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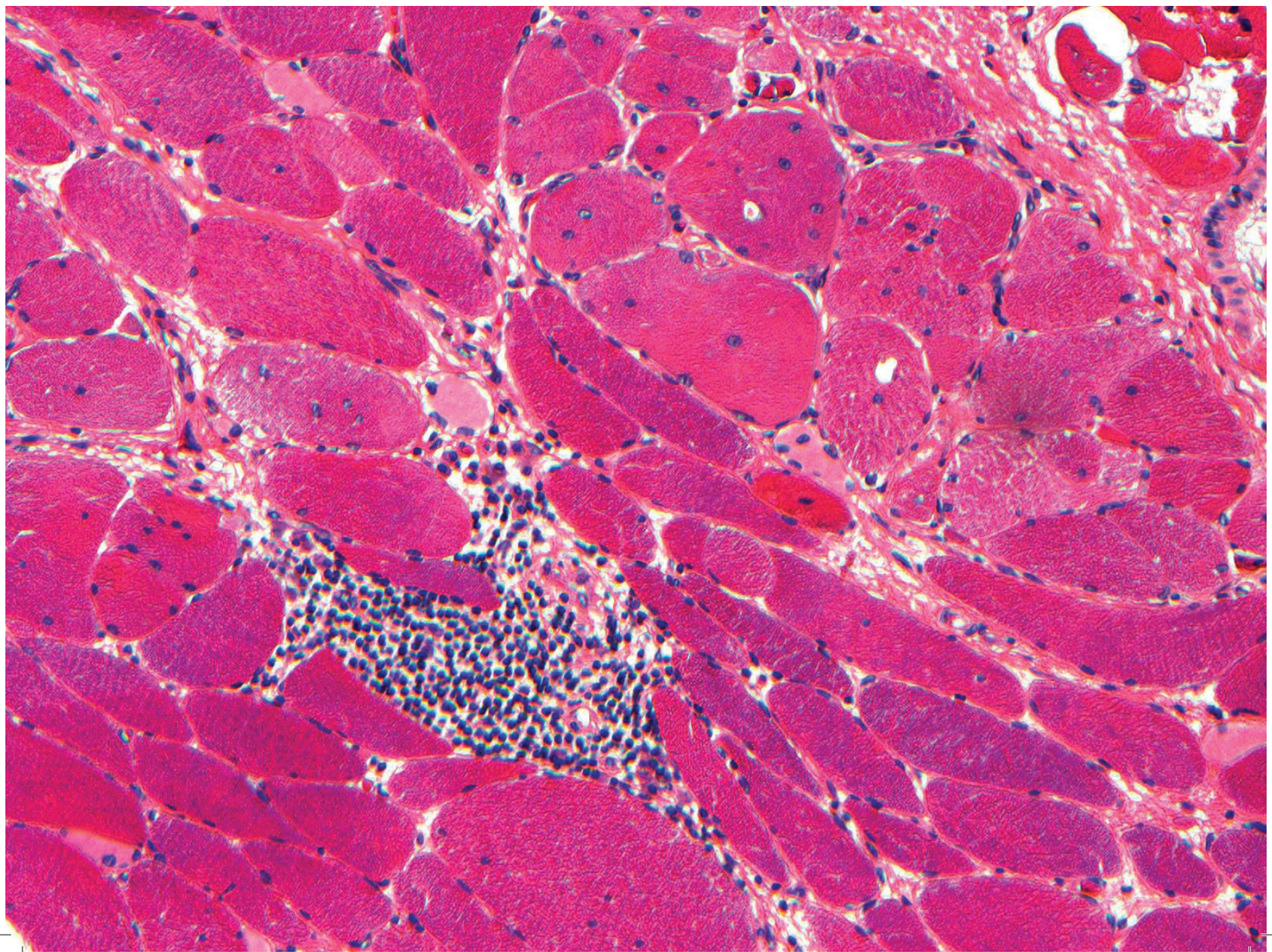
Cleveland Clinic

Rheumatology Connections

An Update for Physicians | Spring 2025



From the Chair of Rheumatic and Immunologic Diseases

Dear Colleagues,

As our team puts the finishing touches on this issue of *Rheumatology Connections*, we look forward to rejuvenation — both the kind we feel in spring and the sort we experience when we gather to share ideas and conversation. Two Cleveland Clinic conferences, Biologic Therapies Summit XI and Vasculitis 2025, will take place May 8-10, drawing national and international experts to Cleveland to discuss news and insights in their fields. We look forward to seeing many of you online or here in person. You can find more details on page 10.

Researchers in the Elaine Husni Laboratory continue to advance their studies of signaling pathways implicated in the development of psoriatic arthritis (PsA). Recent research (page 3) has identified the axis of tumor necrosis factor-alpha receptor 2 and dendritic cells as a mechanism driving PsA. This discovery could help deliver new therapies that improve patients' lives.

For more than two decades, Cleveland Clinic has included bone health assessments for all individuals being considered for lung transplants in an effort to protect them against osteoporosis-related fractures. In this issue, Dr. Sarah Keller writes about her recent research (page 6) on risk factors for transplant-related bone breaks as well as the safety and efficacy of denosumab to strengthen bones after transplant.

Dr. Emily Littlejohn offers an uplifting look (page 14) at extraordinary quality-of-life improvements experienced by a patient who received CAR T-cell therapy for lupus in spring of 2024. Her experience offers hope to others with the disease. Other case studies featured in this issue include scleromyxedema (page 5), relapsing polychondritis (page 8) and Bethlem myopathy (page 13).

Last fall, Dr. Carol Langford became the 88th President of the American College of Rheumatology (ACR). In the Q&A that begins on page 11, Dr. Langford articulates the values and strengths of the ACR and shares her plans for highlighting education, research and connection.

With every issue of *Connections*, we hope to convey a sense of the great work we do here at Cleveland Clinic. We welcome opportunities to help you meet the needs of your patients.

Respectfully,

Abby Abelson, MD
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On the cover
A muscle biopsy image shows an example of myositis, a condition with which the patient featured on page 13 was initially diagnosed. Read more to find out what her Cleveland Clinic team discovered through genetic testing.

