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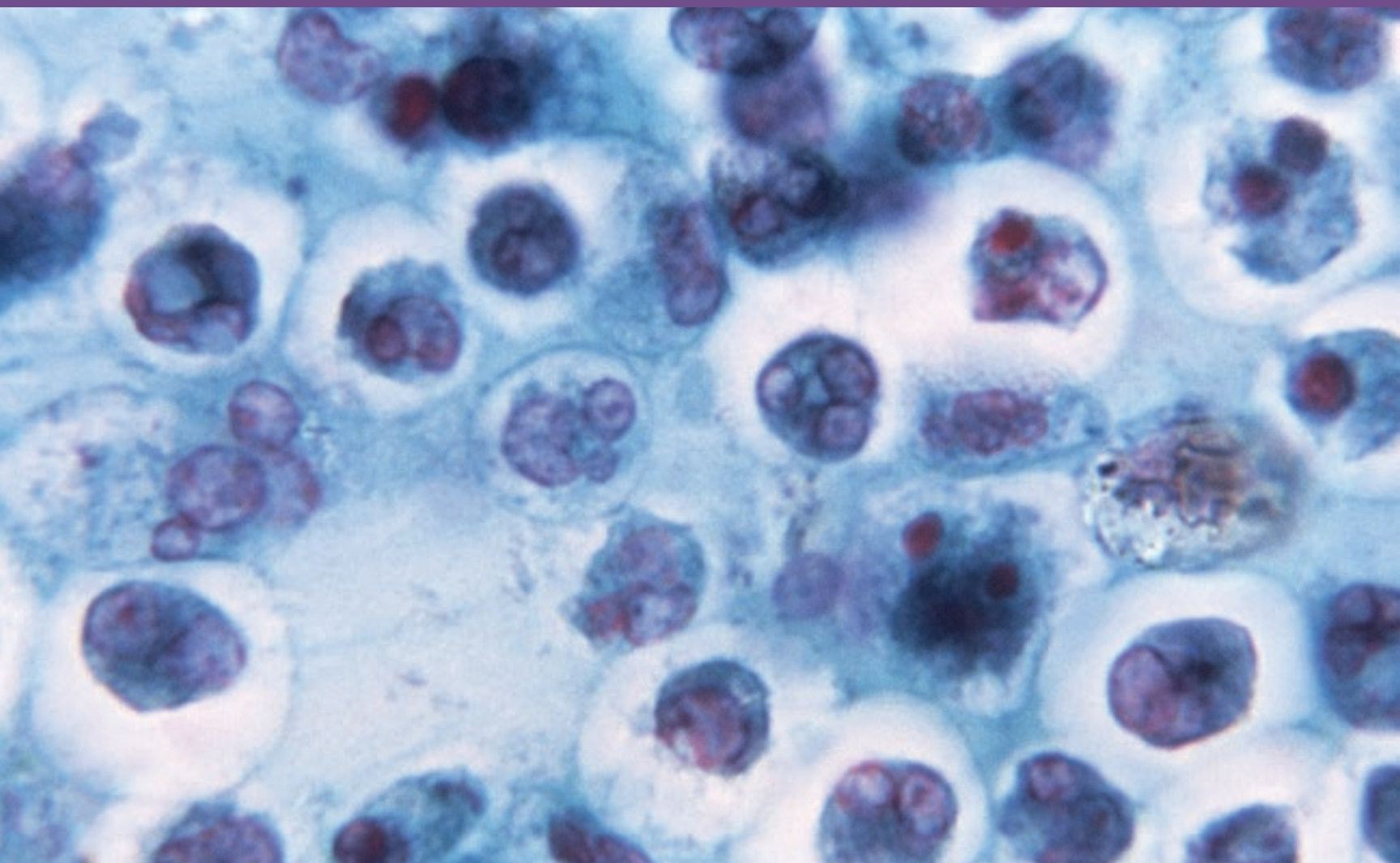
Cleveland Clinic

Rheumatology Connections

An Update for Physicians | Winter 2018



From the Chair of Rheumatic and Immunologic Diseases

Dear Colleagues,

At Cleveland Clinic, the knowledge that tomorrow's medical innovations spring from today's laboratories and clinical trials drives us continually toward fulfilling our mission. In this issue of *Rheumatology Connections*, our staff demonstrate just how deeply this understanding resonates in the Department of Rheumatic and Immunologic Diseases.

Several articles provide a sampling of our diverse research initiatives:

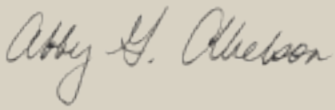
- **M. Elaine Husni, MD, MPH**, describes advances in translational science and clinical trials that will benefit our many patients with rheumatoid, psoriatic and osteoarthritis.
- **Alexandra Villa-Forte, MD, MPH**, reports on the first study to address the rate of venous thromboembolism recurrence in patients with granulomatosis with polyangiitis.
- **Carol A. Langford, MD, MHS**, outlines the results of a multicenter trial examining the safety and efficacy of mepolizumab in eosinophilic granulomatosis with polyangiitis.
- **Rula Hajj-Ali, MD**, shares findings from the longest reported follow-up of patients with primary angiitis of the central nervous system.

Our robust research program is but one aspect of how we fulfill our tripartite mission. Our team's skillful and consistent application of yesterday's research to today's caregiving is evident in the following cases:

- **Soumya Chatterjee, MD, MS**, shares a case that illustrates the mortality of a disease once considered largely benign. His patient with amyopathic dermatomyositis reminds us that despite more advanced immunotherapies, investigations are necessary if we are to improve prognosis.
- **Apostolos Kontzias, MD**, reports the second case ever documented of mosaicism causing tumor necrosis factor receptor-associated periodic syndrome (TRAPS), encountered in our Clinic for Adult Autoinflammatory Diseases.
- **Leonard Calabrese, DO**, collaborates with allergist and immunologist **James Fernandez, MD, PhD**, to share a case of specific granule deficiency from the Adult Immunodeficiency Clinic within Cleveland Clinic's R.J. Fasenmyer Center for Clinical Immunology.
- **Lisa Zickuhr, MD**, one of our fellows under the mentorship of **Howard R. Smith, MD**, describes a multidisciplinary approach in concert with colleagues in obstetrics to managing reproductive health in a patient with systemic lupus erythematosus.

My hope is that this issue of *Rheumatology Connections* demonstrates the breadth and depth of our work caring for the sick, investigating their conditions and educating those who serve. I welcome your feedback as we collaborate to advance rheumatologic care and research.

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: Trichrome-stained photomicrograph of leukocytes. *Source: CDC Public Health Image Library.*

LONG-TERM OUTCOMES FOR PATIENTS WITH PACNS

A better outlook

By Rula Hajj-Ali, MD

Primary angiitis of the central nervous system (PACNS) remains one of the most complex forms of vascular inflammatory disease. Multiple factors contribute to our relatively limited understanding of the disease, including its rarity, the lack of an efficient noninvasive test, a paucity of pathological material to study and the absence of animal models simulating the disease.

Cleveland Clinic has been a leader in care and research in the field of central nervous system (CNS) vasculitis for more than 25 years, developing criteria for its diagnosis that are widely employed today. We have recently begun to report on long-term outcomes of these patients to better understand this rare disease.

From postmortem diagnosis to effective treatment

Historically, patients with PACNS vasculitis were diagnosed postmortem. The first report describing sustained clinical remission in four patients in 1983 by Cupps et al.[1] brought more enthusiasm to the possibility of treating this disease. Since then, clinicians have elucidated many clinical manifestations of and much of the diagnostic approach toward this disease, but little is known about the overall outcomes of these patients. Recent cohort studies have described a generally favorable disease course.

Although most of what we know about this very rare disease is from these large cohorts, there remains no consistency in the studies' diagnostic approaches, where less than half of the patients had brain biopsies. Therefore, the outcomes depicted may not be generalizable.

In addition, more recent advances have discerned the importance of ruling out reversible cerebral vasoconstriction syndrome (RCVS), a major angiographic mimic of PACNS. The definition of RCVS as an entity in 2007 is considered a major breakthrough in understanding and eliminating the mimics of PACNS. Prior to 2007, RCVS was not well-characterized, which may have added to the contamination of some PACNS cohorts.

Long-term outcomes

We have recently elucidated patients' functional capabilities, quality of life and frequency of depression for our strong cohort of patients with PACNS. We have only included in this cohort patients whose diagnosis was established by brain biopsy (74.1 percent) or by the presence of both abnormal cerebral angiography and cerebrospinal fluid findings (25.9 percent).

We mailed four questionnaires to patients to assess their disability (Barthel Index), quality of life (EQ-5D) and depression (PHQ-9) scores. The Modified Rankin Scale, a disability assessment, was obtained during the last visit.

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 using the Modified Rankin Scale showed that the majority of PACNS patients had mild long-term disability, with a median disability score of 1. Approximately 70 percent of patients had minimal or no depression. Mortality was 11 percent.

This is the longest reported follow-up of patients with PACNS in the literature to date and the first evaluation of the quality of life and incidence of depression in these patients. Most of the patients had mild long-term disability and no difficulty with walking, usual activities and self-care, which may be reflective of improved management of this disease or earlier diagnosis and recognition. Rates of depression and mortality represent opportunities for improved diagnosis and treatment of patients with PACNS.

