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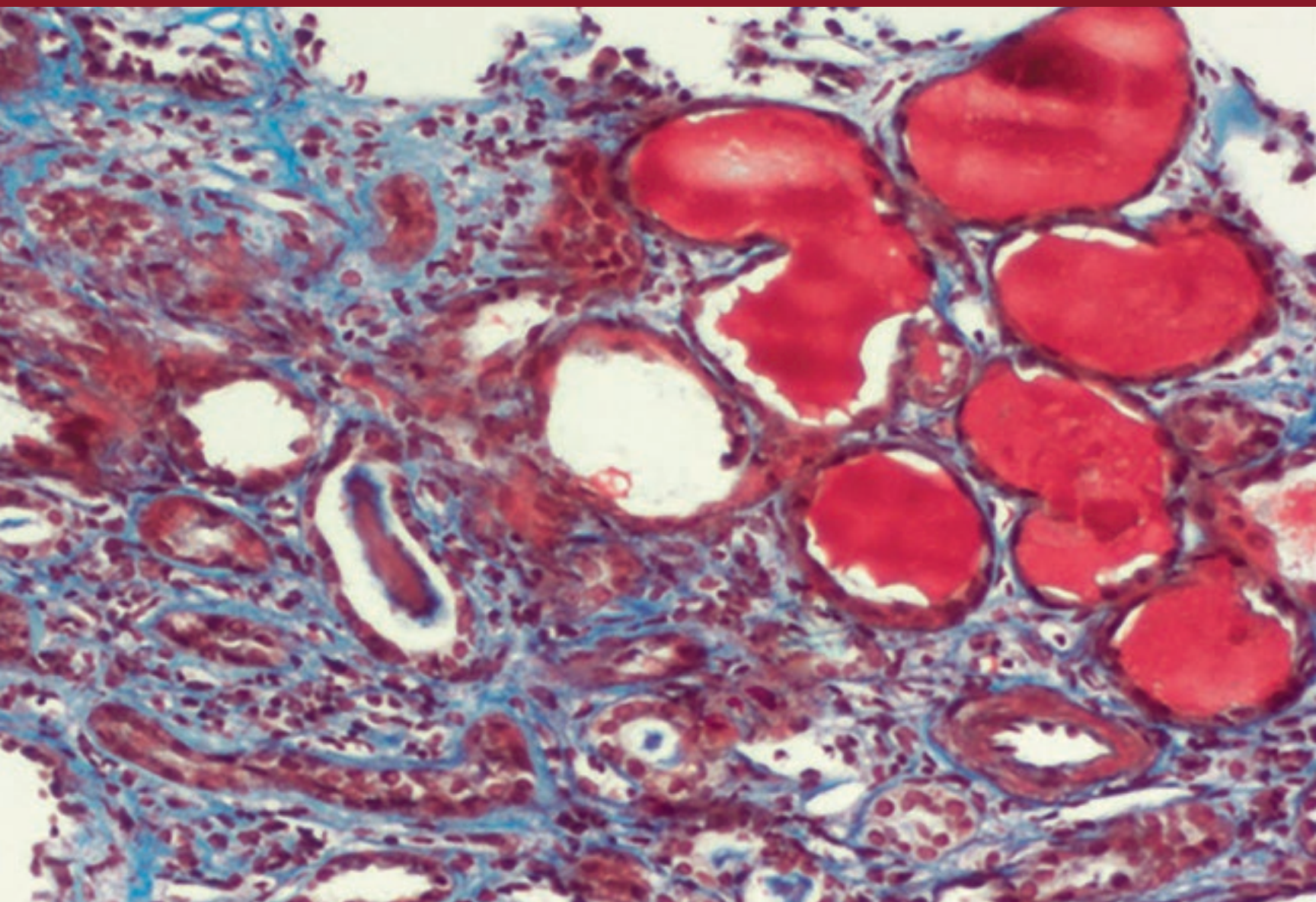
Cleveland Clinic

Rheumatology Connections

An Update for Physicians | Summer 2022



From the Chair of Rheumatic and Immunologic Diseases

Dear Colleagues,

Welcome to the Summer 2022 *Rheumatology Connections*. This issue is packed with illuminating case reports that we hope will pique your interest and expand our shared understanding of the field.

A recent Cleveland Clinic collaboration with colleagues from other medical centers examined the ability of patient-reported outcomes to differentiate between states of low disease activity and remission in psoriatic arthritis. Drs. Elaine Husni and Juliette Yedimenko share the findings.

Drs. Emily Littlejohn, Saja Almaaitah and John Myles discuss a rare case of acute onset class II lupus nephritis with podocytopathy and collapsing glomerulosclerosis as the initial presentation of systemic lupus. Collaboration was key to the plan of care that stabilized the patient.

In a case reported on by Dr. Carol Langford, a patient with Takayasu arteritis arrived at the emergency room with acute chest pain, and pulmonary embolism was considered. The answer was in the imaging.

Dr. Ahmed Elghawy is a member of our staff who earned his Sports Medicine certificate after completing his Rheumatology Fellowship. His unique perspective provides an excellent resource for us as we collaborate in the care of patients with rheumatic diseases who pursue athletic activities. In this issue, he presents two stories that illustrate the importance of widening the diagnostic lens when we care for these patients.

There is still much to be learned about long-term therapies that use the immunosuppressant mycophenolate mofetil (MMF). Dr. Soumya Chatterjee provides an analysis of Epstein-Barr virus-associated primary central nervous system lymphoma in a patient who had been receiving MMF to manage diffuse scleroderma.

The differential diagnosis of systemic vasculitides includes a number of autoimmune disorders, various malignancies, and infections such as infective endocarditis. A case presented by Dr. Kinanah Yaseen demonstrates how endocarditis symptoms can mimic primary systemic vasculitides.

Finally, education is a foundational value at Cleveland Clinic and within the R.J. Fasenmyer Center for Clinical Immunology. As the center's director, Dr. Leonard Calabrese has led a vigorous and expanding immunologic CME program. It's gratifying to see how the impact has grown even during the pandemic.

Innovative educational modalities are highlighted in our profile of Dr. Adam Brown, who shares his infectious passion for the mysteries of immunology through books, CME courses and his Healio podcast, "Rheuminations."

I'm so proud of the work by our team in the Department of Rheumatic and Immunologic Diseases, and by the dedication of those who work across the field to improve patients' lives. I hope that you will find the stories that follow an opportunity to connect, collaborate and consult with our team.

Respectfully,

Abby G. Abelson

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BEST HOSPITALS U.S.News & WORLD REPORT RHEUMATOLOGY 2021-22

Cleveland Clinic's Rheumatology Program is ranked among the top 2 in the nation in *U.S. News & World Report*'s "America's Best Hospitals" survey.

On the cover:
A view of a glomerulus with a suggestive collapsing lesion. See article, page 4.

Rheumatology Connections, published by Cleveland Clinic's Department of Rheumatic and Immunologic Diseases, provides information on leading-edge diagnostic and management techniques as well as current research for physicians.

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Rheumatology Connections is written for physicians and should be relied on for medical education purposes only. It does not provide a complete overview of the topics covered and should not replace the independent judgment of a physician about the appropriateness or risks of a procedure for a given patient.

Correction:
The Winter 2022 edition of *Rheumatology Connections* contained incorrect author attribution and an incorrect photo for the article titled "Case Report: Common Variable Immunodeficiency and Lung Disease," which appeared on page 6. The article was written by James Fernandez, MD (fernanj2@ccf.org, 216.444.6933), Staff Physician in the Allergy and Clinical Immunology Department.

The Potential for Patient-Reported Outcomes to Distinguish Between Low Disease Activity and Remission in Psoriatic Arthritis

by M. Elaine Husni, MD, MPH, and Juliette Yedimenko, MD

Rheumatologists rely on several composite instruments to measure disease activity in patients with psoriatic arthritis. These tools typically examine the number of swollen and tender joints, as well as the number of tendons and percentage of skin involved. However, very few composite instruments include patient-reported outcomes, which may have the potential to determine low disease expression or remission.

