In this issue of Grand Rounds from HSS/Management of Complex Cases, we feature four patients who represent three challenging diseases, along with discussion of their evaluation and management.

Case 1, presented by Kyriakos A. Kirou, MD, Steven P. Salvatore, MD, and research fellow Naveed Chaudhry, MD, describes a patient with severe lupus nephritis and catatonia that responded to prompt and aggressive treatment.

Alana B. Levine, MD, discusses Case 2, a woman who came to HSS for a second opinion regarding her diagnosis of polymyalgia rheumatica in the setting of a leg rash and a host of additional symptoms. After admission with acute renal failure and fever, cardiac evaluation identified a large vegetation, and blood cultures confirmed a diagnosis of subacute bacterial endocarditis.

Case 3 from Susan M. Goodman, MD, and rheumatology fellow Karima Becetti, MD, describes two interesting patients with severe joint pain who had been exposed to the Chikungunya virus during recent travels.

We hope you enjoy reading about the management of these challenging and interesting cases, and invite you to review archived issues at www.hss.edu/complexcases and provide feedback to complexcases@hss.edu.
CASE REPORT: A 34-year-old woman was diagnosed with systemic lupus erythematosus (SLE) in 2011 after she presented with arthritis, photosensitivity, alopecia and oral ulcers, and was treated with short courses of prednisone. Her serologic profile was positive for ANA, anti-dsDNA, anti-Sm and anti-RNP antibodies. In January 2013, she was admitted to another hospital for left popliteal vein deep vein thrombosis (DVT) and pulmonary embolism (PE). She was also noted to have nephrotic range proteinuria and pleuropericarditis. She was treated with anticoagulation (enoxaparin to warfarin) and prednisone 60 mg/day with improved symptoms. She first presented to us in February 2013 with marked leg edema and dyspnea on exertion. Past medical and family histories were unremarkable. Her blood pressure was 112/82, pulse 85, and she had 2+ leg edema. Her Hgb was 13.9 gm/dl, serum creatinine (Cr) 0.64 mg/dL, albumin 1.7 gm/dl, cholesterol 366 mg/dl, ESR 72 mm/hr, C3 167 mg/dL, C4 64 mg/L, and anti-DNA 2+. Her urine sediment was bland, but her urine protein-creatinine ratio (UPCR) was 5.2. She was on prednisone 50 mg/day, and mycophenolate mofetil (MMF) was added to her regimen. Her edema got much worse, however, and she was readmitted 3 weeks later (March 2013) with severe anasarca. She received IV methylprednisolone 500 mg daily for 3 days and, after switching warfarin to heparin, a renal biopsy was performed. This revealed ISN/RPS Class V membranous lupus nephritis (Figures 1-3). MMF was discontinued because of diarrhea, and mycophenolate mofetil (MMF) was added to her regimen. Her edema got much worse, however, and she was readmitted 3 weeks later (March 2013) with severe anasarca. She received IV methylprednisolone 500 mg daily for 3 days and, after switching warfarin to heparin, a renal biopsy was performed. This revealed ISN/RPS Class V membranous lupus nephritis (Figures 1-3). MMF was discontinued because of diarrhea, and she was treated with IV cyclophosphamide (IVCY). The patient was discharged on dexamethasone 9 mg, losartan 25 mg, bumetanide 1 mg, warfarin, atorvastatin 40 mg, calcium, vitamin D3, and alendronate 70 mg weekly. She was readmitted to the hospital in early April 2013, after she developed symptoms of mania, depression, and psychosis with paranoia. She was also noted to have severe edema, and pneumonia. She was treated with IV antibiotics and diuretics, and glucocorticoids were continued. After treatment with haloperidol, she developed catatonia with motor rigidity, immobility, staring, mutism, and negativism. She was not hyperthermic and creatine kinase and electroencephalogram were normal. She was treated with IV lorazepam 2 mg and high dose glucocorticoids were continued. Her mental status normalized after a few days. Pulmonary infiltrates cleared 11 days later and she was given her 2nd IVCY dose as well as IV rituximab 1000 mg. She was discharged on prednisone 40 mg daily with a slow taper. She continued with monthly IVCY for a total of 5 cycles (last August 2013) and had gradual improvement of proteinuria and edema. By Sept 2013 her UPCR was 0.37 and her albumin normalized (Figure 4). At that point, she was started on azathioprine 50 mg BID as maintenance treatment while prednisone was tapered to 5 mg/day. Warfarin was discontinued without recurrent thrombosis. Her antiphospholipid antibodies, including lupus anticoagulant, have remained negative. The patient was able to go back to her job full-time.

