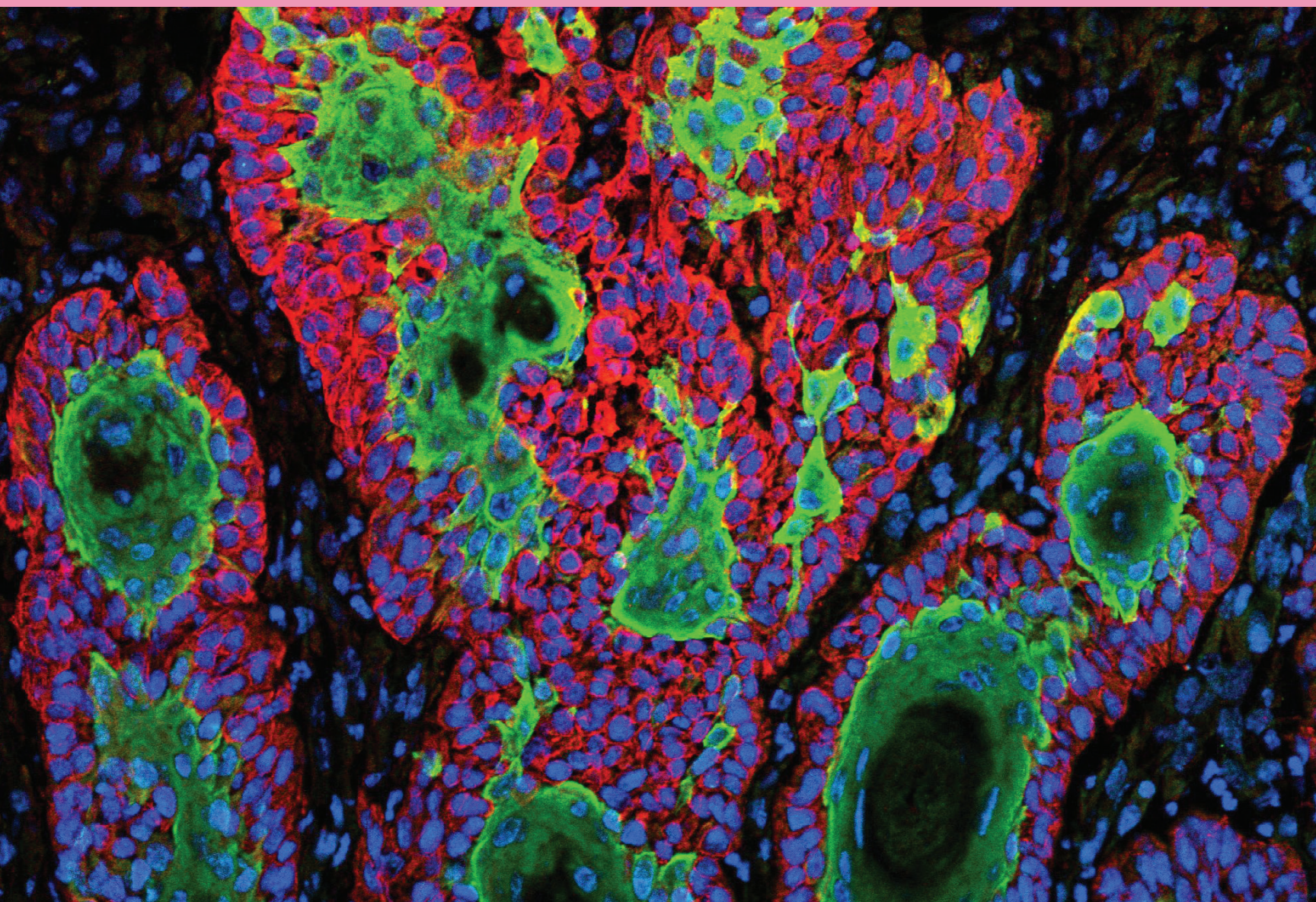
IN THIS ISSUE:

Cleveland Clinic

Rheumatology Connections

An Update for Physicians | Winter 2024



From the Chair of Rheumatic and Immunologic Diseases

Dear Colleagues,

Welcome to our winter 2024 issue of *Rheumatology Connections*.

In our cover story (page 3), Dr. Carol Langford presents a patient who is being treated with azathioprine for his granulomatosis with polyangiitis (GPA). Immunosuppression puts some patients at higher risk for skin cancer, which he has developed on several occasions. Dr. Langford's consultations with the patient's dermatologist demonstrate the importance of collaborative care, close surveillance and counseling for patients receiving immunosuppressive therapies.

This issue also offers other intriguing case reports with valuable clinical insights.

On page 8, Dr. Soumya Chatterjee presents a case of a patient with systemic sclerosis who was treated with pantoprazole for her gastroesophageal reflux symptoms related to her disease. During a routine endoscopy, Candida albicans was found on her esophagus. Dr. Chatterjee discusses the finding and its connection to disease treatment.

Dr. Aditi Patel and colleagues review the case (page 12) of a patient with mixed connective tissue disease with features of overlap myositis. The patient received care in Cleveland Clinic's Rheumatic Lung Disease program, an interdisciplinary clinic where patients with rheumatic diseases with pulmonary involvement see both rheumatologists and pulmonologists working collaboratively.

In our recurring Case Conference series (page 14), Drs. Adam Brown and Komal Ejaz discuss the process of diagnosing urticarial vasculitis, in which systemic involvement may include angioedema.

Other topics in this issue:

- Dr. Emily Littlejohn, director of our Lupus Clinic (page 6), explains the clinic's multidisciplinary approach and how our robust biobank supports both patient care and research.
- Dr. Cassandra Calabrese (page 9) shares details about the establishment of Cleveland Clinic's new Oncology Pharmacovigilance Clinic. With the advent of checkpoint inhibitors to treat cancer, we have seen a rise in the number of patients experiencing immune-related adverse events (irAEs), many of which mimic rheumatic disease. These patients now can receive coordinated care in managing their irAE symptoms as well as their malignancy in this interdisciplinary program.
- Drs. Elaine Husni and Shashank Cheemalavagu report their findings from research about factors associated with the transition that is seen in patients with psoriasis (PsO) who develop psoriatic arthritis (page 10).

Thank you for taking time to catch up on the important work we are doing. As always, please reach out if you see opportunities to collaborate with us.

Respectfully,

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On the cover:
This image shows the uncontrolled growth of cells in squamous cell carcinoma (SCC), the second most common form of skin cancer. Patients with immunosuppression are at a higher risk for developing SCC.
See story, page 3.

This image is part of the *Life: Magnified* collection. Credit: Markus Schober and Elaine Fuchs, The Rockefeller University.

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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.

