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Dear Colleagues,

I am thrilled to share this latest edition of our Cleveland Clinic *Rheumatology Connections* with you. If you were not able to join us in person or virtually for the Tenth Biannual Biologic Therapies Summit X and Vasculitis 2023 in May, please be sure to review the impressive presentations at clevelandclinic.org/rheumcme. You can also read more details about the Summit on page 7 of this issue.

In our Connections cover story, Dr. Rula Hajj-Ali shares a case of a man in his 30s initially diagnosed with primary central nervous system vasculitis. A workup at Cleveland Clinic’s Center for Vasculitis Care and Research revealed the vasculitis mimic that explained his presentation.

Dr. Elaine Husni writes about a Cleveland Clinic trial of a web-based wellness e-coaching program for patients with psoriatic disease. Up to 20% of those with psoriatic disease report poor mental health, making the development of new treatment tools a pressing need.

Interstitial lung disease is a prevalent complication among patients with systemic sclerosis, and Dr. Souryna Chatterjee describes the most effective screening and diagnostic protocols, as well as the importance of multidisciplinary patient care.

The last 25 years have seen significant advances and an increase in options for managing vasculitic diseases. Dr. Carol Langford emphasizes the importance of addressing the multiple comorbidities to optimize care, and she cautions about the need to differentiate active vasculitis from other etiologies.

Presentations of drug-induced vasculitis (DIV) vary, and DIV often can look like primary systemic vasculitis. Dr. Kinanah Yaseen reviews the drugs implicated in vasculitis of large, medium and small vessels.

After decades of limited advancements in the treatment of systemic lupus erythematosus, new therapies have emerged to offer cause for optimism. Dr. Emily Littlejohn provides an overview of five newer therapies, and results of studies to date.

Finally, Dr. Adam Brown brings the second installment of Case Conference, our new series highlighting selections from weekly case presentations at the R.J. Fasenmyer Center for Immunology. He shares a case in which the interdisciplinary conference with Neurology was key to the diagnosis.

We hope you find pearls of interest and inspiration in the work we do at Cleveland Clinic’s Department of Rheumatic & Immunologic Diseases. Please reach out if you see opportunities to collaborate.

Respectfully,

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Boosting Mental Health Access for Patients with Psoriatic Disease

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

The association of psoriatic disease with depression and anxiety has long been established, but providing mental health support for patients with psoriatic disease remains a significant challenge. Despite treatment advances, up to 20.7% of psoriatic disease patients report poor mental health compared to 7.1% of the general population.

Increasing evidence suggests that along with medication and talk therapy, optimizing sleep, physical activity, stress and nutrition may improve mental well-being. While numerous online health programs have emerged to help patients strengthen these behaviors, very little exists for those with psoriatic disease.

Now a new Cleveland Clinic trial will study a 12-week, web-based e-coaching program called Immune Strength, which is tailored for those with psoriatic disease. Immune Strength uses self-directed patient empowerment to enhance mental wellness.

One hundred participants with psoriatic diseases will be randomly assigned to the 12-week Immune Strength program (intervention group) or to a waiting list (control group). Control group subjects will receive access to Immune Strength 12 weeks after the study commences.

Program participants will have 24/7 access with weekly contact to a certified health coach. Support teams will include mental health counselors, dietitians, sleep psychologists and exercise physiologists.

The program’s patient content focuses on four areas:

- **Stress management.** Patients receive education on mindfulness and meditation practices to reduce stress; activation practices to reduce and manage pain and fatigue; positivity; guided imagery.

- **Sleep.** Patients receive directed education on insomnia, tracking sleep quality, managing sleep hygiene and the link between sleep and health.

- **Nutrition.** Patients receive education on topics such as diet and inflammation, eating habits, stress and food, and mindful eating.

- **Exercise.** Patients receive guidance on exercises tailored to their fitness level, focusing on strength, range of motion and chair yoga, plus education on the disease-related benefits of exercise.

Changes in mental health burden will be measured using well-validated measures of mental health as the primary outcome at baseline and at the end of the study. Secondary outcomes will include validated self-efficacy and patient-reported outcomes.

The goals of the study are to determine the improvement of behavioral health, feasibility and practicality of an e-coaching program in patients with psoriatic diseases.
Multidisciplinary Management in Scleroderma-Associated Interstitial Lung Disease

Patient experience improves with a multidisciplinary approach

By Soumya Chatterjee, MD, MS, FRCP

Interstitial lung disease (ILD) can be a prevalent and challenging pulmonary manifestation of systemic sclerosis (SSc), a rare autoimmune rheumatologic disease characterized by inflammation, fibrosis of the skin and internal organs, and an occlusive microvasculopathy. Timely detection and delivery of therapy can be advantageous for patients with scleroderma-associated interstitial Lung disease (SSc-ILD) and the physicians who treat them. To facilitate this, a multidisciplinary approach — focusing on rheumatologists, pulmonologists, gastroenterologists and radiologists — should be used for diagnosing and assessing patients with SSc-ILD.

