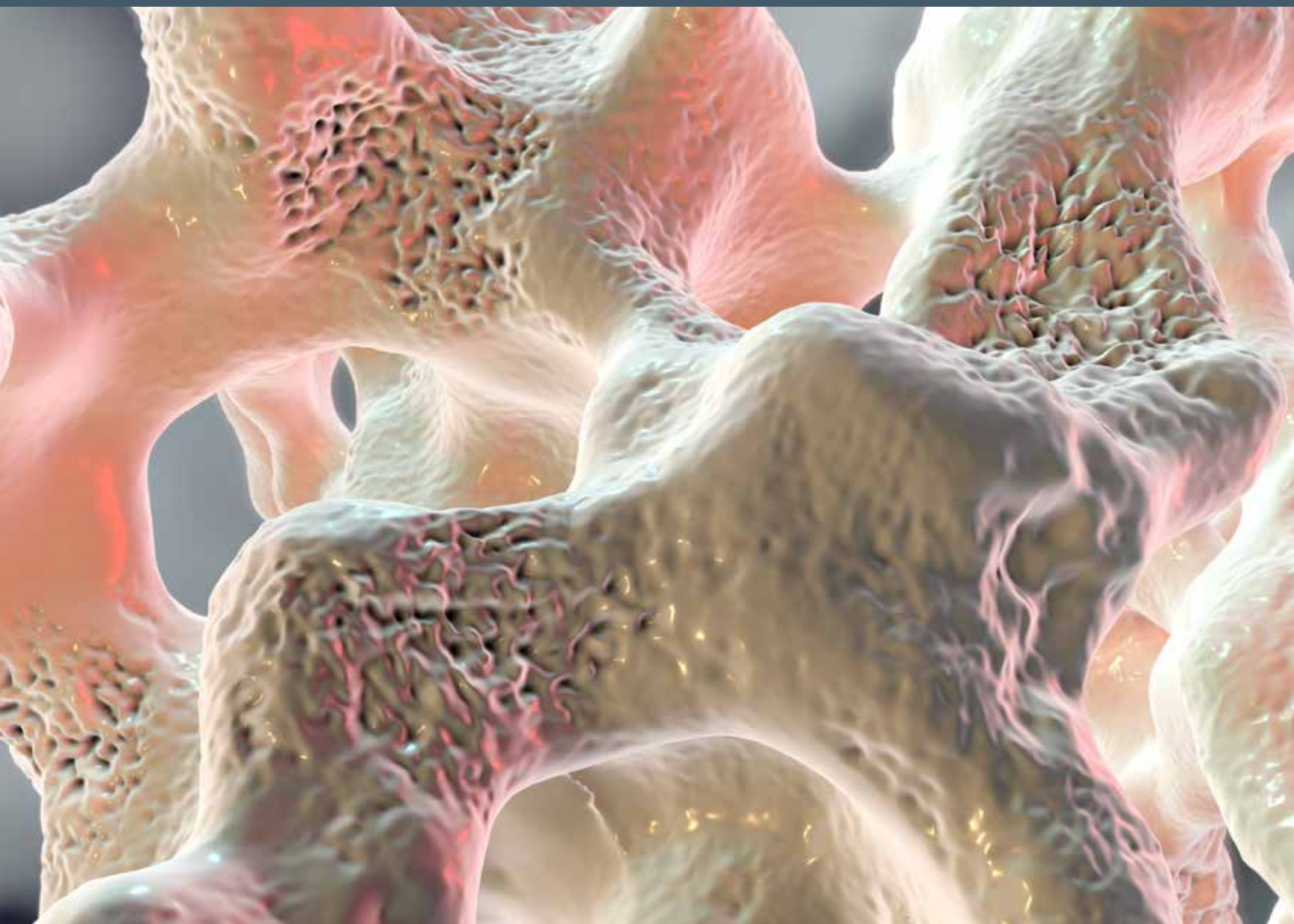
IN THIS ISSUE

Cleveland Clinic

Rheumatology Connections

An Update for Physicians | Winter 2020



From the Chair of Rheumatic and Immunologic Diseases

Dear Colleagues,

It is my pleasure to share the Winter 2020 issue of *Rheumatology Connections* from Cleveland Clinic's Department of Rheumatic and Immunologic Diseases. In 2019, our department was again ranked among the top 2 rheumatology programs in the nation in *U.S. News & World Report*'s "America's Best Hospitals" survey. It is our honor to care for all patients with the diversity of rheumatic diseases, from common conditions to rarer manifestations of the most complex diseases.

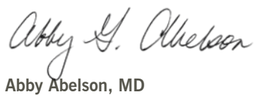
Our robust and diverse staff allows us to consult with experts in myriad rheumatologic subspecialties. Each article in this edition illustrates the medical complexity and interdisciplinary connectedness that are the hallmarks of our specialty. This issue begins with an article by Dr. Carol Langford, who shares the fascinating historical background of and intriguing developments in the management of polyarteritis nodosa (p. 3). Drs. Cassandra Calabrese and Leonard Calabrese provide an update on best practices in the management of immune-related adverse events related to checkpoint inhibitor therapy (p. 4). Dr. Chad Deal details the promising trial outcomes of a newly approved osteoporosis treatment (p. 6). On page 8, Dr. Soumya Chatterjee discusses a case of acro-osteolysis, a rare condition that impacts our patients.

We also share updates on some of our diverse research initiatives. Dr. Alexandra Villa-Forte outlines a multidisciplinary study of the microbiome of the temporal arteries in patients with giant cell arteritis (p. 7). Dr. Rula Hajj-Ali presents the longest reported follow-up of patients with primary angiitis of the central nervous system (p. 10). Dr. Elaine Husni highlights her lab's latest translational work, which aims to develop a personalized approach to treating psoriatic diseases (p. 11). Additionally, Dr. Emily Littlejohn discusses her current research into the role of antinuclear antibodies in lupus patients through the course of their disease (p. 12).