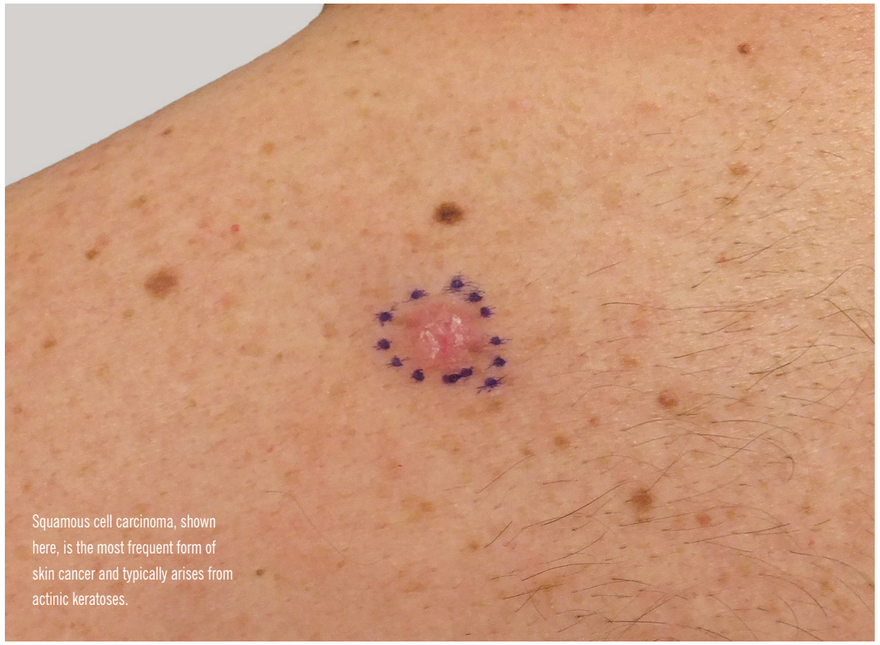
CME Opportunities: LIVE AND ONLINE

Visit clevelandclinic.org/rheumcme for the full slate of continuing medical education from Cleveland Clinic's R.J. Fasenmyer Center for Clinical Immunology. Among current offerings from the Biologic Therapies Summit X and Vasculitis online series:

- Current Issues in ANCA-Associated Vasculitis
- Organ-Specific Issues in Vasculitis
- Lupus: Advances in Diagnosis and Management
- Key Issues in the Differential Diagnosis of Vasculitis
- CNS Vasculitis

Skin Cancer Risk in Immunosuppressed Patients

by Carol A. Langford, MD, MHS



Squamous cell carcinoma, shown here, is the most frequent form of skin cancer and typically arises from actinic keratoses.

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

You take care of a 72-year-old male with granulomatosis with polyangiitis (GPA). He presented with severe disease involving the lung and kidney nine years ago, requiring admission to the intensive care unit. Within the first year, he experienced one relapse after maintenance therapy was held for a serious infection. Since that time, he has remained in remission on azathioprine. He experienced chronic renal insufficiency from his initial presentation and now has a baseline creatinine 1.9 ml/dL with eGFR 35 ml/min, which has been stable. His quality of life has been excellent and in prior discussions he has expressed his wish to remain on azathioprine with the goal of reducing his risk of relapse. As a young man, he worked outdoors and had significant sun exposure with the later development of numerous actinic keratoses (AK). He now sees a dermatologist every three months to monitor for skin cancers, which he develops on a regular basis. His dermatologist contacts you to discuss his management.

Skin cancer and immunosuppression

Skin cancer is the most common cancer in the United States, with current statistics suggesting that one in five Americans will develop skin cancer in their lifetime[1]. Squamous cell carcinoma (SCC), the most frequent form of skin cancer, typically arises from AK, which consist of aberrant epidermal keratinocytes that develop in response to prolonged ultraviolet (UV) radiation exposure. AK are considered the initial lesion in a disease continuum that may progress to SCC. Early detection plays a key role in minimizing the spread of skin cancers and providing the patient with the widest range of options for treatment.

People of all skin tones can develop skin cancer, with higher risk being seen in patients who have increased UV exposure from sunlight or use of indoor tanning beds, blond or red hair, and skin that burns easily. Treatment with immunosuppressive medications also represents

an important risk factor for skin cancer development, making skin cancer of even greater relevance to patients with rheumatic disease. The largest body of supportive evidence for this association comes from organ transplant recipients, for whom the risk of skin cancer is up to 100-fold higher than the general population.[2-4]

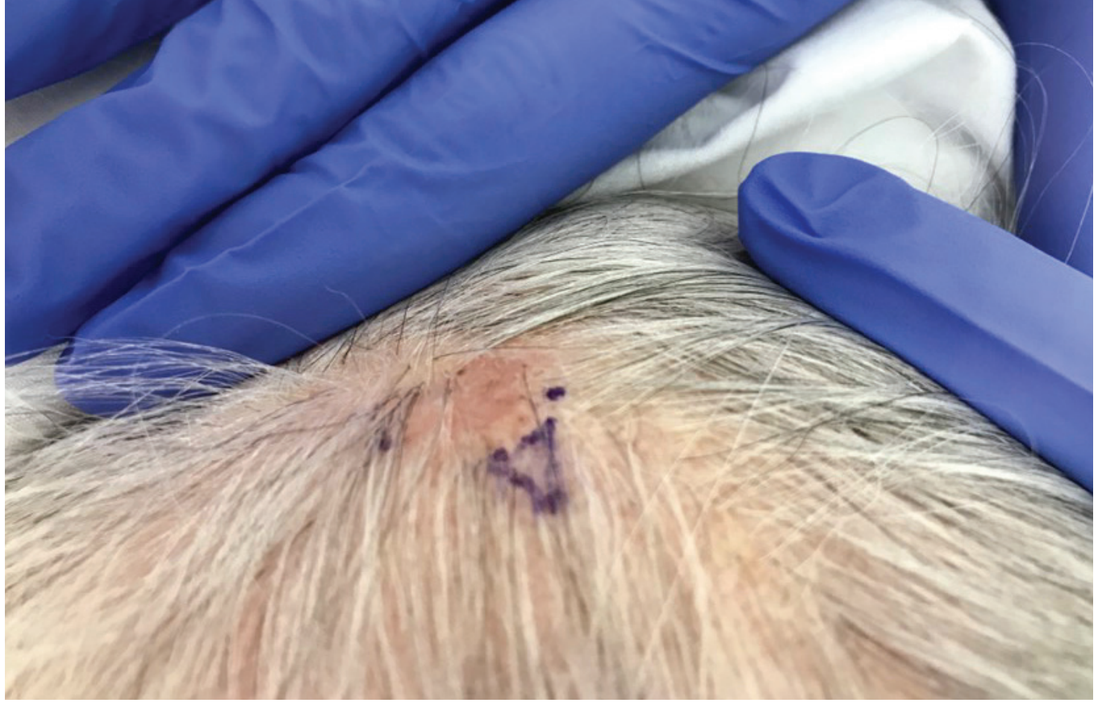
The mechanism through which immunosuppression increases skin cancer development is likely multifactorial, with reduction of host defense mechanisms that allow the body to detect and eliminate abnormal cells playing a prominent role. Immunosuppressive medications may also hasten the progression of AK to SCC and may themselves have properties that influence mutagenic potential. In transplant patients, the duration and dosage of immunosuppressive medications have been found to correlate with skin cancer risk as well as the type of immunosuppressive drug. Skin cancer development has been well-described with conventional immunosuppressive agents such as cyclophosphamide, azathioprine, methotrexate, mycophenolate and calcineurin inhibitors. Although it is less clear that a similar association exists with biologic agents and small molecule inhibitors, taking a cautious approach that any medication that impacts host defense may increase skin cancer risk offers an opportunity to protect our patients against this common malignancy.