Pulmonary complications such as pulmonary hypertension (PH) and ILD are the leading causes of death in patients with SSc. The prevalence of ILD in SSc may be as high as 52.3%, and although it can occur at any time, it is usually an early manifestation of SSc.

Patient presentation

As a systemic disorder, SSc has a heterogeneous range of manifestations: the lungs, kidneys, heart and gastrointestinal tract all may be affected, complicating disease management. Manifestations may include skin thickening, Raynaud’s phenomenon, ischemic fingertip ulcers, secondary Sjögren’s syndrome, musculoskeletal manifestations, gastrointestinal problems and lung disease.

Patients often are referred to pulmonologists if they have pulmonary symptoms, bibasilar crackles on auscultation, lung abnormalities on a high-resolution computed tomography (HRCT) scan, and/or impaired lung function on pulmonary function tests.

It is important to note that even in combination with a chest X-ray, the physical examination has sub-optimal sensitivity to detect SSc-ILD, and should not be used as a screening strategy.

Physical examination and pulmonary function tests

Patients with SSc-ILD commonly present with exertional dyspnea and cough, but some patients with early SSc-ILD are asymptomatic. As the extent of pulmonary involvement progresses, patients usually report fatigue and dyspnea on exertion and eventually at rest. In addition, chest auscultation may reveal dry crackles at the bases of the lungs.

Spirometry is non-invasive and cost-effective but has limitations in the setting of SSc-ILD. Assessment of forced vital capacity (FVC) lacks sensitivity, particularly in the early stages of the disease, and may be falsely normal in patients with coexisting emphysema or falsely reduced in patients with extrapulmonary restriction.

An assessment of functional capacity should be performed during SSc-ILD diagnosis. A cardiopulmonary exercise test can provide excellent information on functional status, but it may not be feasible due to resource limitations. However, a simple six-minute walk test can be performed in the office.

Resting and walking oximetry should be considered in patients with respiratory symptoms or abnormalities in imaging or spirometry. The reliability of finger oximetry is compromised in patients with poor peripheral circulation or Raynaud’s phenomenon. An earlobe or forehead probe should be considered.

Radiologic features of SSc-ILD

High-resolution computed tomography (HRCT) is the gold standard for diagnosing SSc-ILD. On HRCT, most patients with SSc-ILD have non-specific interstitial pneumonia (NSIP) pattern of lung injury, while a usual interstitial pneumonia (UIP) pattern is found in a minority (7.5%) of cases. Ground-glass opacification (GGO) is the dominant feature of NSIP. It is usually symmetric in distribution and primarily subpleural, but can be diffuse, with a lower lobe predominance.

During the early stages of SSc-ILD, prone images help differentiate between an increased density due to ILD and gravity-dependent atelectasis at the posterior lung bases.
Multi-compartment involvement in HRCT scans suggests an underlying autoimmune rheumatologic disease. Esophageal dilatation on HRCT scans is predictive of an SSc diagnosis. An increased diameter of the main pulmonary artery (MPA), or the ratio of the MPA diameter relative to that of the ascending aorta, indicates PH. A high MPA diameter and a segmental artery-to-bronchus diameter ratio above one in three to four pulmonary lobes has very high specificity for PH. Pulmonary venoocclusive disease (PVOD) is an essential consideration in SSc because PVOD-like involvement has been associated with a worse prognosis.

**Pathologic features in SSc-ILD**

A surgical lung biopsy is rarely, if ever, required to establish a diagnosis of SSc-ILD. Given the morbidity and mortality associated with the procedure, surgical lung biopsy should only be performed in exceptional cases, such as to exclude malignancy or where there is a suspicion of PVOD.

**Gastrointestinal (GI) manifestations of SSc-ILD**

Up to 90% of patients with SSc have GI tract involvement. Diagnosing and managing GI manifestations of SSc, such as gastroesophageal reflux disease (GERD) and esophageal dysmotility, is of paramount importance, as repeated microaspirations from poorly controlled GERD may lead to more rapid progression of ILD. A gastroenterologist with expertise in GI dysmotility should evaluate all patients with SSc early in the disease course.

**Screening for and monitoring SSc-ILD**

The high prevalence of ILD among patients with SSc, and the significant morbidity and mortality associated with SSc-ILD, make it essential to screen for SSc-ILD. Different approaches exist, but some form of advanced imaging is necessary.

Protocols based on a limited number of slices seem to perform similarly to traditional HRCTs and are associated with radiation exposure similar to a plain chest X-ray. Lung ultrasound is operator-dependent, and its validity and reliability in detecting SSc-ILD require further investigation, but it performs well in the hands of experienced operators.

In a Delphi consensus study, experts in the field of SSc-ILD recommended that all patients with SSc be screened for ILD with thoracic HRCT as the primary tool, supported by assessment of symptoms, auscultation, and pulmonary function testing.