Finally, Dr. Adam Brown shares his novel efforts to attract more medical students and residents into our specialty (p. 14). His new book, *Rheumatology Made Ridiculously Simple*™, summarizes the complex conditions we manage and is getting positive reviews from our trainees and attending physicians alike.

I hope that you find in these pages an opportunity to connect, collaborate or consult with our team, so please reach out to me if you would like more information or to contact our colleagues.

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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Polyarteritis Nodosa – Everything Old Is New Again

NEW DEVELOPMENTS IN AN UNCOMMON DISEASE

By Carol A. Langford, MD, MHS

CASE

A 40-year-old male presents to the emergency department with a severe headache. On arrival his blood pressure is 220/120. He describes a two-week history of feeling ill with loss of appetite, intermittent right flank pain and areas of numbness over his bilateral lower extremities. On exam he is tachycardic and appears unwell. In addition to the hypertension, his examination is notable for decreased sensation along his anterior lower extremities and weakness in right foot dorsiflexion. Computed tomography (CT) of the abdomen reveals bilateral wedge-shaped infarcts in the renal parenchyma. A CT angiogram (CTA) is normal. You are contacted with the question as to whether the normal CTA has ruled out polyarteritis nodosa (PAN).

An uncommon but potentially life-threatening entity

PAN is a disease with a historical past and an intriguing future. Although Virchow and Rokitansky described pathologic arterial changes later recognized to be due to vasculitis, the detailed clinical and histopathologic report of periarteritis nodosa by Kussmaul and Meier in 1866 is generally recognized as the seminal published report that introduced this unique and life-threatening disease entity.[1] In the early 1900s, the name was modified to polyarteritis nodosa in recognition that inflammation was not confined to the adventitia and occurred throughout the vessel.

Since that time, the concept of PAN has continued to evolve as our understanding of this disease has grown. Following the description of PAN, most instances of vasculitis were referred to using this terminology. During 1920-1940, individual forms of vasculitis affecting the small- to medium-sized vessels began to be described. Pearl Zeek in 1952 presented the first classification system that separated other forms of vasculitis from PAN.[2] The most significant nomenclature changes impacting PAN occurred with the Chapel Hill Consensus Conference (CHCC) definitions published in 1994 in which PAN was differentiated from microscopic polyangiitis (MPA).[3] Although a microscopic variant of PAN associated with glomerulonephritis and pulmonary capillaritis had been recognized since the 1940s, the CHCC formally identified MPA as being a unique disease entity separate from PAN. The most recent CHCC vasculitis nomenclature published in 2013 defines PAN as a "necrotizing arteritis of medium or small arteries without glomerulonephritis or vasculitis involving arteries, capillaries or venules and not associated with antineutrophil cytoplasmic antibodies (ANCA)."[4]

Diagnosing PAN

As currently defined, PAN is an uncommon entity but remains potentially life-threatening with features that can affect the peripheral and central nervous system, heart, gastrointestinal tract and renal vessels. Renal involvement can manifest as hypertension, renal infarcts, perinephric hematuria and renal insufficiency. The diagnosis of PAN is established by the constellation of clinical features, usually in combination with consistent histologic or arteriographic findings. Because PAN affects the medium-sized vessels, visualization typically requires catheter-directed dye arteriography as vessels of this size cannot currently be visualized by CTA or magnetic resonance arteriography. In applying this to our case patient, the normal CTA does not rule out PAN, and this should be further pursued with a catheter-directed dye arteriogram given the patient's suggestive clinical features.

Treatment of PAN is based on the degree of disease severity, with organ- or life-threatening disease usually being treated with glucocorticoids and cyclophosphamide.

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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.

Rheumatic irAEs from Checkpoint Inhibitor Therapy

A FORMIDABLE CHALLENGE FOR RHEUMATOLOGISTS

By Cassandra Calabrese, DO, and Leonard H. Calabrese, DO

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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.

While the mainstream use of checkpoint inhibitors and other immunotherapy strategies is now considered a major pillar of cancer treatment, the immune-related adverse events (irAEs) — namely a wide spectrum of autoimmune diseases including a variety of rheumatic diseases — have been referred to as its possible Achilles' heel. It is now evident that we, as a general medical community and rheumatologists in particular, will have an ever-increasing role in the management of such patients.

Since 2011 the field of cancer immunotherapy has grown rapidly, with many new drugs and strategies being approved for many different malignancies, including the first-ever FDA approval for treatment agnostic of tumor type and instead based on a common biomarker for the PD-1 inhibitor pembrolizumab. It is now estimated that 43.5% of cancer patients are eligible for checkpoint inhibitor therapy.

For rheumatologists, the emergence of irAEs represents a formidable challenge in terms of both patient care and the need for continuing medical education. In patient care, we are seeing a rapid rise in new-onset inflammatory rheumatic diseases in patients who cannot wait a long time for appointments. Educationally, we need to keep up with the rapid pace of new knowledge regarding clinical and immunologic issues. We have been committed to meeting these challenges since 2016, when we developed a specialized interprofessional clinic to evaluate such patients and created new formats for interprofessional education and research.

In September 2017, a monthly conference was developed at our institution dedicated to the presentation and management of irAEs. This tumor board consists of clinicians from numerous departments with known interest and experience in irAEs. The goal is to discuss new and/or challenging cases of irAEs, review the extant literature and receive input on interprofessional management. On average, we discuss six cases at each conference. Approximately six months after the tumor board began, we surveyed participants to assess its educational value and appraise the board's impact on their confidence in managing irAEs. Our survey results indicated that 66.7% of physicians felt attending the tumor board significantly increased their awareness of the scope and presentation of irAEs, and 41.7% reported significantly increased confidence in diagnosing and managing certain irAEs. Most (75%) felt that the conference format/content was superior to other conferences in terms of interest and practical content. When queried about what aspects they valued most, participants most often noted the multidisciplinary nature of the conference. Now, two years later, we suspect these results would be even more impressive, as attendance has increased to standing room only.

