

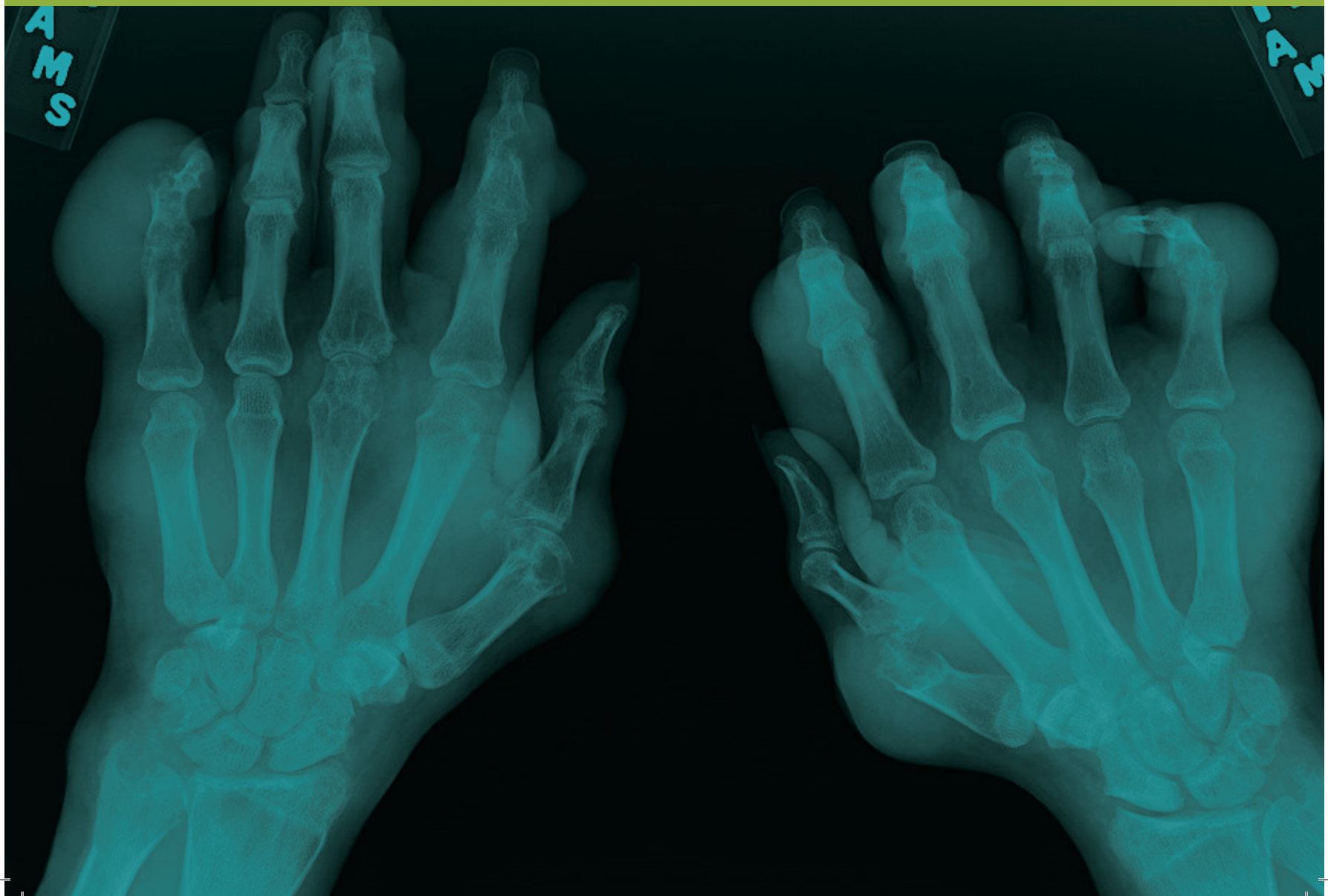
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Rheumatology Connections

An Update for Physicians | Winter 2023





From the Chair of Rheumatic and Immunologic Diseases

Dear Colleagues,

Welcome to the Winter 2023 *Rheumatology Connections*. We begin this issue with Dr. Carol Langford's insightful perspective on the process of preparing "The Year in Review" for the American College of Rheumatology's 2022 ACR Convergence conference. Her review of key developments in rheumatology provides inspiration about the exciting future of our field.

Advances in prevention and treatments for COVID-19 have been transformative, but the future of the pandemic remains uncertain, especially for our immunosuppressed patients. Drs. Leonard Calabrese and Cassandra Calabrese address continued challenges and share results of a study of breakthrough COVID-19 in B-cell depleted patients who received pre-exposure prophylaxis with tixagevimab/cilgavimab. While this pre-exposure prophylaxis is no longer effective for current vaccine variants, the positive results provide insights into future opportunities.

Dr. Ambreesh Chawla presents a patient who developed eosinophilic fasciitis after a recent case of COVID-19, an important example of the myriad post-COVID rheumatologic conditions.

For up to half of patients with psoriatic arthritis, TNF α blockers offer little or no relief to patients, yet there exists no currently clinically available test to predict which patients will benefit from individual agents. A team led by Dr. Elaine Husni is studying genetic polymorphisms in the hope of devising a personalized therapeutic approach for psoriatic arthritis.

A compelling report by Drs. Ahmed Elghawy, James Vondenberg and Vishwanath Ganesan examines how socioeconomic and mental health factors can create barriers to optimum care in a patient with severe gout. And Dr. Soumya Chatterjee reviews a case of yellow nail syndrome, a rare disorder that typically occurs in individuals who are 50 and older.

Among the highlights of practicing at Cleveland Clinic is the ability to work with specialists from across the system to help patients with requiring multimodal therapies. Dr. Patompong Ungprasert describes the operations of one such clinic, which is devoted to patients with sarcoidosis.

Finally, I hope you will enjoy the new feature based on our weekly educational Case Conferences. Drs. Adam Brown and Taylor Koenig explain a bit about the history of presenting complex, real-world cases for discussion, and share a recently presented case. We look forward to presenting a selection of others in upcoming issues.

I am grateful for the opportunity to share a portion of the work we do here in Cleveland Clinic's Department of Rheumatic & Immunologic Diseases. As always, we welcome the opportunity to connect and collaborate with you.

