



Grand Rounds from HSS

MANAGEMENT OF COMPLEX CASES | RHEUMATOLOGY

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FROM THE EDITORS



Dr. Mary K. Crow



Dr. Edward C. Jones

We are pleased to present the first issue of *Grand Rounds from Hospital for Special Surgery* that is devoted to complex cases managed by our rheumatologists. HSS Rheumatology fosters a collaborative approach to patient care that is supported by the deep expertise of our faculty, the enthusiastic engagement of our rheumatology fellows, and close interaction with orthopaedic surgeons, internal medicine specialists, expert radiologists and musculoskeletal pathologists. The four cases presented demonstrate the value of this multidisciplinary and interactive approach for excellent patient outcomes.

The first case, a woman with severe rheumatoid arthritis who underwent bilateral knee replacement (TKR), discusses some issues considered when weighing the risks and benefits of simultaneous bilateral TKR in a patient with a significant rheumatologic disease. The second case, a young woman with systemic lupus erythematosus who developed pulmonary hypertension, describes the excellent clinical outcome that followed aggressive medical therapy. The third case, a young woman who developed a monoarticular synovitis that was initially diagnosed as pigmented villonodular synovitis, was later determined to have rheumatoid arthritis with a good response to therapy. The fourth case describes an excellent clinical response to tumor necrosis factor (TNF) inhibition in a patient with sarcoidosis and discusses the growing support in the literature for use of TNF antagonists in this inflammatory disease. We hope you enjoy reading about these complex cases, and we encourage readers to provide feedback through complexcases@hss.edu.

Mary (Peggy) K. Crow, MD
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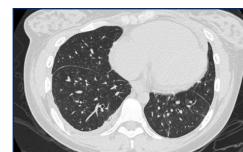
Edward C. Jones, MD, MA
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in this issue



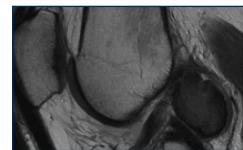
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Bilateral Knee Replacement in Rheumatoid Arthritis

Case presented by Susan M. Goodman, MD; Linda A. Russell, MD; and Mark P. Figgie, MD



Figure 1: Bilateral standing views of the knees demonstrate marked joint space narrowing with severe diffuse periarthritis osteoporosis and no osteophytes.



Figure 2: Lateral views of the knees demonstrate diffuse joint space narrowing and periarthritis osteoporosis.



Figure 3: Standing AP radiograph demonstrating normal alignment of the bilateral arthroplasties, utilizing constrained Zimmer components due to the patient's flexion-extension imbalance.

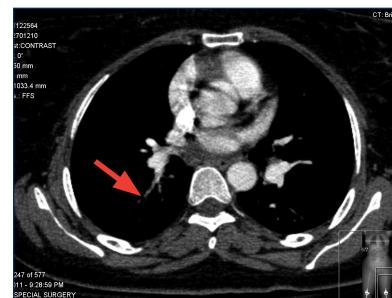


Figure 4: A CT pulmonary angiogram reveals linear filling defect within the posterior segmental artery of the right lower lobe (arrow) and subsegmental artery (not shown).

CASE REPORT: A 44-year-old woman with severe rheumatoid arthritis (RA) was referred to HSS for bilateral knee replacement (TKA) surgery. The patient had erosive RA which had responded poorly to aggressive therapy. Her medication regimen at the time of surgery consisted of golimumab and leflunomide. She had failed to benefit from adalimumab, etanercept, or methotrexate. She was wheelchair-bound due to knee pain and flexion deformities, but could transfer with the aid of a walker.

Her exam revealed boggy synovitis of the wrists and metacarpophalangeal joints. She had a 30 degree flexion contracture of the right knee and 20 degrees on the left, with further flexion to 110 degrees bilaterally. Bilateral effusions with crepitus were noted. Foot, ankle and hip exams revealed normal motion. Bilateral knee radiographs revealed advanced severe diffuse joint destruction (Figures 1 and 2).

Preoperative evaluation included a normal stress test and echocardiogram. Flexion extension views of the cervical spine were normal without instability. She discontinued her golimumab one month prior to surgery and continued her leflunomide until the day of surgery.

