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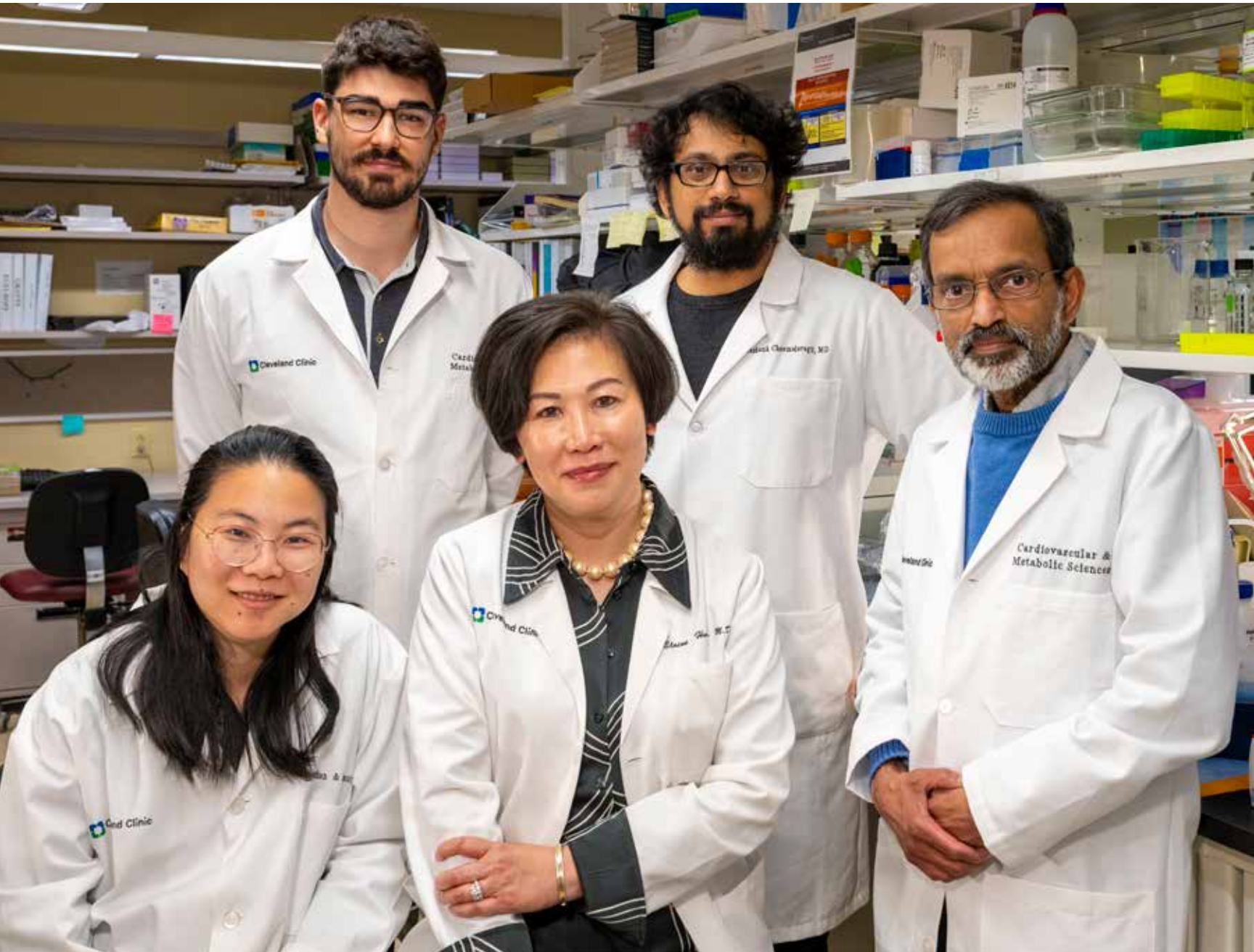
Cleveland Clinic

Rheumatology Connections

An Update for Physicians | Summer 2024



From the Chair of Rheumatic and Immunologic Diseases

Dear Colleagues,

Those of us who have the privilege of caring for individuals with rheumatic diseases have been fortunate to experience the profound and positive impact that basic, translational and clinical discoveries have had on our patients' lives. Individuals who had suffered from chronic multisystem immune-mediated diseases have benefited from the scientific advancements in our field, and they are now experiencing improvement in their pain, function and longevity. In this issue of *Rheumatology Connections*, we share some articles about exciting areas of research in our department that are examples of these initiatives.

Our cover story (page 8) highlights the work of Dr. Elaine Husni and her colleagues in the Husni Laboratory. The team's translational research focuses on psoriatic disease. Here you will read about their study of the pathogenic roles of specific TNF-α receptors as a well as biomarkers that might predict which patients with psoriasis are likely to develop psoriatic arthritis.

On page 3, Dr. Emily Littlejohn discusses the evolution of CAR T-cell therapy and the rationale for its use in treating systemic lupus erythematosus. Positive results from a small study in Germany have led to a multicenter research study in which we are proud to be participating.

I am very pleased to share progress on two of our programs aimed at streamlining and enhancing care for focused patient populations. Dr. Melany Gonzalez Orta discusses the work being done at our new Hispanic clinic for rheumatology (page 5) to eliminate language, cultural and accessibility barriers. And Dr. Adam Brown explains the importance of coordinated care in treating patients with Ehlers-Danlos syndrome (page 12).

Case studies by Dr. Soumya Chatterjee and by Drs. Taylor Koenig and Kinanah Yaseen offer insights into the coexistence of erythromelalgia and Raynaud's phenomenon (page 11) and ulcerative keratitis in untreated rheumatoid arthritis (page 14), respectively.

We offer a look at the ever-popular Basic and Clinical Immunology for the Busy Clinician symposium, begun more than a dozen years ago by Dr. Leonard Calabrese, head of Clinical Immunology and the R.J. Fasenmyer Chair of Clinical Immunology (page 7).

Finally, I hope you will join me in celebrating Dr. Carol Langford's recent appointment to the Editorial Board of *Harrison's Principles of Internal Medicine*, 22nd Edition. In our Q&A (page 10), Dr. Langford shares insights into her history with this valuable resource.

As always, I encourage you to contact me with feedback about this issue or if you see an opportunity to collaborate or consult with our team.

Respectfully,

Abby G. Abelson

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On the cover
Members of the Husni Laboratory team are pictured clockwise from top left: Vincent Del Signore; Shashank Cheemavalagu, MD; Unnikrishnan Chandrasekharan, PhD; M. Elaine Husni, MD; and Jean Lin, PhD.