Respectfully,

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

On the cover:

Film of a patient who presented at Cleveland Clinic with severe gout and a diagnosis of schizophrenia as well as socioeconomic challenges. See story, page 10.

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Reflections on the ‘Year in Review’

by Carol A. Langford, MD, MHS

This year I was honored to be invited to provide the “Clinical Science Year in Review” at the American College of Rheumatology (ACR) Convergence 2022 meeting. Now that this lecture has come and gone, I have had an opportunity to reflect on what I learned. In addition to knowledge gained from the amazing works of published science, what I found took me back to why I chose to become a rheumatologist.

Medical advances

The past year brought forth significant advancements in rheumatology that had a direct impact on clinical practice or represented innovative approaches warranting further investigation. During this time, the Food and Drug Administration (FDA) approved six new indications impacting management of the spondyloarthritis family of diseases. In systemic lupus erythematosus, investigations included the first study of chimeric antigen receptor (CAR) T cells as well as phase 2 clinical trials of novel agents that target type I interferon pathways and B cells. Based on the results from a randomized trial of intravenous immunoglobulin in dermatomyositis, we also saw the first FDA-approved treatment for an inflammatory myositis. This body of work, as well as many other important contributions, demonstrates how progress in rheumatology continues to grow at a rapid pace.

Risk and benefit

As treatment options expand throughout the rheumatic diseases, weighing risk and benefit has become increasingly important. The assessment of risk needs to include not only short- and long-term toxicities related to the pharmacologic agent but also the risk of inadequately treated disease. During the past year, critical studies in rheumatoid arthritis examined the benefit/harm of glucocorticoids and the safety of a Janus kinase inhibitor. These studies reflect the commitment that rheumatology investigators and practitioners have in seeking information that will inform shared decision-making with their patients.

Bench to bedside

An increased understanding of the pathophysiologic mechanisms of disease was fundamental to many of this year’s clinical trials in generating hypotheses for both efficacy and safety. While the opportunity for advancements through basic,

translational and clinical research has never been greater, our ability to conduct such science has become increasingly difficult. The studies presented in the “Year in Review” exemplify how research funding as well support for junior and senior investigators is critical for future innovations in rheumatology.

The rheumatologist as patient advocate

Throughout the COVID pandemic, rheumatology professionals have played an essential role in providing both care and updated knowledge to their patients. The past year brought constant changes to which the rheumatology community responded. From vaccines to variants to novel pre-exposure prophylactic measures, it was the rheumatologist who our immunosuppressed patients turned to with their questions and concerns. Practicing rheumatologists applying information gained from the Global Rheumatology Alliance, the ACR COVID task force, and other international networks exemplified how our collective mission to keep patients safe can be accomplished by working together.

Rheumatology community

When I first began to consider the “Year in Review,” it became clear that being able to select and present topics required not only an understanding of the individual publications but also the background behind each study. I sought to understand from others what they found important and meaningful during the past year, and they in turn became my teachers. I reached out to a diverse spectrum of people: investigators in academic settings, rheumatologists in practice, trainees and rheumatology health professionals. The response I received was staggering – all busy people, all wanting to help and to share their thoughts. It was only through their guidance that the “Year in Review” was possible.

When I chose to specialize in rheumatology, three key points motivated my decision: the rapid growth of scientific knowledge in the field, the ability to play an impactful role in the lives of patients, and the rheumatology community. What the “Year in Review” affirmed to me is that these elements are not only thriving today but will remain fundamental in propelling rheumatology into its exciting future.



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Optimal Management of High Risk Immunocompromised Patients in the COVID-19 Era

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



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

The COVID-19 pandemic has affected the field of rheumatology in many ways, and while our understanding of the virus has improved, and we now have many effective tools for prevention and treatment, the pandemic will continue to require our focus and expertise.

The future of COVID-19 remains unpredictable, in large part due to the emergence of new variants of concern that may have unpredictable impacts on vaccine protection and effectiveness of treatment and pre-exposure prophylaxis (PrEP). We expect that the pandemic will continue down two paths: one for healthy, vaccinated individuals, and another for those who are immunocompromised and remain at higher risk.

Knowing our immunocompromised patient population

Immune-mediated inflammatory diseases and immunosuppressive therapies used as treatment create a heterogeneous group of immunosuppressed patients, with varying levels of risk for severe COVID-19, largely due to poor vaccine responses. Rheumatologists are now called upon to have knowledge of which patients are more vulnerable and how to counsel on risk, and to recommend vaccination and PrEP when appropriate.

Perhaps most importantly, patients and practitioners must be aware of available treatments and how to get them. Globally, we continue to see gaps in both knowledge and care within this model.

We recently described what we believe to be the optimal role of the rheumatology practitioner in COVID-19. To start, practitioners must have knowledge of available treatments, including oral antivirals and monoclonal antibodies, for whom they are indicated, and how to link patients to care, as these treatments are time sensitive. (Treatment should begin within five days of symptom onset for oral antivirals and seven days for monoclonal antibodies currently in use.)

Patient awareness of these treatment options is crucial, and rheumatology practitioners must educate patients on how to be rapidly diagnosed and treated, including use of home tests, and which practitioner to call in the event of infection.

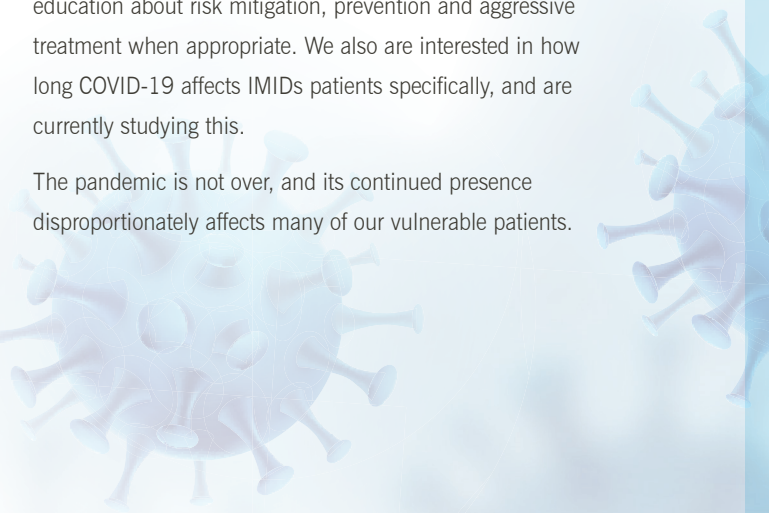
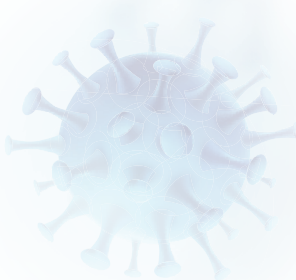
On recommending Evusheld for PrEP

For our most vulnerable (e.g., B-cell-depleted patients), recommending and triaging patients for tixagevimab/cilgavimab (Evusheld™) for PrEP are crucial.

