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Cleveland Clinic

Rheumatology Connections

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From the Chair of Rheumatic and Immunologic Diseases

Dear Colleagues,

As the Summer 2020 issue of *Rheumatology Connections* goes to print, I cannot believe how much has changed in just a few months. These are truly unprecedented times. The evolving COVID-19 pandemic has had a profound impact on clinical care, education and research. I continue to be inspired by the compassion and unwavering commitment of the medical community to serve those in need.

I have great admiration for the physicians who have continued to care for patients with chronic rheumatic diseases with empathy and dedication throughout the pandemic. At Cleveland Clinic, our rheumatologists were nimble and flexible in converting as many patient visits as possible to telehealth consultations. We never stopped seeing new and established patients, and brought patients into the office for treatments to reduce the severity of their conditions on a case-by-case basis. We have managed larger phone and inbox volumes as our patients have needed to discuss critical questions about their immunosuppressive treatments and other issues during this stressful time.

As we begin to resume deferred services, we do so with extreme care. We will continue with a combination of in-person and virtual visits in order to minimize risk to those most vulnerable. We have instituted enhanced cleaning procedures throughout our facilities. In addition, there are several other precautionary measures in place, including mandatory face coverings for all caregivers, reduced occupancy to maintain physical distancing, and thermal screening and symptom checks for all individuals entering our buildings.

Social distancing precautions have led us to consider the plethora of ways in which we are connected to others. Many of the articles in this edition of *Rheumatology Connections* discuss the interconnectedness of rheumatology with other medical specialties. We also highlight recent innovations in medical education.

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

Respectfully,

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BEST HOSPITALS U.S.News & WORLD REPORT NATIONAL RHEUMATOLOGY 2019-20

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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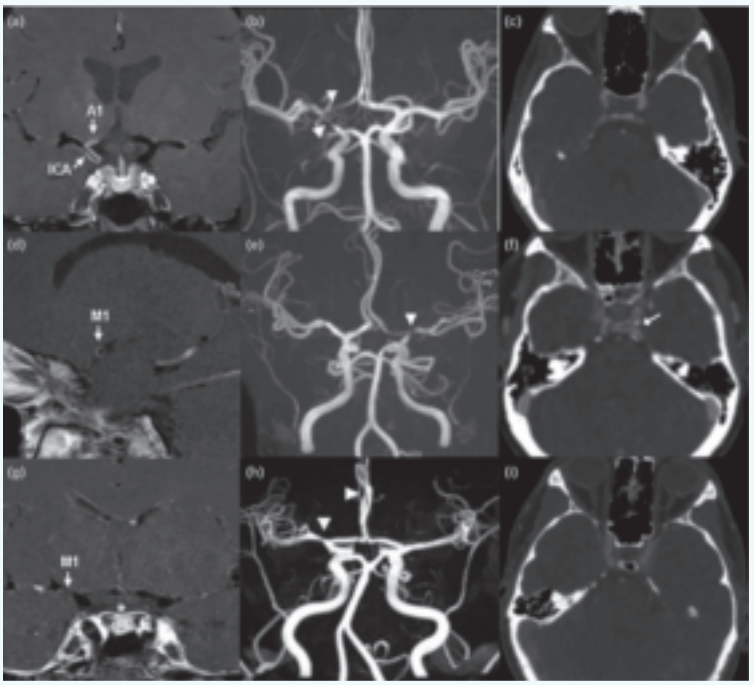
Advances in the Diagnosis of Central Nervous System Vasculitis

by Rula Hajj-Ali, MD, and Leonard H. Calabrese, DO

Arriving at a diagnosis of central nervous system vasculitis (CNS-V) is fraught with challenges. Clinical presentation can be quite variable, and there is no classic presentation. Further complicating matters, the condition has several mimics, brain tissue is inaccessible, and there is no disease-specific test. However, advances in neuroimaging and next-generation sequencing — along with the involvement of a multidisciplinary clinical team — have added formidably to our knowledge of CNS-V.



Representative post-gadolinium contrast high-resolution MRI vessel wall image (a, d, g), 3D time of flight magnetic resonance angiography (b, e, h) and contrast computed tomographic angiography (c, f, i) in patients with intracranial vasculopathy. (a, b, c) A 49-year-old female with central nervous system vasculitis. **(a)** T1-weighted arterial wall coronal image of the right terminal ICA and proximal A1 with strong, smooth, concentric wall enhancement and thickening (arrows). **(b)** Magnetic resonance angiography revealed severe narrowing at the junction of the right terminal ICA, MCA and ACA origin (arrowheads). **(c)** No evidence of intracranial ICA calcification. (d, e, f) A 47-year-old female with intracranial atherosclerotic disease. **(d)** T1-weighted arterial wall sagittal image showed mild wall thickening with eccentric wall enhancement at the left M1 segment (arrow). **(e)** Severe short-segment stenosis was present at the origin of the left MCA (arrowhead). **(f)** Spotty calcification can be observed in the left intracranial ICA lumen (diamond arrow). (g, h, i) A 30-year-old female with reversible cerebral vasoconstriction syndromes. **(g)** T1-weighted arterial wall coronal image showed uniform wall thickening and wall narrowing without enhancement in the right M1 segment. **(h)** Magnetic resonance angiography revealed mild to moderate narrowing in the proximal right MCA and the distal right ACA (arrowheads). **(i)** Intracranial ICA calcification was not present. ; ACA, anterior cerebral artery; ICA, internal carotid artery; MCA, middle cerebral artery.

Systematic approach

Regardless of the scenario, we take a systematic approach to the workup of any patient suspected of having CNS-V. This approach includes a general history and physical exam, with a thorough review of symptoms associated with systemic autoimmune disease (e.g., fever, rash, sinus disease, sicca, joint pain, cough, peripheral neuropathy, orogenital ulcers, inflammatory eye disease, deep venous thrombosis or recurrent miscarriages). Clinicians should look for infectious and/or malignant conditions that might be associated with many of these nonspecific symptoms, especially fever, malaise, joint pain and weight loss. Other important aspects when interviewing patients include eliciting travel history, work hazards, chronic exposure to recreational drugs and family history of neurologic events. This information can reveal rare conditions.

