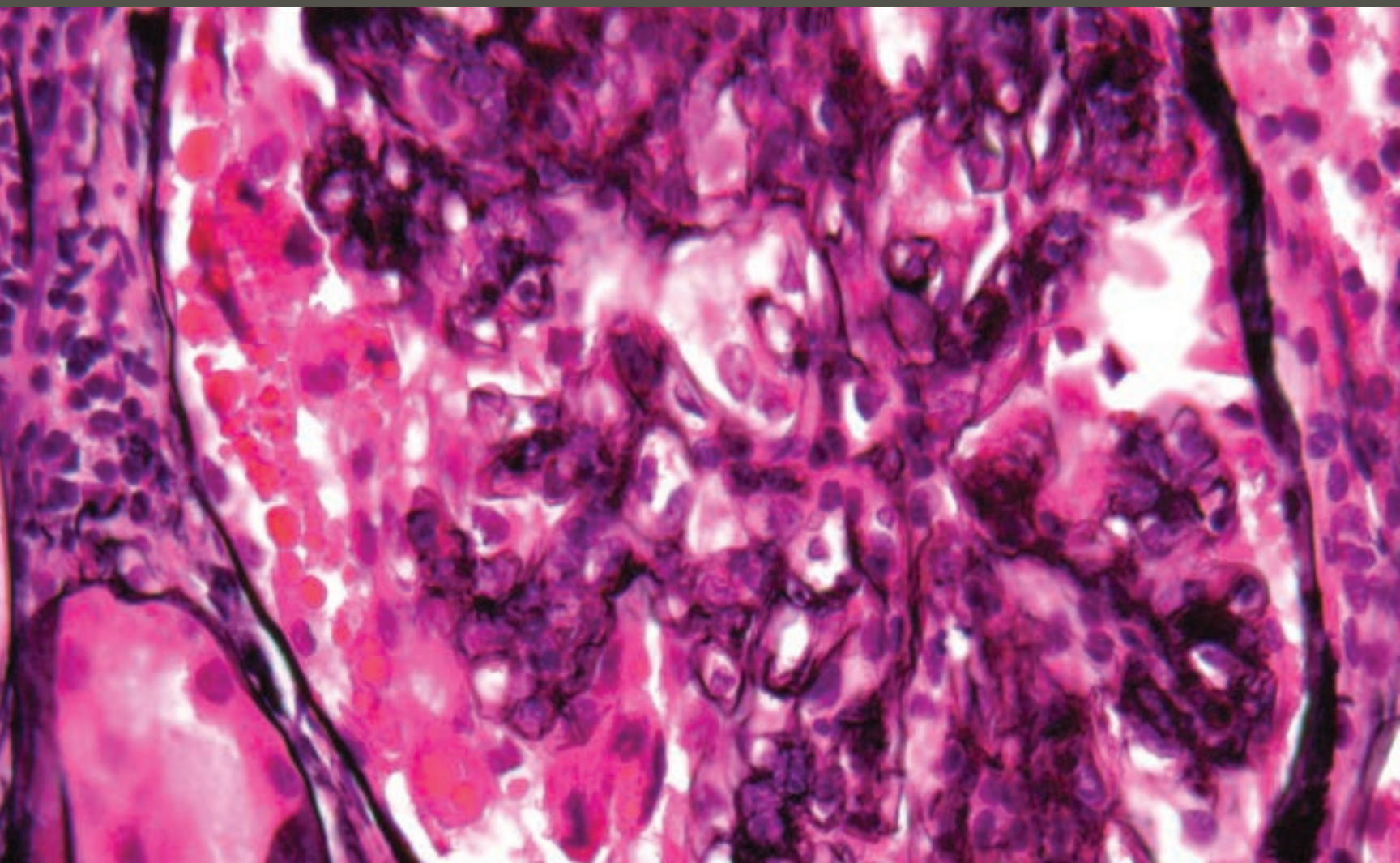
IN THIS ISSUE



Cleveland Clinic

# Rheumatology Connections

An Update for Physicians | Summer 2018



# Dear Colleagues,

## From the Chair of Rheumatic and Immunologic Diseases

Welcome to another issue of *Rheumatology Connections*. I think you'll find our title perfectly apt as you browse these articles, full of connections to an array of other specialties, to our patients and to our clinical, scientific and educational missions.

Dr. Chatterjee's collaboration with the Department of Medical Oncology and Hematology for treating severe systemic sclerosis is but one example of the relevance of our field across disciplines (p. 12). This issue also features a study of psychosocial factors in psoriatic arthritis co-authored by Dr. Husni and a colleague in the Neurological Institute (p. 9). Our connections to neurology become even clearer as Drs. Calabrese and Hajj-Ali offer guidance on distinguishing between a neurological condition and the more fatal, less common rheumatologic one that it mimics (p. 6).

We are always searching for ways to transcend disciplinary boundaries to provide better patient care. Our multidisciplinary style of caring for patients was critical in a case co-authored with a colleague in pathology and Drs. Smith, Littlejohn and Zickuhr (one of our fellows). The case demonstrates that our Lupus Clinic (p. 3) would be incomplete without our colleagues in pathology, nephrology and dermatology, among others.

Dr. Calabrese describes the impact of bench research on and the importance of basic immunology education to our field in his update on advances in IL-6 biology for rheumatologists (p. 10). Dr. Langford collaborates with Dr. Byram, our vasculitis fellow, on an overview of using PET to assess disease activity in large vessel vasculitis (p. 14). All these articles speak to the talent and dedication of our clinicians, researchers, educators and trainees.

I hope that this issue of *Rheumatology Connections* gives you reason to connect with our department in your work, be it in caring for the sick, investigating their conditions or educating those who serve. I look forward to hearing your thoughts, feedback and questions.

Respectfully,

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Cleveland Clinic's Rheumatology Program is ranked among the top 2 in the nation in *U.S. News & World Report*'s "America's Best Hospitals" survey.

*Rheumatology Connections*, published by Cleveland Clinic's Department of Rheumatic and Immunologic Diseases, provides information on leading-edge diagnostic and management techniques as well as current research for physicians.

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On the cover: Figure 1 from p. 4.

# COLLAPSING GLOMERULOPATHY, EXTENSOR TENDON RUPTURES AND AUTOIMMUNE ILD

## Uncommon manifestations of SLE: A case report

By Lisa Zickuhr, MD, Leal C. Herlitz, MD, Emily Littlejohn, DO, MPH, and Howard R. Smith, MD

The Lupus Clinic, part of Cleveland Clinic's Department of Rheumatic and Immunologic Diseases, unites specialists in rheumatology, nephrology and dermatology to care for patients with systemic lupus erythematosus (SLE) and overlap syndromes. Arthritis and malar rash are the most common presentations of SLE, but other organ systems can be involved, sometimes in surprising ways (Table). We share the story of a patient who came to our Lupus Clinic with uncommon manifestations of SLE.

A 49-year-old African American man presented with a history of abnormal liver function tests and inflammatory joint pain. Physical exam confirmed swollen and tender metacarpophalangeal joints, wrists and elbows and revealed cervical lymphadenopathy. Laboratory investigation demonstrated the presence of anti-nuclear, Smith, RNP, SS-A, chromatin and double-stranded DNA antibodies with elevated inflammatory markers. Urine studies identified proteinuria. Renal biopsy showed membranous lupus nephritis, confirming the suspected diagnoses of SLE and lupus nephritis.