We collaborated with colleagues from New York University, the University of Pennsylvania and the University of Utah to study the ability of patient-reported outcomes to independently differentiate between states of low disease activity and remission in psoriatic arthritis based on validated composite indices.

Capturing a more complete picture of the condition

All major treatment guidelines advocate the treat-to-target approach for psoriatic arthritis, which affects the joints, skin, eyes and gastrointestinal system. The goal is to decrease inflammation, reduce radiographic progression and improve function and quality of life. However, it's difficult to capture all the components of this complex inflammatory disease using one of the existing composite tools.

Patient-reported outcomes could indicate the residual impact of psoriatic arthritis on function and quality of life that isn't readily obtained by standard composite instruments, laboratory data and clinical examinations.

Our retrospective cross-sectional study examined data from 2016 to 2019 in a national database of adult psoriatic patients from the four participating institutions, which comprise the Psoriatic Arthritis Research Consortium (PARC). We used three patient-reported outcome tools:

- Patient-Reported Outcomes Measurement Information System (PROMIS) measures of Physical Health, Mental Health and Fatigue
- Routine Assessment of Patient Index Data 3 (RAPID3)
- EULAR Psoriatic Arthritis Impact of Disease (PSAID12)

The study included 227 patients. The team looked for correlations between patients who identify as having low disease activity or remission based on patient-reported outcomes and more objective data, such as physician assessments and lab results.

Study results point to value of patient-reported outcomes

Our initial hypothesis was that subjective, patient-reported outcomes could be influenced by other disease states and therefore might not be able to distinguish between low disease activity and remission. However, the results suggest otherwise.

One of our primary findings is that patients who were in remission as indicated by one of three traditional composite measures — minimal disease activity (MDA), clinical disease activity index (CDAI) or disease activity in psoriatic arthritis (DAPSA) scores — all had significantly better PROMIS scores in the physical, mental and fatigue domains, as well as PSAID12 scores. When considering RAPID3 questionnaires, low disease severity and near remission were reported by nearly all the patients who were in remission according to traditional composite tools.

Potential impact on clinical practice and treatments

Accurate assessment of disease activity in psoriatic arthritis is key in clinical practice so physicians can help guide informed treatment decisions, and adding in the patient's perception of their disease provides another dimension in the assessment. Our study emphasizes the importance of patient-reported outcomes to ascertain remission and low disease activity.

The study is one of several research projects PARC members hope to conduct with the goal of tailoring treatment and perhaps tapering psoriatic arthritis patients with low disease activity and remission off medication.

This case was initially reported in Joint Bone Spine *(2020;87:163-166).*

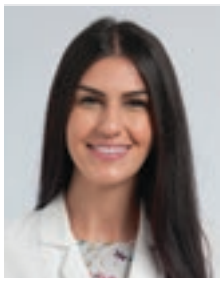
Dr. Husni (husnie@ccf.org; 216.445.1853; @ElaineHusniMD) is Director of the Arthritis & Musculoskeletal Treatment Center in the Department of Rheumatic and Immunologic Diseases, Director of Cleveland Clinic's Psoriatic Disease Biobank and Co-Director of the Cleveland Clinic Dermatology and Rheumatology Collaborative Care Center.

Dr. Yedimenko (yedimej@ccf.org, 216.445.2228) is Associate Staff in the Department of Rheumatic and Immunologic Diseases.

CASE REPORT: LUPUS PODOCYTOPATHY

Multidisciplinary Treatment of a Rare Presentation of Lupus Nephritis

by Saja Almaaitah, MD, Jonathan Myles, MD, and Emily Littlejohn, DO, MPH



Dr. Almaaitah recently completed her fellowship in the Department of Rheumatic and Immunologic Diseases.

Dr. Myles (216.444.2842, mylesj@ccf.org) is a Staff Pathologist in the Department of Anatomic Pathology.

Dr. Littlejohn (littlee3@ccf.org; 216.445.5559; @ELittlejohnDO) is Associate Staff in the Department of Rheumatic and Immunologic Diseases.

Presentation

A 43-year-old female presented to Cleveland Clinic with acute-onset progressive fatigue, generalized weakness and bilateral lower-extremity swelling for one month. On admission, she was found to have elevated systolic blood pressure (160/84 mmHg) and severe acute kidney injury with creatinine of 5.5 mg/dL, from a baseline of 0.7 mg/dL tested one year prior. Urine analysis revealed presence of large blood and large protein. Urine protein creatinine ratio was significantly elevated at 9.9. Autoimmune workup was positive for antinuclear antibodies in addition to positive anti-Smith antibodies, positive anti-chromatin antibodies, positive anti-double-stranded DNA antibodies and positive cytoplasmic perinuclear antibody (p-ANCA). Nephrology and rheumatology teams were consulted and recommended a kidney biopsy that showed mild immune-complex mediated mesangiopathic glomerulonephritis with immunofluorescence staining positive for IgG, IgM, C3 and C1q, in addition to diffuse effacement of epithelial foot processes with possible collapse and segmental scarring, consistent with class II lupus nephritis with podocytopathy and collapsing glomerulosclerosis (Figure 1).

Lupus podocytopathy

Lupus nephritis is one of the most common organ-threatening manifestations of systemic lupus erythematosus, occurring in up to 50% of patients with lupus, with 50% of those diagnosed progressing to end-stage renal disease.[1] Histology of lupus nephritis is characterized by mesangial, subendothelial and subepithelial immune-complex deposition on renal biopsy. Lupus podocytopathy is a rare manifestation of lupus kidney disease occurring in up to 2% of lupus nephropathy[2], and is characterized by diffuse epithelial cell foot process effacement, resembling histologic findings of minimal change disease or focal segmental glomerulosclerosis (FSGS). Collapsing glomerulopathy describes severe injury to podocytes with loss of markers of differentiation, proliferation of podocytes and global or segmental collapse of the glomerular capillary tuft.[3,4] Lupus podocytopathy tends to be steroid responsive, though FSGS and collapsing subtypes are generally resistant to treatment and usually require aggressive immune suppression.

Treatment and collaborative management

Given unusual findings of lupus podocytopathy and collapsing glomerulosclerosis, biopsy results and treatment options were thoroughly discussed with the pathology, nephrology and rheumatology teams. Patient received intravenous (IV) pulse dose methylprednisolone of 1 g daily for three days and was started on IV cyclophosphamide 500 mg every 2 weeks for a total of six doses (EURO lupus protocol). Creatinine increased during hospitalization to a peak of 6.32 mg/dL and started to decline soon after the initiation of treatment. This was associated with improved lower limb swelling and energy level. Good urine output was maintained throughout the patient's disease course. In addition to the cyclophosphamide protocol, the patient was discharged from the hospital on prednisone 60 mg daily as part of a taper regimen. She was also started on hydroxychloroquine, pneumocystis prophylaxis and diuretics.

Patient completed induction therapy with cyclophosphamide infusions over three months. She was subsequently started on mycophenolate mofetil 1,000 mg PO twice daily. Creatinine level returned to normal range (0.84 mg/dL). Proteinuria significantly improved, though persisted, with urine protein creatinine ratio of 2.4. Throughout patient's entire clinical presentation, she never developed other manifestations of lupus, including inflammatory joint pain, mucocutaneous ulcerations, rashes, alopecia or pleuritis. The patient is maintained on mycophenolate mofetil 1,000 mg twice daily, hydroxychloroquine 400 mg daily and prednisone 5 mg daily and continues to do well.

Here we present a rare case of acute-onset class II lupus nephritis with collapsing glomerulosclerosis as the initial presentation of systemic lupus. The complexity and acuity of this patient's disease highlights the need for multidisciplinary management when caring for patients with systemic lupus erythematosus.