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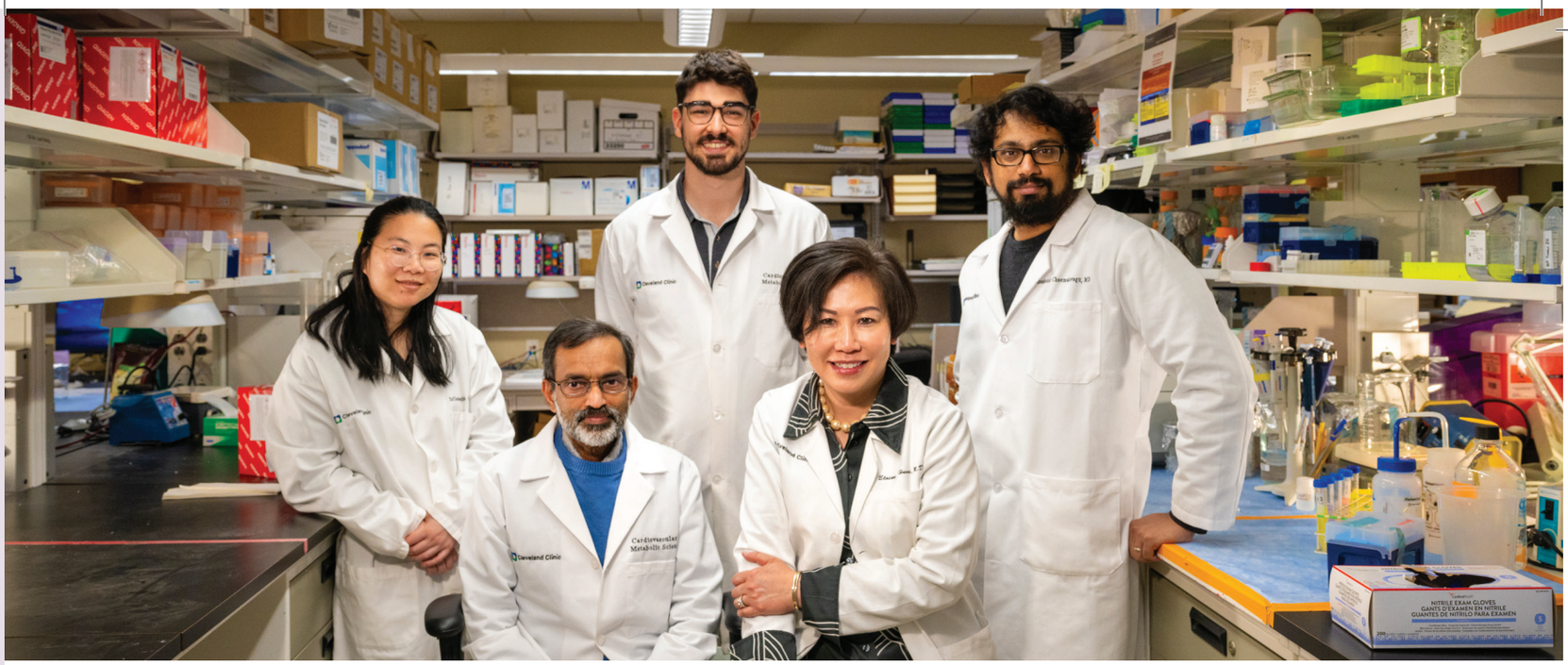
Rheumatology Connections is written for physicians and should be relied on for medical education purposes only. It does not provide a complete overview of the topics covered and should not replace the independent judgment of a physician about the appropriateness or risks of a procedure for a given patient.

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.



Unraveling the Tumor Necrosis Factor Alpha Receptor 2/Dendritic Cell Axis

A novel mechanism in psoriatic disease pathogenesis

M. Elaine Husni, MD, MPH, and Unnikrishnan M. Chandrasekharan, PhD

One of the major focuses of the Husni laboratory is uncovering signaling pathways that drive the progression of psoriatic diseases, focusing specifically on tumor necrosis factor-alpha (TNF-α) receptor signaling. At the beginning of this discovery, we demonstrated that the depletion of TNF receptor 2 (TNFR2), but not TNFR1, significantly reduces psoriasis-like inflammation in a murine model with TNFR knockout (KO) mice. Importantly, this reduction in disease severity correlates with a diminished dendritic cell (DC) population in secondary lymphoid organs, such as the spleen and lymph nodes. This pivotal finding highlights the previously unrecognized role of the TNFR2 DC axis in psoriatic diseases.

TNFR2 promotes PsA-like inflammation potentially through cDC1 activation

Dendritic cells are a heterogeneous subset of antigen-presenting cells linking the innate and adaptive arms of the immune system. DCs have been implicated in numerous inflammatory and autoimmune diseases, including psoriatic arthritis (PsA).

Our current research investigates the role of DC-specific TNFR2 (DC-TNFR2) in PsA. Our results suggest that TNFR2 facilitates PsA-like inflammation by activating conventional dendritic cell type 1 (cDC1), a key subset of antigen-presenting cells. Activated DCs produce pro-inflammatory cytokines such as TNF-α, IFN-γ, IL-12 and IL-23, driving the differentiation of naive T cells into Th1 and Th17 subtypes — critical mediators of psoriatic diseases.

To investigate the role of DC-TNFR2 in PsA, we utilized a mannan oligosaccharide (MOS)-induced model of PsA in DC-TNFR2KO mice. These mice, generated by crossing TNFR2-floxed mice (TNFR2 fl/fl) with CD11c-Cre models, exhibit TNFR2 deletion specifically in DCs. In TNFR2-intact control models, MOS treatment induced pronounced scaling, redness and thickness of the skin, along with joint inflammation (Figure 1). Remarkably, these symptoms were significantly attenuated in DC-TNFR2KO models, as evidenced by reduced cumulative Psoriasis Area and Severity Index (PASI) scores and lower arthritis severity scores on days four and six after MOS treatment. Moreover, MOS induced redness, swelling and inflammation in the paws were attenuated in the DC-TNFR2KO models. Similarly, the mean arthritis severity score significantly decreased in DC-TNFR2KO mice on day four and day six.

Continued on next page

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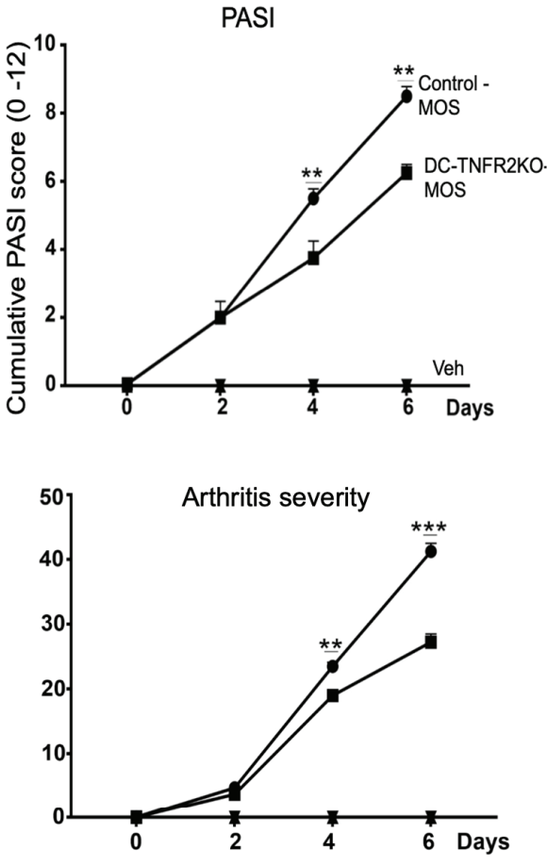


Figure 1. DC-TNFR2 knockout mice showed reduced skin and joint phenotype in the mannan oligosaccharide (MOS)-induced PsA model. The top chart shows the cumulative PASI score (erythema + scaling + thickness) of the ear. The X-axis corresponds to days two, four and six after the MOS injection. The bottom chart indicates the mean arthritis severity score of paws (n = 6, means ± SE, ** $P < .01$; *** $P < .001$).

There are three major DC subsets: plasmacytoid DC (pDC), cDC1 and conventional DC2 (cDC2). MOS-induced PsA increased the cDC1 populations in the spleen of control mice, but not in DC-TNFR2KO mice (Figure 2). Conversely, the cDC2 population did not change significantly, underscoring the specificity of the TNFR2-cDC1 axis in PsA pathogenesis.