She underwent BTKR performed sequentially under epidural anesthesia combined with femoral nerve blocks. A standard peripatellar exposure was performed, but more extensive femoral bone resection was required in order to correct the flexion contractures. A complete synovectomy was performed including the posterior aspect of the knee. In addition, the posterior capsule was released on both sides. Care was taken to protect the bone throughout the surgery as it was severely osteoporotic. Although the implants were sized appropriately, there was a mismatch between the flexion and extension gaps so a Zimmer constrained condylar knee replacement was utilized and fixed with antibiotic impregnated cement (Figure 3).

DVT prophylaxis with warfarin and intermittent pneumatic compression was begun in the recovery room. She was able to ambulate on post-op day two but developed tachycardia. A high resolution CT scan revealed pulmonary emboli (Figure 4); enoxaparin was added. She was discharged to a rehabilitation facility on post-op day seven on coumadin.

DISCUSSION: Although RA patients undergoing arthroplasty should expect significant pain relief from TKA, they may not achieve the same functional outcome as OA patients (1). Reported mortality is increased in RA patients in some series, as are perioperative infections, when compared to non-RA patients (2). Overall, with

widespread use of potent disease-modifying drugs (DMARDs) RA has become less severe and fewer patients are hospitalized for all causes, including arthroplasty (3). Patients such as ours, however, with poor functional status, positive CCP antibody, and persistent joint inflammation are at risk for joint destruction as well as other severe manifestations of RA. Cervical spine involvement is reported in 44 percent of patients screened at the time of arthroplasty with flexion/extension neck films (4). Accelerated atherosclerotic disease may be subclinical, contributing to the excess mortality in RA (6). History may be insufficient to screen for cardiovascular disease in these debilitated patients, and imaging studies may be indicated prior to surgery.

We elected bilateral simultaneous knee replacement in this patient because of her significant flexion contractures, in spite of the increased perioperative risk of thromboembolic events. Unilateral correction of a severe contracture risks recurrence of the deformity and limits ambulation, compromising outcome. Although database analysis reveals that the rate of pulmonary embolus is doubled and mortality increased in patients in whom simultaneous BTKR is performed compared to unilateral procedures, staging the surgery during the same hospitalization does not improve the risk. Anticoagulation decreases the risk, but does not eliminate it (2, 5).

DMARDs may increase the risk of infection and impair wound healing, but medication withdrawal leads to flare, compromising rehabilitation. Although the use of anti-TNF agents such as golimumab have been beneficial in decreasing joint damage, there is a clear increase in infection which may include surgical site infection, currently under study at HSS. Golimumab was held one month prior to surgery, with the plan of restarting it once the sutures were removed and the wound was healing well, typically at two to three weeks. Small studies have reported increased perioperative infections with leflunomide, so this was also held, and restarted once bowel and kidney function were re-established. Given the prolonged half life of leflunomide, this prevents excess accumulation in the event of perturbations of renal function, but does not decrease tissue levels (7).

The patient returned home on post-op day 19 without knee pain, ambulating with a walker. She remains on coumadin and has restarted her leflunomide and was instructed to resume golimumab.

Article and references continued on back page.

Systemic Lupus Erythematosus and Severe Pulmonary Hypertension

Case presented by Lisa Sammaritano, MD; Weijia Yuan, MB; Kyriakos Kirou, MD; James Horowitz, MD; and Evelyn Horn, MD



Figure 1: Chest AP X-ray. The overall cardiovascular silhouette is enlarged. The lungs are well expanded and clear.

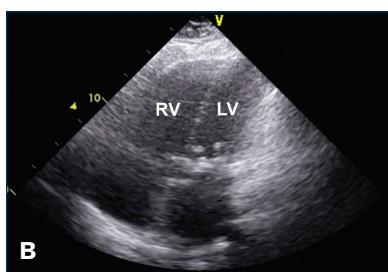
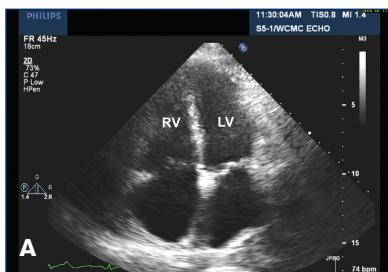


Figure 2: Representative echocardiograms from teaching archives. (2A) Normal echocardiogram: Right ventricle is approximately 2/3 the size of the left ventricle. Atria are normal in size. (2B) Abnormal echocardiogram: Right ventricle is enlarged with reduced function. Right atrium is enlarged.