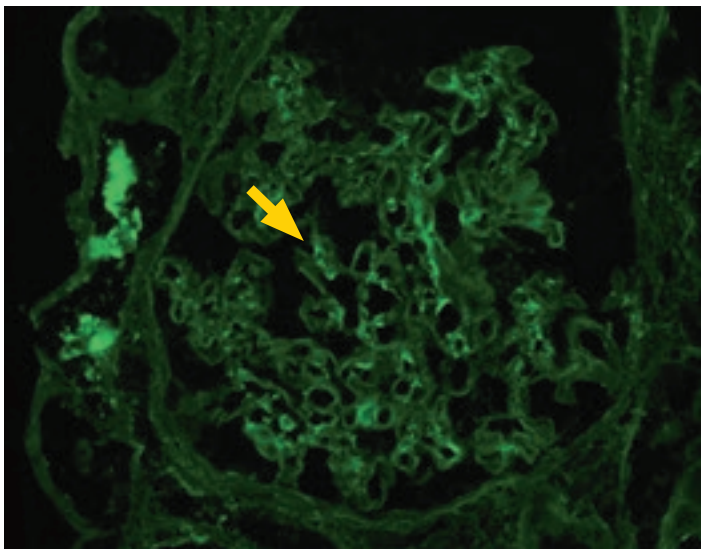


Figure 1: IgG immunofluorescence demonstrates 2+ granular mesangial staining (arrow).

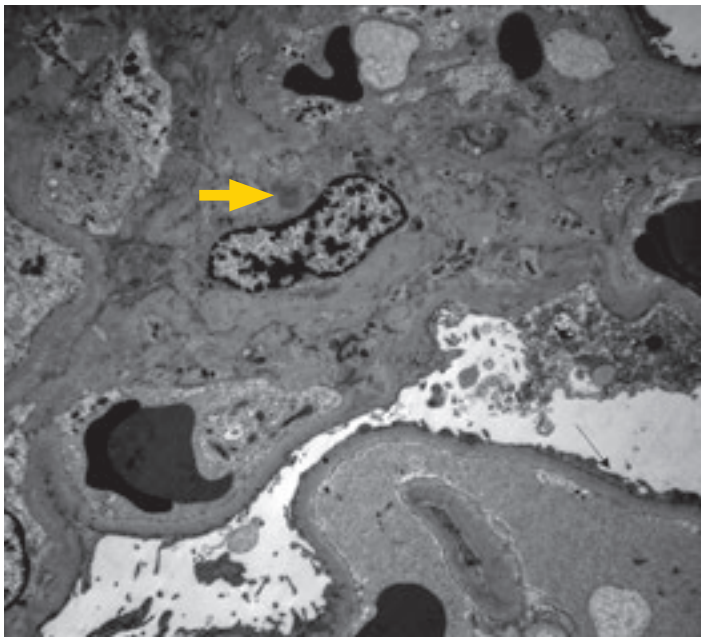


Figure 2: Electron microscope image demonstrates effacement of the epithelial foot processes (small arrows) and some mesangial electron dense deposit (large arrow).

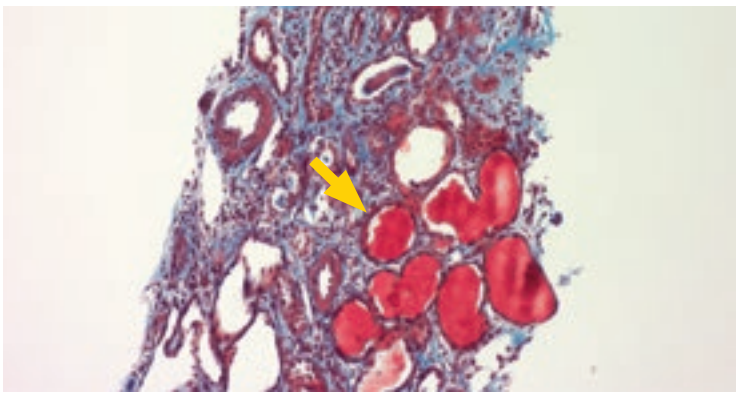


Figure 3: Masson trichrome stain of the interstitium. The collagen stains blue, and initial magnification is times 100. There was 40% interstitial fibrosis. Note the dilated tubules (arrow). Chronic interstitial changes would not be seen in minimal change disease.

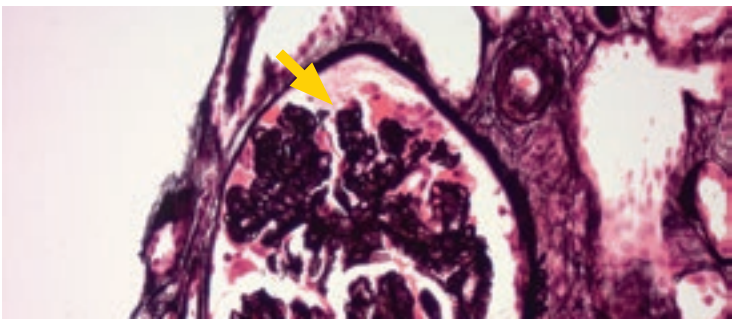


Figure 4: Jones stain (times 200 for the original magnification) demonstrates a view of a glomerulus with a suggestive collapsing lesion. At the top of the glomerulus, individual GBMs collapsing toward the mesangium (arrow) with narrowing of the capillary lumens.

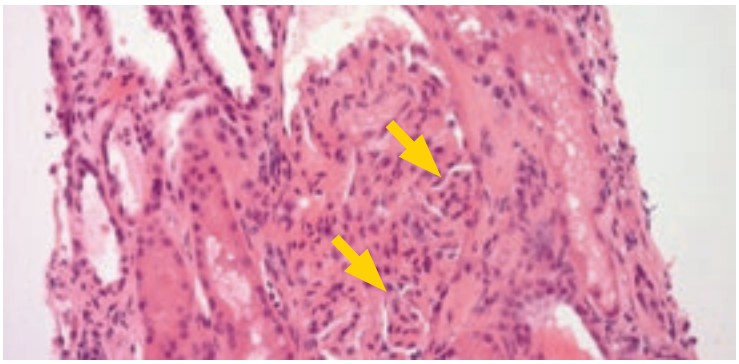


Figure 5: Hematoxylin and eosin stain (original magnification times 200). There is mesangial hypercellularity (arrows).

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Takayasu Arteritis: Pulmonary Embolism or Something Else?

by Carol Langford, MD, MHS, FACP

Dr. Langford (langfoc@ccf.org; 216.445.6056) is Director of the Center for Vasculitis Care and Research at Cleveland Clinic as well as Vice Chair for Research, Department of Rheumatic and Immunologic Diseases.

Case presentation

You receive a call about a 25-year-old female with a three-year history of Takayasu arteritis (TAK) who presents to the emergency room with acute chest pain. Her TAK vascular involvement includes an aneurysm of the aortic root and stenoses of the bilateral subclavian arteries and celiac artery. For this she is receiving treatment with prednisone 5 mg/day and methotrexate 20 mg/week, on which her disease has been in remission. Her only other medications are aspirin 81 mg/day and an oral contraceptive. She was feeling well until this morning, when she experienced the acute onset of pain in the midline of her lower chest. It had a sharp intermittent quality that did not change with breathing and was not associated with dyspnea. On examination she appeared uncomfortable when the pain was present, but she was not hypoxic. Evaluation included normal blood counts, chemistries, sedimentation rate, C-reactive protein, troponin, ECG and chest radiograph. Her d-dimer was mildly elevated at 820 ng/mL FEU (less than 500 ng/mL FEU being the cutoff to exclude a venous thrombotic event (VTE) in patients with low pre-test probability). As she is allergic to iodine-based contrast, she underwent a venous duplex of the lower extremities, which was negative for deep venous thrombosis, and a ventilation/perfusion scan that showed reduced perfusion of the left lung with perfusion defects in the left upper lobe, lingula and left lower lobe. This was interpreted to suggest high probability of a pulmonary embolism. When you see her, the chest pain has resolved.

