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Rheumatology Connections

An Update for Physicians | Winter 2022

A microscopic image showing a dense field of cells. The cells are primarily purple and pink, with some yellow clusters. The background is dark, making the cells stand out.

**COVID-19 Vaccines in
Patients with
Immune-Mediated
Inflammatory Diseases**

p. 3



From the Chair of Rheumatologic and Immunologic Diseases

Dear Colleagues,

It is my pleasure to share with you the Winter 2022 issue of *Rheumatology Connections* highlighting the clinical, research and educational expertise in the Department of Rheumatologic and Immunologic Diseases. This issue powerfully demonstrates the Cleveland Clinic tripartite mission of caring for the sick, investigating their conditions and educating those who serve.

Two articles highlight our expertise in vasculitis. Dr. Rula Hajj-Ali presents research from the Vasculitis Clinical Research Consortium on neurological involvement in ANCA-associated vasculitis (p. 5). Dr. Alexandra Villa-Forte details the optimal approach to treating relapsing and chronic Takayasu's arteritis (p. 14).

Another pair of articles demonstrates the rare and complex cases our clinicians treat on a regular basis. Dr. Soumya Chatterjee presents a closer look at "mechanic's hands," a classic dermatological manifestation of antisynthetase syndrome (p. 8). Dr. James Fernandez offers a glimpse into the clinical challenges associated with diagnosing common variable immunodeficiency and our collaboration with the Respiratory Institute in immunology and interstitial lung diseases (p. 6).

Our lead article from Dr. Cassandra Calabrese describes the ever-evolving American College of Rheumatology recommendations on COVID-19 vaccination for our patients with immune-mediated inflammatory diseases. She offers unique insights as a member of the ACR COVID-19 Vaccine Clinical Guidance Task Force (p. 3). Dr. Adam Brown shares unique historical insights that introduce our medical home for patients with Ehlers-Danlos syndromes (p. 11).

Finally, we continue to excel in clinical and translational research. Dr. Elaine Husni provides an important update on her lab's ongoing efforts to advance research on selective TNF- α inhibition in psoriatic diseases with collaborators Drs. Unni Chandrasekharan, Raminderjit Kaur and Anthony Fernandez (p. 10). Dr. Sarah Keller's clinical research focuses on enhancing understanding of the risk factors associated with osteoporosis and fragility among patients undergoing lung transplantation and developing optimized strategies to prevent bone loss and post-transplant fractures (p. 12), while also providing opportunities to residents with an interest in rheumatology.

I am honored to work with these talented rheumatologists. I hope that you find in the stories that follow an opportunity to connect, collaborate or consult with our team.

Respectfully,

Abby Abelson, MD

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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 Rheumatologic and Immunologic Diseases, provides information on leading-edge diagnostic and management techniques as well as current research for physicians.

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Cover image: Novel coronavirus SARS-CoV-2 — Colorized scanning electron micrograph of a cell (purple) infected with SARS-CoV-2 virus particles (yellow), isolated from a patient sample. Image captured at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland. Credit: NIAID

COVID-19 Vaccines in Patients with Immune-Mediated Inflammatory Diseases

CLINICAL GUIDANCE FOR OUR MOST VULNERABLE PATIENTS

By **Cassandra Calabrese, DO**

Keeping up with the latest data on COVID-19 continues to be a whirlwind, and by the time you read this piece it is likely to be outdated. I have had the privilege of serving as a member of the American College of Rheumatology (ACR) COVID-19 Vaccine Clinical Guidance Task Force along with 12 other specialists from rheumatology, infectious disease and public health. This group had the tall task of drafting guidance for rheumatology providers on vaccinating patients with immune-mediated inflammatory diseases against COVID-19 in the absence of data.

The first iteration was released on Feb. 16, 2021, and published on March 17, 2021. Now we are on version four, updated on Aug. 19, 2021, and it continues to be a work in process as new data accumulate at a rapid pace. This guidance document is meant to serve as just that in the absence of definitive data.

[Evolving understanding of impaired immune response](#)

In the beginning, our knowledge of immune response to COVID-19 vaccines was extrapolated from data on non-COVID-19 vaccines. Now we have a growing amount of COVID-19-vaccine-related data to suggest that rituximab, methotrexate, higher-dose steroids, abatacept and Janus kinase (JAK) inhibitors, among others, inhibit vaccine responses. However, no data suggest that holding any of these medications will boost immune responses to COVID-19 vaccines. Nonetheless, the ACR guidelines recommend holding various biologics and disease-modifying antirheumatic drugs (DMARDs) after COVID-19 vaccines and booster doses (Table 1). The idea is that continuing these medications precludes a boosted immune response, and until we have more data, any potential for increased immune response should be pursued through shared and informed decision-making and in the right setting (disease-activity permitting, etc.).

The ACR guidance document also supports the FDA recommendation for a third COVID-19 mRNA vaccine dose or “booster” for immunocompromised persons, and this includes patients on any biologic, DMARD or chronic glucocorticoids at any dose, and patients with common variable immunodeficiency (CVID).

[Our most vulnerable patients](#)

It has become clear that our most vulnerable patients are those receiving iatrogenic B-cell depleting agents such as rituximab. Numerous studies demonstrate their high risk for poor outcomes with SARS-CoV-2 infection. This became evident during the prevaccine era and unfortunately remains true for fully vaccinated patients receiving these drugs, where breakthrough infections are now well documented, and numerous studies have shown that vaccination within six months of receiving rituximab is strongly associated with significantly reduced humoral response and correlates with the absence of CD19 cells.

