could almost listen to the waves, but classrooms were full! We all woke up early with pleasure to endure a day of classes with great amusement. And there came dr. Bingham's breathtaking class on Cancer and Autoimmunity, and Diet and Gout, and all those precious tips on Sjogren's diet, a new way to think over an old problem, followed by Myosites and Scleroderma, and the morning was gone. Then in a sunny Sunday afternoon in Rio, right across the beach, the plenary was full again to listen to our local residents presenting their amazing case reports, and an intense exchange of information took place.

In this volume, we are pleased to share with you some of the information we could depict from the meeting. Hope you can enjoy it.

Editorial

E como não falar e relembrar todos os momentos do evento mais esperado pela SRRJ? Nosso Reuma Rio deste ano conseguiu superar todas as expectativas! O evento, que sempre foi reconhecido em toda Reumatologia pelo alto nível científico, conseguiu inovar mais uma vez e trouxe a preceptoria do grande e mundialmente reconhecido Hospital Johns Hopkins para o Rio de Janeiro. Com a excelência dos professores escolhidos (Dr. Clifton Bingham, Dr. Thomas Grader-Beck, Dra. Jemima Albaya, Dra. Eleni Tiniakou, Dra. Ana-Maria Orbai e Dra. Julie Paik) pudemos ter acesso à atualizações sobre diversos e relevantes temas, além de nos engajar sobre condutas e protocolos estabelecidos neste renomado centro.

Esta edição, composta por uma versão bilingue, conta com os resumos das aulas apresentadas e observações escritas pelos professores palestrantes da Johns Hopkins e também os casos clínicos apresentados pelos nossos serviços de residência médica da UFRJ, UERJ e IPPMG, este último representando a reumato pediatria. Então, para quem perdeu alguma aula ou não pode comparecer ao evento, aí está nosso "resumão" do Reumario!

Para concluir, ressaltamos que o congresso não só foi uma forma da SRRJ oferecer a todos uma oportunidade única de um certificado internacional de preceptoria sem sair do Rio de Janeiro, como foi um evento pioneiro e inspirador para todo o país!

Aproveitem!

English Version

And how not to talk and remember all moments of the most awaited event by SRRJ? Our Reumario this year has exceed all expectations! The event, which has always been recognized in all Rheumatology for the high scientific level, was able to innovate once again and brought the preceptory of the great and recognized Johns Hopkins Hospital to Rio de Janeiro. With the excellence of the chosen professors - Dr. Clifton Bingham, Dr. Thomas Grader-Beck, Dr. Jemima Albaya, Dr. Eleni Tiniakou, Dr. Ana-Maria Orbai and Dr. Julie Paik - we have access to updates on various and relevant issues. Moreover, we can get involved in conducts and protocols established in this renowned center.

This edition, which is composed of a bilingual version, brings the summaries of the lectures presented and observations written by the professor lecturers of Johns Hopkins lecturers as well as the clinical cases presented by our UFRJ, UERJ and IPPMG residency services, the latter representing pediatric rheumatoid arthritis. Therefore, for those who missed a class or can not attend the event, there is our " big summary" of the Reumario!

Thus, we emphasize that the congress was not only a way for the SRRJ to offer everyone a unique opportunity of an international certificate of preceptorship without leaving Rio de Janeiro. It was also a pioneering and inspiring event for all of us in Brazil.

Have fun!

Plenaria Session

1 - Rheumatoid Arthritis Update 2017: Something New or Déjà vu?
Clifton O. Bingham III MD

The last 20 years have witnessed a number of seminal developments in treating people living withRheumatoid Arthritis, with true sustained disease remission on therapy a reality for many patients. This has been largely made possible by the introduction of a treatment approach grounded in the early introduction of methotrexate and the rapid addition of other conventional synthetic DMARDS (csDMARDS), biological DMARDs (bDMARDS), and most recently targeted synthetic DMARDs (tsDMARDs, e.g. Jak kinase inhibitors). Guidelines from around the world have become harmonized in terms of general approaches grounded in treating patients to a measurable target of therapy, namely the lowest possible level of disease activity and true remission (absence of arthritis) if possible. These guidelines recommend ongoing monitoring and changes in therapy if patients are not at target, using combinations of csDMARDs, bDMARDs, and tsDMARDs. The remarkable response data with TNF inhibitors (TNFi's), first seen in clinical trials in the late 1990's, showed remarkable similarities as new TNFi's were introduced. These early studies were also important in showing that even in patients with longstanding disease considerable improvements in signs and symptoms as well as reduction in rates of radiographic progression were possible. As these agents were studied in patients with early RA, the responses were even more impressive. Results with biosimilars TNFi's have been identical in terms of efficacy, and without any newly recognized adverse events or immmunogenicity in those agents that have reached the approval standards of the US Food and Drug Administration (FDA). As new classes of agents that targeted other mechanisms of action (T-cell co-stimulation, B cells, IL-6, Jak kinases), the responses seen were virtually overlapping with the responses originally shown with TNF inhibitors. While TNFi's remain the "first line biological class for many practitioners, the data would suggest that all agents perform roughly the same, when tested in head-to- head studies with appropriate comparators.New agents on the near term horizon include additional IL-6 inhibitors (sarilumab and sirkumab) andadditional Jak kinase inhibitors (baractinib and others). These are showing "more of the same", and efficacy results have been consistent to the initial compound approved in their class. Even with more"selective" Jak inhibitors, most of the adverse event profiles have been similar, with the exception ofsome hematological parameters seen less with selective Jak 1 inhibitors. For Jak inhibitors increased viral infections (especially zoster) have been seen, highlighting the importance of appropriate immunizations before starting biologics. Another emerging therapy (mavarilumab) that targets GM-CSF has shown promising early results. In all clinical trials across compounds, most patients have some response (and up to 30-40% in some studies reach LDA/remission), but there were groups of patients who had little or no response, and many others with suboptimal responses. Fortunately in those patients who reach a sustained remission state, tapering biological therapies may be possible, with the best predictor of sustained remission being the depth of initial remission, and some studies suggest that ultrasound may also be useful in guiding tapering.

There is a considerable gap in understanding the predictors of response (but more importantly lack of response) to help inform which patients would be most appropriate for a particular drug. In the arena of biomarkers, there has been limited development in providing predictive biomarkers of response at the individual patient level. Some new biomarkers are now available that can provide additional diagnostic information for early RA or "seronegative" disease, including other citrullinated antigen antibodies (e.g. mutated vimentin), anti-carbamylase P antibodies, and 13-3- 3- eta, which is also increased in some other forms of inflammatory arthritis. In our labs, a group of antibodies that target the citrullinating enzymes themselves (peptidyl-arginine deiminases, PADs) have been recognized and provide prognostic information (early erosions), and a more recently described antibody cross reactiveto PAD3 and 4 which identify a group of patients with an increased risk of interstitial lung disease. Future developments in biomarkers will require systems that can simultaneously.

2 - Psoriatic arthritis – how close is it to RA?

Ana-Maria Orbai, MD MHS
Assistant Professor of Medicine
Director Psoriatic Arthritis Program
Johns Hopkins Arthritis Center

Psoriatic arthritis (PsA) and Rheumatoid arthritis (RA) are both forms of inflammatory arthritis. Obesity, smoking, genes, and alterations in the human microbiome are risk factors for both RA and PsA. People with psoriasis have the greatest risk of acquiringPsA which is as high as 30%. Nail psoriasis and certain types of skin psoriasis (scalp, inter-gluteal) further increase this risk. Pathophysiological models of disease led to development of new therapeutics however mechanisms of disease initiation and chronicity are not fully understood.

For both RA and PsA traditionally non-targeted disease modifying rheumatic drugs have been used, particularly methotrexate which in US is FDA approved for RA as well as for psoriasis. Sulfasalazine has limited efficacy in PsA and RA and no efficacy for psoriasis. Leflunomide has modest benefits for RA, PsA and psoriasis. Targeted therapies represent the biggest development in RA and PsA therapeutics and for the past 20 years they are increasingly diversified.

For rheumatoid arthritis potential initiating cytokines are IL6, IL17, IL21 while cytokines leading to chronicity and maintenance of inflammatory activity are IL6 and TNF alpha. This model is supported by the therapeutic success of targeted therapies. TNF and IL6 cytokine inhibitors in maintain disease control and decrease long term damage in RA. Many other classes of therapeutics are effective in RA including anti-B and anti-T cell therapies as well as JAK/STAT inhibition.