Also, we are involved in a national tumor board started at MD Anderson with rheumatologists from institutions all over the country, including Mayo Clinic, Johns Hopkins, NYU, Stanford and others. We meet monthly on a web-based platform to discuss complex rheumatic irAE cases and brainstorm on opportunities to collaborate through research. Leonard Calabrese, DO, is also a member of the European League Against Rheumatism Task Force, which is developing the first rheumatology-specific guidelines for management of irAEs.

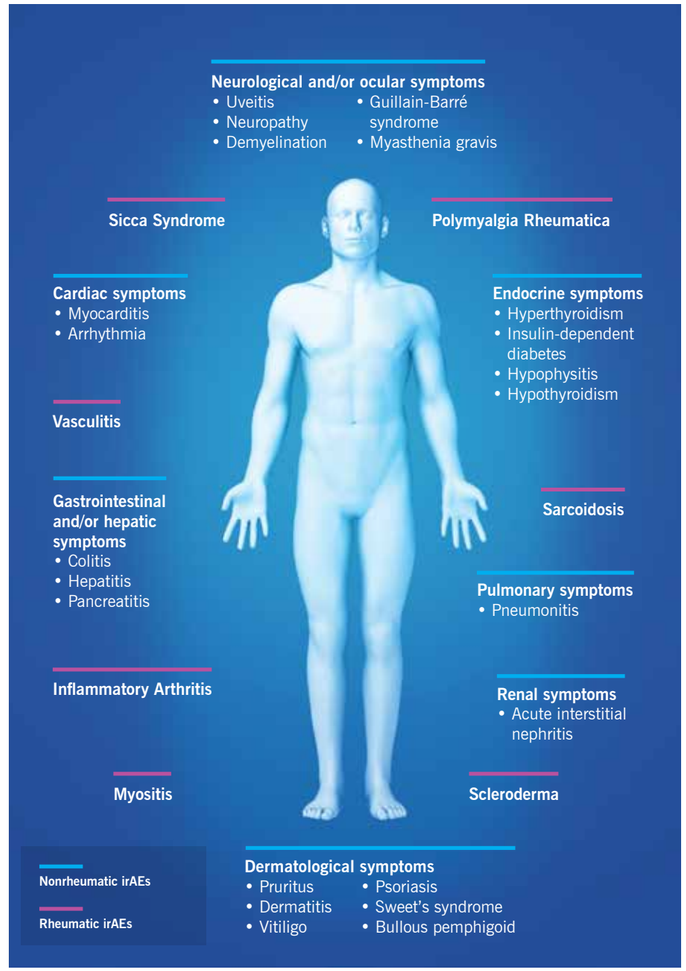
Rheumatologists play an important role in the management of irAEs

The diagnosis and management of patients who develop irAEs from checkpoint inhibitor therapy require multidisciplinary care, and rheumatologists play an important role. Patients who develop irAEs from checkpoint inhibitor therapy need to be triaged and seen by the appropriate subspecialist immediately. With the ever-present patient access issue in our current healthcare system, this can be a problem. At Cleveland Clinic, a multidisciplinary referral system was created to help efficiently triage these patients. Cassandra Calabrese, DO, works directly with the immune-oncology teams to get these patients seen promptly. She sees an average of 10 new immunotherapy patients per month, and this number is expected to grow as rheumatologists will be increasingly called on to participate in the care of these patients.

irAEs are a new area of medicine that require multidisciplinary collaboration for investigation and optimal management. The multisystem involvement and autoimmune, inflammatory mechanisms of these complications make rheumatologists valued — if not critical — partners in both patient management and research. Novel venues for educational interchange are needed to further this evolving field.

Educational opportunities for a rapidly changing field

In Cleveland Clinic's rheumatology department, a morning lecture series has been a great venue for learning about irAEs and immunotherapy. Dr. Cassandra Calabrese presented an introduction to irAEs for the fellows in August, followed by a deeper dive into underlying basic and clinical immunology by Dr. Len Calabrese. In September, we were fortunate to host visiting professor Khashayer Esfahani, MD, from McGill University, who spoke both to the rheumatology department and at Taussig Cancer Center. He is co-leader of one of Canada's largest biobanking/research platforms on irAEs. The focus of his visit was to explore the underlying biology for the use of targeted therapies to treat irAEs over and above glucocorticoids and TNF inhibitors.



Symptoms of irAEs

Along with Pauline Funchain, MD, and Laura Wood, RN, from Taussig Cancer Center, Dr. Cassandra Calabrese is planning Cleveland Clinic's first live CME event exclusively dedicated to irAEs. The course will be held on March 6, 2020, at the Cleveland Intercontinental Hotel and Convention Center.

This will be an interdisciplinary conference, geared toward oncologists and nononcologists, with representation from oncology, rheumatology, dermatology, endocrinology, ophthalmology, pulmonary, gastroenterology and cardiology.

Romosozumab: A New Era in Osteoporosis Treatment

DUAL-ACTING DRUG INCREASES BONE FORMATION WHILE DECREASING RESORPTION

By Chad Deal, MD

Dr. Deal (dealc@ccf.org; 216.444.6575; @CLDeal) is Director of the Center for Osteoporosis and Metabolic Bone Disease.

A new anabolic agent for the treatment of postmenopausal women at high risk for fracture was approved by the FDA in April 2019.

Romosozumab at a glance

Romosozumab is a monoclonal antibody against sclerostin — a cytokine, produced mostly by osteocytes, that regulates bone formation. The Wnt signaling pathway controls osteoblast formation and activity; sclerostin is an inhibitor in the pathway. Sclerosteosis is a rare disease caused by a genetic defect in the gene that codes for sclerostin. Patients with sclerosteosis have very high bone mass and are fracture resistant since osteoblast activity is upregulated in the absence of sclerostin. Romosozumab has the effect of removing sclerostin and upregulates bone formation.