DISCUSSION: We have described a complex case of lupus with active disease in several organs and excellent response to prompt and aggressive management. She first presented with nephrosis and secondary DVT-PE. Then she developed pleuropericarditis and finally neuropsychiatric (NP) SLE with bipolar symptoms, psychosis, and catatonia. Although glucocorticoids may cause psychosis, they were unlikely the culprit here as they had
CASE REPORT: A 70-year-old woman was referred to the HSS Division of Rheumatology for a second opinion regarding polymyalgia rheumatica (PMR). She had been diagnosed with PMR at another hospital eight months prior to presentation based on fatigue and an elevated ESR. Her fatigue resolved rapidly after starting prednisone 20 mg daily which was tapered off over two months. Fatigue recurred after discontinuing steroids and the patient was restarted on prednisone plus, eventually, methotrexate.

One month prior to presentation at HSS, the patient developed a new non-painful, non-pruritic leg rash. Skin biopsy revealed leukocytoclastic vasculitis. At the time she was taking prednisone 5 mg daily which was increased to 40 mg daily, and the rash resolved.

On presentation to HSS the patient complained of severe fatigue, nocturnal fevers to 101°F, night sweats, and anorexia with a 20 pound weight loss. The patient’s past medical history was significant for mitral valve prolapse and osteopenia. She had dental work one month prior to PMR diagnosis and had two caesarian sections in the past. Her medications included methylprednisolone 4 mg daily, rabeprazole 20 mg daily, and calcium supplementation.

On physical examination, the patient was in no acute distress. Her blood pressure was 110/65 mm Hg, pulse 112, and temperature 100.2°F. She weighed 104 pounds and was 62 inches tall. Her exam was remarkable for a loud systolic murmur, heard throughout the precordium but most pronounced at the apex. She had fingernail clubbing and several non-blanching 2 mm palpable purpuric lesions over the shins. Her lung exam was unremarkable, pulses were strong throughout and without bruits, and she had no synovitis. The differential diagnosis at that time included systemic vasculitis, malignancy, and endocarditis.

Labs were significant for hemoglobin 8.7 g/dL, serum creatinine 2.2 mg/dL (0.9 mg/dL one month prior), rheumatoid factor 222 IU/mL, ESR 53 mm/hr, CRP 125 mg/L, C3 31 mg/dL, and C4 7 mg/dL. Urinalysis showed 2+ protein, 3+ blood, >30 WBC/hpf and >30 RBC/hpf. Antinuclear antibodies, double-stranded DNA antibodies, extractable nuclear antigens, and anti-CCP antibodies were negative.

The patient was admitted for evaluation of acute renal failure. Multiple sets of blood cultures were drawn and held for slow-growing organisms and the patient was started on broad spectrum antibiotics. A renal ultrasound was unremarkable. A transthoracic echocardiogram showed severe mitral regurgitation with a 1.9 x 1.8 cm vegetation on the posterior mitral leaflet. Blood cultures grew gram-variable rods which were later speciated as Suttonella indologenes. Due to the size of the vegetation and severe mitral regurgitation, the patient was recommended for mitral valve replacement surgery.

DISCUSSION: Subacute bacterial endocarditis may cause a constellation of symptoms, including fatigue and malaise, fevers, valvular

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CASE REPORT 1: A 59-year-old woman with systemic lupus erythematosus (SLE) presented with joint pain and fever after visiting Puerto Rico. The patient was diagnosed with SLE in October 2013 when she presented with symmetric polyarthritis of small and large joints, Raynaud’s, palatal ulcers, and an ANA of 1:2560. She improved with hydroxychloroquine and naproxen. In July 2014 she developed severe polyarthritis, fever and a maculopapular rash one week after visiting Puerto Rico. A lupus flare was suspected, but she failed to improve with corticosteroids. Testing revealed positive Chikungunya titers; IgM 1:640 and IgG 1:20. Three months later the patient continued to have joint pains despite therapy with naproxen, prednisone and hydroxychloroquine.