For PsA, mechanical stress and microdamage are seen as potential initiators of the inflammatory response in PsA. Enthesial sites are especially prone to microdamage due to mechanical stress. Healing processes in the presence of IL23 activate resident T cells towards the Th1 and Th17 differentiating pathways specific to the PsA immune response (1). This response ultimately leads to propagation of inflammatory changes from enthesial tissues to synovium. In addition, PsA heterogeneity requires that assessment and treatment take into consideration multiple areas involved including peripheral joints, entheses, spine, skin and nails (2). Distinct classes of targeted PsA therapeutics are TNF inhibitors, IL17 ihibitors, IL12/23 inhibitor, with an IL 23 inhibitor (approved for psoriasis in the US) entering phase III clinical trials in PsA.

A treat-to- target has shown efficacy in both RA and PsA. The treatment target is low disease activity or remission and validated scores exist to determine the patient's state at the clinic visit and adjust therapy. For RA we discussed CDAI, DAS28; and for PsA, we discussed DAPSA and MDA. Of importance is the fact that 28 joint counts underestimate articular involvement in PsA and 66/68 joint counts should be always performed – this is why preferred indices in PsA should not include limited 28 joint counts.

Cardiovascular risk is increased in both RA and PsA. Specifically for myocardial infarction the risk if 68% higher in a metaanalysis of acute coronary events in people with PsA compared to the general population (3).

3 - Gout: New trends in diagnosis and management

Jemima Albayda

Gout is the most common inflammatory arthritis worldwide, with increasing prevalence. Despite available treatments, it continues to be suboptimally managed. Newer tools for diagnosis and disease monitoring, as well as newer therapeutic agents will be highlighted.

The diagnosis of gout is easy to make in the presence of acute joint inflammation,
evidence of hyperuricemia, and detection of urate crystals in a symptomatic joint.
Imaging with radiographs serves as an adjunct to detect effects of gouty inflammation with damage to the joint. Erosions are well-displayed in established gout with overhanging edges and sclerotic margins. Newer modalities of ultrasonography and dual energy CT can show the morphologic burden of urate deposition as well as provide objective and quantitative measures for monitoring progression/effect of treatment.

With ultrasound, a double contour sign (an irregular hyperechoic enhancement over the surface of the hyaline cartilage, independent of the ultrasound beam) is the required finding. It indicates uric acid layering over the hyaline cartilage, which can at times be seen even in cases of asymptomatic hyperuricemia. Other findings of gout which can be picked up by ultrasound are the presence of tophi (snowstorm pattern), bone erosions, synovial hypertrophy and Doppler enhancement. Screening for tophi at the first MTPs and a double contour at the ankle may be a potential screening test for gout.

Dual energy CT is a newer modality which has become useful in the evaluation of gout. It uses two xray beams with two different energies which allow distinction between chemical entities. The acquired datasets are then reconstructed in the required planes and processed with dual energy software utilizing a two-material decomposition algorithm designed to separate MSU from calcium using soft tissue as the baseline. Urate deposition is then defined as the presence of color-coded urate at articular or periarticular sites, and seen very nicely on images. Urate deposits can be differentiated from calcium pyrophosphate deposits and can be helpful clinically. Studies done with DECT imaging for gout show that tophaceous deposits are seen not only in joints, but also in ligaments, bursae and tendons, with the deposits seen in the lower extremities more than upper extremities. The first MTPs are still the most common area to find urate deposition.

In terms of treatment, urate lowering agents including xanthine oxidase inhibitors, uricosuric agents and uricases. Xanthine oxidase inhibitors (XOI) include allopurinol as well as the newer agent Febuxostat. Allopurinol is effective therapywhich is rarely optimized to doses above 300mg to reach the target of <6ng/ml of uric acid. Although there are concerns for hypersensitivity syndromes, particularly in those with renal insufficiency, recommendations to prevent this complication are to start no higher than 100mg/day in these patients. The dose is then slowly uptitrated over the ensuing weeks with monitoring of urate levels as well as metabolic panel. Doses needed for allopurinol can go as high as 800mg daily. If patients fail allopurinol, therapy can be switched to an alternative XOI—febuxostat with doses of 40mg, 80 mg or 120mg daily. Febuxostat is metabolized by hepatic conjugation and potential hepatotoxicity can occur, but provides an alternative agent when renal issues are present.

Uricosuric agents have been garnering more attention due to genome wide association studies showing that multiple renal urate transporters contribute to the regulation of serum uric acid levels. Diminished renal clearance of uric acid promotes hyperuricemia in at least 90% of patients with gout. To detect if underexcretion of uric acid is present, urinary uric acid can be checked (low or normal uric acid excretion in the presence of high uric acid in the blood). Benzbromarone is an agent that has been taken off the market in the US due to hepatotoxicity, hence we have no experience with this agent. Probenecid is a URAT 1 inhibitor which is dosed anywhere from 250mg twice a day and can go as high as 2g per day

(2-4x a day). Due to inhibition of other renal transporters OAT1 and OAT3, more drug-drug interaction are seen with this agent. Lesinurad is another URAT 1 inhibitor which has recently come to the market and shows superiority for lowering down uric acid levels when combined with allopurinol, compared to allopurinol alone. It comes in a 200mg dose and must be combined with an XOI as there were more adverse events seen when used alone, particularly for increased serum creatinine. There is a concern for kidney stones with the use of uricosurics, hence adequate hydration is required when using these agents. Also, morning dosing may be preferable given that urinary pH is highest in the morning with less potential for stone formation.

For refractory gout, polyethylene glycolated uricases (pegloticase) can be used. It stimulates uric acid metabolism and converts this to allantoin which is water soluble and easily excreted through the urine. Although it is an 8mg IV dose given every 2 weeks, it is not a long-term drug due to the risks of immunogenicity. Formation of antibodies against the drug lead to inefficacy of the medication and higher risk of adverse events. It leads to rapid debulking of tophaceous gout, which can then be maintained with traditional agents following its discontinuation.

For treatment of the acute flares of gout/prophylaxis, standard agents such as colchicine, NSAIDS, and steroids are still the first line. The use of the particular agent is dictated by the severity of the manifestations, comorbidities and contraindications. In those where contraindications exist to the use of these agents, off-label use of IL-1 inhibitors can be considered, particularly Canakinumab (150mg subcutaneous once) which is a long acting IL-1 inhibitor and endorsed by the European Medicines Agency. A clinical trial has shown some benefit whencompared to 40mg of triamcinolone, but at more expense and with more side effects. Anakinra is a short acting Il-1 inhibitor, with no clinical trials to date, but anecdotal evidence by case reports of efficacy in gout. When used, 100mg SC for 3 days would be recommended to abort a gout attack. Rilonacept is another IL-1 inhibitor (soluble receptor preventing binding) which showed no superiority when compared with 150mg of indomethacin.

4 - Sjögren's Syndrome and SLE – autoantibodies and their clinical correlation

Thomas Grader-Beck

Autoantibodies in primary Sjogren's syndrome (pSS) and Systemic Lupus Erythematosus are importanttools to determine diagnosis, clinical phenotype and disease activity. In pSS, anti-Ro/La antibodies are present in75-80% of patients, about 20% of patients are seronegative. Anti-Ro/La antibodies appear in the serum of patientsup to 18 years before diagnosis and around the time of diagnosis antibody expression is nearly complete. Anti-Ro/La positivity is associated with younger age at diagnosis, higher degree of exocrine gland dysfunction, recurrentparotid gland swelling and extraglandular manifestations. The seronegative patient group demonstrates lower focus scores on minor salivary gland biopsy, lower prevalence of severe sicca symptoms and extraglandulardisease. Anti-La positivity has been removed as a classification criterium for pSS in the 2016ACR criteria. This isbased on the finding that the phenotype of isolated anti-La positive patients does not differ from seronegativepatients. Anti-centromere positive patients represent 1-13 % of the pSS population. These patients suffer frommore severe disease with higher focus score, worse exocrine gland function and are at risk of lymphomadevelopment. Patients with cryoglobulins (9-15%) are also at high risk for extraglandular disease, vasculitis,lymphoma and have increased mortality. The clinical phenotype of anti-CCP positive pSS patients (3-10%) iscomparable to the anti-CCP negative population with an increased prevalence of non-erosive arthritis. Anti-CCP positive patients may have a 2 fold increased risk to develop an inflammatory arthritis that can be classified as Rheumatoid arthritis according to ACR2010. Anti-mitochondrial antibodies (AMA) are found in 1.7-13% of patients.Up to 60 percent of AMA positive patients have liver enzyme abnormalities (ALP, AST, and ALT). Liver biopsytypically demonstrates florid duct lesions with granulomatous inflammation consistent with stage I findings ofprimary biliary cirrhosis. Histological changes appear to progress little over time. Autoantibodies blocking themuscarinic type 3 Acetylcholine receptor (AchR) pathway are frequently found in pSS patients and may play a

pathogenic role. However, the exact target of these antibodies and standardized methods for detection requirefurther studies. Antibodies targeting Salivary Protein 1, carboanhydrase 6 and parotid secretory protein aremarketed in the United States as a panel to detect early Sjogren's syndrome. However, the underlying scientificstudies deliver insufficient evidence and further research needs to be completed to determine the role of these antibodies in pSS.

