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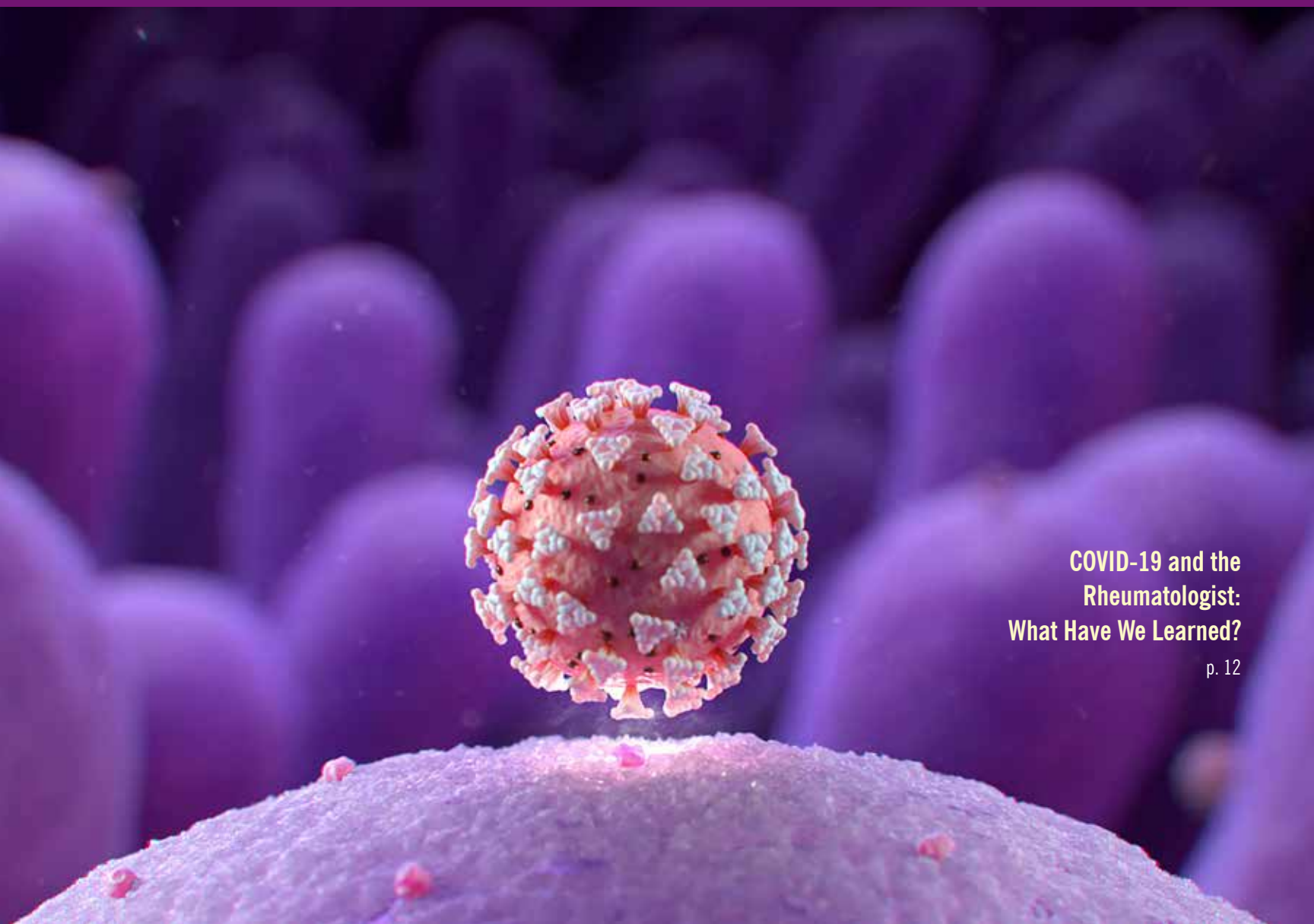
Cleveland Clinic

Rheumatology Connections

An Update for Physicians | Summer 2021



COVID-19 and the Rheumatologist: What Have We Learned?

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From the Chair of Rheumatic and Immunologic Diseases

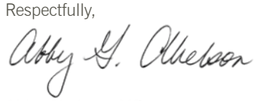
Dear Colleagues,

As March 2020 descended, and the COVID-19 pandemic engulfed us and our patients with disease and fear, who would have dared to hope that rheumatology would be the field that offered the science and clinical perspective that would bring light and hope to the pandemic darkness? As our patients desperately called our phones, messaged our EMRs and came to our visits and infusion appointments, we were always here for them, in person and virtually. As our hospitals filled with patients whose immune systems were raging in cytokine storms, our colleagues asked us to participate in the care of the sickest, deteriorating patients as we collaborated to bring the science of immunology to their bedsides. The treatments we had used for years, as well as new ones based on our understanding of immunopathogenesis, were employed in the care of COVID-19 patients, and we rheumatologists were here to share our experience with complex multisystem immune-mediated diseases and immunologic reactions. As many departments in our hospitals were deferring care, our patients and colleagues needed us more than ever before. And with the myriad questions regarding COVID-19 vaccines and post-disease sequelae, we came through!

As you can see from this issue of *Rheumatology Connections*, the last year has been a fulfilling and productive year for Cleveland Clinic's Department of Rheumatic and Immunologic Diseases in terms of COVID-19-related activities as well as so many other exciting aspects of rheumatology. In this issue we share the diverse accomplishments of our colleagues in rheumatology research and care, including the impact of COVID-19, complex cases and diagnostic challenges. Also in this issue, we discuss impacts of both disease-related symptomatology and the available treatments on the quality of life of those in our care.

Within these pages, I hope you find an opportunity to connect, collaborate or consult with our team. Please reach out to me if you would like more information or to contact a colleague.

Respectfully,



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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.

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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Predicting Major Adverse Cardiac Events in Patients With Arthritis

By M. Elaine Husni, MD, MPH

Patients with chronic systemic inflammatory states may be at increased risk of developing cardiovascular (CV) disease, which has implications for drug therapy and can put patients at risk of premature death. The ability to predict which patients with RA or OA are most likely to experience a major adverse cardiac event (MACE) may help rheumatologists risk stratify these patients early.