Many studies now show that while humoral immune responses are severely impacted, T-cell responses may be robust. However, the clinical significance of these data remains unclear given the incidence of breakthrough infections and their associated high morbidity and mortality. The need to time administration around the last dose of rituximab (waiting as long as possible to vaccinate — six months if disease activity allows) has made it challenging to vaccinate this population and has also highlighted the importance of early diagnosis and aggressive outpatient management of COVID-19 with monoclonal antibodies, which are effective in reducing viral load, symptom duration, and disease progression to hospitalization and death.

In collaboration with the Lederman/Freeman lab at Case Western Reserve University, we have a pilot



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Table 1. Guidance related to the timing of COVID-19 vaccination in relation to use of immunomodulatory therapies in RMD patients

MEDICATION(S)	COVID-19 VACCINE ADMINISTRATION TIMING	LEVEL OF TASK FORCE CONSENSUS
Hydroxychloroquine; sulfasalazine; leflunomide; apremilast; IVIG	Do not delay or adjust vaccine administration timing.	Strong
Methotrexate; mycophenolate mofetil; azathioprine; cyclophosphamide (IV or oral); TNFi; IL-6R; IL-1R; IL-17; IL-12/23; IL-23; belimumab; JAK inhibitors; 11 abatacept (IV or SC); oral calcineurin inhibitors; GCs (prednisone-equivalent dose < 20 mg/day)[†]	Do not delay or adjust vaccine administration timing.	Moderate
Rituximab	Assuming that a patient's COVID-19 risk is low or can be mitigated by preventive health measures (e.g., self-isolation), schedule vaccination so that the vaccine series is initiated ~4 weeks prior to next scheduled rituximab cycle.	Moderate

* COVID-19 = coronavirus disease 2019; GC = glucocorticoid; IV = intravenous; IVIG = intravenous immunoglobulin; JAK = Janus kinase; RMD = rheumatic and musculoskeletal disease; SC = subcutaneous; TNFi = tumor necrosis factor inhibitor

† Examples of cytokine and kinase inhibitors include the following: for interleukin-6 receptor (IL-6R), sarilumab and tocilizumab; for IL-1 receptor antagonist (IL-1Ra), anakinra and canakinumab; for IL-17, ixekizumab and secukinumab; for IL-12/IL-23, ustekinumab; for IL-23, guselkumab and risankizumab; for JAK inhibitors, baricitinib, tofacitinib and upadacitinib. Consensus was not reached for patients receiving glucocorticoids at prednisone-equivalent doses of ≥ 20 mg/day.

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study underway examining humoral and cellular immune responses to mRNA COVID-19 vaccination in patients receiving iatrogenic B-cell depleting therapy as well as in patients with CVID. In addition, we are examining immune responses after a third mRNA vaccine dose. We are also evaluating clinical outcomes of breakthrough COVID-19 in B-cell depleted patients at Cleveland Clinic.

The most important message for patients is that no matter the degree of vaccine response, nonpharmacological interventions such as masking are still of the utmost importance. Informing, advocating for and helping protect our vulnerable patients during the pandemic has been a full-time job and will continue until the end is in sight.

Neurologic Involvement in ANCA-Associated Vasculitis

RAISING AWARENESS OF A COMMON MANIFESTATION

By Rula Hajj-Ali, MD

Neurologic involvement is well documented in ANCA-associated vasculitis (AAV), but its prevalence has not been well characterized. My colleagues from the Vasculitis Clinical Research Consortium (VCRC) and I recently presented data at the 2021 American College of Rheumatology Convergence from a multicenter longitudinal observational study that allows us to understand more clearly the prevalence and types of neurological involvement and its associations with other manifestations of vasculitis.

A large, multi-institutional cohort

Our study analyzed data from 1,368 adult patients with AAV (granulomatosis with polyangiitis [GPA], microscopic polyangiitis [MPA] or eosinophilic granulomatosis with polyangiitis [EGPA]) collected from 2006-2021. Just over a third of patients had neurological involvement. Of this 34%, 46.2% had EGPA, 46% had GPA and 7.8% had MPA. In the overall cohort, 27.3% of patients experienced peripheral nervous system (PNS) involvement, and 3.4% had neurological involvement in the central nervous system (CNS) (3.2% unclassified). Most patients with CNS involvement had GPA (78%, compared with 19% with EGPA and 2% with MPA), while EGPA was the most common diagnosis for patients with PNS involvement (51%, compared with 40% with GPA and 8.8% with MPA).

We observed no significant difference in rates of neurological involvement by patient sex or race, though the cohort was overwhelmingly white (88.7%). The mean age at diagnosis was higher for patients with neurological involvement than without (51.4 vs. 47.0 years, $P < 0.001$).

We also discovered that neurological involvement was significantly associated with skin (49.4% vs. 29.5%, $P < 0.001$) and cardiovascular (15.5% vs. 7.2%, $P < 0.001$) involvement as well as venous

thrombosis (12.8% vs. 8.6%, $P = 0.016$). Neurological involvement was negatively associated with renal (45.6% vs. 55.9%, $P < 0.0001$) and eye (20% vs. 28%, $P < 0.001$) involvement.

In patients with GPA, neurological involvement was associated with musculoskeletal, skin and kidney involvement and venous thromboses. Patients with EGPA were more likely to experience skin and kidney issues if they had neurological involvement. Patients with MPA with neurological involvement were more likely to have constitutional and musculoskeletal symptoms.

Finally, we found that patients who experienced neurological involvement were more likely to have pANCA pattern (43.1% vs. 31.2%, $P = 0.008$) and anti-MPO (44.4% vs. 30%, $P < 0.001$) compared with patients without neurological involvement.