Venous thrombotic events and vasculitis

An increased frequency of VTE has been observed in a number of different forms of vasculitis.[1] The strongest associations have been VTE in ANCA-associated vasculitis[2] and Behçet's disease, where both venous and arterial thromboses can occur.[3] For these entities, VTE are often seen in the setting of active vasculitis. For large vessel vasculitis, the association with VTE is less well established. In giant cell arteritis, database and cohort studies have suggested a greater risk of VTE than for the general population[4], but the published literature on TAK remains small. Another confounding variable in young women with TAK is the potential use of hormonally based contraceptive methods.

Spectrum of vascular involvement in Takayasu arteritis

TAK is a primary large vessel granulomatous vasculitis that has an estimated incidence of 150 new cases each year. TAK occurs predominantly in women, with the age of onset between 10 and 40 years old. TAK can affect the aorta, its major branches and the pulmonary arteries, where it manifests as vascular stenoses or aneurysms. The frequency of pulmonary artery involvement in TAK has ranged from 14% to 40% in published series and is likely underappreciated.[3] Pulmonary artery stenoses may not be readily visualized in the computed tomography angiography (CTA) or magnetic resonance arteriography (MRA) examinations performed in TAK to assess large vessel involvement. The pulmonary arteries represent a different vascular bed than the aorta and its branches, such that contrast injection timed specifically for these vessels is required in order for them to be clearly imaged.

While pulmonary artery involvement in TAK often lacks symptoms, it can present with chest pain, shortness of breath, palpitations, hemoptysis or signs of pulmonary hypertension. In acute settings, pulmonary artery involvement can mimic a pulmonary embolism in both symptoms and imaging findings.[5, 6] Reduced blood flow in perfusion scans can be seen with pulmonary embolism but also with pulmonary artery involvement in TAK. Arteriography, usually with CTA, can support the absence of arterial thrombus as well as other features of TAK, including a thickened arterial wall and tapered narrowing of the vessel.

Return to the patient

The possibility that pulmonary artery involvement in TAK was the cause of this patient's imaging findings was investigated. After receiving premedication prophylaxis, she safely underwent a CTA. This study was negative for pulmonary embolism and showed stenosis and wall thickening of the

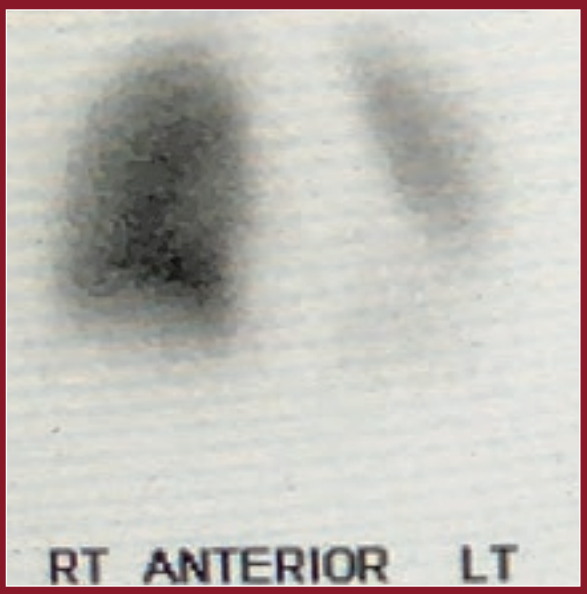

Figure 1: Perfusion scan showing decreased perfusion of the left lung.

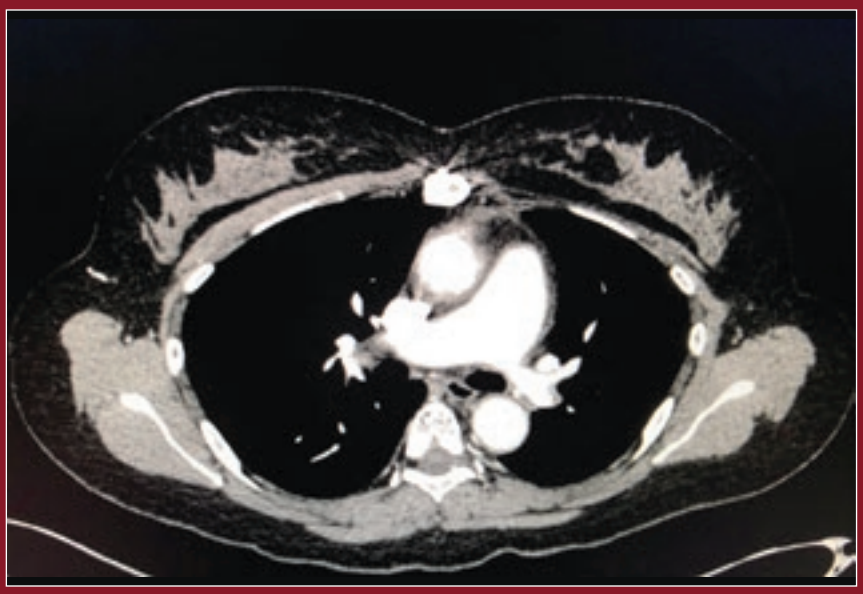

Figure 2: Computed tomography angiography showing stenosis of the left pulmonary artery with vessel wall thickening.

main left pulmonary artery with reduced blood flow corresponding to the abnormal perfusion scan. Using computerized visualization techniques, it was possible to determine that the pulmonary artery stenosis had been present at the time of the original diagnosis for which she had been treated. In order to reassess her disease activity status, she underwent an MRA of the aorta and branch vessels, which revealed no new changes. She was maintained on the same treatment for TAK, as she was not felt to have active arteritis. With follow-up, it was determined that her acute chest pain was likely due to esophageal spasm, with the perfusion imaging findings being unrelated to her reason for seeking urgent medical attention.

This patient illustrates that when perfusion imaging suggests a pulmonary embolism in a patient with TAK, further consideration should be given to the possibility of pulmonary artery involvement.

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WHERE SPORTS MEDICINE MEETS RHEUMATOLOGY

Recognizing Rheumatic Disease in Injured Athletes

by Ahmed Elghawy, DO

Dr. Elghawy (216.444.3876, elghawa@ccf.org) is Associate Staff in the Orthopaedic & Rheumatologic Institute. He is board certified in rheumatology, sports medicine and internal medicine.

CASE 1

A 20-year-old female has sought medical care at Cleveland Clinic's Arthritis and Musculoskeletal Center for intermittent low back pain for 18 months. She is a former high school gymnast with a history of spondylolysis at age 16 from repetitive lumbar hyperextension injuries sustained during her floor routines. This was treated conservatively, with complete resolution of symptoms. Similar symptoms recurred 18 months ago, though this time without any known hyperextension injury, and were described as intermittent, achy, worse in the morning, improved throughout the day and with naproxen (440 mg, twice a day as needed). One month after symptoms started, she was evaluated by her primary care physician, who ordered a lumbar radiograph that was reportedly unremarkable as per the patient, told that this was likely an exacerbation of her previous spondylolysis, advised to limit aggravating activities and was referred to physical therapy for rehabilitation. Unable to tolerate therapy at first, the patient was offered a muscle relaxant, which did not alleviate her symptoms. After completing eight weeks of therapy without relief, the patient slowly started to become more sedentary for fear of exacerbating her low back pain. Since this started, the patient admits to a 40-pound weight gain due to inactivity. Unable to tolerate performing her activities of daily living, the patient presented here for a second opinion. The patient had no known family history of autoimmunity.

Physical exam was significant for tenderness to palpation along the bilateral sacroiliac joints and right piriformis, without tenderness along the lumbar spine. A positive FABER (flexion abduction external rotation) test was noted bilaterally as was a Schober's test with 4 cm.