Evusheld consists of two Fc-modified fully human monoclonal antibodies administered via IM injection. It is authorized for COVID-19 prevention in patients who are moderately to severely immune compromised and are unlikely to mount an adequate COVID-19 vaccine response. We have successfully administered Evusheld to more than 500 high risk patients in Cleveland Clinic's Rheumatology Department since it was first authorized in January 2022, and we have reported our real-world experience. (See next page.)

The R.J. Fasenmyer Center for Clinical Immunology operates in the space intersecting rheumatology and infectious diseases. We are well-poised to tackle COVID-19 and its impact on patients taking immunomodulatory drugs (IMIDs). We have an important role in patient and practitioner education about risk mitigation, prevention and aggressive treatment when appropriate. We also are interested in how long COVID-19 affects IMIDs patients specifically, and are currently studying this.

The pandemic is not over, and its continued presence disproportionately affects many of our vulnerable patients.



Real World Experience with Tixagevimab/Cilgavimab in B-Cell-Depleted Patients

by **Cassandra Calabrese, DO**

Patients receiving B-cell-depleting therapies (BCDT) for immune-mediated inflammatory diseases (IMiDs) and patients with inborn errors of humoral immunity (IEI) have high risk of poor COVID-19 outcomes. Risk mitigation strategies are of the utmost importance for this vulnerable group.

Pre-exposure prophylaxis (PrEP) with tixagevimab/cilgavimab (Evusheld™) has been available in the United States under FDA Emergency Use Authorization since December 2021. This preventive treatment is administered to patients who have been vaccinated, and to those with contraindication to vaccination, who are unlikely to respond to COVID-19 vaccination.

As of January 18, 2022, Cleveland Clinic has made tixagevimab/cilgavimab available to patients receiving BCDT and other select high risk patients. By Oct. 31, 2022, we had administered at least one dose to 600 Cleveland Clinic rheumatology patients.

We sought to describe the clinical outcomes of breakthrough COVID-19 in B-cell-depleted patients, either iatrogenic or from IEI. We retrospectively searched all pharmacy records for patients who met criteria to receive tixagevimab/cilgavimab (as defined by Cleveland Clinic’s COVID-19 Pharmacy & Therapeutics sub-committee) and who subsequently were diagnosed with COVID-19. From this list, we manually reviewed electronic medical records to extract data on infection, vaccination status and outcomes as assessed by an eight-point NIH ordinal scale (Table 1).

Between January 18 and May 28, 2022, a total of 417 patients received tixagevimab/cilgavimab across the rheumatology (n=261), allergy/immunology (n=78) and neurology (n=78) departments. From this cohort, 13 patients (3%) experienced breakthrough COVID-19 after receiving PrEP. All patients had been vaccinated against COVID-19. Six of 13 patients developed infection a median of 19 days (range 13-84) after receiving 150/150 mg of tixagevimab/cilgavimab. Seven of 10 patients developed

infection a median of 34 days (19-72) after either a single dose of 300/300 mg or after a second dose of 150/150 mg.

Overall, 12 patients had a mild course and recovered at home, and one patient was hospitalized and required high flow oxygen. There were no deaths. Nine patients received appropriate outpatient treatment with oral antivirals, monoclonals or both.

Our early experience suggests that COVID-19 infection after tixagevimab/cilgavimab occurs infrequently, and with standard-of-care outpatient management, infection is mild in severity. Unknown at present is how effective this preventive strategy will be against newly circulating variants of concern.



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Table 1. COVID-19 outcomes and treatment

NIH COVID-19 Ordinal Scale ¹	Mild ² Score 1-3	Moderate Score 4-5	Severe Score 6-8
All patients	12	0	1
COVID-19 treatment	9	0	0
Monoclonals	8	0	0
Oral antivirals	3	0	0

¹NIH COVID-19 ordinal scale

1. Not hospitalized and no limitations of activities
2. Not hospitalized, with limitation of activities, home oxygen (O2) requirement, or both
3. Hospitalized, not requiring supplemental O2 and no longer requiring ongoing medical care
4. Hospitalized, not requiring supplemental O2 but requiring ongoing medical care
5. Hospitalized, requiring any supplemental O2
6. Hospitalized, requiring noninvasive ventilation or use of high-flow O2 devices
7. Hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation
8. Death

²Score 1 = 6 patients, Score 2 = 6 patients, Score 6 = 1 patient

New Onset Eosinophilic Fasciitis After COVID-19 Infection

by Ambreesh Chawla, MD



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Eosinophilic fasciitis, also known as Shulman syndrome, is a rare autoimmune disorder that involves inflammation of the fascia overlying muscle, resulting in edema and deep induration of the extremities. It is typically symmetric and involves all four extremities. In contrast to scleroderma, the digits are typically spared and there is no association with Raynaud's phenomenon or microscopic nailfold capillary changes.

Eosinophilia is a characteristic laboratory finding in the early phase; however, it is not always present in early cases and is less prominent in later stages. Some cases of eosinophilic fasciitis can be associated with underlying hematologic disorders such as lymphoma, leukemia or aplastic anemia. Diagnosis is normally based on a deep excisional biopsy of the skin that includes the fascia.

Case report

A 46-year-old female with a recent diagnosis of COVID-19 presented to Cleveland Clinic's Rheumatology Clinic with new-onset worsening distal upper and lower extremity pain and discomfort. She noted that shortly after her diagnosis of COVID-19, she began to experience severe allodynia to light touch over her forearms and shins.