CASE REPORT 2: A 47-year-old healthy woman presented with severe joint pain of 1 month’s duration. The patient first developed fever, a diffuse erythematous rash (Figure 1), joint pain and swelling of her hands and feet during a visit to the Dominican Republic. Her symptoms resolved with acetaminophen and NSAIDs. One month later her joint pain recurred. There was involvement of multiple large and small joints in a symmetrical pattern with 2-3 hours of morning stiffness. The patient complained of fatigue but had no fever or rash. Labs were normal except for elevated inflammatory markers. Chikungunya titers were positive; IgM 1:1280 and IgG 1:2560. The patient was unable to tolerate high dose NSAIDs, so prednisone 10 mg daily was initiated for symptom control. Symptoms persisted 3 months after diagnosis.

DISCUSSION: Chikungunya is an RNA arbovirus and is included among the arthritogenic alphaviruses. The Tanzanian word Chikungunya means “to walk bent over,” and refers to the incapacitating joint pain experienced by patients with this infection. Two to 12 days after transmission by Aedes mosquitoes, the clinical onset is abrupt with high fever (100% of cases), joint pain (78-100% of cases), rash (40-50% of cases, commonly pruritic and maculopapular), headaches and back pain (50-70% of cases). Gastrointestinal, hemorrhagic and neurologic complications such as meningoencephalitis are less frequent [1]. While this is usually a self-limited illness, in one severe epidemic more than 60% of cases required hospitalization. Risk factors for severe outcomes included older age and higher prevalence of other comorbidities such as diabetes. Radiographs and routine laboratory testing are generally normal, although moderately elevated inflammatory markers are often seen. Lymphopenia, elevated liver enzymes and creatinine kinase are less common findings [1]. Diagnosis can be confirmed by 2 methods: virus identification during the initial viremic phase using polymerase chain reaction (PCR), and serologic testing (Figure 2). IgM antibody is detectable after an average of 2 days of the acute illness and remains elevated for several weeks to 3 months [1]. There is no effective antiviral therapy; treatment is symptomatic and supportive with NSAIDs and corticosteroids [1]. Chloroquine was suggested as a therapeutic agent given its anti-inflammatory and anti-viral properties but was not effective in a double-blind randomized trial, and was not useful in our case [1].
been previously tolerated well, and her NP symptoms occurred concurrently with disease activity in other organs. Catatonia is a rare NP manifestation of SLE, often associated with an underlying bipolar disorder [1]. It may be triggered by antipsychotics like haloperidol and often responds to lorazepam as in our case. Treatment of lupus with glucocorticoids, IVCY, and/or plasma exchange is also effective [1]. Catatonia may be life-threatening when of the malignant type, in which case it requires electroconvulsive therapy. Pure membranous lupus nephritis when accompanied by nephrotic range proteinuria is also a severe manifestation of SLE and demands treatment with MMF, IVCY, or cyclosporine [2, 3]. We used IVCY, as our patient could not tolerate MMF. Finally, we added rituximab as it is often effective in severe lupus as well as NPSLE [4].

REFERENCES:

AUTHOR DISCLOSURES:
Dr. Naveed Chaudhry does not have a financial interest or relationship with the manufacturers of products or services.

The joint pain in Chikungunya usually affects small distal joints of the hands and feet, but larger joints including knees can also be affected [1]. 68% of sero-positive patients in the Reunion Island epidemic had persistent joint pain at 18 months. In a retrospective study performed in South Africa, 12% of patients had persistent symptoms 3–5 years after the acute illness [1]. The development of classic rheumatoid arthritis has also been reported with positive RF, ACPA antibodies and radiographic erosions [1]. Arthritogenic alphaviruses can infect osteoblasts in the periostem and joints which can lead to an increase in pro-inflammatory cytokines and chemokines including IL-6. This disrupts the RANKL/osteoprotegerin ratio and promotes osteoclastogenesis, bone loss, erosions and ongoing musculoskeletal pain [2]. Since the Chikungunya virus was first isolated in 1953, epidemics have occurred in Africa, India and Asia. Since 2006, the US had an average of 28 imported cases per year from endemic areas. However, both mosquito vectors, A. albopictus and A. aegypti, are now found in the US. Local transmission of the virus was reported in Florida in July 2014, raising concern that this virus is now endemic (Figure 3) [3]. Climate change may have contributed to the increased risk of Chikungunya epidemics, since viral replication increases with every 1-2 degree increase in temperature, and viral load contributes to infectivity [4]. Early diagnosis, public health interventions including vector control, and the development of vaccines and anti-viral therapies will be required to prevent outbreaks in previously non-endemic countries.

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AUTHOR DISCLOSURES:
Dr. Karima Becetti does not have financial interest of relationship with the manufacturers of products or services.

Dr. Susan Goodman does not have financial interest of relationship with the manufacturers of products or services.
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