Figure 3: Chest CT without contrast. Possible trace right pleural effusion vs. pleural thickening seen on the limited thoracic CT images. Minor left basilar linear scarring is noted. No evidence of interstitial lung disease. Small pericardial effusion is noted.

CASE REPORT: A 27-year-old woman was admitted to HSS in June 2009 with syncope and severe dyspnea on exertion (DOE). The patient was diagnosed with systemic lupus erythematosus (SLE) in 2003 with manifestations including malar rash, photosensitivity, Raynaud's, pericarditis, arthritis and positive autoantibodies (anticentromere antibody, anti-dsDNA and anti-RNP). Symptoms were controlled with hydroxychloroquine and intermittent steroids until January 2008, when she developed new DOE during her fourth week of pregnancy. By March 2008, she could walk only one block. Pulmonary embolism and interstitial lung disease were excluded by computed tomography (CT) scans, and right heart catheterization (RHC) in May 2008 showed pulmonary artery mean pressure of 30 mm Hg, PVR 6 mm Hg. An echocardiogram showed estimated pulmonary arterial systolic pressure (PASP) 65 mm Hg. The patient's pregnancy was terminated and she was started on sildenafil. However, following her pregnancy termination, she was lost to follow-up and not compliant with this therapy. In October 2008 she was restarted on sildenafil but clinically deteriorated when she ran out of medication.

In May 2009 repeat RHC was performed for worsening DOE and revealed PASP of 93 mm Hg, and in June 2009 she was admitted for profound dyspnea and syncope. An examination revealed a heart rate of 118/min, loud P2 and scattered dry crackles in bilateral lungs. Oxygen saturation was 97 percent on 50 percent face mask. The patient also had a new malar rash and synovitis of the bilateral elbow, metacarpophalangeal and proximal interphalangeal joints. Lab tests revealed a lowered platelet count (69,000/ μ l), hypocomplementemia (C3 53.2 ng/ml, C4 4.1 ng/ml), 10 to 25 urine red blood cells per high-powered field and new proteinuria (1.6 g/24 hours). A chest X-ray demonstrated mild enlargement of the cardiovascular silhouette, otherwise normal (Figure 1). An echocardiogram showed normal ejection fraction, a dilated right ventricle/right atrium, and severe pulmonary hypertension (Figure 2); a chest CT was positive for pleural effusion/thickening (Figure 3). The patient was started on intravenous (IV) methylprednisolone 16mg q8h for active lupus. Two days into treatment, she was weaned off oxygen and could walk 20 feet. Before discharge, sildenafil and ambrisentan were started and she began a six month course of monthly IV cyclophosphamide with prednisone taper, followed by mycophenolate mofetil maintenance therapy. In addition to medical therapy, the patient and her family were counseled regarding the nature of the disease and necessary lifestyle adjustments. The patient returned to work as a nurse in June 2010. RHC in October 2010 showed PASP of 52 mm Hg.

Currently, she is able to walk several miles and climb three flights of stairs.

DISCUSSION: Dyspnea is a frequent complaint in SLE patients: 50 to 70 percent of SLE patients exhibit respiratory manifestations during their disease course. Typical symptoms of pulmonary arterial hypertension (PAH) include dyspnea, chest pain, fatigue and decreased exercise tolerance. These nonspecific symptoms mimic a wide range of lupus-related cardiopulmonary disorders, making early diagnosis challenging. An uncommon but severe complication, SLE-PAH affects 0.5 to 14 percent of patients (1); it is associated with presence of antiphospholipid antibodies and Raynaud's syndrome (2).