Patients with SLE frequently display autoantibodies years before diagnosis, in particular anti-Ro/La and anti-phospholipid antibodies. Rising titers of anti-dsDNA antibodies are frequently found before renal and non-renal flares in SLE patients, typically 3-6 months in advance. However, it remains unclear, which degree of increase is most suitable to define a high risk for flare. This depends partly on the assay used to measure anti-dsDNA antibodies. Further studies need to be done to determine whether prophylactic therapy in patients with rising anti- dsDNA titers reduces flare rates without increasing medication exposure and adverse events. Rising titers of anti-C1q antibodies are strongly associated with a renal flare of proliferative glomerulonephritis, however current assays are not standardized and widespread use of this assay is not possible at this point. The combination of rising titers of anti-dsDNA, anti-C1q along with hypocomplementemia is the strongest predictor of impending renal flare.

5 - Role of Ultrasound in predicting RA prognosis

Jemima Albayda

In rheumatoid arthritis, ultrasound (US) has found a role in disease evaluation and management. Some of the findings that can be seen in RA include synovial hypertrophy (grey scale synovitis), synovitis with Doppler enhancement, tenosynovitis, erosions and effusion. It has been found that US is 10x better than clinical exam for detecting synovitis, 7x more sensitivie at detecting small erosions than xrays, and is comparable for subclinical inflammation with MRI for US accessible joints. It provides objective quantification of inflammation and improves the accuracy of joint aspirations and injections. It is also reflective of actual pathology in that synovial thickness and Doppler signal correlated with synovial density and blood vessel density in knee synovial biopsies of early RA. Power Doppler was also seen to correlate to TNF-, IL-1, IL-6 and VEGF gene expression.

In RA, US can help us determine prognosis in the early undifferentiated arthritis window, during treatment, and during remission. In early arthritis <12 weeks, some patients can resolve spontaneously or progress to erosive disease. Studies have shown that patients with + CCP or RF in the presence of hand pain < 12 weeks and morning stiffness, progression is almost 100%. In the seronegative group however, the addition of ultrasound findings (grey scale synovitis =3, power Doppler +, and erosion), the probability can now go up to 50-94% from only 2-30% when only clinical finidngs and CRP are known. Similarly, in 100 patients with nonspecific musculoskeletal complaints and a positive CCP, about half were found to develop RA in a median of 8 months. Tenderness of the hand or foot joints, early morning stiffness >30 minutes and a positive power dopper synovial signal were predictors for high risk of progression to established arthritis. Ultimately, in early arthritis, detecting grey scale synovitis >/=2, power Doppler, or erosions are prognostic markers for development of RA.

During treatment, US can be used to assess clinical activity and modestly correlates with clinical scores such as DAS28 (SJC more than TJC). It can be helpful, particularly in cases with concomitant fibromyalgia to assess true inflammatory activity. Factors associated with structural damage include presence of power Doppler signal, presence of bone erosions at baseline and presence of extensor carpi ulnaris tenosynovitis. However, despite ultrasound being more sensitive than clinical exams for detecting disease activity, recent studies have shown that targeting remission by clinical criteria or ultrasound criteria

had no difference. No improved outcomes were seen with targeting imaging remission and may lead to overtreatment and inefficient use of resources.

When patients are in remission, the presence of subclinical power Doppler synovitis is an independent risk factor for relapse in those in clinical remission. In those whose clinical activity and Doppler score are well-controlled, the presence of bone erosion may be predictive of relapse.

In conclusion, US in another tool that aids in our assessment and treatment of patients with RA. It provides us with objective evidence of inflammation which correlates with synovial inflammation. The presence of power Doppler signal seems to be the most predictive of ongoing activity and potential for structural damage. However, US does not always correlate with clinical scores and its role in treat to target strategy is as of yet unclear.

6 - Idiopathic Inflammatory Myopathies: Diagnosis and Treatment

Eleni Tiniakou, MD

Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of autoimmune syndromes characterized by (i) chronic muscle weakness and (ii) skeletal muscle inflammation of unknown cause.

Historically, the first diagnostic criteria were developed by Peter and Bohan in 1975 and are in use until this day. Nevertheless, these criteria evoke only two subtypes, polymyositis (PM) and dermatomyositis (DM), and do not take into consideration neither myositis specific autoantibodies (MSA) nor specific muscle histology. The European Neuromuscular Center International Workshop (ENMC) has developed classification criteria based on the muscle histopathology with six definite categories of IIM. Concurrently, a plethora of MSAs have been discovered that can lead to subgrouping of the myopathies based on similar clinical phenotype.

The rudimentary differential of myopathies include IIMs, inherited diseases (e.g. Muscular dystrophies, enzyme deficiencies, mitochondrial diseases), motor neuropathies (e.g. spinal muscular atrophy, myasthenia gravis), active endocrinopathy (thyroid, hyperparathyroid, Cushing's), drugs and toxins or infectious etiologies. History, physical examination and laboratory work up at the initial visit ought be oriented into ruling out myositis mimics. Further evaluation with EMG/NCS, muscle MRI and muscle biopsy depends on the clinical scenario. Of note, negative ANA does not preclude the presence of IIM, as it is common for the MSA to have a cytoplasmic pattern. MRI can be useful to support the diagnosis, increase the yield of the muscle biopsy and even monitor response to treatment. STIR sequence with fat suppression can highlight muscle edema, indicative of inflammation. Muscle biopsy is an invasive procedure and we usually reserve it for cases with atypical presentation, pure polymyositis, high clinical suspicion but negative MSA panel, to differentiate from an inherited condition, elucidate isolated CPK elevations or for recalcitrant IIM. The final reading of the muscle biopsy ought to be based on the combination of specific histopathologic and/or pathognomonic findings, as inflammation on its own is not diagnostic.

Myositis-specific autoantibodies can be an important tool to support diagnosis of myositis and can be associated with distinct clinical associations. For example, MDA-5 is associated commonly with amyopathic DM, rapidly progressive interstitial lung disease and unique cutaneous manifestations. The utility of MSA is not limited to diagnosis, but an also lead to targeted screening for potential other organ involvement and specific treatment.

Inclusion body myositis (IBM) is a common PM mimicker and early diagnosis is important, as immunosuppression can lead to earlier difficulty in ambulation. Characteristic findings include finger flexor and knee extensor weakness. Vacuoles can be found on muscle biopsy, but they are not specific for the disease, and ultimately is a clinical diagnosis. Red flags for the disease include PM resistant to treatment, dysphagia, facial involvement, foot drop, falls, and hand weakness. All newly diagnosed myositis patients should undergo malignancy screening. There are no specific guidelines, but it is common practice to order a full body CT scan and pelvic ultrasound, on top of age appropriate screening.

As pathogenetic mechanisms are poorly understood in IIM, immunosuppression treatment is not targeted. As a general rule, we begin with steroids as bridging treatment giving time for steroid sparing agents to manifest their full effect. First line treatment would include azathioprine, methotrexate, mycophenolate, followed by IVIG, Rituximab, Tacrolimus and for severe cases cyclophosphamide.

