At Hospital for Special Surgery our rheumatologists care for some of the most complex and challenging patients, including those with life-threatening autoimmune and inflammatory diseases. We draw on our rich multidisciplinary professional resources, particularly our collaborating specialists in nephrology, cardiology, pulmonary medicine, dermatology and others, to achieve the best outcomes for our patients. Our strong translational research focus adds to our comprehensive consideration of the best management plan for our patients.

In this issue of Grand Rounds from HSS/Management of Complex Cases in Rheumatology, we feature three of our recent cases, all with a satisfactory outcome. Case 1, presented by Nancy Pan, MD, a recent graduate of our Pediatric Rheumatology Training Program, Kyriakos A. Kirou, MD, and their colleagues, describes a woman with lupus nephritis who developed a dramatic exacerbation of her disease, including life-threatening hypertension and massive proteinuria. Two renal biopsies, performed during two distinct flares, demonstrated the evolution of changes consistent with chronic damage. Aggressive immunosuppressive and antihypertensive therapy, using multiple agents, resulted in significant clinical improvement.

Case 2, described by two of our stellar rheumatology fellows, Danielle Ramsden-Stein, MD and Sonali Narain, MD, along with Michael D. Lockshin, MD, presents a woman who developed a dramatic necrotizing skin rash and numerous clinical and serologic manifestations that suggested a diagnosis of granulomatosis with polyangiitis. However, review of the skin biopsy with our pathologist revealed a classic picture consistent with an alternative diagnosis.

Sergio Schwartzman, MD, presents a patient who developed hand arthralgias and diffuse edema of the lower extremities during a trip to Asia. History, physical exam and laboratory data were quite unremarkable, other than extensive non-pitting edema of the legs and an elevated aldolase. A diagnosis of eosinophilic fasciitis was made based on MRI and skin biopsy, the patient responded well to steroid therapy, but any potential link between the patient’s travel and the development of the illness remained undefined.

We hope you will enjoy reading about our interesting patients and our approach to management.

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Severe Lupus Nephritis (LN) with Response to Aggressive Multimodal Management

Case presented by Nancy Pan, MD, Steven Salvatore, MD, Surya V. Seshan, MBBS, James M. Chevalier, MD, and Kyriakos A. Kirou, MD

CASE REPORT: A 31-year-old previously healthy Caucasian woman was diagnosed with systemic lupus erythematosus (SLE) in October 2007 after she presented with a malar rash, generalized edema, small pericardial effusion, with positive ANA and anti-double-stranded (ds) DNA antibodies. Renal biopsy demonstrated diffuse proliferative (class IV-G) and membranous (V) lupus nephritis with focal fibrocellular crescents, wire loop lesions, inflammatory cells in most glomeruli, and a “full house” pattern of immunofluorescence (IF). Activity index (AI) was 10/24 and chronicity index (CI) 2/12. She was enrolled in the Lupus Nephritis Assessment with Rituximab (LUNAR) Study and received induction therapy with rituximab and mycophenolate mofetil (MMF). She achieved complete remission and eventually was weaned off MMF by September 2010.