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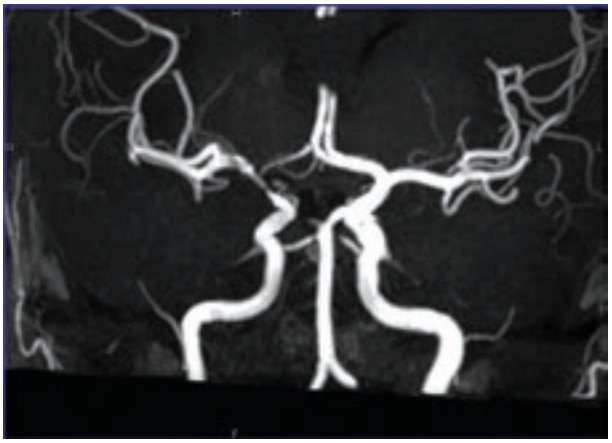

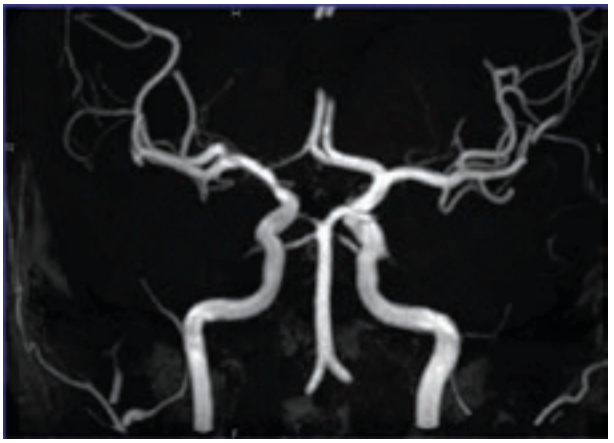

Figure. Magnetic resonance angiogram with PACNS revealing attenuation of the caliber at the junction of the right middle cerebral artery origin and right terminal internal carotid artery (*left*), with improvement in the vessel caliber after treatment (*right*).

TREATMENT OF EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS

Findings from a recent randomized trial investigating mepolizumab

By Carol A. Langford, MD, MHS

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

CASE PRESENTATION

A 55-year-old female was diagnosed with eosinophilic granulomatosis with polyangiitis (Churg-Strauss, EGPA) five years ago. Her features included an eight-year history of asthma, sinus congestion with nasal polyps, eosinophilia, cutaneous small-vessel vasculitis with abundant tissue eosinophils, and a sensory neuropathy. Testing for antineutrophil cytoplasmic antibodies (ANCA) was negative, and echocardiogram was normal. She was initially treated with prednisone and methotrexate which was switched to azathioprine for intolerance. Although this treatment provided good control of the vasculitic features, she continued to have recurrent asthma despite optimized inhaled regimens, requiring frequent glucocorticoid bursts and prednisone > 10 mg/day and impacting her quality of life. She has questions today about whether there are other treatment options.

Challenges in the management of EGPA

EGPA is a clinically diverse disease characterized by allergic, eosinophilic and vasculitic manifestations. Although it is within the family of ANCA-associated vasculitis, it is phenotypically and therapeutically different from granulomatosis with polyangiitis (Wegener's, GPA) and microscopic polyangiitis (MPA).

A similarity in treatment between EGPA, GPA and MPA is the use of glucocorticoids and cyclophosphamide (CYC) in patients with life-threatening vasculitic manifestations. In EGPA, an important manifestation where this regimen is commonly applied is in active cardiac involvement which can be associated with poor outcomes. When CYC is used, it is typically given for three to six months, followed by a maintenance approach with azathioprine, methotrexate or mycophenolate.

While rituximab has been proven to be as effective as CYC in GPA and MPA, there remains a limited body of published data with rituximab in EGPA. Although rituximab has been used in EGPA for patients who cannot take CYC or have mild-to-moderate vasculitic features despite other conventional immunosuppressives, there is currently insufficient evidence to support its use in life-threatening disease in patients where CYC would be an option.

A unique aspect of management in EGPA is the treatment of the allergic and eosinophilic sinus and asthmatic features. For some patients with EGPA, these remain the most problematic manifestations that may limit the ability to taper glucocorticoids to acceptable dosages. For such features, it is important to optimize the use of inhaled glucocorticoids and bronchodilators, working in close collaboration with an asthma specialist. Beyond glucocorticoids, the effectiveness of other conventional immunosuppressive agents for the asthmatic features is variable between patients. There has been insufficient information to establish whether rituximab provides benefit for these features.

Investigation of mepolizumab in EGPA

Mepolizumab is a monoclonal antibody that binds to interleukin-5 (IL-5) and prevents interaction with its receptor on the eosinophil surface. IL-5 plays an integral role in the maturation, proliferation and differentiation of eosinophils, which has made this an intriguing agent to investigate in eosinophilic diseases. In 2015, mepolizumab was approved by the FDA for the treatment of severe eosinophilic asthma in patients over the age of 12.

A multicenter, international, double-blind, randomized trial was recently conducted to examine the safety and efficacy of mepolizumab in EGPA following encouraging results in pilot studies.[1] The trial enrolled 136 patients at 31 sites. Patients had to be 18 years or older with non-life-threatening relapsing or refractory EGPA on a stable dose of prednisone/prednisolone 7.5-50 mg/day for at least four weeks.

Participants underwent blinded randomization to receive mepolizumab 300 mg subcutaneously or placebo every four weeks for 52 weeks. The glucocorticoid dose had to remain stable

between randomization and week four following which this could be tapered at the investigator's discretion using a standardized reduction schedule. Patients who were on a maintenance immunosuppressive continued this agent at the same dose. In this study, remission was defined as a Birmingham Vasculitis Activity Score (BVAS) = 0 with a prednisone/prednisolone dose of < 4.0 mg/day with relapse being active vasculitis BVAS > 0; active asthma or active nasal/sinus disease leading to an increase in prednisone/prednisolone > 4.0 mg/day; addition of another immunosuppressive; or hospitalization.

In terms of efficacy, mepolizumab resulted in more weeks of remission with 28 percent having > 24 weeks of accrued remission compared to 3 percent in those who received placebo ($P < 0.001$). It also led to a higher percentage of patients in remission at both weeks 36 and 48 compared to placebo (32 vs 3 percent, $P < 0.001$). Overall, remission did not occur in 47 percent of those who received mepolizumab as compared to 81 percent who received placebo. An average dose of prednisone < 4.0 mg/day was reached during weeks 48-52 in 44 percent of those receiving mepolizumab compared to 7 percent for placebo ($P < 0.001$). In terms of safety, there was no significant difference in the percentage of adverse events between those who received mepolizumab and placebo with the most common events being headache, nasopharyngitis, arthralgias and upper respiratory tract infection.

What is the role of mepolizumab in EGPA?

The role of mepolizumab in the treatment of EGPA remains yet to be defined (mepolizumab is not FDA-approved for EGPA). In the EGPA randomized trial, mepolizumab resulted in more weeks in remission with a higher percentage of patients in remission than those who received placebo, and showed efficacy for all primary and secondary endpoints. However, only half of the patients who received mepolizumab had a protocol-defined remission.

> Mepolizumab resulted in longer remission, with 28 percent having > 24 weeks of accrued remission compared to 3 percent in those who received placebo.

As patients with organ- or life-threatening EGPA were excluded from the mepolizumab trial, mepolizumab should not be used in this setting. In the EGPA trial, mepolizumab was given at a dose of 300 mg every four weeks which is higher than the FDA-approved asthma dosage of 100 mg every four weeks. Although patients with mild-to-moderate vasculitis were eligible for this study, the efficacy of a lower dose for managing vasculitic manifestations is unknown such that use of conventional immunosuppressive agents remains the best evidence-based approach at this time. Should mepolizumab become FDA-approved for EGPA and available at 300 mg every four weeks, consideration of use for mild-to-moderate vasculitis should continue to be viewed with caution on a case-by-case basis examining the nature of the disease features, the past disease history, and whether there have been relapses or contraindications to conventional immunosuppressive agents.

In our patient with relapsing eosinophilic asthma who is unable to taper glucocorticoids to an acceptable level, mepolizumab would be a consideration given the proven experience in asthma combined with the encouraging experience in the EGPA trial. In such a setting, careful ongoing monitoring for emergence of new EGPA features would remain important.

The investigation of mepolizumab has provided valuable information in EGPA not only in demonstrating therapeutic efficacy but also for the ability to conduct blinded, randomized trials in this rare and diverse disease. Although there remain ongoing questions to be answered regarding the role of mepolizumab, this body of work provides exciting evidence of what lies ahead in the understanding and management of this complex vasculitic disease.

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Disclosure

Dr. Langford and Cleveland Clinic were members of the EGPA mepolizumab study team participating in the clinical trial funded by GlaxoSmithKline and the linked mechanistic studies funded by the National Institute of Allergy and Infectious Diseases.

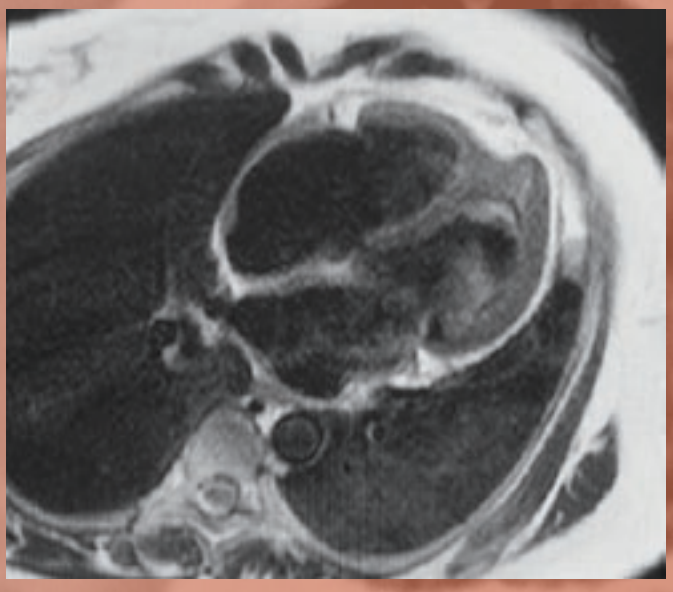

Figure. Cardiac MRI demonstrating complications from heart involvement in EGPA (Churg-Strauss). This patient has endomyocardial fibrosis at the left ventricular apex with a large apical thrombus. Image and caption reprinted with permission from Elsevier.

GPA: A PERSISTENT RISK FACTOR IN RECURRENT VTE

Toward an evidence-based approach

By Alexandra Villa-Forte, MD, MPH

Dr. Villa-Forte (villaa@ccf.org; 216.445.9437) is staff in the Center for Vasculitis Care and Research.