An echocardiogram is an effective screening tool; pulmonary function tests and chest CT scans are necessary to rule out other etiologies. Definitive diagnosis requires right heart catheterization. Although survival has improved with new therapies, connective tissue disease-associated PAH has a poorer prognosis than idiopathic PAH (iPAH). Prognosis for SLE-PAH is better than for systemic sclerosis (SSc)-PAH, however: Three-year survival rates for SLE-PAH and SSc-PAH are 75 percent and 47 percent respectively (3).

Standard treatments (endothelin receptor blockers, prostacyclins and phosphodiesterase-5 inhibitors) are effective for SLE-PAH (4). In contrast to iPAH and SSc-PAH, immunosuppressive therapy is frequently effective for SLE-PAH. Jais et al. described 23 SLE and MCTD patients treated with cyclophosphamide/steroid, alone or in combination with vasoactive therapy for six months. Fifty percent of patients treated with immunosuppressive therapy alone showed improved six minute walk tests and mean PA pressures; the best responses were in patients with the least severe disease at the baseline (5).

In this patient, PAH presented during pregnancy, which may make diagnosis difficult: dyspnea and fatigue are common in pregnancy. Maternal mortality with severe PAH is high (50 percent), with typical sudden postpartum deterioration, and termination of the pregnancy is generally recommended.

Although SLE-PAH may respond to immunosuppressive therapy, our patient had a dramatic and rapid response to intravenous solumedrol, suggesting an additional inflammatory component, perhaps the acute reversible hypoxicemic syndrome described by Abramson et al. (6). They reported on SLE patients hospitalized with severe lupus flares with documented hypoxemia, absence of parenchymal disease, and increased C3a levels. Hypoxemia was attributed to leukoagglutination and complement activation within the pulmonary vasculature, and patients responded to steroids within 72 hours.

Article and references continued on back page.

AUTHOR DISCLOSURES:

Drs. Sammaritano, Yuan, Kirou, Horowitz and Horn do not have a financial interest or relationship with the manufacturers of products or services.

Rheumatoid Arthritis Mimicking Pigmented Villonodular Synovitis

Case presented by Michael D. Lockshin, MD; Alana B. Levine, MD; and Edward F. DiCarlo, MD

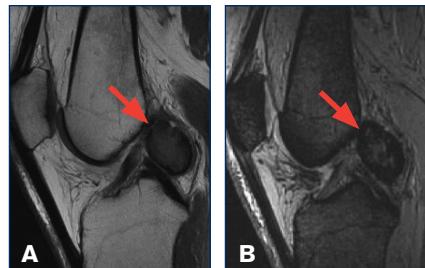


Figure 1: Sagittal moderate echo time MR image (1A) and T2-weighted gradient echo sagittal image (1B) demonstrate an intracapsular soft tissue mass (arrow), consistent with PVNS. Note the lower signal intensity on 1B due to the paramagnetic effect from hemoglobin degradation products.

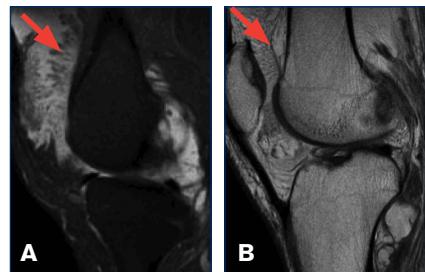


Figure 2: Fat suppressed T2-weighted time sagittal MR image on the left (2A) and moderate echo time sagittal image on the right (2B) demonstrates diffuse bulky synovitis without a nodular morphology, consistent with an inflammatory synovitis of the rheumatoid type.

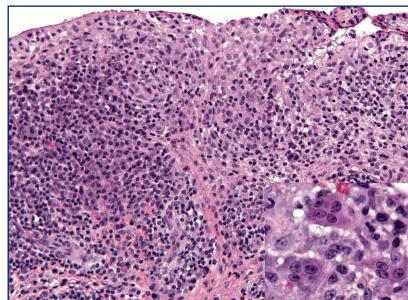


Figure 3: This intermediate-power photomicrograph of the synovial shavings shows focally marked hyperplasia of the lining layer at the top with intense lymphoplasmacytic inflammation in the left side of the image and scattered chronic inflammatory cells intermixed with the synovial lining cells on the right. The insert shows three multinucleate synovial giant cells within the hyperplastic lining layer from elsewhere in the specimen. (H&E, x20; insert x40)

