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CHEST Special Feature

Update in the Diagnosis and Management of Pulmonary Vasculitis*

Stephen K. Frankel, MD, FCCP; Gregory P. Cosgrove, MD, FCCP; Aryeh Fischer, MD; Richard T. Meehan, MD; and Kevin K. Brown, MD, FCCP

The term *vasculitis* encompasses a number of distinct clinicopathologic disease entities, each of which is characterized pathologically by cellular inflammation and destruction of the blood vessel wall, and clinically by the types and locations of the affected vessels. While multiple classification schemes have been proposed to categorize and simplify the approach to these diseases, ultimately their diagnosis rests on the identification of particular patterns of clinical, radiologic, laboratory, and pathologic features. While lung involvement is most commonly seen with the primary idiopathic, small-vessel or antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides of Wegener granulomatosis, microscopic polyangiitis, and Churg-Strauss syndrome, one should remember that medium-vessel vasculitis (*ie*, classic polyarteritis nodosa), large-vessel vasculitis (*ie*, Takayasu arteritis), primary immune complex-mediated vasculitis (*ie*, Goodpasture syndrome), and secondary vasculitis (*ie*, systemic lupus erythematosus) can all affect the lung. However, for the purpose of this review, we will focus on the ANCA-associated vasculitides.

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Key words: antineutrophil cytoplasmic antibody; antineutrophil cytoplasmic antibody-associated vasculitis; Churg-Strauss syndrome; lung; microscopic polyangitiis; pulmonary; vasculitis; Wegener granulomatosis

Abbreviations: ANCA = antineutrophil cytoplasmic antibody; ATG = antithymocyte globulin; c-ANCA = cytoplasmic antineutrophil cytoplasmic antibody; p-ANCA = perinuclear antineutrophil cytoplasmic antibody; CSS = Churg-Strauss syndrome; DAH = diffuse alveolar hemorrhage; ELISA = enzyme-linked immunosorbent assay; EUVAS = European Vasculitis Study Group; MMF = mycophenolate mofetil; MPA = microscopic polyangitiis; MPO = myeloperoxidase; PR = proteinase; RPGN = rapidly progressive glomerulonephritis; SLE = systemic lupus erythematosus; TNF = tumor necrosis factor; T/S = trimethoprim/sulfamethoxazole; WG = Wegener granulomatosis; WGET = Wegener Granulomatosis Etanercept Trial

Learning Objectives: 1. Indicate pulmonary involvement in patients with vasculitis most commonly seen in small vessels or anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis. 2. Identify randomized controlled trials used in new evidence-based recommendations for the evaluation and treatment of small vessels or ANCA associated vasculitis.

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis can be difficult to diagnosis even for the most experienced of clinicians given the (1) multifaceted and variable presentations, (2) the overlap of signs and symptoms with much more common entities such as infection, malignancy, thromboembolic disease, and the connective tissue diseases, and (3) the low frequency of vasculitis in the general population (on the order of 20 to 100 cases per million population).[1–4] Nevertheless, certain clinical scenarios should raise the specter of vasculitis and prompt an aggressive evaluation.

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Clinical Scenarios Suggestive of Vasculitis

Diffuse Alveolar Hemorrhage

Diffuse alveolar hemorrhage (DAH) is a triad of diffuse alveolar infiltrates (although rarely unilateral), hemoptysis (not always necessary), and a drop in hematocrit and/or hemoglobin level. DAH can also be suggested by an increase in the diffusion capacity of > 30% over baseline. Pathologically, capillaritis (*ie*, neutrophilic vasculitis of the capillaries and venules), bland hemorrhage, or diffuse alveolar damage with hemorrhage can all be seen. Although the vast majority of the ANCA-associated vasculitides that present with DAH will have capillaritis identified on surgical lung biopsy specimens, partially treated vasculitis can demonstrate bland hemorrhage on biopsy specimens. The finding of isolated pulmonary capillaritis without a systemic vasculitis is termed *idiopathic pauci-immune pulmonary capillaritis*, a disorder classified within the family of idiopathic, small-vessel vasculitis, despite generally being ANCA-negative.