Laboratory testing revealed 25% eosinophils on complete blood count with mildly elevated markers of inflammation and borderline positive rheumatoid factor. Because of worsening allodynia, polyarthralgia and polymyalgia with persistent eosinophilia, the patient underwent an aggressive workup for eosinophilic-related conditions, including parasitic infections/Strongyloides, vasculitis/eosinophilic granulomatosis with polyangiitis, blood disorders/hypereosinophilic syndrome, and allergy testing.

On a follow-up rheumatology evaluation, a physical exam revealed skin thickening and deep induration of her distal extremities (sparing her hands and feet) with a peau d'orange appearance of the skin of her forearms and shins. Magnetic resonance imaging revealed fascial thickening and edema predominantly involving the deep peripheral fascia superficial to the muscles in the forearms and lower legs.



Distal extremities with peau d'orange indurated appearance (top) and groove sign (bottom).



The patient subsequently underwent a full thickness biopsy, consisting of skin, fascia and superficial muscle, which demonstrated perivascular infiltration of histiocytes, eosinophils, lymphocytes and plasma cells. Based on these findings, she was diagnosed with eosinophilic fasciitis. The patient was then started on high doses of oral prednisone (1mg/kg/day) in addition to methotrexate. Treatment led to normalization of the eosinophil count and skin softening on subsequent evaluation.

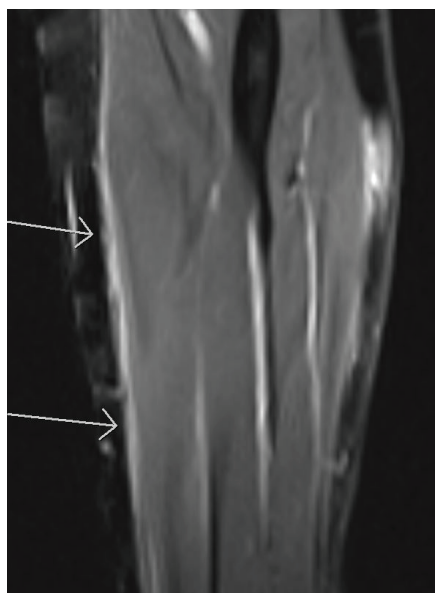
Clinical implications

While many autoimmune and rheumatologic conditions after viral infections have been described in the literature, to our knowledge this is the first case reported of eosinophilic fasciitis after primary COVID-19 infection. Development of new-onset autoimmune skin conditions has been reported following various vaccinations. Eosinophilic fasciitis has been documented after influenza vaccination and, more recently, has been described after a patient had received the COVID-19 mRNA vaccine. Other cutaneous disorders, such as morphea and discoid lupus, also have been described in the literature following various vaccinations.

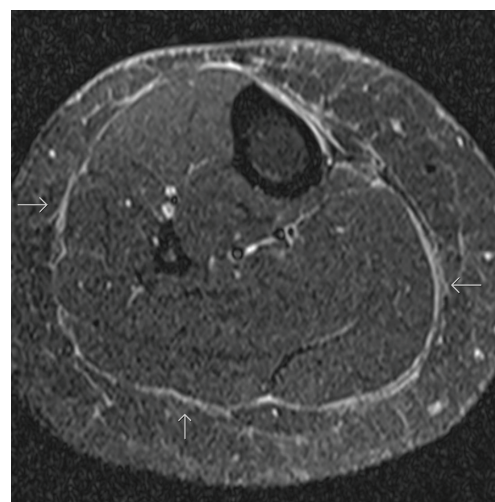
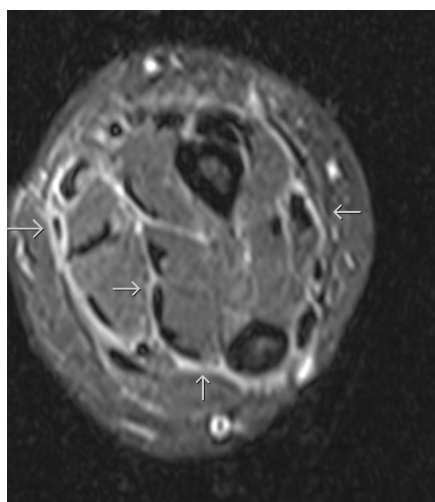
The sequential association presented here between COVID-19 and newly diagnosed eosinophilic fasciitis could be coincidental. It is also possible that the COVID-19 primary infection triggered a phenotypic expression of a previously existing undiagnosed disease.

Patients with eosinophilic fasciitis typically respond with loosening of the skin to

prolonged courses of high doses of steroids in conjunction with steroid-sparing agents such as methotrexate, mycophenolate mofetil and others. Treatment is typically required for several months to years. The condition overall carries a favorable prognosis, although joint contractures may persist if treatment is delayed.



MRI of lower leg with thickening/edema involving the deep peripheral fascia.



Building a Personalized Medicine Approach to PsA Treatment

Genetic polymorphisms and response to TNF α blockers

by M. Elaine Husni, MD, MPH, James K. Sullivan, BA, and Unni M. Chandrasekharan, PhD



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As we improve our understanding of the pathogenesis of psoriatic diseases, our treatment management can be refined as well. Our hope is to move away from the “one size fits all” approach and begin a new era of a more individual approach to treatment. Over the course of 20 years and according to the ACR/NPF guidelines,¹ tumor necrosis factor alpha (TNF α) blocking agents have become first-line treatment for patients with moderate to severe psoriatic arthritis (PsA). Research supports TNF α blockers (TNFi therapy) as safe and effective in relieving a wide spectrum of symptoms and inhibiting PsA-related joint damage.

For 40%-50% of patients² with PsA, however, TNF α blockers work insufficiently, lose efficacy over time or are not effective at all, and no clinical test exists to predict who will or won't benefit from TNF α blocking therapy.

At Cleveland Clinic's Orthopaedic & Rheumatologic Institute, we are studying genetic polymorphisms for clues that we hope will lead to improved understanding of why some individuals do not respond to TNF α blockers, more treatment predictability and, ultimately, allow for a personalized therapeutic approach for those with PsA.