For patients who do develop non-melanoma skin cancers, withdrawal of immunosuppressive medications is often not an option in cases where the patient has a rheumatic disease where these are necessary to control the underlying inflammatory process. In most instances, it may also not be a good option to switch to a different agent in a patient who is doing well, as making a change will not eliminate the risk of skin cancer, the alternative also may not control the underlying disease to the same degree, and it will be associated with its own toxicities that could pose a greater threat than skin cancer where there is a careful program of monitoring and early detection.

Keys to minimizing skin cancer risk

The first step toward reducing skin cancer risk for immunosuppressed patients comes in recognizing this association and providing proactive patient education. Preventive strategies include avoidance of indoor tanning beds. When outdoors, clothing should be used to cover as much exposed skin as possible. To protect skin not covered by clothing, it's a good idea to wear a wide-brimmed hat and sunglasses with UV protection, and apply a broad-spectrum, water-resistant sunscreen with an SPF of 30 or higher. In addition to protection against skin cancer, these strategies have additional benefit in rheumatic diseases associated with photosensitivity and where patients are receiving medications that can increase the risk of sunburn (NSAIDs, sulfonamides, methotrexate are examples). Regular use of sunscreen is important but often underutilized by immunosuppressed patients. An ever-increasing number of skin care products and cosmetics incorporate a sunscreen, making this easier to include in daily life. While older patients may have already sustained solar skin damage many years ago, reducing further injury is beneficial. For younger patients, early adoption of sunscreen use will provide later benefits.

Preventive strategies include avoidance of indoor tanning beds. When outdoors, clothing should be used to cover as much exposed skin as possible. It's a good idea to wear a wide-brimmed hat and sunglasses with UV protection, and sunscreen with an SPF of 30 or higher.



Opportune times to provide reminders about solar protection include office visits going into summer months and when the patient mentions a planned vacation to a sunny location; it should be emphasized, though, that UV exposure occurs outside regardless of the weather conditions. If a patient comes to a clinic visit with a sunburn, it provides an occasion to discuss with them that this represents skin damage and increases the potential for skin cancer.

Monitoring for skin cancer is also essential. Self-checks looking for changes in size, shape or color of a skin lesion, new lesions, or a sore that doesn't heal can be valuable in early detection. Emphasizing that immunosuppressed patients should receive an annual skin assessment by a dermatologist is also important. For those who have demonstrated a propensity to develop skin cancers, more frequent dermatology visits may be necessary to detect early cancers and monitor evolving AK lesions.

Return to our case patient

This patient exemplifies the risk of skin cancer that can be seen in immunosuppressed individuals. He sustained significant cutaneous solar damage in his youth with the development of AK later in life. Following the addition of immunosuppression that was lifesaving in the management of his GPA, he is now developing skin cancers, which was discussed with his dermatologist. In shared decision making with the patient, we concluded that it was in his best interests to remain on azathioprine, which has been otherwise well tolerated, and which has controlled his disease activity. He continues to maintain skin protective measures and receive regular dermatology assessments.

Skin cancer is a common and possibly underappreciated risk in immunosuppressed people with rheumatic disease. Patient education is important as the use of preventive and monitoring strategies can lessen the risk of skin cancer development and allow detection of lesions at an early point where these may be most effectively managed.

Because of the increased risk of skin cancer, patients should be counseled to perform self-checks and to have skin assessments by a dermatologist once a year – more often if they have shown a propensity to develop cancers.

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Coordinated Care, Education and Research

Lupus Clinic providers collaborate to advance treatment and understanding

by Emily Littlejohn, DO, MPH

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

In the Lupus Clinic, Dr. Littlejohn uses a dermatoscope to examine a discoid on a patient's back.

Since the first description of systemic lupus erythematosus (SLE) by Laurent Théodore Biett nearly two centuries ago, the medical community has achieved great strides in the understanding and management of lupus. Advances in drug therapies have improved morbidity and health-related quality of life. That said, this enigmatic disease continues to challenge us to improve on early diagnosis, anticipating and preventing flare-ups, optimizing old and new drugs and, most importantly, finding a cure.

At Cleveland Clinic, specialists in our Lupus Clinic are collaborating to advance science and patient care with the goal of reducing and eventually eliminating the toll lupus takes on an estimated 5 million people worldwide.

Here are a few highlights of what we are doing in our Lupus Clinic.

Shoulder to shoulder on patient care

Our multidisciplinary clinic operates under the direction of rheumatologist Emily Littlejohn, DO, MPH, in collaboration with Laura Provenzano, MD, a specialist in lupus nephritis. The clinic was born of the wish for closer collaboration among physicians who treat patients with complex disease and multiple organ involvement.

Lupus Clinic patients meet with both specialists on the same day, allowing for clear, immediate communication. This is especially important for patients with lupus nephritis, which can damage the kidneys and put patients at higher risk for some cancers and cardiovascular complications. Between 30% and 50% of patients with lupus will develop related kidney disease. It is the lupus manifestation that is most urgent to control.

Patients seen in the clinic also benefit through our team's involvement in trials for lupus and lupus nephritis. They're at the cutting edge of potential new research trials.

Biobank

Within the 22,000-square-foot Cleveland Clinic BioRepository, the lupus biorepository banks blood and urine specimens of our lupus patients. Specimens are tagged with information about general health, lupus activity, smoking and recreational drug use, exposure to heavy metals and other substances, reproductive health history, medications and more. This provides longitudinal data on nearly 400 participating patients across multiple races and ethnicities.

This resource is invaluable. Uncommon diseases present challenges for collecting specimens longitudinally and for establishing cohorts. We collect specimens from a given patient about every six months – sometimes sooner if they're experiencing a flare-up. This rich research platform has provided insight into variables that affect lupus activity and can identify changes in markers for disease over time. It also provides blood and urine specimens for myriad future research projects.

The Lupus Clinic and the biobank also are resources for medical students and medical residents on rotation. Students get hands-on experience with lupus patients and have access to the biobank for use in clinical and translational research projects.