Venous thrombotic events (VTE) can manifest as recurrent disease associated with significant morbidity and mortality. Patients with granulomatosis with polyangiitis (GPA) have a higher incidence of VTE, but the rate of first VTE recurrence has not been studied. As rheumatologists, we often treat these patients in collaboration with vascular medicine or hematology without scientific data to support decision-making. As an initial step toward an evidence-based approach to anticoagulation therapy for our patients, we aimed to first determine the incidence rate of first VTE recurrence in patients with GPA.

Treating VTE in GPA patients is complex

Anticoagulation therapy in the general population aims to prevent VTE recurrences. Standardized guidelines from groups like the American College of Chest Physicians address the duration of anticoagulation for pulmonary embolism, proximal provoked and unprovoked deep vein thrombosis (DVT), and distal DVT. Multivariable risk models have been designed to predict the rate of recurrence of unprovoked VTE in the general population.

Merkel et al. first reported a high incidence of VTE in patients with GPA (7 per 100 person-years; 95% CI, 4-11.4) in a large prospective study in 2005.[1] The study found a higher incidence rate of first VTE as compared with the general male population and with patients with systemic lupus and rheumatoid arthritis (Table). This study was a turning point in the daily care of GPA patients, as it recognized VTE as an important comorbid disorder in this population.

Furthermore, patients with active GPA are at a higher risk not only for VTEs, but also for bleeding, specifically those with severe lung manifestations (large cavities, diffuse alveolar hemorrhage), severe renal failure (uremia) or reno-pulmonary syndrome. For this reason, acute management of thrombotic events as well as duration of anticoagulation therapy is particularly challenging.

Establishing higher recurrence rates

Knowing that the VTE event rate is higher in GPA patients than in the general population and is related to active disease, we hypothesized that the recurrence rate is also higher. To answer this question, we conducted a retrospective study at Cleveland Clinic's Center for Vasculitis Care and Research. We included patients evaluated between 2002 and 2016. Patients were included if they:

TABLE. VENOUS THROMBOTIC EVENT INCIDENCE RATES FOR GPA COHORT AND COMPARISON GROUPS

POPULATION	DATES OF STUDY	FIRST VTE INCIDENCE RATE (95% CI) PER 100 PERSON-YEARS	PARTICIPANTS	MEAN AGE AT START OF OBSERVATION, y	MEN, %
Patients with GPA	2000-2002	7.0 (4-11.4)	167	50	60
General population	1963-1993	0.3 (0.2-0.4)	855	50	100
Hopkins Lupus Cohort	1997-2002	1.0 (0.6-1.5)	764	39	7
Etanercept treatment cohort	1993-2002	0.3 (0.1-0.5)	1,271	52	23
Patients with previous VTE	1998-2002	7.2 (5.1-9.8)	253	53	47

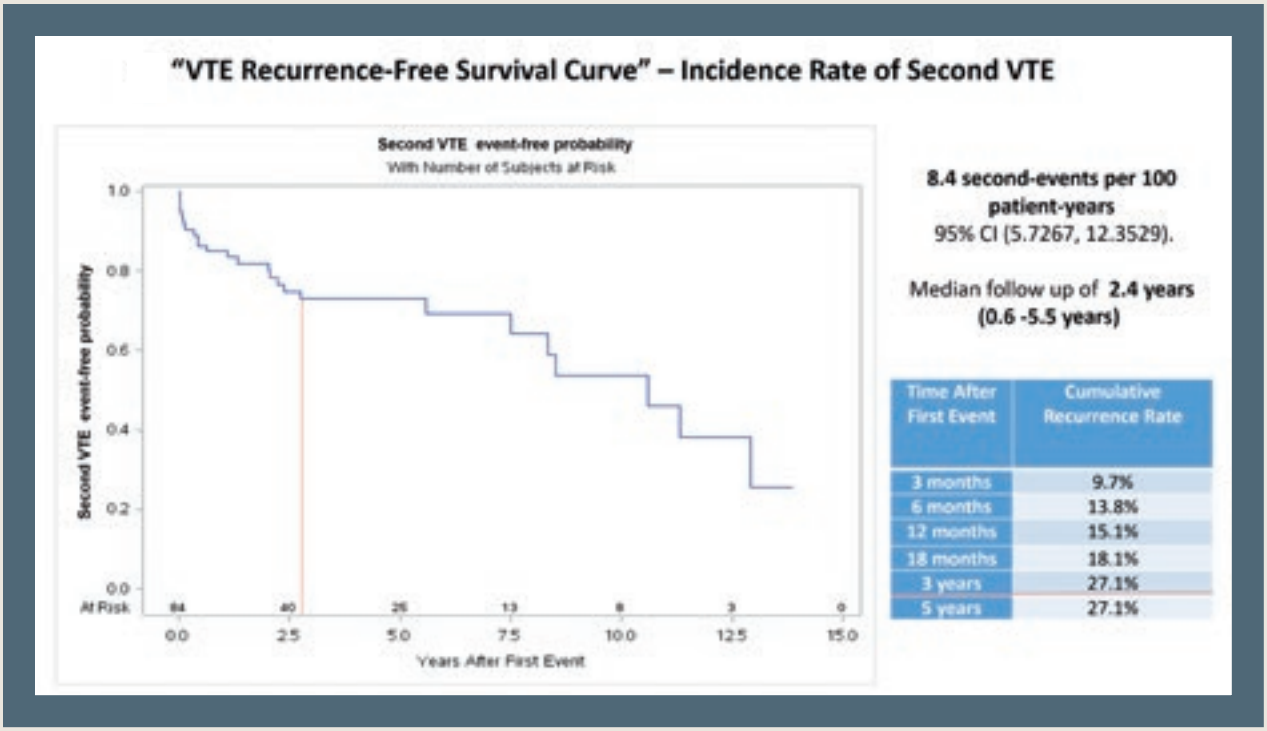

Figure. Second VTE event-free probability with number of subjects at risk.

1. Met the 1990 American College of Rheumatology criteria or the 2012 Revised International Chapel Hill Consensus Conference nomenclature for GPA,
2. Had ≥ two follow-up visits at our center,
3. Had ≥ one VTE documented during the study period, and
4. Had VTE occurrence after diagnosis of GPA or within three months before GPA diagnosis.

Kaplan-Meier was used to estimate first VTE recurrent-event-free survival rates. Disease activity was defined as Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG) of ≥ 1 within three months of VTE.

Of 137 patients with GPA and at least one VTE, 84 met inclusion criteria. Most patients were Caucasian (97.6 percent) and male (56 percent). Incidence of first VTE recurrence was 8.4 events per 100 patient years (95% CI, 5.7-12.3) over a median duration of a 2.4-year observation period (0.6-5.5 years) (Figure).

Events were not related to clinically apparent active disease in almost half of first recurrence cases. The cumulative recurrence rate at three years was 27.1 percent. Time to second event was significantly shorter for patients with BVAS ≥ 15 at diagnosis, and for males compared with females.

Implications of our findings

GPA patients have a higher rate of VTE recurrence than does the general population with unprovoked VTE (3.9 recurrent events per 100 person-years, IC 3.3-4.6). The rate is actually closer to that of first VTE recurrence in patients with active cancer (9.6 per 100 person-years, IC 8.8-10.4), which indicates the magnitude of this comorbidity.[2]

These results show that VTE is a recurrent disease in GPA patients, more so during the first three years after the first event, and that perhaps we should consider GPA as a persistent risk factor for VTE rather than as a transient risk that fades during disease remission.

Our study is the first to address the rate of VTE recurrence in patients with GPA, and our results emphasize the need for prospective studies evaluating duration of anticoagulation, risk stratification for VTE recurrence, and safety of anticoagulation after first VTE in patients with GPA. It is our hope that as we continue to study these patients and learn more about risk factors for VTE recurrence, risk stratification tools can be designed to shift the management of VTE in GPA to an evidence-based approach.

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AMYOPATHIC DERMATOMYOSITIS: LESS BENIGN THAN WE BELIEVED

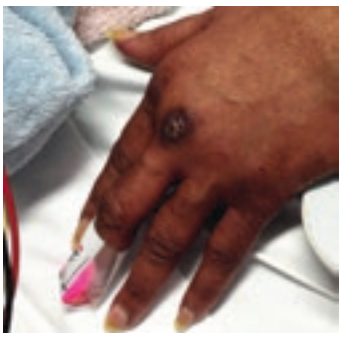
Case illustrates mortality of severe disease

By Soumya Chatterjee, MD, MS, FRCP

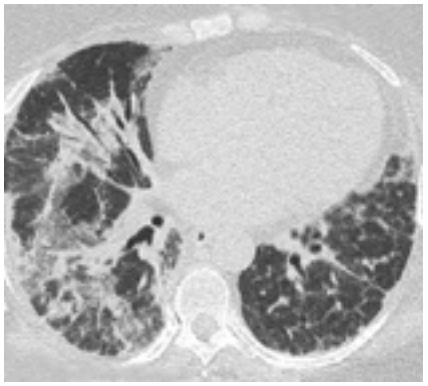
Dr. Chatterjee (chattes@ccf.org; 216.444.9945) directs the Scleroderma Program in the Department of Rheumatic and Immunologic Diseases.

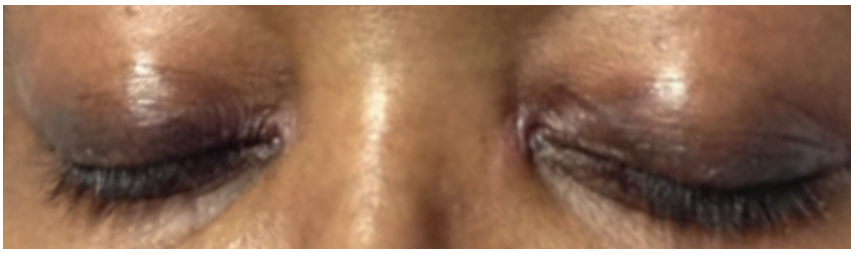
A 58-year-old female was admitted with shortness of breath and a rash that had been present for three weeks.