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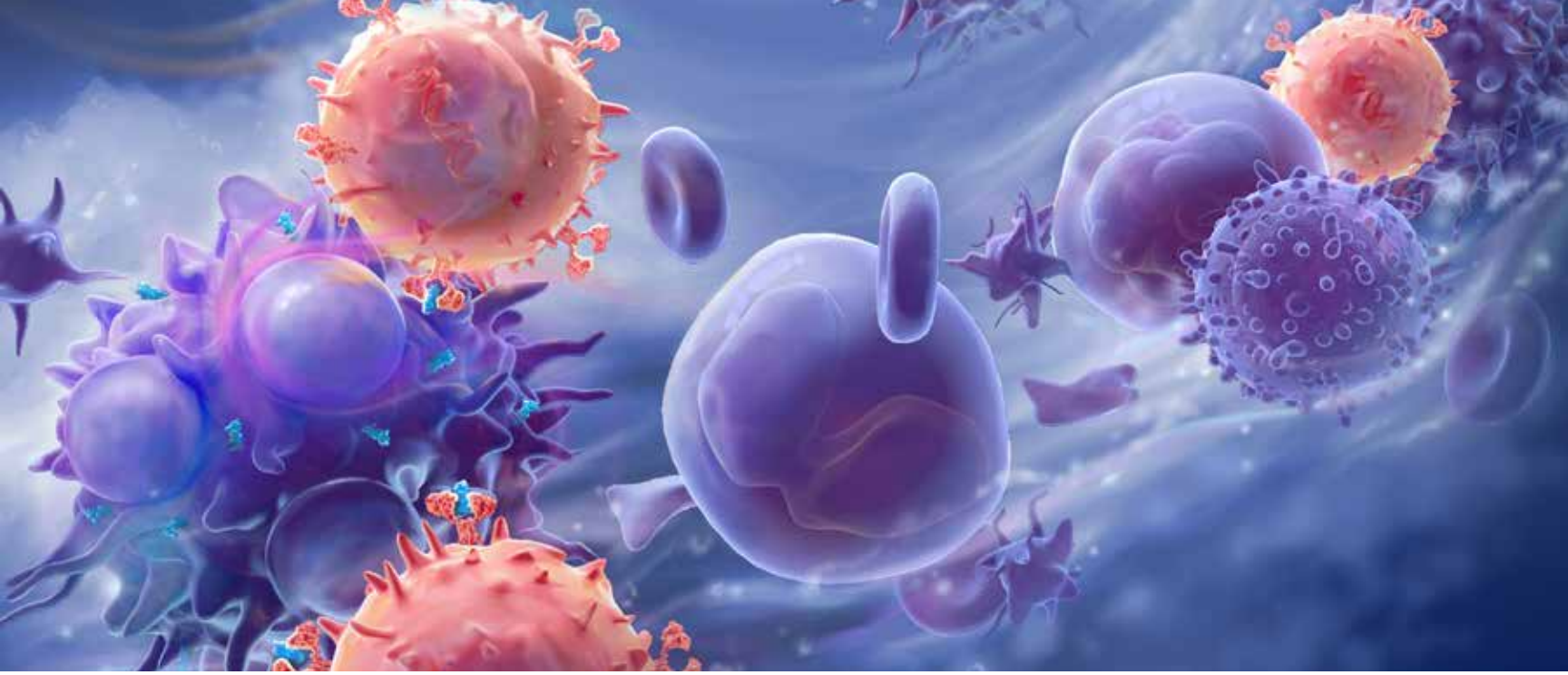
CME Opportunities: LIVE AND ONLINE

Visit clevelandclinic.org/rheumcme for the full slate of continuing medical education from Cleveland Clinic's R.J. Fasenmyer Center for Clinical Immunology. And save the date for Cleveland Clinic's Biologic Therapies Summit XI & Vasculitis 2025. The conference will take place May 8-10, 2025 at the InterContinental Hotel & Conference Center in Cleveland, OH.



The CAR T-Cell Therapy Evolution and Its Use in Systemic Lupus Erythematosus

by Emily Littlejohn, DO, MPH

Dr. Littlejohn (littlee3@ccf.org; 216.445.5559) is Staff in the Department of Rheumatic and Immunologic Diseases.

International research is underway to examine the use of engineered T-cell therapy for adults with severe, refractory systemic lupus erythematosus (SLE). This presents an opportunity to consider chimeric antigen receptor (CAR) T-cell treatment in a larger context, and what it might mean for the future management of autoimmune diseases.

Beginning in 2017, CAR T therapies have been approved for treatment of blood malignancies. Phase 2 and 3 trials are now taking place to examine CAR T for a number of solid cancers as well as for human immunodeficiency virus (HIV).

For those of us in rheumatology working to advance options for our patients with SLE, an ongoing international phase 1 trial[1] at Cleveland Clinic is expected to supply much-needed data on safety, efficacy and follow-up. As we consider the potential of CAR T therapy for autoimmune diseases, it is important to review and understand what we have learned so far.

Living drugs

CAR T cells are sometimes referred to as "living drug" immunotherapy. Chimeric antigen receptors (also referred to as chimeric immunoreceptors, chimeric T-cell receptors or artificial T-cell receptors) are proteins that have been engineered to give T cells the new ability to target a specific antigen. They are chimeric because they combine both antigen-binding and T-cell-activating functions.

Treatment begins with isolating a patient's white cells through apheresis and then selecting the T cells (CD4+ and CD8+) to be transfected with the coding DNA necessary to produce a new receptor capable of recognizing a target antigen. (In the case of current SLE trials, that is anti-CD19.) CAR T cells are then expanded ex vivo.

Next, the patient is given intravenous chemotherapy for leukodepletion, with the intention to make space for T-cell expansion and "prime" the cytokine environment. The CAR T cells are then reinfused into the patient. Once the CAR cells bind to target cells, the innate signaling can turn on machinery to destroy the cell that is recognized (B cells).

With every new medical treatment or therapy comes risk of side effects. In the case of CAR T therapy, there are two that are most worrisome: cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS).

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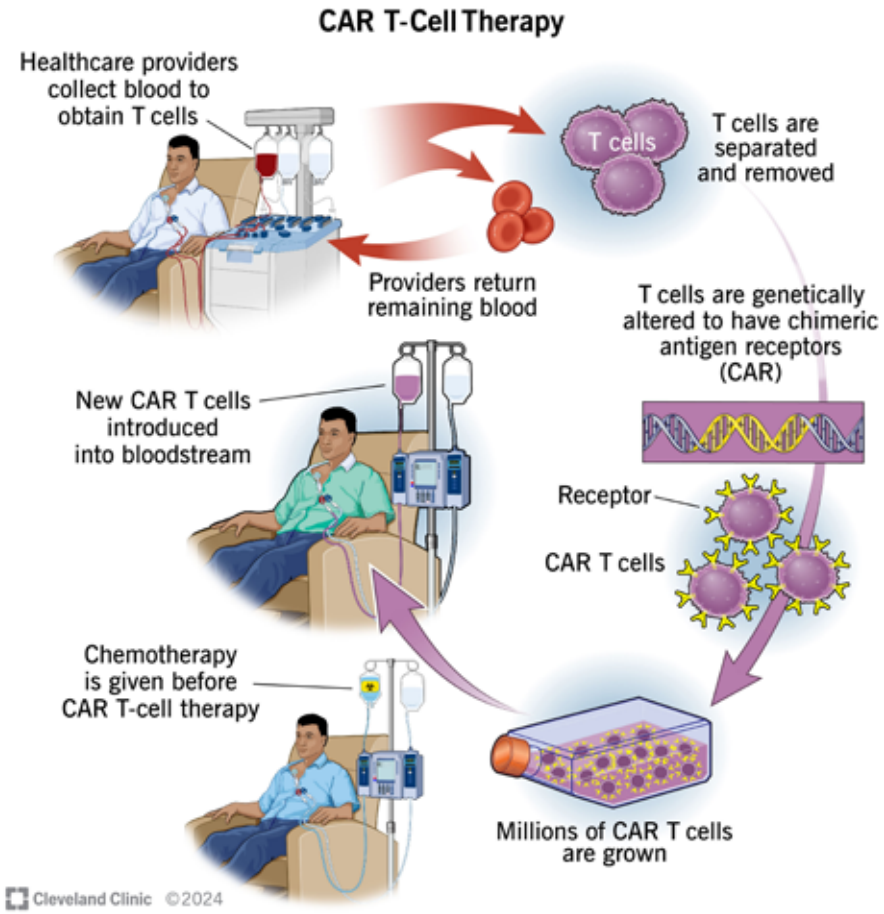