Physicians recommended treatment with hydroxychloroquine, high-dose glucocorticoids and mycophenolate, but the patient was lost to follow-up. A few weeks later, he came to the hospital with acute renal failure requiring dialysis. Repeat kidney biopsy showed collapsing glomerulopathy (CG), a podocytopathy, superimposed on membranous lupus nephritis (Figures 1-3). Treatment with pulse steroids and cyclophosphamide was begun, and he was transitioned to mycophenolate upon completion of cyclophosphamide induction. Renal function recovered, proteinuria improved and liver function tests normalized. Unfortunately, his renal disease relapsed about 18 months later. Tacrolimus was added to his regimen, with clinical improvement.

Our patient's SLE was not confined to joint and renal manifestations. He also developed extensor tendon ruptures in his hands and right patella, thought to be from SLE and glucocorticoid use (Figure 4). About a year after his

| MANIFESTATION | At onset no. (%) | During evolution no. (%) |
|---|---|---|
| Malar rash | 401 (40) | 579 (58) |
| Discoid lesions | 63 (6) | 104 (10) |
| Subacute cutaneous lesions | 27 (3) | 56 (6) |
| Photosensitivity | 294 (29) | 453 (45) |
| Oral ulcers | 108 (11) | 238 (24) |
| Arthritis | 689 (69) | 840 (84) |
| Serositis | 172 (17) | 364 (36) |
| Nephropathy | 160 (16) | 393 (39) |
| Neurologic involvement | 117 (12) | 268 (27) |
| Thrombocytopenia | 94 (9) | 220 (22) |
| Hemolytic anemia | 38 (4) | 82 (8) |
| Fever | 361 (36) | 524 (52) |
| Raynaud phenomenon | 184 (18) | 339 (34) |
| Livedo reticularis | 47 (5) | 137 (14) |
| Thrombosis | 42 (4) | 137 (14) |
| Myositis | 38 (4) | 86 (9) |
| Lung involvement | 29 (3) | 73 (7) |
| Chorea | 9 (1) | 16 (2) |
| Sicca syndrome | 47 (5) | 161 (16) |
| Lymphadenopathy | 70 (7) | 119 (12) |

**Table.** Clinical manifestations at time of onset and during evolution of disease in 1,000 systemic lupus erythematosus patients. Republished with permission from Cervera et al.[6]

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initial presentation, he reported a dry cough, and chest imaging showed interstitial changes in a nonspecific interstitial pneumonia pattern, consistent with autoimmune interstitial lung disease from SLE (Figure 5). Mycophenolate and tacrolimus were used to treat both his lung and renal manifestations.

Several aspects of this case deviate from the classic SLE presentation. First, our patient's male gender is uncommon. SLE predilects female patients, and the estimated ratio of prevalence is 9:1.[1] Second, spontaneous tendon ruptures occur uncommonly in SLE patients. In a review of the literature, Alves et al identified only 55 published cases of spontaneous tendon ruptures in SLE patients and demonstrated that the phenomenon often occurs concomitantly with Jaccoud's arthropathy.[2] Third, interstitial lung involvement is not seen as often in SLE as it is in other autoimmune diseases, such as systemic sclerosis. The prevalence of interstitial lung disease in SLE is estimated at 3 percent over the course of the disease.[3]

Finally, membranous glomerulonephritis is a less common manifestation of lupus nephritis than proliferative glomerulonephritis. Not only did our patient suffer membranous glomerulonephritis, but his second biopsy, performed in the face of rapid clinical deterioration, showed the development of a rare form of glomerular injury, CG. CG is a podocytopathy that is associated with several etiologies, including viral infections, medications and autoimmune disorders such as SLE. In their analysis of CG in SLE patients at a single center, Salvatore et al identified 19 cases, predominantly of African ethnicity.[4] Controlled trials have not been performed in SLE patients with either membranous glomerulonephritis or CG, but consensus suggests treatment with tacrolimus in addition to the traditional choices of cyclophosphamide and mycophenolate is helpful.[5]

This case is not the only example of uncommon manifestations of SLE that we see in the Lupus Clinic. Our Lupus Clinic also fosters a cohort of patients who volunteer to join our Lupus Registry. Our registry is diverse, containing more than 150 patients diagnosed with SLE and overlap syndromes. The Lupus Registry collects both patient-reported outcomes data and biologic samples in the hopes of advancing basic science and clinical knowledge of SLE pathophysiology and treatment.

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**Figure 1**

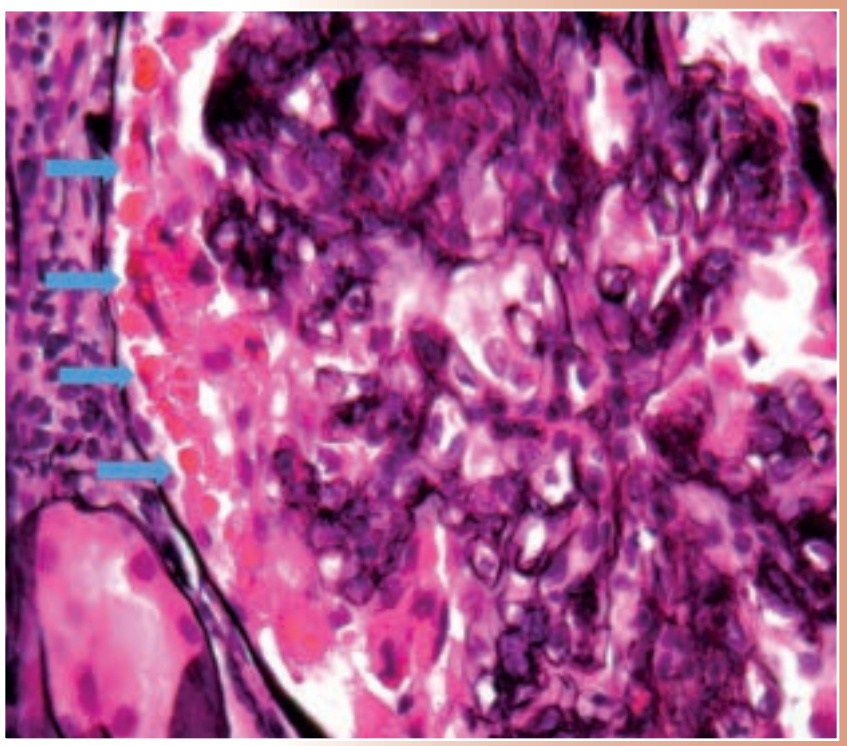
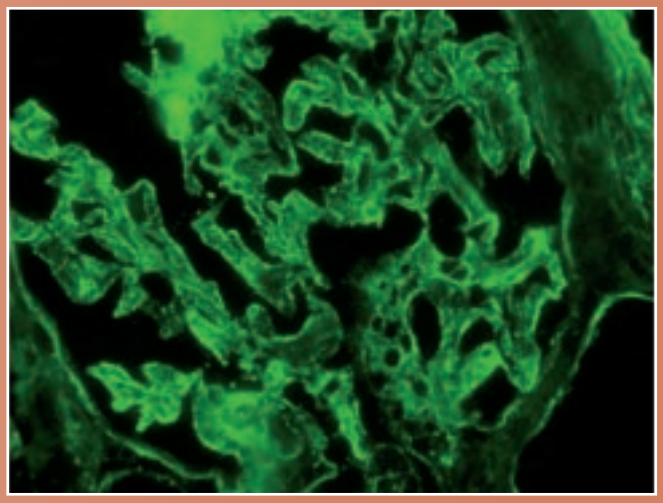
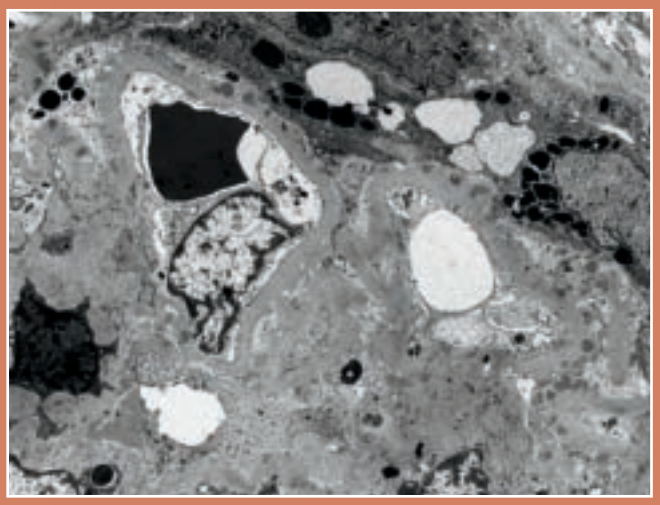
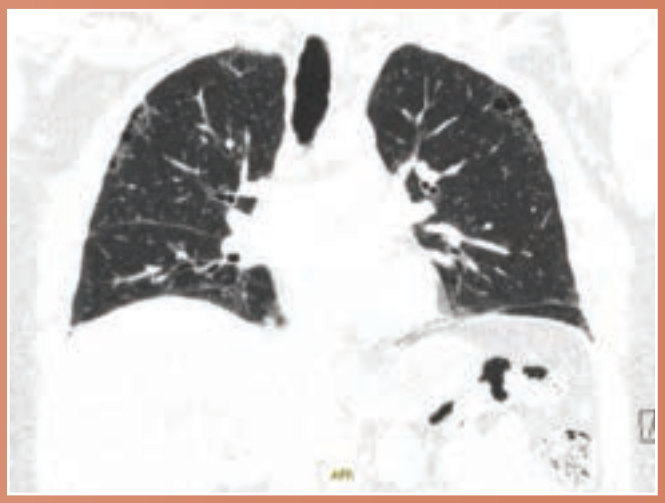