Our findings establish the TNFR2/cDC1 axis as a previously uncharacterized mechanism driving PsA. This discovery opens exciting avenues for therapeutic innovation. Selectively targeting TNFR2-dependent cDC1 activation pathways may offer a more precise and safer alternative to global anti-TNF agents, which inhibit both TNFR2 and TNFR1, often leading to adverse effects. By focusing on this pathway, future treatments could potentially attenuate PsA pathogenesis while preserving essential immune functions, thus revolutionizing the management of psoriatic diseases.

These findings illuminate a transformative path in our understanding of PsA, offering hope for novel and highly targeted interventions that could improve patient outcomes and quality of life.

Lab members Raminderjit Kaur, PhD; Vincent Del Signore, BS; Jean Lin, MD; and Shashank Cheemalavagu, MD, contributed to this research.

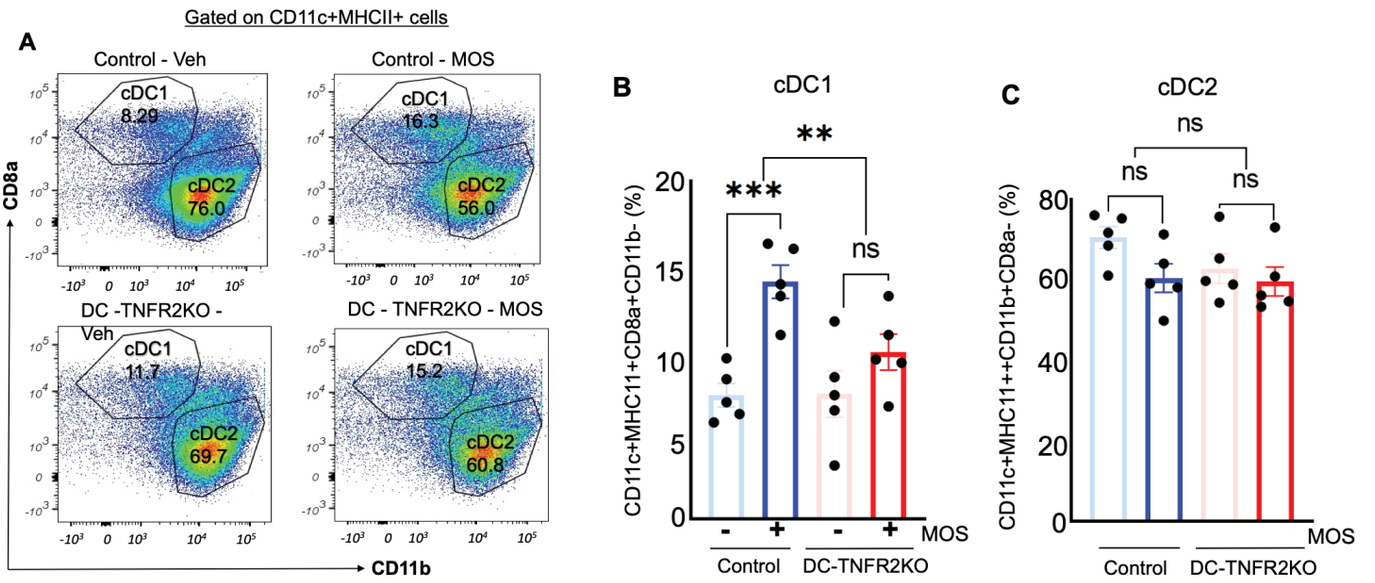


Figure 2. Increase in conventional DC1 (cDC1) population in the PsA model is reduced upon DC-specific TNFR2KO.
(A) Representative figure showing the percentage of cDC1 and cDC2 cells.
(B,C) Percentage of cDC1 and cDC2 in control and DC-TNFR2KO mice ± MOS
(n = 5, means ± SE, ** $P < .01$, *** $P < .001$)

Case Study: Skin Papules, Hand Neuropathy and Monoclonal Gammopathy

Soumya Chatterjee, MD, and Anthony P. Fernandez, MD, PhD

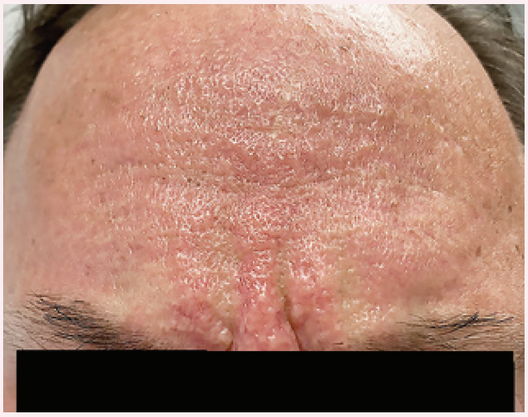
A 53-year-old man presented to the rheumatology clinic with a three-year history of an itchy rash, Raynaud's phenomenon, dysphagia and a burning sensation in his hands.

Physical examination was notable for firm, greasy papules across his forehead that led to the formation of glabellar grooves (A). There were waxy papules on his hands with associated skin thickening and finger flexion contractures (B). Similar skin changes were seen on his nose, lips, ears, trunk and feet. There was no telangiectasia or calcinosis.

Sensory neuropathy was present in his hands, arms and face. Tests of thyroid function were normal. Serum protein electrophoresis with immunofixation identified an IgG-λ monoclonal gammopathy, and a bone marrow biopsy was normal.

A subsequent skin-biopsy sample obtained from the right side of the neck showed dermal spindle-cell proliferation, thickened collagen fibers, fibrosis and perivascular inflammation (C, hematoxylin and eosin stain), as well as increased dermal mucin deposition (D, colloidal iron stain). A diagnosis of scleromyxedema was made.

Scleromyxedema is a primary cutaneous mucinosis typically associated with a paraproteinemia. This type of sclerosing skin disorder may cause extracutaneous symptoms, as was seen in this patient. Although infusions of intravenous immune globulin provided minimal relief initially, treatment with lenalidomide resulted in abatement of symptoms and reduction in paraproteinemia after four months.



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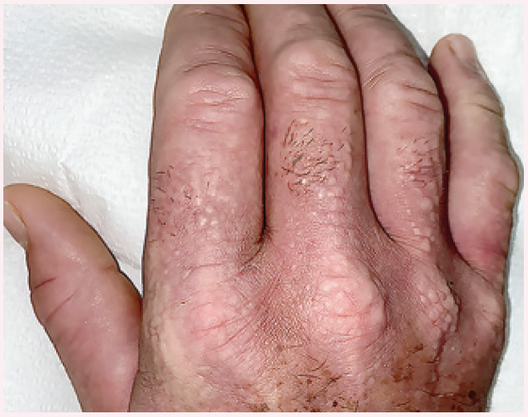

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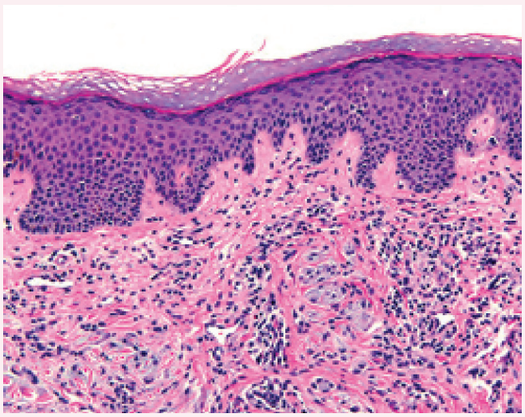