The search for predictive biomarkers

Although validated risk stratification methods exist, such as the Systematic Coronary Risk Evaluation, Framingham risk score and Reynolds risk score, they tend to underestimate CV risk in patients with arthritis.[1] There remains a need to identify other prognostic indicators of CV risk to help mitigate this risk early on in this patient cohort.

Testing for high-sensitivity cardiac troponin T (hscTnT) allows the measurement of cardiac troponin concentrations below conventional levels, and can be used to assess the severity of subclinical myocardial damage. Meanwhile, high-sensitivity C-reactive protein (hsCRP) is traditionally applied in CV risk stratification. In order to evaluate the prognostic relevance of these biomarkers, we evaluated data from the PRECISION biomarker substudy, looking for associations between hscTnT, hsCRP and MACEs. Our results were presented at ACR Convergence 2020.[2]

Baseline high-sensitivity cardiac troponins associated with MACEs

We measured hscTnT and hsCRP in a subset of RA (N = 636) and OA (N = 6,269) patients in the PRECISION trial. The PRECISION trial was a randomized, controlled, noninferiority clinical trial conducted worldwide involving patients who had RA or OA and increased CV risk. The primary CV outcome was MACE, which we defined as CV death, non-fatal myocardial infarction or non-fatal stroke, re-vascularization, hospitalization for unstable angina or transient ischemic attack with at least 18 months of follow-up.

Within this cohort, 58% of patients were female, 80% were Caucasian and the mean age was 63.6 ± 9.4 years. Eighty percent of patients in this cohort had hypertension, 36.5% had diabetes and 17.8% had known coronary artery disease.

Looking at the biomarkers, the median baseline hscTnT was 6.3 ng/L, which was similar in the RA cohort (5.6 ng/L) and the OA cohort (6.4 ng/L). Baseline hscTnT was a significant predictor of MACE during the 18-month follow-up for patients in both the RA cohort (HR 1.60; 95% CI 1.06-2.41) and the OA cohort (HR 1.23; 95% CI 1.04-1.46). The association between hsCRP levels and MACE was weaker for patients with RA (HR 1.36; 95% CI 1.05, 1.75) and not significant for patients with OA (HR 1.09; 95% CI 0.99, 1.21).

In this study, we found hscTnT to be independently associated with MACE in both RA and OA. Further prospective studies to address the predictive role of hscTnT for CV events in RA and OA patients can expand preventive treatment strategies.

Given the increased CV risk in patients with chronic arthritic conditions, physicians should strive to actively manage traditional risk factors while optimizing disease control. Interventions aimed at modifying risk factors of coronary artery disease include smoking cessation, controlling cholesterol and weight, maintaining a healthy (perhaps anti-inflammatory) diet and moderate exercise.

Note: Co-authors include Daniel H Solomon, MD, MPH; Mingyuan Shao, PhD; Katherine E Wolski, MPH; Steven E Nissen, MD; Stanley L Hazen, MD, PhD; and WH Wilson Tang, MD, on behalf of the PRECISION trial investigators.

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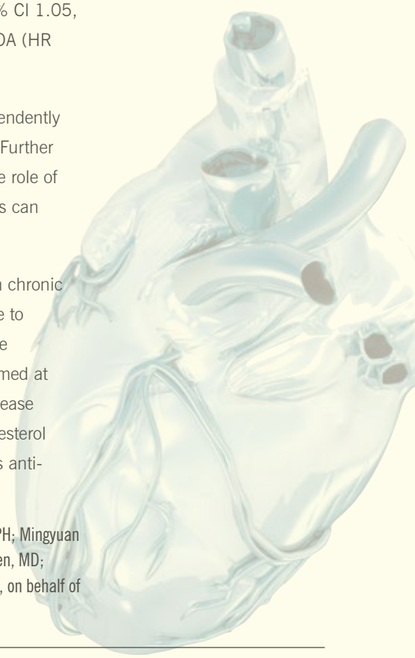

For a complete list of references, please visit https://consultqd.clevelandclinic.org/tag/rheumatology-connections-summer-2021.

Vasculitis or Vasculopathy?

By Carol A. Langford, MD, MHS

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CASE PRESENTATION

You are asked to see a 55-year-old male who presented to the emergency room with acute abdominal pain. He was previously well prior to the onset of the pain and had no significant medical or surgical history. Computed tomography angiography revealed evidence of hemoperitoneum from a ruptured splenic artery aneurysm with evidence of dissections involving the superior mesenteric artery and left renal artery. He was taken to surgery, and his team consults you on the question of whether these vascular abnormalities are due to vasculitis.

Is this vasculitis?

In considering the cause of aneurysms, dissections, stenoses or occlusions in the large- or medium-sized vessels, it is appropriate to include vasculitis in the differential diagnosis. However, in addition to atherosclerosis, there are a range of less common vasculopathic disease entities that should also be considered, particularly if features atypical for vasculitis are present (Table 1). The importance of identifying a vasculopathy is that these would not be treated with systemic immunosuppression and may have their own approach to management.

What features should make clinicians suspect a vasculopathy rather than a vasculitis? Dissections can occur in vasculitis, but they are uncommon and when present should always raise consideration of a vasculopathy. This is particularly true when dissections involve the visceral circulation or if there are dissections that appear to be of different ages. The presence of aneurysms alone without vascular stenoses is also unusual for vasculitis. The lesion location has importance as some vasculopathies will predominantly affect a certain vascular territory. It is essential to review the overall clinical picture, looking for symptoms or signs present immediately prior to the discovery of the vascular disease or in the past. This should include careful review for abnormalities of nonvascular tissue or organs; medical, surgical and obstetric history; and family history. In examining laboratory findings, while vasculopathies are usually associated with a normal erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level, these can be elevated in an acute setting if bleeding or organ infarction has occurred.