Research

Two exciting new clinical trials are getting underway in fall 2023:

- Brain fog in lupus. Neuropsychiatric lupus (NPSLE) is among the most vexing conditions for patients and their physicians. A high percentage of patients with lupus experience the associated memory problems, difficulty finding words and sense of decline in mental acuity. However, these symptoms do not always correlate with lupus activity in the blood, and the mechanisms involved are unknown. NPSLE remains hard to define, diagnose and treat. ClearMEMory is a phase 1 randomized, placebo-controlled trial to test the safety and efficacy of memantine to treat cognitive impairment in systemic lupus erythematosus. The primary outcome is the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) total index at 12 weeks in the memantine and placebo groups for those with substantial neuropsychiatric manifestations of lupus.
- CAR-T therapy in multi-organ disease refractory lupus. A pivotal study done in Germany under Georg Schett published in 2022 in *Nature Medicine* reported on five patients with severe lupus involving multiple organs who entered remission after receiving chimeric antigen receptor (CAR) T cell therapy. Cleveland Clinic will begin a dose-ranging study exploring the potential utility of depletion of CD19+ B cells and plasmablasts with CD19-specific CAR T cells to induce disease remission. CD19-Targeted Nex-T Chimeric Antigen Receptor (CAR) T Cells, in Participants with Severe, Refractory Systemic Lupus Erythematosus is a phase 1 study of SLE in patients who have a severe, life-threatening disease course and have been refractory to currently available therapies.

Our Lupus Clinic creates an environment that allows us to give today's patients with SLE the best care available while we pursue the newest science and train the minds that will yield benefits for the patients of tomorrow.

Left: Dr. Littlejohn reviews a chest x-ray with a patient recently diagnosed with pneumonia.

Below: Dr. Littlejohn assesses the overhead range-of-motion of the patient's shoulder joints.

Esophageal Plaques in a 68-Year-Old Woman with Systemic Sclerosis

by Soumya Chatterjee, MD, MS, Tarik M. Elsheikh, MD, and Donald F. Kirby, MD, FACP

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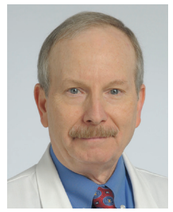
Dr. Elsheikh (elsheit@ccf.org; 216.444.3704) is Staff in the Department of Anatomic Pathology.



Dr. Kirby (kirbyd@ccf.org; 216.445.6609) is Director of the Center for Human Nutrition in the Department of Gastroenterology, Hepatology and Nutrition.

A 68-year-old woman with a 20-year history of systemic sclerosis suffered from chronic iron-deficiency anemia and required multiple iron infusions and packed red blood cell transfusions. Repeated upper endoscopies had shown active gastric antral vascular ectasias, a known complication of systemic sclerosis that causes chronic gastric blood loss.

She had undergone intermittent upper endoscopic ablation using argon plasma coagulation to control the persistent blood loss from gastric antral vascular ectasias. In addition, she needed pantoprazole 40 mg twice daily to control her acid reflux symptoms adequately. During her recent upper endoscopy for routine argon plasma coagulation, she was found to have localized white plaques in the middle third of the esophagus that could not be washed away with water irrigation. On microscopy of the brushings from the white plaques, fungal organisms morphologically consistent with Candida species were detected.

Fungal cultures grew Candida albicans. Based on the patient's reduced creatinine clearance, she was treated with oral fluconazole 100 mg daily for two weeks, followed by nystatin suspension 500,000 units swish and swallow prior to bedtime for three months.

Esophageal involvement in scleroderma can manifest as dysphagia (esophageal dysmotility), gastroesophageal reflux disease, odynophagia (ulcerative esophagitis), pill esophagitis, esophageal stricture, Barrett's esophagus, and rarely, adenocarcinoma.[1] Long-term proton pump inhibitor use is recommended in scleroderma patients, as esophageal dysmotility and lower esophageal sphincter dysfunction usually lead to gastroesophageal reflux disease and can result in the above complications.[1] However, it may not be commonly known that long-term proton pump inhibitor use is also a risk factor for esophageal candidiasis.[2,3]

Most cases of esophageal candidiasis are asymptomatic and incidentally discovered during an upper endoscopy performed for another reason, such as in this case.[3] However, sometimes patients develop odynophagia, dysphagia and retro sternal pain.[3] Esophageal ulceration and stenosis are rare.[3]

Other risk factors for esophageal candidiasis include human immunodeficiency virus infection, diabetes mellitus, smoking, glucocorticoid use, antibiotic use, esophageal achalasia, malignancy, radiation therapy, atrophic gastritis, advanced gastric cancer and gastrectomy.[2]

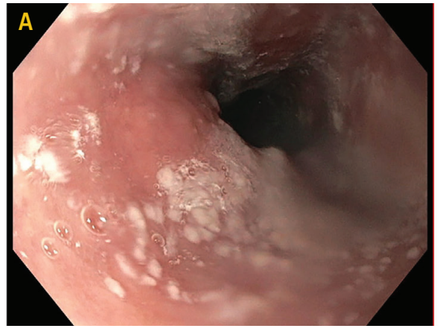


Figure A: Upper endoscopy in a 68-year-old woman with systemic sclerosis, showing localized white plaques in the middle third of the esophagus that were adherent to the mocosa and could not be washed off with water irrigation.

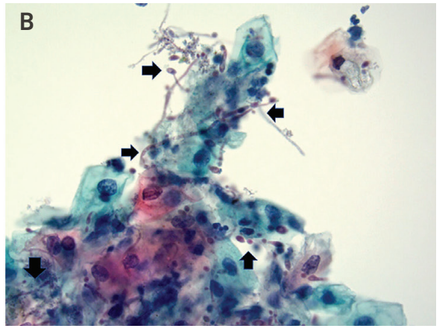


Figure B: Esophageal brushing cytology: *cytologic* examination revealed benign squamous cells and occasional neutrophils. There were numerous admixed fungal spores and pseudohyphae (arrows) staining red, morphologically consistent with Candida spp. (ThinPrep, Papanicolaou stain; 400£).

Diagnosis of esophageal candidiasis requires either cytology of brushing or biopsy of the white plaques seen on esophagoscopy, the former being more sensitive.[4] Cytology demonstrates the fungal elements of Candida species. Fungal cultures confirm the diagnosis, help determine the Candida species, and allow antifungal susceptibility testing. Conversely, a mucosal biopsy is required to diagnose other etiologies of white esophageal plaques, such as epidermoid metaplasia, eosinophilic esophagitis and esophagitis dissecans superficialis.

During the passage from the oral cavity to the esophagus, the brush is protected by a sheath, eliminating the possibility of contamination by oral Candida. Systemic antifungal treatment is necessary to prevent complications such as esophageal stricture formation or perforation; for example, oral fluconazole, 200-400 mg daily for 14 to 21 days.[5] However, the dose needs to be adjusted for impaired renal function.[5] Also, drug-drug interactions may affect therapy. If oral therapy is not tolerated, intravenous fluconazole, an echinocandin, or even amphotericin B, can be used.[5]

This case provides evidence that occasionally, an esophageal problem in a scleroderma patient can be caused by their treatment, not their disease.

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First of Its Kind: Oncology Pharmacovigilance Clinic

Multidisciplinary care for patients with immune-related adverse events

by Cassandra Calabrese, DO

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The cancer treatment landscape was forever changed in 2011 with approval of the first checkpoint inhibitor, nivolumab. These drugs rev up the immune system to target tumor cells and have provided options for durable treatment responses for patients with previously untreatable cancers.