Cytokine release syndrome

When CAR T cells bind to their target antigen, they proliferate and produce cytotoxic molecules that mediate the destruction of tumor or target cells: interferon-γ, granulocyte macrophage colony-stimulating factor, IL-10 and IL-6. Cytokines and/or cytokine storms can cause increased vascular permeability and third-spacing of fluid, which can result in vasodilation, decreased cardiac output, and intravascular volume depletion. Common features of CRS include fever, hypotension and hypoxia. Severe CRS can evolve into fulminant hemophagocytic lymphohistiocytosis (HLH), which requires inpatient treatment.

Management of CRS typically includes use of tocilizumab with steroids. Other agents, including siltuximab (Sylvant), infliximab (Remicade), etanercept and anakinra also have been used in clinical trials. Tocilizumab has not been shown to adversely affect the efficacy of CAR T-cell therapy.

Because corticosteroids are known to suppress and/or kill T cells, it is prudent to avoid their use for non–CAR T-cell–related adverse effects.

Immune effector cell–associated neurotoxicity syndrome

More serious side effects can include neurological symptoms, with or without CRS. Symptoms may include confusion, agitation and delirium and, in severe cases, receptive or expressive aphasia, obtundation, convulsive or nonconvulsive seizures, and cerebral edema. This may be due to greater blood-brain permeability allowing the therapeutic treatment to reach the central nervous system.

Management depends on severity. Low-grade neurologic events can be managed primarily with supportive care. For patients with grade ≥ 1 neurologic events with concurrent CRS, tocilizumab is recommended. Neurologic events without concurrent CRS do not respond to anti–IL-6 therapy. Grade ≥ 2 neurologic events not associated with CRS can be treated with corticosteroids, dose dependent on the grade of the event.

The rationale for use of T-cell therapy for autoimmune diseases

The hallmark association of systemic lupus erythematosus with a diverse range of autoantibodies (anti-dsDNA and anti-Sm antibodies), and the presence of immune complex deposition in various tissues, makes depletion of B cells of interest in treatment of SLE. B cells and their multiple subtypes, including plasmablasts, have pathogenic capabilities beyond antibody production. This has led to an interest in them as therapeutic targets.

Histopathology studies of patients with antisynthetase syndrome have shown the presence of B cells and plasmablasts adjacent to T cells in the affected muscles. This condition is also associated with changes in the profile of peripheral B cells. B-cell–depleting therapy with rituximab has been efficacious in a subset of patients with antisynthetase syndrome, which supports the pathogenic role of autoreactive B cells.

Many previous B-cell-directed therapies have not reached primary endpoints or produced positive or consistent results. They have failed to achieve deep tissue depletion of B cells and shown an inability to target late-stage B cells such as plasmablasts, which are implicated in disease pathogenesis.

State of the research

Results of recent studies of CAR T-cell therapy in SLE and antisynthetase syndrome have offered rationale for further research.

In 2022, *Nature Medicine* published results of a study[2] from a single site in Germany, in which four women and one man, aged 18 to 24, received compassionate use of anti-CD19 CAR T therapy for their severe, refractory SLE. All had multiorgan involvement and failed to respond to

multiple therapies, including pulsed glucocorticoids, hydroxychloroquine, belimumab, azathioprine, mycophenolate mofetil, cyclophosphamide and rituximab.

Following treatment, nephritis ceased in all five patients. Arthritis, fatigue, fibrosis of cardiac valves and lung restriction/diffusion impairment disappeared. INF-α, which had been present in three patients at enrollment, was undetectable in all patients at follow-up. All DMARD/immunomodulatory drugs, including hydroxychloroquine and steroids, were discontinued. Two patients sustained mild CRS. Of note, CRS risk appeared to be much lower than what is seen in studies of CAR T-cell therapies for malignancies.

The study was limited by its small sample size and follow-up data, which ranged from five to 17 months. More recent data indicate that one patient has remained in drug-free remission for 600 days. As of early 2024, all patients with SLE had met Definition Of Remission In SLE (DORIS) criteria. Median follow-up was 15 months.[3]

A study[4] assessing the efficacy of the therapy on two patients with antisynthetase syndrome showed similar results. Both patients experienced normalization or significant reduction in CK levels (patient 1: CK+120 days: 70 U/L; patient 2: CK+60 days: 311 U/L) and were able to stop all immunosuppressive therapy. Follow-up CT scans of the lung and MRI of the thigh done in patient 1 showed resolution of alveolar inflammation and mitigation of inflammatory changes in the thigh muscles and the hamstrings. Highly positive anti-Jo1 antibodies (331 U/L) disappeared after CAR T. Both patients reported near-total elimination of their severe symptoms within about four months of dosing. At the latest follow-up (120 days and 60 days), both patients were in drug-free remission.

Multicenter studies using CAR T therapy that are now under way in the U.S. and Europe stand to offer new insights into approaches for addressing unmet needs in some of rheumatology's most difficult diseases. It is our hope that CAR T therapy will one day be a life-changing therapeutic option for all our patients.

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A Rheumatology Home for Spanish-Speaking Patients

Dr. Melany Gonzalez Orta meets with a patient at the Hispanic clinic.

When healthcare providers speak of the importance of "meeting patients where they are," they often mean communicating with empathy and understanding about an individual's mindset or emotional state. It can be just as crucial, however, to literally meet patients in their own neighborhoods, and to remove language and cultural barriers that can get in the way of the best care.

With that in mind, Cleveland Clinic rheumatologist Melany Gonzalez Orta, MD, now spends one day each week at the health system's Lutheran Hospital, located in a West Side neighborhood that is home to higher percentages of Cleveland's Hispanic and Latino communities. Starting in February 2024, rheumatology joined other specialties—internal medicine, urology, female incontinence, psychiatry and psychology, and nephrology—at Lutheran's Hispanic clinic.

The purpose of the clinic is to meet the unique needs of the Hispanic community, both through physical proximity and by ensuring that patients can meet with Spanish-speaking staff and receive written information in Spanish.

Dr. Gonzalez became interested in providing such a service while she was doing her rheumatology fellowship at Cleveland Clinic's main campus.

"One of the reasons why rheumatology is fascinating is that our diseases don't tend to be clear cut," she says. "Getting a detailed history is key to building a differential diagnosis. Testing can be confusing for patients to interpret, and treatment can be challenging to navigate. Hispanic populations rely on multiple idioms, depending on the country of origin, to communicate."

Even with excellent interpreters, sometimes patients can struggle to communicate about the nuances of symptoms and care.

Continued on next page

As a clinician who speaks Spanish, Dr. Gonzalez often saw the Spanish-speaking patients.