**Figure 1**. Photomicroscopy of a glomerulus from a patient with lupus. The glomerular tuft is partially collapsed and covered by podocytes containing prominent protein resorption droplets (blue arrows). No significant endocapillary proliferation is seen. This lesion could be mistaken for a crescent, as there are cells in Bowman's space, but no glomerular basement membrane rupture or other proliferative features are evident (Jones silver stain x400 magnification).

**Figures 2 through 5** run clockwise starting with **Figure 2** in upper lefthand corner.







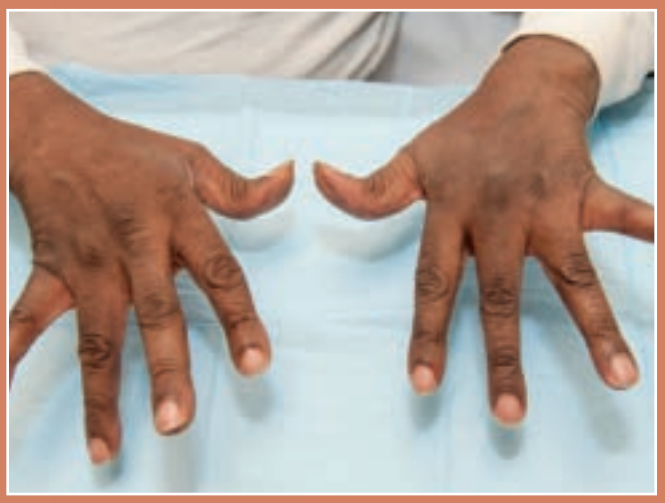


**Figure 2**. Immunofluorescence staining of glomerulus from patient with lupus. Immunofluorescence staining for IgG shows finely granular subepithelial deposits, consistent with an underlying membranous lupus nephritis (x400 magnification).

**Figure 3**. Electron microscopy of glomerulus from patient with lupus. Electron microscopy shows global podocyte foot process effacement with podocytes showing large electron-dense protein resorption droplets. Scattered subepithelial electron-dense deposits are also seen. Even in areas without subepithelial deposits, the podocyte foot process effacement is severe (x2900 original magnification).

**Figure 4**. Spontaneous tendon ruptures in a patient with SLE.

**Figure 5**. Computed tomography of the lungs. Computed tomography of the lungs without contrast demonstrates lower lobe predominant traction bronchial atelectasis with peribronchial and peripheral groundglass opacities, consistent with a nonspecific interstitial pneumonia pattern.

# PACNS OR RCVS?

## How to tell the difference and why it matters

By Rula Hajj-Ali, MD, and Leonard Calabrese, DO

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Primary angiitis of the central nervous system (PACNS) is a devastating disease in which exclusive inflammation and destruction of vessels in the CNS cause progressive, debilitating neurological deficits. Prognosis improves greatly with proper treatment, but with nonspecific tests and many confounding mimics, diagnosis can be tricky.

One of PACNS's closest mimics is reversible cerebral vasoconstriction syndrome (RCVS). The distinguishing characteristic of this group is the "thunderclap" headache — sudden, severe and with or without neurological deficits. Originally, rheumatologists treated RCVS as benign angiopathy of the CNS. In 2007, Calabrese et al set forth RCVS as a concept encompassing several syndromes with unifying clinical, laboratory and radiologic features.[1] The clinical features and diagnostic criteria described in that paper have been considered the standard since its publication.

Distinguishing between RCVS and PACNS is critical because the treatment protocol is vastly different. Misdiagnosing PACNS as RCVS can deprive a patient of medications that prolong survival and improve outcomes. These conditions are close mimics, but the astute clinician has several tools in her armamentarium to distinguish between them. We offer a brief overview below.[2]

### Clinical presentation

Patients with PACNS are more commonly male and trend older with a mean age of 50 years at onset, while patients with RCVS are more likely to be female and a bit younger. Patients with either condition almost always present with headaches, but the differences in onset and type are important to distinguish between the mimics. Patients with PACNS experience subacute onset of headaches with focal and nonfocal deficits; a patient with sudden-onset, severe, thunderclap headaches should be considered for RCVS whether or not neurological deficits are present. RCVS is monophasic, but patients with PACNS will experience these symptoms chronically.

When patients present with these symptoms, diagnostic tests can help eliminate the mimics and guide clinicians toward a precise diagnosis.

### Test results

An extensive workup is required to rule out PACNS mimics and common and secondary causes of CNS vasculitis.

Cerebrospinal fluid (CSF) analysis is essential in the differentiation between PACNS and RCVS and in excluding infections and malignancies. PACNS cases will show lymphocyte-predominant pleocytosis, elevated protein levels and normal glucose levels. In RCVS, normal CSF is the rule, unless the CSF is contaminated by subarachnoid or parenchymal hemorrhages.

