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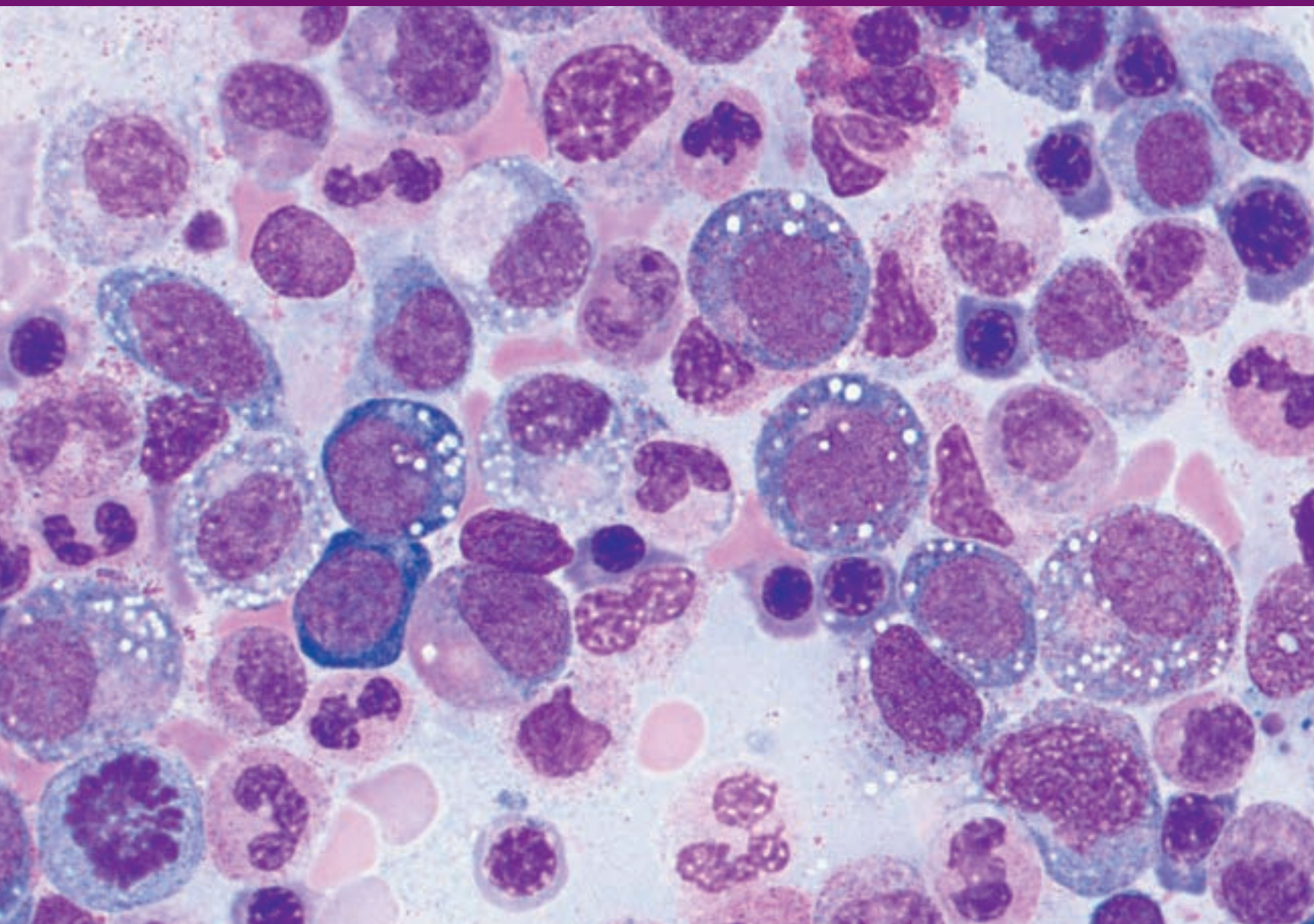
Cleveland Clinic

Rheumatology Connections

An Update for Physicians | Winter 2021



From the Chair of Rheumatic and Immunologic Diseases

Dear Colleagues,

Welcome to the Winter 2021 issue of *Rheumatology Connections*. I am pleased to share this collection of articles highlighting the clinical work and research by staff in Cleveland Clinic's Department of Rheumatic and Immunologic Diseases.

In this issue, we highlight several fascinating clinical cases. Dr. Carol Langford discusses VEXAS syndrome, a multisystem disorder recently identified by the National Institutes of Health that may be mistaken for relapsing polychondritis. Drs. Sarah Keller, Lelia Khan and Chad Deal present a patient with Erdheim-Chester disease, which can mimic rheumatologic processes. Drs. M. Elaine Husni and Anthony Fernandez explore a complex presentation of psoriatic arthritis at the intersection of rheumatology and dermatology. Finally, Dr. Chatterjee shares a patient whose symptoms of a viral infection resembled a systemic autoimmune disease. Each case illustrates the skillful and consistent application of current evidence and the multisystemic nature of our specialty.

At Cleveland Clinic, we embrace opportunities to partner within and across disciplines to improve the care of all patients. Our model of collaborative care is evident in our multidisciplinary clinics, which include combined clinics with specialists in dermatology, endocrinology, immunodeficiency, infectious disease, nephrology, neurology, ophthalmology, pulmonology and more. We are fortunate at Cleveland Clinic to have so many superb subspecialty colleagues to share the care of our complex rheumatology patients in settings where the patients are able to witness the discussion about diagnostic and treatment issues.

This issue also includes an update on Dr. Husni's research of patient-reported outcomes in psoriatic arthritis, a review of the association between asthma and systemic lupus erythematosus, balancing the benefits of biologic therapy against risks of mycobacterial infection, and empathy in medical education.

It is our honor to care for all patients with the diversity of rheumatic diseases, from common conditions to rarer manifestations of the most complex diseases. I welcome your feedback as we collaborate to advance rheumatologic care and research.

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.

Cover image courtesy of Katherine Calvo, MD, PhD, and Marcela Ferrada, MD, National Institutes of Health.

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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Nontuberculous Mycobacterial Infections Potentiated by Biologic Therapy

by Cassandra Calabrese, DO

Since the approval of etanercept in 1998, use of biologic therapy to treat rheumatoid arthritis (RA) and other autoimmune diseases has rapidly expanded. Five tumor necrosis factor-α inhibitors (TNFis) are now available, as well as drugs that target interleukins, Janus kinases and cytotoxic T-lymphocyte-associated protein 4.