Implications for clinical practice

These data demonstrate that clinicians should consider neurological involvement common in their patients with AAV, especially in those with EGPA. Neurological symptoms like symmetrical polyneuropathy, paresis, headaches and cognitive impairment should be considered potential evidence of vasculitis in patients with other classic signs of the disease as well as complications to watch for in patients with established diagnoses. The relationships between neurological involvement and other manifestations of disease observed in this study warrant further investigation.

Collaboration with colleagues in neurology is critical for the rheumatologist treating patients with AAV. Cleveland Clinic's Center for Vasculitis Care and Research collaborates with the Cerebrovascular Center in the Neurological Institute to determine the most appropriate course of treatment for these patients.



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Case Report: Common Variable Immunodeficiency and Lung Disease

MULTIDISCIPLINARY TREATMENT OF RARE AND COMPLEX IMMUNODEFICIENCIES

By James Fernandez, MD, PhD



Dr. Fernandez (fernanej2@ccf.org; 216.444.6933) is staff in the Department of Allergy and Clinical Immunology.

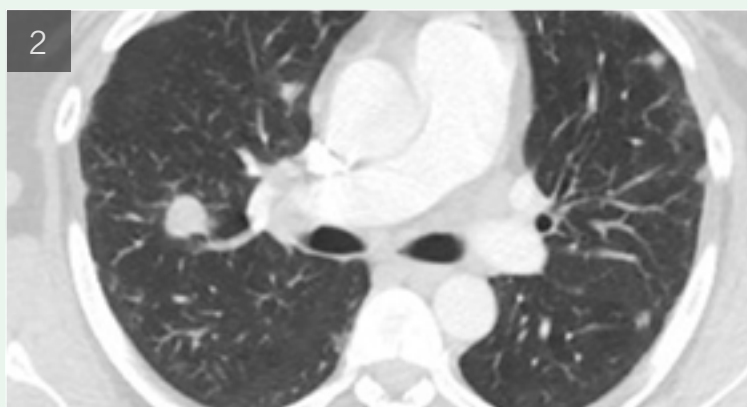
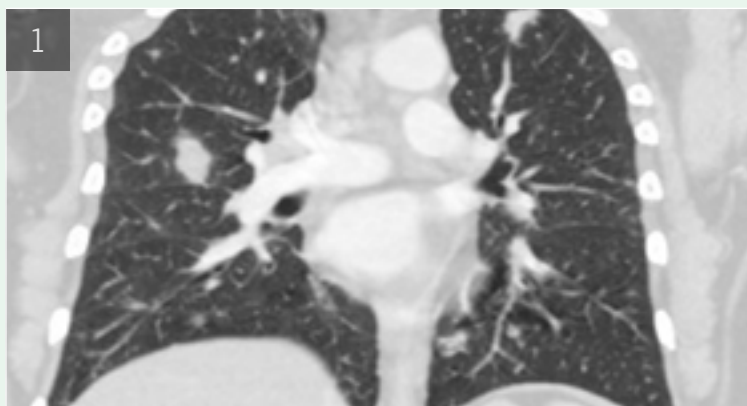
PRESENTATION

A 36-year-old female presented to Cleveland Clinic Respiratory Institute's immunology clinic as a referral for immune dysfunction. Her medical history had been unremarkable except for a recent fall from her horse. Routine testing in an outside emergency department had uncovered a platelet count of 46 k/uL. She was then diagnosed with immune thrombocytopenia and treated appropriately. She was referred to our clinic for long-term management.

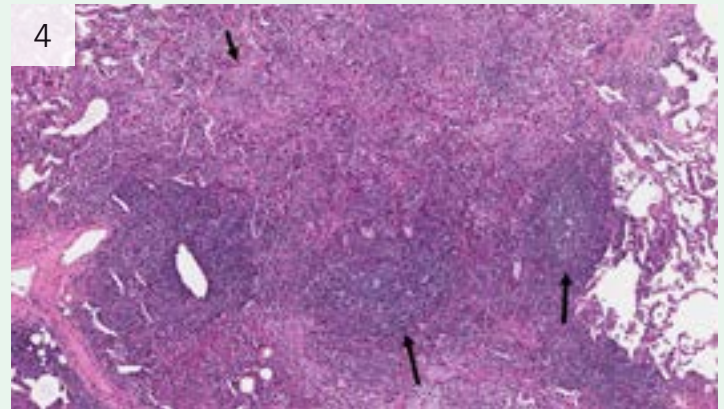
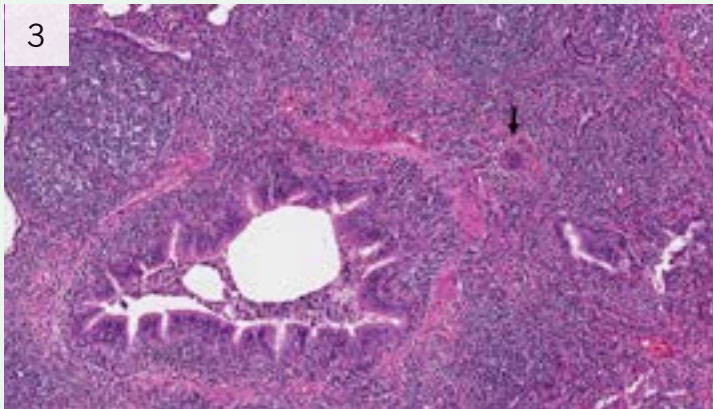
Our clinic ordered further lab testing, which revealed an IgG of 191 mg/dL, an IgA of 26 mg/dL and an IgM of 55 mg/dL. After showing poor response to multiple vaccine challenges, she was diagnosed with common variable immunodeficiency (CVID) and began intravenous IgG.

Soon after, she developed bloody diarrhea. Abdominal computed tomography (CT) showed multiple lung nodules and diffuse adenopathy. A CT chest confirmed the nodules (Figures 1, 2).