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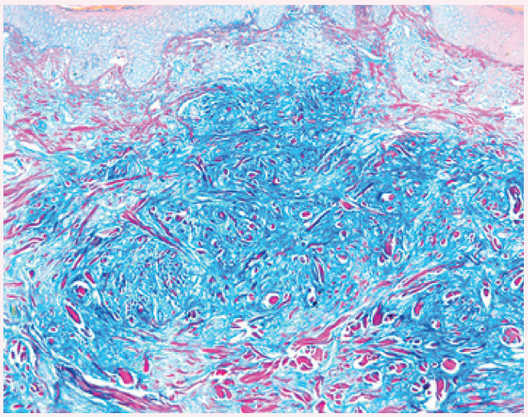

D

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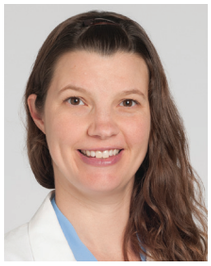
Reducing the Risk of Osteoporotic Fractures Following Lung Transplantation

Sarah Keller, MD



Dr. Keller (kellers@ccf.org; 216.445.5880) is Staff in the Department of Rheumatic and Immunologic Diseases.

People don't always consider bone health in relation to end-stage pulmonary disease and lung transplantation, but it is important to do so. Medications and comorbidities associated with lung disease elevate risks for osteoporosis (OP) and bone fracture. The high-dose glucocorticoid (GC) therapy that follows transplantation can sharply affect bone loss and increase the likelihood of fractures, leading to lengthy hospital stays or even death.

Proactive bone-health management may reduce morbidity and mortality in lung transplant patients, but a more widespread understanding of the risks is needed.

A recent study by Cleveland Clinic's Osteoporosis and Metabolic Bone Disease Center identifies strong predictors of post-transplant fracture and highlights the importance of osteoporosis management before and after transplant. Our research team also analyzed post-transplant use of denosumab — an inhibitor of receptor activator of nuclear factor kappa-B ligand (RANKL) — and found it was associated with a 65% reduction in the odds of having an osteoporosis-related fracture.

Background

From 1992 to 2001, the median survival after lung transplant (LT) in the U.S. was 4.7 years. From 2010 to 2017, that rose to 6.7 years, and the risk of fracture from related OP has increased along with it.

Bone health studies of LT patients have been limited, but risk factors for OP and fractures among this population include lung disease pathology; low body mass index; a sedentary lifestyle; chronic hypoxia/hypercapnia; tobacco and alcohol use; medications (use of glucocorticoids, loop diuretics and calcineurin inhibitors); calcium and vitamin D deficiencies; inadequate post-transplant ambulation and rehabilitation; and acute and chronic organ rejection that requires increased GC doses.

In end-stage pulmonary disease, OP and fragility fractures can occur before LT or as a complication soon after transplant, or later. In a meta-analysis, the incidence of vertebral fractures was 19.5% before transplant and 50.4% after.[1] In the first year post-LT, the rate of fracture was 18% to 37%.[2]

Vertebral fractures are common and can cause compression and curvature of the spine and reduced lung capacity. In older patients, hip fractures carry the greatest mortality risk. Consequences can include stress-related strokes or heart attacks that take place at the time of the break or afterward. A broken hip may lead to surgery, which can put a patient at risk for blood clots or bleeding related to blood thinners. During recovery, patients may spend a long time sedentary, which raises cardiovascular risk and can cause loss of independence.

Given the odds of developing serious osteoporosis and fracture, we know that long-term health of patients who undergo lung transplant depends in part on protecting their bone health.

Study details

Our team's retrospective cohort study was conducted at Cleveland Clinic's transplant center, and included adults who had lung transplants between Jan. 1, 2010, and Dec. 30, 2020. Patients who died within the first year after transplant and those who had a previous lung transplant were excluded. Out of 1,223 patients who had transplants, 1,054 met the inclusion criteria.

Before transplant, 366 patients (35%) had osteopenia; 254 patients (24%) had osteoporosis; and 131 patients (12%) had had at least one fracture, most commonly vertebral (67; 51%). Pre-LT, 403 patients had been treated with these OP medications:

- Abaloparatide, 4
- Alendronate, 225
- Denosumab, 17
- Ibandronate, 40
- Raloxifene, 2
- Risedronate, 29
- Teriparatide, 26
- Zoledronic Acid, 67

After transplant, there were 243 fractures. Additionally, 641 patients received post-LT OP medications:

- Abaloparatide, 8
- Alendronate, 292
- Calcitonin, 4
- Denosumab, 195
- Ibandronate, 28
- Pamidronate, 4
- Raloxifene, 2
- Risedronate, 18
- Teriparatide, 38
- Zoledronic acid, 101

Among denosumab patients, there were 11 episodes of hypocalcemia (one hospitalization) and 23 patients (12%) had cellulitis.

In the denosumab fracture analysis, there were a total of 182 fractures. (Fractures that occurred before or after the denosumab treatment were excluded.) Of those fractures, 21 were in patients who had received denosumab and 161 were in patients who had not. Use of denosumab was associated with 65% (OR: 0.35, 95% CI: 0.21-0.58) lower risk of post-transplant fracture after adjusting for other covariates.

In addition, we found that pre-transplant osteopenia, osteoporosis, and a history of smoking and alcohol use are strong predictors of post-transplant fracture.

Cleveland Clinic's program

Along with Annmarie Miranda, PC-C, our research team included *Abby Abelson, MD; Marie Budev, DO; Chad Deal, MD; Komal Mushtaq, MD; Adil Vural, MD; and Chao Zhang*. Our results underscore the need for bone-health programs such as Cleveland Clinic's, which was launched in 2002 through a cooperative relationship between transplant and metabolic bone specialists.

Every Cleveland Clinic patient who is considered for lung transplant is evaluated in our clinic for overall bone health, which includes a detailed medical history to reveal risk factors, bone-density scans and imaging. For every transplant patient, we develop a medication and follow-up plan.

Patients who go through lung transplants need not have their health jeopardized by osteoporosis-related fracture and frailty. Today, we have some medications that can decrease the risk of fracture by nearly 70%. Expert bone-health care before and after surgery can help improve the chances of a strong recovery.

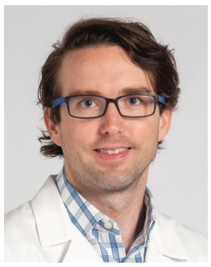
References

1. Caffarelli et al., *Journal of Clinical Medicine*. 2020. 9(9)
2. Stein et al. *Endocrinology and Metabolism Clinics of North America*. 2007. 07.008

CASE CONFERENCE

Unusual Disease Pattern, Vague Symptoms and Striking Imaging

Adam Brown, MD, Ahmed Abuyakoub, MD, and Matthew Mandell, DO



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Background

A 41-year-old Caucasian male with a history of asthma and gastroesophageal reflux disease presented with generalized body pain, neck pain, shortness of breath, episodic chest pain, articular and nasal pain, and unintentional weight loss for one year. Because of the weight loss and concern for malignancy, a chest CT was performed, revealing right-greater-than-left perihilar lymph nodes as well as chronic calcification of the tracheal rings (Pictures 1,2). A bronchoscopy with bronchial alveolar lavage was negative for infection, and ultrasound-guided biopsy of hilar adenopathy revealed reactive changes. Additional imaging of the patient's abdomen revealed para-aortic retroperitoneal lymph nodes. The patient was transferred to Cleveland Clinic for consideration of an additional tissue biopsy.