Advances in diagnostic testing

Diagnosing CNS-V requires multiple modalities to exclude other conditions, including autoimmune serology to rule out systemic disease, as well as hypercoagulable

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Association of Anti-PM-Scl Antibody-Associated Systemic Sclerosis and Inclusion Body Myositis

By Soumya Chatterjee, MD, MS, FRCP

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Two female patients with anti-PM-Scl (polymyositis-scleroderma overlap) antibody-associated scleromyositis developed progressive proximal myopathy. Both patients had profound muscle weakness that was refractory to treatment with glucocorticoids with or without other oral immunosuppressive agents. In this article, we describe these two cases of anti-PM-Scl antibody-associated scleromyositis in which a muscle biopsy unexpectedly showed features of sporadic inclusion body myositis (sIBM).[1]

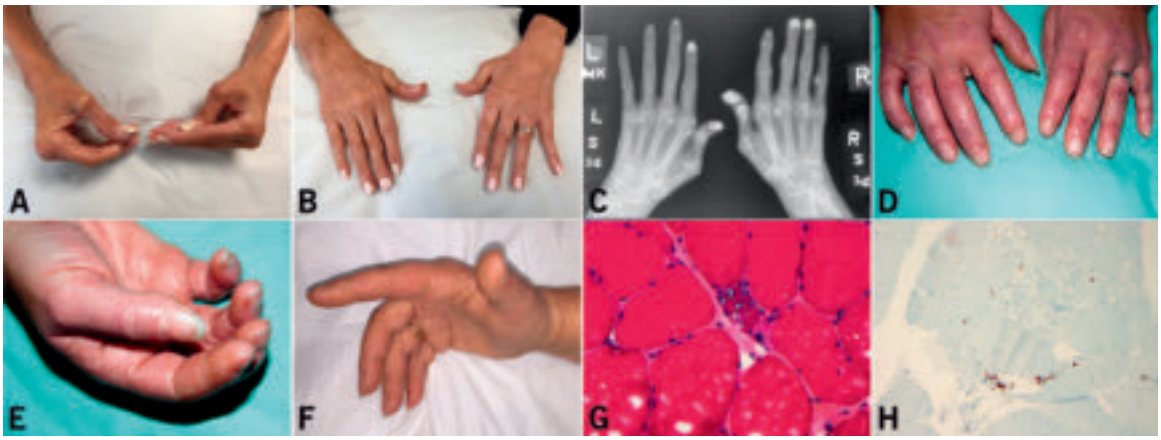
PATIENT 1

Patient 1 (P1) is a 54-year-old female who presented with complaints of polyarthralgia, profound muscle weakness, Raynaud's phenomenon and dysphagia. Her symptoms had an insidious onset when she was 37 years old. Examination revealed mild sclerodactyly but no proximal skin tightness. She had an ulcer on her right thumb with underlying calcinosis. Nailfold capillaroscopy revealed a paucity of capillaries but no dilated loops or hemorrhages. P1 also had a profound proximal weakness, with some distal muscle weakness. Although she did not have the characteristic flexion contractures of systemic sclerosis, she was unable to make a fist, which was attributed to finger flexor weakness. Tendon reflexes and sensory exams were normal, as were exams of the cardiovascular, respiratory and gastrointestinal systems. Relevant laboratory studies included normal muscle enzymes, a positive antinuclear antibody and a positive anti-PM-Scl antibody. Left quadriceps muscle biopsy revealed endomysial inflammation and rimmed vacuoles in scattered muscle fibers, which is consistent with a diagnosis of sIBM.

When P1's muscle weakness did not improve on high-dose glucocorticoids, she refused a trial of methotrexate or azathioprine. However, she did start high-dose monthly intravenous immunoglobulin (IVIG) infusions at 2 g/kg/cycle. In the four years since, P1 notes stabilization of muscle weakness; however, the severe proximal myopathy of her lower extremities and weakness in finger flexors and shoulder abductors persist.

PATIENT 2

Patient 2 (P2) is a 44-year-old female with a nine-month history of symmetrical polyarthritis, proximal muscle weakness, Raynaud's phenomenon and dysphagia with frequent episodes of choking. The patient was initially seen by Rheumatology at 37 years old. Exam revealed sclerodac-



A: Asymmetric weakness of deep finger flexors (left > right) in P1. B: Finger flexion in P1 is not due to contracture associated with systemic sclerosis, as seen here. C: Hand radiographs in P1 showing calcinosis cutis. D: Cuticular overgrowth with periungual erythema and nailfold capillary abnormalities in P2. E: Mechanic's hands in P2. F: Weakness of the deep flexors of right index finger in P2. G: Muscle biopsy in P2 showing rimmed vacuoles (hematoxylin and eosin stain, original magnification 400x). H: CD3 positive T lymphocytes in muscle biopsy in P2 (immunohistochemical stain, original magnification 200x).

tyly without proximal skin tightness; an erythematous, dry and scaly rash over the extensor aspects of the bilateral metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints; and cuticular overgrowth with periungual erythema and telangiectasias and mechanic's hands. Nailfold capillaroscopy revealed dilated loops, dropouts and hemorrhages. P2 had clinical synovitis of the bilateral MCP and PIP joints, knees, and ankles. Additionally, she had severe proximal and some distal muscle weakness. Weakness in her finger flexors, especially on her right side, led to an inability to make a fist. Tendon reflexes and sensory exams were normal, as were exams of the cardiovascular, respiratory and gastrointestinal systems. Notable laboratory results include elevated muscle enzymes and positive serologies (rheumatoid factor, anti-CCP antibody, ANA and anti-PM-Scl antibody).

P2 was diagnosed with seropositive rheumatoid arthritis (RA) (for which she was treated with oral methotrexate 20 mg weekly and six monthly cycles of rituximab; each cycle included two 1,000 mg intravenous infusions two weeks apart) and sclerodermatomyositis (for which she was treated with high-dose oral prednisone and monthly high-dose IVIG infusions). Over several months, her RA synovitis improved and her dermatomyositis rash cleared up; however, her proximal and distal muscle weakness continued to progress. A left quadriceps muscle biopsy revealed focal endomysial chronic inflammation and rimmed vacuoles, suggestive of sIBM.

