Abatacept for Nonsevere GPA: Encouraging Pilot Study Prompts Randomized Trial 3
Why a Multidisciplinary Team Matters in CNS Vasculitis 4 | Case Study: Rare Diagnosis Presents as Monoarthritis in Well-Controlled RA 6 | Carotid Ultrasound Unmasks Cardiac Prevention Needs in Psoriatic Arthritis 8 | Raynaud Phenomenon in Scleroderma: Keeping Digital Ischemia at Bay 10 | New Clinic for Adult Autoinflammatory Diseases 12
Preventing Morbidity in Vasculitis — Remember Pneumocystis 14
Dear Colleagues,

The whole is greater than the sum of its parts. Nowhere is that adage more true than in medicine — at least the way we like to practice medicine in Cleveland Clinic’s Department of Rheumatic and Immunologic Diseases.

At Cleveland Clinic, we look for ways to better serve patients by transcending disciplinary boundaries and actively collaborating across specialties. We’re convinced this culture of team-based, cooperative care benefits beyond just the sum of diverse specialists’ expertise. We believe it leads to exchanges that produce richer ways of approaching complex cases and that open new windows on clinical problem-solving.

This issue of Rheumatology Connections profiles several examples of this culture of collaborative care:

- On page 4, Drs. Rula Hajj-Ali and Leonard Calabrese outline the rationale and benefits of the multidisciplinary team they’ve assembled to ensure timely care for patients with central nervous system vasculitis.
- On page 8, Dr. Elaine Husni and one of our rheumatology fellows share insights from their collaboration with Cleveland Clinic cardiologists to bring carotid ultrasound to bear in screening for cardiovascular risk in psoriatic arthritis patients.
- On page 12, Dr. Qingping Yao spotlights our new Clinic for Adult Autoinflammatory Diseases, which pools the expertise of rheumatologists, genetics specialists and pathobiologists to care for patients with these rare, complex disorders.

In each of these cases, patients benefit from the way our care model fosters interdisciplinary collaboration, as also exemplified in the remaining articles:

- On page 3, Dr. Carol Langford shares promising results from a pilot study of abatacept for nonsevere relapsing granulomatosis with polyangiitis (GPA), a condition with a wide spectrum of manifestations that can involve multiple organs.
- On page 6, Dr. Carmen Gota and a recent rheumatology fellow discuss a fascinating case of a rare malignancy presenting as monoarthritis in a patient with well-controlled rheumatoid arthritis, requiring a number of consults to reach the diagnosis.
- On page 10, Dr. Soumya Chatterjee details the meticulous, multidisciplinary management needed for scleroderma-associated severe digital ischemia.
- On page 14, Dr. Langford closes the issue with reflections on an opportunistic infection that can threaten GPA patients regardless of disease severity or treatments.

It is a pleasure to share these activities and observations with you, and I welcome your feedback on the work my Cleveland Clinic rheumatology colleagues do for our patients.

Sincerely,

Abby Abelson, MD
Chair, Rheumatic and Immunologic Diseases
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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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Cleveland Clinic’s Rheumatology Program is ranked among the top 2 in the nation in U.S. News & World Report’s “Best Hospitals” survey.
Abatacept in Nonsevere Relapsing Granulomatosis with Polyangiitis (Wegener’s):
Encouraging Pilot Study Paves the Way for a Randomized Trial

By Carol A. Langford, MD, MHS

Although treatment options for granulomatosis with polyangiitis (GPA) have increased, 50 to 70 percent of patients continue to experience a disease relapse following successful remission induction. Relapses can be similar to or different from the patient’s initial presentation and can range from mild to severe. Nonsevere relapses in particular remain a common occurrence which can result in incremental damage and require long-term use of glucocorticoids. Nonsevere disease covers a wide spectrum of disease manifestations (Figure), which can have a substantial impact on patient quality of life. Management of nonsevere relapses has remained a challenge for which there has been an unmet therapeutic need.

The Vasculitis Clinical Research Consortium (VCRC) conducted a pilot study examining abatacept in nonsevere relapsing GPA, the results of which were recently published in *Annals of the Rheumatic Diseases* (Langford et al. *Ann Rheum Dis.* 2013 Dec 9 [Epub ahead of print]). Support for this study and the VCRC was provided by the National Institutes of Health.