Unfortunately, due to their mechanism, they are attended by a spectrum of adverse events that mimic immune-mediated diseases (such as rheumatoid arthritis and colitis), and these are called immune-related adverse events (irAEs). With the increasing approval of new checkpoint inhibitor therapies for an ever-expanding list of indications, we are seeing a rise in referrals for irAE diagnosis and management, in rheumatology and other specialties.

In 2017, Cleveland Clinic created a multidisciplinary monthly tumor board, which continues to serve as a venue for discussion of challenging cases, review the extant literature and receive input on interprofessional management. In the past year, almost one third of the cases discussed at irAE tumor board are rheumatologic irAE cases.

Major academic centers have varying triage and referral processes for care of patients with irAEs. Cleveland Clinic is the first to create a multidisciplinary clinic to serve this purpose. In September 2023, the Oncology Pharmacovigilance Clinic was created in the Taussig Cancer Center under the guidance of Wen Wee Ma, MBBS, the inaugural Director of the Novel Cancer Therapeutics Center in Taussig. This clinic is in Taussig and occurs one half-day per week. It is staffed by myself, endocrinologist Keren Zhou, MD, and coordinated with Oncology.

Patients with irAEs are often acutely symptomatic with symptoms interfering with activities of daily living and disrupting their cancer treatment. Many are experiencing irAEs involving multiple systems. For these reasons, it is important there be timely access for their evaluation by oncology and appropriate subspecialists, and ideally in a coordinated fashion.

The goal of the Pharmacovigilance Clinic is to serve as a space for exactly that, fostering excellent patient care and in-person interactions between subspecialists. This type of clinic for irAE care exists nowhere else in the world, and we are proud to be involved in this ground-breaking endeavor. After this initial phase, the goal is to introduce additional specialists such as gastroenterology, cardiology and beyond.

Unlocking the Age Factor

Older Psoriasis Patients May Experience Quicker Transition to Psoriatic Arthritis

by M. Elaine Husni, MD, MPH, 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.

Psoriatic arthritis (PsA) is a condition that affects up to 30% of individuals with psoriasis (PsO). Typically, PsA emerges approximately seven to 10 years after the onset of PsO. However, the timing of transition can vary significantly, leading to delays in diagnosis and high rates of undiagnosed PsA.

In this study, we aim to identify clinical and demographic factors associated with the time it takes for PsO to transition to PsA.

Methods

In our longitudinal psoriatic disease cohort, we identified individuals with both PsO and PsA diagnoses. We measured the duration between the dates of PsO and PsA diagnosis, treating it as a continuous outcome variable using multivariable linear regression analysis.

Our list of candidate predictors included: gender, age at PsO diagnosis, family history of PsO, BMI, treatment, cardiovascular disease, hypertension, diabetes, dyslipidemia, nail involvement, Dermatology Life Quality Index (DLQI), elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), alcohol use and smoking habits.

We also created a subgroup model utilizing individual data with body surface area (BSA) data, and narrowing down the predictors to age at PsO diagnosis, smoking habits, elevated ESR/CRP, BMI, and family history of PsO. Model results were presented using coefficient estimates and respective 95% confidence intervals. Variables were also ranked based on their relative contribution to the models, as assessed by Akaike Information Criterion (AIC). All tests were two-sided, assuming an alpha level of 0.05.

Results

Our analysis included a cohort of 384 patients with a median age at PsO diagnosis of 30.4 years, and 52.2% of patients were female. Importantly, we found that age at diagnosis of PsO is significantly linked to the time it takes for PsO to progress to PsA. For example, when patients reach an age of around 42 (Q3), they experience, on average, approximately 12 fewer years between their PsO to PsA diagnoses compared to patients diagnosed at 18.9 years (Q1), even after controlling for relevant variables in the model (-11.88 (-13.64, -10.12); $p < 0.001$).

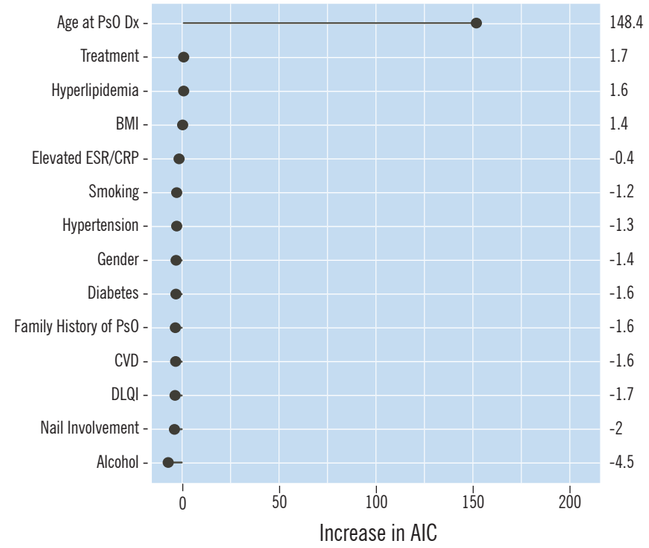
Furthermore, our findings regarding use of biologic disease-modifying anti-rheumatic drugs (bDMARDs) revealed that these individuals tend to experience a shorter time frame, averaging 4.5 fewer years between PsO to PsA compared to patients on NSAIDs only, after controlling for other variables in the model (-4.52 (-8.3, -0.74), $p = 0.02$).

Although the use of bDMARDs demonstrates a trend toward shorter transition period (4.5 years) compared to non-bDMARDs, the overall effect of treatment was not statistically significant. Similarly, patients with BSA of 5% (Q3) have on average 1.1 more years from PsO to PsA than patients with BSA of 0.5% (Q1) after controlling for other variables in the model (1.11 (-0.44, 2.65), $p = 0.16$), although the overall effect of BSA is not statistically significant.

The analysis revealed that the most influential factor in the model, as indicated by the AIC, was the age at which PsO was diagnosed. An AIC score exceeding or equal to 2 suggests a statistically enhanced model, thus emphasizing the value of incorporating age as a variable in the model.

Conclusion

Our study offers compelling evidence that the age at which psoriasis first appears serves as an important predictor for the transition from psoriasis to psoriatic arthritis. Older individuals diagnosed with PsO tend to progress to PsA more rapidly. The time difference is not only statistically significant but also carries crucial clinical implications. Compared to their younger patient cohort (diagnosed at 18.9 years, Q1), older patients (diagnosed at 42.6 years, Q3) develop PsA an average of 12 years sooner.