PsA symptoms and comorbidities

PsA is a seronegative inflammatory arthritis that affects up to 30% of patients with psoriasis and 0.25% of the United States population. It can be debilitating, with symptoms that include pain and swelling in the joints (commonly hands, feet, wrists, ankles and knees) and lower back; reduced range of motion; inflammation of the entheses, and dactylitis. Dermatologic symptoms commonly include scaly areas on the scalp, elbows, knees and lower spine; papules on the arms, legs and torso; and pitting or detachment of fingernails and toenails.

PsA also can significantly reduce quality of life and increase overall risk of mortality in younger patients compared to the general population. Increased risk of cardiovascular disease is the largest contributor to mortality in this population,³

and currently available assessment tools such as the Framingham Risk Score underestimate cardiovascular risks for patients with PsA.

Genetic polymorphisms and PsA

Polymorphisms in the TNF α receptor 2 (TNFR2) gene have long been implicated in the pathogenesis and response to treatment for immune-mediated diseases, including rheumatoid arthritis, inflammatory bowel disease, ankylosing spondylitis and psoriasis.^{4,5} There are limited studies on TNFR2 polymorphisms in PsA and conclusions are not definitive, as the sample sizes are small and the definition of TNFi response is unclear.

In a limited sample of patients with PsA, preliminary data from the Husni laboratory at Cleveland Clinic identified a relationship between a particular TNFR2 gene polymorphism (rs1061622) and response to anti-TNF α therapy. The rs1061622 represents T/G polymorphisms at exon 6 (chromosome 1) in the TNF receptor superfamily member 1B gene, which encodes TNFR2.

The majority of individuals express the T SNP (>80%), while less than 20% encode the G SNP, resulting in a methionine or arginine, respectively, at position 196 in TNFR2 polypeptide (Figure). Even a single allele of the 196R variant significantly reduced response to anti-TNF α treatment in patients with PsA.

The Husni lab also has found that TNFR2 M196R may confer constitutive pro-inflammatory activity in vitro, which suggests a potential mechanism underpinning a reduced response to anti-TNF α therapy.

TNF α is associated with systemic lipid handling,⁶ and variability of the TNFR2 gene is associated with hypercholesterolemia.⁷ However, specific TNFR2 polymorphisms have not been examined. Therefore, in addition, we propose that the gain-of-function activity of TNFR2 M196 may be a factor in altering lipid profile and metabolism.

Based on our preliminary results, we hypothesize that adults with PsA who have TNFR2 M196R (minor variant) show a poor response to anti-TNF α therapy and dysregulated lipid profiles compared to those without the M196R variant because of constitutive pro-inflammatory activity of TNFR2 M196R.

Study goals

Our study goal is to establish the mechanistic relationships of these genetic markers to anti-TNF α therapy. We will accomplish this by accessing Cleveland Clinic's Psoriatic Disease Biorepository and determine the following:

- The impact of a specific polymorphism (rs1061622) on anti-TNF α therapy response.
- Differences in signaling pathways by which rs1061622 polymorphism (T allele versus G allele) modulates response to TNF α inhibition.
- The association of rs1061622 polymorphism with serum lipid profiles of patients with PsA.

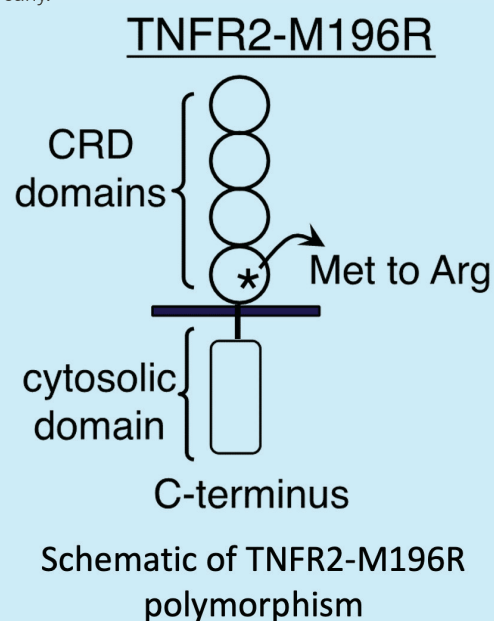
If data support the predictability of poor response to TNF α therapies in certain patients with TNFR2 polymorphisms, an inexpensive and efficient test could be performed on any patient with PsA.

Defining predictability has the potential to risk stratify those PsA patients who may benefit from TNFi therapy versus those who would not benefit from TNFi therapy. This would reduce considerable suffering and unnecessary expense in those with PsA who may need to cycle through many different medications for relief. Trials of TNF α blocker(s) therapy require up to three months time to demonstrate efficacy, during which patients may require time off for either IV infusions performed at infusion center or need teaching visits for self-injections. In cases of treatment

failure, patients continue to experience symptoms, and may face another three-month cycle of different medication – without indication of whether it will work better than the first.

Those for whom anti-TNF α treatment fails have limited options, although new drugs are approved almost every year. Therapies that could be introduced after anti-TNF α failures include anti-interleukin 23 medications such as guselkumab (Tremfya[®]), risankizumab (Skyrizi[®]) and ustekinumab (Stelara[®]); anti-interleukin 17 medications such as secukinumab (Cosentyx[®]) and ixekizumab (Taltz[®]); as well as in combination with other oral DMARDs such as methotrexate.

Similarly, identification of an association of rs1061622 polymorphism with dysregulated lipid metabolism may help to identify PsA patients at risk of related cardiovascular disease and this may lead to reduce mortality, if intervened early.



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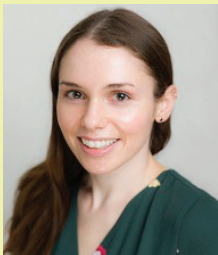
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A Multidisciplinary Approach to Mental Health and Socioeconomic Obstacles in Severe, Diffuse Tophaceous Gout

by James Vondenberg, DO, Vishwanath Ganesan, MD, and Ahmed Elghawy, DO



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CASE

A 43-year-old-male was admitted to Cleveland Clinic for gout flare. The patient, who lives alone, had a history of coronary artery disease post-percutaneous coronary intervention, hyperlipidemia, schizophrenia and long-standing, severe polyarticular and tophaceous gout.