The exploration of abatacept in GPA was based on a mechanistic rationale that supported a role for activated CD4 T cells in the pathogenesis of GPA. By containing CTLA4, abatacept blocks the engagement of CD28 with its ligand, thereby inhibiting T cell activation. Based on reasoning that blockage of T cell activation might impact GPA disease pathogenesis, together with the favorable side effect profile seen with its use in rheumatoid arthritis, abatacept was an attractive agent to explore in nonsevere GPA.

This open-label pilot study enrolled 20 patients with nonsevere relapsing GPA. All patients received IV abatacept 10 mg/kg on days 1, 15 and 29, and every four weeks thereafter. Prednisone up to 30 mg daily was allowed within the first two months, and patients on methotrexate, azathioprine or mycophenolate mofetil at enrollment continued these agents without dosage increase. Patients remained on study medication until meeting criteria for early termination or until common closing, which was six months after enrollment of the final participant.

High Rates of Improvement and Remission

Of the 20 patients, 18 (90 percent) had disease improvement, 16 (80 percent) achieved remission (defined as a Birmingham Vasculitis Activity Score for Wegener’s granulomatosis [BVAS/WG] of 0) and 14 (70 percent) reached the study common closing date. Six patients (30 percent) met criteria for early termination due to increased disease activity; three of these six achieved remission prior to relapse. During the study, 11 of the 15 patients on prednisone (73 percent) reached 0 mg.

Patient safety was good during the course of the trial, with nine severe adverse events occurring in seven patients.

In this study of 20 patients with nonsevere relapsing GPA, abatacept was well tolerated and was associated with a high frequency of disease remission and prednisone discontinuation. While encouraging, this experience remains insufficient to recommend the use of abatacept in clinical practice. It does, however, support the pursuit of a randomized trial to determine more definitively the effectiveness and safety of abatacept in nonsevere GPA.

New Study to Begin in 2014

In pursuit of these goals, the Abatacept (CTLA4-Ig) for the Treatment of Relapsing, Non-Severe GPA (ABROGATE) trial has been designed and is anticipated to begin in 2014. This study will enroll 150 patients with nonsevere relapsing GPA and includes a ran-
The exploration of abatacept in GPA was based on a mechanistic rationale that supported a role for activated CD4 T cells in the pathogenesis of GPA.

The ABROGATE trial will join other ongoing VCRC clinical trials in GPA that include:

- An International, Open Label, Randomized Controlled Trial Comparing Rituximab with Azathioprine as Maintenance Therapy in Relapsing ANCA-Associated Vasculitis (RITAZAREM)
- Plasma Exchange and Glucocorticoid Dosing In ANCA-Associated Vasculitis (PEXIVAS)
- The Assessment of Prednisone in Remission Trial (TAPIR)

Physicians with questions about these studies or who want to make referrals should contact Dr. Langford at 216.445.6056 or langfoc@ccf.org.

Dr. Langford is Director of the Center for Vasculitis Care and Research as well as Vice Chair for Research, Department of Rheumatic and Immunologic Diseases.

Central Nervous System Vasculitis:
Multidisciplinary Team Facilitates Timely Approach for a Challenging Disease

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

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 employed widely today. We recently established a multidisciplinary care team that is highly qualified to evaluate and treat patients with suspected CNS vasculitis. Taking a multidisciplinary approach is enormously important in evaluating these patients to ensure the right diagnosis in this tremendously challenging disease.

Vasculitis affecting the CNS remains one of the most complex forms of vascular inflammatory disease. Multiple factors contribute to our relative lack of understanding of CNS vasculitis, 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.

Vasculitis affecting the CNS can be classified into primary and secondary forms:

- Primary angiitis of the CNS (PACNS) is vasculitis confined to the CNS, including the brain and spinal cord and their coverings.
- Secondary vasculitis of the CNS implies vascular inflammation of the CNS as part of a larger process such as infection, connective tissue disease or other systemic disorders.

A Condition Rife with Diagnostic Challenges

Although several tools are available to assist in the diagnosis of CNS vasculitis, many challenges remain in critically assessing their diagnostic sensitivity and specificity. Diagnostic studies include routine laboratory testing, cerebrospinal fluid assessment, neuroimaging studies, cerebral angiography and biopsy of CNS tissues. Screening laboratory studies performed on blood have little positive predictive value. Also, the specificity of these tests is too low to secure a diagnosis. Various tests for chemistries and autoantibodies as well as cultures and other investigations are useful for ruling out infectious, systemic inflammatory diseases and other hereditary syndromes.