Rimmed vacuoles may indicate an acquired myositis

Our study indicates that, when anti-PM-Scl antibody-associated scleromyositis is treatment-refractory and involves distal muscles, it is prudent to obtain a muscle biopsy to ensure that the myositis is not due to sIBM rather than recalcitrant polymyositis or dermatomyositis. However, we have to keep in mind that rimmed vacuoles may sometimes be missed due to a sampling error. In the future, along with the anti-cytosolic 5'-nucleotidase 1A (anti-cN1A) antibody (seen in a subset of patients with sIBM), it may be appropriate to order an anti-PM-Scl antibody, especially in relatively younger sIBM patients with clinical characteristics suggestive of concomitant systemic sclerosis.

1. *Chatterjee S, Prayson RA. Concurrent anti-PM-Scl antibody-associated systemic sclerosis and inclusion body myositis — report of two cases and review of the literature.* Semin Arthritis Rheum. *2020 Jun;50(3):498-502.*

Advances in the Diagnosis of Central Nervous System Vasculitis

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profile, thoracic or transesophageal echocardiography, and an ECG and electrophysiologic evaluation to rule out thrombotic/embolic conditions. Sampling cerebrospinal fluid (CSF) is indispensable in ruling out mimics like infection or malignancy. Fluid biomarkers of CSF have been ellusive, although recent investigations have found IL-17, Th17, complement system activation and amyloid-beta A4 protein. Importantly, metagenomic next-generation sequencing for an unbiased search for pathogens is quick and is becoming less expensive. Such sequencing may reduce the need for expensive and risky testing, including brain biopsy.

Ocular imaging techniques can aid in the noninvasive diagnosis of CNS-V. Although primary CNS-V does not involve the ocular system, ocular imaging may help distinguish primary CNS-V from other mimics, such as sarcoidosis, Susac syndrome or primary CNS lymphoma.

High-resolution vessel wall MRI (HR-MRI) adds diagnostic value by showing distinguishing vessel wall patterns for CNS-V and other, noninflammatory diseases (e.g., reversible cerebral vasoconstriction syndromes). With HR-MRI, one can visualize the wall of large and medium intracranial vessels and may be able to distinguish between disparate vascular diseases with similar angiographic findings. HR-MRI has become part of imaging protocols for detecting causes of ischemic stroke, mainly in a research setting but is increasingly asked for (and used) in clinical practice. Its precise role and added value for prognosis and patient care needs further elucidation.

As CNS-V can be potentially aggressive; prompt, accurate diagnosis is important. Advances in molecular biology (e.g., next-generation sequencing) and neuroimaging contribute greatly to resolving the diagnostic dilemma. Next-generation sequencing can enhance our ability to diagnose, interrogate and track infectious diseases and may help avoid brain biopsy in certain cases.

Note: Images reused with permission. Hajj-Ali R, Calabrese LH. Central nervous system vasculitis: advances in diagnosis. Curr Opin Rheumatol. *2020 Jan;32(1):41-46.*

Pregnancy and Rheumatoid Arthritis

By Emily A. Littlejohn, DO, MPH

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CASE VIGNETTE

KC is a 36-year-old female with a history of hypothyroidism and rheumatoid arthritis (RA). She was diagnosed with RA at age 33 when she presented with two months of swelling of her ankles and feet and was subsequently found to have a positive rheumatoid factor and anti-cyclic citrullinated peptide (CCP) antibodies, with florid inflammation on blood work. X-rays of her ankles and feet did not show evidence of erosions. She was placed on a course of prednisone and oral methotrexate; however, she was unable to tolerate methotrexate. She was switched to adalimumab 40 mg subcutaneously every two weeks, which was eventually increased to weekly dosing. She went on to achieve tight disease control on adalimumab therapy. At that time she was cleared to attempt conception. Shortly after finding out she was pregnant (estimated at four weeks gestation), she stopped adalimumab. She developed progressive stiffness and swelling of her joints. At an acute visit in our clinic, she had polyarticular swelling of her hands and wrists, with synovitis throughout her bilateral metacarpophalangeal joints. What do we know about treatment of pregnant, flaring RA patients and how can this be prevented?

Women with RA who are of childbearing age face many challenges throughout pregnancy and extending into the postpartum period, from fertility to birth outcomes and control of the disease. With appropriate preconception counseling and tight control of disease activity, it is still possible to achieve good pregnancy outcomes for our patients. This is the topic of a recent review article published in *Best Practice & Research: Clinical Obstetrics & Gynaecology* to raise awareness of this subject matter and update both rheumatologists and obstetricians.[1] With new information available regarding outcomes and safety, physicians should feel renewed confidence to guide management of these patients.

Fertility

Infertility rates are 2.3 times higher in women diagnosed with RA during childbearing years compared with those diagnosed following their childbearing years; however, there appear to be additional factors — besides infertility — contributing to the smaller number of pregnancies and births among women with RA. Research indicates that women with RA have fewer children than the general population for a number of physiological reasons including ovulatory dysfunction, endometriosis, alterations of cytokines (critical to embryonic implantation), aberrant functioning of T-cells, and chronic use of NSAIDs or glucocorticoids. Some psychological factors include decreased sexual desire as well as concerns about their ability to care for children, that their medications might harm a developing fetus or that they might pass RA on to their offspring.

Disease activity during pregnancy

Research indicates that disease activity improves for about 60% of women with RA during pregnancy and flares in 46.7% during the postpartum period.[2] RA flares occurred in 29% of women during pregnancy, most commonly during the first trimester. Risk factors associated with these flares were active disease and elevated CRP in early pregnancy and the discontinuation of tumor necrosis factor inhibitors (TNFi). In this study, 20% of patients discontinued TNFi treatment when they received a positive pregnancy test. Disease flares can be treated during pregnancy; however, continuing TNFi treatment throughout pregnancy may help reduce risk of flares.

Importance of patient education

Many women are not provided with adequate information about the risks and benefits of continued

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Innovations in Rheumatology Education

By Abby Abelson, MD, and Adam J. Brown, MD

In the past decade, innovations in technology have changed nearly everything about the way we communicate, read and learn. Medical education has not been exempt in this time of dramatic change. Perhaps one of the most poignant examples of innovation in medical education is the state-of-the-future, interdisciplinary Health Education Campus (HEC) on Cleveland Clinic's main campus.