These agents have transformed care, but they also are associated with higher risks of serious and opportunistic infections than are traditional disease-modifying anti-rheumatic drugs. A new review provides insights for clinicians on balancing benefits of biologics for RA against risks of tuberculosis (TB) and nontuberculous mycobacterial (NTM) infections.[1]

Tuberculosis

Of all the TNFis, etanercept carries the lowest risk of TB and is the treatment of choice for patients with RA who are at risk for TB, if a TNFi is needed. It is a soluble receptor fusion protein and causes less complement-mediated cytotoxicity and apoptosis of affected cells than do monoclonal TNFis, such as infliximab and adalimumab. Few patients with latent TB are seen in Cleveland Clinic's Department of Rheumatic & Immunologic Disease because the disease is not endemic to the United States. Risk factors include emigrating from an endemic country or being in close contact with someone with active TB.

Nontuberculous mycobacterial infections

In contrast to TB, NTM infections are ubiquitous in the United States, often found in water and dirt. Because they are not transmittable person to person, these infections are not reportable; hence, getting a handle on incidence is difficult. Some reports do exist, however, linking NTM infections with RA and its treatment.

RA itself may be a risk factor for NTM infection, which is not surprising because chronic lung disease is common in patients with RA. Data from population-based studies suggest that the incidence of NTM infections may be upward of 100 per 100,000 patient-years in individuals with RA who are taking TNFis — double that of RA patients not exposed to the drugs.

Risk factors for NTM infection include lung disease, diabetes and hypertension. The number one concern, however, is concomitant treatment with steroids.

Who is at risk?

There are no formal recommendations for screening for NTM infection prior to starting a patient with RA on biologic therapy. Nevertheless, clinicians should be hypervigilant about assessing for risk factors and monitoring for symptoms of infection in individuals being treated with the drugs. The most common symptom is a chronic cough but disseminated disease can present with cutaneous manifestations. Diagnostic testing for an NTM infection includes chest X-ray, computed tomography, sputum culture, and a bronchoscopy with cultures and staining.

Balancing benefit and risk

For physicians, the keys to balancing benefit and risk of biologic therapy are the following:

- Screen patients for latent TB before starting biologic treatment.
- Assess risk for latent TB according to Centers for Disease Control and Prevention-defined risk factors, such as having spent prolonged time in an endemic country, having spent time in a homeless shelter or jail, and being a healthcare worker.
- Counsel patients about the infection risk before prescribing biologics.
- Once patients are on a biologic, have a low threshold for ordering a chest X-ray, if a chronic unexplained cough develops.

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1. *Calabrese C, Winthrop KL. Mycobacterial infections potentiated by biologics.* Infect Dis Clin N Am. *2020 Jun;34(2):413-423.*

Relapsing Polychondritis or Something More?
Identification of a Novel Disorder: the VEXAS Syndrome

By Carol A. Langford, MD, MHS

Dr. Langford (langfoc@ccf.org; 216.445.6056) is Director of the Center for Vasculitis Care and Research at Cleveland Clinic as well as Vice Chair for Research, Department of Rheumatic and Immunologic Diseases.

CASE

You are asked to see a 72-year-old male who has just moved to your community. Three years ago he developed a systemic inflammatory illness characterized by fevers, skin lesions and arthralgias/arthritis of the knees, ankles, wrists and elbows. Labs were notable for a macrocytic anemia, elevated sedimentation rate and C-reactive protein, with negative RF, anti-CCP, ANA and ANCA. Biopsy of the skin lesions revealed a neutrophilic dermatosis. Two years ago he developed dyspnea with pulmonary infiltrates unrelated to infection. Last year he had a deep venous thrombosis (DVT) with no evidence of a hypercoagulable state. He has been treated with prednisone on which he improves but requires doses above 20 mg/day, and he has also received methotrexate and azathioprine without benefit. He is now hospitalized after developing a fever, thrombocytopenia and worsened joint pain while on prednisone 25 mg/day. Assessment for infection has been negative. He notes new swelling over the nasal bridge and external ear. His medical team consults you for the question of whether he has a rheumatic disease.

Relapsing polychondritis

In considering the clinical features of this patient, the recent development of nasal and ear swelling raises the possibility of relapsing polychondritis. Relapsing polychondritis is a complex disease characterized by inflammation of cartilage within the ear, nose, joint and respiratory tract, often with multisystem disease involving the eyes, skin, nerves, heart and vascular system.[1-3] There is no single confirmatory test for relapsing polychondritis with the diagnosis being established by the constellation of clinical findings, laboratory data, imaging and, when possible, biopsy of an involved cartilaginous site.

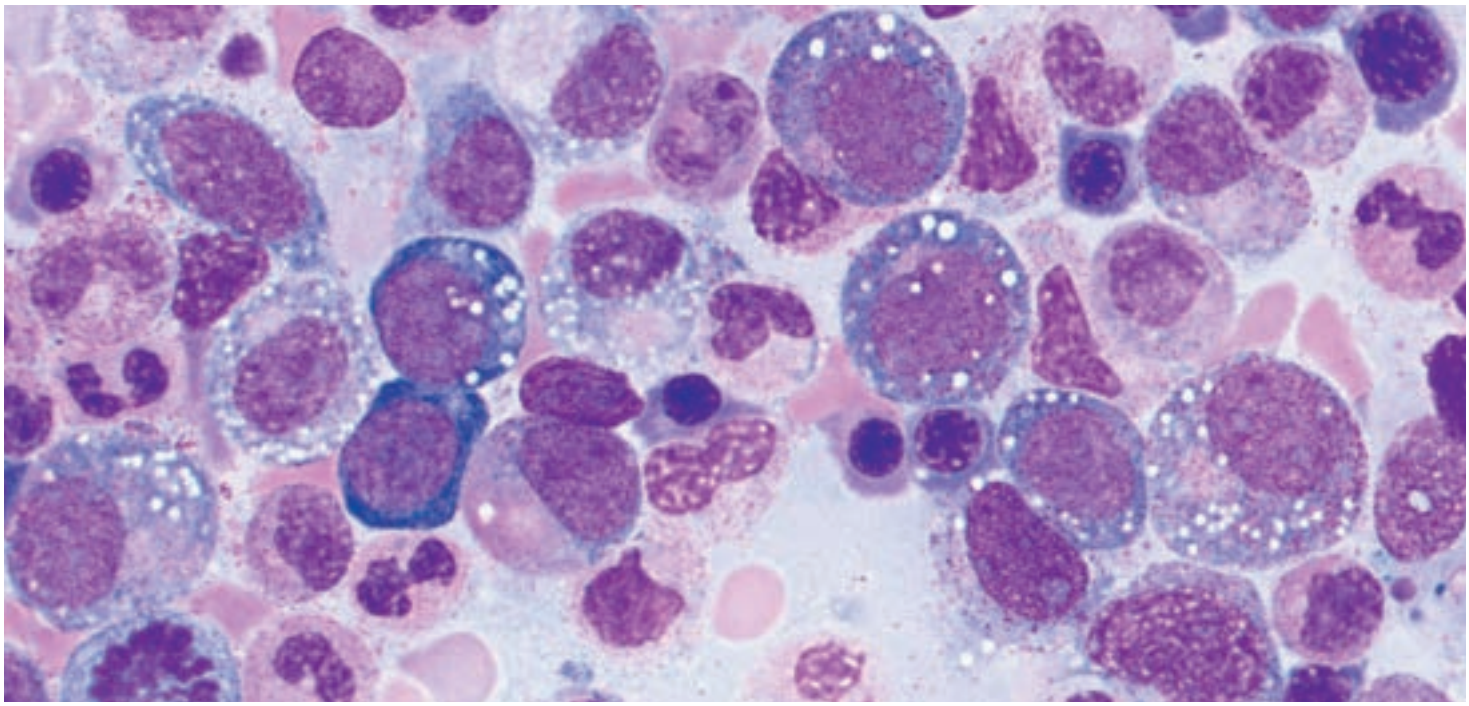
While many of this patient's symptoms and signs could fit relapsing polychondritis, others such as the pulmonary infiltrates, DVT and hematologic findings raise the question of whether there may be a different underlying diagnosis.