A positron emission tomography (PET) scan demonstrated patchy increased metabolic uptake in the cervical spine along with the bilateral sacroiliac (SI) joints, anterior costovertebral joints, and external auditory canal cartilaginous segments (see pictures).

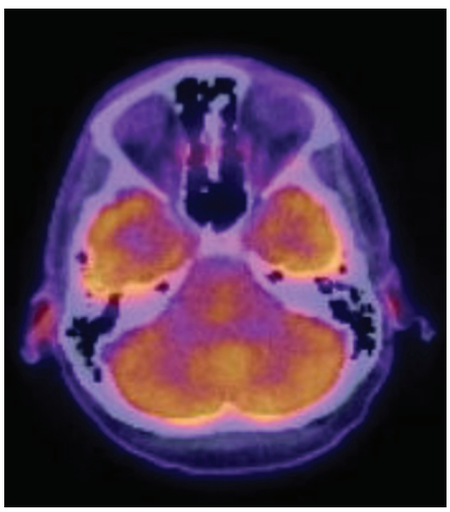
The unusual pattern of PET scan uptake with axial involvement raised questions about underlying spondyloarthritis, and Rheumatology was consulted. At this point the patient was still feeling generalized weakness along with pain primarily in his neck.

During a rheumatologic evaluation, the patient also noted nasal and auricular pain. On exam he had saddle nose deformity and erythema with swelling of the right ear, and pain to palpation of both. His neck had a limited range of motion. He did not have appreciable synovitis on his extremities. His muscle strength was normal in the upper and lower extremities. His labs were notable for an elevated white blood cell count and elevated inflammatory markers. Autoimmune serologies, including ANCA, and syphilis testing were negative.

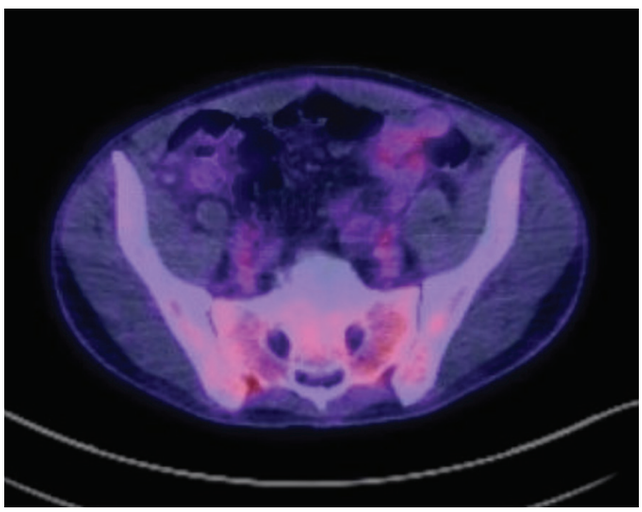
What is going on with this patient?

With the weight loss, weakness, lymphadenopathy and elevated inflammatory markers, the initial concern about underling malignancy was understandable. He also had clear nasal and auricular chondritis as well as imaging (PET and MRI) evidence of axial inflammatory arthritis. The previous chest images also revealed evidence of calcifications of the trachea, which can be seen in relapsing polychondritis (RP). Considering the unremarkable lymph node biopsy, the most likely diagnosis was thought to be RP with axial involvement (cervical and SI joints).

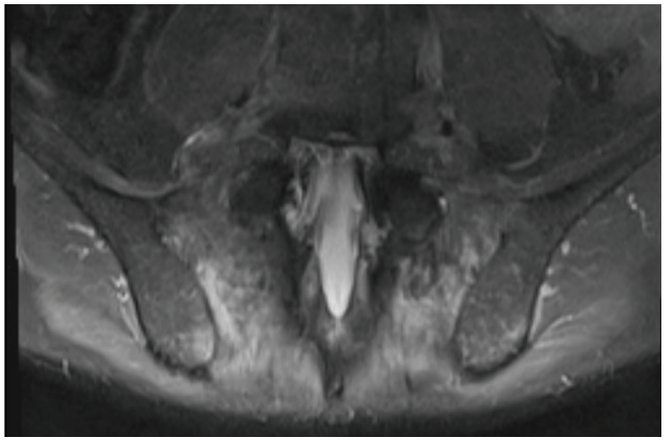
The patient was started on IV methylprednisolone 125 mg IV for three days, followed by 60 mg prednisone daily, along with methotrexate 15 mg daily and one dose of infliximab 7.5 mg/kg.



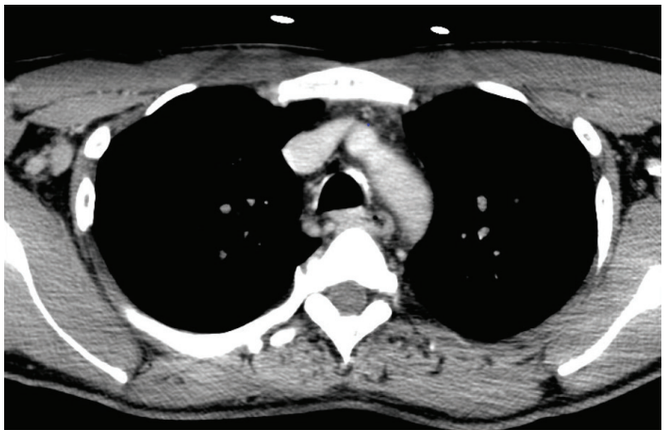
Picture 1. Uptake in the auditory canal cartilaginous segments



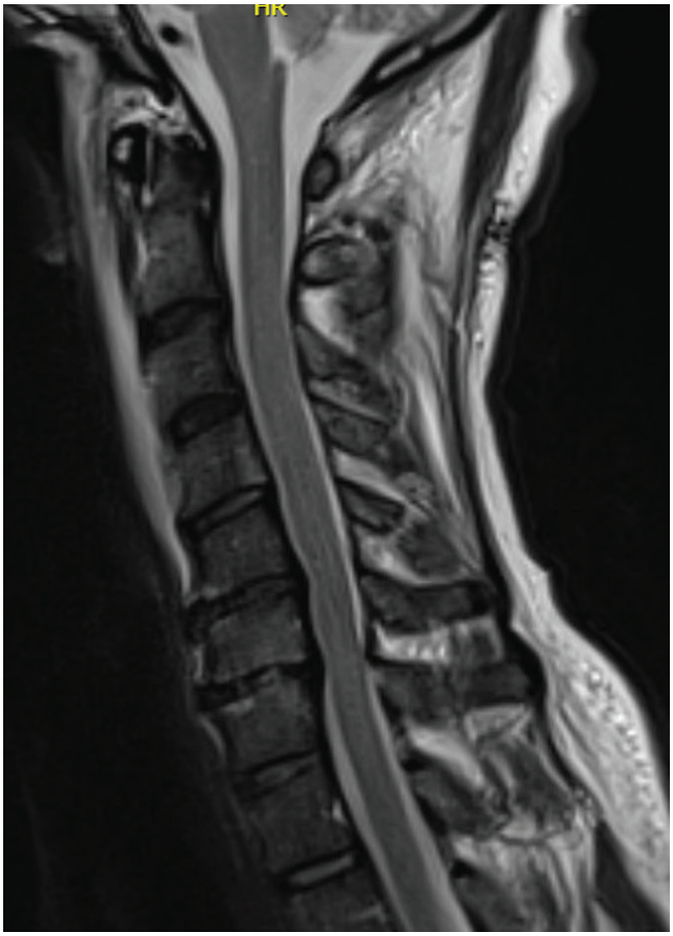
Picture 2. Uptake in the bilateral sacroiliac joints