Fecal analysis showed *Campylobacter* and Shiga toxin-producing *E. coli*, and an infectious disease specialist prescribed levofloxacin. Axillary lymph node biopsies showed follicular hyperplasia. Shortly after, she developed worsening shortness of breath. An open lung biopsy showed chronic lymphocytic bronchiolitis with areas of organizing pneumonia and lymphoid hyperplasia (Figures 3, 4).



Figures 1 & 2. Pre-treatment. CT chest shows numerous bilateral upper lung and lower lung pulmonary nodules without cavitation or calcification, measuring up to 17 mm.



Figures 3 & 4. Wedge biopsies of upper and lower lobes of right lung. **3.** Lymphocytic bronchiolitis with a giant cell (arrow). **4.** Organizing pneumonia characterized by alveolar plugs of fibromyxoid tissue (short arrow) in association with the lymphoid follicles (long arrows).

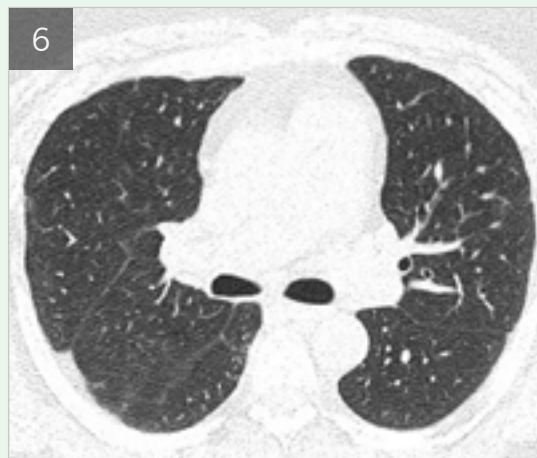
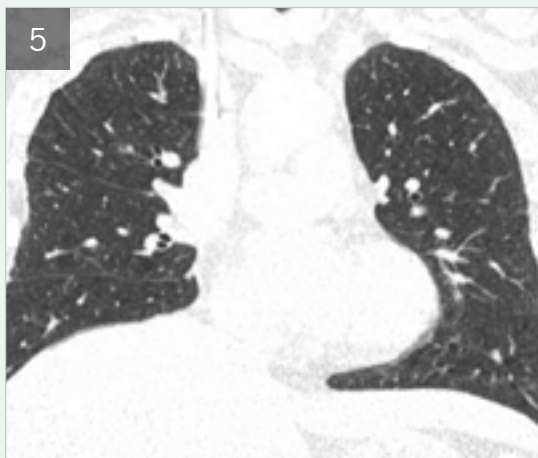
Managing CVID and comorbidities

Managing a patient with CVID, lung nodules and lymphadenopathy with potential for lymphoma requires a multidisciplinary approach. About one-third of patients with CVID have developed chronic pulmonary disease by the time of diagnosis. Furthermore, lymphomas also occur at much higher rates in patients with CVID, so a lymph node biopsy is important early in the course of treatment. A swift diagnostic and treatment approach is important in all immunodeficient patients.

This patient's disease was originally treated with prednisone and had responded well, but shortness of breath recurred upon weaning to 5 mg every other day. Her reactive lymphadenopathy also responded well to the steroids.

The patient was presented at a weekly interstitial lung disease (ILD) clinic meeting, and the team decided to treat her with rituximab. Shortly thereafter, she received her first course, with excellent response clinically and radiographically (Figures 5, 6). She receives periodic dosing (approximately once a year) of rituximab with continued control of her respiratory disease.

This patient is one of many with rare and complex immunodeficiencies seen in our immunology and ILD clinics each week. This expertise has allowed Cleveland Clinic to take a team approach with immunologists, pulmonologists, hematologists, oncologists and other subspecialty physicians who are uniquely familiar with these types of patients.



Figures 5 & 6. CT chest showing significant improvement in number and size of pulmonary nodules.

Case Report: Antisynthetase Syndrome and Mechanic's Hands

LOOK BEYOND SKIN CHANGES

By Soumya Chatterjee, MD, MS, FRCP



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PRESENTATION

A 37-year-old male presented to our rheumatology clinic with a history of over a year of painful, cracked and thickened skin on his fingertips. In addition, he experienced difficulty raising his arms above his head and rising from a chair as well as intermittent low-grade fevers.

Examination revealed weak proximal hip and shoulder muscles as well as hyperkeratotic, thick, fissured and scaly skin on the fingertips of both hands (Figures 1, 2). Laboratory testing revealed a creatine kinase level above 20,000 U/L, negative antinuclear antibody and rheumatoid factor tests, and positive tests for anti-Jo-1 (anti-histidyl-transfer RNA synthetase) and anti-SSA (Ro-52) antibodies. In addition, computed tomography (CT) of his lungs showed lower-lobe-predominant peripheral ground-glass opacities, traction bronchiectasis and subpleural reticulation, all suggestive of interstitial lung disease (ILD). These findings taken together confirmed a diagnosis of antisynthetase syndrome (ARS).

Antisynthetase syndrome and 'mechanic's hands'

ARS is a relatively rare autoimmune disease characterized by ILD, myositis, inflammatory arthritis, Raynaud's phenomenon and mechanic's hands — the hyperkeratotic, scaly skin seen on this patient's hands (Figures 1, 2). Eight autoantibodies to aminoacyl-transfer RNA synthetases have been described so far: Jo-1, PL-7, PL-12, EJ, OJ, YRS, KS and Zo. Morbidity and mortality in this idiopathic inflammatory myopathy is mainly related to pulmonary complications.