Unlike the parathyroid hormone (PTH) analogs (teriparatide and abaloparatide), which increase both formation and resorption, romosozumab increases formation and decreases resorption; hence, the "dual effect" noted in the label. In clinical trials, this resulted in a large bone build. The drug is given once per month as two subcutaneous injections for 12 months, and is paid under Medicare B plans.

Clinical trial outcomes

Romosozumab was approved following three clinical trials: FRAME, ARCH and STRUCTURE. FRAME compared romosozumab to a placebo for 12 months, followed by an additional 12 months of denosumab in all patients.[1] Vertebral fractures were reduced by 73% at 12 months and 75% at 24 months in the romosozumab/denosumab arm. However, there was not a significant nonvertebral fracture reduction, which was felt to be a result of the low baseline fracture risk in the trial (most patients had a FRAX® 10-year risk that was less than the treatment thresholds set by the National Osteoporosis Foundation). This may be in part due to the geographic distribution of the patients, as 39% were from Latin America. A post hoc analysis excluding Latin American patients shows a significant nonvertebral fracture reduction.

ARCH was an active comparator trial: 12 months of romosozumab versus 12 months of alendronate, followed by 12 months of alendronate in all patients.[2] Patients in this trial had a much higher risk for fracture than those in the FRAME trial. The risk reduction for patients on romosozumab was 0.5 (50%) for vertebral fracture and 0.62 (38%) for hip fracture. (Remember that alendronate reduced vertebral and hip fracture in its registration trial by 50%.) An unexpected increase in major adverse cardiovascular events (MACE – MI, stroke and cardiovascular death; relative risk 1.87) occurred in ARCH, and the label carries the related warning: "Evenity® should not be initiated in patients who have had a myocardial infarction or stroke in the preceding year." Since there were only 41 events in the romosozumab-treated patients, risk factors that might predict who would be likely to develop a MACE could not be identified.

STRUCTURE compared patients previously treated with an oral bisphosphonate who were transitioned to either romosozumab or teriparatide.[3] Bone density increases in the spine and hip were greater with romosozumab (lumbar spine 9.8% versus 5.4%). Areal bone mass by CT scan was significantly greater in romosozumab treated patients. Finite element analysis (FEA) in hips — a measure of strength — increased with romosozumab and declined with teriparatide.

The foundational effect of using romosozumab is shown by analysis of fractures in year two of the FRAME and ARCH studies. All patients in year two of FRAME were on denosumab. The increase in bone mass in year two was the same as in patients who had been on romosozumab or placebo in year one, yet the risk reduction for vertebral fracture in year two was 0.19 (81%). The increase in bone mineral density in FRAME was 13.1% at 12 months, which is equivalent to the increase in bone mass after 4.5 years of treatment with the most potent antiresorptive agent, denosumab.

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Microbiome in Patients with Giant Cell Arteritis

TEMPORAL ARTERY MICROBIOME DIFFERS FROM THAT OF HEALTHY CONTROLS

By Alexandra Villa-Forte, MD, MPH

Researchers have long suspected that microorganisms play a role in the development of giant cell arteritis (GCA), and new data showing that patients with the disease have a distinct microbiome are the first step toward determining that function.

GCA occurs most often in the extracranial branches of the carotid arteries near the temple and is the most common large vessel vasculitis. Evidence suggests that infectious agents may provide antigenic stimulation in GCA. With this in mind, we recently analyzed bacterial sequences and abundance in patients with GCA (N = 24) and compared them with patients without GCA (N = 23).[1]

The etiology of GCA is unknown, but the immunologic features of the disease suggest that microorganisms may play a role. However, a distinct vascular microbial environment could also be a secondary result stemming from injury to the vessel itself.

Histopathology and biopsies

Histopathology of the temporal artery (TA) of the nine patients with a final diagnosis of biopsy-proven GCA revealed arteritis, with mononuclear cell inflammatory infiltrates localized to the media and adventitia, varying amounts of intimal proliferation and fibrinoid necrosis, and fragmentation of the internal elastic lamina.

All biopsies from biopsy-negative patients with clinically positive GCA revealed arteriosclerosis, with intimal thickening and rare, focal calcification; 20 of 23 control TAs without GCA also shared these findings. Three TAs from controls were normal.

Microbiota differences

We compared the relative abundances of bacterial operational taxonomic units in the TAs of patients with and without GCA. At least two classes of Firmicutes were relatively over-represented at the phylum level in GCA TAs compared with those without GCA. Two other classes of Firmicutes were relatively under-represented in TAs with GCA compared with TAs without GCA.

In TA samples from patients with GCA, Proteobacteria and Actinobacteria were relatively under-represented. At the genus level, Granulicatella and Streptococcus in phylum Firmicutes were relatively over-represented. Parasutterella, in phylum Proteobacteria, and Bifidobacterium, in phylum Actinobacteria, were relatively under-represented in TA samples from patients with GCA.

Not a sterile environment

Overall, we learned that TAs are not sterile, as previously assumed, but rather are inhabited by communities of bacteria in both the control and diseased states. We also found that the microbiomes of biopsy-negative, clinically confirmed GCA TAs were similar to those of biopsy-positive GCA TAs, and together these two groups were distinct from those in control group samples. All of this leads us to wonder why there are histopathologic differences between biopsy-positive and biopsy-negative individuals with GCA.

One idea is that microbiomes may play a permissive role in the pathogenesis of GCA, to be later followed by a histologically apparent inflammatory response. If this were true, the well-known "skip lesions" in GCA biopsies could result from a stepwise inflammatory response.

Dr. Villa-Forte (villaa@ccf.org; 216.445.9437) is staff in the Center for Vasculitis Care and Research.