Laboratory findings were significant for a positive HLA-B27 with normal sedimentation rate and C-reactive protein. Radiographs of the sacroiliac (SI) joints demonstrated sclerosis along the iliac margins of the SI joints, and MRI of the pelvis (Figure 1) demonstrated evidence of active sacroiliitis. The patient was diagnosed with axial spondyloarthritis and was started on adalimumab 40 mg subcutaneously every two weeks. Upon reevaluation at eight and 12 weeks, the patient's low back pain had resolved and she was performing her activities of daily living without pain or loss of function.

CASE 2

A 22-year-old male presented to Cleveland Clinic's Arthritis and Musculoskeletal Center with left knee pain

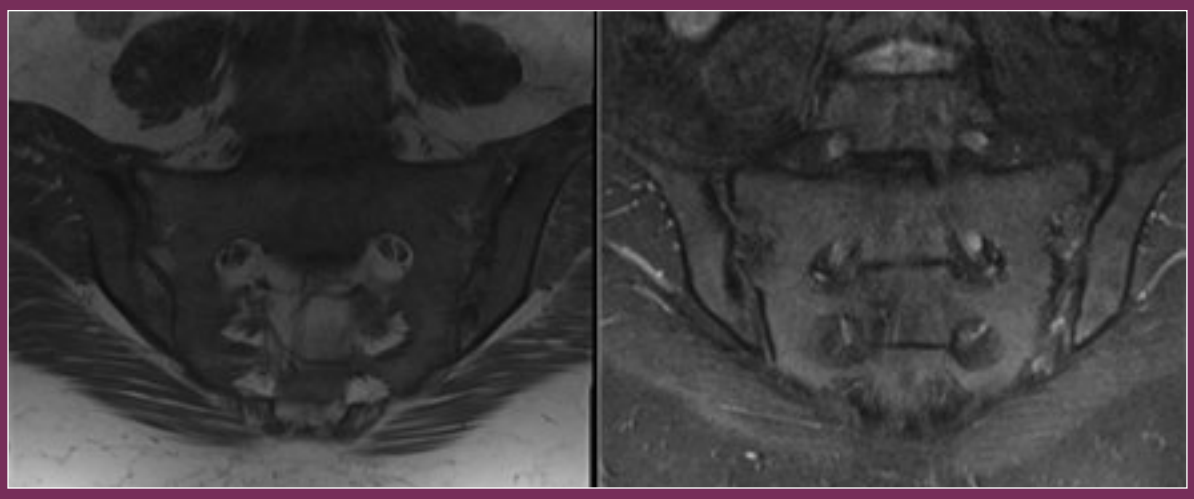


Figure 1: MRI Pelvis in coronal oblique views demonstrating sacroiliitis in T1 (left) and STIR (right).

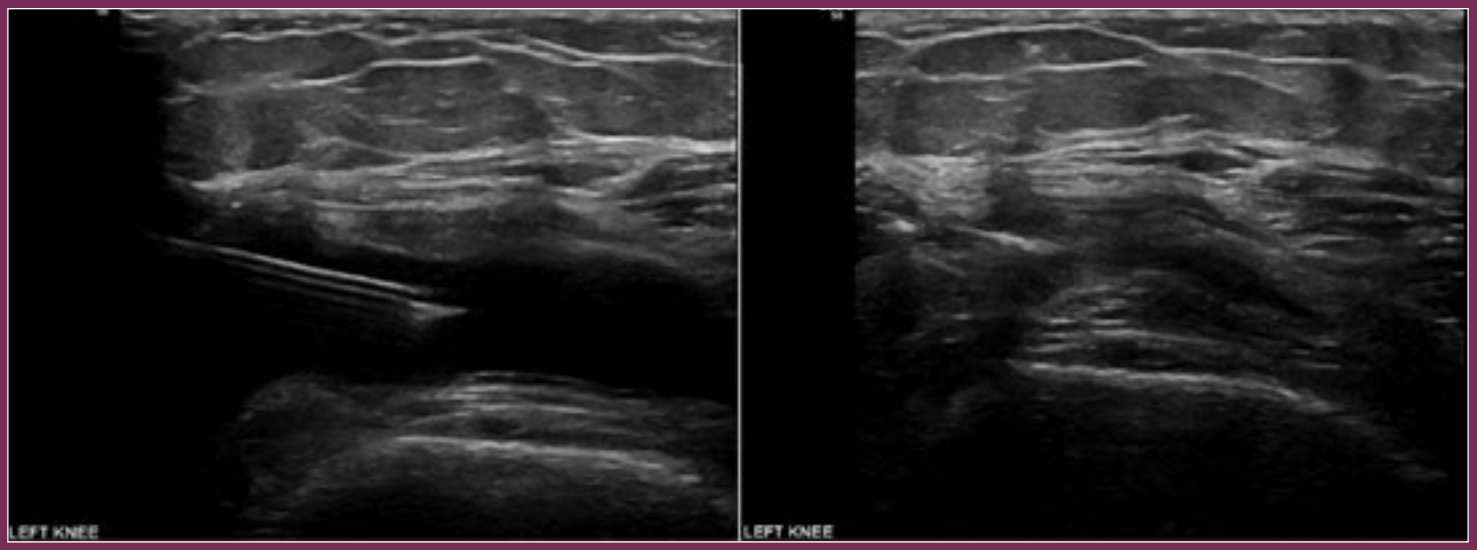


Figure 2: Ultrasound left knee – moderate knee effusion before and after knee aspiration.

and swelling. The patient is an in-season college wrestler who is on holiday break. The patient reports that three days ago, he developed sudden-onset left knee pain, swelling, redness and difficulty in flexing or extending the knee. He denies any inciting event, trigger or injury to his knowledge. He has not taken any medications for relief, and has tried to ice, though he notes that even touching the knee is exquisitely painful. He notes that he had similar symptoms two months ago that resolved on their own after a few days with ibuprofen. The patient denied any fever or chills. Interestingly, he noted that he had a similar episode of pain in his left first toe last year that he attributed to "turf toe."

On exam, the knee was diffusely tender to palpation, warm and erythematous and had evidence of effusion. There was difficulty flexing the knee beyond 80 degrees due to pain, and the patient was unable to tolerate provocative exams to test for ligamentous derangement.

A knee radiograph was unremarkable, and musculoskeletal ultrasound (Figure 2) demonstrated a moderate knee effusion. The knee was aspirated, yielding 34 cc of cloudy, turbid synovial fluid. Fluid analysis demonstrated < 2,000 RBC/uL, 35,616 total nucleated cells/uL with 76% neutrophils, negative Gram stain and culture, and presence of intracellular monosodium urate crystals. A serum uric acid level of 7.4 mg/dL was noted.

Upon further questioning, the patient admitted that he had difficulty reaching his desired weight for his weight class in wrestling and was taking furosemide in an effort to reach that weight. He had obtained this from other members of his team and admitted that he used it last year as well. The patient was placed on oral colchicine for his gout flare, with complete resolution of his symptoms. Prompt discontinuation of furosemide was advised, and the patient was counseled that if he develops frequent flares, urate-lowering therapy could be considered. Radiographs of his feet did not demonstrate any erosive changes, but it was discussed that his previous history of "turf toe" may have actually been a gout flare.

Athletes are strong and resilient but not impervious to rheumatic disease

Competitive athletes are typically highly motivated and adherent to advice and treatment plans formulated by the medical team. Often this is in line with their goals of a quicker recovery and return to sport. But sometimes the road to recovery is impeded – sometimes even misdirected with a wrong turn, leading to treatment delay and potentially more harm.

In the first case, we have a former gymnast with a previous low back injury in her teenage years that was successfully managed conservatively. Understanding that spondylolysis is a common hyperextension injury in gymnasts is vital in noting that her current complaint started without any new injury. Recognizing that her pain was present in a different location than what was

continued on page 11

First Report of EBV-Associated Primary CNS Lymphoma in a Patient with Diffuse Scleroderma on Long-Term Mycophenolate Mofetil

by Soumya Chatterjee, MD, MS, FRCP

Dr. Chatterjee (chattes@ccf.org; 216.444.9945) directs the Scleroderma Program in the Department of Rheumatic and Immunologic Diseases.