Picture 3. Inflammatory changes in the paravertebral lymph nodes



Picture 4. Tracheal calcification musculature and posterior (ligamentous part) of SI joints



Picture 5. Edema in the C2-C4 anteriorly, mostly representing ligamentous inflammation, and in the cartilaginous part of the vertebrae

He rapidly responded to immunosuppressive therapy with resolution of pain and improvement in inflammatory markers and was discharged home with a steroid taper.

A neck CT showed small, non-enhancing fluid collection/effusion in the retropharyngeal space spanning from approximately the C2 vertebral body level through the inferior aspect of C4.

Commentary

This patient's unusual pattern of disease and striking imaging findings are a reminder of the diverse way relapsing polychondritis can present. The patient presented with rather nonspecific symptoms — fatigue, unintentional weight loss and joint pain. Although the initial concern was for underlying malignancy, the nasal bridge inflammation, ear swelling and neck stiffness turned the differential diagnosis to potential RP. The differential diagnosis for nasal bridge inflammation and auricular swelling is relatively narrow, most commonly RP, granulomatosis with polyangiitis (GPA), or syphilis, although the latter two were less likely in the context of negative serologies.

Auricular chondritis is the most common and characteristic manifestation of RP, noted in 85% to 95% of patients, with nasal chondritis only slightly lower at 60% to 75% of patients (reference). Respiratory chondritis occurs in 30% to 60% of patients, involving either upper or lower airway, and can be difficult to distinguish from the subglottic stenosis seen in GPA. GPA is typically localized in the subglottic airway and is circumferential, whereas RP is more tracheal and often more localized anteriorly with calcifications, which this patient had.

Some aspects of his presentation, however, are unusual. On physical exam, the patient had limited ability to rotate his neck, and the MRI demonstrated an edema-like signal change along the anterior longitudinal aspect of the upper cervical spine. The patient also complained of years of low back painand evidenced sacroiliac pain with palpation. A pelvic MRI showed edema-like changes surrounding the SI joints, predominantly in the posterior ligamentous portion, rather than inflammation in the joints themselves, which is typically seen in spondyloarthritis. There were similar edema changes in the paravertebral muscles and ligaments at multiple levels. Axial involvement in RP is a rare manifestation.

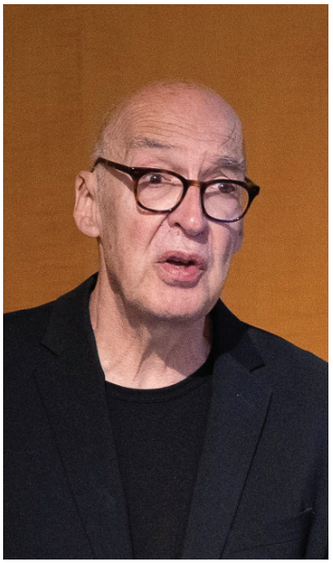
Reassuringly, the patient responded rapidly to glucocorticoids and tumor necrosis factor (TNF) inhibition and was able to be discharged. Upon follow-up, his glucocorticoids were tapered to nearly zero. He was tolerating TNF inhibition, his pain had diminished, and his range of motion had substantially improved.

References

Mertz P, Costedoat-Chalumeau N, Ferrada MA, *et al.* Relapsing polychondritis: clinical updates and new differential diagnoses. *Nat Rev Rheumatol*. 2024 Jun;20(6):347-360.

Biologics XI and Vasculitis 2025

Summit offers insights from bench to patient care and beyond



Dr. Leonard Calabrese

Dr. Rula Hajj-Ali

It can be nearly impossible for clinicians to keep up with the cascade of information and advances in the care of patients with rheumatic and immunologic diseases. At Cleveland Clinic's Biologic Therapies Summit XI and Vasculitis 2025, internationally recognized faculty will bring focus and up-to-date insights to discussions around the most important science, clinical care and patient quality-of-life issues of the day.

The conferences will be May 8-10, 2025, in person at the InterContinental Hotel & Conference Center in Cleveland and livestreamed free.

"This is a clinical conference that takes complex immunologic topics and translates them for the frontline practitioner — both physicians and advanced practitioners," says Leonard Calabrese, DO, Director of the R.J. Fasenmyer Center for Clinical Immunology.

Vasculitis 2025: Advances and Controversies

The weekend begins Thursday with Vasculitis 2025: Advances and Controversies, a daylong symposium dedicated to this family of rare and challenging diseases. Cleveland Clinic's Center for Vasculitis Care and Research is a leader in research, patient education and clinical care for vasculitis patients.

"Our goal is to bring up-to-date information to the community of rheumatologists," says Symposium Chair Rula Hajj-Ali, MD, Associate Director of Cleveland Clinic's Center for Vasculitis Care and Research and an expert in the field of vasculitis. "We focus on highly specialized topics and complex vasculitides, especially to support the general rheumatologist, nephrologist and pulmonologist."

Key topics and presenters include:

- Emergent Treatment in Small Vessel Vasculitis by Benjamin Terrier, MD, PhD, Professor of Medicine at Cochin Hospital in Paris and President of the French Vasculitis Study Group
- Emergent Treatment in Large Vessel Vasculitis by Carol Langford, MD, MHS, Director of the Center for Vasculitis Care and Research at Cleveland Clinic and President of the American College of Rheumatology
- Advances in the Management of Eosinophilic Granulomatosis With Polyangiitis by Michael Wechsler, MD, MMSc, Professor of Medicine and Director of The Cohen Family Asthma Institute at National Jewish Health
- Glucocorticoid Use in Small Vessel Vasculitis by Dr. Terrier and in Large Vessel Vasculitis by Tanaz Kermani, MD, Founder and Director of the Vasculitis Program at the University of California, Los Angeles
- Imaging of Large Vessel Vasculitis by Kaitlin Quinn, MD, Staff Clinician at Vasculitis Translational Research Program at the National Institute of Arthritis and Musculoskeletal and Skin Diseases

Afternoon sessions are presented by expert Cleveland Clinic and guest faculty and focus on diagnostic modalities in systemic vasculitides, with presentations on large vessel vasculitis imaging, kidney pathology in small vessel vasculitis, pathology in large vessel vasculitis and ophthalmologic assessment in giant cell arteritis.