Neuroimaging in PACNS cases is always abnormal. Ischemic infarctions are the most common lesions and are often multiple and bilateral. Nonspecific high-intensity lesions are also common in PACNS as visualized on T2-weighted magnetic resonance imaging (MRI) with a fluid-attenuated recovery sequence. RCVS is usually but not always abnormal on neuroimaging.

## CLINICAL PRESENTATION

| | PACNS | RCVS |
|---|---|---|
| **Gender** | Male | Female |
| **Mean age at onset** | 50 years | 42 years |
| **Headache** | Insidious, with subacute onset of headache with focal and nonfocal deficit | Acute onset of thunderclap headache with or without neurological deficit |
| **Course** | Chronic, relapsing | Monophasic, nonrelapsing |

## TEST RESULTS

| | PACNS | RCVS |
|---|---|---|
| **CSF** | Lymphocytes, protein ↑ | Normal |
| **Neuroimaging** | Ischemic, high-intensity T2/FLAIR lesions, abnormal MRI in 100% of cases | Ischemic, edema, cSAH, ICH, initial MRI normal in 20% of cases |
| **Vascular** | Abnormal in 2/3 of cases | Abnormal in all cases |
| **Histological** | Vasculitic changes | Normal |

## MANAGEMENT

| | PACNS | RCVS |
|---|---|---|
| **Immunosuppressive therapy** | Essential | Not indicated |
| **Prognosis** | Improved with immunosuppressive therapy | Majority of patients have no disability |

Upon initial presentation, 20 percent of patients may have normal neuroimaging. Edema is a common finding, and computed tomography can show convexity subarachnoid hemorrhage or intracranial hemorrhage, both more common in RCVS.

Cerebrovascular imaging is always abnormal in RCVS and usually abnormal in PACNS. Stenosis and dilation visualized by direct or indirect angiography are not specific to either condition. Involvement of vascular beds in RCVS is usually bilateral and affecting multiple territories, which may not be true in PACNS. Further, the cerebrovascular abnormalities in RCVS are dynamic and improve over time.

In the lab, both PACNS and RCVS will test normal for C-reactive protein, erythrocyte sedimentation rate, complete blood count and complete metabolic profile. Serologic tests for rheumatologic, autoinflammatory, autoimmune, malignant and infectious diseases are negative in PACNS and RCVS.

Advances in neuroimaging such as the use of 3-Tesla high-resolution MRI specifically to assess the vessel wall hold promise in differentiating between the conditions. The vessel walls in RCVS do not show enhancement, while in PACNS, enhancement occurs.

### A note on the gold standard

Brain biopsy is the often-feared, underutilized gold standard in the diagnosis of PACNS. An open-wedge procedure is considered low risk, and an experienced neurosurgeon working as part of a multidisciplinary team can perform a biopsy with greater than 80 percent sensitivity and 90-100 percent specificity. Finding inflammation in the vessel wall is characteristic of PACNS, while brain biopsies are normal in RCVS.

### Management and outcomes

Before the advent of immunosuppressive therapies, the prognosis for PACNS was dismal. Survival improves with aggressive therapy. The use of immunosuppressive therapy is not indicated in RCVS, as the pathogenetic mechanisms are related to vasospasm and not inflammation; calcium channel blockers are commonly used to control headaches.

We have recently elucidated functional capabilities, quality of life and frequency of depression for our strong cohort of patients with PACNS in the longest reported follow-up in the literature to date and the first evaluation of the quality of life and incidence of depression in these patients. Of 78 patients, 27 responded to the questionnaires (34.6 percent). Mean follow-up was 5.5 years (± 4.7). Seventy percent had mild disability, and 5 percent had severe disability. Around half of the patients had no mobility problems and no problems with usual activities, and two-thirds had no problems with self-care. Physician assessment with the Modified Rankin Scale showed that the majority of PACNS patients had mild long-term disability with a median dis-

ability score of 1. Approximately 70 percent of patients had minimal or no depression. Mortality was 11 percent.

## Better tools for the future

As our experience with and knowledge of PACNS and RCVS have grown, rheumatologists and neurologists alike grow closer to demystifying these mimics and providing precise diagnoses for affected patients. Much work remains to be done to assess the pathogenesis and etiologies of both conditions. At the R.J. Fasenmyer Center for Clinical Immunology's CNS Vasculopathy Program, we are currently looking for biomarkers in CSF to better elucidate these mechanisms.

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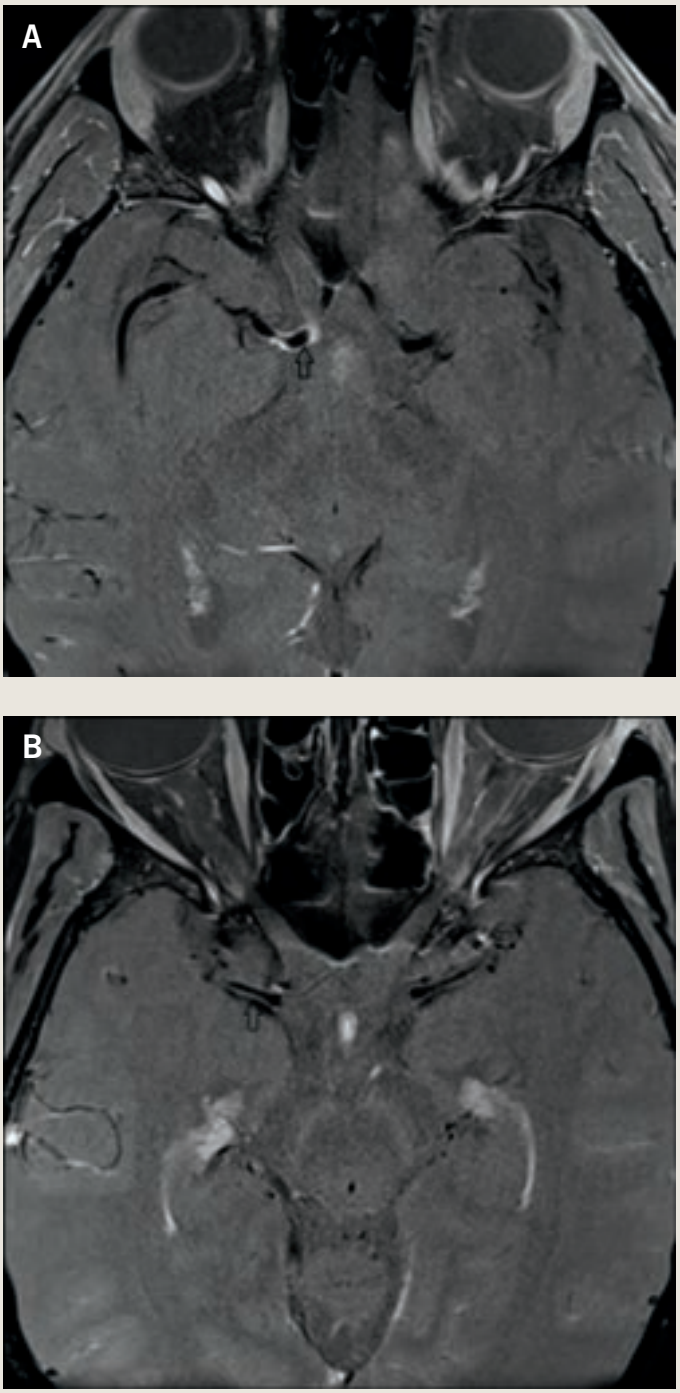