Immersive medical education

The HEC, which opened to students in the summer of 2019, reflects the collaborative efforts of Case Western Reserve University and Cleveland Clinic to prepare students to lead in a new era of healthcare delivery. Home to Case Western Reserve University's dental, medical and nursing schools, including the Cleveland Clinic Lerner College of Medicine (CCLCM), the campus is designed to encourage interprofessional education and facilitate innovative thinking about some of the most complex issues in healthcare. Working with the latest technology, including digital anatomy lessons and medical simulation, students develop the skills they need to thrive in their respective fields.

Faculty from Cleveland Clinic's Department of Rheumatologic and Immunologic Diseases are quite involved in the training of first- and second-year CCLCM students, who benefit from this new learning environment. In the first year, Chad Deal, MD, teaches about bone turnover and issues related to metabolic bone diseases. In the second year, we provide a variety of interactive seminars. For example, Leonard H. Calabrese, DO, and Emily Littlejohn, DO, MPH, present on lupus; Abby Abelson, MD, conducts a targeted therapy seminar; and Carol Langford, MD, teaches about vasculitis. At the end of each topic, we have students come into our clinics to meet with patients whose conditions they have been studying. Our patients share their experience of the condition with the students, including everything from their symptoms and the journey to diagnosis to the cost and side effects of medications. This is a powerful experience for our learners and patients alike. Students enjoy the variety and interaction, and our patients view it as an opportunity to teach future physicians what it is like to live with chronic rheumatic diseases.

Varied platforms give us wide reach

We are also reaching a wide audience through a podcast from Adam Brown, MD. The podcast is an excellent teaching tool in the field of medicine that allows students and trainees from all levels to hear interesting cases and expert opinions. Medical professionals also listen to podcasts to keep up to date in a rapidly changing field or to hear an interesting case presentation. Medical students find podcasts appealing as the learning can be done at their convenience, with episodes replayed at leisure that can be listened to while enjoying other activities such as exercise.[1] In the podcast, Dr. Brown discusses the rare conditions that we see at Cleveland Clinic routinely, and interviews other rheumatologists in the department to get a variety of perspectives. Dr. Brown has also recently published a book titled *Rheumatology Made Ridiculously Simple*. The engaging text and illustrations aim to make rheumatology more approachable to medical students and residents.

In addition to our rheumatology fellowship, our involvement with CCLCM and Dr. Brown's outreach efforts complement our other professional activities, illustrating our commitment to Cleveland Clinic's tripartite mission: to provide better care for the sick, investigate their problems and further educate those who serve. As we engage people in the interesting complexity of diagnosis and management of patients with rheumatic, we hope these educational interactions intrigue medical students, residents and APPs to lead them to choose rheumatology as their professional focus.

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1. *Cho D, Cosimini M, Espinoza J. Podcasting in medical education: a review of the literature.* Korean J Med Ed. *2017;29(4):229-239.*

Pregnancy in Vasculitis: Issues to Consider

By Carol A. Langford, MD, MHS

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CASE

A 34-year-old female you have followed for granulomatosis with polyangiitis (GPA) comes to your clinic to discuss whether she is able to pursue a pregnancy. She was diagnosed with GPA at age 30 and presented with features that included sinus disease, pulmonary nodules, arthralgias, glomerulonephritis with a peak creatinine of 3.0 mg/dL, and a positive PR3-cANCA. For this she was treated with prednisone and rituximab, on which her creatinine improved to a baseline of 1.7 mg/dL. She has remained in remission since that time on her current medications of azathioprine 150 mg daily, lisinopril 20 mg daily and an oral contraceptive. What are the key points you need to discuss with your patient?

With the evolution of management options, pregnancy has become a feasible and realistic goal for many women with vasculitis. Most forms of vasculitis can impact women capable of having a child but prominently include Takayasu arteritis and ANCA-associated vasculitis.[1-3] The published literature on pregnancies in vasculitis remains small and often encompasses all these diseases, although there are some unique differences.[3]

For young women with vasculitis, it is important to begin the discussion about the potential for pregnancy early in their disease course. This is not only related to the teratogenicity of some medications, but also because careful planning and counseling prior to pursuing conception provides a woman and her child with the greatest potential for a safe outcome. When a woman begins to plan for a future pregnancy, there are several key issues that should be discussed:

- **Pregnancy timing.** The recency of the patient's active vasculitis and the overall disease course should be examined in evaluating the timing and advisability of pregnancy. As some series have found improved outcomes with disease control prior to pregnancy, achieving a stable remission before pregnancy is strongly recommended.
- **Organ damage.** Underlying permanent organ or blood vessel damage is one of the most important factors to be weighed in the safety of pregnancy for a woman with vasculitis. Renal insufficiency can occur as a consequence of many forms of vasculitis. During pregnancy, there is the potential for worsening renal function, pre-eclampsia or eclampsia. Women with renal disease should be seen by a nephrologist for preconception counseling as well as for monitoring during the pregnancy. Decreased diaphragmatic excursion during pregnancy can impact those with severe lung disease. For women with Takayasu arteritis, the location of large vessel involvement and how this would be impacted by a pregnancy must be examined. The abdominal aorta and its branches play a very significant role during pregnancy, both in terms of providing placental circulation to the fetus and the potential for further reduction in blood flow to the mother through these vessels from the gravid uterus. As pregnancy can impact blood pressure and blood flow, it must be carefully evaluated how this would impact women with aortic aneurysms or stenotic vessels providing brain perfusion. New or worsening hypertension is a significant concern during pregnancy. It is believed to impact outcome in pregnant women with Takayasu arteritis but can factor into the pregnancy course of all forms of vasculitis.
- **Medications.** As most forms of vasculitis carry the potential for relapse, whether to continue remission maintenance medication during pregnancy must be considered. Factoring into this is that a number of medications that are used in vasculitis cannot be taken during pregnancy. The American College of Rheumatology recently published guidelines for the management of reproductive health, which includes valuable information applicable to medication decision-making for pregnant women with vasculitis.[4]

- **Potential for relapse.** It is unclear how or whether a pregnancy impacts the risk for a vasculitis disease relapse. The potential that a relapse could occur during pregnancy should be openly discussed prior to conception. Individual factors that should be examined include whether the patient has had prior relapses, how these have manifested and what therapies they have needed to control them. Should a relapse occur during a pregnancy, treatment considerations would depend on multiple factors including the type of vasculitis, severity of the relapse and the pregnancy trimester in which the relapse was occurring.
- **Pregnancy management.** It has been my recommendation that all women with vasculitis who are considering a pregnancy receive preconception counseling from a high-risk obstetrician and have such a specialist involved during their pregnancy. While it is the hope that high-risk skills will not always be needed, patients with vasculitis can present with complex and unpredictable medical issues. In addition to a vasculitis care provider, the need for other specialists to play an active role during pregnancy will be based on patterns of organ or vessel involvement. The method of delivery would be individually determined. It is not mandatory for all women with vasculitis to undergo a cesarean section, although this may provide advantages for women where a controlled delivery optimizing management of blood pressure is desirable.