Determining with certainty whether a patient has vasculitis or a vasculopathy can be difficult. Narrowing the differential based on the features found by history, examination, labs and imaging can provide a starting point from which additional testing can be pursued. The presence of characteristic histologic findings can be diagnostic in some instances. However, examining tissue may not be possible unless vascular surgery is required or there is an abnormality of a nonvascular tissue that is amenable to biopsy. When vascular tissue is obtained, examining many different

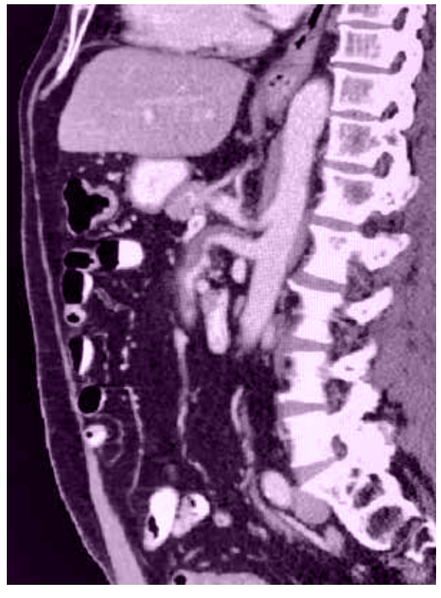

Figure 1. CT abdomen – sagittal view demonstrating dissection of the superior mesenteric artery.

sections is important as characteristic changes can be patchy in both vasculitis and vasculopathies. Genetic testing should be performed if there is a degree of suspicion for a heritable collagen defect or other genetically linked disorder. In some instances, imaging of extravascular organs that are commonly affected in the suspected diagnosis may be informative.

Return to our case patient

In reviewing the key elements in our patient, he was well until he experienced the severe onset of abdominal pain. There were no prodromal features or prior vascular events. His ESR and CRP were elevated on first measurement but rapidly returned to normal. Review of the vascular lesions was notable for vessel dissections involving more than one vessel, predominantly in the visceral circulation. Multiple tissue sections were reviewed from his emergency surgery, which revealed areas of medial breakdown in the muscular arteries with associated aneurysm formation and adjacent areas of organizing granulation tissue. Collectively, these features argued against a vasculitis and supported a diagnosis of segmental arterial mediolysis (SAM).

Table 1. Causes of vasculopathy that can affect the medium- to large-sized vessels

Atherosclerosis
Heritable vascular disorders - Vascular Ehlers-Danlos syndrome - Marfan syndrome - Loeys-Dietz syndrome - Grange syndrome - Neurofibromatosis - Pseudoxanthoma elasticum - Arterial tortuosity syndrome
Erdheim-Chester disease
Fibromuscular dysplasia
Segmental arterial mediolysis (SAM)

Segmental arterial mediolysis

SAM is a rare, noninflammatory vascular disorder of unknown cause that manifests as an arterial dissection, aneurysm, stenosis or occlusion involving muscular arteries. This most commonly involves the visceral arteries and less often the renal, coronary or cerebral circulation.[1,2,3] In adults, SAM may present at any age and has a slightly higher frequency in men. Presentations are typically acute and can be severe, with visceral organ infarction, vascular dissection or intra-abdominal hemorrhage. The diagnosis of SAM is based on histology, where it is defined by the presence of vacuolar degeneration of the vessel media with subsequent mediolysis. This can lead to "gap aneurysms" that are at risk of rupture as well as mural hemorrhage or dissecting hematomas of the artery wall. In the reparative phase, fibrous granulation tissue replaces areas of medial loss. Treatment is based on management of the acute event, cautious application of treatment principles for dissection when present, and optimization of vascular risk factors such as blood pressure and atherosclerosis.

SAM presents a significant diagnostic challenge as it is rare, it can present in a similar manner to other more common disease entities, and obtaining tissue for histology is frequently not possible.[4] The diagnosis of SAM as well as other complex medium- and large-vessel vascular disorders requires a multidisciplinary approach involving rheumatology, vascular medicine, vascular and cardiothoracic surgery, radiology, and genetics. Particularly in the setting of acute presentation, such collaboration is essential in establishing the most likely diagnosis and optimizing patient management.

For a complete list of references, please visit: https://consultqd.clevelandclinic.org/tag/rheumatology-connections-summer-2021.

Patients Report Positive Experiences With Patient-Reported Outcome Measures in Rheumatology Clinics

By Brittany Lapin, PhD, and Abby Abelson, MD

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Patients overwhelmingly perceive patient-reported outcome measures (PROMs) as useful, easy to understand and informative, according to a study we recently published in *Quality of Life Research*.[1] To our knowledge, this is the first study to examine the perception of and experience with PROMs in such a large series of rheumatology patients.

The main goal of the study was to assess the patients' experiences with completing PROMs. An additional goal was to assess the patients' perception/acceptance of additional questions that were recently added to rheumatology-specific PROMs across Cleveland Clinic.

The utility of PROMs in rheumatology

Prior to rheumatology visits, patients are asked to complete PROMs through MyChart or on tablets in the waiting room. The PROMs include a depression screen and surveys assessing physical function, fatigue, pain interference and overall health-related quality of life. The purpose of PROMs in clinical practice is to evaluate the impact of disease from the patients' point of view in order to monitor response to treatment and overall progress in controlling their disease. Additional goals of these detailed questionnaires are to facilitate patient-provider communication, help clinicians gain a better understanding of the patients' overall health, and empower patients to participate in shared decision-making.

PROMs have proved especially relevant in rheumatology due to their ability to convey a patient's perspective on their health, irrespective of clinical findings. Clinical tests are not always indicative of how a patient is feeling day to day, so PROMs really help clinicians understand the patient experience. PROMs are used enterprise wide at Cleveland Clinic; our rheumatology PROMs also contain condition-specific measures where patients respond about fatigue and pain interference. At 76%, our response rate is considered very high.

Since rheumatic diseases affect many different organ systems in the body, getting an accurate assessment at the point of care of all the ways in which the disease affects the patient is critical. PROMs ask: How do you feel now? We find that when you start every encounter with that question, it focuses the whole visit on the patient.

Patients welcome PROMs, find them useful

Our retrospective cross-sectional study included 12,597 adult (76% female and 84% white) rheumatology patients seen across Cleveland Clinic rheumatology clinics between Jan. 1, 2017 and June 30, 2017. Patients included in the study completed at least one patient-reported experience question after completing their PROMs. They overwhelmingly found PROM questions to be useful (84%) and easy to understand (97%). Furthermore, 78% of patients felt that PROMs improved their physician's understanding of their health and their communication with the provider.