In July 2011, during a routine follow-up visit, she was noted to have new microscopic hematuria and proteinuria of 7g/day. She was treated with pulse glucocorticoids (GC), oral prednisone 60mg, MMF 1500mg, lisinopril 20mg and furosemide 20mg daily. Upon evaluation at our institution three weeks later, there was progressive severe edema, a 30-pound weight gain, and blood pressure (BP) of 160/100. Pertinent laboratory data included Hgb 9.8g/dl, Cr 1mg/dl (increased from baseline 0.6mg/dl), albumin 1.6g/dl, cholesterol 324mg/dl, proteinuria 14g/day with active urine sediment, C3 51mg/dl, C4 4.3mg/dl, and high anti-dsDNA titers. MMF was increased to 3000mg daily and prednisone was changed to dexamethasone (DEX) 8mg daily in order to minimize mineralocorticoid (MC) effects, including infertility and malignancy, with excellent clinical response to an induction regimen of rituximab and MMF, in addition to GC and HCQ. Her presentation was clinically severe because of refractory hypertension, marked edema, nephrosis, and increased Cr. In addition, the kidney biopsy also showed an increased CI, which was favored over intravenous cyclophosphamide (IVCY), because of previous response and fertility concerns. She was discharged on daily DEX 8mg, hydroxychloroquine (HCQ), lisinopril, furosemide, amlodipine, trimethoprim/sulfamethoxazole, atorvastatin, calcium and vitamin D, and weekly risedronate. By one month of follow-up, furosemide had been gradually tapered off without residual edema, her BP remained well-controlled, proteinuria improved to 5g/day, and complement levels were normal (Figure 4). By six months, while on prednisone 2.5mg daily, the patient was clinically well with improved Cr to 0.7mg/dl, albumin 3.9g/dl, 1.4g/day of proteinuria, normal C3/C4, and no change in anti-dsDNA titers.

DISCUSSION: This patient presented with two severe LN flares, four years apart, with excellent clinical response to an induction regimen of rituximab and MMF, in addition to GC and HCQ. Her presentation was clinically severe because of refractory hypertension, marked edema, nephrosis, and increased Cr. In addition, the kidney biopsy was consistent with severe disease, classified as mixed ISN/RPS class IV and V LN with crescents, which carries a worse prognosis than Class IV alone (1, 2). Of note, the second biopsy had fewer active lesions compared to the first, as well as some crescents in the healing stages, possibly related to therapy with oral and pulse GC prior to the biopsy. Interestingly, the repeat biopsy also showed an increased CI, which is typical with repeated flares of LN (3).

Although IVCY has been the mainstay of therapy for severe proliferative LN for many decades because of suboptimal effectiveness and significant adverse effects, including infertility and malignancy,
CASE REPORT: A 47-year-old woman with recurrent sinusitis and bronchitis, intermittent febrile rashes and depression presented to an outside hospital with rapidly progressing skin rash after eating at a seafood restaurant, consisting of bruises on her left shoulder, left thigh and under her left breast accompanied by fever to 102°F, arthralgias and fatigue. The rash worsened within 24 hours to involve her upper and lower extremities, cheeks, ears, breasts and abdomen. She denied trauma, toxic exposures, new medications, sick contacts, or recent travel.

On examination, she had saddle nose deformity and necrotizing purpura as shown in the figures, with bullae developing over the dependent areas. She had proteinuria and pancytopenia. Lumbar puncture was negative but chest X-ray showed left lower lobe consolidation. She was started on ceftriaxone/vancomycin. She developed cough with blood tinged sputum and gross hematuria. Head CT scan showed pansinusitis. Intravenous methylprednisolone 40mg every six hours was prescribed. The lesions progressed from pruritic to tender, with darkening of color to purple, peaking on the third day of hospitalization, affecting approximately 70 percent of her body surface area. Biopsy revealed leukocytoclastic vasculitis and the patient requested transfer for further management.

On admission corticosteroid was continued, since new onset granulomatosis with polyangiitis (Wegener’s) was suggested by the rash, nose deformity, proteinuria and recurrent sinusitis. Antibody to proteinase 3 was strongly positive. Review of her pathology slides deemed the underlying process to be classic for a cocaine-induced vasculitis. After an initial dose of pulse methylprednisolone, patient was started on oral prednisone 1mg/kg dose tapered over a 20-day period. There was very slow improvement in the cutaneous lesions, for which, she eventually underwent multiple sessions of skin grafting. At the time of discharge, there was marked improvement with mild scarring. Despite repeated questioning, the patient did not admit to cocaine use.