In addition, all patients with SSc without a diagnosis of ILD should be screened regularly with pulmonary function tests. Spirometry and carbon monoxide diffusing capacity (DLCO) should be assessed every three to six months for the first three to five years after diagnosis.

SSc-ILD patients should be closely monitored for progression. Unfortunately, there is no established protocol for monitoring patients with SSc-ILD. Therefore, a multifaceted approach is required. It is generally recommended that symptoms, FVC and DLCO, and exercise-induced oxygen desaturation be assessed every six to 12 months, with repeated thoracic HRCT scans as clinically indicated.

**The multidisciplinary approach**

SSc-ILD requires collaboration among, at a minimum, a rheumatologist, a pulmonologist and a radiologist. Assessment of the severity of ILD and risk factors for progression can have important implications for the patient’s monitoring, management and prognosis. Close collaboration between rheumatology and pulmonology may result in earlier referrals for therapies such as hematopoietic stem cell transplantation and lung transplantation.

Given the systemic nature of SSc, a multidisciplinary approach is also essential for assessing other organ manifestations. A gastroenterologist should evaluate all patients with SSc early in the disease course. Patients with SSc and potential cardiac involvement should be evaluated by a cardiologist.

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This article was edited and adapted for Rheumatology Connections from “Viewpoint: A Multidisciplinary Approach to the Assessment of Patients with Systemic Sclerosis-Associated Interstitial Lung Disease,” by Soumya Chatterjee, Apostolos Perelas, Ruchi Yadav, Donald F. Kirby and Amandeep Singh. It was first published online October 21, 2022 in Clinical Rheumatology. To view the original article, including citations and supplemental information, visit https://link.springer.com/article/10.1007/s10067-022-06408-4.
Management options for many of the vasculitic diseases have rapidly grown over the past 25 years. While novel treatment approaches represent important advances, the potential for relapse, treatment-related toxicity, permanent organ damage, and the emergence of other disease processes remain active issues that can result in morbidity or mortality. Because of these factors, optimizing care in people with vasculitis includes not only the selection of medications but other steps to detect or prevent future concerns.

Evidence-based treatment

The expansion of treatment options for vasculitis has raised many questions. Utilizing evidence-based therapeutic regimens provides the best means of approaching immunosuppression for these potentially life-threatening diseases. With the goal of providing guidance to health care providers, the American College of Rheumatology (ACR)/Vasculitis Foundation have recently published management guidelines for a number of the vasculitic diseases. 1-4

Monitoring

Monitoring is an essential part of care for people with vasculitis. Identification of active disease as early as possible may reduce the potential for organ damage. Monitoring also plays a critical role in detecting medication toxicity or the development of other diseases.

Regular physician visits represent the foundation of monitoring to assess the patient’s symptoms and signs. The frequency of visits will vary based on many factors, most significantly the recency of active disease or other acute issues. Regular laboratory monitoring is also critical. The typical labs I obtain include a complete blood count with differential, complete metabolic panel/chemistries (to include renal and hepatic studies and glucose), erythrocyte sedimentation rate and/or C reactive protein, and a urinalysis in patients with any form of vasculitis that can affect the kidneys. How often labs are obtained will vary based on the medications the patient is receiving and where they are in their treatment course. In people receiving cyclophosphamide or with recently active disease, I obtain labs every one to two weeks, with labs once a month in the setting of other therapies. In patients with large vessel vasculitis, vascular imaging to look for new vascular lesions in new territories represents one of the main means of assessing for active disease.

Given that vasculitis is not only an inflammatory disease but one that affects the blood vessels, it is important to monitor lipids and blood pressure for cardiovascular health. This is particularly notable as some medications used in vasculitis can directly impact these modifiable parameters.

People with vasculitis remain at risk of the same health issues that can affect all people. At the time of their appointments, it is helpful to remind patients to keep up to date with health care screenings for the early detection of malignancy. As many immunosuppressive agents can increase the risk of skin cancers, regular skin checks by a dermatologist should be strongly encouraged.

Use of prophylactic and preventive strategies

Assertive use of available strategies that can minimize or prevent medication toxicities is important. Infection represents one of the greatest risks of the immunosuppressive agents used to treat vasculitis. Prophylaxis against Pneumocystis pneumonia should be given to patients receiving regimens known to place patients at increased risk of this opportunistic infection. Use of non-live vaccines represents another means of lessening preventable infections.

Some medications have toxicities for which an effective prevention strategy exists. Examples include taking daily oral cyclophosphamide in the morning with a large amount of fluid to prevent urothelial toxicity or the use of folic acid with methotrexate. A recently updated ACR guideline for the prevention and treatment of glucocorticoid-induced osteoporosis was presented at ACR Convergence 2022.