Multivariable Analysis of Risk Factors Associated with the Time to Develop Psoriatic Arthritis in Patients with Psoriasis

Factor	Level	Estimate (95% CI)	Pvalue	Omnibus test of the variable
Sex	F (v M)	0.85 (-1.44, 3.13)	0.468	0.468
Age	IQR Increase	-11.88 (-13.64, -10.12)	*<0.001*	*<0.001*
Family History of PsO	Yes (v No)	-1.77 (-7.62, 4.08)	0.554	0.554
BMI	IQR Increase	-1.19 (-2.49, 0.11)	0.074	0.074
Treatment	oral DMARD (v NSAID only)	-3.36 (-7, 0.27)	0.07	0.065
	bDMARD (v NSAID only)	-4.52 (-8.3, -0.74)	0.02	
Nail Involvement	Yes (v No)	0.16 (-4.06, 4.38)	0.942	0.942
DLQI	IQR Increase	0.03 (-0.08, 0.15)	0.578	0.578
CVD	Yes (v No)	1.27 (-2.97, 5.51)	0.558	0.558
Hypertension	Yes (v No)	1.14 (-1.53, 3.82)	0.402	0.402
Diabetes	Yes (v No)	1.05 (-2.16, 4.27)	0.522	0.522
Hyperlipidemia	Yes (v No)	2.51 (-0.14, 5.15)	0.064	0.064
Elevated ESR/CRP	Yes (v No)	1.57 (-0.89, 4.03)	0.21	0.211
Alcohol	Often (v Never)	1.21 (-2.44, 4.87)	0.516	0.689
	Occasional (v Never)	-0.61 (-3.5, 2.28)	0.678	
	Quit (v Never)	-0.1 (-4.61, 4.41)	0.966	
Smoking	Ever (v Never)	0.97 (-1.27, 3.22)	0.396	0.396

These remarkable findings underscore the importance of early screening for PsA, especially in older patients diagnosed with PsO. By identifying and addressing this age-related factor, healthcare professionals can enhance the early detection and management of PsA, ultimately improving the quality of life for those affected by these conditions.

A Little Bit of Everything: Mixed Connective Tissue Disease

by Aditi Patel, MD, Sameep Sehgal, MD, Kristin Highland, MD

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A 67-year-old female was referred to our rheumatology clinic after she reported a history of new onset Raynaud phenomenon for two months. In addition, she reported hand puffiness, heartburn, dyspnea on exertion and a rash over lateral thighs.

The examination revealed puffy hands, erythema around the nailbeds, rash over the lateral aspect of her thighs, weak proximal hip muscles, and crackles at the base of the lung fields. Laboratory evaluation was notable for elevated creatinine kinase at 2034 U/L, positive ANA, titer >1:1280, nuclear fine speckled pattern, and ribonucleoprotein (RNP) antibody. Additional workup included a magnetic resonance imaging (MRI) of her thighs, which showed myositis and computed tomography (CT) of the chest, which showed mild reticulation with ground glass opacity within the lower lobe peripheral lung fields. This was suggestive of interstitial lung disease (ILD) and reduction in diffusion capacity.

A skin biopsy was notable for interface dermatitis with increased dermal mucin and chronic perivascular inflammation. The patient also was noted to have absent esophageal contractility on manometry testing. With her constellation of symptoms, she was diagnosed with mixed connective tissue disease (MCTD) with features of overlap myositis.

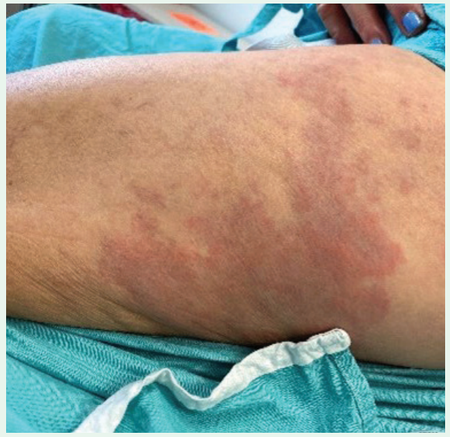
Mixed connective tissue disease

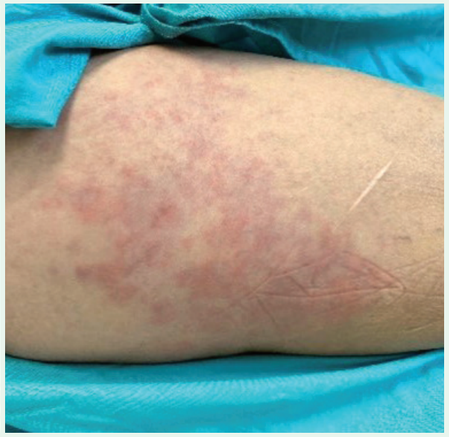
MCTD describes a disorder characterized by features of systemic sclerosis, systemic lupus erythematosus and inflammatory myopathy. Typical symptoms include Raynaud syndrome, inflammatory arthritis, swollen hands, muscle weakness, difficulty swallowing, heartburn and dyspnea. Skin changes such as systemic sclerosis or lupus-like rashes also can be seen. Pulmonary involvement in the form of ILD and pulmonary hypertension are often causes of mortality in these patients.

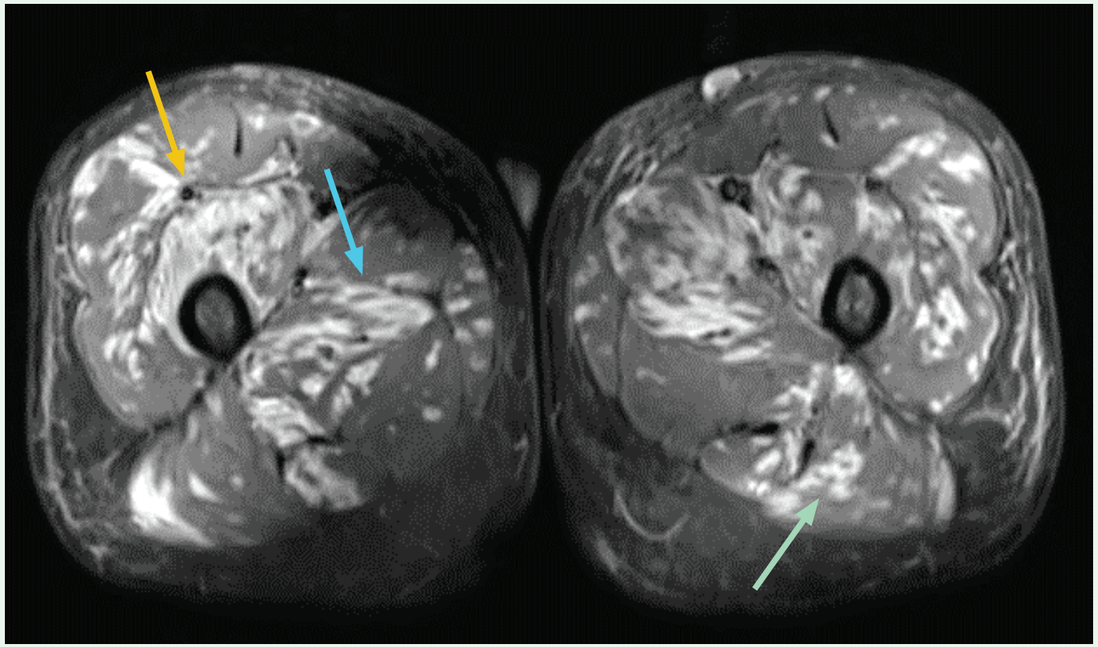
Treatment

The patient was treated with high doses of corticosteroids, mycophenolate mofetil (MMF) and intravenous immune globulin. MMF was switched to intravenous rituximab every six months due to leukopenia. She had complete resolution of her respiratory symptoms, CT chest findings and myopathy.