**Figure 1**. High-resolution MRI brain axial section post gadolinium contrast. (A) Vasculitis patient shows vessel wall enhancement and thickening (arrow) while RCVS patient (B) shows minimal wall enhancement (arrow). Image and caption republished with permission from Hammad and Hajj-Ali.[2]

# THE PSYCHOSOCIAL BURDEN OF PSORIATIC ARTHRITIS

## How and why to assess and treat

By M. Elaine Husni, MD, MPH, and Sarah Davin, PsyD, MPH

Patients diagnosed with psoriatic arthritis (PsA) experience significantly poorer health-related quality of life (QoL) than the general population and than those with psoriasis alone. Appropriate management from a multidisciplinary team of clinicians can reduce the psychosocial burden of this disease. We recently published a review of the literature regarding PsA and QoL and made recommendations based on our observations and clinical experiences to help physicians manage their patients with PsA.[1]

### Diminished QoL

Quality of life is significantly diminished in patients with PsA. Patients experience:

- More comorbidities, with cardiovascular disease as the most common.
- Cosmetic effects that negatively impact self-image and emotional health.
- Pain, which has a bidirectional association with depression in patients with PsA.
- Sleep disorders, which are common in patients with PsA and contribute to diminished QoL and increased pain.
- Higher risk of depression, making adherence to treatment (and thus pain management and functional improvement) more difficult.
- Diminished physical function and productivity, which impacts self-worth and increases economic burden.

Delays in diagnosis and treatment can significantly impact these QoL issues in patients with PsA. Delays in treatment mean more bone erosion and functional decline and further negative impacts on mental health and QoL. These delays are common given the lack of laboratory or imaging tests for the early diagnosis of PsA and given how difficult the disease can be to diagnose, especially in early stages. The latest Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) treatment guidelines recognize the major challenges inherent in early identification of PsA and call for better diagnostics and faster treatment as key research imperatives.[2]

### Recommendations to assess and address QoL

Based on our literature review and clinical experiences, we recommend always assessing psychological parameters in addition to overall function in your patients with PsA. The patient interview is crucial and should include questions about familial relationships as well as further inquiry into symptoms that patients may tend to minimize on written assessment tools.

Physicians should assess physical function, dermatology-specific measures, sleep and fatigue, depression and anxiety, and QoL in all PsA patients. Validated measures to assess psychosocial burden in patients with PsA include:

- Short Form-36 (SF-36)
- Psoriatic Arthritis Quality of Life (PsAQoL) instrument
- Health Assessment Questionnaire (HAQ)
- Pain Disability Index (PDI)
- Dermatology Life Quality Index (DLQI) for patients with skin involvement (supplemented with an evaluation for itch)
- Psoriasis Area and Severity Index (PASI)
- Functional Assessment of Chronic Illness Therapy-fatigue (FACIT-fatigue) scale
- Depression, Anxiety and Stress Scales (DASS-21)
- Goldberg Anxiety and Depression scale-7 (GAD7)
- EuroQol 5 Domain (EQ-5D®)
- PsA Impact of Disease (PsAID) (a recently developed tool that needs further evaluation)

With a wealth of assessment tools at the rheumatologist's disposal, a collaborative approach involving primary care, dermatology and behavioral health will allow the best assessment and treatment of psychosocial burden in patients with PsA. PsA is chronic, and assessment should be continuous. At Cleveland Clinic, patients complete questionnaires at each outpatient visit that focus on gathering information on how they are living with their current immune-mediated diseases. Queries include level of pain, quality of life and mental health. This information is available to physicians during the visit to add the patient's perspective to clinician evaluations and to laboratory and imaging results.

### QoL in clinical trials, management algorithms

This literature review is but a first step toward further research on QoL concerns in patients with PsA. We believe that future clinical trials must include evaluation of QoL concerns based on a core set of variables and assessment tools recently defined by a joint dermatology-rheumatology board.[3] A recent, OMERACT-endorsed (Outcome Measures in Rheumatology) update to the PsA core domain set[4] establishes evaluation of pain, global assessment, physical function, health-related QoL and fatigue as imperative to include in all studies, and emotional well-being, participation and economic cost as highly recommended. It's also key that future care paths and management algorithms for the disease incorporate the psychosocial assessments mentioned above and the management of psychological, functional and physical concerns.

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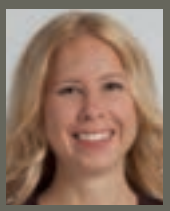

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# ADVANCES IN IL-6 BIOLOGY FOR RHEUMATOLOGISTS

## It's more than inflammation

By Leonard Calabrese, DO

Dr. Calabrese (calabrl@ccf.org; 216.444.5258) directs the R.J. Fasenmyer Center for Clinical Immunology.

When interleukin 6 (IL-6) was discovered in the laboratory in the 1980s, it was considered a cytokine that primarily offered help to B cells in the process of making immunoglobulin. Since then, it has become clear that IL-6 is not only a key mediator in the inflammatory response, but also a link between the immune system and a variety of viserosomatic tissues with far-reaching biology.

2017 was a big year for IL-6 biology, with the approval of two new indications for tocilizumab, the lead compound in a class first approved to treat rheumatoid arthritis over a decade ago. This potent agent is now approved for inducing long-term, steroid-sparing remissions in giant cell arteritis and also for treatment of cytokine storm, which often accompanies the use of chimeric antigen receptor T cells, a major, recent breakthrough in the field of cancer immunotherapy.

I've worked with several collaborators, including Stefan Rose-John, PhD, from University of Kiel and a pioneer in IL-6 biology and its signaling, as well as Ernie Choy, MD, University of Cardiff, and Kevin Winthrop, MD, University of Oregon Health Sciences Center, on a series of reviews that discuss numerous recent observations pertinent to rheumatologists and immunologists who employ anti-IL-6-based strategies in their practice.[1-3] I've highlighted the most compelling here.