DISCUSSION: Although we were unable to confirm that the presentation of this rash, in our patient, was related to cocaine use, the pathology report prompted us to understand the pathophysiology of cocaine induced vasculitis. Unlike granulomatosis with polyangiitis, cocaine induced vasculitis, is less commonly a true vasculitis, but rather a vasculopathy with thrombosis. Its occurrence is associated with cocaine that has been contaminated with levamisole, a veterinary antihelminthic agent (1-2) although recently it has been hypothesized that cocaine itself may enhance complement synthesis and trigger the formation of C5b-9, resulting in endothelial cell injury. Accelerated apoptosis results in the formation of antibodies associated with the apoptotic microenvironment, such as antiphospholipid antibodies and antineutrophil cytoplasmic antibodies. While levamisole has been acknowledged as possessing immunomodulatory properties since the 1960s, the mechanism is not well understood. It was once used in the treatment of autoimmune conditions such as rheumatoid arthritis. However, in 1999 this drug was removed from US markets for use in humans due to adverse side effects. It reportedly potentiates the psychotropic effects of cocaine and therefore makes it highly desirable to manufacturers of illegal cocaine. Reports consistently state that it is added to approximately 70 percent of cocaine available in the United States.

In cocaine-induced disease, tender purpuric lesions occur on the ears, cheeks and often the extremities. The classic skin finding is that of retiform purpura, a net-like pattern of irregular nonblanching violaceous plaques. Skin biopsy shows a very distinctive intravascular occlusion without vasculitis, termed vasculopathy.
CASE REPORT: The patient is a 23-year-old female who first noted joint pain in her hands two months prior to presentation at HSS while traveling in Asia. Over time, she noted similar symptoms in her feet and developed diffuse swelling of her lower extremities, including her feet. However, she noted no swelling in her hands. These symptoms progressed and worsened while she was traveling, and upon her return to the United States, the symptoms became even more pronounced. In addition to diffuse swelling in her lower extremities, she developed lower extremity pain. The patient had a 15 pound weight gain.

The patient denied any dry eyes, dry mouth, oral ulcers, lymphadenopathy, or pleuritic-type chest pain. She had not had any cough or shortness of breath. She denied any night sweats. She noted no fevers or known infections. The patient did not have any clotting or bleeding problems in the past. She denied any history of red or hot joints and had no history of muscle weakness or any history of DVT, PE, MI, or stroke. There was no history of any pregnancies. She did not use birth control pills and did not smoke. There was no history of exposure to animals or dust. She had not used any medications, including statins or L-Tryptophan. Her past medical history was only remarkable for exercise-induced asthma. Family history was remarkable for an uncle with SLE. She had several evaluations, including bilateral Dopplers and a CT of the abdomen and pelvis that were negative, and was noted to have normal laboratory test results and serologies. She’d had prior evaluations by multiple (non-HSS) subspecialists; ID, GI and renal and workup was nondiagnostic. The patient was treated with furosemide 40mg a day by her internist with a subsequent 4 pound weight loss.

Initial clinical evaluation at HSS was remarkable for acne rosacea and marked non-pitting edema of the arms and legs, which was much more dramatic in the lower extremities. Equivocal synovitis was present in the wrists. Laboratory workup at HSS revealed normal serologies, chemistry profile, CBC ESR of 37, a positive Quantiferon with a negative PPD, an Aldolase of 15.6 U/L (Ref: <8.1), CPK <20. A CT of the chest was performed that was normal, and a repeat evaluation by an infectious disease subspecialist revealed a negative repeat Quantiferon, negative Filaria and Chikungunya antibodies. Ultrasound and MRI of the lower extremities revealed extensive subcutaneous soft tissue edema from the thighs to the calves that was consolidated to the superficial fascia without intramuscular enhancement consistent with an inflammatory fasciitis. Skin, fascial and muscle biopsies showed focally intense inflammatory infiltrates in the deep dermis, fascia and muscle interstitium without myositis. The infiltrates consisted mostly of small lymphocytes, with variably dense accumulations of macrophages, few plasma cells, and rare eosinophils. The patient underwent therapy with prednisone at an initial dose of 60mg per day and physical therapy and had an almost immediate clinical response with resolution of pain and edema and a return to baseline weight. Aldolase levels normalized. Corticosteroids were tapered over a 6-month period of time.