Diagnosis of ARS requires a positive test for an antisynthetase antibody and both ILD and inflammatory myopathy, or one of those major criteria plus two

minor criteria: polyarthritis, mechanic's hands and Raynaud's phenomenon.

Almost all patients presenting with mechanic's hands have an inflammatory myopathy; it tends to be more common in ARS patients. Topical steroids can address the skin changes. Still, systemic treatment is often warranted as mechanic's hands may be the most visible but not the only manifestation of ARS.

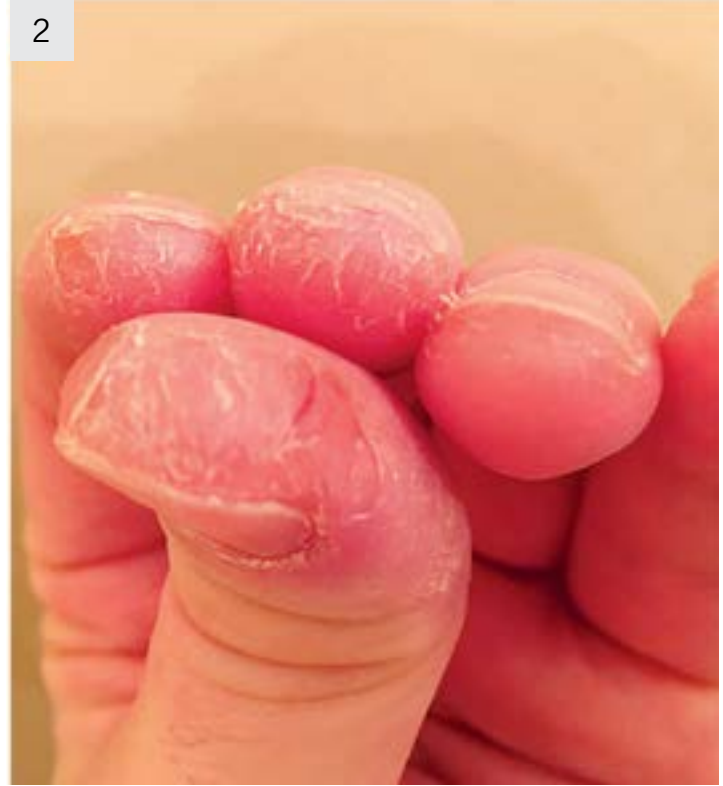
Treatment and collaborative management

For this patient, a month of daily oral prednisone 60 mg and azathioprine 150 mg resolved the mechanic's hands as well as the myositis and ILD. We were able to taper him off the glucocorticoid and begin an ongoing treatment regimen of intravenous rituximab once every six months. The patient remains symptom free.

We often utilize our joint rheumatology-pulmonology clinic to manage patients with ARS, as ILD can be one of the most debilitating symptoms. In this clinic, decisions about the investigation and management of complicated cases like this are made jointly by two different subspecialists who can combine their respective perspectives. Patients appreciate getting collaborative opinions about their care from specialists with distinct areas of expertise who are experienced in managing different aspects of their disease.

Moreover, rheumatology trainees benefit from the unique opportunities to learn about the methods involved in such complex decision-making and the abundant opportunities for fellowship research projects.

This case was originally published in the New England Journal of Medicine (384;6), and figures are reprinted with permission from Massachusetts Medical Society.



Figures 1 & 2. Hyperkeratotic, thick, fissured and scaly skin on the fingertips of both hands of patient.



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Advancing the Research on Selective TNF- α Inhibition in Psoriatic Disease

THE POTENTIAL FOR SAFER THERAPIES

By **M. Elaine Husni, MD, MPH**; Collaborators: **Unni Chandrasekharan, PhD**; **Raminderjit Kaur, PhD**; and **Anthony Fernandez, MD, PhD**



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The latest clinical practice guidelines issued jointly by the American College of Rheumatology and the National Psoriasis Foundation recommend tumor necrosis factor alpha (TNF- α) inhibitors or soluble TNF- α receptors as first-line therapy for active psoriatic disease. Five anti-TNF medications approved by the FDA to treat psoriatic disease — etanercept, adalimumab, golimumab, infliximab and certolizumab pegol — act by binding to circulating TNF- α and blocking the association between TNF- α and its two immune cell surface receptors, TNFR1 and TNFR2. However, various studies to date have raised questions about whether long-term global TNF- α inhibition may be associated with the development of potential serious adverse effects, including serious infections and malignancies, in which the action of TNFR1 has a protective role.

The Husni lab

Our lab at Cleveland Clinic has recognized this unmet need for safer therapies and is currently focused on studying the mechanisms of selective inhibition of TNF- α in psoriatic disease. Our team postulates that global TNF- α inhibition may not be necessary to effectively treat psoriasis, and that selective inhibition of one of the receptors — TNFR2 — could potentially reduce the signs and symptoms of psoriatic disease while preserving the protective effects of TNF- α and its interaction with TNFR1. In one of our recent studies, we identified arginine methyltransferase 5 (PRMT5), an enzyme downstream of TNF- α signaling, as critical for TNF- α -mediated signaling pathways, which makes it a suitable target for treating TNF- α -dependent inflammatory diseases.

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 using 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.

PRMT5 inhibition, TNFR1 and TNFR2 signaling

In continuation of this research, our team recently presented data at the GRAPPA 2021 annual meeting and symposium. We examined how inhibition of PRMT5 activity will influence the expression of psoriasis-related genes and aimed to further clarify the role of PRMT5 in TNFR1 and TNFR2 signaling. Gene expression studies conducted in human endothelial cells found that PRMT5 indeed has a critical role in TNF- α induction of gene expression at varying levels. Namely, PRMT5 depletion causes a significant percentage reduction in the expression of IL-8 (67.3%), IL-6 (73.7%), CXCL11 (88.23%), E-selectin (66.3%) and VCAM-1 (75.2%), all of which are implicated in psoriatic disease.