Finally, in Debates in Vasculitis, faculty will appraise the pros and cons of controversial topics in the diagnostic and treatment approaches for various vasculitides to provide in-depth review of these discussions.

"This symposium addresses topics most important to the management of patients and brings therapeutic advances to clinicians," says Dr. Hajj-Ali. "Attendees will hear about very challenging cases and how the experts approached them. And just as importantly, we present an opportunity for them to converse and make connections with highly specialized colleagues in the field."

Biologic Therapies Summit XI

The biennial Biologic Therapies Summit takes place Friday and Saturday, May 9-10.

"It is dedicated to the intersection of advances in biologics and immune-based therapies and the practitioner in the broad field of rheumatology and clinical immunology, particularly for those who are not research based and without laboratory backgrounds in the field," says Dr. Calabrese.

"Most noteworthy to me in this conference is the opening session, Advances in Basic and Translational Immunology for the Clinical Rheumatologist," he adds. "The people we've invited are renowned scientists working in some relevant clinical space of immunology, and are known for their ability to translate their work so that this target audience can get a lot out of it."

Deepak Rao, MD, PhD, will present the keynote, Immune Profiling of Patients With Autoimmune Diseases: Defining Metrics of Immune Dysregulation. Dr. Rao is a rheumatologist and immunologist at Brigham and Women's Hospital and Co-Director of the Center for Cellular Profiling.

Other opening session topics include:

- The Evolution of Immune Effector Cell Therapies for the Treatment of Autoimmune Diseases, presented by Maximilian F. Konig, MD, Director of the Cellular Therapy Program in the Department of Medicine at the Johns Hopkins University School of Medicine
- IL-23 – Advances in Basic and Clinical Immunology, presented by Christopher Ritchlin, MD, MPH, of the University of Rochester
- New Insights Into the Role of EBV in Autoimmune Diseases, presented by William Robinson, MD, PhD, Chief of the Division of Immunology and Rheumatology at Stanford University

The Biologics conference also will provide an opportunity for rheumatology trainees from across the country to apply to present during a scientific abstract session. Those accepted will receive scholarships to help offset the cost of attending the conference.

"We have always made the meeting registration free for physicians in training," says Dr. Calabrese. "And we have one of the lowest cost structures of any meeting in this class."

For those who can't attend in person, the entire meeting is available online free with full CME credit.

"We market this conference internationally so that many clinical immunologists and rheumatologists in resource-poor areas can take full advantage of it," Dr. Calabrese says. "And since the very beginning, we have posted our meeting immediately as an enduring educational activity for free. Part of the mission of the R.J. Fasenmyer Center is to educate the broad community of clinicians, patients and other allied health professionals at no cost when we can do it."

"Biologic therapies have transformed the treatment of millions of people with immune-based diseases around the world," says Dr. Calabrese. "Now scores and scores of biologic therapies are either approved or in advanced trials.

"In the past three years, we're now in a second revolution of advances, both at the basic level and in the introduction of these advanced cellular and immune-based therapies," he adds. "They have the prospect of not only far deeper remission than we ever considered, but the possibility of cure."

Dr. Langford discusses her vision and goals at the ACR Business Meeting in November 2024 after being inducted as the 88th ACR president. (Picture courtesy of the American College of Rheumatology)

Becoming President of the American College of Rheumatology

A conversation with Dr. Carol Langford

In November 2024, Carol Langford, MD, MHS, was inducted as the 88th president of the American College of Rheumatology (ACR), becoming the first ACR President from Cleveland Clinic. We spoke to Dr. Langford about the ACR, her involvement with this organization, her goals for the next year, and the history between the ACR and Cleveland Clinic.

Can you tell us about the ACR?

The ACR is a not-for-profit professional association committed to advancing the specialty of rheumatology that serves more than 10,000 physicians, rheumatology professionals, researchers and scientists worldwide. In doing so, the ACR offers education, research, advocacy and practice management support to help its members continue their innovative work and provide quality patient care. The ACR was founded in 1934 and went through name changes as it evolved, becoming known as the American College of Rheumatology in 1988.[1] An interesting historical point for me was learning that one of the first meetings of this fledgling organization was held in 1934 in Cleveland.

Continued on next page

How did you get involved with the ACR?

My first exposure to the ACR was in 1991, attending the annual meeting as a fellow. Seeing the rheumatology community come together through the ACR in a setting where fellows, expert practicing clinicians, investigators conducting clinical and basic research, and rheumatology professionals could all learn from each other, was an eye-opening experience. It was at that point that I knew the ACR was an organization I wanted to be a part of. My first volunteer experience came in 1995, when I was asked to be a vasculitis abstract reviewer. From that point on, I was engaged with the ACR in different volunteer positions on subcommittees, committees, journals, guidelines, the board of directors, and the executive committee, gaining something new and valuable in every role.

Why has involvement in the ACR mattered to you, and would you suggest this to others?

The ACR has been a wonderful experience for me in being able to meet people from broad geographic areas who have different skill sets and perspectives. Learning from them brought tremendous professional and personal growth in ways that I would not have otherwise had a chance to experience. I truly believe that others would find this as meaningful as I have, and I would encourage all rheumatologists and rheumatology professionals to consider volunteering with the ACR, the Association of Rheumatology Professionals (ARP) or the Rheumatology Research Foundation.

What are your goals for your President year?

The mission of the ACR is to empower rheumatology professionals to excel in their specialty. During this year, it is my goal to shine light on three focus areas. The opportunity for lifelong learning is one privilege of being a rheumatologist. My first goal is to highlight the many ways the ACR can meet each person's educational objectives and be the place they choose to come to increase their knowledge. Research is the catalyst through which novel innovations are made that impact our patients. My second goal is to highlight how the ACR supports investigators to conduct, present and publish their research. Finally, my third goal is to enhance connections between the ACR and its members, such that everyone within our rheumatology community sees their objectives and priorities reflected through the ACR's commitment to its mission.

How has Cleveland Clinic been engaged with the ACR?

Cleveland Clinic has a wonderful history with the ACR, and I have very much followed in the footsteps of those around me. Our Chair, Dr. Abby Abelson, has been inspirational as an ACR volunteer and past president of the Rheumatology Research Foundation. Many of my Cleveland Clinic colleagues have served in important volunteer positions, including on committees and on the board of directors for the ACR, ARP and Foundation. Additionally, our fellows have been engaged in fellow in training volunteer roles with the ACR. Most importantly, department faculty and fellows have actively engaged in education and research published through ACR journals and presentations at ACR Convergence, the ACR's annual meeting, through which they advanced rheumatology and made a difference in the lives of patients.

Reference
1. Pisetsky, D. *The ACR at 75*. Hoboken, NJ: Wiley & Sons; 2009.

Cleveland Clinic faculty and fellows attend the ACR Business Meeting in November 2024. (Picture courtesy of the American College of Rheumatology)

Muscle Weakness Does Not Always Mean Myositis

Jennifer Elise Abdalla, MD, and Ambreesh Chawla, MD

A 45-year-old female with a history of previously diagnosed juvenile myositis in the 1980s presented to our rheumatology clinic for further evaluation of inflammatory myositis. Her symptoms began at age 7, when she had hand weakness and difficulty rising from a chair in conjunction with recurrent falls, and she ultimately required use of a wheelchair. She also exhibited a toe-walking gait, which led to Achilles tendon-lengthening surgery. A muscle biopsy of her calf performed at the time noted "polymyositis," and for many years she was treated for presumed juvenile polymyositis with prednisone, methotrexate and mycophenolate mofetil. Her creatine kinase (CK) level ranged from 200 U/L to a maximum of 583 U/L (reference range 42-196 U/L). Upon examination, she displayed diffuse, symmetric weakness of both proximal and distal muscle groups as well as bilateral elbow contractures.