Presentation and initial management

A 46-year-old woman presented to our rheumatology clinic with Raynaud phenomenon, sclerodactyly, rapidly progressive skin tightness, polyarthralgia with morning stiffness, proximal myopathy, dry eyes and mouth, and gastroesophageal reflux disease.

Laboratory testing showed positive antinuclear antibody and positive anti-RNA polymerase III antibody. Her anti-SS-A and anti-SS-B antibodies were negative. Her blood count, comprehensive metabolic panel and inflammatory markers were normal. A pulmonary function test and 2D echocardiogram were also normal.

Based on these findings, she was diagnosed with diffuse cutaneous systemic sclerosis (dcSSc) with secondary Sjögren syndrome.

Her modified Rodnan skin score (mRSS), a measure of skin tightness, was 17/51 at initial presentation and rapidly increased to 27/51 by eight months. She also developed severe pruritus and progressive joint contractures.

She was started on 2 g daily of mycophenolate mofetil (MMF), which effectively slows down progressive skin tightness in dcSSc. MMF has become the first-line immunosuppressive therapy for interstitial lung disease (ILD) in scleroderma and also the first-line therapy used by many scleroderma experts to treat diffuse and rapidly increasing skin tightness in dcSSc.

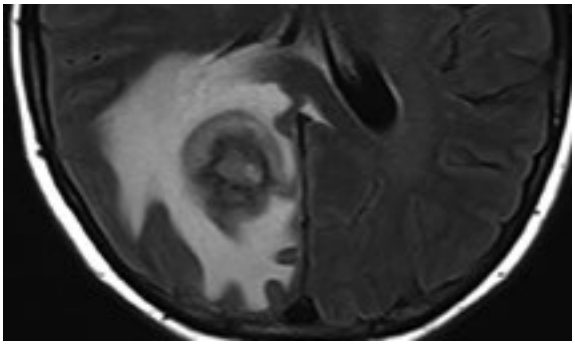


Figure 1: MRI scan of the brain revealed a solitary 2.4 cm peripherally enhancing right parietal lobe lesion with centrally restricted diffusion and significant adjacent vasogenic edema and local mass effect.

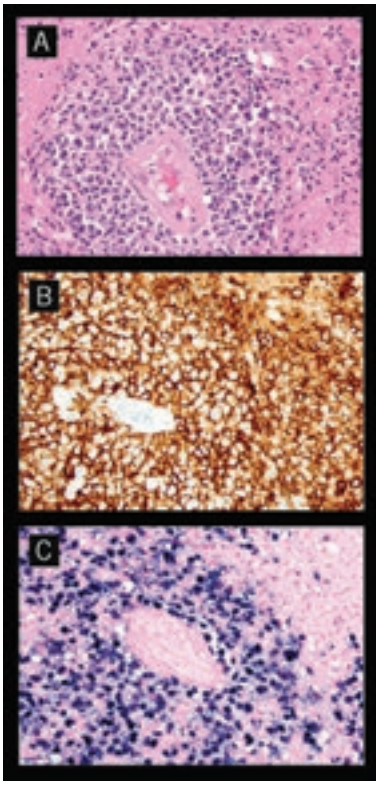


Figure 2:
A. Hematoxylin and eosin stain shows atypical perivascular cells.

B. The atypical perivascular cells are positive for CD20 by immunohistochemistry.

C. The atypical perivascular cells are EBER-CISH (chromogenic in situ hybridization for EBV-encoded RNA) positive.

After eight months of treatment, she had an mRSS of 8/51, a remarkable regression. Her widespread skin tightness diminished from her face, extremities and trunk to just her fingers. In addition, her joint pains, contractures, proximal myopathy, pruritus and fatigue improved substantially.

We advised her to continue MMF 2,000 mg daily to maintain her improved mRSS. In addition, her Raynaud phenomenon was well controlled on amlodipine 2.5 mg daily; she took omeprazole for acid reflux disease and pilocarpine tablets for her dry mouth.

Lymphoma develops

For five years, the patient's condition was stable. She then developed intermittent right-sided headaches similar to her previous migraines. She soon presented to her local emergency room with an onset of neurological symptoms: more severe headaches, nausea, vomiting, gait instability, lightheadedness, blurry vision (worse on leftward gaze) and word-finding difficulty. Physical examination showed left homonymous hemianopia.

She underwent an MRI of her brain (Figure 1), revealing a single 2.4-cm peripherally enhancing right parietal lobe lesion with centrally restricted diffusion and significant adjacent vasogenic edema with local mass effect. Chest CT showed a few indeterminate subcentimeter pulmonary nodules and mild interstitial fibrosis. CT of the abdomen and chest was normal.

A biopsy of the right parietal lobe mass was performed and confirmed a diagnosis of diffuse large B-cell lymphoma associated with Epstein-Barr virus (EBV) (Figure 2). As a result, her MMF treatment was discontinued.

Clinical implications

This is the first report of EBV-associated primary central nervous system lymphoma (ePCNSL) in a dcSSc patient receiving long-term MMF treatment. ePCNSL has been increasingly reported in patients receiving immunosuppressive agents following organ transplants or for autoimmune diseases. In addition to MMF, other immunosuppressive agents associated with development of ePCNSL include methotrexate, azathioprine and cyclophosphamide.

This case raises concerns about the safety of MMF. A safe dose and duration of long-term therapy with MMF are unknown. In the ePCNSL cases reported so far, the duration of MMF treatment ranged from one to five years. At the rheumatology clinic, we are vigilant in monitoring patients on long-term MMF for signs of ePCNSL, including focal and nonfocal neurological deficits, so that they can be recognized and treated promptly to prevent permanent neurological deficits. We also consider stopping MMF after three to four years of continuous treatment if no additional benefit is anticipated.

This case was initially reported in Joint Bone Spine *(2020;87:163-166).*

WHERE SPORTS MEDICINE MEETS RHEUMATOLOGY

continued from page 9

previously reported should prompt a search for an alternative diagnosis. From a rheumatic perspective, she is well within the age range for inflammatory spondyloarthropathy, and this is further supported by her physical exam, laboratory findings and imaging results. For the patient's part, a known previous injury that was once successfully treated tends to impart confidence that repeating the same treatment plan will fix the issue once again. This can lead to a delay of diagnosis and, ultimately, a slow functional decline that can be debilitating not only to the athlete's physical well-being, but their personal identity as a competitive athlete.

In the second case, we have an active, competitive wrestler who, in an attempt to lose weight in order to compete in his desired weight class, sought out diuretic therapy to help. Athletes are under immense stress to wrestle at the lowest possible weight class that they can manage in order to gain a competitive advantage. Unfortunately, this can lead some wrestlers to seek means that are not only illegal in their sport but dangerous to their overall health. It is well documented that diuretics like furosemide can induce hyperuricemia by increasing urate reabsorption via volume contraction.[1] In a patient like this who already has a family history of gout, there is already a strong predisposition for the personal development of hyperuricemia, likely unmasked even earlier in his life due to diuretic use. It is important to discuss the effects of improper medication use, as well as the long-term sequelae of uncontrolled crystal arthropathy so that the patient is able to not only compete safely and ethically during his athletic career, but also develop an understanding that his choices today can have serious consequences for his health and well-being long after his career has ended.

Knowing how to differentiate a mechanical sports injury from a potential rheumatic disease that may require lifelong therapy can be the difference between disability and health. It is our duty to ensure that we protect not only their well-being but also their long-term function.