Reproductive health risks from medication and underlying disease also need to be recognized in people with vasculitis. In young women, discussions about the need for pre-conception planning to optimize pregnancy safety for both
mother and child should start at an early point following diagnosis. Use of medications that impact fertility or that carry teratogenic potential must be weighed carefully, with application of risk mitigation strategies when these agents are required to treat vasculitis.

**Recognition that not everything is active vasculitis**

Determining whether new symptoms, signs, laboratory, and/or imaging findings are indicative of active vasculitis can be very difficult. Particularly in immunosuppressed patients, the possibility that a new or persistent feature could represent something other than vasculitis must always be considered. Permanent damage, infection, medication toxicity or another medical diagnoses can all have similar presentations to what can be seen with active vasculitis. How to differentiate these will vary depending on the presenting features, but recognition of this potential is an essential first step in this process.

**Patient and family education**

Educating the patient and their family about vasculitis and the medications used to treat it begins on the first encounter and continues during each visit thereafter. Facing the uncertainty of what lies ahead when confronted by a medical illness is a challenge shared by all people. Knowledge is empowering, and regular discussion of those factors we understand and can control provides a means of combating such uncertainty. These discussions also provide a valuable tool in understanding the patient's concerns and priorities that can help to guide management through shared decision making now and in the future.

**References**


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**CME Webcasts Available**

Continuing medical education from Cleveland Clinic’s R.J. Fasenmyer Center for Clinical Immunology is available in a variety of modes, including webcasts. Visit clevelandclinic.org/rheumcme. From there, you can browse offers by specialty. These and other topics can be viewed:

**Through July 12, 2023:** How Do I Recognize and Treat the VEXAS Syndrome? Faculty: Peter Grayson, MD.

**Through Aug. 20, 2023:** What Dose and Duration of Glucocorticoids Should Be Used in ANCA-Associated Vasculitis? Faculty: Peter Merkel, MD.

**Through April 21, 2025:** Advances in Immunology for the Non-Immunologist: The Human Immune Response at 30,000 Feet. Faculty: Leonard Calabrese, DO.

**Video Case Studies**

Cleveland Clinic’s Department of Rheumatic and Immunologic Diseases has a rich library of case study videos on YouTube. Visit clevelandclinic.org/rheummdvideos, where you can see the following cases and more.

Kinanah Yaseen, MD, discusses a case that highlights that 25% of antineutrophil cytoplasmic antibody-associated vasculitis cases may present initially with nonspecific symptoms such as migratory polyarthritis, fatigue and fever. Increased awareness of such presentation is needed for early diagnosis and management to prevent any chronic damage.

Cassandra Calabrese, DO, shares a complicated case study involving a 53-year-old man being treated for seropositive rheumatoid arthritis. After presenting with fevers, rigors, night sweats and shortness of breath, he was diagnosed with histoplasmosis. The case illustrates why histoplasmosis complicates TNF inhibitor therapy.

Adam Brown, MD, presents a fascinating look at a patient in her 60s with a new onset rash (below) and unusual labs. Her symptoms suggested systemic vasculitis. Further testing revealed something else altogether.
Recognizing Drug-Induced Vasculitis
By Kinanah Yaseen, MD

The Chapel Hill Consensus Conference nomenclature divided vasculitides based on several combinations of features. One of these divisions is primary versus secondary, based on whether the vasculitis is associated with or caused by a systemic disease or drug. Secondary vasculitides can be associated with and/or caused by infections such as hepatitis B, causing cryoglobulinemic vasculitis; underlying autoimmune disorders such as rheumatoid vasculitis; certain drugs, such as cocaine, causing anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV); and malignancies.

The clinical presentation of secondary vasculitides may share symptoms as well as laboratory, radiographic and pathological findings with primary vasculitides. Identifying the potential cause, such as a drug or underlying autoimmune disorder, is extremely important for management and prognosis.

In "A Spotlight on Drug-Induced Vasculitis," we highlighted common drugs known to cause vasculitis based on the size of the affected vessels and involved organs. We further discussed clinical phenotypes, risk factors, treatments and outcomes. What follows is a more abbreviated look at drug-induced vasculitis (DIV).

**Drug Induced Small Vessel Vasculitis**

Small vessel vasculitis predominantly affects intraparenchymal arteries, arterioles, capillaries and venules which may or may not involve immune complex deposition in vessel walls.

- **Drug Induced ANCA-Associated Vasculitis:** Hydralazine, propylthiouracil and cocaine are considered the most common drugs to be associated with AAV. The clinical presentation varies from non-severe vasculitis to potentially life-threatening multi-organ involvement. Clinical suspicion should be high when leukopenia, thrombocytopenia, dual-positive ANCA patterns, and overlapping serologies between AAV and systemic lupus erythematosus are present, which all are uncommon in primary AAV.

- **Drug-Induced Small Vessel Vasculitis with Immune Complex Deposits:** Immunoglobulin A vasculitis is an immune complex-mediated, small vessel vasculitis with IgA1-dominant immune deposits. It has been associated with infections, malignancies and autoimmune diseases. It can be caused by exposure to medications including quinolones and clarithromycin, furosemide, nonsteroidal anti-inflammatory drugs (NSAIDs), tumor necrosis factor-α (TNF-α) inhibitors, and many other drugs.