One of the more exciting findings here, in our opinion, is the predictors of who had a more positive experience. These predictors included patients who were younger, were nonwhite, had lower income, were depressed and reported a lower quality of life. We believe PROMs are especially important in these patient populations that frequently face health disparities, and completing PROMs may be a simple and effective way to reduce these disparities.

An additional finding was that the younger, lower income and more depressed patients were more likely not to complete PROMs even though they were more likely to benefit from them. Our findings suggest that there should be greater outreach to all patients to make sure they are completing PROMs.

1. *Lapin BR, Honomichl R, Thompson N, et al. Patient-reported experience with patient-reported outcome measures in adult patients seen in rheumatology clinics.* Qual Life Res. *2021 Apr;30(4):1073-1082.*

Recognizing Noninfectious Autoimmune Scleritis

By Rula Hajj-Ali, MD

CASE VIGNETTE 1

A 57-year-old patient you have been treating for rheumatoid arthritis (RA) presents for a scheduled follow-up with a complaint of eye pain that has gradually increased over two weeks. The pain is sharp and sometimes wakes her up at night. She reports sensitivity to light and indicates that she isn't seeing as well as she once did. On exam, the patient has bilateral redness in her eyes. What's your next move?

CASE VIGNETTE 2

A 68-year-old patient has been referred to you by ophthalmology for workup to identify possible systemic associations with newly diagnosed scleritis. Your colleague in ophthalmology has ruled out infection and malignancy as sources of the inflammatory ocular disease and is looking for other potential causes. The patient recounts her history of sudden-onset, severe pain in both eyes. She has no history of sinus problems, no joint pains, no rashes, no weight loss, no neuropathy symptoms, no gastrointestinal or pulmonary symptoms. What tests do you order?

Workup for patients presenting to rheumatology with "red-eye"

Rheumatologists may encounter patients with symptoms of scleritis as part of ongoing care for patients with systemic conditions, or as a referral from ophthalmology for workup of systemic associations and assistance with immunosuppression.

When assessing a patient for red-eye with severe ocular pain, rheumatologists should have a high index of suspicion for scleritis. If you have already diagnosed your patient with an autoimmune disease (as in the first case vignette), prompt ophthalmic assessment is warranted.

If the patient has been referred to you by ophthalmology (as in the second case vignette), review the patient's symptoms, noting the presence or absence of sinus disease (which might indicate granulomatosis with polyangiitis [GPA] or sarcoidosis) as well as orogenital ulcers (inflammatory bowel disease [IBD] or Behcet's syndrome), shortness of breath (sarcoidosis), neuropathy and rashes (GPA or sarcoidosis), and a history of joint pain (rheumatoid arthritis or inflammatory arthritis).

Tests to consider include complete blood count, acute phase reactants, creatinine, anti-neutrophilic cytoplasmic antibodies (ANCA) and urinalysis. In patients with oligo- or polyarthritis or recent-onset polyarthralgia, consider testing for rheumatoid factor and anticitrullinated peptide antibody. If the review of systems or other laboratory results suggest systemic lupus erythematosus, an anti-nuclear antibody test should be performed. When ocular or systems findings suggest sarcoidosis or GPA, pursue chest CT without contrast. Very rarely, ANCA will return positive in patients with scleritis without any systemic symptoms. Many of these patients, when followed, will develop systemic GPA. Given the systemic nature and the involvement of vital organs of ANCA-associated vasculitis, we recommend testing all patients with scleritis for ANCA.

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Figure 1. Nodular anterior scleritis in a patient with Behcet's syndrome. Images used with permission. Originally published in Nevares A, Raut R, Libman B, Hajj-Ali R. Non-infectious Autoimmune Scleritis: Recognition, Systemic Associations, and Therapy. *Curr Rheum Rep*. 2020 Mar 26;22(4):11.

continued on page 11

Chronic Glucocorticoid Use for Management of Systemic Lupus Erythematosus 5 Times More Likely in Black Patients

By James K. Sullivan, BA, and Emily A. Littlejohn, DO, MPH

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After adjusting for validated measures of systemic lupus erythematosus (SLE) disease activity, recent hospitalization, disability and SLE medications used (hydroxychloroquine and conventional disease-modifying anti-rheumatic drugs [cDMARDs]), Black participants were more than five times likelier to use chronic glucocorticoids for management of SLE, according to an unpublished data analysis conducted at Cleveland Clinic. In addition to showing Black patients have an increased risk of adverse outcomes specific to SLE disease activity, these data indicate Black patients may face increased morbidity and mortality from chronic steroid use.

Significant racial disparities exist in SLE

SLE is a multisystem inflammatory autoimmune syndrome with higher morbidity and mortality rates than those for many other major rheumatologic conditions.[1,2] Significant racial disparities exist in SLE incidence, long-term outcomes and mortality. In particular, Black patients with SLE have up to fourfold greater SLE-related mortality,[3] threefold higher incidence of end-stage renal disease[4] and higher incidence of cardiovascular and neuropsychiatric SLE manifestation[5] compared with white patients with SLE. Given these trends, recent research has sought to identify modifiable factors related to the medical management of SLE that underlie these disparities. While glucocorticoids are a potent therapeutic to ameliorate acute SLE flares, chronic long-term use has been associated with poor health outcomes, particularly among those with minimal SLE disease activity.[6]

Chronic glucocortiocoid use in patients with SLE

We sought to quantify chronic glucocorticoid use among Black and white patients with systemic lupus erythematosus (SLE) within a prospective Cleveland Clinic registry. We conducted multivariable logistic regression of race and glucocorticoid use, adjusting for covariates exhibiting a bivariate association with glucocorticoids at a significance level of $P < 0.10$.