"I noticed some patients were not very compliant with recommendations made by other providers," she says. "When I started talking to them, it became clear it didn't have anything to do with the providers themselves. It was that the patients felt that they couldn't really express themselves fully. So that sometimes resulted in not following through or non-adherence to medications."

In addition to communication barriers, traveling to appointments across town also was complicated for patients from lower-income households, who often have to rely on public transportation.

A place that feels like home

Reducing barriers around medical visits can make a substantial difference in the patient experience.

"For a Spanish-speaking person going into Lutheran, it is like another world. Every corner has a Spanish-speaking provider, so you feel part of that community," says Dr. Gonzalez. "That encourages patients to actually go to their appointments because they don't find barriers. If they have to leave the exam room to get labs or X-rays, they'll still find staff members who speak Spanish. And when I see Spanish-speaking patients, I make sure discharge instructions are in Spanish and all communications in my chart are also in Spanish."

Statistics on incidence of rheumatic illness among Spanish-speaking populations are in short supply.

"We see a lack of appropriate representation of Hispanic patients in trials and studies because of socioeconomic limitations," she says. "Many of them live in poor socioeconomic conditions. They may lack health insurance, so they underuse health services."

One of her goals is to learn more about the prevalence of rheumatic diseases in the Hispanic population, she says.

Getting the word out

The first steps necessary to starting the rheumatology clinic at Lutheran Hospital included carving out space and putting the scheduling apparatus in place. Now patients with rheumatologic issues are offered an appointment there, regardless of whether they speak Spanish.

Promotional efforts include updating Dr. Gonzalez's biographical information and publishing news of the clinic in a Spanish-language newspaper in Cleveland.

The question of how to measure success will evolve as use of the clinic evolves.

"I will consider it successful if I am able to help the Hispanic population feel better managing their chronic rheumatic diseases without a language barrier," she says. "We hope this results in increased treatment adherence and fewer disease flare-ups and complications."

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Basic and Clinical Immunology for the Busy Clinician

12 years (and counting) of bringing new knowledge to the fore

Years ago, Leonard Calabrese, DO, head of Cleveland Clinic's Section of Clinical Immunology and the R.J. Fasenmyer Chair of Clinical Immunology, believed that advances in basic and clinical immunology were occurring so rapidly that many busy clinicians were being overwhelmed by data. Especially for those who never spent time in basic research or who worked outside of academic programs that routinely discussed such developments, it could be difficult to stay on top of important developments.

New targeted therapies, new immunologic pathways and, more recently, findings surrounding the biology of COVID-19 can hinder clinicians' confidence in treating patients with immune-mediated inflammatory diseases.

To address this unmet need, Dr. Calabrese collaborated with well-known immunologists and master teachers on a plan to present new data in a readily translatable manner and style. Together with William F.C. Rigby, MD, of Dartmouth; Gregg Silverman, MD, of New York University; and R. John Looney, MD, of the University of Rochester, Dr. Calabrese developed an annual symposium, Basic and Clinical Immunology for the Busy Clinician.

In February 2024, the 12th such meeting took place in Arizona (and online), and the program is still going strong.

Cleveland Clinic rheumatologist M. Elaine Husni, MD, MPH, eventually became a course director, focusing on advances in targeted therapies with world-class teachers who approach these new developments in a similar fashion.

Most recently, Cassandra Calabrese, DO, a dually trained rheumatologist and infectious disease specialist, joined the course and highlights the intersection of infections and immune-mediated diseases, including the rapidly changing landscape of COVID-19 and autoimmunity.

The meeting remains small and intimate by design, allowing maximal contact between attendees and faculty. The venue has changed over the years. Meetings in Florida, Arizona and Las Vegas all have been held during the winter, allowing a welcome break for attendees and guests. Most recently, the course became one of the first in the rheumatology community to provide free virtual attendance for full CME credit.

Over the past five years, the course has included a closing session on evidence-based advances in the field of immunologic wellness and its application in clinical care through evidence-based integrative medicine within the scope of rheumatologic practice. This segment has generated overwhelming interest.

"Rheumatologists and other specialists caring for patients with immune-mediated diseases have increasingly recognized that targeted therapies and beyond have transformed our ability to control inflammation," says Dr. Leonard Calabrese. "However, there are still gaping holes in our understanding and capacity to manage problems that are really important to patients, including fatigue, pain, sleep and neurocognition."

Many clinicians are interested in this area, he adds, but are missing both declarative and procedural-skills knowledge in these areas. "This course helps fill these gaps," says Dr. Calabrese.

In the future, organizers hope to expand this weekend course by attracting trainees, who can attend tuition-free, and more advanced practitioners—a rapidly growing segment of the rheumatologic care community.

Plans soon will be finalized for the February 2025 symposium.

"It will be in a nice warm place, and tuition will be minimal by industry standards," says Dr. Calabrese. "And of course the science will be world class."

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

Dr. Cassandra Calabrese (calabrc@ccf.org; 216.445.6996) is Associate Staff in the Department of Rheumatic and Immunologic Diseases.

Novel Drug Targets and Early Biomarkers of Psoriatic Diseases

by M. Elaine Husni, MD, MPH; Unnikrishnan M. Chandrasekharan, PhD; Vincent Del Signore, BS; and Shashank Cheemalavagu, MD

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Dr. Cheemalavagu (cheemas@ccf.org; 216.310.2491) is Associate Staff in the Department of Rheumatic and Immunologic Diseases.

Dr. Chandrasekharan (chandru@ccf.org; 216.444.0534) is an assistant professor in the Department of Molecular Medicine at Cleveland Clinic Lerner College of Medicine.

Vincent Del Signore is a research technician at Lerner Research Institute.

In the Husni Laboratory, our translational research encompasses two primary objectives: identification of safer drug targets for individuals afflicted with psoriatic disease, and the discovery of precise biomarkers capable of forecasting treatment outcomes and the onset of disease comorbidities.

The Husni Lab has been focused on the mission to transform psoriatic disease management and treatment.

TNFR2 in psoriatic disease

Our research aims to elucidate the distinct roles of two tumor necrosis factor alpha (TNF-α) receptors in the pathogenesis of psoriatic disease. Utilizing murine models treated with imiquimod (IMQ), we have identified the crucial role of TNF-α receptor-2 (TNFR2), as opposed to TNFR1, in orchestrating the pathogenesis of psoriatic disease. Our investigations have revealed that TNFR2-dependent activation of dendritic cells (DCs) serves as a pivotal driving force in the manifestation of psoriasis (PsO). Dendritic cells, which are upregulated in psoriatic disease, play a central role in the polarization and activation of naïve T cells into psoriatic disease-promoting effector Th1 and Th17 cells.[1,2]

Our murine models have demonstrated an increase in various DC subtypes during PsO, with this surge significantly inhibited in TNFR2 knockout mice (Figure 1). In addition, recent findings indicate that genetic depletion of TNFR2 in DC alone can curtail psoriatic arthritis (PsA)-like disease in mice. We are currently pursuing studies using preclinical models and human PBMC-derived DC to understand mechanisms that underlie the TNFR2-dependent regulation of DC subtype expansion during psoriatic disease. Our findings underscore TNFR2 as a promising new target for combating psoriatic diseases. By selectively targeting TNFR2 while preserving TNFR1 function, we anticipate reduced adverse effects compared to conventional anti-TNF therapies, which often affect TNFR1-dependent host-defense mechanisms.