A novel discovery: the VEXAS syndrome

An exciting discovery recently published in the *New England Journal of Medicine* was the identification at the National Institutes of Health (NIH) of a novel disorder that connects seemingly unrelated adult-onset inflammatory syndromes.[4] This disorder has been named the VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome. In this study, 25 men were identified who possessed somatic mutations affecting methionine-41 in UBA1, the major E1 enzyme that initiates ubiquitylation. These patients presented with a treatment-refractory inflammatory syndrome that developed in late adulthood with clinical features that included fevers, neutrophilic cutaneous and pulmonary inflammation, chondritis, and vasculitis together with hematologic abnormalities of cytopenias, vacuoles in myeloid and erythroid precursor cells, dysplastic bone marrow, or multiple myeloma.

From a diagnostic standpoint, recognizing the constellation of clinical manifestations is the first essential step in identifying patients with the VEXAS syndrome. For rheumatologists, the VEXAS syndrome should be considered in a male patient with characteristics that suggest relapsing polychondritis, polyarteritis nodosa, Sweet syndrome, adult-onset Still disease or giant cell arteritis which is occurring in conjunction with one or more of the following:

- Hematologic abnormality: cytopenias, macrocytic anemia, myelodysplastic syndrome, monoclonal gammopathy of unknown origin or multiple myeloma
- Fevers
- Venous thrombotic events
- Pulmonary infiltrates
- Cutaneous lesions: neutrophilic dermatoses, leukocytoclastic vasculitis, medium-vessel arteritis
- Treatment resistance



Vacuoles in myeloid cells in a patient with VEXAS syndrome (image courtesy of Katherine Calvo, MD, PhD, and Marcela Ferrada, MD, National Institutes of Health).

While these are the currently identified manifestations of the VEXAS syndrome, additional clinical features may be found as more patients are tested and identified. For patients who have bone marrow biopsies performed, the precursor cells should be carefully examined to look for vacuoles, which are characteristic of the VEXAS syndrome. Genetic testing to confirm the diagnosis can be performed by contacting the NIH team who described the VEXAS syndrome.

In the 25 described patients with the VEXAS syndrome, treatment-refractory disease was typical. Glucocorticoids at high doses often provided improvement, with many patients having also received multiple other immunomodulatory agents. Ten of the 25 patients died either as a result of their disease or from treatment-related complications, which speaks to the severe nature of this disorder. At this time the optimal treatment for the VEXAS syndrome remains unclear, although the article notes that approaches to target the somatic process should be considered.

The identification of the VEXAS syndrome is a very important discovery for multiple reasons. This work utilized a genotype-first, phenotype-neutral strategy to identify the cause of a severe adult-onset disease, an exciting approach that could open the door for many future insights into human disease. Significantly for patient care, the VEXAS syndrome provides a diagnostic explanation for a complex range of seemingly unrelated clinical features. Recognition of this disorder will help physicians, patients and their families in having the first step of knowing the cause of their illness and in beginning to work together toward an approach to treatment.

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2. *Horváth A, Páll N, Molnár K, et al. A nationwide study of the epidemiology of relapsing polychondritis.* Clin Epidemiol. *2016 Jun;8:211-230.*
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Assessing the Relationship Between Systemic Lupus Erythematosus and Asthma

By Patompong Ungprasert, MD, MS

Dr. Ungprasert (ungprap@ccf.org; 216.445.4745) is associate staff in the Department of Rheumatic and Immunologic Diseases.

Systemic lupus erythematosus (SLE) is one of the most common autoimmune connective tissue diseases among women of reproductive age. Despite decades of research, the exact etiology and pathogenesis of SLE remain unknown. It is clear that multiple factors, including genetic, hormonal, immunologic and environmental factors, play a role in the development of this autoimmune disease. Previous studies suggest an association between asthma, which affects approximately 4% of the population, and elevated risk of certain chronic diseases including diabetes mellitus,[1] inflammatory bowel disease,[2] coronary artery disease[3] and SLE.[4-13] However, the relationship between asthma and SLE remains unclear as some studies suggest a positive association,[5,12,13] while others demonstrate a nonsignificant negative association.[6,7]

The study

Our recent epidemiologic work attempts to shed more light on the pathogenesis of SLE.[14] Through systematic review and meta-analysis, we identified all existing cohort and case-control studies that investigate whether patients with asthma have an increased risk of SLE compared with individuals without asthma. Qualifying cohort studies included one cohort of patients with asthma and another cohort of comparators without asthma. Additionally, qualifying cohort studies compared the incidence of SLE between the groups. Qualifying case-control studies consisted of patients with SLE and controls without SLE. Further, the case-control studies had to compare the prior history of asthma between the two groups in order to be included.

We screened more than 20,000 articles from PubMed/Medline and EMBASE, and identified 10 qualifying studies. The pooled results from those 10 studies show that the odds of developing SLE later in life are 37% greater for individuals with asthma than for those without asthma (pooled odds ratio of 1.37 with 95% confidence interval of 1.14–1.65, moderate statistical heterogeneity with I^2 of 67%). No evidence of publication bias was detected using funnel plot visualization.