CASE REPORT: A 22-year-old female swimmer presented to HSS Rheumatology with three years of right knee pain and swelling. An MRI performed at an outside institution three years earlier showed synovitis and a large effusion. Serologic studies for rheumatic diseases were negative. Arthroscopic synovectomy revealed reddish-brown areas of synovium suggestive of pigmented villonodular synovitis (PVNS). After surgery, the patient was asymptomatic and resumed swimming until swelling returned one year later. Repeat MRI suggested possible recurrence. Reevaluation of pathology slides at a second institution was again found to be consistent with PVNS. Shortly thereafter the patient developed new onset left knee, right elbow, neck and back pain with swelling. A rheumatologist diagnosed juvenile arthritis and initiated methotrexate, which provided only modest relief of symptoms.

Medical history was otherwise significant for asthma. Her medications included methotrexate 20 mg intramuscular weekly, folic acid, fluticasone/salmeterol, montelukast and albuterol as needed. The patient is an elementary school teacher. She did not drink alcohol, smoke tobacco, or use illicit substances. There was no family history of rheumatic disease.

She was a well-appearing young woman with vital signs within normal limits. Her general physical examination was unremarkable. The musculoskeletal exam revealed swelling and tenderness bilaterally in the wrists, knees and ankles with decreased range of motion.

Re-examination of the original synovial biopsy at HSS did reveal focal hemosiderosis and giant cells, but was most notable for synovial hypertrophy and an intense lymphoplasmacytic infiltration, most consistent with rheumatoid arthritis. Methotrexate was discontinued and adalimumab and prednisone were initiated. The patient responded well and adalimumab was discontinued after six months of treatment. The patient remains on low doses of prednisone.

DISCUSSION: This patient has a polyarticular inflammatory arthropathy with pathologic evidence of inflammatory synovitis. Given its duration, the differential diagnosis for this condition includes rheumatoid arthritis and spondyloarthropathy. While the patient originally presented with a monoarthritis and was thought to have PVNS, the evolution to a polyarthritis makes this diagnosis unlikely.

Pigmented villonodular synovitis, a benign proliferation of synovial tissue, is divided into three forms, including an isolated tenosynovitis,

a diffuse form commonly involving the knee, and a localized form that projects into the joint space, causing signs and symptoms of a loose body. Initial evaluation of this patient suggested the diffuse form of PVNS in the knee.

Pigmented villonodular synovitis is almost always monoarticular. There are rare reports of polyarticular PVNS in the literature (1, 2). While not apparent on plain radiographs, PVNS typically appears as a soft tissue mass with a characteristic appearance on T2-weighted magnetic resonance imaging (Figure 1, image from a different patient), in contrast to the bulky inflammatory synovitis seen in rheumatoid arthritis (Figure 2, image from a different patient). On gross pathology, PVNS tissue is thickened and reddish-brown, owing to hemosiderin deposition, with villous or nodular proliferation depending on the site of involvement. Histopathology shows proliferation of synovial cells, multinucleated giant cells, and an intermixed inflammatory infiltrate of lymphocytes, plasma cells, fibroblasts, and large epithelioid histiocytic (foam) cells that can contain fat or hemosiderin (3). Surgical treatment for diffuse PVNS of the knee involves open or arthroscopic synovectomy, and recurrence is not uncommon. There may also be a role for external beam radiation therapy. One report describes the use of infliximab for refractory PVNS of the knee with significant clinical and histopathological improvement (4).

This patient's synovial tissue showed a hyperplastic lining layer containing intense lymphoplasmacytic infiltration including synovial giant cells (Figure 3). Presumably, the presence of these giant cells, along with focal hemosiderosis in the tissue, led to the initial interpretation as PVNS. For a histopathologic diagnosis of PVNS, however, the giant cells must be intermixed with epithelioid macrophages in sheets or aggregates deep to the lining layer; this was not seen in this specimen. The presence of hemosiderosis is nonspecific. The hyperplastic lining layer and intense inflammatory infiltrate support a diagnosis of inflammatory arthritis, such as rheumatoid arthritis, which can also have foci of hemosiderosis as well as superficial giant cells in the lining layer.