Return to the case patient

Each of these issues was carefully discussed with the patient. As she was in a stable remission, it was an appropriate time for her to consider a pregnancy. The main concern was her renal insufficiency, for which she was seen by Nephrology prior to conception. In addition to discussion about the potential impact of pregnancy on her kidney function, the lisinopril was stopped — as this cannot be taken during pregnancy — and replaced by labetalol with home blood pressure monitoring. She was also seen by high-risk obstetrics. After counseling, the patient chose to pursue conception and remain on azathioprine during her pregnancy.

As more women with vasculitis are choosing to pursue pregnancies, it is critical for us to gain a greater understanding of their experiences. The Vasculitis Pregnancy Registry (V-PREG) that is being conducted through the Vasculitis Patient-Powered Research Network is an important initiative that will provide valuable prospective information on how vasculitis impacts reproductive health and pregnancy outcomes. Further information on the registry and how your patients can participate can be found at https://www.vpprn.org/vpreg.

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2. *Fredi M, Lazzaroni MG, Tani C, et al. Systemic vasculitis and pregnancy: a multicenter study on maternal and neonatal outcomes of 65 prospectively followed pregnancies.* Autoimmun Rev. *2015;14(8):686–691.*
3. *Comarmond C, Mirault T, Biard L, et al. Takayasu arteritis and pregnancy.* Arthritis Rheumatol. *2015;67(12):3262-3269.*
4. *Sammaritano LR, Bermis BL, Chakravarty EE, et al. 2020 American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases.* Arthritis Rheumatol. *2020;72(4):529-556.*

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therapy throughout pregnancy, nor are they educated on the medications that are safe for pregnancy. The use of anti-TNF therapy and other medications deemed safe for pregnancy is a newer concept; the American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases was only recently released. With this new information on hand, a thorough discussion about the risks and benefits of continuing therapy needs to take place in the preconception period.

Pregnancy outcomes

Compared with the general population, pregnant women with RA have been shown to have a higher prevalence of hypertensive disorders, premature rupture of membranes, antepartum hemorrhage, preterm delivery, intrauterine growth restriction and cesarean delivery.[3] Several studies suggest that tight disease control may improve birth outcomes.

Although further research is needed in this area, the literature should motivate rheumatologists and obstetricians to strive for low levels of disease activity before and throughout pregnancy.

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2. *Jethwa H, Lam S, Smith C, Giles I. Does rheumatoid arthritis really improve during pregnancy? A systematic review and metaanalysis.* J Rheumatol. *2019 Mar;46(3):245-250.*
3. *Kishore S, Mittal V, Majithia V. Obstetric outcomes in women with rheumatoid arthritis: results from nationwide inpatient sample database 2003-2011.* Semin Arthritis Rheum. *2019 Oct;49(2):236-240.*

The Role of Chronic, Systemic Inflammation in Rheumatic Disease

By Leonard H. Calabrese, DO

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Over the past generation we have witnessed marked progress in our understanding of the inflammatory process and how it relates to health and disease. While intermittent inflammation in reaction to injury or infection can aid survival, chronic, lower-grade inflammation has been shown to be associated with chronic diseases, such as rheumatoid arthritis (RA), psoriatic arthritis (PsA) and psoriasis.[1]

The biologic underpinnings of how behavior influences integrated immune health are becoming clearer and involve complex biologic pathways. Advances in genomics have helped us identify physiological patterns of biological differences between individuals with chronic stress (e.g., loneliness, poverty, bereavement, post-traumatic stress disorder) and those without such chronic stressors. Studies show that the genes upregulated in adversity are associated with inflammation, and those downregulated in adversity are enriched with transcripts related to Type 1 interferon responses.[2]

Additionally, the literature suggests both endogenous and nonendogenous factors are associated with chronic inflammation.[1] While the endogenous factors, such as aging, oxidative stress and DNA damage, are difficult to control on an individual level, the nonendogenous factors, such as microbiome dysbiosis, stress, environmental pollutants,[3] obesity and physical inactivity, may be altered to help lower the inflammatory response and potentially improve health and relieve symptoms from some of these disorders. In the case of RA, for example, traditional treatment with disease-modifying anti-rheumatic drugs might be complemented with behavioral interventions, such as an anti-inflammatory diet, an exercise plan and cognitive behavioral therapy.