Further testing revealed that PRMT5 depletion significantly inhibited TNFR2-mediated, but not TNFR1-mediated, NF κ B activation. This finding is particularly interesting as we recently found that targeting TNFR2, but not TNFR1, alleviates psoriasislike disease in a mouse model. In future studies, we will use this information to help personalize therapy with PRMT5 inhibition and compare the effectiveness and side effect profile of this strategy to those of current therapies.

Taken together, these findings support the potential role of the TNFR2/PRMT5 axis in the pathogenesis of psoriatic disease and point to the possibility of developing new targeted therapies with safer side effect profiles. Our team is committed to advancing this research further with the hope of providing safer therapies for patients suffering from psoriatic diseases.

A Medical Home for Patients with Ehlers-Danlos Syndromes

COORDINATING COMPLEX CARE ACROSS MULTIPLE DISCIPLINES

By Adam Brown, MD

Niccolò Paganini (1782-1840) was a violinist who played with such speed, bravado and dexterity that he earned the moniker “the devil’s violinist,” and some even consider him to be the first rock star. Paganini was tall and lanky and often performed in a black suit, giving him a sinister appearance. Paganini could contort his hands and fingers in ways that seemed impossible, stretching his fingers across the violin, jumping between notes rapidly, in ways that no one had seen before.

Although his inherent flexibility allowed him to appear supernaturally talented at the violin, his flexibility came with a cost as he developed crippling joint pain at an early age, making it more difficult to practice and play for an audience.

We will never know with certainty, but based on observations of the violinist, he likely had an Ehlers-Danlos syndrome (EDS). EDSs are a heterogeneous group of connective tissue disorders leading to abnormal collagen synthesis affecting skin, ligaments, joints and sometimes blood vessels. Multiple types of EDS exist, including some with known genetic mutations that can be tested for, but most patients do not have a known genetic abnormality despite clear familial inheritance.

Joint pain common among multiple complications

As we saw with Paganini, the laxity of the joints caused by EDSs leads to premature wear and tear, often resulting in joint pain at an early age. Sometimes the cause is clearly osteoarthritis, but most of the time the pathology of the pain is not completely understood. Patients with an EDS often suffer from multiple joint dislocations, resulting in premature osteoarthritis that often requires repeated surgeries. EDS patients can suffer for years or even decades with body aches without knowing the cause.



Paganini (1782-1840) was an Italian violinist and composer.

Multiple medical complications can arise in patients with EDSs. Joint pain is the most common, but more life-threatening complications are possible. The collagen synthesis abnormalities can result in cardiac and valvular abnormalities, autonomic instability leading to postural orthostatic tachycardia syndrome (POTS), skin abnormalities leading to excessive tearing and bleeding, and vascular abnormalities leading to aneurysm formation and rupture, which can cause hemorrhage and potential death.

Cleveland Clinic’s EDS coordinated care program

Depending on the major presenting problem for the patient, specialties like vascular medicine or surgery may take care of the patient, but the majority of patients with joint laxity do not have a medical home. The goal of Cleveland Clinic’s EDS coordinated care program is to provide that medical home. Our team evaluates each patient and assesses their needs. We help with joint pain through physical therapy

and use joint preservation strategies like ankle orthotics to prevent recurrence. We help coordinate care with orthopaedic surgery, cardiology, neurology for POTS evaluation and vascular medicine, if needed.

Paganini never knew why he suffered from crippling joint pain at a young age. We now know a great deal about the types of EDS but still have much to learn. One of the most important advances we have made is recognition. A diagnosis of an EDS, after years of mysterious symptoms, can have a profound impact on a patient’s life. A diagnosis identifies a medical cause for physical symptoms and allows clinicians to provide more focused care. As we expand our knowledge of and therapies for EDSs, our coordinated care program provides a central resource and care team for patients whose multisystem symptoms warrant multidisciplinary care.



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Lung Transplantation and Metabolic Bone Disease

ADVANCING OUR KNOWLEDGE OF RISK FACTORS

By Adil Vural, MD, and Sarah F. Keller, MD



Dr. Vural is a resident in the Department of Internal Medicine.

Patients with end-stage pulmonary disease awaiting lung transplantation (LT) are more likely to have osteoporosis and fragility fractures than the general population. The prevalence of osteoporosis among these patients is anywhere from 30% to 60%,¹⁻⁷ and vertebral fractures were detected in 29% of patients with chronic obstructive pulmonary disease and in 25% of patients with cystic fibrosis (CF) awaiting LT.² As rheumatologists, we play a critical role in the evaluation and optimization of bone health in these patients.

Pretransplant risk of bone density loss

LT candidates have a high risk of osteoporosis and metabolic bone disease, a risk that increases post-transplant. All patients with end-stage pulmonary disease awaiting transplant should be evaluated and treated prior to transplantation. At Cleveland Clinic, all patients who are evaluated for LT undergo a bone density scan and evaluation by an expert in osteoporosis at the Center for Osteoporosis and Metabolic Bone Disease as part of their pretransplant evaluation.