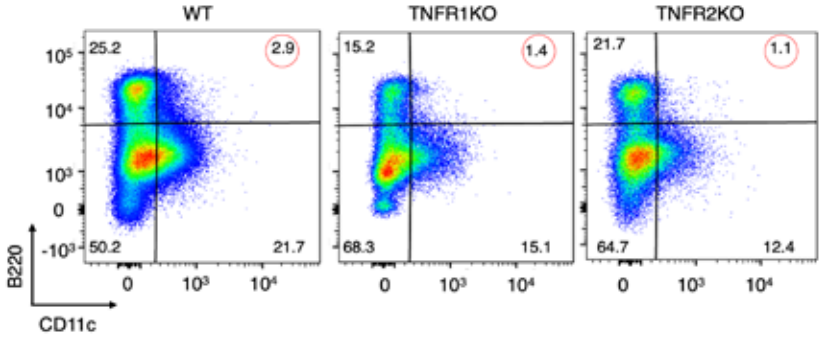
Biomarkers of PsO to PsA transition

In approximately 30% of cases, PsO can progress into PsA.[3,4] Unfortunately, reliable biomarkers for predicting this transition are lacking. The temporal gap between the onset of PsO and PsA presents an opportunity to identify biomarkers that can predict which PsO patients are prone to developing PsA.

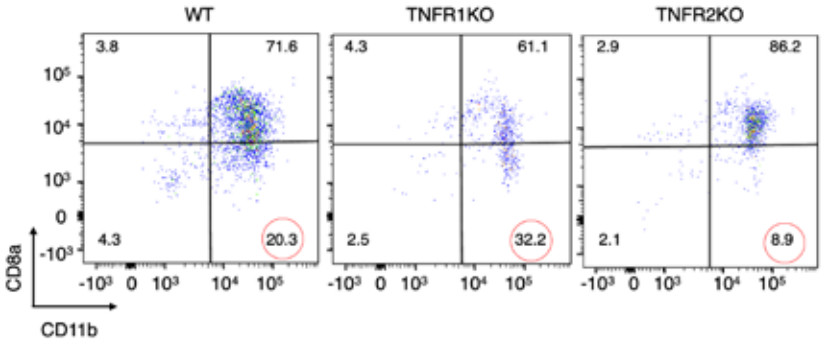
To this end, we employed single-cell RNA sequencing (scRNAseq) technology on PBMCs obtained from treatment-naïve patients categorized into three groups, based on clinical assessments. We divide our clinical cohorts into low risk, high risk and established PsA.

Our unbiased scRNA-seq transcriptomic analysis enabled the stratification of specific immune cell subtypes in PBMCs (Figure 2A), leading to the identification of certain

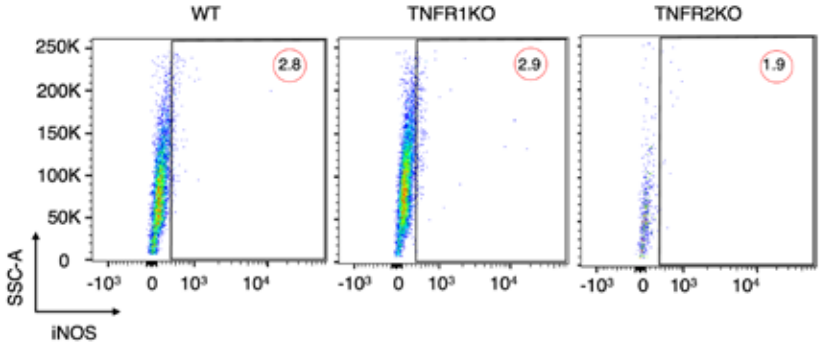
1A. pDC (circled)



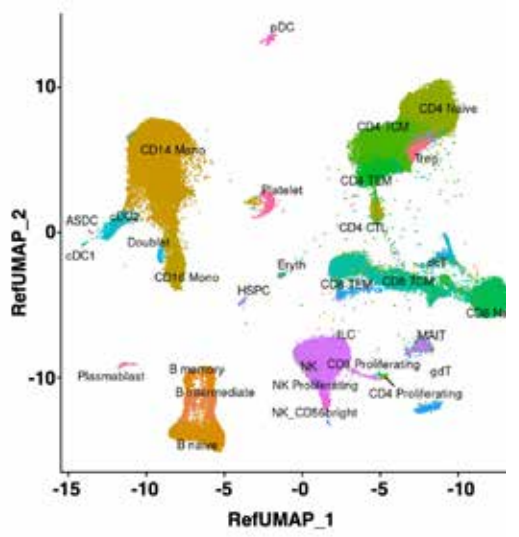
1B. MDC (circled)



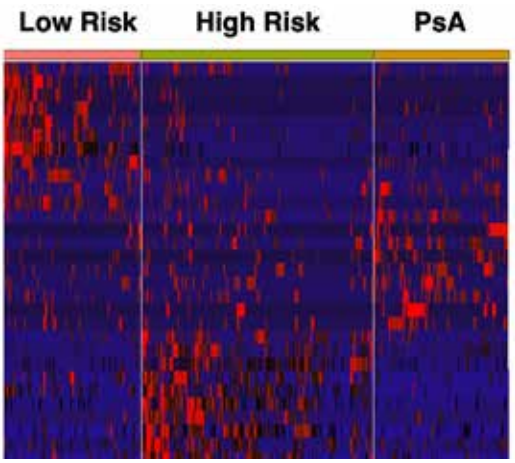
1C. Tip DC (circled)



2A. All cohorts (high risk, low risk & established PsA)



2B.



immune cell types that are enriched with marked differences in gene expression across the three groups (Figure 2B). Ongoing immunophenotyping on patients' PBMCs and skin samples aims to validate our findings. We believe that the insights gleaned from this study have the potential to facilitate the development of bioassays capable of predicting psoriatic arthritis years before clinical detection.

This research has been made possible by funding from NIH RO1, the Arthritis Foundation and the National Psoriasis Foundation.

FIGURE 1. Regulation of dendritic cell populations by TNFR2 in PsO. A. Plasmacytoid dendritic cells (pDC), B. myeloid DC (MDC) and C. TNF inducible nitric oxide synthase-producing DC (Tip-DC) are reduced in the lymph nodes of TNFR2KO mice during imiquimod (IMQ)-induced PsO-like inflammation in mice. WT: Wild type mice, TNFR1KO: TNF-α receptor 1 knockout mice, TNFR2KO: TNF-α receptor 2 knockout mice.

FIGURE 2. Representative figures of single cell RNA sequencing analysis. A. Two-dimensional plot (UMAP) highlighting distinct immune cell clusters. B. Gene expression heat map showing differential gene expression pattern of a candidate immune cell type enriched in high risk-PsO patients.

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Harrison's Principles of Internal Medicine

A Conversation with Dr. Carol Langford

Carol Langford, MD, MHS, is Director of Cleveland Clinic's Center for Vasculitis Care and Research and Vice Chair for Research, Department of Rheumatic and Immunologic Diseases. Dr. Langford recently was named to the Editorial Board of *Harrison's Principles of Internal Medicine*, 22nd Edition. In this interview, she offers insights into the history of the publication and the importance of continuing its founding principles.