Timely diagnosis is extremely important to ensure accurate treatment before irreversible brain damage occurs. Few clinicians are highly experienced with this disease. The care and diagnosis of patients with CNS vasculitis require a team of experts who are familiar not only with this disease but also with its mimics to ensure an accurate diagnosis and workup.
Central Nervous System Vasculitis: Multidisciplinary Team Facilitates Timely Approach for a Challenging Disease

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

specialists and rheumatologists (see sidebar). This team provides personalized, complete care that is coordinated with the right providers, eliminating needlessly long delays between appointments. This allows patients to meet the medical team with expertise in CNS vasculitis to optimize and improve their outcomes.

Exploring Pathogenesis and More

This multidisciplinary approach empowers us to focus not only on patient care but also on striving to clarify the mechanisms and pathogenesis of CNS vasculitis. We are building a repository of clinical data, radiologic findings and biological samples from patients with CNS vasculitis and its mimics. Our goals include investigation of long-term outcomes, discovery of biomarkers and exploration of radiologic studies that may distinguish CNS vasculitis and other mimics.

By investigating biomarkers to aid in the diagnosis of CNS vasculitis and develop therapeutic targets against it, we hope to better distinguish it from other cerebral arteriopathies. This, in turn, may lead to reduced costs and morbidity, more effective diagnosis and, ultimately, identification of appropriate therapies.

To refer a patient for comprehensive CNS vasculitis assessment or care, contact Dr. Hajj-Ali at hajjalr@ccf.org or 216.444.9643.

Dr. Hajj-Ali is a staff physician in the Center for Vasculitis Care and Research, Department of Rheumatic and Immunologic Diseases (contact info above). Dr. Calabrese is Director of the R.J. Fasenmyer Center for Clinical Immunology in the Department of Rheumatic and Immunologic Diseases. He can be reached at calabrl@ccf.org or 216.444.5258.

A Team Structure to Streamline Care

At Cleveland Clinic’s R.J. Fasenmyer Center for Clinical Immunology, our multidisciplinary team includes neurologists with interest in cerebrovascular and neuroimmunologic diseases, neuroradiologists and interventional radiologists, neurosurgeons, infectious disease specialists and rheumatologists (see sidebar). This team provides personalized, complete care that is coordinated with the right providers, eliminating needlessly long delays between appointments. This allows patients to meet the medical team with expertise in CNS vasculitis to optimize and improve their outcomes.

Exploring Pathogenesis and More

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Dr. Hajj-Ali is a staff physician in the Center for Vasculitis Care and Research, Department of Rheumatic and Immunologic Diseases (contact info above). Dr. Calabrese is Director of the R.J. Fasenmyer Center for Clinical Immunology in the Department of Rheumatic and Immunologic Diseases. He can be reached at calabrl@ccf.org or 216.444.5258.
Investigation of Persistent Knee Pain and Swelling Leads to Uncommon Diagnosis

By Nilofar Syed, MD, and Carmen Gota, MD

Case Study:

A 73-year-old woman presented to Cleveland Clinic with persistent left knee pain and swelling. Her history was notable for seropositive erosive rheumatoid arthritis diagnosed in 1980. She initially was treated with nonsteroidal anti-inflammatory drugs and hydroxychloroquine. In the mid-1980s, she was switched to oral methotrexate 12.5 mg weekly. She was maintained on monotherapy with methotrexate, and her disease was felt to be in remission for years. Her family history was notable for malignancies in three siblings — one each with lung, rectal or prostate cancer.

Her knee pain and swelling began approximately four months before her presentation to our rheumatology clinic. She said the pain was worse with activity and improved with rest. She denied having pain or swelling in other joints. She also denied fevers, chills, morning stiffness or rash. Initial X-ray showed medial compartment narrowing and osteophyte formation. She was treated with an anti-inflammatory medication and physical therapy.

Follow-Up Four Weeks Later

She returned to the clinic four weeks later without improvement of her symptoms. Arthrocentesis yielded minimal fluid; cell count could not be obtained, but cultures were negative. A new erythematous nodule was noted on the anteromedial aspect of the left knee. Biopsy revealed necrotizing granulomatous inflammation consistent with a rheumatoid nodule. She was treated for a relapse of rheumatoid arthritis with a short course of prednisone and two doses of etanercept.

She denied any improvement with prednisone. As she continued to have pain and swelling, she was admitted to the hospital for further evaluation. Laboratory studies revealed elevated ESR (41 mm/hr) and C-reactive protein (6.6 mg/dL). MRI of the left knee showed evidence of synovitis and erosions (Figure 1). Ultrasound-guided arthrocentesis again yielded minimal fluid. Routine cultures were negative, as were fungal and acid fast bacilli smear and cultures. Orthopaedic surgery staff were consulted, and the decision was made to proceed with synovectomy for further evaluation.