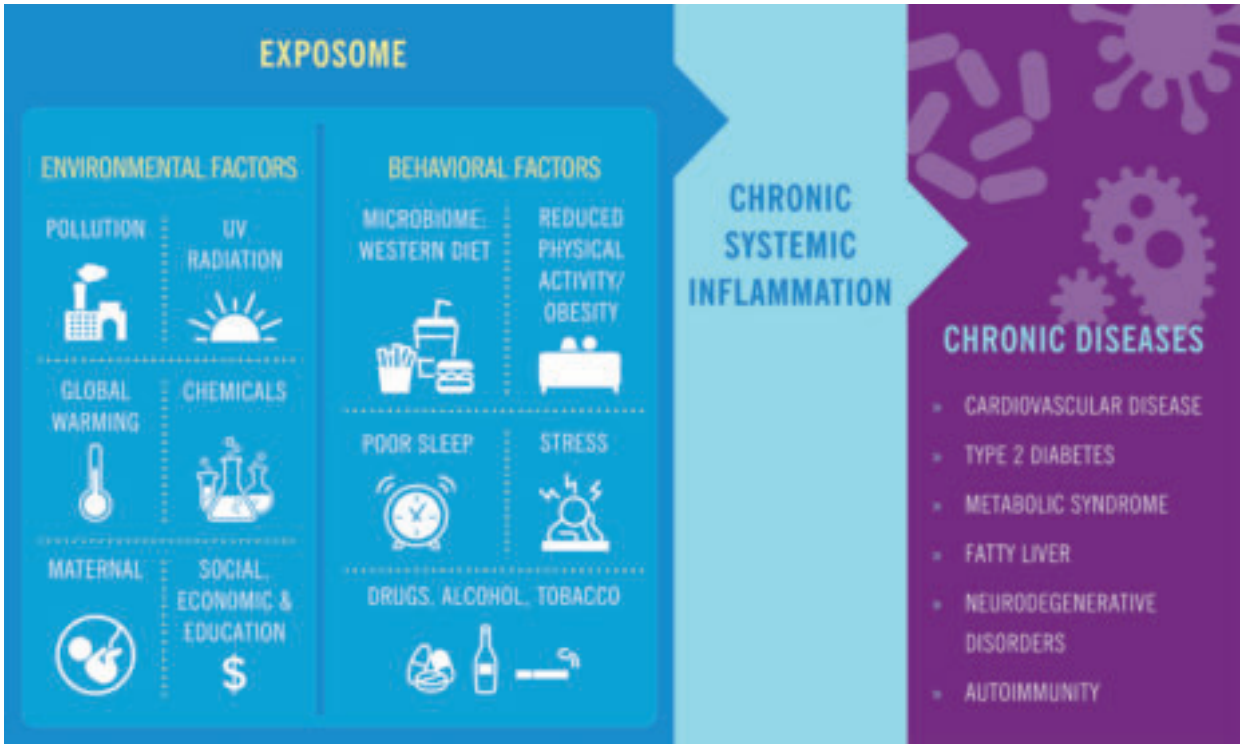
The diet-inflammation axis

A growing body of data derived from preclinical investigations as well as observational and interventional studies provides evidence that the Western diet (WD) is a major driver of chronic, low-grade, metabolic inflammation.[4] The WD includes highly processed, convenience foods and sweetened beverages — all of which are high in calories, sugars, trans fats and saturated fats, salt, and other food additives. The mechanisms contributing to these pro-inflammatory effects are multiple. First, consumption of the WD has been demonstrated to lead to both quantitative and qualitative changes in our microbiome, which in turn helps shape our integrated immune response. Such dietary patterns also lead to disruption of gut-barrier integrity,[5] allowing harmful translocation of microbial products, which can induce inflammation.

Finally, perhaps one of the most remarkable developments in our understanding of the diet-inflammation axis is inflammation's demonstrated capacity to serve as a danger signal to the innate limb of immunity. Innate immunity — our early line of defense against infectious danger signals — was traditionally understood as lacking a memory component.[6] Over the past decade, mounting evidence has demonstrated that innate cells (e.g., myeloid cells) can "memorize" inflammatory encounters with pathogens, creating long-lasting changes in the way the cells respond to subsequent challenges. Similarly, a series of studies have demonstrated that innate immunity can also respond with "trained memory" to sterile challenges, such as uric acid and cholesterol crystals.[1,7] Bringing this back to our dietary patterns, based on preclinical experimental modeling, the innate immune system appears to mistakenly recognize the WD as a threat and responds vigorously with an inflammatory response as the result of metabolic and epigenetic reprogramming.

The pro-inflammatory diet pattern is associated with increased seropositive RA risk in women ≤ 55 years old, according to a large study of over 170,000 women with up to 30 years of follow-up.[8] Interestingly, the association can be partially attenuated by decreased body mass index. No association between the pro-inflammatory diet pattern and RA risks was found in

women over the age of 55. A recent review supports an adjunctive role of a prudent diet enriched with unsaturated fat content, and minimized for high salt content and stripped carbohydrates as an important adjunct in the treatment of inflammatory arthritis.[9] This same review further asserts that clinicians who treat immune-mediated diseases are poorly prepared to provide such counsel. Future research might focus on the impact of an anti-inflammatory diet (i.e., a high ratio of monosaturated fats to saturated fats; high consumption of whole grains, legumes, fruits and vegetables; low consumption of meat; moderate consumption of milk and dairy products) on RA risk, symptom severity and quality of life.



Interventions to reduce chronic inflammation

We are beginning to see more high-quality studies demonstrating the capacity of diet,[8] exercise,[10] sleep[11] and stress modification[12] to influence not only biomarkers of inflammation, but also many of the diseases of chronic inflammation and general quality of life. In one small randomized clinical trial (N = 20), patients who practiced tai chi twice weekly over 12 weeks reported statistically significant improvements in scores of disability, vitality and depression compared with a control group.[10] Another study (N = 131) found that RA patients who received eight weekly, two-hour cognitive behavioral therapy sessions for pain management had decreased mitogen-stimulated levels of interleukin 6 (IL-6) production and improved self-reported pain control at six months.[13] In a New Zealand study of patients with RA (N = 51), participants randomized to a mindfulness-based stress reduction intervention showed greater improvements in the four-variable Disease Activity Score in 28 Joints-C-reactive protein (DAS28-CRP) immediately following the intervention and at four- and six-month follow-up.[12] These early studies are intriguing. Certainly, larger randomized control trials of behavioral interventions aiming to increase quality of diet, sleep, exercise and mindfulness should be explored.

Exploring the role of behavioral modification

I am writing a six-part series for Consult QD on systemic inflammation and chronic disease that will explore the role of behavioral modification in addressing chronic inflammation and immune health, and how healthcare providers, payers, the pharmaceutical industry and patients can come together to improve global health. Topics will include diet, exercise, sleep, chronic stress and behavioral economics.

See reference list at ***consultqd.clevelandclinic.org/chronic-inflammation-the-exposome-and-the-epidemic-of-chronic-disease-across-our-life-span***

Predicting Anti-TNF-Therapy Responsiveness

By Elaine Husni, MD, MPH, and Unni Chandrasekharan, PhD

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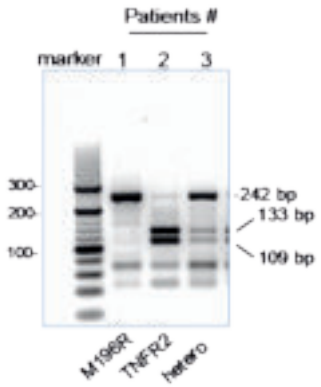
Although tumor necrosis factor (TNF) inhibiting agents have revolutionized our treatment of patients with rheumatoid and psoriatic diseases, up to 40% of patients do not respond or only partially respond, or lose efficacy of therapeutic response over time. We need to better understand how to provide personalized care for patients, rather than continue the current trial-and-error approach, to improve quality of life and clinical outcomes.