Can you tell us about the origin of *Harrison's Principles of Internal Medicine*?

Harrison's Principles of Internal Medicine has a wonderful history where it has served as an authoritative educational resource for the past 74 years. The 1st Edition of *Principles of Internal Medicine* was published in 1950 under the leadership of Editor-in-Chief Dr. Tinsley Harrison. Dr. Harrison was a cardiologist who is widely regarded as one of the most influential physicians of the 20th century. One of the groundbreaking concepts of this textbook that was introduced by Harrison and his colleagues was the inclusion of how current knowledge of pathophysiology impacted the clinical expression and management of disease. This was quite remarkable, when you reflect on the fact that this foresight occurred during the same period that penicillin first became widely available.

What has been the more recent history of *Harrison's Principles of Internal Medicine*?

Following the success of *Principles of Internal Medicine*, subsequent editions followed. Beginning with the 6th Edition, the book became known as *Harrison's Principles of Internal Medicine*, by which it has been recognized ever since. To date, there have been 21 editions of *Harrison's* under the leadership of 19 editors, which have documented the remarkable advances that have occurred in the practice of internal medicine. The great strength of *Harrison's* has always been the quality of its chapters, which are written by disease experts under the direction of the *Harrison's* editors. The shared commitment of the contributors and editors to provide clinically meaningful content that reflects the current art and science of internal medicine is what has made *Harrison's* a global resource of medical knowledge.

What has been your individual history with *Harrison's Principles of Internal Medicine*?

In many ways, *Harrison's* has been with me throughout my career. As a medical student, I remember going to the campus bookstore and picking up my first copy (it was the 10th Edition). From that point on, *Harrison's* was where I went to read and learn about the medical issues my patients were facing. Over time, newer editions continued to have a place on my desk. After completing internal medicine and rheumatology training, I joined the National Institutes of Health (NIH) for my first faculty position within the National Institute of Allergy and Infectious Disease, working in the vasculitis section under Dr. Anthony Fauci.

Dr. Fauci became a *Harrison's* editor beginning with the 11th Edition. During my time at the NIH, I had the privilege of joining him as a chapter contributor for "The Vasculitis Syndromes" and saw first-hand the high level of quality that was expected of a *Harrison's* chapter. I later had the opportunity to learn further from Dr. Fauci in the compilation of *Harrison's Rheumatology*, derived from chapters within the main textbook. This year, it was a tremendous honor for me to be joining Dr. Fauci as a member of the editorial team for the 22nd Edition, together with Drs. Dan Longo, Dennis Kasper, Stephen Hauser, J. Larry Jameson, Joseph Loscalzo and Steven Holland.

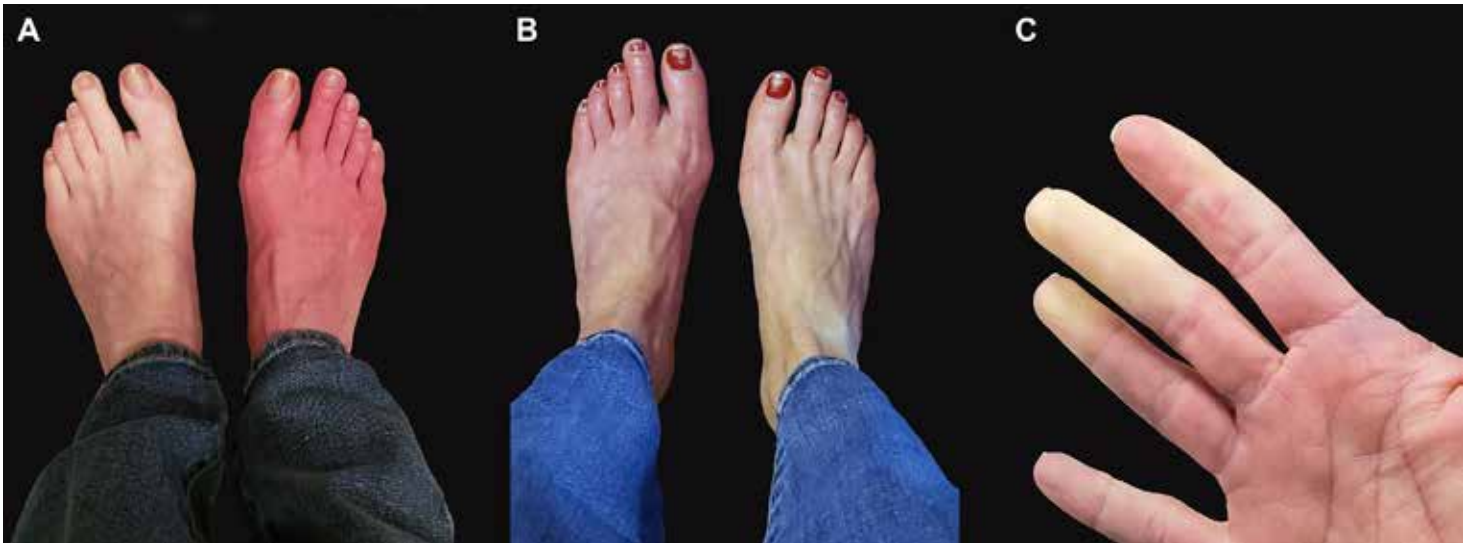
What do you see as the future of *Harrison's Principles of Internal Medicine*?

In current day, *Harrison's* reaches a worldwide audience both through the printed textbook and electronically through AccessMedicine. As an editor, it will remain my foremost priority to carry forward the core principles of excellence and reliability that *Harrison's* was founded on and maintained by its past and current editors. It remains my hope that future generations will continue to see *Harrison's Principles of Internal Medicine* as the resource that first draws them to this fascinating field and that remains where they go to learn medicine throughout the course of their career.

Dr. Langford can be reached at langfoc@ccf.org or 216.445.6056.

Coexistence of Erythromelalgia and Raynaud's Phenomenon

by Soumya Chatterjee, MD, MS



Erythromelalgia (EM) is a rare neurovascular disorder characterized by spontaneous episodes of redness, heat, swelling and intense burning pain in the extremities. Symptoms are exacerbated by warmth, pressure, exercise, stress, alcohol, caffeine or dependency of the affected extremity, whereas cooling and limb elevation relieve the pain. EM can be primary or secondary. Primary EM is caused by mutations in the voltage-gated sodium channel a-subunit gene *SCN9A,*[1] which may be familial (autosomal dominant inheritance) or sporadic. Secondary EM can result from myeloproliferative disorders, small fiber neuropathy, medications (calcium channel blockers, bromocriptine, pergolide and topical isopropanol), mushroom or mercury poisoning, and various autoimmune diseases.

Raynaud's phenomenon (RP) is characterized by constriction of small arterioles triggered by cold exposure or emotional stress, causing pallor of the fingers or toes, followed by cyanosis and/or rubor. RP may also be primary (Raynaud's disease) or secondary. The latter is associated with systemic sclerosis, mixed connective tissue disease (MCTD) or lupus, and less often with thromboangiitis obliterans, thoracic outlet syndrome, paraneoplastic syndrome, hypothyroidism, or use of vibrating machinery or vasoconstrictors.