Pathology Findings and Diagnosis

Pathology results revealed an atypical lymphoid infiltrate consistent with diffuse large B cell lymphoma (Figure 2, left image). The cells were positive for CD20 and Epstein-Barr virus (EBV) by chromogenic in situ hybridization (Figure 2, right images). The patient underwent staging with a PET scan and a bone marrow biopsy, neither of which revealed evidence of neoplasm elsewhere. She was started on chemotherapy (rituximab-CHOP regimen) with a plan for post-chemotherapy radiation treatment.

Comment: Non-Hodgkin Lymphoma of the Synovium Is Rare

In the setting of well-controlled rheumatoid arthritis, pain in one joint out of proportion to that in other joints is a red flag. This case...
In the setting of well-controlled rheumatoid arthritis, pain in one joint out of proportion to that in other joints is a red flag.

reflects the importance of considering other causes of chronic monoarthritis.

Primary non-Hodgkin lymphoma originating in the synovium is very rare. Only a few cases have been reported in the literature. The risk of non-Hodgkin lymphoma is increased approximately twofold in patients with rheumatoid arthritis and is especially pronounced in those with higher inflammatory activity. The potential role of disease-modifying antirheumatic drugs and biologics in the development of malignancies is not known, and the link between EBV and the development of lymphoma in rheumatoid arthritis is also unclear.

Suggested Reading


The authors thank Soumya Chatterjee, MD, for his editorial input on this article.

Dr. Syed is a recent graduate of Cleveland Clinic’s rheumatology fellowship. She has accepted a position as an assistant professor in the Department of Rheumatology at UT Southwestern in Dallas.

Dr. Gota is a staff physician in the Department of Rheumatic and Immunologic Diseases. She can be reached at gotac@ccf.org or 216.444.0564.

Figure 2. Pathology findings following synovectomy. (Above) Disruption of synovial tissue by an atypical lymphoid infiltrate composed of large cells with vesicular chromatin and multiple prominent nucleoli (H&E, 500× oil). (Top right) Cells positive for CD20 (CD20, 500× oil). (Bottom right) Cells positive for Epstein-Barr virus by chromogenic in situ hybridization (EBER-CISH, 500× oil).
Risk for cardiovascular disease is elevated in patients with psoriatic arthritis (PsA) relative to the general population and is a major source of morbidity and mortality in these patients. Subclinical atherosclerosis in PsA has been shown to be prevalent even without existing classic cardiovascular risk factors, suggesting a role for systemic inflammation in patients with psoriatic skin and joint disease.

Unmet Needs in Cardiovascular Risk Assessment in PsA

The most commonly used methods of evaluating cardiovascular risk in the general population have recently been found to significantly underestimate the risk of cardiovascular disease in patients with psoriasis, PsA and rheumatoid arthritis. In spite of this, no clear guidelines exist for assessing or managing cardiovascular risk in patients with systemic rheumatic disease such as PsA.

There is an urgent need to identify coronary artery disease in its early forms, before clinical events, which will help guide therapy, particularly in patients with known increased risk, such as those with PsA. Carotid ultrasound findings have been shown in the general population to correlate highly with future cardiovascular events. As a result, physicians in Cleveland Clinic’s Department of Rheumatic and Immunologic Diseases are investigating whether screening of asymptomatic PsA patients for carotid plaque would alter medical management to address known cardiovascular risk.

Carotid Ultrasound as a Risk Screening Tool

We conducted a cross-sectional investigation of all PsA patients who were recruited for our Cardiometabolic Outcome Measures in Psoriatic Arthritis Study (COMPASS).

We identified PsA patients who were at least 18 years of age with subclinical cardiovascular disease from among 86 patients from our PsA registry who underwent voluntary carotid duplex ultrasound (CDU). Patients were screened for the presence of carotid artery plaque using the Mannheim consensus criteria, and arterial wall thickness was quantified by the carotid intima-media thickness measurement (Figure 1).

All patients also were offered a preventive cardiology consult automatically through the electronic health record, and results of the carotid scans were sent to the patient and his or her primary care physician. As per our PsA registry protocol, repeat CDU was performed at 12 to 24 months in 38 of the 86 patients. Demo-

Figure 1. Carotid artery ultrasound images from a control patient (left) and from a PsA patient with carotid artery plaque and a thickened arterial wall CIMT measurement (right). CIMT = carotid intima-media thickness.
Carotid plaque was identified in 34 of 86 PsA patients (40 percent) at baseline carotid artery screening.