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Systemic Sclerosis: Critical Digital Ischemia with Acro-Osteolysis

SEVERE PAIN AND ULCERATION AFFECTING FINGERTIPS

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.

CASE

A 58-year-old female with an 18-year history of limited cutaneous systemic sclerosis presented with severe pain and ulceration affecting the tips of her fingers.

On examination, there was evidence of auto-amputation of some of her distal phalanges (Panel A: 1, 2 and 3) and ulceration of the overlying skin.

Hand radiographs demonstrated resorption of the first and fourth distal phalanges as well as the second, third and fifth middle phalanges of the right hand, in addition to resorption of the first, second, fourth and fifth distal phalanges as well as the third middle phalanx of the left hand (acro-osteolysis), along with resorption of overlying soft tissues (Panel B).

These changes had developed insidiously because of severe persistent digital ischemia associated with systemic sclerosis.

Panel A: Auto-amputation of distal phalanges

Pain relief from intravenous prostaglandin analogs

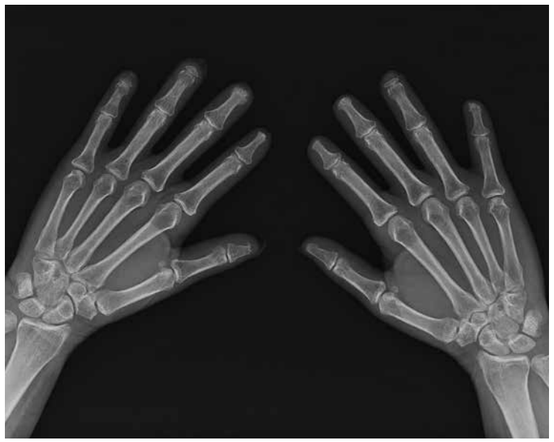
The patient did not get maximum pain relief with trials of various oral vasodilators, such as calcium channel blockers, alpha-blockers, losartan, pentoxifylline, phosphodiesterase-5 inhibitors and topical nitroglycerin. Intravenous prostaglandin analogs — such as prostacyclin, alprostadil and treprostinil — are useful for the treatment of severe digital ischemia in systemic sclerosis. Thus, she was admitted for a five-day course of continuous intravenous alprostadil infusion, which was chosen for its ease of use and lower price.[1] It provided substantial pain relief lasting for several months.

A rare condition that can co-occur with systemic sclerosis

Acro-osteolysis is associated with a diverse group of illnesses, such as scleroderma spectrum disorders, psoriasis, hyperparathyroidism, diabetes mellitus, leprosy, thermal burns, frostbite and chronic polyvinyl chloride exposure. It can also occur in rare genetic disorders such as progeria, pyknodysostosis and Hajdu-Cheney syndrome.

Systemic sclerosis is an autoimmune disease of unclear etiology characterized by progressive fibrosis of skin and various internal organs (mainly the lungs, heart, gastrointestinal tract and kidneys), a widespread occlusive microvasculopathy and presence of certain autoantibodies.

Acro-osteolysis is estimated to occur in about 20% to 25% of patients with systemic sclerosis.[2,3] It is believed to result primarily from hypoxia-induced upregulation of vascular endothelial growth factor, leading to increased osteoclastogenesis and enhanced osteoclastic bone resorption.[4] However, although acro-osteolysis is assumed to result from critical digital ischemia, it often develops even without digital ulcers, indicating that other factors may also play an essential role in its pathogenesis.[4]



Panel B: Resorption of overlying soft tissues. Reprinted with permission from Chatterjee S. Clinical Image: Acro-osteolysis. *ACR Open Rheumatology*. 2019 Aug 25. https://doi.org/10.1002/acr2.11072

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Polyarteritis Nodosa – Everything Old Is New Again

continued from page 3

New developments

The most recent intriguing development in the PAN story has been the recognition of a PAN-like vasculitis being described in conjunction with deficiency of adenosine deaminase type 2 (DADA2).[5] Patients with DADA2 usually present in childhood with a variable pattern of clinical involvement that includes ischemic and hemorrhagic strokes, skin findings, portal and systemic hypertension, hematologic abnormalities, immune deficiency, and vascular pathology. At a plenary session of the 2018 American College of Rheumatology annual meeting, results were presented of a study in which 117 patients with idiopathic PAN were screened for mutations in ADA2. Of these 117 patients, eight were identified as having a missense variant in ADA2, suggesting that DADA2 accounts for a subset of patients with idiopathic PAN.[6] This is important as TNF inhibitors have potential efficacy in DADA2, which would not be the usual treatment for PAN. These findings suggest that DADA2 should be considered in patients with idiopathic PAN, especially in those who present with early-onset disease.

PAN remains a complex disease whose story has continued to evolve over time. The rich history of PAN serves as a reminder that every disease provides opportunities for novel insights that may beneficially impact patient management and outcome.

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The Search for Prognostic Markers in Patients with PACNS

NEW LONG-TERM OUTCOMES DATA OFFER INSIGHTS

By Rula Hajj-Ali, MD

Dr. Hajj-Ali (hajjalr@ccf.org; 216.444.9643; @RulaHajjAliMD) is Associate Director of the Center for Vasculitis Care and Research at Cleveland Clinic.

As Associate Director of the Center for Vasculitis Care and Research at Cleveland Clinic, I see many patients with both common and rare vasculitides. The patients I diagnose with primary angiitis of the central nervous system (PACNS) often present with severe functional and cognitive symptoms, and we are only beginning to understand the long-term outcomes of this disease. My colleagues and I recently published the longest reported follow-up of patients with PACNS in *Clinical and Experimental Rheumatology.*[1] We found that long-term disability is mild, perhaps thanks to improvements in diagnosis and treatment, but that opportunities remain to improve patient quality of life and identify prognostic markers.