Overlapping immunogenic pathways

Our observation may help illuminate the pathogenesis of SLE by highlighting the role of the overlapping immunopathogenic pathways between asthma and SLE. Increased levels of T_H2 class cytokines, including IL-4, IL-5 and IL-13, have been observed in both asthma and SLE patients.[15,16] Therefore, it is possible that upregulation of T_H2 activity along with increased circulating inflammatory markers in asthma patients could trigger systemic inflammation and, subsequently, SLE in the same individuals later in their lives. This hypothesis would emphasize the role of T_H2 class cytokines in the pathogenesis, which may warrant more attention from investigators.

Shared environmental risk factors

However, it is also possible that increased risk of SLE is a function of shared common environmental risk factors rather than shared immunopathogenic pathways. Cigarette smoking, for example, is a well-known risk factor for asthma.[17] Smoking is also associated with a significant increase in risk of SLE, which is probably mediated by oxidative stress causing DNA damage, epigenetic changes and the formation of anti-dsDNA and dysfunctional T and NK cells.[18]

Surveillance bias less likely

Lastly, it is also plausible that the observed increased risk of SLE in asthma patients was partly due to surveillance bias since patients with asthma are more likely to receive continuous medical care because of the chronicity of the disease. Nevertheless, it is unlikely that surveillance bias alone would entirely explain the increased risk, as patients are usually symptomatic from SLE and most patients would eventually seek medical attention.

Note: For a complete list of references, please visit: https://consultqd.clevelandclinic.org/assessing-the-relationship-between-systemic-lupus-erythematosus-and-asthma/

Case Report: Malar Rash, Polyarthritis, Positive ANA

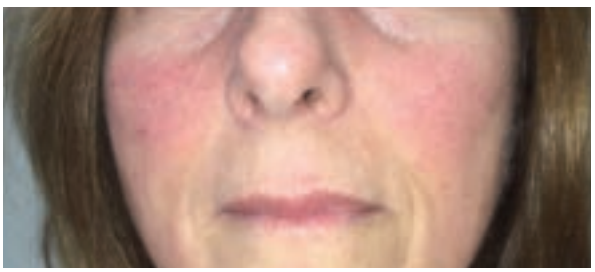
By Soumya Chatterjee, MD, MS, FRCP

A 58-year-old female with a history of cervical spondylosis and hypothyroidism presented with a two-week history of joint pain.[1] She reported that her pain and swelling began in the right knee, migrated to the right ankle, and finally to the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints of her fingers. On exam, the patient was afebrile with a malar rash. She had swollen and tender MCP and PIP joints. She had difficulty making a fist and extending her fingers.

Approximately two weeks before the patient's symptoms began, her 5-year-old grandson developed a febrile illness with headache, body aches, malaise, and rash on the cheeks, trunk and extremities, but no joint symptoms. The patient's 10-month-old granddaughter developed a similar illness 10 days later. Eight days before the patient presented, her 25-year-old daughter developed headache and malaise, with pain and stiffness of the wrists and knees, but no rash or fever. All the symptoms of her family members resolved spontaneously within seven days.

Initial laboratory studies revealed a mild normochromic normocytic anemia with a hemoglobin level of 11.5 g/dL, normal white blood and platelet counts, and normal results for a comprehensive metabolic panel. She had a positive antinuclear antibody (ANA) result (1:160 [homogeneous pattern; negative <1:80 serum dilution]). Her rheumatoid factor (RF) was negative; levels of inflammatory markers (ESR and C-reactive protein) were normal.

It was felt that with the pertinent recent family history, it would be premature to give her a diagnosis of a chronic autoimmune rheumatologic disease, such as systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA). On the other hand, the recent family history of exposure to children with fever and a facial rash suggested a possible diagnosis of erythema infectiosum (fifth disease).



Malar rash in a 58-year-old woman.

Laboratory studies reveal antibodies to parvovirus B19

Further laboratory studies revealed significant titers of IgM (15.04 index value) and IgG (6.45 index value) antibodies to parvovirus B19. Antibodies to cyclic citrullinated peptide, double-stranded DNA and antibodies to extractable nuclear antigens were all negative. The patient's symptoms resolved with prednisone 35 mg daily, which was tapered over a week. Six months later, repeat laboratory studies were negative for IgM antibodies to parvovirus B19 and ANA.

Symptoms of a viral infection may mimic the onset of a systemic autoimmune rheumatologic disease

Erythema infectiosum is common in children and is caused by human parvovirus B19. The infectious phase of the virus generally begins 24–48 hours before the earliest detectable symptoms and lasts until the associated rash resolves. Symptoms include fever, headache, sore throat, itching, cough, upset stomach, sneezing, conjunctivitis and muscle aches. These flu-like symptoms last approximately 5–7 days before the classic "slapped cheek rash" develops (which was thought to be a malar rash in our patient), which is sometimes followed by a maculopapular rash on the rest of the body. Although rare in children, joint symptoms are common in adults and tend to occur more frequently in women than men.[2] The nonerosive, often symmetric, arthropathy generally lasts for 1–3 weeks;[2] however, they can be more protracted and may mimic the onset of a systemic autoimmune rheumatologic disease such as RA or SLE. Both ANA and RF can be transiently positive, further confusing the picture. Other viral infections that can cause arthralgia and arthritis include Rubella, Hepatitis B and C, HIV, Chikungunya, Dengue, Ebola, Adenovirus, Enteroviruses and Herpesviruses.

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Collaborative Rheumatology-Dermatology Clinic Improves Outcomes

By Anthony Fernandez, MD, PhD, and M. Elaine Husni, MD, MPH

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CASE

A 49-year-old woman with psoriasis and psoriatic arthritis (PsA, arthritis mutilans subtype) sought care at Cleveland Clinic for active joint and skin symptoms. She was on infliximab at presentation, but was developing ongoing erosive disease.

Finding good treatment options for this patient was not straightforward. While living in China she had contracted latent tuberculosis (TB), which required adequate treatment before she could safely be started on many of the systemic medications that would be expected to improve her psoriatic disease. The patient sought the opinions of internists and dermatologists, who prescribed topical treatment. She also consulted with rheumatologists, who felt that although she continued to experience mutilans, there was no active joint disease to justify biologics in the setting of TB. The patient's quality of life worsened, and she withdrew from social activities due to flares of psoriasis and limited her travel due to worsening joint pains she suffered from long plane rides. Her joint exam remained quiet, with no active synovitis or enthesitis, but she did have persistent, intermittent right shoulder pain.

After evaluating the patient and discussing her case together, we initiated a systemic treatment (apremilast), which we felt had the efficacy and safety profile she needed. Although there are other treatment options that may have more robust response in terms of skin and joint efficacy, it took a collaborative approach with a dermatologist and rheumatologist to weigh the risks and benefits of further immunosuppression versus initiating another therapy and monitoring response. The patient's shoulder pain, which we could have easily attributed to PsA, was evaluated by an MRI. After further evaluation, she required rotator cuff repair. Three years later, the patient remains on apremilast and continues to enjoy relief from the painful skin lesions and disabling joint symptoms she had suffered from previously.