Prevalence of Carotid Plaque and Other Risk Factors

Carotid plaque was identified in 34 of 86 PsA patients (40 percent) at baseline carotid screening. This prevalence of carotid plaque is similar to that in other cohorts of PsA patients and higher than in the general population.

When we analyzed the 38 patients who underwent repeat carotid screening, 18 had plaque at baseline that persisted on the second scan. Of the remaining 20 patients without plaque at baseline, three (15 percent) had new plaque formation on repeat ultrasound. In the group with plaque, mean LDL cholesterol was 120 mg/dL (vs. 102 mg/dL in the no-plaque group), mean HDL cholesterol was 55 mg/dL (vs. 55 mg/dL) and mean triglycerides were 203 mg/dL (vs. 96 mg/dL). Mean ESR was 8 mm/hr in patients with plaque and 6 mm/hr in those without plaque.

Better Prevention Strategies Needed

Overall, 24 of 36 patients (67 percent) with repeat screening and LDL measurements had an LDL greater than 100 mg/dL, yet only 12 (33 percent) were on statin therapy and only 10 (27 percent) were on antiplatelet medication (Figure 2). Of the 21 patients identified with carotid plaque within the repeat-screening group, only seven (33 percent) were using statins; none were on maximum doses.

Despite the offer of automatic referral for all 86 patients screened, only 11 patients were seen by our preventive cardiology section. Fourteen others were seen by a cardiologist for other reasons, including hypertension, syncope, arrhythmias and valvular disease.

Clinical Implications, Next Research Steps

Carotid ultrasound is a pragmatic modality that allows better estimation of cardiac risk than do traditional risk factors alone in PsA, and it presents an opportunity for early interventions. Low utilization of preventive services was observed even in patients with definitive evidence of atherosclerotic disease by plaque identification. A majority of patients exceeded stated preventive cardiology goals (in terms of LDL cholesterol), yet few were on statin or antiplatelet therapy.

Our research highlights the need to improve proactive modification of cardiovascular risk in PsA patients. Cleveland Clinic researchers are committed to characterizing these lapses in referral, and we recommend continued research to fill gaps in knowledge regarding short- and long-term cardiac risk assessment in our patients.

Accelerated cardiovascular disease remains a major problem for patients with PsA. Future work should focus on refining cardiac risk assessment tools to make them more specific for patients with systemic rheumatic diseases such as PsA.

The authors gratefully acknowledge the technical assistance of Alex Massiello.

Dr. Husni is Director of the Arthritis and Musculoskeletal Treatment Center and directs Cleveland Clinic’s Psoriatic Disease Biobank. She can be reached at husnie@ccf.org or 216.445.1853.

Dr. Lucke is a senior rheumatology fellow in the Department of Rheumatic and Immunologic Diseases. He has been an active investigator in the area of cardiovascular risk stratification and subclinical atherosclerosis in patients with psoriatic arthritis.
Scleroderma-Associated Severe Digital Ischemia:
Pharmacologic Intervention Often Needed

By Soumya Chatterjee, MD, MS, FRCP

Raynaud phenomenon (RP) results from intense vasospasm of digital arteries on exposure to cold or with emotional stress. It leads to well-defined triphasic color changes of fingers and toes (white, blue, dusky red) in association with paresthesia and ischemic pain (Figure 1). RP may be primary (Raynaud disease) or secondary to autoimmune rheumatic diseases such as scleroderma.

Although Raynaud disease is thought to be a result of exaggerated vasospastic response of digital arterioles to cold temperatures, RP in scleroderma often results from an underlying vaso-occlusive process. As a result, ischemic symptoms are more severe and persistent, often necessitating pharmacologic intervention.

Treatment: Start Conservative When Possible

A conservative approach is often attempted first in all cases of RP.

Nondrug measures. Even in RP in scleroderma, certain general measures may be adopted to reduce the frequency, severity and duration of RP attacks, such as avoiding cold temperatures and temperature fluctuations, alleviating stress and adopting measures to keep the core body temperature and fingers warm. Tobacco exposure, sympathomimetic drugs and vibrating tools should be avoided.