**Drug Induced Medium Vessel Vasculitis**
Polymyxin nodosa (PAN) is the most common primary medium vessel vasculitis. Historically, minocycline is reported to be the drug most frequently drug associated with PAN. Most cases reported to date are isolated cutaneous.

The clinical presentation of secondary vasculitides may share symptoms, laboratory, radiographic and pathological findings with primary vasculitides. Identifying the potential cause ... is extremely important for management and prognosis.

PAN followed by systemic vasculitis with multiple organ involvement such as nerves, muscles or kidneys. In contrast to primary PAN, patients with minocycline-induced medium vessel vasculitis are commonly found to have positive ANCA antibodies. Prognosis is favorable, as complete resolution has been reported in most cases of minocycline-induced PAN.

**Drug-Induced Large Vessel Vasculitis**

Large vessel vasculitis affects the aorta and its major branches. The most common forms are giant cell arteritis, Takayasu’s arteritis, and isolated aortitis.

Aortitis and large vessel vasculitis are rarely reported complications of granulocyte colony-stimulating factor...
and other cancer-related therapies, including gemcitabine and immune checkpoint inhibitors (ICIs). Most of the reported cases manifested as fever of unknown origin, unexplained weight loss and lethargy in addition to localized symptoms based on the vascular territory involved. Vessel wall thickening was the most reported finding on different imaging modalities.

**Drug Induced Single Organ Vasculitis involves:**

- **Drug Induced Cutaneous Vasculitis** presenting as ulceration, digital ischemia or purpuric rash, which may be triggered by antibiotics, NSAIDs, TNF-α inhibitors and various other medications.

- **Drug-Induced Cerebral Vasculitis** presenting as new onset headache, focal neurological symptoms, seizure or change in mental status, which is typically associated with amphetamines and cocaine abuse.

- **Drug-induced Vasculitic Neuropathies** presenting as mononeuropathy, mononeuritis multiplex or sensorimotor polyneuropathy. Drugs implicated as triggers of non-systemic vasculitic neuropathies, which are quite rare, are TNF-α inhibitors, ICIs (nivolumab, pembrolizumab), and minocycline.

A high index of suspicion for DIV is required for prompt diagnosis and treatment, which begins with removing the inciting drug. Administering glucocorticosteroids is recommended in non-severe cases. Addition of a second agent may be necessary in severe presentations with organ or life-threatening vasculitis.

**References**

Emerging Treatments for Systemic Lupus Erythematosus

By Emily Littlejohn, DO, MPH

The heterogeneity of lupus, both clinically and immunologically, makes disease management and drug development a challenge. For decades, only a handful of FDA-approved drugs existed for this disease, including antimalarials, corticosteroids, aspirin and cyclophosphamide.

By 2020, however, we began seeing a surge in drug development, including:

• Belimumab, a human monoclonal antibody that binds to soluble B lymphocyte stimulator (BLyS) to treat systemic lupus and lupus nephritis.

• Voclosporin, a calcineurin inhibitor approved for lupus nephritis.

• Anifrolumab, a human monoclonal antibody that binds to the type I interferon receptor and is indicated for treatment of systemic lupus.

These drugs have led a long line of therapies that are now emerging for treatment of systemic lupus erythematosus.

The pathogenesis of lupus is complex. It involves pathways starting from exposure of the immune system to autoantigens, presentation of autoantigens to self-reactive T cells, the interactions of T and B cells, and the production of pathogenic autoantibodies by plasma cells. Autoantibodies scavenge autoantigens, producing immune complexes, which interact with plasmacytoid dendritic cells and induce type I interferon.

Type I Interferons are heavily involved in pro-inflammatory pathways, including production of pro-B cell survival cytokines (APRIL, BLyS), pathogenic activation of T cells, and signal transduction using the Janus kinase/signal transducer and activation of transcription pathway.

The pathogenic pathways involved in the perpetuation of chronic inflammation in lupus present myriad therapeutic targets, many of which are being explored in phase 1, 2 and 3 trials.

Obinutuzumab

One noteworthy emerging therapy is obinutuzumab, a humanized anti-CD20 monoclonal antibody. This is distinct from other anti-CD20 antibodies (such as rituximab and ocrelizumab) in that it provides greater B-cell cytotoxicity and depletion. NOBILITY, a phase 2 trial using obinutuzumab with mycophenolate mofetil for lupus nephritis class III-IV, met primary endpoint of complete renal response at week 52. Further improvement was evident by week 104.1

Obinutuzumab resulted in greater improvements from baseline in C3, C4 and anti-dsDNA antibodies at weeks 4 through 104, and urine protein-creatinine ratio at weeks 52...
through 104. We anticipate positive results from the phase 3 trial ALLEGORY, which is ongoing.