Below: Bilateral lateral hip skin rash suggestive of Holster sign





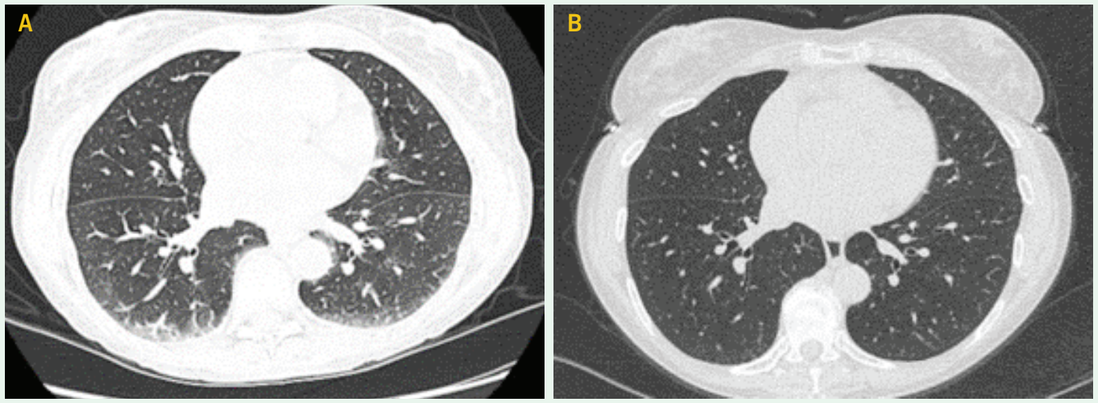


Collaborative management

Our patient was seen in Cleveland Clinic's Rheumatic Lung Disease program, which involves a rheumatologist, pulmonologist and other subspecialists. Patients with pulmonary manifestations from rheumatic diseases such as systemic sclerosis and inflammatory myopathies receive comprehensive care. This integrated, team approach provides expertise for patients with multisystem complex diseases. Specialists with distinct areas of expertise deliver care efficiently and with the goal to improve patient outcomes. The clinic also provides unique opportunities for clinical research and for trainees to be involved in understanding complex medical decision-making.

Above: Axial MRI of Thighs: Streaky Short-T1 Inversion Recovery (STIR) signal changes involving bilateral anterior (yellow arrow), medial (blue arrow), and posterior (green arrow) compartments consistent with myositis.

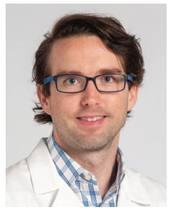
Below: A) CT chest with changes of nonspecific interstitial pneumonia (NSIP); B) Complete resolution of CT findings at one-year follow-up



Joint Pain, Angioedema, Abdominal Pain, Confusing Rash

Symptoms complement one another

by Komal Ejaz, MD, and Adam Brown, MD



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We present the case of a 44-year-old male who came to Cleveland Clinic for evaluation of inflammatory arthritis, rash, facial swelling, abdominal pain and weight loss.

The patient was in his usual state of health until October 2022, when he developed inflammatory pain involving small joints of the hands and feet. He was found to have rheumatoid factor, an anti-cyclic citrullinated peptide positivity, along with likely rheumatoid nodules on his elbows. He was diagnosed with rheumatoid arthritis and started on methotrexate, but couldn't tolerate it and was transitioned to leflunomide.

Within weeks, the patient developed further complications of multiple raised skin lesions (Fig. 1) and erythematous plaques with central clearing, which was present for multiple days, and left hyperpigmented, ecchymotic-appearing lesions (Fig 2). Along with the skin rash, he developed episodes of facial and tongue swelling (Fig. 3) and severe abdominal pain.

He was evaluated at an outside hospital, where he was diagnosed with angioedema. Imaging of his abdomen at the time revealed mural thickening through the ileum, duodenum and ascending colon. He underwent esophagogastroduodenoscopy and colonoscopy with biopsy without a clear diagnosis; angioedema of the gut was thought to be the most likely process. He was given glucocorticoids and fresh frozen plasma with some improvement in symptoms. No cause of the angioedema was found and no diagnosis for the rash was made at this time.

The patient was discharged with a prednisone taper, but his rash and abdominal pain persisted. Loss of appetite had led to a 40-pound weight loss within a span of three months. This prompted him to be admitted to Cleveland Clinic, where he was evaluated by multiple specialties, including internal medicine, rheumatology, gastroenterology, dermatology and allergy/immunology.

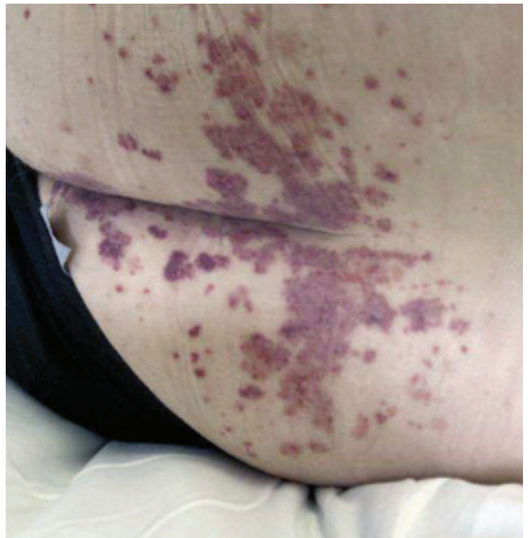
Fig. 1: The patient first experienced joint pain, and within weeks developed raised skin lesions and erythematous plaques.

During the patient's second hospitalization, he continued to have joint pain, mostly in his hands, wrists and ankles. He did not have any fresh skin lesions; only the hyperpigmented lesions remained. Dermatology clinicians made a major contribution when they speculated that the lesions were most likely urticarial, despite not migrating and lasting for greater than 24 hours.

A biopsy revealed leukocytoclastic vasculitis. Considering the appearance and characteristics of the lesions and the histological findings, a diagnosis of urticarial vasculitis was made. Additional testing revealed low C3 and C4, further classifying the diagnosis as hypocomplementemic urticarial vasculitis, potentially secondary to seropositive rheumatoid arthritis. The patient had normal renal function and normal urinalysis. He was treated with high-dose glucocorticoids and dapsone, leading to rapid resolution of his symptoms, including abdominal pain.