Pharmacologic measures. We use dihydropyridine calcium channel blockers (CCBs) (e.g., nifedipine, amlodipine) first, as they are by far the most commonly studied and prescribed class of agents for treatment of RP. For patients who do not respond adequately or cannot tolerate a CCB, we try other classes of drugs that have been effective, such as topical nitrates (transdermal nitroglycerin patch), alpha-receptor antagonists, angiotensin receptor blockers, selective serotonin reuptake inhibitors or pentoxifylline.

In refractory cases of secondary RP with intractable digital ischemia often leading to digital ulceration or gangrene (Figure 2), we consider one of the more expensive second-line agents, such as a phosphodiesterase-5 inhibitor (e.g., sildenafil, tadalafil), an endothelin receptor antagonist (e.g., bosentan) or an IV prosta-cyclin analog (e.g., epoprostenol, alprostadil). These agents are either used alone or added to the first-line agents. We also ensure adequate pain control. Superadded infection, which is sometimes deep-seated, is identified and often requires prolonged courses of IV antibiotics.

Critical Digital Ischemia Requires Meticulous Management

Severe digital ischemia can threaten the viability of a digit and is considered an emergency. Early intervention is paramount to prevent irreversible tissue loss.

Our approach is to hospitalize the patient, ideally in a private room, with the room temperature kept warm. A thorough evaluation is carried out to identify and, if possible, correct any secondary reversible cause that may be contributing to the crisis. This includes careful evaluation for correctable macrovascular disease, superadded infection (skin and deeper structures), severe anemia, any cause of systemic hypoxia or a hypercoagulable state.

We ensure adequate analgesia with appropriate means and often need to use oral or parenteral narcotic analgesics. If the patient is not already on a long-acting dihydropyridine CCB and an anti-platelet agent (e.g., aspirin), these are started as initial therapies. Often a second vasodilator is necessary. The choice is between a transdermal nitroglycerin patch and a phosphodiesterase-5 inhibitor.

Because Raynaud phenomenon in scleroderma often results from an underlying vaso-occlusive process, ischemic symptoms are more severe and persistent. If these measures still do not reverse the ischemia, we consider a trial of continuous IV infusion of alprostadil (prostaglandin E1) for five days. In this situation, the patient is transferred (or directly admitted) to a telemetry bed in one of our cardiac step-down units (due to the increased level of hemodynamic monitoring required). Alprostadil induces vasodilation and also inhibits platelet aggregation. Close monitoring is needed to watch for alprostadil’s hemodynamic side effects, such as hypoten-sion (which can be dose-limiting) and flushing. Other dose-limiting effects include nausea, headache and diarrhea. Due to the potential for hypotension, blood pressure and heart rate are monitored frequently.

We typically use peripheral IV access to administer alprostadil. Infusion is avoided if systolic blood pressure is less than 90 mm Hg. The starting dose of alprostadil is 0.5 to 1 ng/kg/min, which is titrated up by 1 ng/kg/min every two to four hours if the patient tolerates it (i.e., has no hypotension, headache or nausea). We
titrate the dose based on improved perfusion, decreased pain and patient tolerance, with the goal of using the maximum tolerated dose. We do not exceed a maximum infusion rate of 6 ng/kg/min. The infusion is maintained for five days and then titrated down by 1 ng/kg/min every two to four hours while we closely monitor the affected digit for pain and other signs of worsening ischemia.

When the Digit Is Nonsalvageable

If the digital ischemia is advanced and irreversible, then a portion of the digit becomes necrotic and is nonsalvageable, regardless of all medical measures. In this situation, autamputation is preferred to recover maximum perinecrotic tissue, provided the gangrenous area is dry and well-demarcated and pain and infection are controlled adequately. To reduce the ischemic penumbra, alprostadil is continued.

If all medical measures fail, surgical amputation of the affected part of the digit becomes the only therapeutic option, as advanced and irreversible digital ischemia leading to gangrene is unavoidable.

Dr. Chatterjee directs the scleroderma program in the Department of Rheumatic and Immunologic Diseases. He can be reached at chattes@ccf.org or 216.444.9945.

Figure 1. Raynaud phenomenon (pallor phase) in a patient with limited systemic sclerosis.