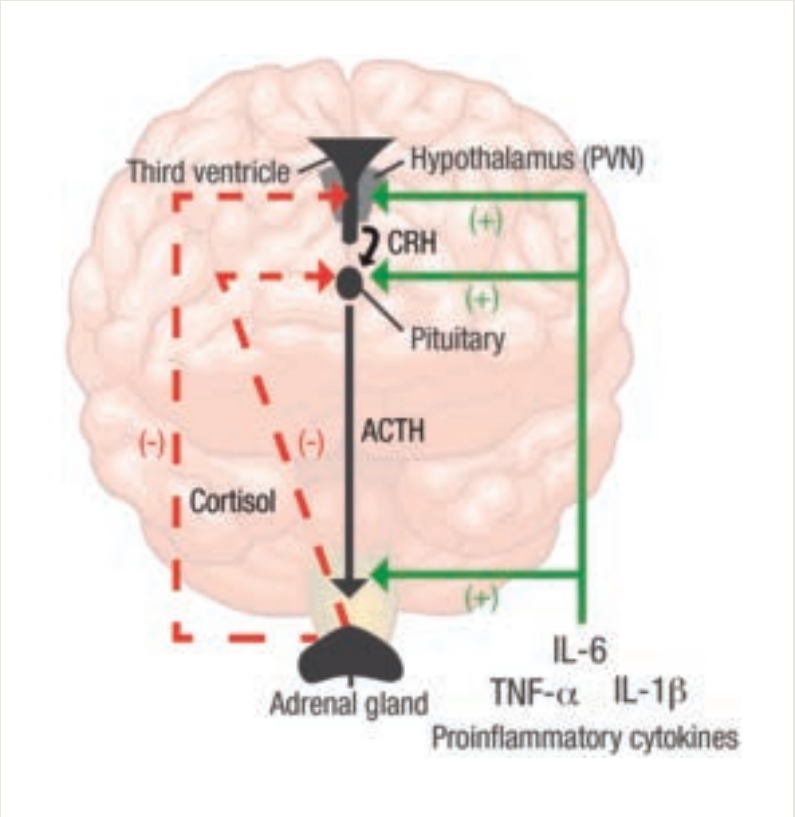


**Figure**. The hypothalmic-pituitary-adrenal (HPA) axis in RA. Pro-inflammatory cytokines such as IL-6, TNF-α and IL-1β stimulate cortisol and CRH release by acting at all three levels of the HPA axis (solid green lines). As a result, glucocorticoids regulate their own production through negative feedback on the upper levels of the HPA axis, including CRH in the PVN of the hypothalamus and ACTH in the anterior pituitary (dashed red lines). ACTH: adrenocorticotropic hormone; CRH: corticotropin-releasing hormone; PVN: paraventricular nucleus. Image republished with permission from Oxford University Press.

### The role of IL-6 in pain, fatigue and mood

Recent work on the biology of IL-6 has demonstrated a key role in a wide variety of bodily systems, including vascular, lipid metabolism, insulin resistance and neuropsychological behavior. IL-6 has also been demonstrated to be intimately involved in the interplay between the central nervous system and the immune system (Figure). In rheumatoid arthritis (RA) and many other inflammatory conditions, there is dysregulation of the hypothalamic pituitary axis, and increasing evidence points to a critical role of inflammatory cytokines, especially IL-6. These effects likely belie the role of IL-6 in the domains of pain, fatigue and mood, which are critical to quality of life in patients with inflammatory diseases such as RA.

In terms of pain, preclinical models have suggested that IL-6 sensitizes animals to pain, as glial cells and dorsal root ganglia express gp130 and thus can be activated via trans-signaling with IL-6. In these experimental models of arthritis, IL-6 knockouts that are unable to respond to IL-6 significantly attenuate pain behavior. Clinical studies with biologics such as tocilizumab, sarilumab and sirukumab all support a potent capacity for IL-6 inhibition to mediate pain directly as well as via its key anti-inflammatory role in disease.

Fatigue is also a major comorbidity in numerous inflammatory conditions. Studies of normal volunteers infused with IL-6 demonstrated both disturbed sleep and fatigue. Fatigue in RA correlates with mood, pain and disability; thus, targeting IL-6 may be useful in approaching fatigue both directly and indirectly as a therapeutic strategy. It has been postulated that IL-6 may mediate this effect by directly disrupting the hypothalamic-pituitary axis, which has been shown to be dysfunctional in patients with chronic fatigue syndrome.

Accordingly, it has become increasingly important to assess pain not only in clinical trials but also in the clinic. At Cleveland Clinic's Department of Rheumatic and Immunologic Diseases, all patients are screened with quality of life measurements that center on the use of PROMIS® (Patient-Reported Outcomes Measurement Information System), a set of person-centered measures that evaluate and monitor physical, mental and

social health in adults and children. To date, we have such measures on over 35,000 patient visits. Increasing evidence suggests enhanced patient engagement when they are able to see and reflect on issues that are important to their overall wellness, not merely the activity of their disease.

Finally, more than one-third of patients with RA have mood disorders, and depression ranks top among these. Numerous studies in animals and humans suggest a role for IL-6 in the development of depression and anxiety. IL-6 is a sensitive biomarker in depression and in healthy individuals, and experimental administration of IL-6 significantly suppresses self-reported mood markers. In clinical trials, targeting of IL-6 in RA has been associated with significant improvements in mood scores and has been superior to an anti-TNF comparator. Though the mechanisms involved are poorly understood, a clinical trial of the IL-6 receptor antagonist sirukumab for treatment-refractory depression is ongoing and nearing completion.

Experimental administration of IL-6 significantly suppresses self-reported mood markers.

The IL-6 space, including its basic, translational and clinical immunology, is rapidly changing, and numerous additional biologics are under development and soon may be available. Clinicians using these agents need to maintain a robust knowledge base in the field to better care for our patients. We highlighted some of these developments at the 6th Annual Basic and Clinical Immunology for the Busy Clinician, held March 9-10 in Miami, where over 120 clinical immunologists gathered for an immunology boot camp designed to strengthen skills in immunology as it relates to practice.

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# AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION FOR SEVERE SYSTEMIC SCLEROSIS

## Way of the future? A closer look at a promising therapy

By Soumya Chatterjee, MD, MS, FRCP, and Navneet Majhail, MD, MS

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Systemic sclerosis (systemic scleroderma, SSc) is an autoimmune disease of unclear etiology characterized by progressive fibrosis of skin and various internal organs (mainly the lungs, heart, gastrointestinal tract and kidneys), a widespread occlusive microvasculopathy and presence of certain autoantibodies. Despite significant medical advancements in the past century, so far no therapy has proven consistently effective in altering the natural history of this devastating disease. The available immunosuppressive, antifibrotic and vasoactive therapies offer modest benefit at best. Moreover, they are fraught with side effects that are often unacceptable for the marginal degree of stabilization or improvement that they may provide.

In the past decade, autologous hematopoietic cell transplantation (AHCT) has gained progressive acceptance as a form of salvage therapy for severe autoimmune diseases. The mechanisms underlying the benefit of AHCT in autoimmune diseases are still not fully elucidated. Increasing evidence supports the hypothesis that it helps in re-establishment of immunological tolerance in addition to its nonspecific immunosuppressive effect.

In the absence of potentially effective, disease-modifying therapy that can prevent SSc from progressing or reverse damage to the internal organs, high-dose chemotherapy in conjunction with AHCT has been investigated in several observational and clinical studies. Based on these studies, the European League Against Rheumatism (EULAR) issued evidence-based practice guidelines for the treatment of SSc that recommend AHCT for the treatment of selected patients with rapidly progressive disease at risk of irreversible organ failure.[1]

### The evidence at hand

Several observational and uncontrolled phase 1/2 trials have suggested the efficacy of AHCT in patients with severe scleroderma. A retrospective study compared the outcomes of 18 AHCT recipients with rapidly progressive, diffuse scleroderma to a demographically and clinically matched group of 36 patients receiving conventional therapies.[2] Compared to the AHCT group, the control patients had significantly lower overall survival (hazard ratio [HR] 6.94, $P < 0.002$), including the subset who had received cyclophosphamide-based regimens (HR 5.98, $P < 0.006$). AHCT recipients had a significantly higher likelihood of improving skin tightness and preserving lung function.