A case illustrating the coexistence of EM and RP and its possible pathomechanisms is described here.

Case report

A 49-year-old female with mixed connective tissue disease (MCTD) presented to the rheumatology clinic with episodic attacks of RP and EM. Her illness started when she was 45 and experienced new onset of RP and inflammatory polyarthritis. She had dilated capillary loops and cuticular hemorrhages on nailfold capillaroscopy, a positive antinuclear antibody (1:320, homogeneous pattern), and anti-U1-RNP antibody (3.1 AI; ref range: 0–0.9 AI).

She also suffers from severe attacks of EM. When trying to keep her feet and toes warm, if her socks are too thick or too tight, her feet become red, hot, swollen, painful and throbbing. Her legs and feet become intermittently red and hot, but never simultaneously. Warm water and compression gloves cause hot, swollen, painful and red hands. Spicy food causes her face, neck, chest and arms to turn red, splotchy and painful. Extreme temperatures make outdoor activities difficult. Sleep is disrupted as her body is cold but her feet are "on fire."

Cold exposure and stress also trigger RP, but calcium channel blockers cause severe facial flushing from worsening EM.[2-4]

As she had no myeloproliferative disorder, aspirin was ineffective for her EM. Laboratory tests ruled out other causes of EM.

Continued on next page

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ABOVE –A patient with mixed connective tissue disease suffering from an episode of erythromelalgia involving the right foot (A); an episode of erythromelalgia involving the left foot (B); and Raynaud's phenomenon affecting the right third and fourth fingers (C).

EM and RP have specific initiating events and clinical manifestations, although the patient's primary and secondary forms rarely coexist.[4–8] Both start with vasospasm, followed by reactive hyperemia, which is more pronounced in EM. These two seemingly opposite conditions may share some common causative and pathophysiologic mechanisms.[9]

In a subset of EM, increased cutaneous vascular tone lowers the morning basal temperature[9] and is followed by reactive hyperemia later in the day, as in the rubor phase of RP. The initial vasoconstriction results from structural or functional alterations in the endothelium and/or smooth muscle or cutaneous microvascular innervation.[9] Cutaneous vasoconstriction causes the ischemic cells to switch to anaerobic respiration, accumulating nociceptive inflammatory mediators that open up arteriovenous anastomoses.[10]

This scenario may explain why some EM cases respond to calcium channel blockers, similar to RP.

Conversely, the vasoconstriction model does not address perpetually vasodilated EM patients,[5] where calcium channel blockers exacerbate symptoms.[2–5] Vascular studies in warm and cool environments could distinguish the two subtypes of EM and determine whether vasodilation or vasoconstriction will control symptoms.[5]

Optimal management strategies for patients concurrently affected by EM and RP require a more in-depth understanding of the pathomechanisms underlying these two paradoxically opposite conditions.

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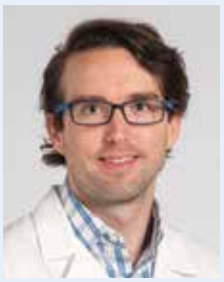
Ehlers-Danlos Program Helps Us Better Meet Patient Needs

by Adam Brown, MD



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Joint hypermobility is the feature most associated with Ehlers-Danlos syndrome (EDS), but being "bendy" doesn't always spur patients or their physicians to investigate EDS. The collagen synthesis abnormalities of EDS can lead to other conditions as well—skin hyperelasticity and damage to ligaments, blood vessels and the heart.

Identifying EDS is a necessary first step for optimizing patient outcomes.

Ehlers-Danlos syndrome describes a group of 13 genetic connective-tissue disorders that affect an estimated 1 in 20,000 people. In addition to previously mentioned symptoms, EDS can lead to dislocations, stretchy and overly thin skin, bruising and scarring, chronic joint and muscle pain, fatigue and brain fog. Dysautonomia and stroke are among more serious complications.

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FIGURE 1 – The Beighton score uses a nine-point system for assessing joint hypermobility.

While there are genetic factors – multiple individuals in families often exhibit hypermobility – genetic panels reveal no known mutation for about 80% of these patients. They are labeled hypermobile Ehlers-Danlos syndrome based on meeting clinical criteria, including results of their Beighton screening test for hypermobility.

The next step is connecting patients with EDS-experienced rheumatologists and other specialists who can help them navigate challenges.

In 2019, Cleveland Clinic started a care program to give patients with EDS a medical home, where they can be assessed, educated about EDS and referred for physical therapy. The program also coordinates with Orthopaedic Surgery, Cardiology, Physical Therapy, Gastroenterology, Neurology and Vascular Medicine so patients can more easily have their EDS-associated conditions addressed by specialists who understand the syndrome.

Focused, coordinated care

Since starting the EDS program at Cleveland Clinic, we have helped hundreds of patients get the coordinated care they need to manage their chronic condition. Our services include:

- Coordinated care with a broad network of providers who can address issues around hypermobility
- Access to vascular medicine specialists for patients with vascular complications such as aneurysms or dissections.
- Access to Orthopaedics for patients with dislocations.
- Access to pain psychology experts for management of chronic pain and fatigue.
- Access to Cardiology and Neurology for help with dysautonomia.
- Physical therapists who are knowledgeable about movement- and pacing-related needs of patients with hypermobility.

Empowering patients with strategies for living

One of the biggest benefits we offer patients in our EDS program is connecting the dots when symptoms develop. Understanding the complexities of the syndrome allows us to keep them from bouncing from specialist to specialist in search of answers.

In addition to treating physiological conditions associated with EDS, we understand the importance of helping patients manage social and psychological effects.

This year we will begin offering shared medical appointments that will enable us to educate newly diagnosed patients efficiently and effectively while connecting them to others with similar experiences.

Some patients have experienced a variety of complications related to EDS but either were never diagnosed or they received care from clinicians lacking EDS expertise. Being listened to and understood brings them an immediate sense of relief.

One of the most important things we do is let them know that their experiences are not all in their head. In some cases, they have been told there's nothing wrong with them. We are able to validate their experiences, offer tools to help them manage and to offer hope that they can feel better.

Cleveland Clinic's Ehlers-Danlos program has been developed with funding support from the family of the late Sophie Herschman, who received care for her EDS at Cleveland Clinic. To learn more about her and the gift that grew out of her EDS experience, visit https://give.ccf.org/fundraiser/3001730.

CASE CONFERENCE

Peripheral Ulcerative Keratitis in Untreated Rheumatoid Arthritis

by Taylor Koenig, MD, and Kinanah Yaseen, MD

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Presentation

An 81-year-old female presented to Ophthalmology with a monthlong history of left-eye blurry vision, foreign body sensation, irritation and photophobia. Her ophthalmologic examination revealed peripheral ulcerative keratitis (PUK) with scleritis of her left eye, which was confirmed on slit-lamp examination with fluorescein staining (Figure 1). Bacterial culture of corneal scrapings was negative. She was started on oral glucocorticoid therapy out of concern for underlying autoimmune etiology of her inflammatory eye disease.