At age 21, the patient was diagnosed with rheumatoid arthritis and had symptoms of inflammatory polyarthritis. This diagnosis was questioned when he was being established at Cleveland Clinic, where a repeat workup demonstrated a negative rheumatoid factor and cyclic citrullinated peptide. His exam was notable for multiple open tophi, confirming a diagnosis of polyarticular tophaceous gout.

Over several years, the patient was trialed on multiple medications, including allopurinol, probenecid, febuxostat, colchicine, pegloticase, anakinra and prednisone. He frequently missed appointments. His response to these therapies, both independently and in combination, has been difficult to assess because of significant psychiatric and socioeconomic barriers that contribute to medication non-adherence.

Physical exam was notable for tophaceous deposits involving bilateral hands, forearms, elbows, ankles, feet, shins and knees, in addition to deposits of the musculature and tendons of the upper and lower extremities. Laboratory findings were notable for elevated uric acid and C-reactive protein. Radiographs of the feet, tibia/fibula, knees, ankles and forearms revealed extensive changes of tophaceous gout [Figures 1-4].

A re-trial of pegloticase was discussed, but the patient expressed concerns that pegloticase had caused him to have a seizure in the past, so he declined. Thorough review of the medical records confirmed that his seizure had been during a hospital admission for pneumonia. The patient received anakinra for his flare and was followed closely.

During outpatient follow-up for injection teaching, the patient disclosed that he had not refrigerated his anakinra for several weeks. He reported that he was living alone without family

nearby and was unable to care for himself. His vital signs at that time were further concerning for hypertensive crisis, for which he was sent to the emergency department.

Over the next few weeks, social work, adult psychology, pharmacology and rheumatology worked to improve the patient's access to care and medication education. At his most recent follow-up, the patient noted improved symptoms and pain control with daily anakinra injections and allopurinol 900 mg daily as urate-lowering therapy; he noted that he was now properly storing his anakinra. The patient is currently engaged in therapy with adult psychology, and strides are being made with social work to provide home assistance in addition to easier transportation and access to care.

Mental health barriers to disease control

Here, we have a male in his 40s with schizophrenia and gout that has been uncontrolled and progressing throughout his lifetime. He experienced no response to multiple therapies because of medication nonadherence and inconsistent follow-up. While his physical exam indicates significant progressive disease, this is likely a consequence of the numerous difficulties the patient faced before receiving multidisciplinary care at Cleveland Clinic.

Mental health can often serve as a significant barrier to care for patients struggling with rheumatic disease. In this patient's case, schizophrenia and limited health literacy hindered control of his disease. For example, the patient's delusions regarding previous treatment with pegloticase made this option difficult to consider even though he may have been an ideal candidate for it. Additionally, the patient may have not had the medical competence to fully appreciate the severity of his disease and how vital his medications were to treatment.

By collaborating with adult psychology, our team was able to communicate regularly and effectively to ensure that the patient fully understood his treatment. Although this is an ongoing process, the foundation of medical care that was missing for years has finally been built.

Socioeconomics and rheumatic disease

When treating patients with rheumatic disease, a multidisciplinary focus can help overcome social and economic factors that would otherwise impede or complicate medical care.

This patient's economic barriers had made getting to appointments a major task. Financial difficulties and inconsistent modes of transportation resulted in missed appointments and inability to continue medications that would treat his rheumatic disease. A combination of polypharmacy and multiple hospitalizations with medication changes often led to the patient experiencing confusion regarding his treatment plan. Without a trusted guardian to aid in his medical decision-making, ensuring consistent medical

care was difficult. Collaborating with social work has provided him with tools to help him properly use his medication and to participate in outpatient follow-up.

The combination of this patient's socioeconomic challenges with his psychiatric history creates a situation with limited treatment options. Our multi-team approach has given this patient a better opportunity to understand the full extent of his disease and take steps to effectively treating it. Caring for such patients serves as a sobering reminder that even with the best therapies available, mental health and socioeconomic obstacles can delay or hinder medical care altogether. At times, the start of therapy must come second to forming a solid therapeutic relationship with our patients.



Figures 1, 2: Image of the hands (A) and plain films of the hands (B) during hospital admission.

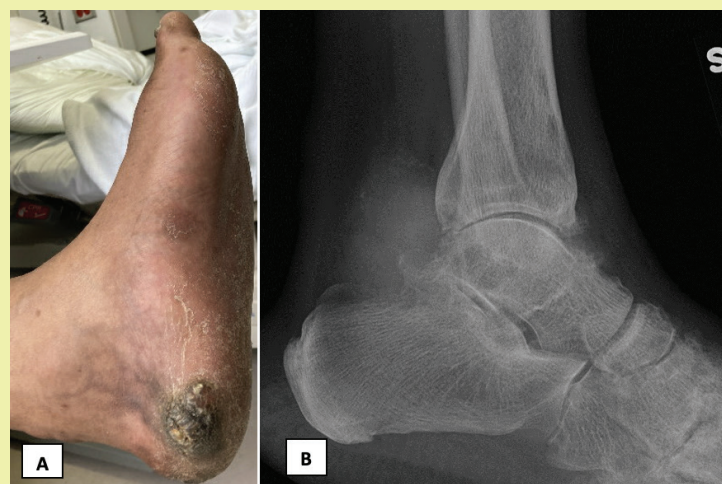
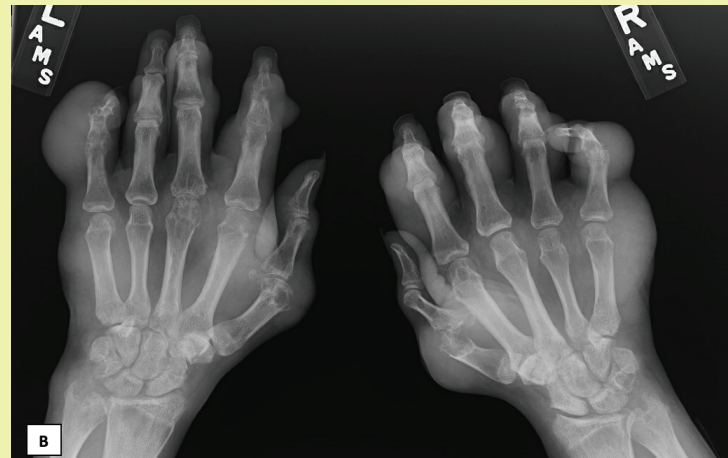


Figure 3: Image of the left foot (A) and plain film of the left ankle (B) during hospital admission.