For instructions on attaining CME credit, see page A-72

Acute Glomerulonephritis

Although rapidly progressive glomerulonephritis (RPGN) represents only a small percentage of patients with renal insufficiency (approximately 5%), these cases must be identified and distinguished from the more common causes of renal insufficiency. RPGN is identified by an active urinary sediment including red blood cell (RBC) casts, hematuria (especially with dysmorphic RBCs), proteinuria (*ie*, > 500 mg/d), and elevated BUN and serum creatinine levels (Fig 1). Clinically, edema and hypertension may occur. To assist with the diagnosis, a microscopic examination of the urine should be performed by skilled personnel on a fresh urine sample before RBC casts or other diagnostic features degenerate. The differential diagnosis of RPGN includes the ANCA-associated vasculitides, idiopathic pauci-immune glomerulonephritis (*ie*, isolated small-vessel renal vasculitis), systemic lupus erythematosus (SLE), Goodpasture syndrome, postinfectious glomerulonephritis, IgA nephropathy, Henoch-Schönlein purpura, essential cryoglobulinemia, and membranoproliferative glomerulonephritis.[5–8]

Pulmonary-Renal Syndrome

The term *pulmonary renal syndrome* refers to patients with both DAH/pulmonary capillaritis and glomerulonephritis. The differential diagnosis includes the ANCA-associated vasculitides, Goodpasture syndrome, and SLE.

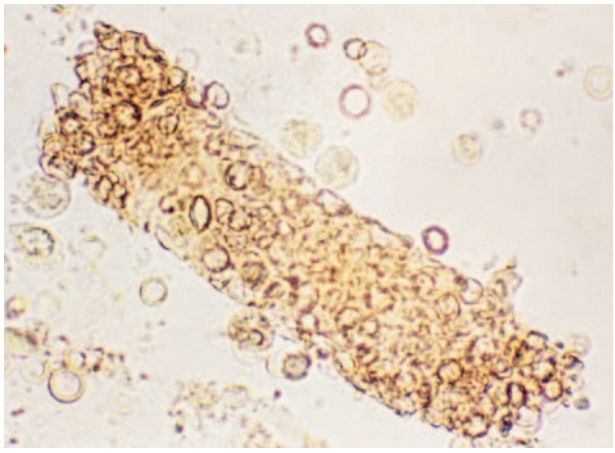

Figure 1. RBC cast from a patient with glomerulonephritis (×100). The figures is published courtesy of Scott Lucia, MD, Department of Pathology, University of Colorado Health Sciences Center (Denver, CO).

Deforming or Ulcerating Upper Airway Lesions

Patients with refractory chronic sinusitis in which infectious, allergic, and anatomic causes have been eliminated and/or in which there are significant ulcerative or destructive soft-tissue or bone lesions should be assessed for an ANCA-associated vasculitis.

Cavitary or Nodular Disease on Chest Imaging

A wide array of nondiagnostic abnormalities on chest imaging may be seen with the ANCA-associated vasculitides. However, the specific identification of cavities and/or nodules carries a more limited differential diagnosis, albeit one led by common entities such as infection and malignancy. In the correct clinical setting, these findings should raise the possibility of an ANCA-associated vasculitis, as nodular disease is found in 55 to 70% of patients and cavitary disease is found in 35 to 50% of patients with Wegener granulomatosis (WG) [Fig 2].[9,10]

Palpable Purpura

The physical examination finding of palpable purpura implies small-vessel, cutaneous vasculitis.[11] Cutaneous (hypersensitivity) vasculitis is commonly seen with drug reactions, but is also found in the setting of ANCA-associated vasculitis, cryoglobulinemia, connective tissue diseases, infections, and malignancy.