Our cohort

We identified patients diagnosed with central nervous system vasculitis by either cerebral angiogram results typical of vasculitis plus inflammatory cerebrospinal fluid (CSF) or findings of vasculitis on pathologic examination of brain tissue. Of 78 patients meeting the inclusion criteria, 27 responded to the four mailed questionnaires: the Barthel Index (to assess disability), the European Quality of Life Questionnaire (EuroQol; EQ-5D™), the Brief Patient Health Questionnaire (BPHQ-9; to assess depression) and a treatment history survey. Researchers also administered the Modified Rankin Scale (mRS; to assess disability). Median follow-up was 60 months (0-204), compared with 35 and 13 months reported in previous cohorts.

Our decision to include only patients whose diagnosis was established by brain biopsy (74.1%) or by the presence of both abnormal cerebral angiography and CSF findings (25.9%) distinguishes our study. Our study is also the first to address patient-centered outcomes.

Long-term quality of life outcomes

Most patients (N = 19; 70.4%) had mild disability, while around one-fifth (N = 5; 18.5%) experienced severe disability. Mobility issues were not present in 51.9% of patients, and 66.7% had no problems with self-care. Fifteen respondents reported no issues with usual activities, and a similar number (51.9%) reported no pain. Almost one-third (29.6%) reported no anxiety, and about 70% had minimal or no depression.

Our search for prognostic markers uncovered two potential targets. We noticed that patients with stroke demonstrated significantly higher rates of depression and/or anxiety, which is expected given that about one-third of stroke patients will experience post-stroke depression. One-third to one-half of patients with PACNS present with stroke, so it seems reasonable that the reported 30% incidence of clinical depression in this population is under-recognized.

The need for prognostic markers

Not long ago, PACNS was only diagnosed postmortem. The progress toward establishing standard diagnostic criteria and effective treatment protocols since Cupps et al. first described sustained clinical remission in 1983 has helped patients achieve a generally favorable disease course.[2] Our efforts in this study to characterize long-term quality of life factors allow us to understand areas of opportunity for improved diagnosis and treatment. Mortality remains high in patients with PACNS (11% of the 78 patients who met our inclusion criteria), and studies of larger cohorts are needed to identify prognostic markers.

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Targeting Tumor Necrosis Factor Pathways in Psoriatic Diseases

HUSNI LAB RECENTLY FUNDED BY NIH-NIAMS

By M. Elaine Husni, MD, MPH

The Husni lab is dedicated to advancing discoveries in psoriatic diseases and related comorbidities. Our lab recently received a grant that allows us to focus on a more targeted approach to treatment that may help reduce the signs and symptoms of psoriasis and psoriatic arthritis with fewer side effects. Together with co-principal investigator Unnikrishnan M. Chandrasekharan, PhD, lead scientist in our lab and staff in the Department of Cellular and Molecular Medicine at Cleveland Clinic's Lerner Research Institute, our lab is working to define novel disease-specific signaling pathways to allow more precisely targeted anti-tumor necrosis factor (TNF) therapy in psoriatic diseases. Although highly effective in treating psoriatic diseases, the chronic use of anti-TNF therapy can cause unwanted side effects because it also blocks TNF-α, a cytokine important in infection regulation and cancer surveillance.

Inhibiting TNFR2 to decrease adverse effects

To that end, our lab is focusing on the cell signaling of TNF-α, as its dysregulation plays a significant role in the skin and joint pathology of psoriatic diseases. Current anti-TNF medications act by binding TNF-α in circulation before it binds to its two immune cell surface receptors, TNFR1 and TNFR2, thus preventing the activity of both receptors. By contrast, our work involves selective inhibition of one of the two TNF-α receptors. This approach will still reduce the signs and symptoms of psoriatic diseases while preserving some protective mechanisms of TNF-α.

Our preclinical models using mice genetically engineered to selectively eliminate TNFR1 or TNFR2 receptors responded differently to a chemically induced psoriasis murine model. The findings suggest that specific blockade of TNFR2 may significantly reduce inflammation and ameliorate signs of psoriatic diseases, while also maintaining normal immune response in the host, including the ability to combat infection and cancer.

Furthermore, we know that some patients do not respond to anti-TNF therapies, and our work has shown that this lack of response may be related to a genetic variant of TNFR2, TNFR2-M196R. Our studies will uncover the mechanisms of TNFR2-M196R that link to this reduced response to anti-TNF agents in certain patients.

The new grant allows us to further develop these findings and ultimately test the hypothesis that inactivation of TNFR2, or chemical inhibition of its signaling intermediates, will relieve psoriatic inflammation in patients. Our study also tests whether TNFR2-M196R polymorphism does, in fact, reduce a patient's response to anti-TNF agents. This may help predict inadequate responders to anti-TNF therapies early on, allowing a more personalized treatment approach.

The grant

The National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health awarded our lab a $1.8 million R01 grant for five years to investigate the mechanisms of TNFR2 activation and its impact on psoriatic pathogenesis. We plan to continue our translational work in both murine models and our patient biorepository. Selective targeting of TNFR2 is a novel approach and can be applied to improving the safety and precision of treating a broad range of immune-mediated diseases.

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Changes in ANA Titers over Time: Preclinical to Clinical Lupus

NEW GRANT TO ASSESS POTENTIAL SIGNIFICANCE OF SERIAL ANA TESTING

By Emily A. Littlejohn, DO, MPH

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CASE 1

D.D. is a 29-year-old African American female with systemic lupus erythematosus (SLE) manifesting with positive antinuclear antibodies (ANA), anti-Smith antibodies, anti-double stranded DNA (dsDNA) antibodies and cytopenias. Clinically, the patient has arthritis, rash, alopecia and oral ulcers. Her ANA titer is > 1:1280, with a homogeneous pattern.

CASE 2

M.A. is a 22-year-old African American female with SLE, with positive ANA, positive anti-dsDNA, low complements, cytopenias with lupus nephritis on hemodialysis, cardiomyopathy and serositis. Her ANA titer is 1:80, with a homogeneous pattern.