7 - Neurological manifestations in lupus and other autoimmune diseases

Thomas Grader-Beck

ACR case definitions for neuropsychiatric SLE (NP-SLE) published in 1999 include 19 manifestations. A subsequent validation study in 2001 recommended to remove headache and anxiety disorder, and to adjust any cognitive dysfunction to moderate/severe, adjust mood disorder to severe depression and require EMG/nerve conduction studies to confirm peripheral neuropathy, in order to better delineate specific NP-SLE manifestations. The 2012 SLICC criteria for Np-SLE include seizures, myelitis, mononeuritis single/multiplex, myelitis, peripheral or cranial neuropathy and acute confusional state. Seizure disorder and stroke represent about 50-60% of all NP-SLE manifestations. Patients with lupus anticoagulant are about 2.5 fold higher risk for intracranial thrombosis. Anti-ribosomal P antibodies confer a 3.9 fold higher risk of psychosis, and high SLEDAI is also associated with NP-SLE activity. Seizures occur most commonly in younger patients (mean age 22 years) and may be the presenting symptom. Generalized and complex partial seizures are most common. Higher SLEDAI scores and active glomerulonephritis are often associated. Most patients experience only one seizure episode, the recurrence rate is 11.7%. In those patients, temporal lobe intericteric abnormal EEG findings are common. Therapy includes phenobarbital, carbamazepine and phenytoin. An attempt to withdraw treatment can be tried after 1 year of therapy without recurrence. In refractory cases iv methylprednisolone and cyclophosphamide can be added. Posterior reversible encephalopathy syndrome (PRES) must be ruled out. PRES occurs in the setting of hypertension, active renal disease, high disease activity and recent initiation of immunosuppressive medications. MRI can be helpful for differentiation, MRI findings typically show bilateral parieto-occipital involvement and vasogenic edema. Therapy of PRES is largely symptomatic. SLE patients are at higher risk for stroke, from 2 fold for ischemic stroke to 4 fold for subarachnoidal hemorrhage. Young patients below 30 years are at up to 30 fold increased risk and stroke occurs more frequently in the first 5 years of disease. The recurrence rate is 35% and mortality is 15-25%. Identification and correction of traditional modifiable risk factors for stroke at diagnosis is critical. Therapy of ischemic stroke in SLE is similar to the general population. Patients with persistent anti-phospholipid antibodies after ischemic stroke are candidates for anticoagulation. Acute myelopathy in SLE is infrequent (1-3%), but early recognition is essential for timely initiation of therapy that limits long-term damage. Acute myelopathy may present with a non-specific prodrome consisting of fever, nausea, and bladder pain. Within hours, muscle weakness, sensory and autonomic deficits can develop that may become irreversible. Rapid recognition and institution of iv steroids and cyclophosphamide is critical. Plasmapheresis, IVIG and Rituximab also play a role in therapy. Psychosis typically presents in younger SLE patients and responds well to immunosuppressive therapy. The recurrence rate is about 1 in 3 patients. Small fiber neuropathy is underdiagnosed in systemic autoimmune diseases, including Sjogren's syndrome and Systemic Lupus Erythematosus. The non-length dependent character of symptoms of patchy pain and allodynia may lead to a presumptive diagnosis of fibromyalgia. .On exam, patients have decreased pinprick sensation and temperature alteration with preservation of light touch, proprioception, vibration sense and motor strength. EMG/nerve conduction studies are normal. A punch biopsy of the skin shows decreased small nerve fiber density. Therapy includes gabapentin, pregabalin, duloxetine and tricyclic antidepressants. IVIG can be beneficial in progressive cases, highlighting the potential autoimmune nature of the disease.

8 - Systemic Sclerosis: How to stop a critical evolution?

Julie J. Paik, MD MHS

Systemic sclerosis is a rare autoimmune disease that is driven by autoimmunity, fibrosis, and vasculopathy. The purpose of this talk is to focus on the skin manifestation of diffuse cutaneous systemic sclerosis, in particular its assessment, management, and treatment.

The natural history of the skin disease in systemic sclerosis is as follows: the skin disease is typically in the edematous phase with rapid progression in the first 12-18 months. After this period, natural remodeling of the skin disease results in gradual softening of the skin disease over a period of 3-5 years. Based on the extent of skin involvement, the classification of diffuse vs. limited cutaneous disease is determined by the rheumatologist. For skin tightening that is contiguous and extends above the elbows or knees, we classify these patients as diffuse cutaneous systemic sclerosis. Those patients who have skin tightening below the elbows and knees +/- face are classified as limited cutaneous systemic sclerosis.

The main difference between those with limited cutaneous systemic sclerosis and diffuse cutaneous systemic sclerosis as noted above is the extent of skin tightness. Other differences include the fact that in limited cutaneous systemic sclerosis, Raynaud's phenomenon typically occur years before the diagnosis and other disease manifestations such as gastrointestinal involvement may occur over many years, making a diagnosis even harder to make. For example, if a patient has only mild puffy fingers with Raynaud's phenomenon but no other symptoms, careful evaluation and follow-up will be needed to make sure the patient is followed for other disease manifestations such as GI dysmotility and PAH.

Autoantibodies in systemic sclerosis can also guide the clinician in determining the clinical phenotype of the patient. In those patients who are Scl-70 positive, patients typically have prominent interstitial lung disease and have diffuse scleroderma. However, this is not absolute and Scl-70 positive patients can have the limited cutaneous subtype. Patients who are positive RNA Polymerase III antibodies have the typical phenotype of rapidly progressive skin disease, high risk for renal crisis, and close temporal association with a malignancy. Centromere antibodies are typically associated with limited scleroderma and have a higher risk of PAH usually 7-10 years after the onset of disease. Therefore, it is routine for our patients to get echocardiograms and PFTs yearly. In those who are at high risk of lung fibrosis, such as in the Scl-70 positive group, PFTs are followed typically every 4-6 months.

In terms of the treatment of the skin disease in diffuse cutaneous systemic sclerosis- Mycophenolate mofetil, MMF, is the typical first line agent in the treatment of skin disease. We typically up titrate to a minimum efficacious dose of at least 2000mg/daily, and as tolerated, gradually up titrate to a maximum of 3000mg/daily. If diarrhea is a limiting side effect, we switch to myfortic. Liquid MMF is also used in certain patients who cannot swallow the drug. IVIG is used as adjunctive treatment for refractory cases and in a retrospective case control study using historical controls, patients who received IVIG had a statistically significant improvement in the modified Rodnan skin score. Cyclophosphamide is also

considered especially if patients have concomitant lung disease and are not an MMF responder. Hematopoietic stem cell transplant has been used in a randomized controlled trial in 2014, and showed there is an improvement in the skin score that was statistically significant. However, there was an increased risk of death in the 1 st year after transplant when compared to the Cytoxan group. Stem cell transplant should be considered in patients who do not respond to first line treatments and do not have other vascular disease manifestations such as severe PAH or renal crisis. Clinical trials should also be considered when first line agents fail. Tocilizumab has been used in Phase II trials, and a Phase Trial is underway. Multiple other agents are being investigated, and referral to a tertiary Scleroderma Center should be considered in these cases.

9 - Health Information Technology Up To Date

Thomas Grader-Beck

The use of modern electronic health record (EHR) systems promises the reduction of medical errors, improvement of communication among clinicians as well as decreasing health care costs, leading to higher quality in patient care and health care overall. The Health Information Technology for Economic and Clinical Health (HITECH) act of 2009 in the United States provided an unprecedented stimulus of almost $30 billion dollars to stimulate pay for performance use of EHR, promote interoperability by establishing state health information exchanges and for standardization and certification of health information systems. A model of meaningful use was established that provided incentives for the correct use of EHR systems according to three successive stages from (i) data capture and sharing to (ii) implementing advanced clinical processes and (iii) demonstration of improved outcomes. Penalties were established for failure to comply. The main difficulties to make modern EHR systems successful are problems with interoperability between systems, which includes the lack of unifying data standards and the lack of a national patient identifier. Furthermore, patient privacy legislation varies from state to state and may prohibit exchange of certain data content. On an individual level (hospital/outpatient) the main difficulties are to implement a new EHR system without disrupting the clinical workflow for providers and clinics, and to teach the necessary skills to master EHR technology. Johns Hopkins implemented the Epic system in 2013 and has since then undergone updates from the Epic 2012 to Epic 2014 version. In September 2017 Epic2017 will be implemented, which will put Johns Hopkins at the forefront of EHR technology in the United States. Epic is the most commonly used EHR system in the United States, both inpatient and outpatient, and over 50 percent of US patients have records in the Epic EHR. At Johns Hopkins, records of over 5 million patients are stored across 93 clinical specialties and over 700 clinical departments. Johns Hopkins Rheumatology is leveraging Epic to improve capture of discrete data elements on all patients seen in the specialty centers of the division. These elements include for example disease classification criteria, disease activity measures and patient reported outcomes, that can be collected in between visits through a patient portal and on tablets at patient visit. The resulting data is stored directly in Epic and can then be reviewed and analyzed. Queries can be implemented that investigate specific patient populations on the fly or using recurrent reports. The resulting knowledge is then reintroduced into the system to help improve patient care and outcomes. Additionally, this knowledge can be utilized as a foundation for research and education. In order to facilitate disease specific content development within the Epic EHR system, the division has appointed Dr. Thomas Grader-Beck. He is a certified Epic physician builder with broad knowledge of the Epic system and expertise in Health Informatics. By using national data standards to code patient clinical data, the division is laying the foundation to maximize efficiency in exchanging data with external patient cohorts. The long-term goal of the division is to combine clinical data along with other data sources (genetics, imaging, pathology, functional biospecimen data) in order to better understand patient phenotypes.