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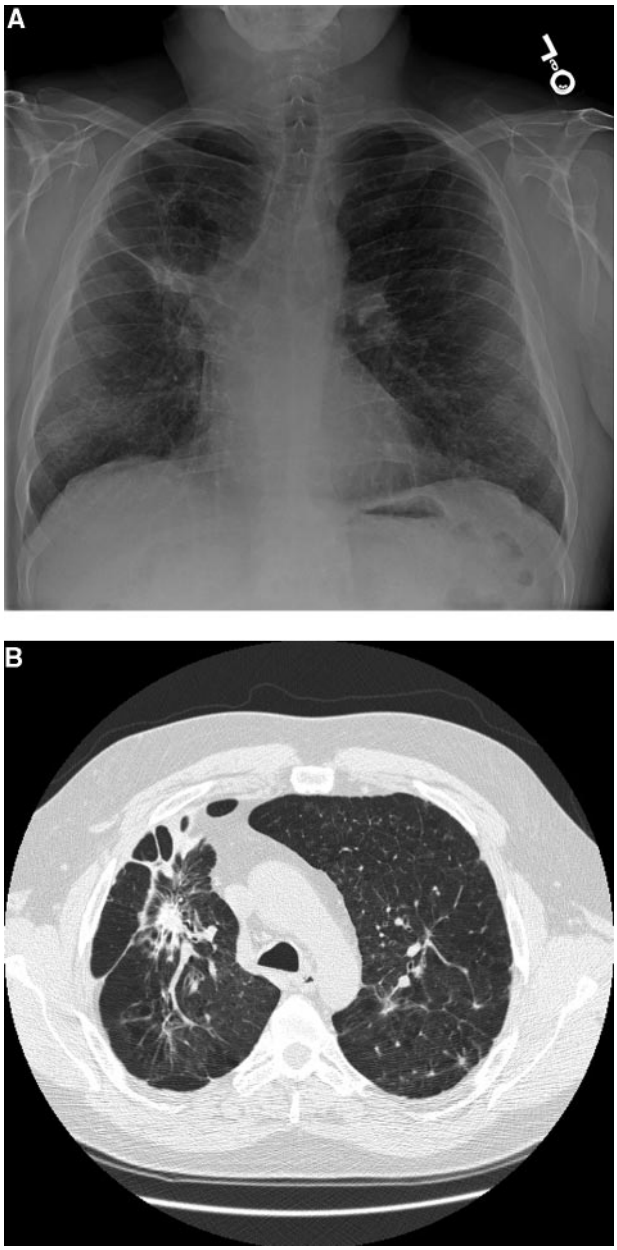

FIGURE 2. *Top*, *A*: chest radiograph of a patient with WG. *Bottom*, *B*: CT scan further delineating the right upper lobe lesion that is radiographically indistinguishable from malignancy or abscess.

Mononeuritis Multiplex

While vasculitis may present with a variety of CNS or peripheral nervous system manifestations, mononeuritis multiplex, in particular, should alert the physician to the possibility of vasculitis.[12,13] The sudden onset of a foot drop or wrist drop is often the result of a vasculitis. Other presentations may include pain, numbness, paresthesias, weakness, or loss of function, which by definition, occur in two or more peripheral nerve distributions.

Multisystem Disease

Unusual constellations of signs and symptoms involving multiple organ systems either simultaneously or over time should raise the possibility of a vasculitis. This requires close attention and a high index of suspicion from the clinician as items such as constitutional symptoms, uveitis (which is rarely described as such), unusual "rashes," arthritis, or "sinus troubles" must be remembered and considered relevant when the clinical presentation is an abnormal chest radiograph finding, shortness of breath, or renal failure.