Comanagement clinics

Patients with psoriatic disease commonly have both skin and joint symptoms with heterogeneous presentations. Optimal treatment should rely on shared decision-making between patients with chronic inflammatory diseases and a multidisciplinary team that includes a rheumatologist and dermatologist.[1,2]

At Cleveland Clinic, we have historically taken a collaborative, multidisciplinary approach to patients with complex disease processes such as PsA. Our collaborative dermatology-rheumatology clinic has increased connectivity between the two disciplines, improved patient outcomes, and increased opportunities for education and research.

Improved patient outcomes

Patients with both skin and joint symptoms of psoriatic disease report a significantly impaired quality of life compared with the general population, including greater emotional burden, worse health status, and increased disability and work impairment.[3] However, patients, rheumatologists and dermatologists seem to perceive

Drs. Husni and Fernandez review a case together in the Cleveland Clinic Dermatology and Rheumatology Collaborative Care Center.

continued on page 11

Elucidating the Pathophysiology of Susac Syndrome

By Adam Brown, MD, Rula A. Hajj-Ali, MD, and Leonard H. Calabrese, DO

A rare immune-mediated disease

Susac syndrome is an uncommon immune-mediated disease affecting the eyes, ears and brain in a triad of vision loss, hearing loss and encephalopathy. It's unclear why these organs are targeted in this condition. In the eye, branch retinal artery occlusions cause ischemia to parts of the retina, leading to patches of vision loss. In the ear, the most distal parts of the blood supply of the cochlea are affected. As a result, the patient experiences low frequency hearing loss, which can be more profound as the disease progresses. When the corpus callosum is involved the symptoms can be broad, ranging from headaches and mood changes to severe encephalopathy.

Diagnosis is often made following MRI of the brain; the ischemic lesions in the corpus callosum are referred to as "snowball lesions."

Susac syndrome is rare; the true incidence and prevalence are unknown. It is more commonly seen in females compared to males in a 3.5-1 ratio.[1]

Alterations of the blood vessels appear to be a focus of the disease pathology, causing decreased blood flow and ischemia to the affected organs. Usually when we're talking about blood vessel pathology in rheumatology, we're referring to a vasculitis, but in Susac syndrome the pathology is noninflammatory, categorized as a vasculopathy and, more specifically, an endotheliopathy. An endotheliopathy occurs when the endothelial cells lining the blood vessel swell, occluding the lumen of the vessel as well as disrupting the normal cell-to-cell barrier of the vessel. The cause of the endothelial swelling is unknown. The histology of the small affected blood vessel of Susac syndrome demonstrates the endothelial swelling, but not an influx of immune cells as is typically seen in a vasculitis.

Cleveland Clinic Susac syndrome team

The best approach to care for patients with Susac syndrome is through a comprehensive team of specialists. At Cleveland Clinic, we have organized a team of specialists including ophthalmology, neuroimmunology, otolaryngology and rheumatology to care for these complex patients. Our Susac team at Cleveland Clinic has evaluated more than 100 patients for suspected Susac syndrome. Our team includes rheumatologists Adam J. Brown, MD, Leonard H. Calabrese, DO, and Rula Hajj-Ali, MD; neuroimmunologists Devon Conway, MD, and Ghulam Abbas Kharal, MD, MPH; ophthamologists Sunil Srivastava, MD, and Sumit Sharma, MD; and otolaryngologists Erika Woodson, MD, Anh Nyguyn-Huynh, MD, and Thomas Haberkamp, MD. Considering the rarity of this syndrome, we will be working with multiple institutions to better understand this disease.

Goals of research

Currently, no robust outcome data exist to outline the disease course or what type of therapy is most effective in Susac syndrome. Treatment consists of aggressive immunosuppression, but the level of aggression depends on the severity of the disease. A patient with only a headache will not be treated as aggressively as a patient with vision loss and confusion.

One goal of our team is to better understand how patients with Susac syndrome do over time, as this will give us a better understanding of how aggressive treatment needs to be upfront and how long therapy needs to be continued.

The pathophysiology of Susac syndrome is incompletely understood. A group in Germany has evaluated the role of CD8+ T cells in Susac syndrome, demonstrating the cells may have a role in the disease, expressing cytokines such as tumor necrosis factor (TNF) and interferon.[2] We have many medications that inhibit specific cytokines in rheumatology; if the cytokines involved in Susac syndrome are better elucidated, a more targeted approach to therapy could be pursued. One of the goals of our team is to better elucidate the underlying cytokine biology using cell-based techniques, such as transcriptomics, to gain insight into the roles of interferon and other cytokines in Susac syndrome, potentially providing new therapeutic targets for this rare condition.

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

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Teaching Empathy to Medical Students

By 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.

What qualities make a good doctor? Medical schools tend to favor students who score high in biology, chemistry or other science; demonstrate leadership; and are driven to succeed. Curiosity, doggedness, a keen memory and the ability to think deductively are also highly valued.

What about empathy? Research has shown empathy in physicians is associated with kindness and a good bedside manner. Empathy also correlates with satisfying personal growth, decreased burnout, increased patient satisfaction and lower rates of being sued. Empathetic medical students appear to be more competent and are likely to receive greater recognition for their achievements.

With so many positive associations, empathy should be as highly valued as other traits. At Cleveland Clinic Lerner College of Medicine (CCLCM), it is. Empathy has been part of the curriculum since the medical school opened in 2002.

Empathy is not an option: It is at the core of what we do, which is why we embrace it.

Empathy in medical students

My interest in teaching empathy to medical students attracted the attention of the American Association of Colleges of Osteopathic Medicine (AACOM), which decided to explore how empathy was being taught to DO medical students nationwide. The resulting Project in Osteopathic Medical Education and Empathy (POMEE) is a groundbreaking, nationwide, multi-institutional study in medical education sponsored by AACOM in collaboration with the American Osteopathic Association, Cleveland Clinic and Sidney Kimmel Medical College at Thomas Jefferson University.

POMEE collected data on nearly 10,000 students from all 41 DO medical colleges in the United States. These data have served as a rich resource for many studies I have undertaken with Dr. Hojat.

One recently published study in *Academic Medicine* explored whether empathy declines during medical education in DO- and MD-granting schools.[1] Previously, a significant decline in empathy scores was documented in year three, when students move from preclinical to clinical phases. The POMEE study suggested that osteopathic medical students underwent a lesser decline in empathy than that previously described in MD students.

Dr. Hojat and I began searching for reasons that might explain this observation, in hopes of finding lessons that could apply to the broader topic of empathy in healthcare.