DISCUSSION: Eosinophilic fasciitis is an uncommon but increasingly recognized illness first defined in 1974. It usually evolves from initial induration of the skin to non-pitting edema and ultimately results in woody induration, skin tightness and the development of flexion contractures. The differential diagnosis may include systemic sclerosis and all of the illnesses and conditions where edema is a clinical finding. There can be associated extra-cutaneous manifestations, including involvement of the musculoskeletal, hematologic and pulmonary systems, and malignancies have been associated with this illness (1). The etiology of this illness is unknown. Potential causes that have been
other therapies—such as MMF and rituximab, have been recently explored in LN (4-6). At present the efficacy of MMF, but not rituximab, has been established. Despite several successful uncontrolled rituximab studies, the LUNAR trial failed to show superiority in renal response in combination with MMF over MMF alone, possibly because of study design problems. Our patient, at six months after therapy, achieved a significant clinical response, although only partial renal response according to LUNAR criteria. Considering the rapid complement normalization and early improvement in proteinuria in this patient, as well as the typically delayed complete proteinuria response, we believe that she will improve further with time (7). Other good prognostic factors include her Caucasian race and early initiation of therapy (8).

In conclusion, we emphasize the importance of prompt detection and aggressive multimodal therapy of LN for optimal outcomes. Management should include adequate immunosuppression, aiming for early correction of hypocomplementemia (6, 7). In addition, therapy should include HCQ, statins, and renin-angiotensin system inhibitors, as well as other anti-hypertensive agents, aiming for BP ≤130/80 (6). In cases of severe edema, DEX might be preferable to other GC given its absent MC effects.

REFERENCES:

AUTHOR DISCLOSURES:
Dr. Nancy Pan does not have a financial interest or relationship with the manufacturers of products or services.
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CASE 2 CONTINUED

primarily targeting capillaries and venules. The process differs from a classic leukocytoclastic vasculitis because of the extent of vascular thrombosis and lack of infiltration of the vessel wall by inflammatory cells. Gross et al. found, in 16 patients, that 13 percent had a pure small vessel vasculitis, 40 percent thrombotic vasculopathy and 47 percent vasculitis and thrombosis (1).

Cocaine/levamisole induced vasculitis is frequently associated with antineutrophil cytoplasmic antibodies (1, 3). In the 16 cases reviewed by Gross et al., 15 (94%) patients were ANCA positive, 10 (63%) were positive for antiphospholipid antibodies and 5 (31%) were positive for ANA, dsDNA or RNP autoantibodies. While ANCA positivity has been documented with both cocaine use and with levamisole use individually, normalization of ANCA and APL antibodies after levamisole exposure tended to take place within 2-14 months in Rongioletti’s study (4). Given this patient’s history, to differentiate whether her presentation was likely drug induced rather than a systemic autoimmune process such as granulomatosis with polyangiitis, repeat serologies at 6-12 months will be useful.

REFERENCES:

AUTHOR DISCLOSURES:
Dr. Sergio Schwartzman is a consultant and speaker for Abbott, Genentech, Amgen, Pfizer, UCB and Janssen.


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Dr. Danielle Ramsden-Stein does not have a financial interest or relationship with the manufacturers of products or services.
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FOR YOU AND YOUR PATIENTS

Advances in Lupus Research: Spotlight on Treatment Webinar
HSS hosted a live webinar, sponsored by the Lupus Foundation of America, which discussed the advances in lupus research. This program was led by Susan Manzi, MD, from Allegheny General Hospital and HSS’s experts Michael D. Lockshin, MD and Jane E. Salmon, MD. An overview of lupus and discussion about current and future therapeutic treatment options are featured in this webinar. Visit www.hss.edu/pped-webinars to view this program.

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The following featured CME symposia, now available for free from HSS e-University, were part of the HSS Alumni Association 93rd Annual Meeting that was held in November 2011.

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