We analyzed data from 114 white participants (mean age 45; standard deviation [SD] 15) and 59 Black participants (mean age 42; SD 14). White participants had a mean score of 3.7 (SD 5.2) on the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K). Black participants had a mean SLEDAI-2K score of 6.3 (SD 6.0). Among Black participants, 43 (72%) utilized glucocorticoids compared with white participants 39 (34%) (unadjusted odds ratio [OR] 5.17; 95% confidence interval [CI] 2.59-10.33). We did not observe differences between unadjusted hydroxychloroquine (OR 0.69; 95% CI 0.28-1.65) or cDMARD (OR 1.07; 95% CI 0.57-2.01) utilization among Black and white participants. SLEDAI-2K, disability, recent hospitalization, and past or present hydroxychloroquine or cDMARD use were included in a logistic regression model. Adjusting for covariates, Black participants were more likely to be on glucocorticoids (adjusted OR 5.69; 95% CI 2.17-14.96; $P = 0.0004$).

Table 1. Current SLE medication use among white and Black participants

Medication	White (N = 114)	Black (N = 59)	*P* value*	Odds ratio (95% confidence interval)
Chronic corticosteroids (oral or intravenous)	39 (34%)	43 (73%)	< 0.0001	5.17 (2.59-10.33)
NSAIDs†	35 (31%)	20 (34%)	0.62	1.19 (0.51-2.33)
Hydroxychloroquine	100 (88%)	49 (83%)	0.40	0.69 (0.28-1.65)
Conventional DMARDs‡ §	58 (51%)	31 (53%)	0.84	1.07 (0.57-2.01)
Biologic DMARDs¶	8 (7%)	3 (5%)	0.75#	0.71 (0.18-2.78)

*All statistical tests performed using Pearson's chi-squared test except where indicated

† NSAIDs stands for nonsteroidal anti-inflammatory drugs

‡DMARD stands for disease-modifying anti-rheumatic drug

§ Conventional DMARDs consist of methotrexate, azathioprine, mycophenolate, leflunomide, cyclophosphamide

¶ Biologic DMARDs consist of rituximab, belimumab

Fischer exact test

Table 2. Multivariable logistic regression of odds of chronic glucocorticoid use among white and Black participants in the SLE registry

Variable	Estimate	Odd ratio (95% confidence interval)	*P* value
Intercept	-2.51		<0.0001
Race (Black)	1.74	5.69 (2.17-14.96)	0.0004
Hospitalization	-0.52	0.60 (0.21-1.69)	0.33
Total SLEDAI-2K* ≥ 6	1.73	5.66 (1.93-16.56)	0.002
Disabled	1.34	3.81 (1.45-10.07)	0.007
Never used hydroxychloroquine	1.24	3.44 (0.59-19.33)	0.17
Ever used cDMARD†	1.75	5.76 (2.20-15.04)	0.0004

Overall model *P* value < 0.0001; Overall model N = 145

*SLEDAI-2K stands for Systemic Lupus Erythematosus Disease Activity Index 2000

†cDMARD stands for conventional disease-modifying anti-rheumatic drug (methotrexate, azathioprine, mycophenolate, leflunomide, cyclophosphamide)

Note: Independent variables include race, hospitalization in the past year, total SLEDAI-2K dichotomized at 6, disability, no current or prior hydroxychloroquine use, and current or prior cDMARDs. Odds ratios and significance are Wald based.

Access may play a role in chronic steroid use

While individuals with active SLE are more likely to require glucocorticoids, these data suggest that after adjusting for measures of disease activity and other factors that might influence chronic glucocorticoid use, Black participants were more likely to use this treatment than white participants. As the chronic use of glucocorticoid medications has been independently associated with increased morbidity and mortality,[6] increased exposure to glucocorticoids among Black patients with SLE may be another driver of the increased morbidity and mortality in this population.

The precise reasons for increased glucocorticoid use among Black registry participants are not entirely clear, but healthcare access may play a role. There are well-documented disparities in healthcare access and utilization between Black and white patients with SLE. Specifically, Black patients with SLE use less specialized ambulatory care and more acute care, driven by lack of access to health insurance, healthcare affordability and other care access issues.[5,7] It is possible that this different pattern of care could lead to increased use of glucocorticoids and a lag in or decreased transition to glucocorticoid-sparing DMARDs, as access to these medications can be predicated on more detailed and complex patient monitoring. Research is needed to identify more precise mechanisms underlying this treatment disparity. Dedicated SLE care coordination by a trained, specialized professional (such as a registered nurse or licensed social worker) may be a reasonable approach to facilitate access to specialist outpatient care and to ensure the periodization of glucocorticoid-sparing medications.

For a complete list of references, please visit https://consultqd.clevelandclinic.org/tag/rheumatology-connections-summer-2021.

Clinical Characteristics of Sarcoidosis in an Asian Population

By Patompong Ungprasert, MD

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Sarcoidosis is a chronic granulomatous disease of unknown etiology believed to result from a complex interaction between host factors and environmental triggers. We know that ethnicity influences the epidemiology and clinical phenotype of sarcoidosis. For instance, the annual incidence of sarcoidosis is as high as 70 per 100,000 population among Black Americans, but is as low as 1-2 per 100,000 population among Asians and Hispanics. In addition, Blacks with sarcoidosis tend to have more advanced stages of pulmonary sarcoidosis, higher frequency of extrathoracic involvement and a higher mortality rate than do whites.[1] However, data on clinical manifestations of sarcoidosis in Asians are still relatively limited.

A 14-year, single-center retrospective cohort study from Thailand

Together with collaborators from Mahidol University, the largest teaching hospital in Bangkok, Thailand, I conducted a study using the medical record-linkage system and the pathology database of Siriraj Hospital. Results from our study were presented in a poster at ACR Convergence 2020.[2]

In our study, we identified and retrieved data on patients with International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes for sarcoidosis (D86–D86.9) treated between 2005 and 2018 using the medical record-linkage system. We also identified and retrieved data regarding patients with histopathology positive for non-necrotizing granuloma or non-caseating granuloma from the pathology database for the same time period. We then reviewed the medical records of all potential cases from either source to confirm the diagnosis of sarcoidosis, which required compatible clinical pictures supported by the presence of noncaseating granuloma, radiographic evidence of intrathoracic sarcoidosis and exclusion of other granulomatous diseases, especially tuberculosis.

We deemed the presence of caseous granuloma as an acceptable alternative if extensive investigations for other causes of granulomatous inflammation, especially tuberculosis, were negative.