SPECIFIC CLINICAL FEATURES

WG

WG is the most common of the ANCA-associated vasculitides. It is clinically characterized by the triad of upper airway involvement (*eg*, sinusitis, otitis, ulcerations, bony deformities, and subglottic or bronchial stenosis), lower respiratory tract involvement (*eg*, cough, chest pain, shortness of breath, and hemoptysis), and glomerulonephritis (Table 1).[8,9,14–16,22–25,36,37,64,112,115–120] The complete triad need not be present at the time of initial presentation, with as few as 40% of patients having renal involvement at the time of first presentation, even though 80 to 90% of patients will ultimately go on to develop renal disease.[14–16] Constitutional symptoms, ocular involvement, and skin and musculoskeletal disease are also relatively common.[8,14–16] Abnormal chest radiography findings are especially common in patients with WG compared with those having other vasculitides and occurs in the majority of patients. That said, patients may present with alveolar, mixed, or interstitial infiltrates, nodular disease, or cavitary disease.[9,10] Pathologically, WG is characterized by small-vessel and medium-vessel necrotizing vasculitis and granulomatous inflammation, often with a geographic appearance (Fig 3).[17,18] Prognostically, poor outcomes correlate with advanced age, more severe renal impairment, alveolar hemorrhage, proteinase (PR)-3 positivity, and a diagnosis of WG (as opposed to a diagnosis of microscopic polyangitiis [MPA] or Churg-Strauss syndrome [CSS]).[19–21]

CSS

Although CSS is also an ANCA-associated vasculitis, its clinical presentation is often quite distinct from that seen with WG, MPA, or idiopathic pauci-immune pulmonary capillaritis (Table 1). Generally, CSS enters the differential diagnosis with the other eosinophilic lung diseases (*ie*, chronic eosinophilic pneumonia, allergic bronchopulmonary mycosis,

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Table 1—*Clinical Characteristics of the ANCA-Associated Vasculitides

Variables	WG	MPA	CSS
Pulmonary	Very common, 70–95% of patients; symptoms may include cough, chest pain, dyspnea, or hemoptysis; tracheobronchial and endobronchial disease also relatively frequent (10–50%)	Moderately common with 10–30% of patients experiencing involvement, most of which demonstrate alveolar hemorrhage	Asthma is essentially universal; patients may also have infiltrates/eosinophilic pneumonia
Renal	RPGN occurs in 50–90% of patients	RPGN is essentially universal	RPGN occurs in 10–50% of patients
Upper Airway	Very common, 70–95% of patients; ulcerating and destructive lesions are suggestive	Variable	Sinusitis occurs in 20–70% of patients but often lacks the destructive nature seen in WG
Constitutional	Common; symptoms may include fatigue, malaise, fevers, and weight loss	Very common and often precedes RPGN	Common
Musculoskeletal	Arthralgias, arthritis and myalgias occur in approximately one half of patients	Arthralgias and myalgias in at least one half of patients	Arthralgias and myalgias reported in up to one half of patients.
Ocular	Common, occurring in 25–50% of patients; sight-threatening disease including uveitis, ocular ulcers, along with a host of other complications may occur	Less common, 0–30% of patients	Uncommon
Cardiac	5–15%.	10–20%	Common (30–50%) and a major cause of mortality in patients with CSS; may present with conduction delay, other ECG abnormality, systolic or diastolic dysfunction, or coronary artery involvement
Gastrointestinal	Uncommon	Common, 35–45%; complications usually resemble those of the other ANCA-associated vasculitides (see CSS), although it is possible to see the visceral aneurysms most commonly associated with classic polyarteritis nodosa	Common (30–60%); another major cause of morbidity and mortality; may present with hemorrhage, abdominal pain, infarct, or perforated viscus
Dermatologic	Common; may include classic palpable purpura, but may also present with ulcers, nodules or vesicles	Common	Common
Neurologic	May present with CNS disease or peripheral nervous system involvement	Mononeuritis multiplex occurs in 10–50%	Mononeuritis multiplex in > 50%
Chest Imaging	Abnormal chest imaging findings are very common (> 80%); may present with alveolar, interstitial or mixed infiltrates, or nodular or cavitary disease	Pulmonary infiltrates occur in 10–30%	Pulmonary infiltrates are common (40–75%); may also see changes consistent with asthma (*eg*, airway wall thickening and hyperinflation)
ANCA	ANCA-positive in > 90% and c-ANCA/ anti-PR3 ELISA positive in > 85% with generalized active disease	ANCA-positive in 50–75% with most of these being p-ANCA/ anti-MPO-positive	ANCA positive in 45–70% with most of these being p-ANCA /anti-MPO-positive