The association between pulmonary disease and decreased bone density is multifactorial. Underlying lung pathology results in chronic hypoxia and hypercapnia.⁷ In CF, additional contributing factors include malabsorption, pancreatic insufficiency, hypogonadism, failure to attain peak bone mass and vitamin deficiencies. Other factors associated with end-stage pulmonary disease such as low body mass index, sedentary lifestyle in patients on chronic supplemental oxygen, older age, female sex and tobacco use also contribute to low bone density.⁷⁻⁹ Medication factors pose additional challenges as patients with lung disease are often prescribed proton-pump inhibitors, glucocorticoids and loop diuretics, all of which are associated with bone density loss.^{7,8}

Post-transplant risk factors

Bone density loss and fractures are also significant problems post-transplant.^{3,4,6,10-13} Post-transplant factors associated with bone density loss include the use of high-dose glucocorticoids, calcineurin inhibitors

and mammalian target of rapamycin inhibitors (mTOR inhibitors);⁹ calcium and vitamin D deficiencies; and difficulty (or failure) in adequately ambulating and rehabilitating following surgery.^{7,9} Furthermore, any episodes of graft rejection increase the overall dose of systemic glucocorticoids and subsequent risk of rapid bone density loss.

Typical immunosuppressive regimens in LT recipients include a combination of high-dose, gradually tapered glucocorticoids, cyclosporine, tacrolimus, mycophenolate mofetil and, rarely, an mTOR inhibitor. Osteoporosis and fragility fractures can occur as an early or late complication following transplantation;⁷ however, the rate of bone loss, and thus fracture risk, is highest immediately following transplantation among patients receiving high-dose glucocorticoids.¹⁴

Osteoporotic fractures increase morbidity and frailty and pose a significant risk to the patient's health and survival post-transplantation. Increased vertebral fracture burden has been associated with reduced mobility and physical function, as well as decreased forced vital capacity and inspiratory time.¹⁵ One study found the incidence of vertebral fractures increased from 19.5% pretransplant to 50.4% post-transplant among LT patients in the first period of follow-up (six to 18 months).⁶ Another review cited a fracture rate of 18% to 37% in the first post-transplant year.⁷ There is clearly a need to decrease bone density decline and fractures following LT.

In addition to the challenges described above, frailty is increasingly recognized as a threat to patients with end-stage pulmonary disease as well as to those patients who undergo LT.¹⁶ An important dimension of frailty assessment is the identification of sarcopenia, a syndrome characterized by decreased muscle mass and progressive decline in physical function that has been associated with fragility fractures, especially in elderly men.^{12,17,18} While there are several methods of measuring sarcopenia, a novel method involves measuring pectoralis muscle area by computed tomography scan



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of the chest.^{19,20} Additional research is urgently required to elucidate the relationships between the pathophysiology and mechanisms of sarcopenia and frailty fracture risk.

Enhancing our understanding of risk factors

We are working with an interdisciplinary group to rigorously examine the risk factors for osteoporosis and fragility fractures among LT recipients at Cleveland Clinic. Cleveland Clinic is an International Center of Excellence for LT and performs a large number annually, nearly 2,000 since the beginning of the 21st century. Our objective is to further elucidate the risk factors for osteoporosis, fragility fractures and frailty by analyzing clinical and demographic characteristics, glucocorticoid and other medication use, biochemical and laboratory data, and bone density scans in this large patient population using our unique experience and patient database.

We are working on this multidisciplinary project with co-investigators Abby Abelson, MD, Chair of the Department of Rheumatologic and Immunologic Diseases; Chad Deal, MD, Head of the Center for Osteoporosis and Metabolic Bone Disease; Marie Budev, DO, Medical Director of the Lung and Heart Lung Transplant Program; and Xiaojuan Li, PhD, Director of the Program for Advanced Musculoskeletal Imaging. By gaining an enhanced understanding of the risk factors associated with osteoporosis and fragility among patients undergoing LT, developing optimized strategies to prevent bone loss and post-transplant fractures, and creating an improved fracture prediction model for this unique population, we hope to decrease the significant disease burden posed by osteoporosis and metabolic bone disease among these patients.

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Treatment of Chronic and Relapsing Takayasu's Arteritis

PREVENTION OF PROGRESSION AND COMPLICATIONS IS THE PRIMARY GOAL

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Takayasu's arteritis (TAK) is an idiopathic granulomatous inflammatory disease that affects the aorta and its primary branches. The disorder is rare, mostly found in young women, and is frequently chronic and relapsing. Physicians can encounter several diagnostic and therapeutic challenges when providing care for these patients.

Diagnostic challenges

One of the main challenges impacting patients with TAK is the difficulty in establishing early diagnosis. Diagnosis is often delayed for many years, and when patients are first identified, they often have irreversible arterial lesions. One reason for the delay in diagnosis is the absence of symptoms until vessel stenosis or occlusion is detected on physical exam or imaging studies. Another reason is the vague nature of symptoms that for years may be described by some patients as fatigue, arthralgias, myalgias, non-specific headaches or dizziness.

Later, symptoms suggestive of ischemia in a young patient, such as carotidynia, syncope or limb claudication, lead to further evaluation with computed tomography angiography (Figure 1) or magnetic resonance angiography, and arterial abnormalities are identified. These modalities are the primary diagnostic tools, along with positron emission tomography-computed tomography, though each modality has its strengths and shortcomings. Digital subtraction angiography is rarely needed for diagnosis.

Laboratory tests are not always helpful in establishing diagnosis or monitoring disease activity as the sedimentation rate (WSR) and C-reactive protein (CRP) may be normal at times of active disease in up to 50% of patients.

Patients may also develop tachycardia with palpitation, chest pain, dyspnea, renovascular hypertension, mesenteric angina and, less commonly, visual disturbances. On physical exam, vascular bruits and absent or asymmetric arterial pulses and/or blood pressure may be noted.

Challenging clinical scenarios

While establishing early diagnosis is difficult, determining and monitoring disease activity in patients with TAK also proves challenging. Patients may be asymptomatic with normal WSR and/or CRP and have evidence of a new arterial lesion, or they may have progression of a previous arterial lesion. Other patients may have elevated WSR and/or CRP without evidence of new or progressive arterial lesions (Figure 2).