On examination, she had swollen eyelids with a violaceous tinge (bottom image); erythema and focal erosions of the neck, submental chin and upper chest; and violaceous plaques overlying the metacarpophalangeal (MCP) joints of her hands (Gottron papules). She was also severely short of breath, requiring supplemental oxygen. She denied fever, but had a cough with minimal expectoration of clear phlegm. There was no clinical synovitis, but she was mildly weak in her proximal muscles. She had diffuse crackles at the lung bases, up to the mid-zones.



> The clinical phenotype represents an overlap of a severe form of vasculopathy and rapidly progressive ILD.





CLOCKWISE

Top left: Ulcerated Gottron papule.

Top right: Papule on lateral aspect of index finger.

Center right: Thoracic HRCT showing ILD.

Bottom: Swollen eyelids with a violaceous tinge.

Laboratory investigations included a negative antinuclear antibody (ANA), antibodies to extractable nuclear antigens (except a low-titer anti-U1 RNP antibody), and the antisynthetase antibody panel. Her creatine kinase was 350 U/L (reference range: 30-220 U/L) and serum ferritin was 1237 ng/mL (reference range: 18-300 ng/mL). Pulmonary function tests showed severe restrictive lung disease, with forced vital capacity at 63 percent of predicted and transfer factor (diffusing capacity of carbon monoxide, DLCO) at 33 percent of predicted. Thoracic high-resolution computed tomography (HRCT) showed evidence of severe interstitial lung disease (ILD) (organizing pneumonia and/or interstitial pneumonitis) mostly involving mid- to lower lung zones (center right image). These findings were suggestive of dermatomyositis (DM) with severe ILD.

MDA-5 dermatomyositis

In the next few weeks, some of the Gottron papules became ulcerated (top left image). She also developed focal and erythematous tender papules of the palms and some fingers (top right image). Based on these findings, she matched the clinical phenotype of melanoma differentiation-associated protein 5 dermatomyositis (MDA5 DM), the diagnosis of which was confirmed when the MDA5 antibody came back positive.

Once infections were ruled out, she was treated with high-dose intravenous methylprednisolone followed by oral prednisone, 60 mg daily. Unfortunately, cyclophosphamide and mycophenolate were denied by her insurance. Based on published data on MDA5 DM, she was started on oral tacrolimus. However, she

did not notice any improvement in her breathing, though her skin disease stabilized. With worsening hypoxia, her home oxygen was titrated up from 3 L/min to 6 L/min. In spite of a good appetite, she kept losing weight.

While her breathing continued to deteriorate, serial thoracic HRCT scans revealed areas of ground glass opacification being replaced by interstitial thickening and dense fibrosis, and eventual progression to diffuse reticular opacities associated with architectural distortion and traction bronchiolectasis. She underwent bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial lung biopsy. Lung biopsy showed reactive type 2 cells with scattered areas of intra-alveolar fibrin and areas of organizing inflammation. Neutrophils were present within the septal capillaries as well as in some areas of the alveolar space.

Ultimately, hypoxia requiring positive pressure ventilation necessitated admission to the intensive care unit. Though BAL was negative for opportunistic infections, broad-spectrum antibiotics were started. Oxygen requirements kept rising. Finally, she showed evidence of multi-organ failure with thrombocytopenia, transaminitis and hematuria. Despite escalation of oxygen therapy, her respiratory status continued to decline, and she developed hypotension requiring vasopressors. She ultimately died of cardiac arrest secondary to respiratory failure.

Distinct features of the disease

In 2005, Sato et al. identified a novel autoantibody recognizing a 140 kDa protein in patients with clinically amyopathic DM (CADM, initially termed CADM-140).[1] The 140 kDa autoantigen was subsequently identified as MDA5. In the initial studies in Japanese cohorts, most patients were clinically amyopathic, and many had rapidly progressive ILD. Ultimately, Fiorentino et al. linked the unusual cutaneous findings of CADM (ulceration and palmar papules) with ILD and described its association with anti-MDA5 antibody.[2]

More recently, based on observational cohort studies, further detailed descriptions of MDA5 dermatomyositis have become available. The clinical phenotype represents an overlap of a severe form of vasculopathy and a rapidly progressive ILD. Unique findings that differentiate MDA5 DM from classical DM include little or no myositis, skin ulceration (affecting lateral nail folds, Gottron papules and elbows), tender palmar papules and severe ILD. Other features include weight loss, oral pain and/or ulceration, mechanic's hands, hand edema, polyarthritis/arthralgia and diffuse alopecia. Hyperferritinemia and negative ANA are common. When lung disease is severe, there may be variable response to mycophenolate and tacrolimus along with high-dose glucocorticoids. Other therapies with some reported success include basiliximab and plasmapheresis. MDA5 DM patients who have a favorable response to an initial treatment may have a better long-term outcome.

There have been significant differences in the phenotype of lung disease between the published Japanese cohorts and those reported in the U.S. Japanese patients quite often have an unfavorable pulmonary outcome. However, in the U.S., the prognosis has been more variable. Some patients with severe immunosuppressant-refractory ILD (including our case) have died from rapidly progressive respiratory failure while waiting for a lung transplant. Other patients have a relatively milder course and respond favorably to immunosuppressive agents. It is not clear why this difference is seen in these different patient populations. It has been proposed that there may be differences in host genetic risk factors and environmental factors that are novel and yet undefined.

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TARGETING BIOMARKERS OF NITRIC OXIDE AND ENDOTHELIAL DYSFUNCTION IN RA AND PsA

Translational human plasma studies

By M. Elaine Husni, MD, MPH, and Unni Chandrasekharan, PhD

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Numerous studies have reported increased cardiovascular (CV) morbidity and mortality in rheumatoid arthritis (RA) and psoriatic arthritis (PsA) patients that traditional risk factors cannot explain. Some have hypothesized that this increased risk is in part due to persistent systemic inflammation. Chronic inflammation promotes endothelial dysfunction with reduced vascular reactivity, leading to CV disease (CVD).

L-arginine metabolism is critical for maintaining normal endothelial homeostasis, and arginases are the central enzymes in the urea cycle that catalyze L-arginine to L-ornithine and urea (Figure 1). Our translational research lab's goal is to identify specific pathways leading to aberrant L-arginine metabolism as a potential cause of the increased CVD risk observed in RA and PsA patients.

From aberrant L-arginine metabolism to CVD

L-arginine is the sole source of nitric oxide (NO), an enhancer of endothelial function as well as modulator of insulin sensitivity, whose production is catalyzed by NO synthase (NOS). Elevated arginase activity diminishes L-arginine bioavailability, thus decreasing NO production. Decreased NO has been associated with endothelial dysfunction, one of the earliest steps in atherosclerosis. Furthermore, elevated arginase activity causes excessive production of ornithine, leading to vascular dysfunction. This study aimed to understand these underlying molecular mechanisms by using human plasma to analyze L-arginine metabolites in PsA and RA.

Translational human plasma studies

We used liquid chromatography-mass spectrometry to measure plasma levels of L-arginine, L-ornithine (arginase catabolic product) and L-citrulline (NOS catabolic product) in the plasma of RA and PsA patients compared with control subjects. We also measured the methylated L-arginine products asymmetric dimethyl arginine (ADMA) and symmetric dimethyl arginine (SDMA), both endogenous inhibitors of NO production.

Furthermore, we measured plasma arginase activity using colorimetric assay. We analyzed correlations between L-arginine metabolites and CV risk factors using Spearman's correlation.

Plasma arginase activity levels increased 400 percent in RA patients (N = 119) and 160 percent in PsA patients (N = 233) as compared with controls (N = 148) (Figure 2). Also, RA patients with prior CVD history had higher arginase activity compared with RA patients without prior CVD.

Compared with controls, the RA patients showed significantly lower levels of plasma L-arginine and elevated levels of ADMA and SDMA. Arginase activity and its catabolic product L-ornithine were elevated in RA, while the level of the NOS catabolic product L-citrulline was diminished. In comparison with controls, PsA patients also showed lower levels of plasma L-arginine, higher arginase activity and elevated levels of plasma ADMA and SDMA.

Closer to precise biomarkers, treatment pathways

This work in human plasma builds on our prior work that found altered L-arginine metabolism in murine models. Our study has the potential to link increased arginase activity and elevated levels of dimethylarginines to the premature vascular dysfunction disproportionally seen in RA and PsA patients. Thus, inhibition of arginase activity and blockade

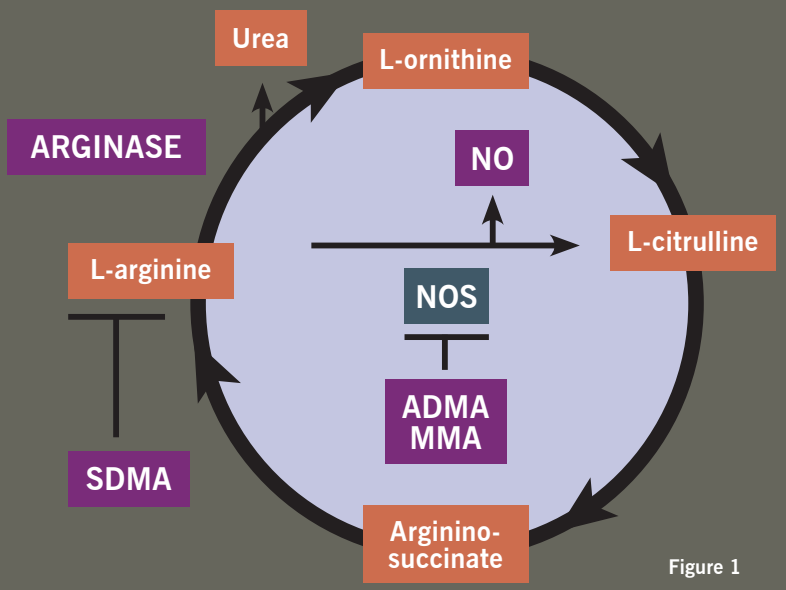


Figure 1

Figure 1. L-arginine is the common substrate of arginase and nitric oxide synthase (NOS). ADMA is a potent inhibitor of NOS, whereas SDMA inhibits NO production by inhibiting L-arginine cellular uptake.

of pathways that generate methylated arginine derivatives have the potential to decrease CV risk in these patients. These elevated arginine metabolites in RA and PsA patients suggest an important avenue for detecting subclinical endothelial dysfunction.