Hot Topics in Rheumatic Disease

SCLERODERMA AND MYOSITIS

Caso 1 (Português)
Apresentação: Dr. Eleni Tiniakou
Moderadora: Dr. Carla Dionello

Foi apresentado um caso de uma paciente que tinha o diagnóstico prévio de polimiosite com acompanhamento irregular. A paciente foi encaminhada para o centro de tratamento JHM em quadro de evolução aguda de insuficiência respiratória, que sofreu rápida regressão após as medidas realizadas em terapia intensiva. Na discussão com os colegas foi questionado a vigência de processo infeccioso e os diagnósticos diferenciais do quadro respiratório, no que se relacionava também a manifestações de pele e outros sintomas.

A Dra Tiniakou mostrou o painel de anticorpos, eletroneuromiografia e padrão de biópsia muscular. Tais exames mostraram alterações que poderiam estar relacionadas à miopatia mitocondrial ou metabólica, além das alterações de miopatia inflamatória.

Caso 1 (Inglês)
Presented by Dr. Eleni Tiniakou
Debated by: Dr. Carla Dionello

It was presented a case of a female patient who was previously diagnosed as polimiositis and was irregularly accompanied by a rheumatologist. The patient was taken to JHM center suffering from acute respiratory failure, which was rapidly reversed by the intensive care. In the discussion with other rheumatologists it was questioned about infection and other possible causes of respiratory failure, since the patient had several other systemic manifestations.

Dr Eleni showed all the exams, the antibodies panel, the electroneuromyography findings and the muscle biopsy pattern. Such exams demonstrated features that assembled mithocondrial or metabolic myopathy, besides inflammatory manifestations.

Caso 2 (Português)
Apresentação: Dr. Julie Paik
Moderadora: Dr. Carla Dionello

Foi apresentado um caso de paciente com esclerose sistêmica grave, estável, que iniciou com sintomas miopáticos como astenia e fraqueza intensas, associada a manifestações cardíacas.

Durante a discussão, foram abordados temas relacionados à miopatia grave em si, no contexto da esclerose sistêmica, em que a principal alteração fisiopatológica parece ser de origem vascular. Sobre o tratamento foi abordado as condutas usuais em casos graves como esse. Foi discutido o emprego de imunoglobulina intravenosa, e também do uso de biológicos como tocilizumabe e rituximabe.

English Version – Case 2
Presented by Dr. Julie Paik
Debated by: Dr. Carla Dionello

The presented case was of a female patient with systemic sclerosis and progressive muscle weakness. There was also several cardiac manifestations. During the discussion with the public it was discussed the muscle symptoms and the relation with the SE. The main pathophysiological aspect was a possible vascular origin of the myopathy. Regarding treatment it was discussed about the options to such severe case, like IV immunoglobulin, tocilizumab and rituximab.

Cancer Associated Rheumatic disorders and Spondylo-arthritis and Infection

Versão em Português
Apresentação: Dr. Clifton Bingham
Moderador: Dr. Bruno Schau

No domingo pela manhã o Dr. Bingham nos apresentou um interessantíssimo caso clínico ilustrando os recentemente relatados paraefeitos subsequentes à imunoterapia oncológica que vem ganhando corpo junto aos pacientes acometidos pelos mais diversos cânceres. A tendência é que o reumatologista se depare cada vez mais com esse novo perfil de paciente, com manifestações inflamatórias e marcadores imunológicos distintos daqueles que nos habitamos no nosso dia a dia. Iremos nos confrontar com a delicada decisão de propor tratamentos imunossupressores para pessoas em tratamento de doenças oncológicas e aprender este equilíbrio entre inflamação e oncologia será primordial para o sucesso do nosso paciente.

Toxicidade associada à imunoterapia com inibidor de ponto de verificação

Os agentes imunológicos de inibição do ponto de controle específicos (checkpoint inhibitors) para o antígeno citotóxico 4 (CTLA-4) associado aos linfócitos T citotóxicos e para os receptores programados de morte celular 1 (PD-1) estão tendo um impacto dramático no tratamento de pacientes com melanoma avançado e estão sendo investigados rapidamente como terapia para outras doenças malignas.

O tratamento está associado a eventos adversos relacionados à imunidade (irAEs) que tipicamente são transitórios, mas ocasionalmente podem ser graves ou fatais. As irAEs mais comuns e importantes são dermatológicas, diarreia / colite, hepatotoxicidade e endocrinopatias, embora outros sistemas também possam ser afetados. Foi observada uma ampla gama de toxicidades reumatológicas com a imunoterapia de inibição do ponto de controle. Estes incluem artrite inflamatória, disfunção da glândula salivar (síndrome sicca) e miosite inflamatória, entre outros. A incidência desses efeitos colaterais não foi claramente determinada. Em geral, o tratamento de irAEs moderadas ou graves requer interrupção do inibidor do ponto de controle e o uso de imunossupressão de corticosteróides. Se os corticosteróides não forem eficazes no tratamento da diarréia relacionada à imunoterapia, após aproximadamente três dias, infliximab (5 mg / kg) pode ser considerado. Infliximab não deve ser administrado a pacientes com hepatite imunomediada.

Cancer Associated Rheumatic Disorders and Spondyloarthritis and Infection

English Version
Presented by Dr. Clifton Bingham
Debated by Dr. Bruno Schau
Dr. Clifton Bingham Clinical Case

On Sunday morning Dr. Bingham presented us an interesting clinical case illustrating the recently reported effects of oncology immunotherapy that has been gaining ground among patients suffering from a variety of cancers. The tendency is that the rheumatologists will increasingly come across this new patient profile, with inflammatory manifestations and immunological markers distinct from those we are used to in our day to day practice. We will be confronted with the delicate decision to propose immunosuppressive treatments for people receiving oncologic treatment and undestanding this balance between inflammation and cancer will be paramount for our patient's success.

Toxicities Associated With Check Point Inhibitor Imunotherapy

Immunologic checkpoint inhibition agents targeting cytotoxic T-lymphocyte- associated antigen 4 (CTLA-4) and programmed cell death-1 (PD-1) receptor are having a dramatic impact on the care of patients with advanced melanoma and are rapidly being explored as therapy for other malignancies.

Treatment is associated with immune-related adverse events (irAEs) that typically are transient, but occasionally can be severe or fatal. The most common and important irAEs are dermatologic, diarrhea/ colitis, hepatotoxicity, and endocrinopathies, although other sites can also be affected.

A wide range of rheumatologic toxicities has been observed with checkpoint inhibition immunotherapy. These include inflammatory arthritis, salivary gland dysfunction (sicca syndrome), and inflammatory myositis, among others. The incidence of these side effects has not been clearly determined.

In general, treatment of moderate or severe irAEs requires interruption of the checkpoint inhibitor and the use of corticosteroid immunosuppression. If corticosteroids are not effective in treating immunotherapy-related diarrhea after approximately three days, infliximab (5 mg/kg) may be considered. Infliximab should not be given to patients with immune-mediated hepatitis.

Dr. Jemima Albayda presented a patient with tophaceous gout, hypertension and alcohol liver disease and discussed the dietary impact on uric acid levels. The focus was on what's to avoid and what you should recommend for the gout patient diet.

Dr. Thomas Grader-Beck presented a Sjögren's patient characterized by sicca symptoms, fatigue and brain fog. The debate was on the dietary recommendations for the symptoms of dryness and other possible dietary modifications to improve fatigue and cognitive disorder.

Dietary Impact in Gout and Autoimmunity

Apresentação: Dr. Jemima Albayda
Moderadora: Dr. Adriana Danowski

Na primeira apresentação, Dra. Jemima Albayda discutiu o impacto da dieta nos níveis séricos de ácido úrico de um paciente com gota tofácea, hipertensão arterial e doença alcoólica hepática. O foco foi tanto no que evitar quanto no que recomendar em termos de dieta para os pacientes com gota.

Dr. Thomas Grader-Beck apresentou um paciente com Síndrome de Sjogren com xeroftalmia, xerostomia, fadiga e distúrbio cognitivo. O debate foi relacionado às recomendações dietéticas para a síndrome seca e outras possíveis modificações dietéticas para melhora da fadiga e distúrbio cognitivo.