Given the atypical features of her case — specifically distal muscle involvement, mildly elevated CK levels < 1000 U/L, and joint contractures — the diagnosis of inflammatory myositis was reconsidered. She was referred to Cleveland Clinic's Neuromuscular Medicine Clinic, where genetic testing corroborated the diagnosis of Bethlem myopathy.

This rare congenital muscular dystrophy is caused by a mutation in the *COL6A* gene, which encodes a critical component of type VI collagen. Bethlem myopathy is characterized by early-onset muscle weakness, typically in the first or second decade of life, along with increased distal joint laxity, joint contractures and muscle-tendon contractures. The disease progresses slowly, and CK levels are often normal or mildly elevated. Many patients eventually require assistive devices.[1] Inherited muscular dystrophies such as Bethlem myopathy sometimes can be misdiagnosed as idiopathic inflammatory myopathies (IIM), as both conditions can present with proximal muscle weakness.

IIM, also known as myositis, is a heterogenous group of autoimmune disorders that can be classified into multiple subgroups: dermatomyositis, polymyositis, anti-synthetase syndrome, immune-mediated necrotizing myopathy and overlap myositis. These conditions are relatively rare, with an incidence of 0.2-2 per 100,000 person-years and an annual prevalence of 2-25 per 100,000 individuals.[2] IIM typically presents over weeks to months with symmetric weakness affecting the proximal muscles of both the upper and lower extremities. Laboratory tests usually show a significant elevation in CK levels (often > 1,000 U/L) and the presence of myositis-specific antibodies in 50% to 60% of cases.[3] Several conditions can present with muscle weakness that may mimic IIM, including (but not limited to) muscular dystrophies, metabolic myopathies, mitochondrial myopathies, and toxic or endocrine-related myopathies.

This case highlights the importance of differentiating between these conditions and IIM to avoid unnecessarily exposing patients without IIM to systemic immunosuppressive treatments. Obtaining and performing a comprehensive medical history, physical examination, laboratory/serologic workup, electromyography, muscle biopsy and genetic testing are often critical to avoid an incorrect diagnosis. Certain clinical features that are incongruent with IIM and might point to an alternative diagnosis include slow evolution of weakness over years, family history of muscle weakness, asymmetrical weakness and predominantly distal muscle weakness.

References

1. Silverstein RS, Wang DD, Haruno LS, Lotze TE, Scott AC, Rosenfeld SB. Bethlem Myopathy (Collagen VI-Related Dystrophies): A Retrospective Cohort Study on Musculoskeletal Pathologies and Clinical Course. *J Pediatr Orthop*. 2023 Feb 1;43(2):e163-e167.
2. Khoo T, Lilleker JB, Thong BY, Leclair V, Lamb JA, Chinoy H. Epidemiology of the idiopathic inflammatory myopathies. *Nat Rev Rheumatol*. 2023 Nov;19(11):695-712.
3. Ghirardello A, Zampieri S, Tarricone E, *et al.* Clinical implications of autoantibody screening in patients with autoimmune myositis. *Autoimmunity*. 2006;39(3):217-221.

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Lupus Case Underscores CAR-T cell Potential for Quality-of-Life Benefit

Emily Littlejohn, DO, MPH

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For years, patient JG experienced severe fatigue, brain fog and numerous other symptoms of systemic lupus erythematosus, which eventually led her to stop working and participating in most normal daily activities. Since receiving CAR T-cell treatment in spring 2024, she has returned to work as well as to exercise and caring for her dogs.

For four years, a woman in her 20s with systemic lupus erythematosus (SLE) experienced a host of symptoms so severe that she was unable to perform basic activities of daily living: work, family celebrations, sports — even simply driving to the store.

That was until March 2023 at Cleveland Clinic, when she became the second participant in an international phase 1 clinical trial of chimeric antigen receptor (CAR) T-cell treatment for severe, refractory lupus. Six months after treatment, she was in drug-free remission and had returned to those activities she enjoyed before her diagnosis, and more.

As clinicians and scientists investigating CAR T-cell therapy for SLE and other autoimmune diseases, we temper hope with an understanding of the need for more research and data. Rigorous clinical trials and lab metrics are necessary to measure safety, efficacy and the longevity of this therapy.

As this patient's experience underscores, however, it is important to acknowledge patient-reported improvements in symptoms such as fatigue, depression and brain fog that are hard to measure with traditional disease activity tools.

Background

In February 2019, JG was diagnosed with autoimmune hepatitis (lupus hepatitis). She was placed on daily azathioprine and tacrolimus and was feeling well until November 2019, when she was found to have proteinuria. Cleveland Clinic nephrologists examined her and performed a renal biopsy was performed; it showed membranous glomerulonephritis with mesangial and subepithelial electron-dense deposits with foot process effacement, consistent with class V lupus nephritis. She was then switched to mycophenolate mofetil from azathioprine.

Around this time, the patient began to report chest pain and difficulty breathing. A chest CT revealed an acute pulmonary embolism causing small infarct and small left pleural effusion. CT also showed bilateral axillary/subpectoral lymphadenopathy. A left axillary lymph node biopsy revealed no evidence of a metastatic neoplasm or granulomatous inflammation. Given the presence of antiphospholipid antibodies, the patient was placed on warfarin.

Over time, she developed severe hip pain, and an MRI showed bilateral avascular necrosis, a known complication of SLE. Over the course of six months, both hips were replaced.

Due to ongoing joint pain and diffuse adenopathy, the patient was eventually given belimumab subcutaneous weekly injections and, later, rituximab infusions, with only some decrease in joint pain.

Unfortunately, she continued to experience the fatigue and brain fog that had caused her to stop work and other activities, such as traveling and working out, for more than four years.

In December 2023, the patient received her last rituximab infusion. In March 2024, she was enrolled in a phase 1 CAR T-cell therapy clinical trial for severe, refractory lupus. She experienced no cytokine release syndrome or immune effector cell-associated neurotoxicity syndrome during or after her CAR T-cell therapy infusion.

At nine months out from CAR T-cell therapy, the patient remained in drug-free remission and had returned to social activities. Seeing her in office, she endorsed less fatigue and an overall sense of well-being and improved mood — something not capturable or reportable by measures of disease activity in SLE, but life-changing for this patient. She was excited to be planning a vacation cruise and coming off disability status to return to work.

Takeaways

For many individuals with lupus, the toll of the disease extends beyond the difficulties of managing organ damage and physical symptoms such as joint pain, rash or alopecia. Those with lupus also suffer from chronic fatigue, brain fog and depression, symptoms that are difficult to measure but significantly impair overall sense of well-being. CAR T-cell therapy not only offers the chance to put severe, refractory lupus into a drug-free remission, but is providing reason for optimism that those with SLE may experience improvement in quality of life.

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