Figure 2. Ischemic ulceration leading to digital gangrene at the tips of the left second and third fingers and the right third and fourth fingers in a patient with diffuse systemic sclerosis. There is a small ischemic ulcer at the tip of the left fourth finger.
Clinic for Adult Autoinflammatory Diseases:  
Taking a Multidisciplinary Approach to Autoinflammatory Diseases/Periodic Fever Syndromes

By Qingping Yao, MD, PhD

Case Presentation

A 57-year-old white woman presented to Cleveland Clinic with a complex disease for consultation. The patient, an internist, had been puzzled by her illness for years. She noticed flexion contractures of her third, fourth and fifth proximal interphalangeal joints of both hands at age 6. She developed inflammatory polyarthritis and intermittent facial erythematous plaques/patches at age 30. Due to cough and dyspnea, chest radiography and CT were ordered. They showed multiple lung nodules without hilar adenopathy noted, and subsequent mediastinal lymph node biopsy revealed noncaseating granuloma. She had dry eyes that were being treated with cyclosporine drops, but she did not have uveitis. There was bilateral parotid gland enlargement with histological evidence of pleomorphic adenoma and scanty granuloma composed of lymphocytes and mixed with debris and rare collections of histiocytes. She had intermittent low-grade fever.

Family history included early-onset flexion contractures of the fourth and fifth proximal interphalangeal joints in her daughter and son. She was negative for antinuclear antibodies. Genetic testing showed presence of the NOD2 variant IVS8+158 in the family (Figure 1).

We diagnosed this as familial Blau syndrome (Figure 2). The patient was referred to Cleveland Clinic’s Genomic Medicine Institute for genetic counseling. She was treated with prednisone and sulfasalazine and achieved reasonable control of her symptoms.

Patients with autoinflammatory diseases typically do not have autoantibodies for autoimmune diseases.

A New Clinic for Adult Autoinflammatory Diseases

This case illustrates the importance of having a dedicated clinic with multidisciplinary management of complex and rare autoinflammatory diseases.

Autoinflammatory diseases, or periodic fever syndromes, are a recently classified and expanding spectrum of rheumatic conditions. Most are hereditary, caused by genetic abnormalities. They are not the same as autoimmune diseases; typically patients with autoinflammatory diseases do not have autoantibodies for autoimmune diseases such as lupus.

Diagnosing and managing autoinflammatory diseases can be complex and challenging, and patients with these conditions often struggle to find specialized care. Now adults with these conditions can get the specialized help they need at the Clinic for Adult Autoinflammatory Diseases in Cleveland Clinic’s Department of Rheumatic and Immunologic Diseases.

We are one of the few centers in the United States to offer expert knowledge and management of these disorders, which we support with genetic testing and counseling as well as with research to further the evolving understanding of these complex conditions. The sidebar lists conditions we treat in the clinic.

Figure 1. Pedigree chart of familial Blau syndrome.

Figure 2. Photo of the hand deformity camptodactyly in a patient with familial Blau syndrome.
Diverse Services from a Multidisciplinary Team

With help from colleagues in Cleveland Clinic’s Pathology & Laboratory Medicine Institute, Genomic Medicine Institute and Lerner Research Institute, we offer adults with autoinflammatory disease the most advanced services available, including:

- Expert diagnosis and treatment
- On-site genetic testing, providing faster results at lower cost
- Genetic counseling
- Scientific research in many of the conditions treated

The Clinic for Adult Autoinflammatory Diseases is part of our Department of Rheumatic and Immunologic Diseases, which led the discovery of NOD2-associated autoinflammatory disease in 2011. I have the privilege of leading this multidisciplinary clinic, and my partners in patient care and research at the clinic (Figure 3) are:

**Felicitas Lacbawan, MD**, Head of Molecular Genetic Pathology. Dr. Lacbawan leads the section that performs molecular tests for indications spanning inherited and genetic disorders to pharmacogenomics. Her section also provides genetic/genomic test review and utilization. She serves as the medical and technical director of laboratory-developed genetic tests.

**Rocio Moran, MD**, Medical Director of General Genetics Clinics in the Center for Personalized Genetic Healthcare. She also is Head of Pediatric Genetics and leads the genetics program for the Sydell and Arnold Miller Family Heart & Vascular Institute. Dr. Moran has been pivotal in improving patient access to genetic testing and educating providers about its role in clinical practice.

**Christine McDonald, PhD**, Associate Staff in Pathobiology. Dr. McDonald coordinates translational research studies in autoinflammatory disease. A major focus of her research is to explore links between dysregulated NOD2 function and autoinflammatory diseases to gain insights into potential novel treatment approaches for patients. Her research program is supported by grants from the National Institutes of Health and the Department of Defense.

**Suggested Reading**


To refer a patient to the Clinic for Adult Autoinflammatory Diseases, call 216.444.5632.