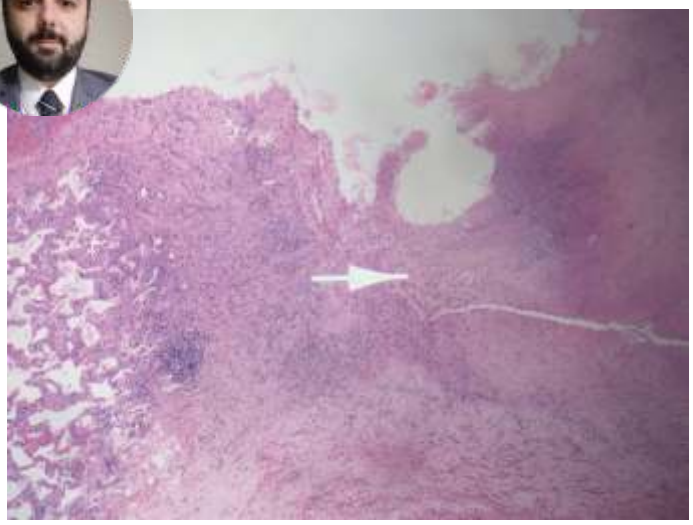
Clinical Cases Discussion

Caso 1

Presented by: Igor Pereira Garcia
From: Hospital Universitário Clementino Fraga Filho – Universidade Federal do Rio de Janeiro

Versão em Português

Mulher, de 45 anos, com artrite reumatoide e tosse seca progressiva



Esse caso descreve a história de uma mulher de 45 anos, com diagnóstico de Artrite Reumatoide há 3 anos e história de tose seca progressiva há 12 meses, associada à dispneia. Estava controlada e sem atividade de doença com o uso de hidroxicloroquina 400 mg diários e de metotrexato, na dose de 15 mg/ semana. Comparece à consulta regular do serviço de reumatologia com queixa de piora da dispneia, associada à febre baixa. Como a paciente vinha de área endêmica, foi iniciado terapia anti-tuberculose e retirado o metotrexato. Após 3 meses dessa intervenção, evoluiu com piora da dispneia. Tomografia de tórax demonstrou opacidades nodulares esparsas, com predomínio em periferia, de dimensões variadas e algumas cavitadas. O diagnóstico diferencial nesse caso incluiu nódulos reumatoides, pneumopatia intersticial, vasculites, infecção ou neoplasias. Testes sorológicos para vasculite foram negativos; histopatológicos e culturas foram negativas para bactéria, fungo e BAAR. A paciente evoluiu com piora do quadro pulmonar, evoluindo para insuficiência respiratória e óbito em dois dias por choque séptico.

Discussão: Pneumopatia intersticial tem sido progressivamente observada como uma complicação de artrite reumatoide (AR), contribuindo significativamente com a sua morbidade e mortalidade. O desafio do diagnóstico inclui a limitação à deambulação, o que pode retardar os sintomas de dispneia. Adicionalmente, infecções, toxicidade das medicações e toxinas ambientais podem, também, mimetizar uma pneumopatia intersticial, o que pode ser um grande dilema diagnóstico para o clínico. Os fatores associados ao desenvolvimento de pneumopatia intersticial em pacientes com AR incluem altos títulos de anti-CCP e tabagismo (>25 maços/ ano) promovem uma chance de 3.8 vezes de desenvolvimento de pneumopatia intersticial em pacientes com AR.

Case 1

English Version

A 45-year- old woman with rheumatoid arthritis and dry cough

A 45-year- old woman had been diagnosed with rheumatoid arthritis based on her clinical symptoms and serological tests, which were positive RA factor and anti-CCP antibodies. Her rheumatoid arthritis activity had been well controlled with hydroxychloroquine and methotrexate. She presented with dry cough. Based on medical history, origin from a region of high prevalence of tuberculosis, methotrexate was disrupt and antituberculous therapy was initiated. After 3 months, her cough persisted, and she became dyspneic climbing a flight of

stairs. Her exam revealed a low-grade fever at 99.6F, and she had bibasilar crackles but no digital clubbing. CT scan of the chest showed cavitating lung nodules, raising concerns for an inflammatory or malignant process. The differential diagnosis included organizing pneumonia, interstitial fibrosis, rheumatoid nodules, airway disorders such as bronchiectasis and bronchiolitis and pulmonary vasculitis. Stains and cultures of the biopsy specimen were negative for bacteria, fungi and acid-fast bacilli. A panel of serological tests for vasculitis were checked and showed negative titers of cANCA and anti-proteinase 3 antibodies. Urine analysis and CT scan of paranasal sinuses was normal. A CT-guided needle biopsy of the largest nodule was undertaken, which showed nonspecific interstitial pneumonia. Three days after, she developed acute pneumonitis resulted in respiratory failure requiring intubation and mechanical ventilation. Diffuse alveolar hemorrhage was excluded. Even though, she died one day after intensive care unit hospitalization due to septic shock.

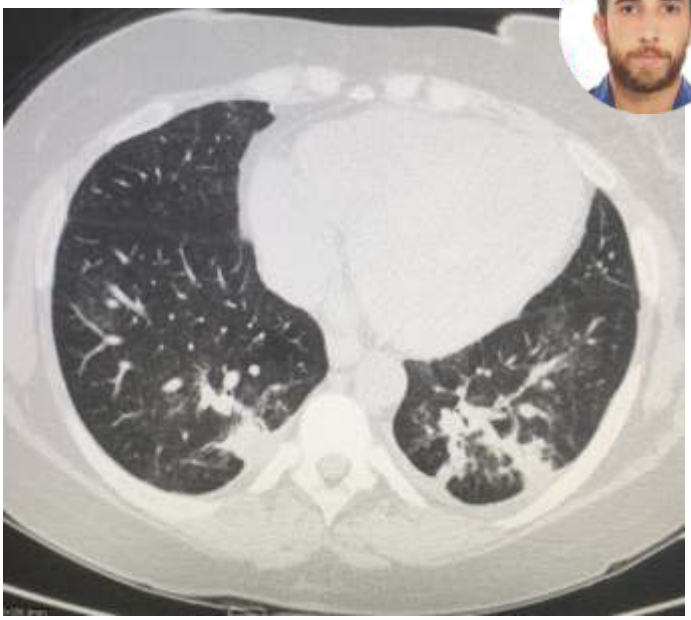
Discussion: Interstitial lung disease (ILD) is an increasingly recognized complication of rheumatoid arthritis (RA) contributing to significantly increased morbidity and mortality. Diagnosis can be challenging since patients are unlikely to report dyspnea due to an overall decrease in physical activity with advanced arthritic symptoms. Additionally, infections, drug toxicity, and environmental toxins can mimic ILD, creating significant diagnostic dilemmas for the clinician. High levels of anti-CCP antibodies have been associated with pulmonary fibrosis, and tobacco abuse (>25 pack years) may have the strongest association with the development of RA-ILD with an odds ratio of 3.8.

Caso 2

Presented by: Matheus Vieira Gonçalves
From: Hospital Universitário Pedro Ernesto

Versão em Português

Mulher de 34 anos, com nefrite lúpica refratária e múltiplas infecções



Este caso clínico ilustra uma paciente com LES cutâneo-seroso e nefrite refratária, responsiva apenas à rituximabe, complicada frequentemente por infecções. Também possuía diagnóstico de SAF soronegativa com morbidade gestacional e duas TVPs. Paciente de 34 anos, feminino, admitida na emergência com quadro de 4 dias de evolução do surgimento de pústulas inframamárias, axilares e inguinais, febre, dispneia, tosse seca e dor pleurítica. Há 1 mês, havia recebido infusão de rituximabe e pulsoterapia com metilprednisolona para nefrite lúpica ativa.

Exame físico mostrava murmúrio vesicular reduzido, edema periférico e as lesões pustulosas. Laboratório revelava neutrofilia leve, VHS elevado, PCR baixa, anti-DNA negativo, C3 consumido e INR no alvo. Radiografia do tórax revelava congestão pulmonar e infiltrado em base direita. Parecer da dermatologia avaliou as lesões cutâneas como pustulose amicrobiana das dobras. Culturas de sangue e urina, swabs mucosos, e sorologias virais e para fungos foram todos negativos.

Foi iniciado cefepime e claritromicina para pneumonia, com boa resposta clínica. No entanto, uremia, sobrecarga volêmica e acidose metabólica se desenvolveram sem motivo aparente, sendo indicada diálise de urgência. A recorrência da dispneia ocorria a despeito da adequada terapia de substituição renal. Foi solicitada tomografia de tórax que revelou opacidades

em vidro-fosco difusas, além de consolidações periféricas, uma das quais com aspecto cavitado. O lavado broncoalveolar foi realizado com bacterioscopia, cultura e BAAR negativos, mas galactomanana positiva, sendo diagnosticada aspergilose pulmonar invasiva. Anfotericina B intravenosa foi feita por 30 dias, seguida por 12 semanas de Itraconazol oral, com melhora clínica definitiva.