Translational work combining these human plasma studies with our previous mouse model data will enable our team to identify new, precise biomarkers and potential treatment pathways that may help pinpoint and treat RA and PsA patients at increased risk of CV disease.

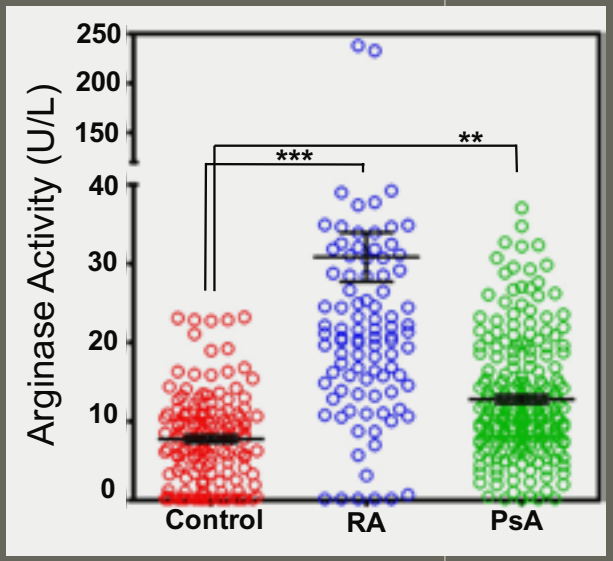
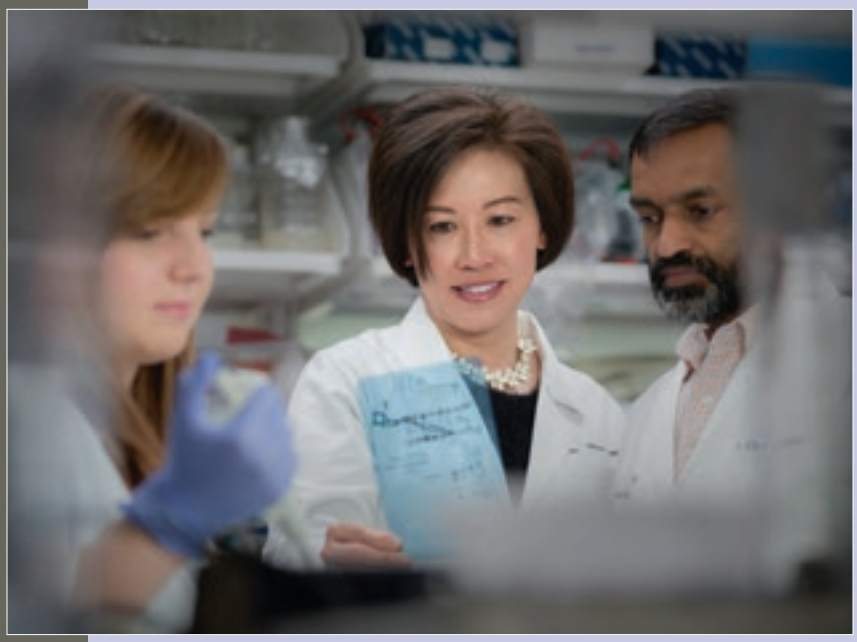


Figure 2. Plasma arginase activity in RA, PsA compared with control ($P > 0.0001$).



Husni Receives Endowed Chair

In July 2017, Dr. Husni was named Endowed Chair of Translational Functional Medicine Research. She will lead collaborative research between Cleveland Clinic's Department of Rheumatic and Immunologic Diseases and Cleveland Clinic's Center for Functional Medicine. Dr. Husni's interdisciplinary, collaborative work focuses on the epidemiology and health outcomes of musculoskeletal and rheumatic diseases, specifically psoriatic diseases, rheumatoid arthritis and osteoarthritis. Her translational research lab in the Lerner Research Institute focuses on the understanding of cellular responses and signaling events initiated by inflammatory cytokines, in particular TNF-alpha, in chronic inflammatory diseases.

This collaborative role aims to bring scientific study to functional medicine modalities for autoimmune diseases.

MANAGING PRIMARY IMMUNODEFICIENCIES

Complex cases requiring multidisciplinary care

By Leonard Calabrese, DO, and James Fernandez, MD, PhD

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Presentation

A 57-year-old man with history of coronary artery disease (CAD) who had COPD and atrial fibrillation after coronary artery bypass grafting (CABG) required admission to the hospital due to worsening cardiac symptoms associated with CAD and aortic insufficiency requiring surgical intervention.

Throughout his teenage years and early 30s, he had necrotic skin ulcerations involving his upper and lower extremities that required two-to-four-week courses of parenteral antibiotic therapy four to five times per year. His symptoms subsided by the age of 40, with spontaneous resolution of his recurrent skin lesions. He had no further history of recurrent infections involving skin or other systems after the age of 40.

However, he developed a severe postoperative infection after a CABG and aortic valve repair performed at age 53, resulting in mediastinitis requiring surgical intervention, skin flap and a prolonged IV antibiotic course. Due to this history of postoperative infection and poor wound healing, he was deemed a high-risk surgical candidate and required preoperative evaluation by immunology and infectious disease.

Evaluation

The physical exam was fairly unremarkable. His labs revealed a WBC of 8.36 x 103/uL, hemoglobin of 10.7 g/dL, hematocrit 33.6 percent, MCV 88 fL, platelets 462 x 103/uL, total protein 6.8 g/dL, and normal liver and renal function tests. Immunologic and infectious workup showed IgE 16.7 mg/dL, IgA 483 mg/dL, IgG 1,020 mg/dL, IgM 69 mg/dL, protective titers against tetanus and pneumococcal serotypes, normal LTT mitogen, syphilis IgG negative, nonreactive HIV, and negative hepatitis screen and fungal battery. He underwent redo open heart surgery consisting of aortic valve replacement and CABG without intraoperative complications.

Postoperative complications

His postoperative course was complicated by leukocytosis (WBC 27.6 x 103/uL, neutrophils 87 percent, lymphocytes 6.8 percent, monocytes 1.4 percent) and increased ESR (39), wound dehiscence, sternal wound osteomyelitis and enterococcal bacteremia. He required treatment with wound vac placement and prolonged IV vancomycin.

> When PID patients experience autoimmune or autoinflammatory diseases, rheumatology's role is to help craft targeted therapies with biologic agents.

Peripheral blood smear showed leukocytosis with neutrophilia, with mature segmented neutrophils. Interestingly, the majority of the neutrophils showed hyposegmentation, particularly bilobed nuclei similar to those found in Pelger-Huët anomaly, and occasionally small, fragmented nuclei (microlobes) were present. All neutrophils demonstrated pale cytoplasm because of a significant decrease in cytoplasmic granulation (Figure 1A-C). Myeloperoxidase stain showed mild myeloperoxidase reaction in neutrophils; however, it was significantly reduced compared with the reactions in normal neutrophils from a healthy donor (Figure 1D). Although only a few eosinophils were present in the peripheral blood smears, cytoplasmic granules appeared decreased. No other inclusions in the granulocytes or immature granulocytes were noted.

A closer look and an answer

Figure 2A-C shows the ultrastructure of granulocytes by electron microscopy, demonstrating mature, segmented neutrophils with many bilobed forms and occasional microlobes. Segmented neutrophils had abundant cytoplasm, rich glycogen particles and Golgi zone. Primary (azurophilic) and tertiary granules were present but decreased in the neutrophils. Secondary (specific) granules were markedly decreased or absent in the neutrophils examined.

A heterozygous variant of unknown significance, c.653T>C (p.Val218Ala), was identified in exon 2 of the *CEBPE* gene. A second mutation of the *CEBPE* gene was not detected via gene sequencing, but deletion/duplication analysis was not completed. The presence of large deletions or duplications could not be ruled out. Other deep intronic pathogenic variants as well as variants in other regulatory regions also could not be ruled out.

All of these findings suggest a diagnosis of specific granule deficiency. This patient experienced significant burden of disease from infancy to adulthood. Even after remission of his skin lesions, he remains at elevated risk for severe infections, as demonstrated by mediastinitis, osteomyelitis and bacteremia after surgical or invasive interventions.

Adult Immunodeficiency Clinic: a collaborative approach

This case demonstrates the complex characteristics of primary immunodeficiencies (PID). Patients with PID often present to rheumatologists with a

variety of symptoms suggestive of autoimmune or autoinflammatory diseases. These patients are at risk of multiple complications, including autoimmune disease, which develops in 20 to 25 percent of patients with PID.

Patients with common variable hypogammaglobulinemia (CVID) require continued monitoring not only for infections but also for granulomatous disease of the lungs, autoimmune disorders, lymphoma, malabsorption and other complications. Patients with CVID may be misdiagnosed as other granulomatous disorders, in particular sarcoidosis, and treatment with glucocorticoids can result in catastrophic complications.

When PID patients experience autoimmune (e.g., cytopenia, vasculitis) or autoinflammatory (e.g., granumomatous infiltration of various end organs) diseases, rheumatology's role is to help craft targeted therapies with biologic agents vital to the management picture. For these reasons, a team approach is vital to the overall care of our PID patients.

The Adult Immunodeficiency Clinic works closely with pulmonologists, rheumatologists, hematologists, oncologists and gastroenterologists to provide the best care for these patients. We frequently make decisions about care as a team, and constant communication among physicians is a necessity.

In the end, patients are better served and appreciate a collaborative effort by multiple physicians with specific expertise in managing their primary immunodeficiency and the complications related to it. With a growing number of adult immunodeficiencies being identified, our Adult Immunodeficiency Clinic is fully committed to advancing the care of patients and initiating new research projects in this growing and exciting field.