We identified a total of 89 confirmed cases of sarcoidosis. Of patients in the cohort, 80.9% were female; the mean age at diagnosis was 46.8 years (standard deviation [SD] 13.9 years) and the mean follow-up time was 5.4 years (SD 4.5 years). The majority of patients in this cohort had intrathoracic disease (81 cases; 91.0%). About half had stage I pulmonary sarcoidosis (43 cases; 53.1%), followed by stage II (32 cases; 39.5%), stage III (five cases; 6.2%) and stage IV (one case; 1.2%). However, fewer than half of patients with intrathoracic disease were symptomatic (34 cases; 41.9%), with dyspnea and cough being the most common symptoms (25.9% and 22.2%, respectively). The yield of intrathoracic biopsy was fair, as histopathology was positive for noncaseating granuloma in 52 of 68 patients (76.5%) who underwent biopsy.

Extrathoracic disease was common in this cohort, accompanying pulmonary sarcoidosis in 53 patients (65.4%). Eight patients had isolated extrathoracic disease. The most common extrathoracic disease was sarcoid uveitis (35 cases; 39.3%; four males and 31 females), followed by cutaneous sarcoidosis (24 cases; 26.9%), extrathoracic lymphadenopathy (18 cases; 22.5%) and sarcoid arthropathy (four cases; 4.5%).

A total of 48 patients (53.9%) received at least one systemic treatment during the course of their illness. Oral prednisolone was the most commonly prescribed systemic treatment (46 cases; 51.7%), followed by methotrexate (16 cases; 17.9%), azathioprine (eight cases; 9.0%) and chloroquine (three cases; 3.4%). Topical and inhaled corticosteroids were also frequently used (31.5% and 6.7%, respectively).

Distinguishing features of sarcoidosis in Thailand

The high prevalence of uveitis and marked female predominance are the most prominent findings in this study. Prevalence of uveitis was almost 40%, which is far higher than previous reports of 10%-15% in Europe and North America. However, a similarly high prevalence of uveitis was previously reported by a study from Japan.[3] Thus, the current study may provide another piece of evidence to support the supposition that uveitis is much more common among Asian patients with sarcoidosis.

This cohort had a female-to-male ratio of about 4:1, which is much higher than the slight female predominance in cohorts of white and Black patients, for which the ratio is less than 2:1.

Hypercalcemia was seen in 16% of patients who had at least one calcium level available in their medical records, which is comparable to reports from North America. Since hypercalcemia in chronic granulomatous disease is driven by vitamin D, one could hypothesize that a geographic area with a higher intensity of sunlight and ultraviolet rays could have a higher prevalence of sarcoidosis-related hypercalcemia; however, the result of this study does not support this theory.

Potential biases

Since our study included a database from only one tertiary care center, the cohort may not be representative of all patients with sarcoidosis in the country (i.e., referral bias). Relying on ICD-10-CM codes also limited the accuracy of diagnosis and completeness of case identification. In addition, there was no specific protocol for documentation, and some important data may not be documented in medical records as a result.

For a complete list of references, please visit https://consultqd.clevelandclinic.org/tag/rheumatology-connections-summer-2021.

Recognizing Noninfectious Autoimmune Scleritis

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Treat to alleviate pain and prevent complications

In scleritis, the treatment goal is to alleviate pain and prevent complications, which are most common in patients with necrotizing and posterior scleritis. Ocular complications include peripheral ulcerative keratitis, vision loss or ocular perforation.

Treatment of scleritis depends on the severity and associated systemic disease. NSAIDs are the first-line therapy for anterior non-necrotizing scleritis. Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) (e.g., methotrexate, azathioprine, mycophenolate); biologic therapy, such as anti-tumor necrosis factor (TNF) drugs (e.g., rituximab, infliximab, tocilizumab); and alkylating agents (e.g., cyclophosphamide) have all been used in refractory disease in addition to glucocorticoids. If there is a risk of perforation, cyclophosphamide is usually the therapy of choice. The American Uveitis Society recommends the anti-TNF agents in ocular inflammatory conditions as second-line corticosteroid-sparing therapy for chronic and severe scleritis, especially in diseases with evidence of efficacy of these medications such as rheumatoid arthritis, Behcet's syndrome and IBD. Data are limited on the effectiveness of csDMARDs in scleritis, and randomized controlled trials comparing DMARDs for the treatment of noninfectious scleritis are needed.

Interdisciplinary management

Along with ophthalmology, rheumatologists play a major role in comanagement of patients with scleritis. It can be challenging to familiarize yourself with diseases that you are unable to fully assess with the tools you have available in your rheumatology clinic. Our practice at Cleveland Clinic is designed to facilitate interconnectedness of rheumatology and other specialties. Methods to facilitate interdisciplinary communication with ophthalmologists include interdisciplinary clinics and case conferences.

COVID-19 and the Rheumatologist: What Have We Learned?

By Cassandra Calabrese, DO

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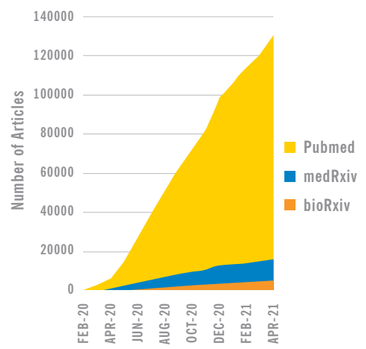
While we continue to encounter more unknowns than knowns with COVID-19, it is incredible to reflect on how much we have learned since the start of the pandemic. Just over one year ago we were bracing our patients for hydroxychloroquine shortages, when it was thought this would be the panacea for COVID-19. Over the past year, we witnessed many of the medications we use in rheumatology (from colchicine to tocilizumab) being studied and used to treat COVID-19. And while there have been many more negative than positive studies, there have been success stories (e.g., dexamethasone).

Despite this work, many unanswered questions remain, in particular about patients with immune mediated inflammatory diseases (IMIDs), including their risk for infection and poor outcomes, management and, perhaps most important, vaccine responses in our IMID patient population.