Case 2
English Version

A 34-year- old woman with lupus nephritis and multiple infections

This clinical case illustrates a SLE patient with skin and serous involvement, as well as refractory nephritis that responded only to rituximab, frequently complicated with infections. Also, she had seronegative APS with pregnancy morbidity and two DVT. A 34-year- old woman was admitted in the emergency room with a four-day onset of inframammary, axillary and inguinal pustules, fever, dyspnea, dry cough and pleuritic pain. She had just received rituximab and methylprednisolone in the past month, for active lupus nephritis.

Physical examination showed reduced breath sounds, bilateral leg swelling and pustules lesions. Laboratory tests revealed mild neutrophilia, high ESR, but low CRP, negative Anti-DNA, low C3, and INR on target. Chest X-ray revealed pulmonary congestion and right-basis infiltrate. The Dermatology staff evaluated the cutaneous lesions as amicrobial pustulosis of the folds. Blood and urine cultures, mucosal swabs, viral and fungi serologic tests were all negative.

Cefepime and Clarithromycin were started for pneumonia and a good initial response was noted. However, uremia, fluid overload and metabolic acidosis developed with no apparent reason, with need for urgent dialysis. Recurrence of the dyspnea occurred despite adequate renal replacement therapy. A CT scan revealed diffuse and random ground-glass opacities and bilateral peripheral consolidations, one of which had a cavitation aspect.

A bronchoalveolar lavage was performed with negative bacterioscopy, culture or acid-fast bacilli, but positive galactomannan, and thus diagnosing Invasive Aspergillosis. Intravenous amphotericin B was performed for 30 days, followed by 12 weeks of oral Itraconazol, with definite clinical improvement.

Caso 3

Apresentação: Kelly Rodrigues Silva
Instituição: Hospital Universitário Clementino Fraga Filho – Universidade Federal do Rio de Janeiro

Versão em Português

Homem de 31 anos, com doença renal crônica pela nefrite lúpica e poliartralgia Paciente masculino, 31 anos, com nefrite lúpica diagnosticada em 1993 e uso prévio de imunossupressão com ciclofosfamida, micofenolato de mofetil, azatioprina e rituximabe. Foi diagnosticado com imunodeficiência comum variável em 2014. Em 2016, compareceu à consulta regular no serviço de reumatologia com quadro de poliartrite de mãos, punhos, tornozelos associado à febre baixa de um mês de evolução. Estava em uso de hidroxicloroquina, ciclosporina, colchicina, azitromicina profilática e imunoglobulina humana. O exame físico evidenciou poliartrite de punhos, metacarpo falangeanas e tornozelos. Os exames laboratoriais mostraram anemia (Hb 9.3, Coombs direto negativo), linfopenia, aumento de PCR e VHS; consumo de complemento, função renal e spot urinário normais. O ultrassom articular (USG) evidenciou sinovite grave nos punhos com Power Doppler (PD) grau 3 sem líquido sinovial puncionável. Instituído tratamento para artrite gonocócica, mas após 3 semanas mantinha o quadro articular com USG PD grau III. Realizada biópsia sinovial e exames mostraram a presença de chikungunya no sangue, além de Zika no sangue, urina e tecido sinovial. Paralelamente, a função renal piorou (Cr 1.6) com início de proteinúria (1.74g), sendo excluídas

causas infecciosas (hemoculturas negativas). Diagnosticado então com coinfecção de Zika e Chikungunya reativando o LES. Diante da gravidade da artralgia de difícil controle e atividade do lúpus, foi realizado pulsoterapia com corticoide e o paciente evoluiu com melhora articular parcial. Recebeu alta com tratamento de indução com micofenolato. Contudo, ao longo de 8 meses ainda manteve poliartralgia de difícil controle, piora da função renal associado à pancitopenia, atribuída ao micofenolato, além de exames que mostraram persistência dos vírus no sangue e urina, evoluindo com óbito por sepse.

Case 3
Presented by: Kelly Rodrigues Silva
From: Hospital Universitário Clementino Fraga Filho – Universidade Federal do Rio de Janeiro

English Version

A 31-year- old man with end-stage renal disease due to lupus nephritis and polyarthralgia

A 31-year- old male patient with SLE-nephritis diagnosed in 1993 and previous use of immunosuppression with cyclophosphamide, mycophenolate mofetil, azathioprine and rituximab, with common variable immunodeficiency diagnosed in 2014, presented for 1 month polyarthritis of hands, wrists and ankles associated with fever at the beginning of the frame. He was using hydroxychloroquine, cyclosporine, colchicine, prophylactic azithromycin, and human immunoglobulin. Physical examination: polyarthritis of wrists, MCFs and ankles. Laboratory tests showed anemia (Hb 9.3, negative direct coombs), lymphopenia, increased CRP and HSV, complement consumption, normal renal function and urinary spot. Articular ultrasound (USG) showed severe synovitis in the handles with power doppler (PD) grade 3 without puncturable synovial fluid. It was established treatment for gonococcal arthritis, but after 3 weeks maintained the articular frame with USG PD grade III. Synovial biopsy and examinations showed the presence of chikungunya in the blood, zika in the blood, urine and synovial tissue. In parallel, renal function worsened (Cr 1.6) with the beginning of proteinuria (1.74g), excluding infection (negative blood cultures). Then, he was diagnosed with Zika and Chikungunya co-infection reactivating SLE. In view of the articular severity with difficult-to- control arthralgia and SLE activity, a pulse therapy with corticoid was performed and the patient presented partial articular improvement. He was discharged with mycophenolate induction treatment. However, over the course of 8 months, the patient maintained a difficult articular condition to control, worsened kidney function associated with pancytopenia (attributed to mycofenolate), besides the tests that showed persistence of the virus in the blood and urine, resulting in death due to sepsis.

Caso 4
Apresentação: Thaissa Amorim Nogueira
Instituição: Instituto de Puericultura e Pediatria Martagão Gesteira - UFRJ

Versão em Português

Menina de 4 anos com história de febre a esclarecer, exantema a nódulos subcutâneos em membros inferiores

Menina, 4 anos, filha de pais não consanguíneos, encaminhada ao ambulatório de Reumatologia Pediátrica, com quatro meses de febre alta intermitente de origem indeterminada, rash livedoide e nódulos subcutâneos nos membros inferiores. Exames iniciais revelaram anemia, reagentes de fase aguda elevados e autoanticorpos negativos (ANA, anti-dsDNA, anti-Sm, anti-RNP, ANCA, anticoagulante lúpico e anticardiolipina). Os pais e irmãos eram saudáveis. Foi diagnosticada poliarterite nodosa cutânea após extenso rastreio de causas infecciosas e outras causas subjacentes. A penicilina profilática e o naproxeno controlaram

apenas parcialmente a febre, rash e alterações laboratoriais. Seis meses após, desenvolveu ptose palpebral direita e diplopia, devido à paralisia do terceiro par craniano. Foram iniciados pulsos de metilprednisolona e ciclofosfamida, prednisolona oral e posterior manutenção com metotrexato, obtendo melhora da ptose e diplopia. Houve piora da febre, nódulos e rash, ao desmame do esteroide. A biópsia excisional do nódulo revelou linfócitos perivasculares, sem vasculite. Entre 9 a 11 anos de idade, apresentou síndrome piramidal, úlceras aftosas orais e episódios de mononeurite multiplex, parcialmente responsivos ao micofenolato mofetil. A ressonância magnética cerebral mostrou infartos lacunares subcorticais e atrofia do nervo óptico direito. Detectadas mutações heterozigotas no gene MEFV (C605G, p.R202Q). Colchicina e infliximabe foram prescritos, com controle satisfatório de febre, manifestações cutâneas e neurológicas. A presença de nódulos subcutâneos, rash livedoide e mononeurite multiplex nos fez considerar a hipótese de poliarterite nodosa associada à mutações MEFV. No entanto, devido à vasculopatia, inflamação sistêmica de início precoce e infartos lacunares, a possibilidade de deficiência de adenosina-deaminase2 também deve ser considerada.