Three randomized controlled trials have compared AHCT and standard of care (cyclophosphamide-based therapy) for severe scleroderma:

(1) American Scleroderma Stem cell versus Immune Suppression Trial (ASSIST)[3]

(2) Autologous Stem cell Transplantation International Scleroderma (ASTIS) trial[4]

(3) Scleroderma: Cyclophosphamide Or Transplantation (SCOT) trial[5]

The patient characteristics and eligibility criteria were similar among the three trials. All three trials validated a benefit in the AHCT arm regarding their primary endpoints (clinical improvement in ASSIST, event-free survival in ASTIS and change in global rank composite score in SCOT). Also, patients receiving AHCT had better overall survival and a lower rate of disease progression. Treatment-related mortality in the AHCT arm was 0 percent at 12 months in ASSIST, 10.1 percent in ASTIS and a much more favorable 3 percent at 54 months in SCOT. It was 0 percent in the cyclophosphamide arms in all three studies. Recurrent disease in the AHCT arm was seen in 0 patients in ASSIST (8/9 patients in the cyclophosphamide arm), 22.4 percent in ASTIS (43.8 percent in the cyclophosphamide arm) and 9 percent in SCOT (44 percent in the cyclophosphamide arm).

A systematic review and meta-analysis included three randomized trials and one comparative observational study.[2-6] Patients in the control arm received monthly cyclophosphamide in all three trials and so also did the majority of patients in the observational study. Compared to controls, patients receiving AHCT had lower all-cause mortality (risk ratio [RR] 0.50; $P = 0.0007$), and improved skin scores, forced vital capacity, total lung capacity and quality of life. In sensitivity analyses that only included data from the randomized trials, the improvement in overall mortality was maintained (RR 0.61, $P = 0.02$).

### The evidence we need

Although it would be too optimistic to call AHCT curative for SSc, it has thus far shown the most promise as a potential disease-modifying therapy. Currently, studies are ongoing to evaluate the effectiveness of continuing immunosuppressive therapy (with mycophenolate mofetil) to help maintain disease remission achieved through AHCT and prevent future relapse. It is clear that patient selection is critical in determining successful outcomes for AHCT.

It cannot be overstressed that for the best results, AHCT should only be performed in centers with sufficient experience and expertise in providing multidisciplinary care for both scleroderma and AHCT. Careful follow-up to evaluate long-term outcomes is essential. Currently, consideration of AHCT has been limited to patients with SSc of four to five years' duration, with mild-to-moderate but progressive internal organ involvement, who have failed to improve (or have worsened) on conventional immunosuppressive therapy. In the future, we need recommendations about whether AHCT should be offered as an upfront treatment option or as salvage therapy.

The cost-effectiveness of AHCT also must be established for third-party payers. Appropriate decision tools are needed to better understand and address the trade-off between the short-term, treatment-related morbidity and mortality

and the long-term benefits of AHCT. Further ongoing research to help refine the treatment protocol involving AHCT is essential to help provide the highest possible benefit with the lowest possible risk in this critically ill patient population.

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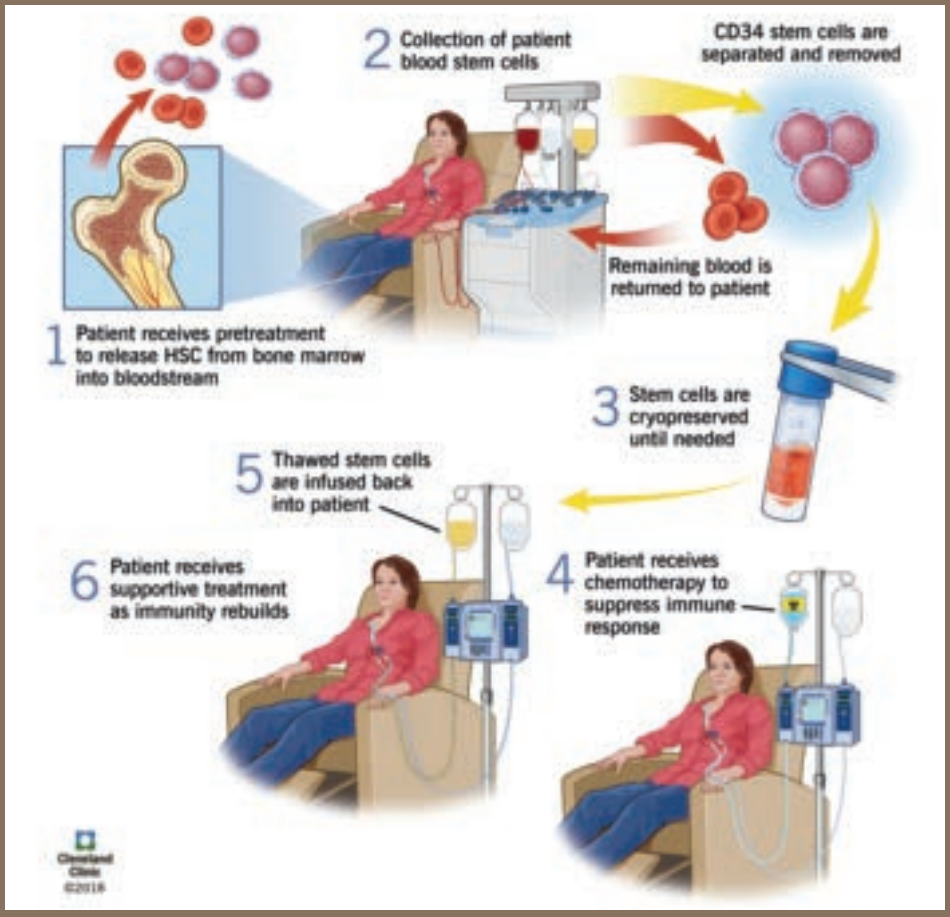


**Figure.** AHCT. Patient will also receive total-body irradiation and antithymocyte globulin to achieve myeloablation.

**Dr. Chatterjee** was awarded the **Bruce Hubbard Stewart Award for Humanistic Medicine** in 2018. This award honors clinicians who manifest compassion, respect, professionalism and integrity in the care of patients; who treat patients with sensitivity and concern for the impact that illness has upon their physical, emotional, social and spiritual lives; who value the uniqueness and individuality of patients; who take time to ensure that patients and their families understand diagnosis, treatment and possible outcome; who are available to their patients throughout all stages of their illnesses; who respect the rights of patients; who respond to the moral aspects of medical practice with wisdom and empathy; and who cooperate in harmony with all who serve the patient.

# POSITRON EMISSION TOMOGRAPHY IN LARGE VESSEL VASCULITIS

## A case report

By Kevin Byram, MD, and Carol A. Langford, MD, MHS

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### Case presentation

A 49-year-old male was diagnosed with Takayasu arteritis (TAK) three years ago. At that time, he presented with headache and was found to have severe hypertension and an absent left radial pulse. His sedimentation rate (ESR) and C-reactive protein (CRP) were elevated, and he had normal renal function. Vascular imaging revealed a stenotic left subclavian artery and an occluded left renal artery with an atrophic left kidney. Following his diagnosis, he was started on glucocorticoids and methotrexate, with medical management of his hypertension. He initially did well, but recent laboratory evaluation revealed mild elevations in his ESR and CRP. He was having no new symptoms and his physical examination was stable, including four-limb blood pressures and bruit evaluation. He had recently read about positron emission tomography (PET) imaging and had questions about its clinical utility.