Figure 1

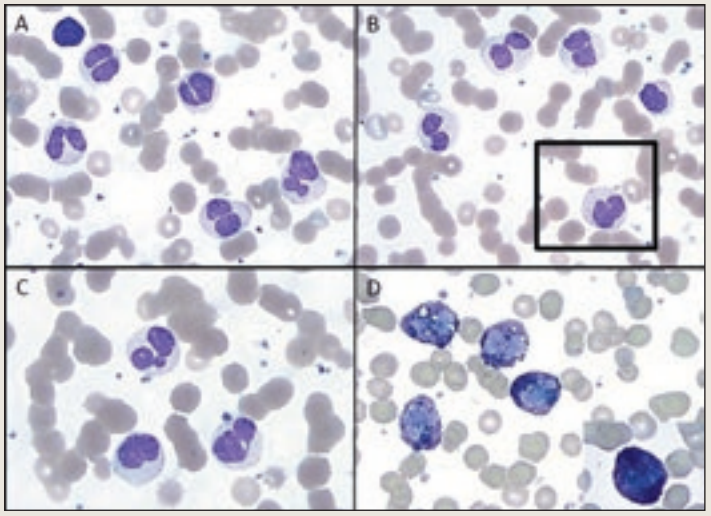

Figure 2

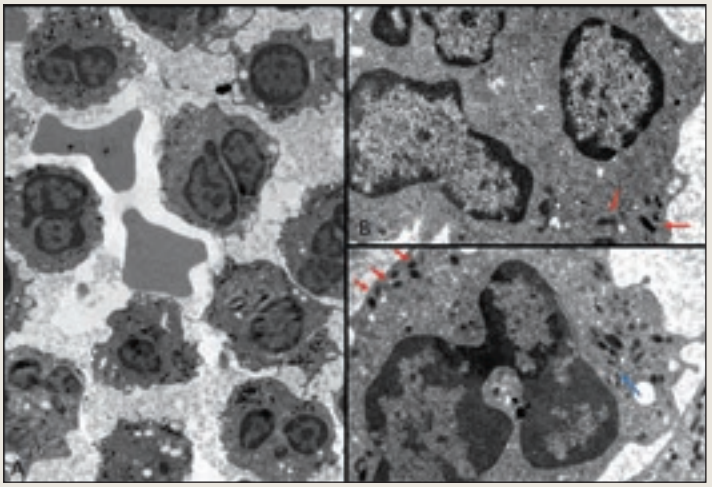

Figure 1. (A-C) Peripheral blood smear of the patient shows hyposegmented neutrophils, particularly with bilobed nuclei, with significantly reduced cytoplasmic granulation (Wright-Giemsa stain, X1,000). (D) Myeloperoxidase stain shows reduced myeloperoxidase reaction compared with those in normally segmented neutrophils in healthy donors (inlet) (x1,000).

Figure 2. (A) Ultrastructure of neutrophils shows predominantly bilobed nuclei with occasional microlobes (x4,800). (B-C) Higher magnification of the neutrophils showed decreased primary (azurophilic; red arrow) and tertiary (blue) granules. Specific (secondary) granules are not present (x23,000).

MOSAICISM AND TRAPS

Second case ever reported highlights complexity, rarity

By Apostolos Kontzias, MD

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A 60-year-old male presented with a six-year history of intermittent daily fever as high as 103.5 F lasting three to four weeks. Associated symptoms included erythematous rash on his torso (Figure 1), peritoneal symptoms, myalgias, arthralgias, bilateral episcleritis (Figure 2) and lymphadenopathy. Neither prednisone nor colchicine proved effective. Extensive workup for fever of unknown origin was inconclusive. His symptoms were reminiscent of tumor necrosis factor receptor (TNFR)-associated periodic syndrome (TRAPS), but TRAPS would be unusual to encounter in late adulthood.

A rare disease among a group of rare diseases

TRAPS is a rare autoinflammatory, autosomal-dominant disease caused by gain-of-function mutations in the *TNFRSF1A* gene, which encodes the 55-kd TNFR type I (TNFRI) protein. Its estimated prevalence is 1 per 1 million individuals. Typically, autoinflammatory diseases (AIDs) lack serologic evidence of adaptive immunity involvement such as high-titer autoantibodies. Nonspecific laboratory evidence of systemic inflammation — high erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), leukocytosis, thrombocytosis — is typical during flares.

Although AIDs usually present in childhood or early adulthood, they are increasingly recognized across age groups with the help of next-generation sequencing (NGS). Many of the prototypic autoinflammatory disorders are caused by mutations in single genes that encode proteins involved in innate immunity pathways. In the genomics era, NGS has become accessible and employed in the rheumatology clinic as a tool to dissect clinical phenotypes that belong to the spectrum of AID. NGS has the capacity to detect any de novo sequence variants beyond what can be represented on single-nucleotide polymorphism arrays. NGS can also detect even low-level mosaicism, the presence of two or more populations of cells with different genotypes in one individual.

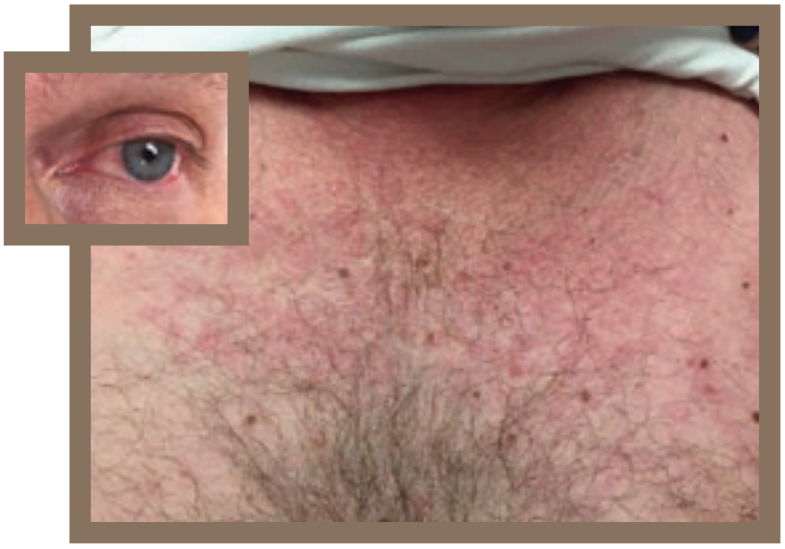

Figure 1. Erythematous rash on the patient's torso.

Figure 2. Bilateral episcleritis associated with intermittent daily fever.

Genetic clues to TRAPS

To diagnose this patient, we worked with Cleveland Clinic's Center for Personalized Genetic Healthcare and the Department of Molecular Pathology. Using NGS, we found evidence of somatic mosaicism on the *F89L* variant, which has been associated with TRAPS.[1] The mutant allele's presence in buccal mucosa and whole blood, and its absence in hair root, supported somatic *TNFRSF1A* mosaicism (Figure 3). In silico prediction modeling with SIFT and Polymorphism Phenotyping-2 prediction modeling showed numerous structural rearrangements from this mutation, resulting in changes in the protein surface profile.[2]

Identifying this variant through NGS allowed us to confirm a suspected diagnosis and provide targeted treatment with canakinumab. With treatment, the patient's symptoms resolved and protein levels normalized. The complete response to an interleukin-1 blocker further supported the TRAPS diagnosis.

Do postzygotic mutations cause TRAPS?

Since autoinflammatory disorders were first described nearly 20 years ago, the causes of these confounding syndromes have at times remained a mystery. Recent advances like NGS have brought welcome news for clinicians and patients, revealing important clues about the genetically mediated aspects of these diseases. Both this and the only other case ever reported[3] suggest that postzygotic mutations may cause TRAPS phenocopies in adulthood, offering yet another clue into the genesis of autoinflammatory disorders. I presented this case with Cassandra Calabrese, DO, a fellow in the Department of Rheumatology, and Yu-Wei Cheng, PhD, staff

in the Genomics Institute, at the Annual European Congress of Rheumatology in 2017, and we are conducting further studies to identify the extent of mosaicism in this patient's cell subsets.

Our Clinic for Adult Autoinflammatory Diseases is one of the very few multidisciplinary clinics in the country focusing on investigating and managing these enigmatic diseases. We believe strongly that multidisciplinary care of autoinflammatory conditions yields the best outcomes and is imperative for proper diagnosis, treatment and genetic counseling for these challenging cases.

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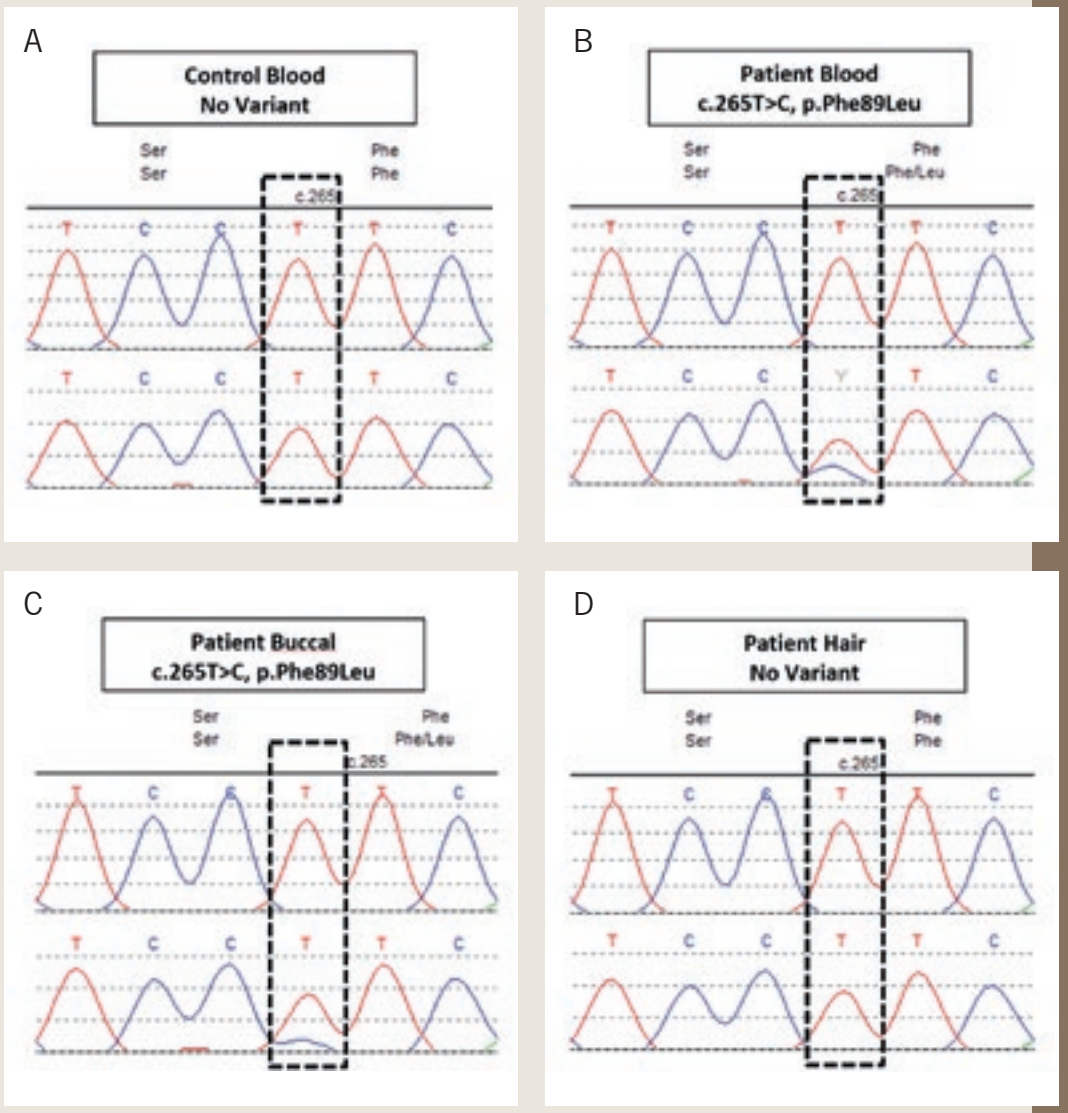