Litifilimab

Litifilimab (BIIB059) is a humanized IgG1 monoclonal antibody targeting blood dendritic cell antigen 2. Phase 2 trials have demonstrated this drug to be effective in both cutaneous lupus and systemic lupus as an add-on to standard-of-care therapy. It has met endpoints of decrease in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) score at week 16 (N = 132) and decrease in number of active joints at week 24 (N = 102).2,3

Deucravacitinib

Deucravacitinib is an oral selective inhibitor of the intracellular signaling kinase, tyrosine kinase 2. Phase 2 trial patients were on background therapy with at least one antimalarial or immunosuppressant drug and could receive up to 30 mg/day of glucocorticoids. Patients treated with deucravacitinib 3 mg twice daily or 6 mg twice daily met the primary outcome of SLE Responder Index (SRI-4) response versus placebo at week 32.

Patients treated with deucravacitinib 3 mg twice daily met all secondary end points, including SRI-4, British Isles Lupus Assessment Group–based Composite Lupus Assessment, Lupus Low Disease Activity State, CLASI-50 response, and reduction in active joint count at week 48.4

Ielanalumab

Ielanalumab is an anti-B-cell activating factor receptor fully human IgG1 monoclonal antibody engineered for direct antibody-dependent cellular cytotoxicity-mediated B-cell depletion. In an ongoing phase 3 study,5 406 patients were given monthly or quarterly subcutaneous injection on top of standard-of-care treatment. Primary outcome is SRI-4 response, defined as Systemic Lupus Erythematosus Disease Activity Index — 2000 (SLEDAI-2K) reduction from baseline of ≥ 4 points, no worsening in British Isles Lupus Assessment Group — 2004, and no worsening in Physician Global Assessment of Disease Activity.

CAR T Therapy

Chimeric antigen receptor (CAR) T cell therapy is the beginning phases as an emerging therapy in rheumatology. CAR T therapy has been used in the oncology space to treat conditions such as B cell non-Hodgkin lymphoma, B cell acute lymphoblastic leukemia and multiple myeloma.

CAR T therapy is considered a “living drug,” in which chimeric antigen receptors (also known as chimeric immunoreceptors, chimeric T cell receptors, or artificial T cell receptors) are engineered to give T cells the ability to target a specific antigen. The receptors are considered chimeric because they combine both antigen-binding and T cell activating functions into a single receptor. First, a patient’s leukocytes are obtained via leukapheresis and CD4- and CD8-positive T cells are isolated. T cells then are transfected with the necessary coding DNA to produce a new receptor capable of recognizing a target antigen — in this case, CD19. Once binding to this antigen is achieved, the innate signaling can turn on machinery to destroy the recognized cell.

A recent study of the use of anti-CD19 CART T therapy for five patients with systemic lupus erythematosus and lupus nephritis yielded exciting results. All patients had SLE according to the EULAR/ACR 2019 criteria, with signs of active organ involvement, including kidney involvement (WHO III or IV). They had failed to respond to multiple immunomodulatory therapies, including pulse dose glucocorticoids, belimumab, azathioprine, mycophenolate mofetil, rituximab and cyclophosphamide. Results were astounding; after three months, all five patients had achieved drug-free remission with decrease in the SLEDAI-2K scores. They also had resolution of proteinuria, improved complement levels, and decreased anti-dsDNA levels.6 These results were maintained over a long-term follow-up, and B cell reconstitution was evident at 150 days.

Long-term follow-up in larger SLE cohorts is needed, and these studies are underway.

The therapies discussed are not exhaustive of the potential therapeutic targets or ongoing clinical trials. A recent systematic review of targeted therapies in clinical development yielded a total of 92 (58 biological DMARDs and 34 targeted synthetic DMARDs) in a total of 203 clinical trials.7

It is an exciting time in the systemic lupus space, and we look forward to more treatment options to offer our patients who suffer from this devastating disease.

References

Holistic Approach Is a Must When Central Nervous System Vasculitis Is Suspected

By Rula A. Hajj-Ali, MD, Komal Ejaz, MD, and Jeffrey Donaldson, MD

Central nervous system vasculitis (CNSV) is fraught with diagnostic challenges. Clinical presentation can be quite variable, and there is no disease-specific test. Furthermore, the condition has several mimics, even with the availability of brain tissue. Clinicians should always be on alert for other diagnostic possibilities that could present as CNSV. Here we present a case in which the diagnosis of CNSV was challenged.

Case Presentation

A 50-year-old male was referred to Cleveland Clinic’s Center for Vasculitis Care and Research for evaluation of four years of neurological symptoms. His initial presentation included intermittent headaches, forgetfulness, and cognitive and personality changes, with right upper and lower extremity weakness, and loss of sensation.