Cases such as these have piqued the interest of rheumatologists in examining the ANA titer and its role in SLE. The patient in case 1 has no end organ involvement of her lupus, yet her ANA titer is > 1:1280. In contrast, the patient in case 2 has multi-organ involvement of SLE, with a low positive ANA titer at 1:80.

Are these ANA titers static? Is the absolute number meaningful? Have the titers increased or decreased over the course of the disease? These uncertainties have yet to be elucidated and are at the core of a recent grant we have accepted from the Lupus Foundation of America.

The diagnosis of SLE is multifaceted, requiring clinical symptoms with support of laboratory data. Although standard dogma among rheumatologists is that patients need only one ANA test throughout their medical workup, serial testing is nonetheless often performed. The ANA test holds so much weight that new European League Against Rheumatism and American College of Rheumatology classification criteria will require a positive ANA test by Indirect Immunofluorescence Assay (IFA) as an entry criterion.[1]

The antinuclear antibodies test

The ANA by IFA is a semiquantitative laboratory test that quantifies the presence of autoantibodies in addition to providing a pattern of nuclear staining. The degree of the ANA titer and the staining pattern portend an increased risk for the development of autoimmune diseases, and research has found that ANA titers were higher in patients with rheumatic diseases than in healthy individuals.[2] The presence and activity of autoantibodies have been implicated as the driving mechanism of injury and inflammation in this disease.[3,4] Nevertheless, we have not fully defined the role of these autoantibodies in lupus patients over time.

While one retrospective study using the Department of Defense Serum Repository suggested a progressive accumulation of autoantibodies before the onset of SLE, there have been no large-scale studies to assess changes in ANA titers in the same individual over time.[5] Another study from this same dataset investigated the use of hydroxychloroquine (HCQ) in the preclinical or asymptomatic phase of patients who went on to develop SLE. Patients who were treated with HCQ had a longer time period before the clinical onset of SLE symptoms compared with those who were not treated with HCQ, and the average number of autoantibodies accrued by the time of diagnosis was higher in patients receiving no pre-diagnosis HCQ.[6] This suggests that an increase in autoantibodies, as reflected by the ANA test, may mirror the onset or worsening of symptoms.[7] Additionally, this study lends evidence that HCQ can slow or alter the accrual of these antibodies. One proposed mechanism is that HCQ alters the pH in intracytoplasmic vesicles and, thus, the processing and presentation of autoantigenic proteins in MHC class II complexes. This results in a decreased stimulation of CD4-positive T cells reactive with self-peptides, decreased release of cytokines and an overall weakening of the autoimmune process.

Do ANA titers change over time?

In accepting the Gary S. Gilkeson Career Development Award from the Lupus Foundation of America, we plan to characterize trajectories of ANA titers over time in patients with SLE, patients with incomplete SLE and ANA-positive controls without rheumatic disease. After identifying these patients within the electronic health record, we will perform longitudinal modeling, stratified by these three patient groups, to statistically define patterns in positivity and strength of ANAs over time, while accounting for intrapatient correlation. As a secondary aim, we will investigate whether HCQ use is associated with changes in ANA positivity or strength, testing the hypothesis that HCQ exposure is associated with a decrease in the prevalence or strength of ANA positivity over time.

This project will allow us to investigate whether ANA titers in the same individual change over time and whether these changes are clinically meaningful. This is timely in the wake of the Choosing Wisely® initiative,[8] which seeks to advance a national dialogue on avoiding unnecessary medical tests, as this grant would address the potential utility of serial ANA testing in lupus patients and provide data to guide decision-making related to ANA ordering.

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Romosozumab: A New Era in Osteoporosis Treatment

continued from page 6

Who is a candidate for romosozumab vs a PTH analog?

There are no guidelines, and the following list is based on expert recommendation only:

- Patients with hip fracture, as ARCH showed a 38% relative risk reduction in hip fracture versus alendronate, and neither PTH analog has demonstrated hip fracture reduction. STRUCTURE showed a significant increase in hip strength by FEA with romosozumab compared with teriparatide.[3]
- Patients with previous radiation, which is a contraindication to PTH analogs.
- Patients who have taken a PTH analog for two years in the past and need additional anabolic medication.
- Patients with chronic kidney disease who have elevated PTH levels that preclude the use of a PTH analog.
- Patients who have side effects with PTH analogs (perhaps 10% of patients discontinue for side effects, usually hypercalcemia, bone pain or vasoactive effects like tachycardia).
- Patients who need an anabolic and have elevated bone resorption markers (i.e., NTX or CTX). Romosozumab may be a better option in these patients since it decreases resorption.
- Romosozumab is less expensive for a course of treatment ($22,000) versus abaloparatide ($48,000) and teriparatide ($86,000).
- Romosozumab is a Medicare B drug and may be less expensive — especially for Medicare patients — than PTH analogs.

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Educational Hurdles Contribute to Workforce Shortage

TEXT AIMS TO MAKE RHEUMATOLOGY MORE APPROACHABLE FOR MEDICAL STUDENTS

By Adam J. Brown, MD

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Rheumatology is a complex, rapidly changing field. We see a wide range of diseases that have heterogeneous presentations with incompletely understood pathophysiology. The laboratory testing that we utilize often is nondiagnostic and requires interpretation within an appropriate clinical context. The medications we prescribe are specialized, requiring a knowledge of immunology and potential side effects and, often, close laboratory monitoring. The majority of our patients are immunosuppressed to some degree, requiring providers to be wary of infectious complications patients may develop while on these specialized medications.

These complexities make rheumatology a difficult field to approach from a learning perspective. Most nonrheumatology physicians do not feel comfortable with the workup, lab interpretation or medications used in the field. When I'm working with internal medicine residents during their rheumatology rotations, a major concern is the lack of educational materials regarding the field, aside from thick, unapproachable textbooks meant for rheumatology fellows and rheumatologists. Students and trainees often are not exposed to the field to a degree that allows them to feel comfortable with the approach and management of these conditions.