The patient reported that she had been diagnosed with rheumatoid arthritis (RA) 20 years before and was treated with intermittent non-steroid anti-inflammatory medications. She had never been treated with a disease-modifying agent or biologic therapy and had not followed up with a rheumatologist since this diagnosis. The patient was referred to Rheumatology, where her evaluation was significant for ulnar deviation of her hands (Figure 2), positive rheumatoid factor of 24 IU/mL (normal range <16 IU/mL), and bilateral hand/wrist radiographs with metacarpal and intercarpal joint space narrowing and erosions (Figure 3).

The patient's peripheral ulcerative keratitis was determined to be an extra-articular manifestation of her long-standing untreated seropositive erosive rheumatoid arthritis. Because of the severity of her disease, she was started on methotrexate and an anti-TNFα inhibitor for long-term treatment; glucocorticoid therapy had not improved her significant ocular disease, and was tapered. Eventually, rituximab was effective in controlling her arthritis as well as PUK.

RA-associated PUK

RA is a chronic autoimmune disease that mostly affects the joints. Extra-articular organ involvement, including ocular and pulmonary manifestations, are common. They can be challenging to manage and associated with increased morbidity and mortality.

Ocular manifestations include sicca symptoms, episcleritis/scleritis and cornea melt, including PUK. Inflammation causes breakdown of collagen and stromal lysis of juxta limbal cornea, which may lead to corneal perforation.

The underlying cause of PUK could be systemic, including infection or non-infectious causes such as RA, granulomatosis with polyangiitis and systemic lupus erythematosus. In RA, PUK can be unilateral or bilateral. Clinical symptoms include redness, ocular pain, tearing and photophobia. With the introduction of biologic therapy, the incidence and morbidity associated with PUK have reduced significantly. Rituximab has shown to be an effective treatment of RA-related PUK.

At Cleveland Clinic, we work closely with Ophthalmology and other specialties in diagnosing and managing challenging rheumatic cases.

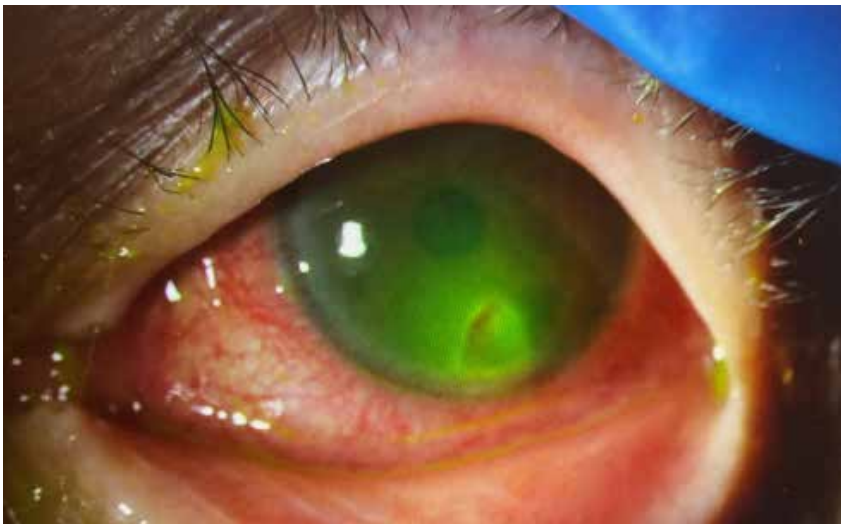

FIGURE 1 – Slit-lamp examination with fluorescein staining reveals peripheral ulcerative keratitis.

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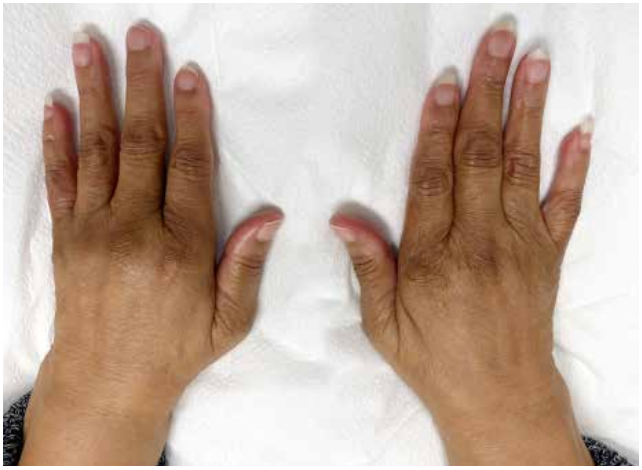

FIGURE 2 – Ulnar deviation can be seen on both hands.

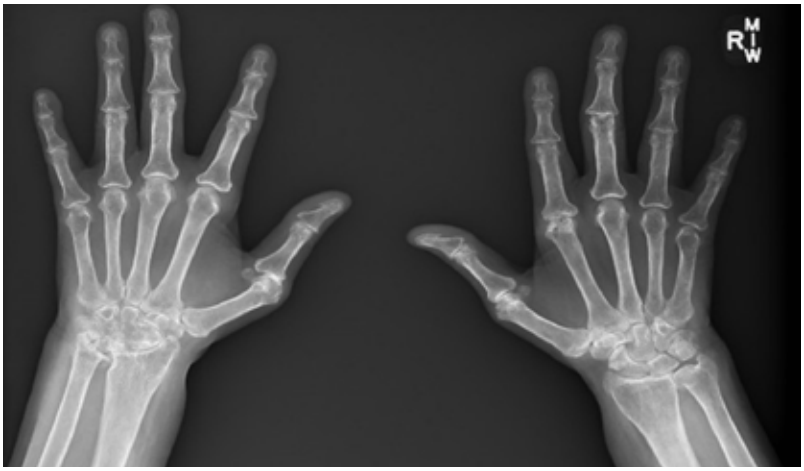

FIGURE 3 – Osseous erosions are noted at the right second metacarpophalangeal joint and first metacarpal head. Advanced diffuse intercarpal and radiocarpal/ulnocarpal joint space narrowing and chronic erosive changes can be seen at the ulnar styloid and at the distal radioulnar joint.

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- FcRN Inhibitors – A New Age in Immune-Based Therapeutics
- Inside the Brain of Abatacept: Multi-Omics Dissection of How it Works to Halt RA Pathogenesis

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Faculty: Neha S. Shah, MD; Philip J. Mease, MD; Pavan Tankha, DO

Session agenda

- Integrative Medicine and Rheumatology: Why It's Important in IMIDS
- Advances in Fibromyalgia: Science and Care
- Multimodal Care of Chronic Pain

Key Issues in the Differential Diagnosis of Vasculitis

Series: Biologic Therapies Summit X and Vasculitis Online Series

Estimated time of completion: 1 hour and 45 minutes

Faculty: Zachary Wallace, MD, MSc; Marcela Ferrada, MD; Adam Brown, MD; Kinanah Yaseen, MD

Session agenda

- IgG4-Related Disease
- Relapsing Polychondritis
- Vascular Ehlers-Danlos Syndrome
- Drug-Induced Vasculitis

Treatment of Psoriatic Disease

Estimated time of completion: 1 hour

Faculty: Anthony P. Fernandez, MD, PhD; Andrew Blauvelt, MD, MBA; Nehal Mehta, MD

Session agenda

Update your knowledge and understanding of both traditional and new therapeutic strategies for a range of critically important medical dermatologic conditions, including rheumatology-dermatology overlap diseases, medical dermatologic diseases, psoriatic disease, and the interprofessional approach to patients on biologics.

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