*Data are from references 8, 9, 14–16, 22–25, 36, 37, 64, 112, and 115–120.

drug reactions, hypereosinophilic syndrome, parasitic infection, and asthma/atopic disease), or in patients with asthma/atopy who develop significant GI disease (*ie*, perforation, ischemia, and bleeding) or cardiac disease (*ie*, conduction abnormalities, systolic dysfunction, or diastolic dysfunction). The syndrome is characterized by its own triad of (1) asthma, (2) hypereosinophilia, and (3) necrotizing vasculitis. While pulmonary hemorrhage and glomerulonephritis may occur, they are much less common than in the other small-vessel vasculitides.[22–25] Mortality and morbidity are often due to cardiac complications (up to half of CSS-related deaths), GI complications, or status asthmaticus and respiratory failure.[22,23,26] Pathologically, both a necrotizing, small-vessel vasculitis and an eosinophil-rich inflammatory infiltrate with necrotizing granulomas are seen.[27,28]

Over the last several years, a number of case reports and case series[29,30] have suggested an asso-

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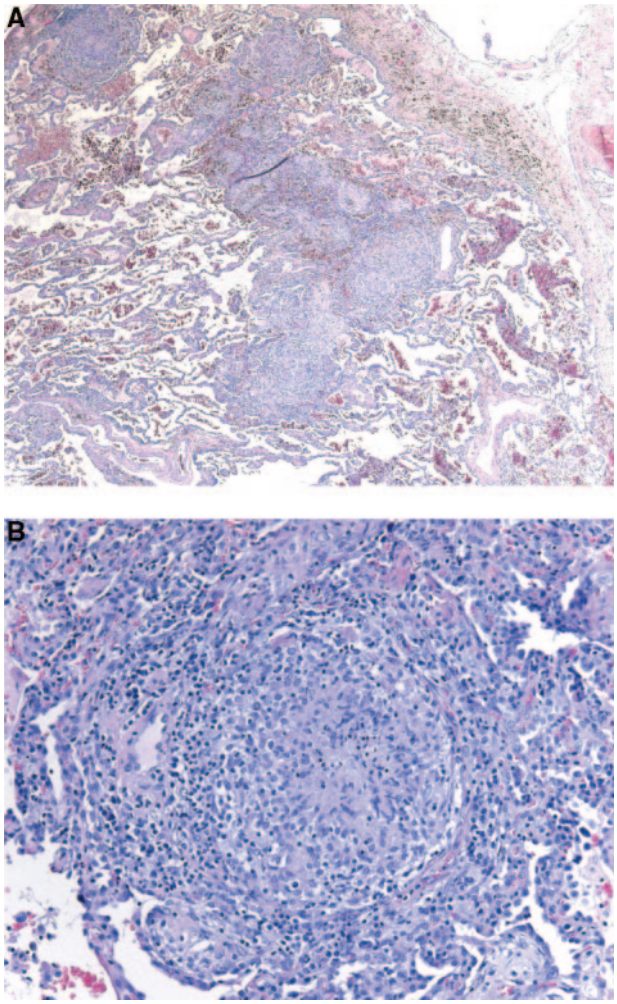