The initial work-up revealed multifocal regions of parenchymal signal abnormality involving the left parietal lobe, frontal lobe, and corpus callosum with scattered areas of restricted diffusion on magnetic resonance imaging (MRI) of the brain (Figures 1 and 2). Cerebrospinal fluid analysis revealed an elevated protein of 233 mg/mL with a white cell count of 34/mm³. A fluorescein angiogram (FA) performed for visual changes revealed retinal vasculitis. A brain biopsy showed small vessel vasculopathy with coagulative type necrosis.

The patient was diagnosed with primary CNSV and treated with high-dose glucocorticoids and oral cyclophosphamide for six months, followed by mycophenolate for maintenance. Despite aggressive treatment measures, his disease continued to progress, with worsening motor weakness and sensory and personality changes.

Serial MRI imaging revealed new lesions and a worsening of existing lesions. He was then treated with one course of rituximab. However, he continued to have clinical and radiographic progression and was subjected to another course of oral cyclophosphamide for six months; mycophenolate was continued.

Unfortunately, he developed complications, including pleural effusion; liver disease (with liver biopsy showing nodular regenerative hyperplasia); hypercalcemia; anemia requiring multiple blood transfusions; bilateral extensive deep venous thromboses requiring anticoagulants and, finally, worsening kidney disease.

Discussion

At our Center for Vasculitis Care and Research, we take a systematic approach in the work-up of any patient suspected of having CNSV. This includes a thorough review of symptoms and radiologic and laboratory findings with detailed evaluation for mimics, including infectious, genetic and malignant causes. It is vital to delineate details of any therapeutic trials and available tissue biopsies.

This case raised multiple flags that called for reconsideration of the diagnosis, including lack of response to multiple rounds of effective treatment, findings of retinal vascular disease and systemic involvement. The differential diagnosis of conditions that affect the brain and the eye includes neurosarcoidosis, Susacs syndrome, demyelinating diseases and lymphoma. The patient lacked specific manifestations of neurosarcoidosis or granulomatous inflammation on biopsy and had a negative positron emission tomography scan. Multiple sclerosis was considered, but the patient lacked the characteristic clinical course and consistent MRI findings.

Refractoriness to adequately dosed immunosuppression, and accompanying liver and kidney disease with anemia, raised suspicion for retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (RVCL-S) caused by TREX1 mutation. Prior brain pathology revealed small vessel vasculopathy with coagulative necrosis, which has been reported in RVCL-S. Magnetic resonance angiography and 7-Tesla MRI of the brain were obtained along with ophthalmology evaluation. The ophthalmologic exam was notable for bilateral severe occlusive vasculitis and posterior uveitis, with FA showing significant disc and large vessel leakage.

This patient did not have a family history to support the typical autosomal dominant inheritance pattern of TREX1 mutation, but a de novo mutation was suspected. De novo
mutations, while rare, have been described as heterozygous frameshift mutations involving \textit{TREX1}. Subsequent genetic testing performed after genetic counseling revealed \textit{TREX1} C-terminal frameshift mutation with a likely pathogenic variant.

Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations is an exceedingly rare and uniformly fatal genetic disease that affects the microvasculature primarily of the brain and eye. The onset of this disease is usually reported between 35 and 50 years. This genetic disease is caused by somatic or, rarely, de novo mutations of the \textit{TREX1} gene, which is involved in DNA repair.

RVCL-S is characterized by visual field defects caused by vascular retinopathy as well as a series of micro-infarcts in the brain leading to encephalopathy, focal neurological signs, or global brain dysfunction leading to cognitive decline. Blood vasculature in other organs can be impacted, leading to liver and renal involvement, anemia, hypertension, thyroid disease, migraines, osteonecrosis, intestinal bleeding and Raynaud’s phenomenon. Unfortunately, life expectancy following symptom onset is reduced to five to 20 years.

Imaging findings of RVCL-S include supratentorial lesions, brain calcifications, and cerebral atrophy. Lesions can display surrounding edema and mass effect. Cerebellar punctate-enhancing lesions are typically seen in patients older than 50.

While there is currently no treatment for RVCL, multiple investigations are underway. An ongoing phase 2 trial is looking at the efficacy and safety of crizanlizumab, a humanized monoclonal anti-P-selectin antibody that prevents leukocyte adhesion to the vascular endothelium, thereby limiting the risk of microvascular occlusion and leading to fewer ischemic brain and eye lesions. Furthermore, researchers at the University of Pennsylvania are investigating the role of delivering therapies to correct the genetic mutation in RVCL, which may prove to be a breakthrough in the near future.

References
CASE CONFERENCE

Getting to the Root of Neuropathic Symptoms
Collaboration was key to identifying source of nerve condition

By Adam Brown, MD

A great example of the multidisciplinary aspect of rheumatology is a case recently presented at our department's Friday morning conference. For this case, the neurology team joined us during the morning conference to help guide us through their thought process and teach during the presentation.