Figure 3. The variant present in the patient's blood (B) versus the control (A) is also present in the buccal sample (C) but not in the hair sample (D).

MANAGING REPRODUCTIVE HEALTH IN PATIENTS WITH SLE

Systemic lupus erythematosus complicates conception, pregnancy

By Lisa Zickuhr, MD, Amanda Kalan, MD, and Howard R. Smith, MD

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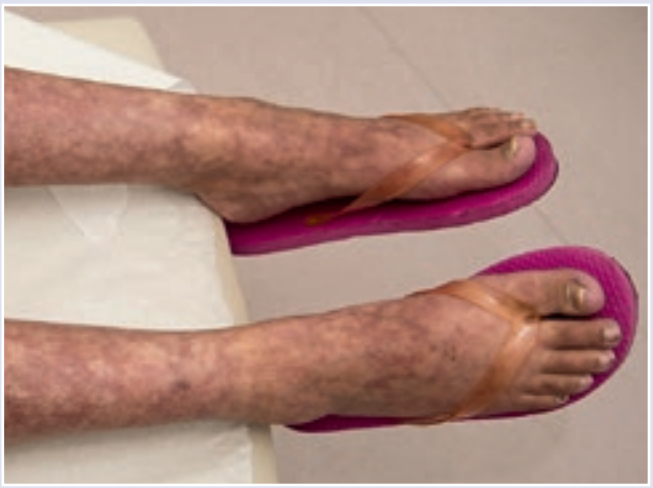
A 25-year-old African American woman was counseled about contraception. She had a history of systemic lupus erythematosus (SLE), manifesting with arthritis, alopecia, Raynaud's phenomenon, leukopenia and lupus nephritis, and her disease was previously well-controlled on hydroxychloroquine (HCQ), mycophenolate mofetil (MMF) and prednisone.

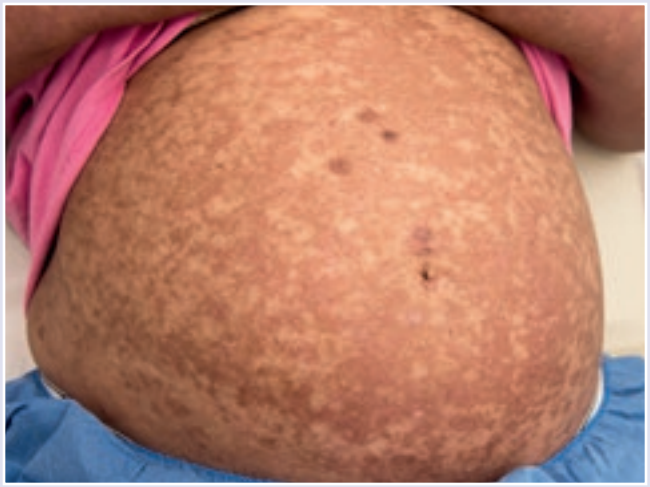
She conceived before beginning the discussed contraception, prompting discontinuation of MMF. Her serum antibody testing revealed the presence of anti-Ro (SSA) and anti-La (SSB) antibodies. Low-dose aspirin and fetal ultrasonographic monitoring were initiated. At the start of her second trimester, widespread lesions of cutaneous lupus erythematosus erupted (Figures 1-4). They responded to high-dose glucocorticoids and azathioprine, but flared when prednisone was weaned. She also developed thrombocytopenia, proteinuria, elevated liver enzymes and hypertension that raised concern for a lupus flare versus preeclampsia. She was admitted to the obstetrics labor and delivery unit for antenatal monitoring of a high-risk pregnancy.

SLE = high-risk pregnancy

Compared with healthy women, pregnant SLE patients with active disease and major organ involvement have a higher risk of thrombosis, premature delivery, preeclampsia, eclampsia, pregnancy loss and maternal mortality. In some studies, maternal SLE is also associated with fetal intrauterine growth restriction. Many immunosuppressive agents that could potentially control active lupus are known teratogens.

To protect mother and fetus, contraception should be discussed with all female SLE patients, and pregnancies should be planned during inactive disease. Combined hormonal contraception is appropriate for any SLE patient without antiphospholipid syndrome (APS). Those with APS should avoid estrogen-containing products. Copper intrauterine devices offer long-acting, reversible and hormone-free contraception that avoids the thrombotic risks of estrogen.





Monitoring a patient with SLE and her fetus during gestation

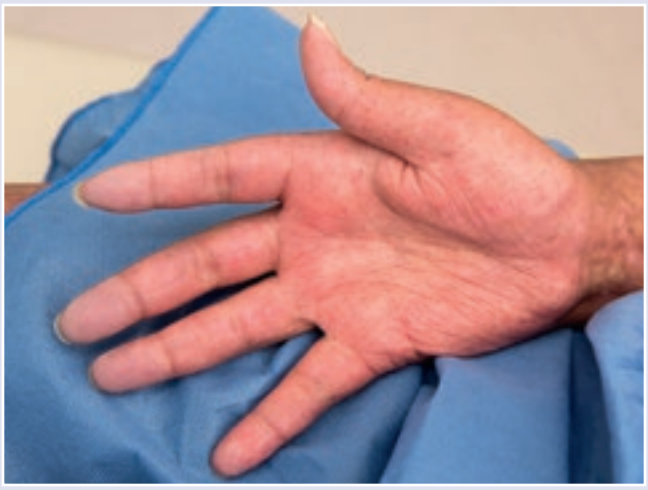
The rate of SLE flares during pregnancy varies among observational studies but is estimated at 30 to 70 percent. Severe flares can have negative consequences, as active lupus nephritis is a positive predictive factor for poor pregnancy outcomes. Careful, routine monitoring of lupus activity is necessary throughout pregnancy.

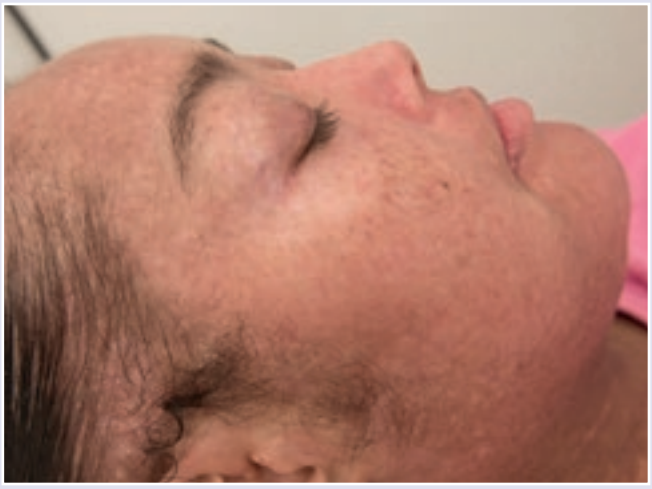
Rheumatologists and obstetricians play an important role in maternal and fetal monitoring. At risk of preeclampsia and eclampsia, mothers should be monitored for hypertension, thrombocytopenia, proteinuria and swelling. These symptoms characterize preeclampsia and eclampsia, but they can also be seen in SLE flares. Anti-dsDNA antibody and complement levels can help differentiate the two, an important task given the difference in treatments.

We recommend serially checking complete blood cell counts, complete metabolic panels for renal and hepatic function, urinalyses, complement levels and anti-dsDNA antibody levels to monitor SLE activity during pregnancy.

Increased plasma volume during pregnancy can cause dilutional anemia and thrombocytopenia and thus mimic SLE and artificially raise the sedimentation rate. Increased plasma volume also raises the glomerular filtration rate, increasing urine protein and creatinine measurements. As a rule of thumb, 24-hour proteinuria greater than 300 mg/dL should be considered pathologic until proven otherwise. Hematuria is abnormal in pregnancy, and lupus nephritis must be ruled out if it is detected. Complement (C3 and C4) levels increase during gestation, as opposed to often decreasing in flares of lupus, but anti-dsDNA antibody levels remain unaffected.

Fetal growth should also be carefully monitored during pregnancy. Additionally, maternal anti-SSA or anti-SSB antibodies can cause neonatal lupus, a syndrome characterized by rash, hemolytic anemia, thrombocytopenia and congenital heart block (CHB). Ultrasound surveillance for fetal growth and CHB is common practice. The latter has an incidence of approximately 2 percent in mothers whose previous pregnancies were unaffected by CHB and approximately 15 percent in those affected. Expectant mothers should be treated with glucocorticoids if CHB is detected.