Figure 1. Cumulative COVID-19 Articles Stratified by Database



It is impossible to keep up with the onslaught of COVID-19-related data. As of April 1, 2021, more than 130,000 COVID-19-related publications have been posted. This number continues to grow (Figure 1) and we wonder if/when it will level out. Here I attempt to highlight where we have been and where we are going in terms of managing patients with IMIDs amid the COVID-19 pandemic.

Vaccination in IMID patients

I have been privileged to be a member of the American College of Rheumatology (ACR) COVID-19 Vaccine Clinical Guidance Task Force, along with 12 other specialists from rheumatology, infectious disease and public health. Led by Jeffrey Curtis, MD, MS, MPH, at the University of Alabama at Birmingham, this group had the tall task of drafting guidance for rheumatology providers on vaccinating IMID patients against COVID-19 in the absence of data. The guidance summary was released on Feb. 11, 2021 and discussed at a town hall hosted by the ACR on Feb. 16. The peer-reviewed manuscript was published in *Arthritis & Rheumatology* on March 17, 2021.[1] We developed this document to provide guidance and to serve as a basis for shared and informed discussion between rheumatologists and their patients. We intend it to be a living document and will update it as new data emerge.

To that end, we undertook a multidisciplinary study to evaluate vaccine response in specific IMID populations. Of pressing clinical concern is our lack of data on vaccine response in numerous special populations that were underrepresented or censored from the pivotal trials of each currently available COVID-19 vaccine. In collaboration with the Lederman/Freeman lab at Case Western Reserve University, this pilot study examines humoral and cellular immune responses to COVID-19 vaccination in anti-neutrophil cytoplasmic autoantibody-associated vasculitis and rheumatoid arthritis patients receiving rituximab, as well as common variable immunodeficiency patients receiving immunoglobulin replacement, in order to increase our understanding of the adaptive immune host response to vaccination, and to provide data and insights for patients and providers regarding vaccination. Thus far, there have been several reports of reduced immunogenicity after a single dose of a COVID-19 mRNA vaccine in solid organ transplant patients.[2,3] Studies examining vaccine responses in IMID patients provide reassurance of safety and efficacy; however, these were small studies.[4,5]

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Bisphosphonates and Atypical Femur Fractures in Osteoporosis

By Chad Deal, MD

JB, an 81-year-old, white female, presented with bilateral thigh pain of three months' duration. She had osteoporosis with a lumbar spine T-score of –3.2 and had been on alendronate for 11 years. X-rays showed bilateral stress reactions in both femurs, on the lateral cortex, below the lesser trochanter consistent with atypical femur fracture (AFF). The left femur had an identified fracture line that did not extend to the endocortex, although the patient had both periosteal and endosteal elevation on X-ray. She was seen in orthopedics and intramedullary rodding was recommended, which the patient refused. She was treated with partial weight bearing and teriparatide for 24 months. The pain resolved in two months in the right thigh and 12 months in the left thigh.

The role of bisphosphonates in atypical femoral fractures

First reported in 2005, AFFs were determined to be related to long-term therapy with bisphosphonates (BP). AFFs have also been reported with denosumab and romosozumab therapy. AFF is extremely uncommon in the first three years of BP therapy; however, the incidence increases with duration of treatment to 113 per 100,000 patient years after eight years.

In the FREEDOM trial open-label extension with denosumab, two participants developed AFFs at three and seven years of treatment, which represents an incidence of 8 per 100,000 participant years.[1] It is important to tell patients at high risk for fractures that the benefit/AFF risk ratio of three to five years of BP favors treatment: For every single AFF, approximately 1,200 osteoporotic fractures are prevented.[2] Because the incidence of AFF increases with duration of therapy, the American Society for Bone and Mineral Research (ASBMR) developed guidelines for drug holidays from BP.[3] For patients with no fractures and mild osteoporosis, ASBMR recommends three to five years of oral and three years of intravenous therapy (zoledronate).[4] For patients with fractures and T-scores of < -2.5, the benefit/risk ratio favors up to 10 years of oral BP and six years of intravenous BP. With discontinuation of BP, the risk of AFF declines rapidly, and is 70% lower 12 months after discontinuation. The rapid decline is somewhat surprising since BP have a long residual half-life in bone, but also means that clinicians need to be alert to the possibility of AFF after discontinuation of BP.

Diagnosis and treatment of atypical femoral fractures

Patients on long-term BP and denosumab therapy who present with thigh pain should have femur X-rays. Negative imaging with high suspicion for AFF warrants further imaging with MRI or CT. MRI scans show a bright signal on T2 images representing bone edema. ASBMR has also published a case definition of AFF, which is important since typical fractures of the femoral shaft occur in patients with osteoporosis.[5]

Providers should look at the dual-energy X-ray absorptiometry (DXA) scans, as review in our patient revealed periosteal elevation on the lateral femur shaft. AFFs occur with no or minimal trauma and always originate on the lateral cortex, with periosteal elevation at the fracture site. They are below the lesser trochanter, and characteristically, when fractures occur they are not or minimally comminuted and transverse. Prodromal symptoms of thigh pain are usually present. Up to 25% of cases are bilateral. Groups at higher risk for AFF include patients on glucocorticoids and patients of Asian ancestry (in North America). In our patient, a DXA scan of the left femur in 2012 showed subtle periosteal elevation of the lateral cortex, which was very prominent on the DXA in 2014.

When an identified fracture line is present, treatment should include intramedullary nailing as many of the fractures will complete. BP or denosumab therapy should be discontinued. In a small series, more than 33% of patients with AFFs completed their fracture without surgery, and another 33% had pain and delayed healing.[6] There is a rationale for anabolic therapy since the mechanism of AFF is thought to be adynamic bone,

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Infective Endocarditis Can Mimic Systemic Autoimmune Conditions

By Adam Brown, MD

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A patient presents to the hospital with a six-week history of malaise, oligoarticular asymmetric inflammatory arthritis, palpable purpura on lower extremities, acute kidney injury and the presence of red blood cell casts on urine microscopy. The patient also has a positive anti-neutrophilic cytoplasmic antibodies (ANCA) test. Although it sounds like ANCA vasculitis, this is actually a great example of a patient with subacute infectious endocarditis (IE). Some clues to the diagnosis may be present, including fever, weight loss, normal platelets (usually high in active vasculitis) and low complements (usually normal in ANCA vasculitis). Although IE can look very similar to a small vessel vasculitis, the consequences of immunosuppressing this patient could be devastating.