Defective TNFR2-myosin interaction and anti-TNF response

There are currently no clinical tests available to predict responsiveness to anti-TNF therapy. Small studies have shown that patients carrying a TNFR2-M196R polymorphic variant demonstrate a higher risk of being an inadequate responder to anti-TNF drugs; however, the underlying mechanisms are unclear.



Restriction Fragment Length Polymorphism (RFLP) analysis

We have shown previously that nonmuscle myosin functions as a negative regulator of TNFR2 activation.[1] In a recent study, presented at the annual meeting of the American College of Rheumatology in November 2019, we tested the hypothesis that a defect in myosin binding to TNFR2-M196R causes TNF-independent pro-inflammatory activity, which leads to reduced responsiveness to anti-TNF agents.[2] The ability to genotype this polymorphism will enable us to predict inadequate responders to anti-TNF therapies early on and help us develop a personalized approach to the treatment of these immune-mediated diseases.

Through co-immunoprecipitation studies, we demonstrated myosin binds to endogenous TNFR2, but not TNFR2-M196R in leukocytes isolated from patients' blood. We also found that TNFR2-M196-expressing cells show TNF-independent, Rho Kinase 1 (ROCK1) activity and pro-inflammatory gene induction (e.g., *ICAM1*, *CXCL10*) in cultured cells. Importantly, a TNF-neutralizing antibody failed to inhibit pro-inflammatory gene induction in TNFR2-M196R-expressing cells. Furthermore, this elevated pro-inflammatory gene induction upon TNF is sustained for a longer time in TNFR2-M196R-expressing cells (8-10 hours) compared with TNFR2-expressing cells (4-6 hours).

Mechanistically, TNFR2-M196R drives cells to a constitutive pro-inflammatory state, potentially due to a defect in myosin binding. Since this constitutive activity is TNF-independent, and given that approximately 20% of the general population carry the TNFR2-M196R polymorphic variant, our findings may potentially explain, in part, why a significant percentage of patients do not adequately respond to anti-TNF therapy.

Toward a more personalized treatment approach

Our mechanism-based approach implicating TNFR2-M196R testing in patients who are candidates for anti-TNF therapy may not only help predict anti-TNF responsiveness, but may also reveal novel pathways that can be targeted to treat inadequate responders of anti-TNF therapy in a subset of patients with rheumatoid and psoriatic diseases. Given the higher cost, longer time, potential serious adverse effects and emotional toll on patients in cycling through multiple disease-modifying agents, identifying genetic biomarkers of treatment response would change our existing practice and facilitate a more personalized treatment approach.

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Can Patient-Reported Outcome Measures Aid Assessment of Disease Activity in Inflammatory Eye Disease?

By Joshua Hedrick, MD, Sunil Srivastava, MD, and Rula Hajj-Ali, MD

Uveitis is a potentially blinding inflammatory eye disease (IED) that requires close interdisciplinary care, with ophthalmologists assessing disease activity and rheumatologists adjusting systemic, potentially toxic, therapies based on exam findings visualized by ophthalmologists. Patient-Reported Outcomes Measurement Information Systems (PROMIS®) may aid in medical decision-making in IED, according to the results of a study we presented at the 2019 American College of Rheumatology Annual Meeting.[1]

PROMIS data have been used to influence medical decision-making in other chronic medical conditions, including rheumatic diseases; however, their utility has not been assessed in patients with IED.

Visible symptoms correlate with perceptions of worse physical health

Our study included 87 patients with a diagnosis of uveitis (N = 74) or scleritis (N = 13), who were seen two or more times by specialists in IED over a 30-month period, and for whom PROMIS data were collected within two weeks of ophthalmologic exam. Demographics and disease characteristics were documented for each patient's initial and subsequent encounters.

There were no statistically significant differences in PROMIS scores in patients with uveitis versus scleritis, nor in patients on biologic versus nonbiologic therapies. Extent of anterior chamber inflammation negatively correlated with physical health PROMIS scores. The presence of vascular leakage on fluorescein angiography was associated with worse physical health PROMIS scores at one-year follow-up, though the association was not seen at other time points.

We evaluated the use of PROMIS data in tracking ocular disease activity and response to therapy in patients with IED in an effort to better understand the patient experience between office visits. Our evaluation did find some significance to patients perceiving their physical health to be worse when inflammation was seen in the anterior chamber of the eye on assessment by Ophthalmology. This may be because anterior chamber inflammation is sometimes associated with redness in the eye. Patients can see this symptom for themselves, which may result in the perception that their health is worse.

Treating IED is of utmost importance to prevent blindness and complications of a systemic rheumatic disease when present. Uveitis has been listed as the cause of blindness in 10% of cases of blindness in the Western world. Additionally, ocular disease can be the first manifestation of multiple diseases and can potentially lead to a systemic diagnosis.

Through this pilot project, we found correlations between PROMIS data and some aspects of IED. Our findings validate patient symptoms in anterior uveitis and will enhance our understanding and recording of disease activity among patients. Additional, larger studies are warranted to further investigate how PROMIS data can assist in monitoring ocular disease activity outside the exam room.

Preventing vision loss

At Cleveland Clinic, a multidisciplinary team composed of rheumatologists and ophthalmologists has facilitated a fast-track approach to evaluating and treating patients with uveitis in a timely manner to prevent vision loss. Utilizing this team-based approach allows advanced evaluations and treatment plans for these complex patients. This established relationship between team members has led to accurate ocular and systemic diagnoses, which facilitates favorable outcomes.