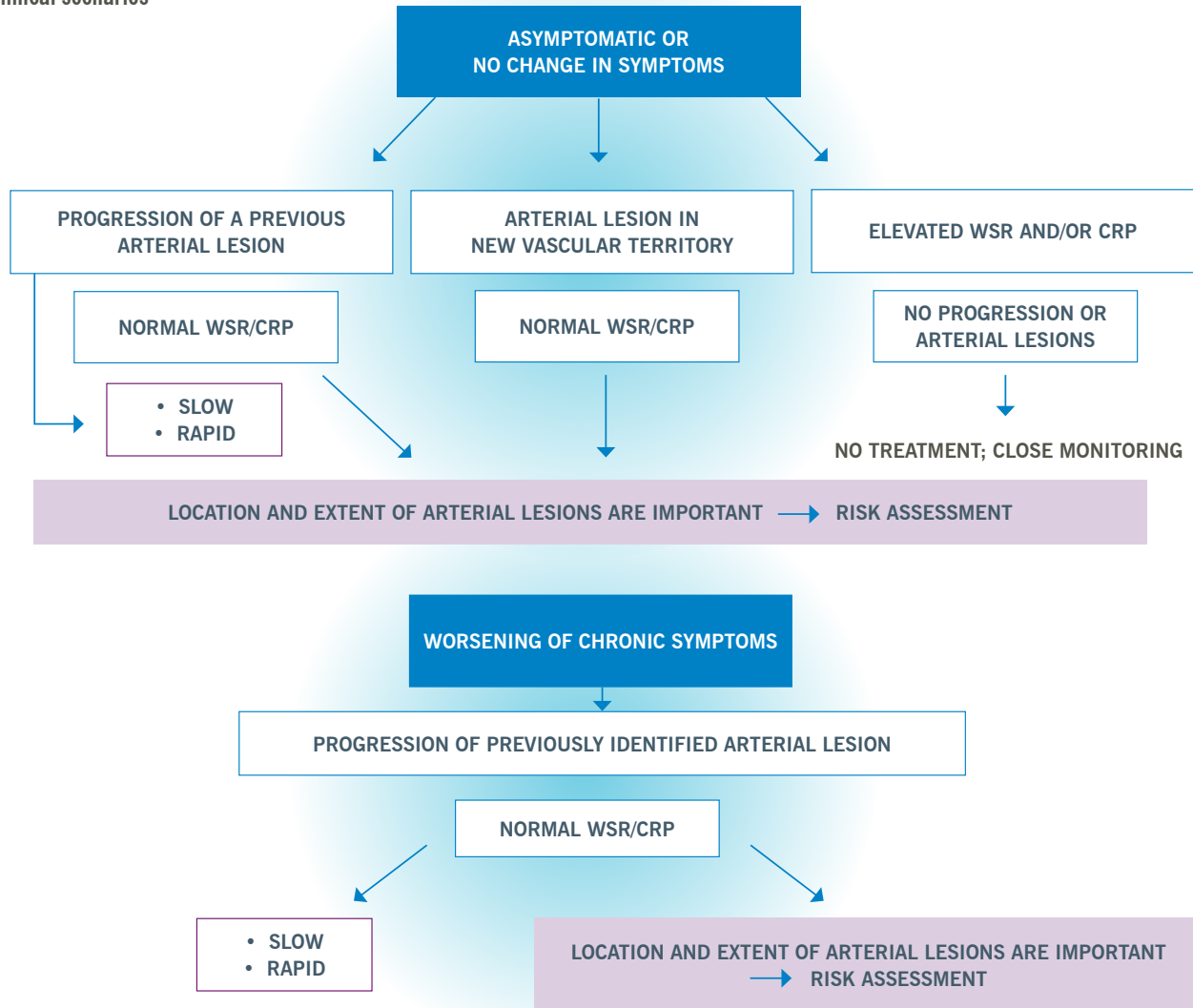
Figure 1. Computed tomography angiography (CTA) of head and neck with contrast showing severe stenosis of the mid right subclavian artery, severe stenosis of the proximal right common carotid artery and complete occlusion of the right cervical through supraclinoid internal carotid artery.

Complications from arterial inflammation differ according to which vessels are affected. They include secondary hypertension, aortic regurgitation, congestive heart failure, aortic aneurysm, stroke and chronic limb claudication, among others. Vessel damage may occur not only from active

inflammation but also from vessel fibrotic remodeling when the disease may be in remission. Patients with TAK are at risk of significant vascular morbidity over the years.

Risk assessment is very important in patients with TAK. The location and extent of arterial lesions should be carefully analyzed with an experienced radiologist to predict risks of major complications such as stroke,

Figure 2. Clinical scenarios



organ infarcts (e.g., kidney), progression of a thoracic aortic aneurysm, cardiac ischemia and severe limb functional disability. Risks from chronic immunosuppression should be incorporated in treatment decisions, especially in light of the young age of many patients with TAK, and all therapy-related risks should be clearly discussed with patients and families and closely monitored on a regular basis. Controlling disease activity, halting vascular lesion progression and preventing complications are the primary goals of treatment.

A chronic and relapsing disease

TAK is chronic or relapsing in the majority of patients, and continuous or multiple courses of treatment are often needed. The care of

these patients relies on close monitoring of the disease over time by combining evaluation of symptoms, vascular physical exam, laboratory tests and sequential imaging tests. Imaging tests at regular intervals allow for evaluation of the location and extent of arterial lesions and the identification of lesions in new vascular territories and progression of previous arterial lesions.

While TAK may be challenging to diagnose and treat, careful monitoring with the appropriate clinical expertise and tools and thoughtful, risk-sensitive treatment can improve outcomes for patients.



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