Subacute IE can be subtle, presenting over months of progressive, nonspecific symptoms. A minority of patients may not even develop a fever. Rheumatologists should be aware of the ways IE can mimic systemic autoimmune conditions.

Historical background of immunologic sequelae

IE produces multiple complications, from embolic disease from valvular vegetations such as cerebrovascular accidents and splenic infarcts to other manifestations that are not clearly secondary to embolism. The immune sequelae of endocarditis were first suspected when biopsy of Osler nodes — the well-known cutaneous manifestations of IE on the fingers and toes — demonstrated a sterile vasculitis. Further traction for the immune etiology of endocarditis-related sequelae came from a paper published in 1962 demonstrating that many patients with endocarditis had low complement levels, and worse renal outcomes in patients with hypocomplementemia.[1] Additional studies showed nearly all patients with IE develop circulating immune complexes, and the glomerulonephritis in many patients with IE has immune complex deposition demonstrated by immunofluorescence.[2,3] It is hypothesized that immune complex deposition plays a role in multiple manifestations of IE, including the peripheral joint involvement.

Joint manifestations

Approximately 30% of patients presenting with IE have articular manifestations, which can be divided into pyogenic and immunologic subtypes. The pyogenic causes of joint pain include direct infectious embolization from the cardiac vegetation into a joint or bone, causing osteomyelitis. Most commonly this occurs in the vertebrae and presents as an acute, focal back pain. Overall, focal vertebral osteomyelitis is the most common articular manifestation of IE. The inflammatory arthritis seen in the peripheral joints is most likely a result of immune complex deposition within the joint triggering monoarticular or asymmetric oligoarticular inflammatory arthritis. The synovial fluid is often mildly inflammatory and almost always sterile and resolves rapidly with the initiation of antibiotic therapy.[4] The peripheral joint involvement of IE is nondestructive, again arguing against a direct infectious process in the septic joint.

Small vessel vasculitis

IE can mimic small vessel vasculitis in a variety of ways, including palpable purpuric rash, inflammatory arthritis, digital ischemia and glomerulonephritis. To further confuse matters, IE can also be associated with positive ANCA serologies as well as positive serum cryoglobulins.[5,6,7] Renal histology can provide insight, as many patients with endocarditis develop an immune complex glomerulonephritis in contrast to the typical pauci-immune glomerulonephritis of ANCA vasculitis; however, pauci-immune glomerulonephritis can also be seen in a subset of subacute bacterial endocarditis that is indistinguishable from ANCA vasculitis. Because of the similarities of small vessel vasculitis and IE, ordering a set of blood cultures in acute presentations of ANCA vasculitis is critical to rule out important infectious mimics as much as possible.

Laboratory

Multiple autoimmune serologies and rheumatologic tests can be positive in patients with IE. Rheumatoid factor is positive in nearly half of patients with IE, which can be tricky as joint manifestations can be an early complaint in patients with IE.[1] Nearly 97% of patients with IE have measurable immune complexes. Immune complex formation is not unique to IE as it is common in autoimmune conditions and in other infections — including sepsis — but the rates of immune complex in IE seem to be much higher than in other infections. Rheumatologists do not typically measure immune complexes in patients, but the downstream consequences of immune complex formation and deposition can be seen in IE with low serum complement levels.[1] In fact, in a patient with suspected ANCA vasculitis, low complement levels can be a clue that IE is the culprit.

Conclusion

Subacute bacterial endocarditis can present with a broad range of symptoms including many that mimic systemic autoimmune diseases. Patients with IE can present with joint pain and may have a positive rheumatoid factor. IE can present with multiple components of a small vessel vasculitis and again have positive ANCAs and serum cryoglobulins. Rheumatologists see many conditions that do not quite fit into a proper category of a systemic autoimmune disease and should have a low threshold for checking blood cultures.

For a complete list of references, please visit https://consultqd.clevelandclinic.org/tag/rheumatology-connections-summer-2021.

COVID-19 and the Rheumatologist: What Have We Learned?

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Post-acute sequelae of COVID-19

Finally, the entity now referred to as post-acute sequelae of COVID-19 (PASC) is one that rheumatologists will encounter with increasing frequency.[6] In PASC, patients suffer from persistent symptoms after recovering from the acute phase of infection. Most commonly, symptoms of PASC include fatigue, brain fog, shortness of breath, musculoskeletal pain and autonomic dysfunction. These lingering symptoms can be debilitating and may prevent previously healthy persons from returning to work. Even more puzzling is that patients with PASC often had a fairly mild infection course with COVID-19.

Cleveland Clinic has launched a ReCOVer Clinic, an effort led by Kristin Englund, MD, for evaluation of patients with PASC, which involves collaboration across specialists from 18 different clinical areas. This is likely to have a great impact on the field of rheumatology, and we are already seeing a growing number of patients. This collaboration not only serves to help patients, but also helps providers gain insight into the many unanswered questions about PASC, including immunopathogenesis, risk factors and optimal management. The clinic is currently seeing patients by referral from Cleveland Clinic providers but plans to expand in the future.

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Bisphosphonates and Atypical Femur Fractures in Osteoporosis

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with accumulation of microcracks that propagate to become a fracture. Numerous reports of PTH analogs have been published with mixed results. Teriparatide may accelerate fracture healing and reduce risk of non-union after treatment of intramedullary rods.

Our patient refused surgery and fortunately did not complete her fracture. In JB's case, PTH analog therapy was associated with increased markers of bone formation, symptom improvement and rapid remodeling of the fracture site with resolution of the fracture line. At the end of teriparatide treatment, her lumbar spine T-score was –2.5. The use of antiresorptive agents would normally be recommended with a T-score of –2.5 and the knowledge that that bone loss will start after teriparatide discontinuation. This decision is always a difficult one when these agents were the initial cause for fracture. In this case, we started JB on raloxifene.

For images and complete list of references, please visit https://consultqd.clevelandclinic.org/tag/rheumatology-connections-summer-2021.

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