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Sorting Out Rheumatic Immune-Related Adverse Events

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

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The emergence of immune-related adverse events (irAEs) from cancer immunotherapy presents a growing challenge for rheumatologists. We still have much to learn about their immunopathogenesis, clinical presentation, diagnosis and optimal management, and we are learning that not all irAEs are the same. irAEs are quite heterogeneous and have been described to affect nearly every organ system and range from mild and self-limiting to severe and life-threatening. Some irAEs mimic de novo autoimmune disease that we see in the absence of immunotherapy, while others seem to represent new nosologic entities. A new classification system for irAEs may help focus discussions of these heterogeneous complications, and three main categories have been proposed.[1] Here we discuss the proposed classification of irAEs.

Proposed classification of immune-related adverse events	
Type 1	irAEs that are self-limiting in their inflammatory phase, either through use of short-term immunosuppression or discontinuation of immune checkpoint inhibitors. This is the most common pattern reported. Type 1 reactions are generally nonspecific in nature and not consistent with traditional classification of autoimmune diseases.
Type 2	irAEs that appear indistinguishable from idiopathic forms of autoimmune diseases and are often identified by the presence of signature autoantibodies, such as antibodies to citrullinated proteins in rheumatoid arthritis, anti-acetylcholine esterase antibodies in myasthenia gravis and anti-islet cell antibodies in Type 1 diabetes. Type 2 irAEs are rare and represent only a small proportion of all irAEs. These tend to be chronic, but the natural history remains poorly characterized.
Type 3	irAEs that are chronic in their inflammatory phase. Based on the current literature, inflammatory arthritis (IA) appears to be the most common irAE to assume this clinical course. Rare reports of chronic and/or relapsing colitis and pneumonitis and dermopathy have been reported. In general, however, aside from descriptive reports of IA, these reports are rare.

Type 1

Type 1 rheumatic irAEs are commonly encountered and often affect patients with grade 1* arthralgias and myalgias. These patients often present with musculoskeletal complaints within months of starting immunotherapy, and respond to nonsteroidal anti-inflammatory drugs, acetaminophen or low-dose steroids that are able to be discontinued.

* Common Terminology Criteria for Adverse Events (CTCAE) grading system for severity of irAEs: grade 1 = mild; grade 2 = moderate; grade 3 = severe; grade 4 = life-threatening; grade 5 = death.

Type 2

Type 2 irAEs mirror our traditional autoimmune diseases, as exemplified in the following case. A 68-year-old male with stage IV renal cell carcinoma was started on nivolumab infusions every two weeks. After the first three infusions, the patient developed insidious onset joint pain in the knees, wrists and fingers. After the fifth infusion, his joint symptoms escalated in severity and were so intense that he required transport to the emergency room by ambulance. On initial presentation, he had marked inflammatory arthritis involving the proximal interphalangeals (PIPs), metacarpophalangeal (MCP), wrists and knees. C-reactive protein was 12 mg/dL, and the erythrocyte sedimentation rate was 93 mm/hr. He was started on prednisone 20 mg with some improvement. Prednisone was tapered to 10 mg daily, and symptoms were present but tolerable. A sixth dose of nivolumab was administered, and explosive joint pain and swelling recurred within one day. He was unable

to perform his activities of daily living. Nivolumab was discontinued. He was evaluated by Rheumatology, found to have severe disease activity and started on prednisone 40 mg daily. Significant laboratory studies included negative antinuclear antibodies, extractable nuclear antibodies and rheumatoid factor (RF); however, anti-citrullinated peptide antibody (anti-CCP) was positive at > 250. Interestingly, the patient had anti-CCP testing prior to starting immunotherapy, and it was positive then at 54.

While traditional autoantibodies are rarely detected in the setting of rheumatic irAEs, this has been described in the literature. Belkhir et al. reported six patients who developed inflammatory arthritis secondary to immunotherapy.[2] All were anti-CCP positive. Three of these patients had anti-CCP testing prior to immunotherapy, and two were positive. This suggests that in certain patients who may be predisposed to autoimmunity, immunotherapy can tigger autoimmune disease.

Type 3

We are learning that a large proportion of rheumatic irAEs persist in a chronic inflammatory state, which is distinct compared to irAEs in other systems.[3] For example, a 62-year-old male with stage IV renal cell carcinoma received combination ipilimumab and nivolumab, which was complicated by grade 3 colitis requiring high-dose glucocorticoids and ultimately four doses of infliximab. The colitis improved, and maintenance nivolumab therapy was initiated. When the prednisone dose was tapered below 10 mg daily, the patient developed polyarticular inflammatory arthritis involving the hands, wrists, ankles and toes. He had prominent stiffness. Anti-CCP and RF were negative. Prednisone could not be tapered due to symptom recurrence, and he was ultimately started on tocilizumab 162 mg subcutaneously every two weeks with improvement in symptoms, and was able to taper prednisone to a lower dose. Immunotherapy was discontinued indefinitely. The patient is currently more than five years out from his immunotherapy and doing great from a cancer standpoint, but continues to require anti-IL-6 therapy to control his chronic inflammatory arthritis.

Clinically challenging cases of irAE will likely be more frequent

Rheumatologists will encounter clinically challenging cases of irAEs such as these with increasing frequency, as the use of checkpoint inhibitor therapy grows in community-based oncology settings. Rheumatologists are now confronted by immediate clinical challenges in both access to evidence-based diagnostic and treatment strategies and in access to high-quality education regarding this emerging field.

While many challenges are posed by irAEs in general, perhaps the greatest clinical concern to rheumatologists are patients in the "Type 3" group (i.e., chronic inflammatory diseases that may persist indefinitely after checkpoint inhibitor therapy). These patients now appear to require chronic and perhaps lifelong therapy for their inflammatory conditions.

It is a challenge to sort out the issues of what appropriate therapy will successfully lower disease activity and improve quality of life without compromising the anti-tumoral response. We are looking for strategies that combine sparing the use of glucocorticoids and employing targeted therapies based on insights from our knowledge of immunopathogenesis, but the work is early in its evolution. We have recently published a review on this challenge for those looking for greater detail.[4]

The irAE clinic in the Department of Rheumatic and Immunologic Diseases at Cleveland Clinic works collaboratively with the immunotherapy group at Cleveland Clinic Taussig Cancer Center. Patients can be referred in real time. In addition, Cleveland Clinic held the first-ever multidisciplinary clinical course on "Management of Checkpoint Inhibitor-Related Toxicity" on March 6, 2020, organized by Pauline Funchain, MD, Laura Wood, RN, and Cassandra Calabrese, DO. This will be an annual conference.

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