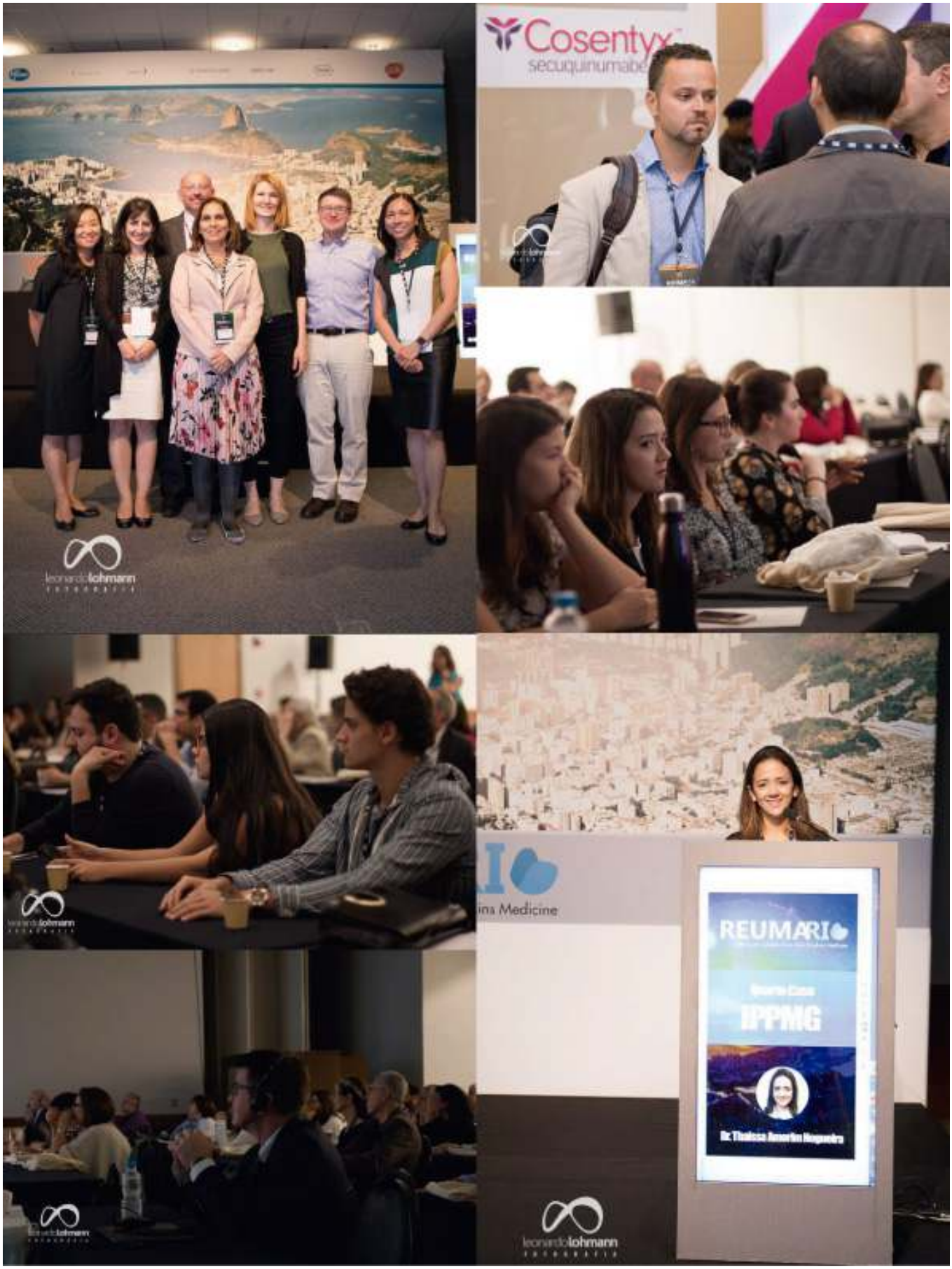
Case 4
Presented by: Thaissa Amorim Nogueira
From: Universidade Federal do Rio de Janeiro

English Version

A 4-year old girl with a four-month history of high intermittent unexplained fever, livedoid rash and subcutaneous nodules on lower extremities.

A 4-year old Latin-American girl, born to non-consanguineous parents, was referred to our Pediatric Rheumatology outpatient clinic, with a four-month history of high intermittent unexplained fever, livedoid rash and subcutaneous nodules on lower extremities. Initial exams revealed anemia, high acute-phase reactants, and negative autoantibodies (ANA, anti-dsDNA, anti-Sm, anti-RNP, ANCA, lupus anticoagulant and anticardiolipin). The parents and siblings were healthy. Cutaneous polyarteritis nodosa was diagnosed after a thorough negative workup for infectious disease and other underlying causes. Prophylactic penicillin and Naproxen controlled only partially the fever, rash, and the elevated acute-phase reactants. Six months later, she developed right palpebral ptosis and diplopia, caused by a third cranial nerve palsy. Methylprednisolone and cyclophosphamide pulses, besides oral prednisolone and later maintenance methotrexate were introduced, with ptosis and diplopia improvement. During steroid tapering, fever, subcutaneous nodules and livedoid rash worsened. Excisional nodules biopsy revealed perivascular lymphocytes, without vasculitis. At 9-11-year old, she had pyramidal syndrome, oral aphthous ulcers and mononeuritis multiplex episodes, partially responsive to mofetil mycophenolate. Magnetic resonance imaging (MRI) of the brain showed small subcortical lacunar infarcts and right optic nerve atrophy. Heterozygous mutations in MEFV gene (C605G, p.R202Q) were detected. Colchicine and infliximab were prescribed with satisfactory control of fever, cutaneous and neurological manifestations. The presence of subcutaneous nodules, livedoid rash and mononeuritis multiplex, made us consider the hypothesis of polyarteritis nodosa associated with heterozygous MEFV mutations. However, considering that she has vasculopathy, early-onset systemic inflammation and lacunar strokes in the absence of true vasculitis, adenosine-deaminase2 deficiency must also be considered.

Entertainment



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Erudite Rheumatology

Tulips
By Sylvia Plath

The tulips are too excitable, it is winter here.
Look how white everything is, how quiet, how snowed-in.
I am learning peacefulness, lying by myself quietly
As the light lies on these white walls, this bed, these hands.
I am nobody; I have nothing to do with explosions.
I have given my name and my day-clothes up to the nurses
And my history to the anesthetist and my body to surgeons.
They have propped my head between the pillow and the sheet-cuff
Like an eye between two white lids that will not shut.
Stupid pupil, it has to take everything in.
The nurses pass and pass, they are no trouble,
They pass the way gulls pass inland in their white caps,
Doing things with their hands, one just the same as another,
So it is impossible to tell how many there are.
My body is a pebble to them, they tend it as water
Tends to the pebbles it must run over, smoothing them gently.
They bring me numbness in their bright needles, they bring me sleep.
Now I have lost myself I am sick of baggage—
My patent leather overnight case like a black pill-box,
My husband and child smiling out of the family photo;
Their smiles catch onto my skin, little smiling hooks.
I have let things slip, a thirty-year- old cargo boat stubbornly hanging on to my name and address.
They have swabbed me clear of my loving associations.
Scared and bare on the green plastic-pillowed trolley
I watched my teaset, my bureaus of linen, my books
Sink out of sight, and the water went over my head.
I am a nun now, I have never been so pure.
I didn't want any flowers, I only wanted
To lie with my hands turned up and be utterly empty.
How free it is, you have no idea how free
The peacefulness is so big it dazes you,
And it asks nothing, a name tag, a few trinkets.
It is what the dead close on, finally; I imagine them
Shutting their mouths on it, like a Communion tablet.
The tulips are too red in the first place, they hurt me.
Even through the gift paper I could hear them breathe
Lightly, through their white swaddlings, like an awful baby.
Their redness talks to my wound, it corresponds.
They are subtle : they seem to float, though they weigh me down,
Upsetting me with their sudden tongues and their color,
A dozen red lead sinkers round my neck.
Nobody watched me before, now I am watched.
The tulips turn to me, and the window behind me

Where once a day the light slowly widens and slowly thins,
And I see myself, flat, ridiculous, a cut-paper shadow
Between the eye of the sun and the eyes of the tulips,
And I have no face, I have wanted to efface myself.
The vivid tulips eat my oxygen.
Before they came the air was calm enough,
Coming and going, breath by breath, without any fuss.
Then the tulips filled it up like a loud noise.
Now the air snags and eddies round them the way a river
Snags and eddies round a sunken rust-red engine.
They concentrate my attention, that was happy
Playing and resting without committing itself.
The walls, also, seem to be warming themselves.
The tulips should be behind bars like dangerous animals;
They are opening like the mouth of some great African cat,
And I am aware of my heart: it opens and closes
Its bowl of red blooms out of sheer love of me.
The water I taste is warm and salt, like the sea,
And comes from a country far away as health.

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