We found that higher scores on the Jefferson Scale of Empathy throughout medical school among DO students appear to be associated with their belief in the osteopathic philosophy of integrative care.

I interpret these findings as support for the notion that illness does not belong solely to the body or to the mind, but rather to the individual as a whole — a philosophy espoused by Eric Cassell in *The Nature of Healing*. I keep a copy of this book on my desk. It guides my personal philosophy of patient care and my goals in teaching the "Art and Practice of Medicine" course.

Another study looked at associations between empathy in patient care and gender, age, race, ethnicity, academic background and career interest in U.S. medical students.[2]

As in previous studies, empathy was found to be more prevalent in women than men and in students with undergraduate majors in social and behavioral sciences and arts and humanities.

But high empathy scores in underrepresented African American and Hispanic medical student groups stood out. Perhaps these students are taking on the role of the "wounded healer": They know about suffering and have a better view of the common experience. We need to explore this further.

Implications

Empathy is not evenly distributed across trainees or practicing physicians and providers. For professors of

medicine, this makes cultivating a climate of empathy a challenge, as well as an opportunity.

There is a growing body of data on how empathy may be cultivated in healthcare. Interventions including cultivating reflective practice through techniques such as appreciative inquiry, engaging in narrative writing, interacting with the arts and practicing mindfulness have the potential to enhance empathy. We explore all these techniques in my CCLCM course entitled "The Art and Practice of Medicine," which I teach to third-year medical students.

Our organization values empathy, which is why we teach relationship-centered healthcare communication to our medical students. I believe we are on the right track for this mission, which is needed as much as science.

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2 *Hojat M, DeSantis J, Shannon SC, Speicher MR, Bragan L, Calabrese LH. Empathy as related to gender, age, race and ethnicity, academic background and career interest: a nationwide study of osteopathic medical students in the United States.* Med Educ. *2020 Jun;54(6):571-581.*

Collaborative Rheumatology-Dermatology Clinic Improves Outcomes

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disease symptom burden and quality of life very differently. To better understand this variability, a study was conducted to survey these differences among the patient, the rheumatologist and the dermatologist, and to identify themes that could improve health outcomes.

Being together and making decisions together about which medicines may best treat the entire patient — what's going on with the skin, joints and other organ systems — can be very beneficial for patients. Real-time comanagement and connectivity may enhance this assessment, accelerating the pace of putting the patient on appropriate medication, switching or adding medications if we need to, educating the patient, etc., depending on the severity of the skin and joint issues.

Tremendous educational experience

Comanagement clinics, where dermatologists and rheumatologists are together with our trainees, can be very educational. With comanagement clinics, dermatology trainees will learn about the perspective of rheumatologists just from the conversations we have in clinic together, and rheumatology trainees will develop an understanding of the dermatologic evaluation and treatment paradigms. This is a tremendous educational opportunity, as these trainees will carry that understanding with them into their future practices.

Increased research opportunities

Although we understand the pathophysiology of these immune diseases much more now than we did just 10 years ago, we still have an enormous need to better delineate their molecular pathways and be more precise in our treatment algorithms. With two physicians from different backgrounds and specialties in the same space, research concepts will emerge, offering more opportunities to grow cross-disciplinary research and ultimately contributing to better understanding and treatment of these diseases.

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Longitudinal Variation in ANA Titers

By Emily A. Littlejohn, DO, MPH

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Risk factors for developing subclinical autoimmunity and predictors for progression to clinical autoimmune phenotypes are poorly understood. An important step is to understand trajectories of antinuclear antibody (ANA) positivity and titers within individuals over time, and factors associated with these changes.

As part of the Gary S. Gilkeson Career Development Award from the Lupus Foundation of America, we performed an exploratory analysis of electronic health record (EHR) data to assess intraindividual variation in ANAs longitudinally. This work is in conjunction with Kelly Speth, MS, Liu Wang, PhD, and Emily Somers, PhD, ScM, of the University of Michigan; and Jinoos Yazdany, MD, MPH, of the University of California, San Francisco.

Utilizing records from 1999 through the present from our academic health centers' EHRs, we extracted ANA (by immunofluorescence assay, IFA) and basic demographic data for all patients with at least one ANA. We also extracted ANA data for a subset of patients with validated systemic lupus erythematosus (SLE) by Systemic Lupus Erythematosus International Collaborating Clinics or American College of Rheumatology criteria. A titer of $\geq$ 1:80 was considered positive and a titer of $<$ 1:80 was considered negative. We investigated the overall trend in ANA titer between each patient's first and last observation by summarizing the number (and percentage) of SLE and control patients with a titer decrease, titer increase or stable titer. We evaluated changes in ANA titer over time using a baseline-category logit mixed model with a patient-level random intercept where a separate fixed parameter for time was obtained for each comparison of a non-negative titer relative to a negative titer. We then estimated the odds of having a decreased titer value relative to a stable/increased titer at the next successive draw for various covariates using a generalized linear model.

A total of 6,546 unique patients had at least two valid ANA-IFA results. A subset of 52 of these patients had validated SLE; the remaining patients were considered controls. Patients were primarily female (85%) and non-Hispanic (90%), with a median age of 50 years. The mean number of valid ANA titers per patient was 2.6 (SD = 1.4), with a range of 2 to 20.

Intra-individual variability

Longitudinally, ANA titer strength varied ($P < 0.001$). With the exception of higher average odds of having a positive titer with each successive year (OR 1.84 [95% CI 1.62 – 2.09]), no clear pattern of change between titers was identified (Figure 1). However, when evaluating the outcome of having a titer decrease (versus stable/increase) at the

Table 1. Summary of changes for ANA titer (as an ordinal variable) from first to last observation over time.

	Controls	SLE	Total
Titer Increase	2,181 (33%)	11 (21%)	2,192 (33%)
No Change	2,129 (33%)	23 (44%)	2,152 (33%)
Titer Decrease	2,184 (34%)	18 (35%)	2,202 (34%)
Totals	**6,494**	**52**	**6,546**

next successive observation, 32% of successive ANA draws had a decreased titer relative to the preceding titer. Among persons who were ANA-positive at baseline, 1,118 (22%) of the control subjects and two (4%) of the SLE subjects subsequently had a negative ANA. Among the SLE cases, titers decreased in 29% of successive draws (Figure 2). Controlling for basic demographic characteristics, being male increased the odds of having a decreased titer at the next successive draw (OR: 1.24 [95% CI: 1.11 – 1.40]). Each successive year between ANA titers increased the odds of having a decreased titer (OR: 1.02 [95% CI: 1.01-1.04]).