This case demonstrates the diagnostic challenges frequently seen in rheumatology. It may take years for many of the rheumatic diseases to truly present themselves and, as in this case, patients may see their diseases slowly evolve and change character over time. A multidisciplinary approach is essential to the diagnosis and management of such patients.

References continued on back page.

Tumor Necrosis Factor Inhibition Therapy for Sarcoidosis Presenting as Transverse Myelitis and Uveitis

Case presented by Arthur M.F. Yee, MD, PhD

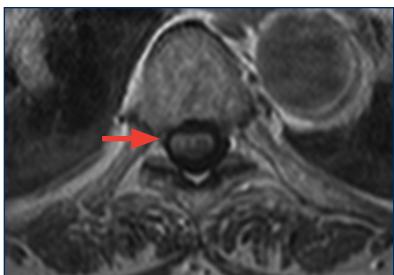


Figure 1: Axial post-gadolinium non-fat-saturated T1-weighted MRI examination demonstrates ventral and lateral cord enhancement with extension into the anterior and lateral cord parenchyma at the level of T7 (red arrow).



Figure 2: Sagittal post-gadolinium non-fat-saturated T1-weighted MRI examination demonstrates ventral cord enhancement with intramedullary extension from levels T5 through T8 (red arrow). The thoracic cord is not enlarged.

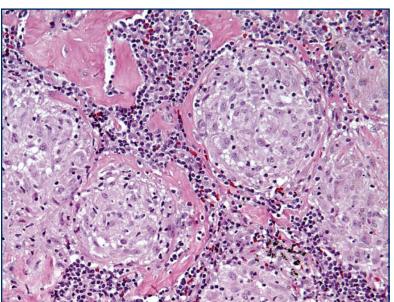


Figure 3: Lymph node biopsy specimen demonstrates multiple non-caseating granuloma pathognomonic of sarcoidosis, showing giant cells well-circumscribed by epithelioid histiocytes and lymphocytes.

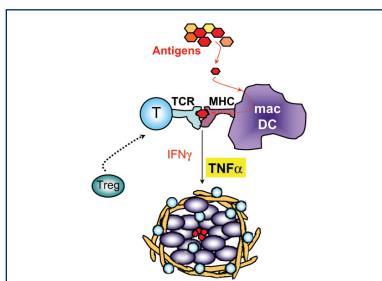


Figure 4: The overproduction of TNF- α by activated macrophages is hypothesized to play a central role in the formation and maintenance of granulomas in sarcoidosis.

CASE REPORT: A 72-year-old previously healthy Greek woman originally presented with bilateral vision changes in the fall of 2007 and was diagnosed with bilateral uveitis and vitreous hemorrhage. She was treated with surgical debridement and topical corticosteroids, but no underlying etiology was identified.

In July 2008, the patient was admitted to a local hospital with acute onset right leg weakness, bilateral lower extremity paresthesias ("cold leg"), and partial bowel and bladder incontinence. An MRI showed transverse myelitis (Figures 1 and 2), and cerebrospinal fluid showed pleiocytosis. She received high-dose corticosteroids to which she had an initial partial response, but subsequently developed multiple adverse effects including Cushingoid changes, obesity, hypertension, diabetes, glaucoma and cataracts. Systemic corticosteroids were discontinued, and the patient's myelitis relapsed. She consulted various neurologists but was given no further treatments outside of physical therapy and eventually became confined to a wheelchair.

In spring 2009, her uveitis recurred, and she was started again on corticosteroid ophthalmic drops. Further investigation at this time revealed mediastinal lymphadenopathy. A lymph node biopsy revealed non-caseating granulomas consistent with sarcoidosis (Figure 3), and the patient was referred to Hospital for Special Surgery.