Figure 4: Image of the lower extremities (A) and plain film of the right knee (B) during hospital admission.

Case Report: When Edema and Dyspnea Accompany Dyschromic Nails

Patient's two-year symptom history leads to an uncommon diagnosis

by Soumya Chatterjee, MD, MS, and Elliott Chandler Dasenbrook, MD, MHS



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For two years, a patient with a history of hypertension and obstructive sleep apnea also has been experiencing new symptoms: nasal congestion, dripping and cough, and discoloration of his fingernails and toenails. A thorough history, physical examination and laboratory exams establish the diagnosis and a successful treatment plan.

Physical examination

The 70-year-old patient presents with no fever, a heart rate of 66 bpm, and a blood pressure of 143/72 mm Hg. He has no chest pain or joint inflammation.

All nails on the patient's fingers and toes have become brittle, thick and yellow, with some showing distal separation from the nail bed. These changes have been accompanied by a chronic cough and nasal symptoms. Diminished breath sounds are evident upon auscultation, but no crackles can be heard. Cardiac and abdominal examinations are normal. Lower extremity non-pitting edema and dyspnea have recently developed.

Laboratory tests show normal complete blood count, thyrotropin and comprehensive metabolic panel results. Other results: erythrocyte sedimentation rate: 2 mm/h; C-reactive protein 0.1mg/dL; antinuclear antibody is positive (1:160, nucleolar pattern); testing for antibodies to extractable nuclear antigens and double-stranded DNA are negative; mildly low C3 complement level (63 mg/dL [reference range, 79-152mg/dL]); normal immunoglobulin and C4 complement level (20mg/dL [reference range, 16-38mg/dL]). A recent chest X-ray to assess a persistent cough did not indicate any obvious cardiopulmonary disease. Electrocardiogram reveals a pericardial effusion with no evidence of tamponade.

Diagnosis

The presence of dyschromic nails, lymphedema, and sinus and lung symptoms point to yellow nail syndrome.

With fewer than 400 cases reported so far, yellow nail syndrome can affect anyone but typically occurs in those 50 and older. Its cause is unknown. It is believed that lymphatic abnormalities lead to the accumulation of lipids which, when

oxidized, cause nails to discolor. As a result, longitudinal growth slows, and nails can double in thickness and cause the cuticle and lunula to disappear.

Several more common conditions, including onychomycosis or psoriasis, can cause similar nail symptoms, but would not account for other symptoms.

When yellow nail syndrome is suspected, the next step is to investigate pulmonary manifestations with a thoracic CT scan. This patient's scan reveals bronchiectasis. Bilateral pleural effusions and a large circumferential pericardial effusion are also present. During thoracentesis, 1,400mL of straw-colored fluid is aspirated from the right pleural space. Nonchylous, exudative fluid with a lymphocytic predominance is drained during a pericardial window procedure. Fluid shows no evidence of malignancy; bacterial and fungal cultures are negative.

About 50% of patients with yellow nail syndrome experience spontaneous remission. This patient's ongoing symptom management includes repeated thoracenteses to relieve fluid buildup, manual lymph drainage, and the use of compression stockings for lymphedema. The patient takes daily vitamin E (1,000 IU) and furosemide and is gradually improving.



The patient's fingernails and toenails showed yellow discoloration and thickening. Few nails showed distal onycholysis.

Multidisciplinary Clinic Brings Specialties Together to Treat Sarcoidosis

by Patompong Ungprasert, MD, MS

Sarcoidosis is a chronic granulomatous disease of unknown etiology that is believed to be a result of complex interactions between genetic predisposition and environmental exposure. This systemic disease can affect virtually any organ in the body. In fact, more than half of patients with sarcoidosis have inflammatory disease from sarcoidosis in two or more organs.¹

The multi-systemic nature of the disease poses a significant challenge to patients and clinicians, and close collaboration between the patient's healthcare providers is often required.

The benefit of a team approach

The concept of a multidisciplinary team approach has gained popularity over the past few decades, particularly for diseases that typically involve psychosocial support and care from healthcare providers across disciplines. This multidisciplinary approach has been linked to better health outcomes, reduced cost and higher patient satisfaction.²

In rheumatology, this model of care is common, as rheumatologic autoimmune disorders tend to affect more than just the musculoskeletal system. At Cleveland Clinic's Department of Rheumatic and Immunologic Diseases, this collaborative approach has been used in many areas, such as the Rheumatology-Dermatology Clinic led by Elaine Husni, MD; the integrative Vascular Neuroinflammatory Clinic, networking with stroke neurology, neuroimmunology, neuroradiology and neuropathology, led by Rula Hajj Ali, MD; and the Systemic Sclerosis-Interstitial Lung Disease, led by Soumya Chatterjee, MD.

Multidisciplinary sarcoidosis care

Cleveland Clinic's multidisciplinary Sarcoidosis Clinic is one of the few such clinics in the country that offer comprehensive care for patients with sarcoidosis. Our team consists of physicians from different specialties who also bring experience in sarcoidosis. Pulmonologists Dan Culver, DO, and Manuel Lessa Ribeiro, MD, bring special expertise in pulmonary sarcoidosis. Cardiologists Christine Jellis, MD, PhD, and Ziad Taimeh, MD, have special expertise in cardiac sarcoidosis and advanced cardiac imaging study. Neurologist Brandon Moss, MD, has special expertise in neurosarcoidosis. And

as a rheumatologist, I bring extensive experience using immunosuppression medications and biologic agents for treatment of musculoskeletal and other manifestations of sarcoidosis.

Care with our clinic starts with a phone consultation with our dedicated registered nurse, who gathers preliminary information from the patient and referring providers. The nurse, in collaboration with physicians, determines which specialists the patient needs to see, as well as necessary laboratory and imaging investigations. Appointments are scheduled to ensure that all of the required care will be completed within a span of a few days, as our patients often travel from different states or even from abroad.

The physician team discusses and formulates a treatment plan together, which is shared with the patient at the end of the visit and again during follow-up by telemedicine.