> We face an impending workforce shortage in rheumatology in the next decade.

Rheumatology can be approachable

Throughout medical school and my residency in internal medicine, I used a popular textbook titled, *Microbiology Made Ridiculously Simple*™. Full disclosure: As an attending rheumatologist, I still have a copy of the latest edition on the bookshelf next to my desk. The textbook is designed to make it easy and enjoyable to learn about the field of infectious diseases. The pictures within the book are farcical, with bacteria, viruses and fungi drawn with scowls and weaponry set to invade the unsuspecting host.

Considering the lack of material for students and residents to learn the basics of rheumatology, I reached out to the microbiology book's publisher to gauge interest in a rheumatology book for the series. The publisher was very interested, and over the course of two and a half years, I wrote *Rheumatology Made Ridiculously Simple*. I drew pictures and made tables with the express purpose of making the topic as easy to understand as possible. I wrote clinical vignettes at the end of every chapter, giving examples of the disease, workup and treatment approaches. At the end of the book I provided multiple-choice questions along with detailed answers, as well as explanations of why the incorrect choices are wrong — all with the goal of making the complex field of rheumatology as approachable as possible.

Not only are medical students and general medicine trainees uncomfortable with rheumatology, but we also face an impending workforce shortage in rheumatology in the next decade.[1] Many older rheumatologists are retiring, and there aren't enough training spots to make up for the growing demand. *Rheumatology Made Ridiculously Simple* simplifies the field in the hopes of allowing general and advanced practitioners to feel more comfortable with the workup and treatment of these patients. Many patients live hundreds of miles from a rheumatologist — this book may be able to help bridge the gap and allow their local providers more familiarity with the patient's condition and management.

My hope is to have students and residents more engaged and excited about the field of rheumatology and appreciate its diagnostic and therapeutic possibilities. Rheumatology is such an incredible specialty with diverse diseases, complex immunological pathways and treatments that can make a dramatic impact on patients' lives. I hope students and practitioners will read this book and feel more comfortable with the diagnostic workup, laboratory interpretation and therapeutic options for patients with rheumatologic conditions, but also be entertained by the material.

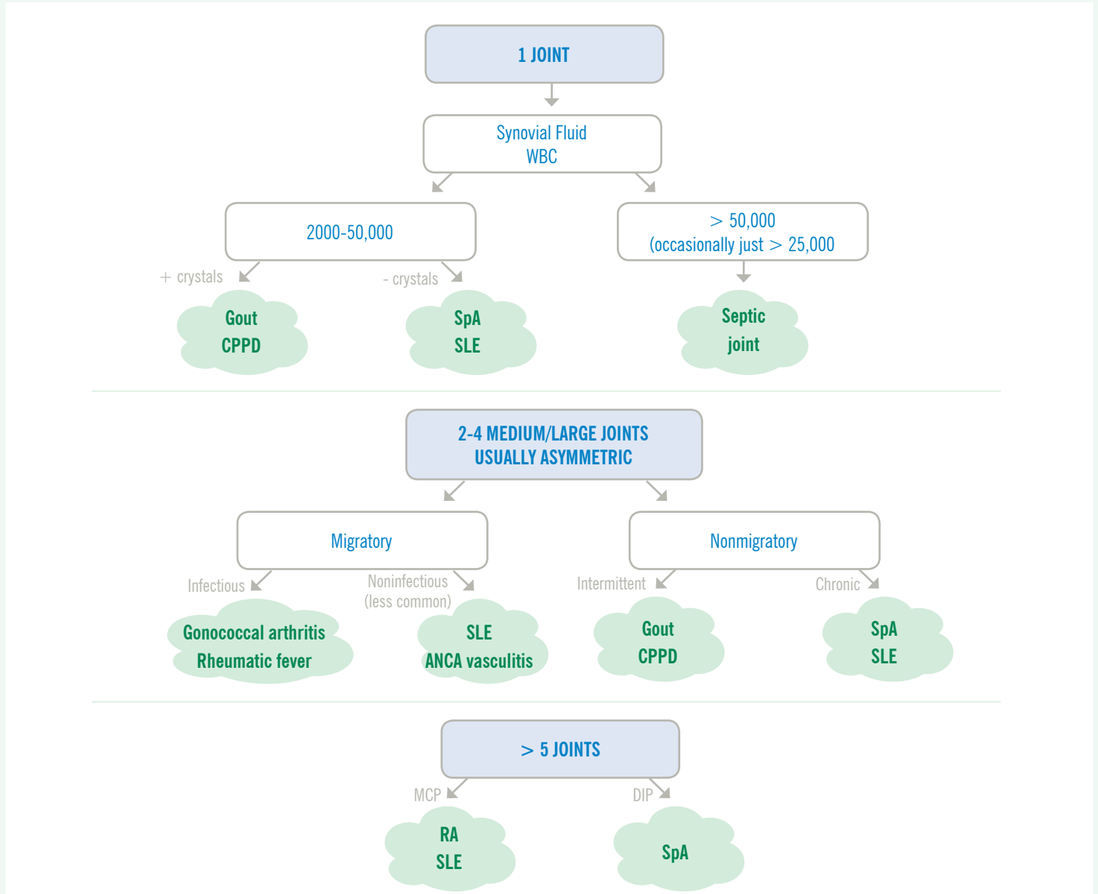

Chart 1. Simplified flowchart of conditions to consider when evaluating a patient, based on the number of joints involved at presentation. ANCA = antineutrophil cytoplasmic antibody; CPPD = calcium pyrophosphate deposition; DIP = distal interphalangeal joints; MCP = metacarpal phalangeal joint; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; SpA = spondyloarthritis; WBC = white blood cell.

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