Although prior series of cross-sectional data suggest that ANAs tend to increase with age, longitudinal data of intra-individual patterns are lacking. Our data provide initial evidence of intra-individual variability. What is most novel about our findings is the downward trend of successive ANA titers and their variability over time. The common clinical perception is that in SLE, ANAs remain positive once antibodies are accrued and that repeat testing would not influence management or alter diagnosis. Our data suggest that ANA titers may be more dynamic than previously accepted. We plan to investigate demographic and other covariates to further discern titers in different clinical phenotypes over time.

Figure 1. Spaghetti plot of ANA titers over time, with nine randomly selected patients per panel, for visualization purposes.

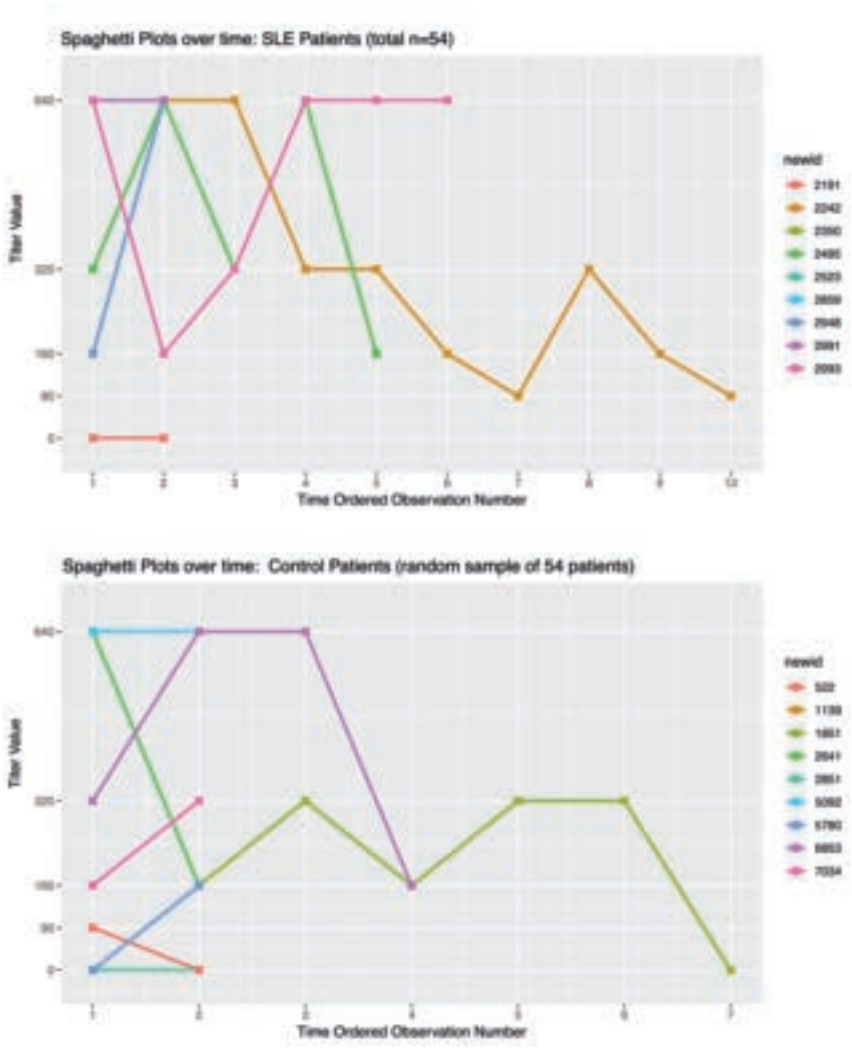
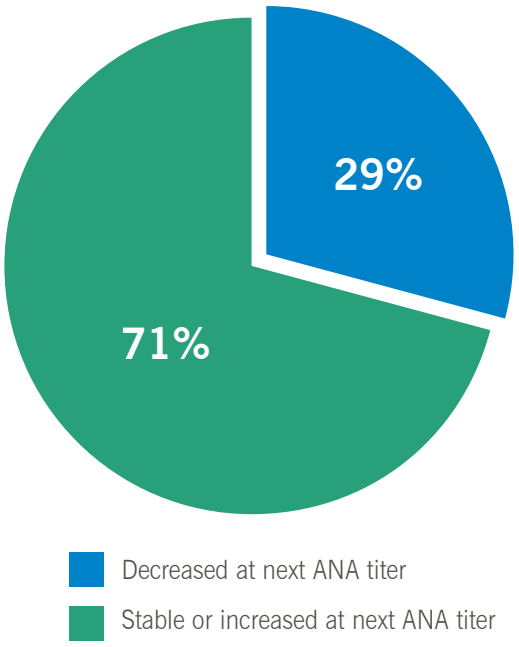


Figure 2. Proportion of SLE patients with changes in successive ANA titers relative to the prior titer.



Paget's Disease in a 36-Year-Old Patient?

By Sarah Keller, MD, MA, Leila Khan, MD, and Chad Deal, MD

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A 36-year-old man presented to the metabolic bone clinic with two years of fatigue in the setting of high serum alkaline phosphatase (149 U/L , normal range 38 - 113 U/L). The patient reported bilateral thigh pain when doing physically intense labor; however, he denied additional symptoms. Medical history included vitamin D deficiency, gastroesophageal reflux disease and depression. There was no history of a fragility fracture. Medications at the time of presentation included vitamin D3 supplementation at a dose of 2,000 international units daily, omeprazole 20 mg daily and fluoxetine 20 mg daily.

Serum vitamin, D 25-hydroxy was 26.7 ng/dL (normal range 31 – 80 ng/mL). Serum calcium and parathyroid hormone were within normal limits. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT) and bilirubin were within normal limits. The bone fractionation of alkaline phosphatase was elevated at 28.6 uG/L (normal range 6.5 – 20.1 uG/L). A whole-body nuclear bone scan obtained at an outside facility and interpreted by a Cleveland Clinic radiologist demonstrated heterogeneous and moderately intense uptake in the calvarium, the bilateral upper extremities (bilateral humeral diaphysis and bilateral radius) and bilateral lower extremities (distal femurs, proximal tibia and distal fibula). Uptake in the left femur was interpreted as having a “blade of grass” appearance, a classic finding in Paget's disease. The impression of the bone scan was that findings could be consistent with the secondary phase of Paget disease; however, evaluation was limited as the study was obtained at another institution. Plain radiographs of the left lower extremity demonstrated patchy areas of sclerosis and lucencies in the distal femur and proximal tibia, corresponding to the regions of increased uptake on bone scan. A positron emission tomography and computed tomography scan obtained at an outside facility concluded that none of the sclerotic lesions demonstrated any fluorodeoxyglucose avidity. MRI of the bilateral lower extremities demonstrated large areas of heterogeneous low T1 signal and increased T2 signal throughout the bilateral femurs, tibia, fibula and visualized pelvis/sacrum. MRI raised the question of a diffuse bone marrow infiltrative process.