Initial physical examination at HSS was notable for flaccidity and paresthesia of an atrophic right leg from the hip girdle distally. Strength in the left leg was normal, but there was mild loss of discrimination between pin-prick and dull-touch. Weekly subcutaneous adalimumab 40 mg was initiated, and the patient regained near-normal sensation and improved strength in the right leg within the first two weeks of therapy, declaring "My leg is warm, and I can stand!" She enjoyed steady improvement without complications until six months later when she developed mild recurrence of her neurologic symptoms. Adalimumab was replaced with monthly intravenous infliximab 10 mg/kg and oral mycophenolate mofetil 500 mg twice daily. The patient was able to recapture and exceed her prior improvement. After 12 months on the current medical regimen, the patient can now support her own weight and ambulate short distances without assistance or assistive devices. The uveitis has also been quiescent.

DISCUSSION: Sarcoidosis is a systemic inflammatory disorder characterized by pathognomonic non-caseating granulomatous inflammation potentially involving any organ system. Clinical presentations can vary widely from patient to patient with regards to severity and to diversity of organ involvement. Accord-

ingly, many patients may need only monitoring, while others require immediate and aggressive intervention. Moreover, this phenotypic heterogeneity presents difficulties in designing and conducting clinical trials, and thus generalizable evidence-based guidelines for treatment are lacking. When treatment is required, systemic or local corticosteroids are typically offered as first-line therapy but are often only temporizing and are associated with unacceptable adverse effects with prolonged use. Steroid-sparing agents, such as methotrexate, azathioprine, and hydroxychloroquine, are commonly used for maintenance therapy (1). However, the few well-controlled trials supporting the use of these agents are typically restricted to narrowly defined patient populations, and applicability to rare or multisystem organ involvement is unclear. Moreover, the specific mechanisms of the therapeutic action of these drugs are not known.

Tumor necrosis factor (TNF) has long been implicated in the pathogenesis of sarcoidosis, and so the advent of anti-TNF therapies has opened an intriguing targeted approach to the treatment of this condition. TNF is necessary for the development and maintenance of granulomas (Figure 4), and mice deficient in TNF fail to generate granulomas in response to antigen challenge (2). In sarcoidosis, macrophage TNF production is higher in patients with active disease than in patients with inactive disease (3).

Since our initial report of the successful treatment of complicated multisystem sarcoidosis using the monoclonal anti-TNF antibody infliximab (4), the potential benefits of TNF-inhibitors in the treatment of challenging sarcoidosis, spanning a diverse range of clinical presentations, have been described in many subsequent case reports and series (1). It is an interesting observation, however, that TNF-inhibitors may not be equally effective. Etanercept, a chimeric soluble receptor for TNF, was not found to be effective in a prospective uncontrolled case series of patients with moderately severe active pulmonary sarcoidosis (5), while infliximab did show benefit in a placebo-controlled double-blinded trial (6). This may relate to the ability of infliximab, but not etanercept, to bind to TNF bound to the surface of inflammatory cells and granulomas, thereby inducing the regression of granulomas and attendant inflammatory burden. The other monoclonal antibodies (i.e., adalimumab, golimumab, and certolizumab) should share similarities to infliximab.

TNF-inhibition offers a very promising targeted approach to a very challenging disease. As illustrated by the presented case, advantages include steroid-sparing capacity, prompt response, and durability of efficacy.

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CASE 1 CONTINUED

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References for Case 1 continue online at www.hss.edu/complexcases.

AUTHOR DISCLOSURES:

Drs. Goodman, Russell and Figgie do not have a financial interest or relationship with the manufacturers of products or services.

CASE 2 CONTINUED

Maintaining a high index of suspicion for PAH in SLE patients with exertional dyspnea is critical for early diagnosis, and institution of early aggressive immunosuppressive therapy in addition to PAH-specific medications increases the likelihood of a favorable clinical outcome.

References for Case 2 appear online at www.hss.edu/complexcases.

DESIGN/PRODUCTION:

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CASE 3 CONTINUED

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AUTHOR DISCLOSURES:

Drs. Lockshin, Levine and DiCarlo do not have a financial interest or relationship with the manufacturers of products or services.

CASE 4 CONTINUED

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AUTHOR DISCLOSURE:

Dr. Yee does not have a financial interest or relationship with the manufacturers of products or services.

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Case 1

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Cases 1-2:

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Case 4:

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