Overview

We all learn in medical school that if you encounter a patient with an urticarial rash and examine them sometime later, the rash will look different because classic urticaria moves from one place to another on the body. Urticarial vasculitis, however, is unique. It remains fixed in place for more than 24 hours, and as it resolves it leaves



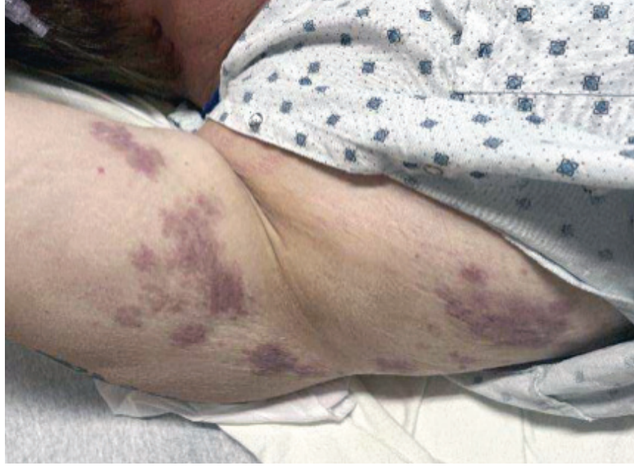


Fig. 2: The raised lesions left hyperpigmented areas that looked like bruising.

Fig. 3: Severe swelling of the face and tongue accompanied the rash.

an area of hyperpigmentation. A biopsy of the rash, even as it's resolving, can establish the diagnosis of urticarial vasculitis[1].

Urticarial vasculitis can occur without an underlying condition, but, importantly, urticarial vasculitis is also associated with underlying systemic autoimmune conditions, such as systemic lupus erythematosus and, rarely, rheumatoid arthritis, as occurred in our patient.

Once a diagnosis of urticarial vasculitis is made, it can be divided into normocomplementemic urticarial vasculitis (NUV) or hypocomplementemic urticarial vasculitis (HUV) based on serum C3 and C4 levels. The distinction is important, as HUV tends to have more systemic involvement compared to NUV. Like in the patient described, HUV can be associated with angioedema and arthritis, but other systemic manifestations also can occur, such as glomerulonephritis and uveitis. NUV, in contrast, tends to be confined to the skin.

Angioedema is a striking feature of HUV. It can be life-threatening and seems to have a relatively unique association with HUV, as it is not commonly seen in other systemic autoimmune processes. The mechanism of angioedema is unclear but is thought to be potentially related to the production of C5a, which could lead to mast cell degranulation. C5a is produced because of the presence of anti-C1q antibodies forming immune complexes with C1q, triggering the classical complement cascade and depleting serum C3 and C4 in the process. C5a is produced in many other conditions that activate complements that are not associated with angioedema, so this is likely not the sole explanation for angioedema in this patient population. Anti-C1q antibodies can be ordered when HUV is suspected as they are often present.

Standard treatment of HUV is not established, but the literature shows that many medications have been used with reasonable success. Initially, as with many of our cutaneous conditions, colchicine or dapsone can be attempted along with antihistamines to help with the angioedema. More aggressive therapy includes disease-modifying anti-rheumatic drugs (DMARDS) and potentially rituximab[2].

Learning points

- Urticarial vasculitis is different than chronic spontaneous urticaria. Urticarial vasculitis is fixed, lasting for greater than 24 hours, and leaves an area of hyperpigmentation upon resolution.
- Differentiating HUV from NUV is important. HUV is associated with systemic involvement, including potentially life-threatening complications such as angioedema.
- The formation of immune complexes generation by anti-C1q antibodies is thought to be a primary mechanism of HUV.
- Treatment is not standardized, but multiple therapeutics have been attempted with varying success, including colchicine, dapsone, DMARDs, and rituximab in more severe cases. Cetirizine and famotidine were given for his angioedema.

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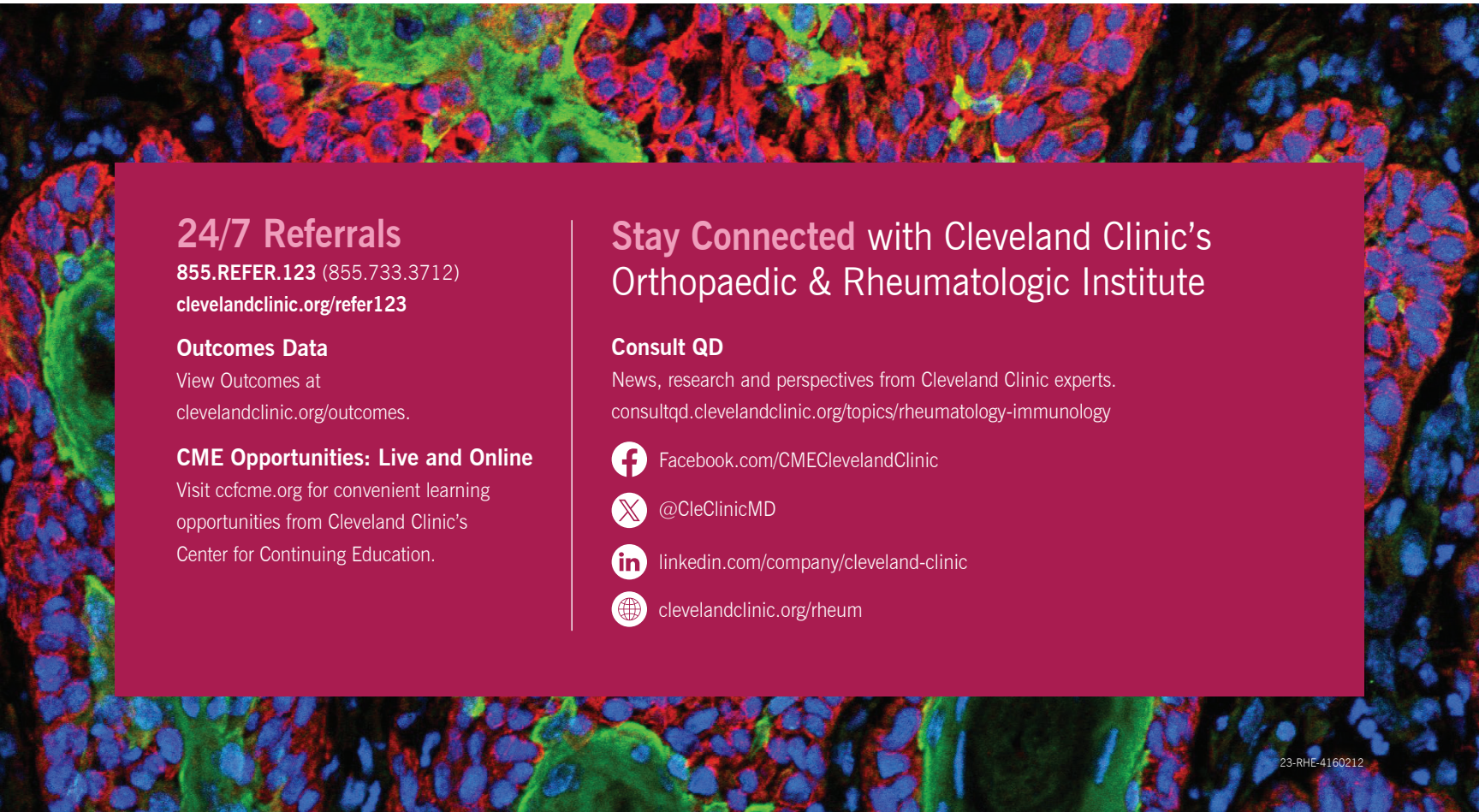

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