Cleveland Clinic's Sarcoidosis Clinic welcomes referrals, especially for challenging cases involving patients requiring multidisciplinary care. We can be reached at 440.613.8891.



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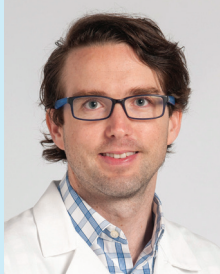
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CASE CONFERENCE

Rheumatology Case Conferences Make for Engaged Learning

by Adam Brown, MD, and Taylor Koenig, MD



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In our digitally focused world, user experience is important, but it isn't limited to computers. At Cleveland Clinic's Department of Rheumatic and Immunologic Diseases, medical fellows employ a century-old tradition – interactive case teaching – to hone medical trainees' clinical reasoning and deepen their diagnostic skills.

Each Friday at the R.J. Fasenmyer Center for Clinical Immunology, residents, fellows and faculty gather for Case Conference, the presentation of a clinical case with sufficient complexity to ignite educationally relevant debate and discussion.

The clinicopathologic conference was introduced at Harvard Medical School around 1900, spurred by student Walter B. Cannon's interest in replacing some of the hours spent listening to lectures with purposeful case conversations. Richard Cabot, MD, then began using the method with third-year medical students at Massachusetts General Hospital.

In Rheumatology at Cleveland Clinic, fellows rotate the responsibility of presenter, choosing a case and establishing the facts: the presenting illness and patient's medical history, as well as details from the physical exam. The

trainees and faculty then discuss and debate differential diagnosis, what next tests and imaging should be pursued, and what treatments may be implemented. The presenter eventually reveals the final diagnosis.

The process makes for a meaningful educational activity because students move step by step through the reasoning they will use every day in practice. When a patient comes to them, what will they do about it? How will they prove one diagnosis or disprove another? They also are typically learning about complex cases, and often those requiring a multidisciplinary approach. Physicians from a variety of specialties often are part of our case discussions.

Case Conference offers an especially rich experience in rheumatology, which can be a confounding and humbling specialty. With that in mind, beginning with this issue, *Rheumatology Connections* will highlight one or more cases from the Friday conference series.

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Residents and faculty members participate in person and online in Friday morning discussions of challenging rheumatology cases.

CASE STUDY PRESENTATION

JOINT PAIN AND EYE REDNESS

We present the case of a 36-year-old male with a history of hyperlipidemia and a childhood penicillin allergy who presented to the Rheumatology Clinic with polyarticular joint pain and bilateral eye redness. This case required collaboration among specialty providers and highlights the multidisciplinary nature of rheumatic disease.

The patient's symptoms started with sore throat and general malaise less than two weeks prior to his initial rheumatology evaluation. His throat culture was positive for streptococcus. He improved on antibiotic treatment with doxycycline. However, 10 days after symptom onset, the patient developed severe polyarticular joint pain and stiffness along with bilateral eye redness.

The patient was started on twice-daily naproxen by his primary care physician (PCP). On day 13, his symptoms continued to progress, and his PCP referred him to an emergency department (ED) for further evaluation.

In the ED, laboratory studies, including complete blood count and comprehensive metabolic panel, were within normal limits, with the exception of elevated C-reactive protein (CRP) at 5.7 mg/dL (normal < 0.9 mg/dL). Electrocardiogram revealed no ST changes and a normal PR interval. Urine tests for gonorrhea and chlamydia were negative. The patient was discharged with referrals to rheumatology and ophthalmology.

The patient was evaluated in the Rheumatology Clinic 14 days after symptom onset. He endorsed pain and stiffness in his hands, wrists, elbows, shoulders, knees, ankles and feet, which progressed in an additive fashion. His pain and stiffness had improved since starting naproxen. He denied eye pain, photophobia and vision loss associated with his eye redness. The patient denied rash, urethral discharge, dysuria, chest pain and gastrointestinal symptoms.

On exam, the patient had bilateral conjunctival erythema. He had synovitis and limited range of motion in his ankles, left wrist and bilateral third PIP joints. He also had tenderness with decreased range of motion in his hands and elbow without swelling. Dermatologic exam was pertinent for hyperpigmented patches over the patient's anterior lower legs – findings that were confounded by a recent episode of poison ivy.

Because acute rheumatic fever was on the differential for this patient, we ordered an echocardiogram to evaluate for subclinical carditis and

referred the patient to Infectious Disease as well as our ophthalmology colleagues, where he was diagnosed with episcleritis. Echocardiogram revealed normal systolic function, no valvular disease, and no pericardial effusion, ruling out subclinical carditis.

For our patient presenting with symmetric polyarthritis and episcleritis in the setting of a recent streptococcal infection, the two main diagnoses debated were acute rheumatic fever (ARF) and post-streptococcal reactive arthritis (PSRA). During the conference, we discussed how the diagnosis of ARF is distinguished from PSRA and how it may change management. We discussed the Jones diagnostic criteria for ARF; the patient only met one major (polyarthritis) and one minor (elevated CRP), making ARF less likely.

Additionally, the classic inflammatory arthritis of ARF is migratory: One joint is involved for a few days, resolves, then a different joint becomes involved. The joint pattern typically seen in PSRA is an additive, symmetric pattern like this patient described.

Importantly, the joint pain in ARF also typically doesn't start until two to three weeks after the sore throat. In contrast, PSRA often starts within two weeks of the sore throat, similar to our patient. The episcleritis is more non-specific and can be seen in both conditions, so this doesn't narrow the diagnosis.

Distinguishing ARF and PSRA is important, because there are treatment implications. In ARF, we would expect the joint pain to be self-limiting, but recurrence of streptococcal infection would put the patient at risk for valvular heart disease, and prophylactic antibiotics may be initiated. In contrast, in PSRA we would not expect cardiac complications, but the articular manifestations may become more chronic requiring immunosuppressive therapy.

With this multidisciplinary evaluation, our patient was diagnosed with PSRA. He has improved on naproxen and will follow up in the Rheumatology Clinic for further management.

This case demonstrates the interdisciplinary nature of rheumatic disease. Clinicians in primary care, infectious disease, ophthalmology and rheumatology all were essential in making this diagnosis and initiating the correct treatment for our patient.



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