Dr. Yao is a staff physician in the Department of Rheumatic and Immunologic Diseases. He can be reached at yaoq@ccf.org or 216.444.5625.
Morbidity Prevention in Vasculitis —
Remember Pneumocystis

By Carol A. Langford, MD, MHS

A 34-year-old woman was diagnosed with granulomatosis with polyangiitis (Wegener’s) (GPA) six weeks ago with features including sinonasal disease, a lung nodule without respiratory compromise, episcleritis, migratory arthralgias and (+) PR3-cANCA. For this, she was treated with prednisone 60 mg daily and methotrexate 20 mg/week. After improvement in her symptoms, she returns with a new cough and dyspnea. She appears unwell and has a pulse oximetry value of 89 percent with chest imaging showing improvement in the prior nodule with new bilateral interstitial infiltrates.

A 65-year-old man experienced a relapse of GPA two months ago manifest as glomerulonephritis with a peak creatinine of 2.6 mg/dL and purpura. For this, he was treated with methylprednisolone 1,000 mg intravenously for three days followed by prednisone 60 mg daily and rituximab 375 mg/m²/week for four weeks. His creatinine improved to 1.3 mg/dL and the purpura resolved. He now presents with dyspnea and has a pulse oximetry value of 85 percent with chest imaging showing bilateral interstitial infiltrates.

Two patients, different degrees of GPA disease severity and different treatments — but the same life-threatening complication: Pneumocystis pneumonia.

**Pneumocystis Pneumonia — A Potentially Life-Threatening Infection**

*Pneumocystis* is a genus of four species of organisms recognized as a fungus based on ribosomal RNA sequences. *Pneumocystis carinii* is the species seen in rats, and although this term was applied to human disease for many years, the designation *Pneumocystis jirovecii* is now used to correctly reflect the species that infects humans. The abbreviation PCP has continued to be used in reference to *Pneumocystis pneumonia* to maintain the accuracy of this abbreviation in older medical literature.

In immunocompromised/immunosuppressed patients, *P. jirovecii* can result in a severe pneumonia. This is characteristically manifested as dyspnea and hypoxia with interstitial infiltrates, although a diversity of radiographic presentations can be seen. *P. jirovecii* is detected by staining or polymerase chain reaction assays of respiratory secretions obtained from induced sputum or bronchoalveolar lavage (Figure). PCP carries a mortality rate of up to 35 percent in some series.

**Risk Not Isolated to Cyclophosphamide-Based Induction**

In patients with GPA or microscopic polyangiitis (MPA) receiving induction treatment, PCP is an important opportunistic infection. As these two cases illustrate, the risk of PCP is not isolated to patients who receive cyclophosphamide-based regimens. It was, in fact, during studies of methotrexate in nonsevere GPA during the 1990s that the significance of this pathogen in GPA came fully to light. More recently, PCP also has been observed in patients treated with rituximab-based induction regimens, providing emphasis that *P. jirovecii* is an organism that rheumatologists should be aware of.

Current data support employing a prophylactic strategy for *P. jirovecii* in all patients with GPA/MPA who are receiving induction therapy for active disease, regardless of whether this consists of cyclophosphamide, rituximab or methotrexate. Prophylactic strategies include trimethoprim/sulfamethoxazole (T/S), dapsone, atovaquone and inhaled pentamidine. In patients without a contraindication, T/S is considered the first-line choice and is typically given at a dose of 800 mg/160 mg three times a week or 400 mg/80 mg daily.

The risk of PCP in vasculitis is not isolated to patients who receive cyclophosphamide-based regimens.

Although there is an interaction between T/S 800 mg/160 mg taken twice a day and methotrexate, prophylactic doses have been well tolerated. However, blood counts should be monitored.

**Cases Continued**

In returning to our two patients, a diverse differential for new pulmonary infiltrates would need to be considered, including recurrent active disease and medication toxicity. However, in an immunosuppressed patient, infection would be a primary concern, which would include *P. jirovecii*. Given the high rate of mortality associated with PCP, it is important for rheumatologists to be aware of this important infection and to use preventive strategies in at-risk patients, which includes GPA/MPA patients receiving any immunosuppressive-induction regimen.
Morbidity Prevention in Vasculitis

Remember Pneumocystis

By Carol A. Langford, MD, MHS

Risk Not Isolated to Cyclophosphamide-Based Induction

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Figure. Image of a broncho-alveolar lavage specimen positive for Pneumocystis jirovecii (GMS stain). Courtesy of Sandra S. Richter, MD, Cleveland Clinic.

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THE CLEVELAND CLINIC WAY
By Toby Cosgrove, MD,
CEO and President, Cleveland Clinic
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