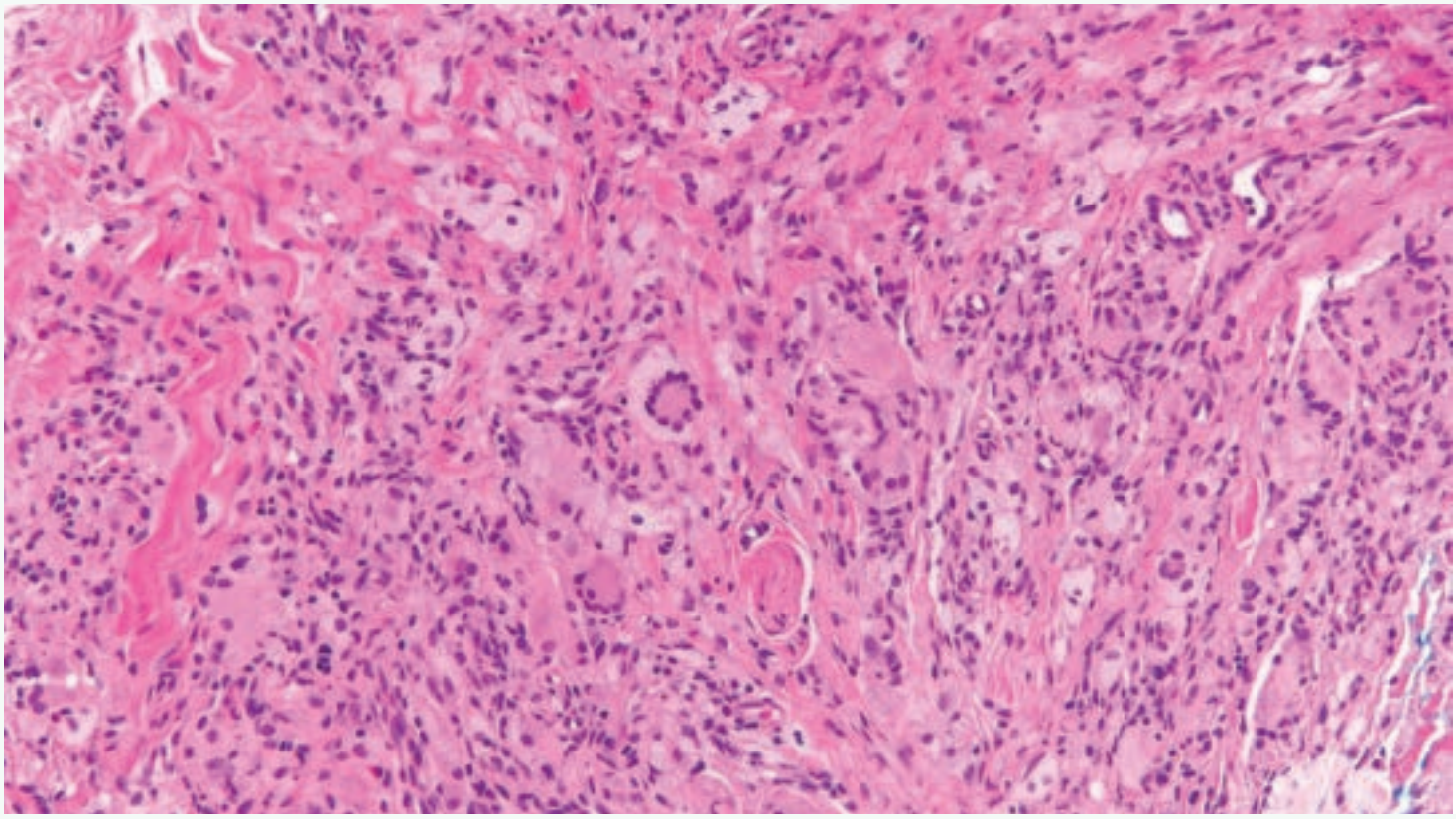
More information needed

The constellation of findings in this case was puzzling. While the elevated alkaline phosphatase and the findings on the bone density scan and radiographs raised the question of Paget's disease, several aspects of this case did not fit with this diagnosis. First, Paget's disease is rarely diagnosed before the age of 40, with increasing incidence over the age of 60.[1] Second, despite the “blade of grass” finding, the high intensity of uptake on the bone scan was more suggestive of that seen in metastatic disease or bone marrow reconversion and was not typical of Paget's disease.[1] The lucency and symmetry of lesions in the appendicular skeleton led to the following potential causes: medullary bone infarctions, malignancy, bone marrow reconstitution and Erdheim-Chester disease (ECD). Given the need for more information, the decision was made to pursue a CT-guided bone biopsy.

An unusual diagnosis

Bone biopsy of the femur demonstrated fibrohistiocytic proliferation of CD68-positive foamy histiocytes mixed with fibrosis and occasional lymphocytes. The pathologic diagnosis was ECD.

A malignancy of histiocytes from the monocyte-macrophage lineage, ECD is caused by mutations of *BRAF* and other signaling molecules in myeloid progenitor cells. While ECD is reported as a rare disease, its true incidence is not known, and it is thought that the disease incidence is under-represented in the literature.[2] According to one systematic review of 259 patients with ECD, the long bones were almost always involved, and the most common clinical manifestations included skeletal involvement (26%), neurologic symptoms (23%), diabetes insipidus (22%), constitutional symptoms (20%), retroperitoneal involvement (14%), pulmonary symptoms (12%), cutaneous involvement (11%), cardiovascular manifestations (6%) and other pituitary involvement aside from diabetes insipidus (3%).[2]



Punch biopsy shows diffuse dermal infiltrate of bland cells with pale cytoplasm. This image was originally published in Morgan E, Patel S. Erdheim-Chester disease. *ASH Image Bank.* 2018;00061844. ©The American Society of Hematology.

A multidisciplinary approach is essential

ECD is primarily treated by oncology, and this patient was referred to oncology following bone biopsy for staging and chemotherapy.[3] However, the complications that can arise in this disease and the myriad clinical manifestations require a team approach. In this case, ECD has been further complicated by the development of diabetes insipidus, for which the patient is being treated with desmopressin, as well as by primary hypogonadism, for which he will likely be treated with testosterone, highlighting the need for close follow-up with endocrinology.

This case underscores the need to maintain a high index of suspicion for diseases that can mimic rheumatic processes as well as the essential nature of the multidisciplinary approach to the evaluation and management of patients with complex presentations of rare diseases.

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