1. Pascual E, Perdiguero M. Gout, diuretics and the kidney. Ann Rheum Dis. *2006 Aug;65(8):981-982.*

Stoking Curiosity and Feeding Knowledge

Adam Brown, MD, shares his passion for solving rheumatologic mysteries

Adam J. Brown, MD, is passionate about rheumatology. When he talks about understanding its complexities, he tends to interrupt himself to add cheerfully, "but no one really understands rheumatology." The puzzles — along with case varieties and differential diagnoses – are part of what he loves about the specialty.

Dr. Brown is on staff in Cleveland Clinic's Department of Rheumatic and Immunologic Diseases. In addition to his clinical practice, he's a natural educational ambassador.

- He wrote the book *Rheumatology Made Ridiculously Simple* (Medmaster Inc.) to make the topic more approachable for medical students and residents.
- He hosts Healio's "Rheuminations," a podcast on "medical mysteries and other ripping yarns about the immune system gone awry." It has featured experts from the National Institutes of Health, Mass General, Cleveland Clinic and elsewhere, and has garnered 150,000 downloads across more than 60 episodes.
- With Leonard Calabrese, MD, Dr. Brown has been working on content for Cleveland Clinic's rheumatology channel on VuMedi, a video education platform for physicians.
- He is the editor and creates quiz materials for Healio's Rheum+Boards, an education platform helping physicians study rheumatologic topics.

Adam J. Brown, MD

Dr. Brown was in the second year of his internal medicine residency at Georgetown University Hospital, and expecting to pursue cardiology, when he was assigned to a rheumatology rotation. He soon found himself working on a variety of fascinating cases.

"We had a young woman presenting with a stroke that actually resulted in a diagnosis of central nervous system vasculitis, which is very rare," he says. "I didn't really know much about vasculitis at the time. I knew it could cause inflammation of the blood vessels, but I didn't know it could cause stroke. This young woman got started on immunosuppression, and she did fantastic."

In rheumatology, he discovered challenging cases, opportunities to improve patients' lives, and a specialty full of persistent questions.

"Rheumatoid arthritis is relatively common," he says. "We can tell you about the different cytokine abnormalities within the joints, we can target the cytokines and stop them from causing an inflammatory response and greatly impacting the quality of patients' lives, but I still cannot tell you why it all happened in the first place. Hopefully, we start chipping away at why this happens."

Dr. Brown is also interested in medical history and explores the history of rheumatology in the "Rheuminations" podcast. He devoted two podcast episodes to the history of gout, during which he covered the 1962 study that confirmed that uric acid triggers the disease. Drs. James S. Faires and Daniel J. McCarty Jr. each injected uric acid into their knees to see if it triggered an inflammatory response. They had to abandon their original plan to simply observe, rather than treat, the progression of any inflammation. "Within two hours, they were both lying on the hospital floor, unable to move because their knees were so swollen and they were in such intense pain," says Dr. Brown.

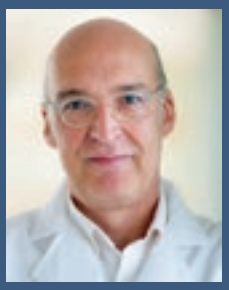
In general, he says, he wants other young physicians to learn more about rheumatology early enough to pique their interest in pursuing it as a career. That doesn't always happen.

"A big barrier is that people don't feel comfortable with it and they aren't exposed to it," he says. "So if my educational content is fun and accessible, then hopefully we can catch a few more people and get them excited about it."

Growing the Immunology Knowledge Quotient

Immunologic CME programs expand through online and live events

by Leonard H. Calabrese, DO



Dr. Calabrese (calabrl@ccf.org; 216.444.5258; @LCalabreseDO) directs the R.J. Fasenmyer Center for Clinical Immunology and is Vice Chair of the Department of Rheumatic and Immunologic Diseases.

In 2021, when Cleveland Clinic's R.J. Fasenmyer Center for Clinical Immunology presented its 10th Biologic Therapies Summit, the year-old pandemic informed the event in important ways. First, COVID-19 and autoimmunity became a significant focus of the program. Additionally, the event was livestreamed and, for the first time, presented at no cost to participants — extending access worldwide, including to colleagues in underresourced regions.

This was our way to express gratitude to the growing community of physicians and allied health workers who have joined our efforts over the years to expand the understanding of immunologic diseases.

Education is at the core of our mission. Since the Fasenmyer Center opened in 2005, we have been leveraging advances in communications technology, have conferred thousands of CME credits and reached hundreds of thousands of participants. More than 10,000 people are registered within our online rheumatology space. And so far this year, we have garnered more than 70,000 Twitter impressions and are increasing our social media outreach.

Our anchor events are the biennial Biologic Therapies Summit and the Annual Basic & Clinical Immunology for the Busy Clinician — our Clinical Immunology Boot Camp. Additionally, we have won several recent educational grants, including one for a project now being developed on outcomes in rheumatoid arthritis management for the patient and the practitioner. This will focus on the power of relationship-centered care, a discipline pioneered by Cleveland Clinic.

Annual Basic & Clinical Immunology for the Busy Clinician

Developed 11 years ago, this symposium addresses essentials of basic clinical and translational immunology with both immunologists and nonimmunologists in mind. We highlight the biology of rheumatic illness and other autoimmune and autoinflammatory diseases, as well as biologic therapies. Over the past five years, we also have shared evidence-based wellness topics, including the impact of diet, exercise, sleep and stress modification on the immune response.

More than 500 people from 66 countries attended our 10th boot camp, which was livestreamed on Feb. 26, 2022. This year's presentations focused entirely on the intersection of COVID-19 and immune-mediated inflammatory diseases. In addition to panel discussions and Q&A sessions, lecture topics included:

- COVID-19 at two years: politics, science and challenges
- Vaccine response in IMIDS - challenges and strategies
- Breakthrough COVID in IMIDS
- COVID-19 intersections with multiple sclerosis, irritable bowel syndrome and dermatologic disorders

Biologic Therapies Summit

The two-day biennial Biologic Therapies Summit was begun in 2005 to coincide with the launch of the Fasenmyer Center. It has grown from a primarily local gathering to an international conference, reflecting both Cleveland Clinic's expertise and the growth of the importance of biologic therapies in managing immunologic disease. The next Biologic Therapies Summit will be May 11-13, 2023.

Our 2021 meeting focused on immune-based inflammatory disease through the lens of COVID-19 and vasculitis treatment. Lectures included:

- How Does the Treatment of Behçet's Disease Differ Based on Disease Manifestations?
- COVID-19 and Autoimmunity
- Maintenance Rituximab in ANCA-Associated Vasculitis: Dose, Frequency and Duration — How Do We Decide?

These educational series remain available for two years at clevelandclinicmeded.com.

We are proud to be able to provide free online education in the evolving field of immunology and to bring nonimmunologists up to speed in this most fascinating and complex area. In the era of COVID-19, we are all immunologists.

Infective Endocarditis Mimicking Polyarteritis Nodosa

by Kinanah Yaseen, MD

Dr. Yaseen (yaseenk@ccf .org, 216.213.0011) is Staff in the Department of Rheumatic and Immunologic Diseases.

The vasculitides are a rare group of disorders that cause inflammation of the blood vessel wall (vasculitis) that can lead to vessel destruction, resulting in either stenosis or aneurysm. The differential diagnosis of systemic vasculitides is broad and includes autoimmune disorders such as systemic lupus erythematosus sarcoidosis, various malignancies, and infections such as infective endocarditis and mycobacterial or fungal disease.

Herein we report on a patient who was referred for evaluation of possible polyarteritis nodosa (PAN).

Presentation

A 70-year-old male with a medical history significant for aortic valve replacement presented to Cleveland Clinic for evaluation of acute-onset abdominal pain, high grade fever, chills and unintentional weight loss over a one-month period.

Physical examination on presentation was notable for temperature of 102°F, heart rate of 120 beats per minute, mild abdominal tenderness without guarding or rebound, normal arterial pulses without bruits, and a 3/6 systolic murmur best heard at the right upper sternal border.