### Challenges in the assessment of patients with large vessel vasculitis

Giant cell arteritis (GCA) and TAK are the two most common forms of primary large vessel vasculitis (LVV). Assessment of disease activity in patients with LVV is an ongoing challenge. Currently, the clinician integrates information from the history, physical examination, laboratory and available imaging to reach a conclusion regarding ongoing inflammatory disease activity.

From an imaging standpoint, computed tomography angiography (CTA) or magnetic resonance angiography (MRA) are the main modalities used to assess the vascular lumen in patients with LVV. Detection of a new stenosis or aneurysm on serial imaging is usually considered to be indicative of disease activity necessitating treatment. However, once these lesions develop, vascular damage has already occurred, such that there is interest in techniques that could identify vascular inflammation prior to the development of a stenosis or aneurysm in patients with LVV.

### Investigation of PET imaging in large vessel vasculitis

Position emission tomography (PET) is a mode of imaging utilizing 18F-fluorodeoxyglucose (FDG) uptake to determine the metabolic demands on various body tissues. Hypermetabolic tissues will demonstrate increased FDG uptake on PET scans, potentially providing insights into the biological processes occurring at a particular site of interest.

The established clinical indication of FDG-PET is for the assessment of oncological diseases. The use of FDG-PET in inflammatory diseases is a subject of ongoing investigation. In LVV, the unique metabolic mechanism of PET imaging has raised interest in whether it could provide a means for clinicians to identify vascular inflammation and prestructural disease activity.

A large prospective, observational study was recently conducted at the National Institutes of Health (NIH) to characterize the role of PET imaging as a biomarker in patients with LVV.[1] The study enrolled 67 patients with GCA and 44 with TAK, with a comparator group comprised of healthy controls (N = 7), patients with hyperlipidemia (N = 35) and patients with disease mimicking LVV (N = 7).

Prior to and independent of imaging studies, disease activity was determined by clinical history, physical examination and laboratory assessment. FDG-PET was performed at baseline and at each follow-up visit. PET studies were examined by nuclear radiologists and determined dichotomously to be positive for vasculitis and negative for vasculitis. A novel assessment tool defined in this study was the PET Vascular Activity Score (PETVAS), a semi-quantitative score rating PET uptake intensity relative to the liver on a 0-to-3 scale in nine vascular territories (0 = no FDG uptake, 1 = less than liver, 2 = equal to liver, 3 = more than liver).

In this study, FDG-PET had a sensitivity of 85 percent and specificity of 83 percent when differentiating active LVV from comparator groups. The sensitivity dropped to 42 percent when differentiating active LVV from those patients with LVV in remission. Some patients with LVV who were in clinical remission maintained persistent FDG uptake signal on follow-up PET scans. The researchers also found an association between relapse risk and PETVAS score in which more patients who had a PETVAS greater than or equal to 20 relapsed compared to those with PETVAS less than 20 (45 vs. 11 percent, $P = 0.03$).

### What is the role of PET imaging in large vessel vasculitis?

The role of PET imaging in patients with LVV has yet to be clearly defined. In the NIH study, although FDG-PET demonstrated reasonable ability to discriminate patients with active LVV from other disease settings and healthy controls, FDG uptake was also seen in some patients with atherosclerosis and other mimicking disease processes. FDG-PET did not reliably differentiate patients with active LVV from those in remission, and more studies are needed to better understand whether persistent PET uptake represents increased metabolic activity from vascular remodeling or subclinical active inflammation.

A key issue that remains is whether FDG-PET characteristics, such as PET uptake and PETVAS score, correlate with the later development of structural arterial consequences, such as a new stenosis or aneurysm. Longer-term, serial follow-up from the NIH and other cohorts may provide answers to this important question in this complex patient population.

Until there are more definitive answers regarding the utility of FDG-PET in LVV, the decision about whether to pursue such imaging should be made on an individual basis. Factors to weigh include the specific question being asked and the currently available evidence, as well as

cost and access issues. If PET is performed, this information should be used adjunctively with CTA or MRA, as these methods of imaging remain critical in order to assess vascular anatomy.

## Next steps in the case presentation

To assess the disease activity of our patient with TAK, we recommended MRA of the entire aorta and branch vessels, which did not reveal any new vascular lesions. While slightly elevated, his inflammatory markers were at his baseline. Given no new symptoms, stable labs and unchanged vascular lumen imaging, he was deemed to be in clinical remission, and no changes were made to his medical regimen. In the six-month interim, he is still in clinical remission. In the absence of new symptoms or signs, we will plan to repeat his MRA every 12 months.

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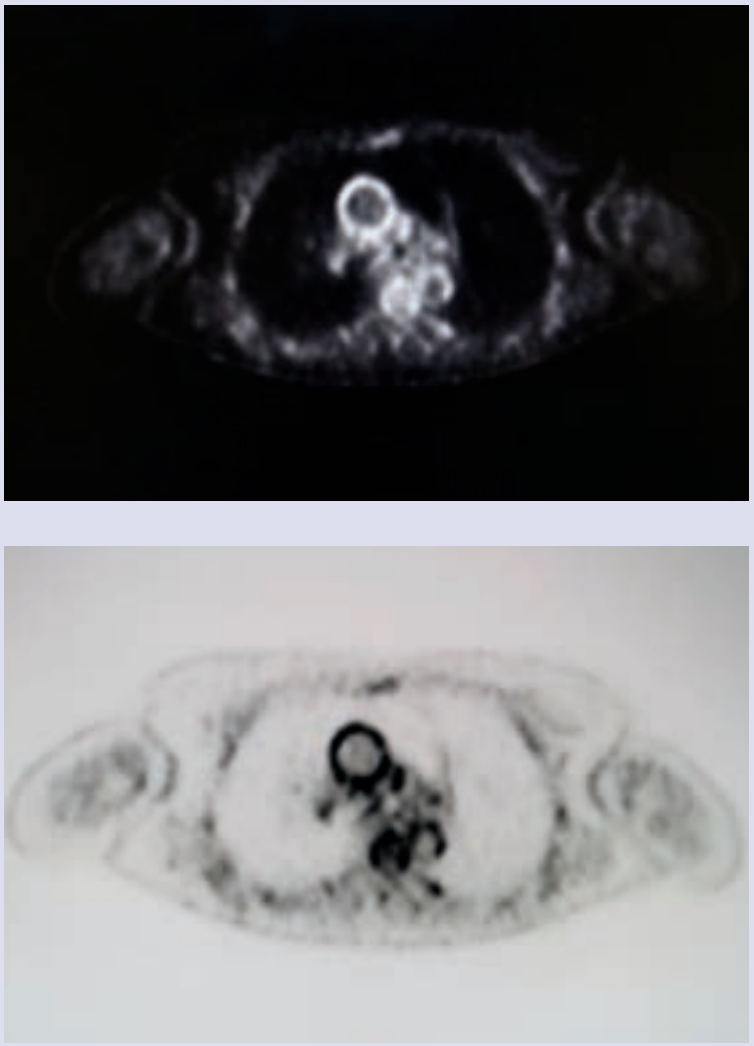

**Figure**. Axial FDG-PET images from a patient with aortitis demonstrating increased FDG uptake in the aortic root and ascending aorta.

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