The case

A man in his mid-30s with no significant medical history presented to an outside emergency room with bilateral hand numbness that had begun five weeks earlier. At first, the patient thought the hand numbness was carpal tunnel syndrome from using heavy tools in his construction job. The numbness persisted, spreading to the left side of his face and then to the front of his thighs. He also felt weakness in his hands and was having trouble gripping tools.

The progression of symptoms prompted him to be evaluated in the ER, where he was noted to have sensory loss to all the areas he complained about as well as bilateral grip weakness.

In the ER, an MRI of his brain and spine was performed and read as normal. He was transferred to Cleveland Clinic and evaluated by Neurology.

Once evaluated by Neurology at the main campus, it was noted, the patient had sensation loss to his hands, on the left side of his face in V2 and V3 distribution, and in a large patch on the anterior thighs. Importantly, the patient also had significant proprioceptive loss in his fingers and wrists. When he closed his eyes, his arms demonstrated pseudoathetoid movement; they drifted aimlessly. The patient couldn’t tell where his arms and feet were in space, which explains his pseudoathetoid movements and ataxia.

It was previously noted that the patient had weakness in his hands, but when he was asked to look directly at one of his hands and then grip the examiner’s hand, motor strength was normal.

Breaking it down

First, let’s consider non-length-dependent versus length-dependent sensory neuropathy. This patient’s sensory loss followed a patchy distribution, starting in his hands, traveling to half his face, then reaching his thighs. The areas of sensory loss were not dependent on the length of the nerve. In contrast, most neuropathies are length-dependent, meaning the sensory loss starts at the farthest nerves of the feet, such as that seen with diabetic neuropathy.

Next: Consider large-fiber versus small-fiber sensory neuropathy. There are multiple sizes of sensory fibers, each responsible for different aspects of sensation, but we can simplify it to large- and small-fiber sensory nerves. Small-fiber sensory nerves detect pain and temperature. When they’re involved, it’s typically a painful neuropathy. Large-fiber sensory nerves, in contrast, are primarily responsible for proprioception and detecting vibration. In this case, the patient demonstrated very poor proprioception — indeed, so severe that he couldn’t tell where his arms and feet were in space, which explains his pseudoathetoid movements and ataxia.

Upon initial clinical examination, his loss of sensation in the hands made it seem that he was weak. This illusion was overcome by asking the patient to look at his hand while squeezing. Because of the loss of sensation and proprioception, he couldn’t feel the examiner’s hands to squeeze, but once he looked at his hands to squeeze he was able to perform normally.

Most neuropathies are length-dependent, meaning the sensory loss starts at the farthest nerves of the feet, such as that seen with diabetic neuropathy.
Now we know he has a primary large-fiber sensory neuropathy with intact motor function.

He does not have any upper motor neuron signs, such as hyperreflexia or spasticity. His brain MRI and spine were normal.

So where are the lesions?

**Putting it together**

Clinical evidence points to primary large-fiber, sensory non-length-dependent neuropathy. This is consistent with the destruction of the dorsal root ganglion, the bean-shaped bundle of sensory nerves lying adjacent to the spinal cord at multiple levels of the cord. This phenomenon is called a sensory ganglionopathy, and the differential is rather limited.

This is how Rheumatology gets on board.

The differential of a sensory ganglionopathy is limited to malignancy, vitamin toxicity, chemotherapy toxicity, celiac disease or Sjögren’s syndrome. During the workup of this patient, he was found to be SSA-positive. Rheumatology was consulted, and we learned that the patient had been experiencing a multiple-month history of dry eyes and dry mouth preceding his neuropathy symptoms but didn’t think much of it. He was evaluated by Ophthalmology. Objective measures demonstrated eye dryness.

MRI of the spine is typically normal, so the diagnosis is made clinically.

The treatment is not standardized, but most experts agree with aggressive immunosuppression upfront in hopes of stopping inflammation and further damage. Pulse dose regimens of methylprednisolone, rituximab, IVIG and plasmapheresis have all been used.

**In conclusion**

Rheumatologists encounter a diversity of pathology, and interdisciplinary care is a critical component of care. In our Friday morning presentation of this case, a Neurology team was present to guide us through the neurologic findings and explain how the exam changed the differential and workup, narrowing the diagnosis. A rapidly progressive neurologic presentation was worked up and found to be secondary to a primary systemic autoimmune disease. Working with our Neurology colleagues, we developed and initiated an immunosuppression regimen we hope will halt the progression of sensory loss for the patient.

Sensory ganglionopathy is a rare complication of primary Sjögren’s syndrome. The pathogenesis is unclear, but it is likely an autoimmune attack on the dorsal root ganglia and primarily the large-fiber sensory nerves. As occurred in this patient’s case, most people with Sjögren’s syndrome commonly don’t know they have it until neuropathy develops and they’re worked up with an anti-SSA.

Why does this occur? We don’t know for sure, but the blood supply of dorsal root ganglia is unique, as the ganglia are not protected by the blood-brain barrier and have fenestrated capillaries, potentially making them more vulnerable.
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