Treatment of SLE during pregnancy

HCQ prevents flares and controls disease activity and can improve outcomes during pregnancy. Low-dose aspirin protects against premature delivery and preeclampsia in healthy pregnant women and is thus assumed effective in SLE and APS patients.

Glucocorticoids, azathioprine, tacrolimus and cyclophosphamide (after the first trimester, but only in those with severe or life-threatening disease) can be used to treat active lupus during pregnancy. As every medication carries the potential for side effects, disease flares should be treated with agents that have the least potential for causing complications. Intravenous immunoglobulins have been used in refractory cases of SLE in pregnant patients.

Methotrexate, leflunomide, MMF and cyclophosphamide (during the first trimester) should be avoided because of their abortifacient and teratogenic effects. The effects of rituximab and belimumab during pregnancy are not well-understood.

The complexity of pregnancy in a patient with SLE clearly warrants management by a multidisciplinary team of expert rheumatologists and obstetricians. Either condition alone can be complicated, and together they can present a challenge for the clinician, patient and fetus.

> Many immunosuppressive agents that could potentially control active lupus are known teratogens.

CLOCKWISE FROM TOP LEFT

Bilateral hypo- and hyperpigmentation and erythematous livedo reticularis representing active cutaneous lupus erythematosus.

Palmar erythema with area of desquamation from active cutaneous lupus erythematosus.

Alopecia and areas of chronic hyperpigmentation from active SLE.

Pregnant abdomen with hypo- and hyperpigmentation indicating healing cutaneous lupus erythematosus.

RELIEVING KNEE OSTEOARTHRITIS PAIN: IS THERE A BETTER WAY?

Examining PT + HA

By M. Elaine Husni, MD, MPH

Dr. Husni (husnie@ccf.org; 216.445.1853) is Director of the Arthritis and Musculoskeletal Treatment Center and Endowed Chair of Translational Functional Medicine Research at Cleveland Clinic.

Knee osteoarthritis (OA) is a common disease associated with significant morbidity, including daily pain and decreased mobility. As the aging population increases, knee OA prevalence and knee replacement surgeries have increased in the U.S. Although risk factors for cartilage loss in OA (including obesity, repetitive activities and gender) have been established, the determinants of pain and disability are less clear.

Recent attention has focused on the need for nonsurgical, effective, yet sustainable management for individuals suffering from knee OA. Current guidelines from the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) emphasize the importance of including physical therapy (PT) and exercise as first-line treatment. The benefits of PT have been well-studied, including increased muscle strength, improved range of motion and pain relief.

Another significant modality to treat knee OA pain is an intra-articular injection of hyaluronic acid (HA). HA is believed to provide a variety of mechanistic benefits including joint lubrication, anti-inflammatory effects, cartilage matrix benefits and promotion of proteoglycan synthesis. Although many HA preparations are FDA-approved for the treatment of knee OA, the overall clinical benefit has been less clear.

Currently there is no cure or disease-modifying agent for knee OA. Our team hypothesized that the addition of intra-articular HA injections to physical therapy would have a synergistic effect in alleviating pain and reducing disability in patients with knee OA.

Adding HA injections to physical therapy

We compared the use of hylan-GF20 (Synvisc One®) injection with placebo control in conjunction with standardized PT in patients with knee OA. To our knowledge, this was the first randomized, single-blind study that compared the addition of hylan-GF20 intra-articular injection with a sham injection, used in conjunction with standardized PT for knee pain and function. This study was performed on 42 symptomatic patients and included 24 weeks of follow-up. The patients were randomly divided into two treatment groups: Patients in group one were given intra-articular treatment with hylan-GF20 during the baseline visit, and group two received a sham injection during the baseline visit. Both groups received standardized physical therapy treatment using a knee OA protocol.

The Knee Injury and Osteoarthritis Outcome Score (KOOS) patient questionnaire was our primary outcome measure. We compared results at baseline and week 12 between the two groups. In addition, we compared survey responses at 24 weeks to examine the longer interval from baseline treatment response. Clinical assessments for each patient were made at one, three, six, nine and 12 weeks using the following measures: KOOS, timed up-and-go, 36-item short-form survey (SF-36), visual analog scale (VAS) and standard PT measures.

Numerical difference not statistically significant

The patient characteristics were similar between the two groups at baseline. Although greater mean level improvement was seen at 12 weeks in all KOOS subscales, timed up-and-go and VAS scales, these differences did not reach statistical significance between the hylan-GF20- and sham-treated groups. No significant differences were observed at week 24 between the two treatment groups, perhaps due in part to the small sample size.

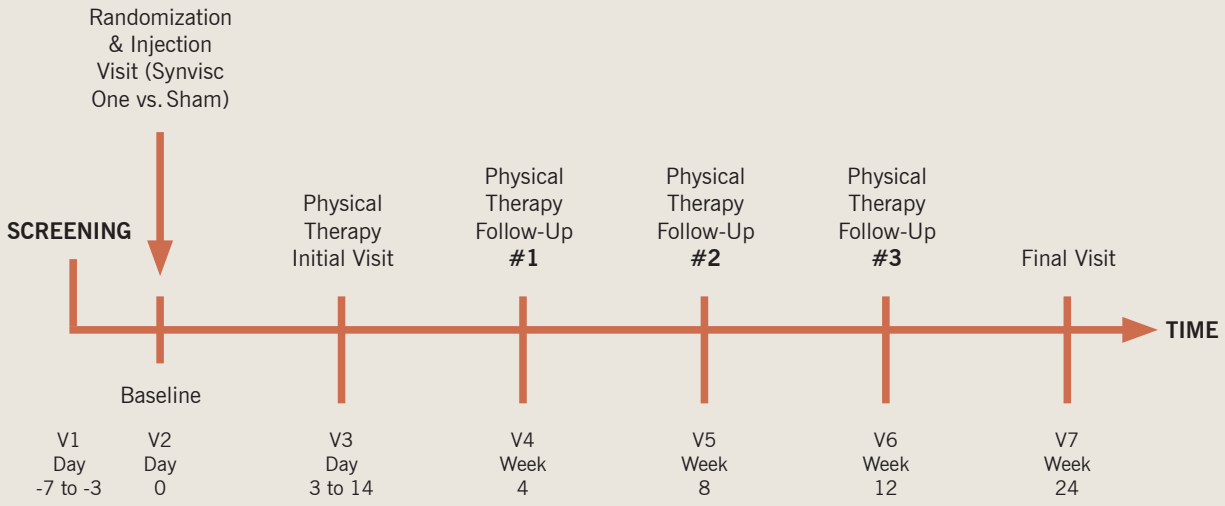
Interestingly, the quadriceps strength observed at 45 and 90 degrees was statistically different among the groups. Further analysis is needed to determine whether the hylan-GF20 group's greater mean strength improvement in the quadriceps is beneficial.

HA injections conditionally recommended

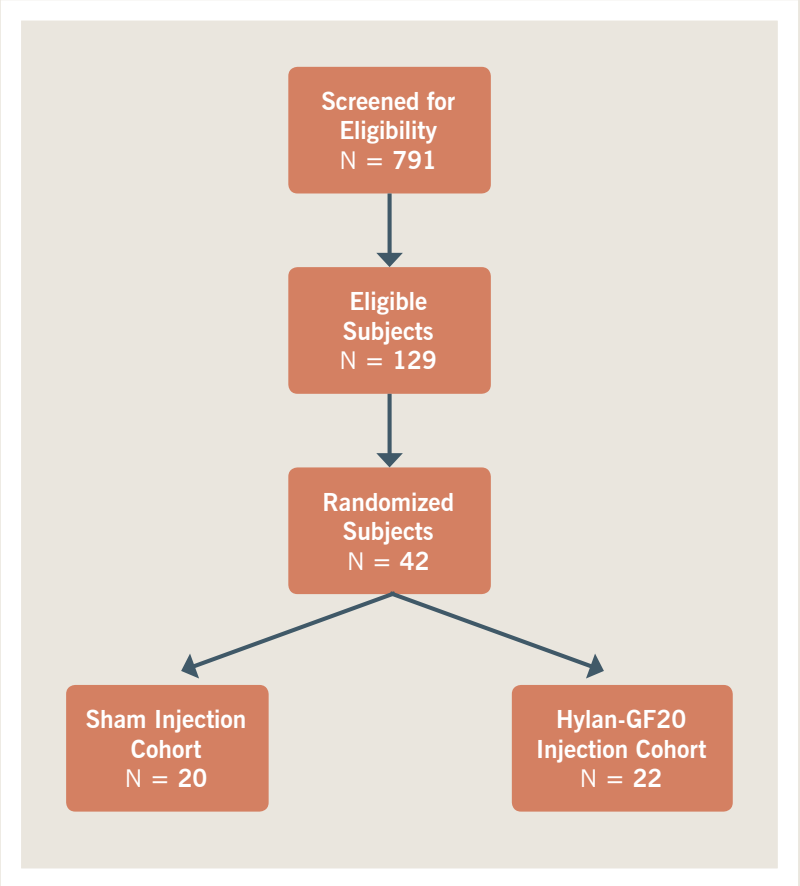
This study was performed to evaluate whether standardized physical therapy and the intra-articular use of hylan-GF20 in knee OA would reduce pain and improve knee function when implemented together. This pilot demonstrated the safety and tolerability of hylan-GF20 in our patients. Hylan-GF20 was generally well-tolerated, and no serious adverse events were found or caused patient withdrawal. Additionally, the numerical difference in the KOOS pain scale of patients in the hylan-GF20 group showed the potential of HA in conjunction with PT.

Overall, hylan-GF20 can be conditionally recommended if patients have an inadequate response to a trial of analgesics. It remains unclear which specific patients (age, grade of knee OA) would benefit the most from hylan-GF20 and concurrent PT. Large-scale, longitudinal studies are critically needed to examine the role of physical therapy and intra-articular HA in patients with knee OA.

SCHEMATIC PRESENTATION OF STUDY DESIGN



FLOW DIAGRAM OF RANDOMIZATION AND FOLLOW-UP



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17-RHE-1237