Laboratory testing revealed white blood cell count 25k (neutrophils 96%), hemoglobin 8.5 g/dL, elevated sedimentation rate 77 mm/hr, C-reactive protein 17 mg/dL, and normal lipase, kidney and liver function. He tested negative for hepatitis B and C and had a normal hypercoagulable panel. Blood cultures were sent from the emergency department upon admission.

Imaging revealed hemorrhagic cholecystitis on right upper quadrant ultrasound with computed tomography arteriogram showing severe acute pancreatitis, 80% stenosis of the celiac artery at the origin, irregularity of the splenic artery without clear dissection, splenic infarction, a small aneurysm of the inferior pancreaticoduodenal artery, and a 3-cm aneurysm of the distal right hepatic artery.

Transthoracic echocardiogram showed a decreased left ventricular ejection fraction of 40%, moderate-severe aortic insufficiency, thickened mitral valve leaflets and mild mitral regurgitation without vegetations. Later, blood cultures grew Enterococcus faecalis; transesophageal echocardiogram revealed large vegetations on prosthetic aortic valve.

He was diagnosed with endocarditis. Management included embolization of his right hepatic artery aneurysm by interventional radiology, redo aortic valve replacement and intravenous (IV) antibiotics for six weeks.

Infective endocarditis mimicking polyarteritis nodosa

endocarditis is a great imitator of the primary systemic vasculitides clinically, radiologically and histopathologically through two mechanisms: embolic phenomena or immune-complex formation. Due to septic embolization of vegetations to the arterial vasa vasorum, mycotic aneurysms can occur as a rare complication of endocarditis.

The most common causative pathogens are *Staphylococcus*, *Streptococcus* and Gram-negative bacilli in IV drug users. Mycotic aneurysms favor arterial branching points and may occur in any vessel; however, the most commonly involved vessels include the aorta and the femoral, cerebral and visceral arteries (renal, hepatic and superior mesenteric artery). Aneurysms due to endocarditis carry a risk of rupture in up to 24% of cases, which is associated with a 66% rate of mortality.

The clinical presentation is diverse and consists of localized symptoms depending on aneurysm location and systemic symptoms such as fever, myalgia and weight loss, which are also frequently found in patients with PAN. Patients with endocarditis and mycotic aneurysms may have leukocytosis, anemia, thrombocytosis and elevation of acute-phase reactants similar to PAN. However, in contrast to PAN, endocarditis may cause leukopenia and thrombocytopenia, which are not usually seen in primary systemic vasculitides.

Aneurysms in endocarditis usually manifest as saccular aneurysms with concentric or eccentric periaortic gas and inflammatory soft tissue stranding in 48% of cases, which may help in differentiating from aneurysms related to PAN.

Despite such a distinction, it remains challenging to differentiate both conditions based on radiographic findings only. Notably, these aneurysms typically lack calcification or thrombus as is usually seen in atherosclerosis.

Endocarditis may also mimic anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis by causing constitutional symptoms, cutaneous purpura, digital ischemia, pulmonary cavitary lesions, pauci-immune glomerulonephritis, and positive ANCA testing.

Hence, ruling out endocarditis is essential when evaluating for systemic vasculitis by sending blood cultures and performing transthoracic and/or transesophageal echocardiography.

At Cleveland Clinic's Center for Vasculitis Care and Research, we work closely as a multidisciplinary team with vascular medicine physicians, cardiologists, cardiovascular surgeons and others in diagnosing and managing challenging vasculitis cases and to rule out vasculitis mimics.

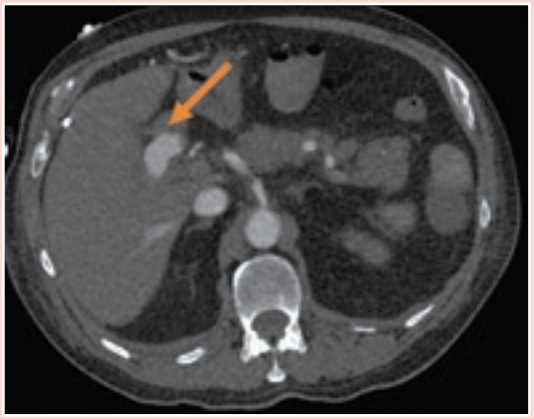


Figure 1: Inferior pancreaticoduodenal artery aneurysm.

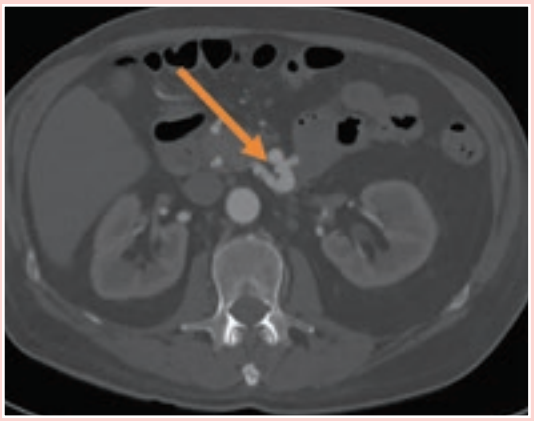


Figure 2: Distal right hepatic artery aneurysm.

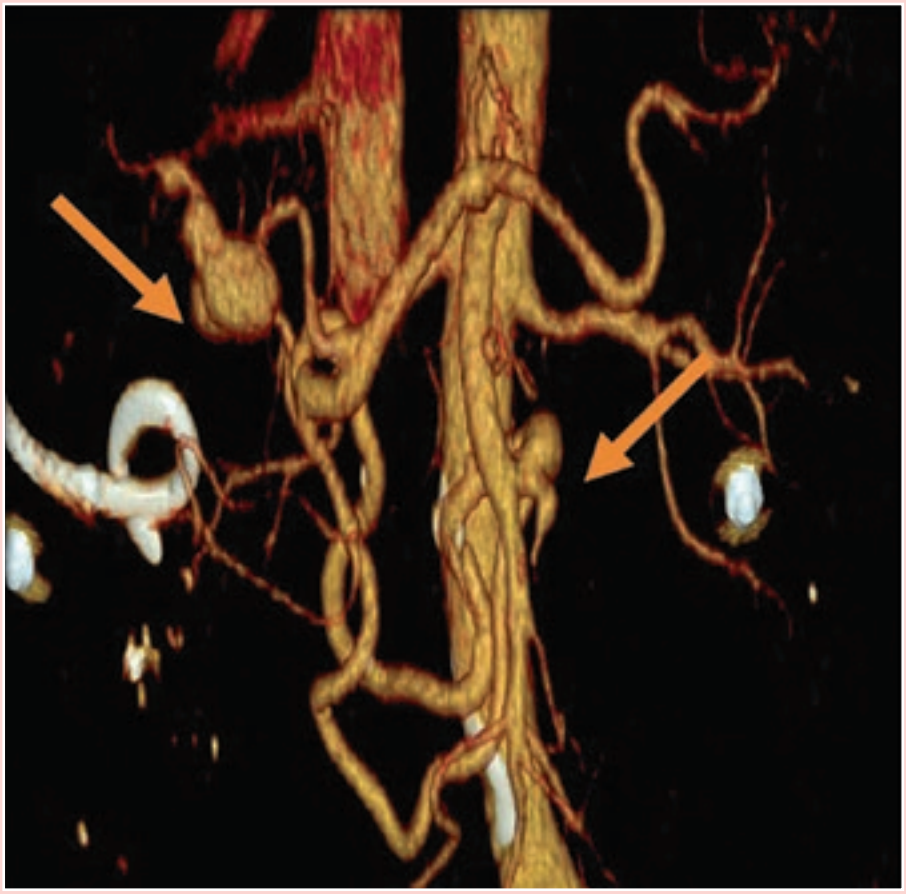


Figure 3: Distal right hepatic artery aneurysm and inferior pancreaticoduodenal artery aneurysm.

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