FIGURE 3. Histopathology of a patient with WG. *Top*, *A*: low-power view demonstrating patchy, "geographic" necrotizing vasculitis and granulomatous inflammation (×4). *Bottom*, *B*: high-power view of granulomatous inflammation (×40).

ciation between the use of leukotriene inhibitors and CSS. This in turn led to the development of the following two competing hypotheses: (1) that the introduction of therapy with leukotriene inhibitors permits oral corticosteroid dose reductions in patients with severe asthma, which then unmasks previously treated but unrecognized CSS; or (2) that leukotriene inhibitors promote the biological conversion of severe asthma/atopic disease toward CSS.[31] More recently, the analysis of postmarketing surveillance data and a number of patient cohorts offer no compelling evidence of a pathogenic role for leukotriene receptor antagonists in the development of CSS, but rather support the "unmasking hypothesis."[32–35]

MPA

Clinically, MPA is often heralded by a long prodromal phase that is characterized by profound constitutional symptoms followed by the development of RPGN. RPGN is essentially universal in MPA, whereas pulmonary involvement occurs in only a minority of patients (10 to 30%).[36–38] In those patients who do develop lung involvement, DAH/capillaritis is the most common manifestation.[38] Joint, skin, peripheral nervous system, and GI involvement are also relatively common.[37] Pathologically, a focal, segmental necrotizing vasculitis and a mixed inflammatory infiltrate without granulomas is seen.

EVALUATION

Clinical Assessment

The clinical evaluation of the patient with suspected vasculitis begins with a detailed and thorough medical history and physical examination. Close attention must be paid to seemingly unrelated signs and symptoms as both vasculitis and conditions mimicking it (*eg*, connective tissue diseases, infection, malignancy, drug toxicity, sarcoidosis, and interstitial lung diseases) present with a variety of potentially confusing manifestations. Infection can be particularly problematic in that it may cause both a positive ANCA response and a leukocytoclastic vasculitis, and therefore needs to be ruled out before being treated with aggressive immunosuppressive therapy. A medication history that includes not only current medications, but any medications that could produce significant side effects such as vasculitis (*eg*, propylthiouracil) is required. Similarly, a careful and thorough physical examination may reveal evidence of otherwise asymptomatic extrapulmonary disease that assists with developing a comprehensive clinical picture.

Laboratory testing is critical. A CBC count with a differential metabolic panel, liver function testing, and urinalysis with microscopic examination are required to help identify hematologic, renal, hepatic, and metabolic abnormalities. Cryoglobulinemia and hepatitis B and C infection should be ruled out. Besides ANCAs, and anti-PR3 and anti-myeloperoxidase (MPO) enzyme-linked immunosorbent assay (ELISA) testing (see next section), rheumatologic serologies may be useful and an initial screen should include antinuclear antibody, rheumatoid factor, and antiphospholipid antibody testing. Depending on the clinical scenario, additional rheumatologic serologies may also be useful, including the following: anticyclic citrullinated peptide for rheumatoid arthritis, anti SS-A/Ro and anti-SS-B/La for SLE and Sjögren syndrome, anti-Scl-70 (topoisomerase) and anticentromere antibodies for systemic sclerosis (scleroderma), aldolase and creatinine phosphokinase for polymyositis, and complement levels for SLE. In

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addition, antiglomerular basement membrane antibodies, which are indicative of Goodpasture syndrome, are helpful when evaluating alveolar hemorrhage, hematuria, or pulmonary renal syndrome.

ANCAs

ANCAs have developed a prominent role in the diagnosis of small-vessel or ANCA-associated vasculitis, and new data suggest a pathophysiologic role in their development.[39] The following two distinct staining patterns have been described, cytoplasmic ANCA (c-ANCA); and perinuclear ANCA (p-ANCA). c-ANCAs have since been shown to primarily recognize the enzyme PR3, and their presence often suggests a diagnosis of WG, whereas p-ANCAs have been shown to interact with a number of distinct antigens, but most commonly MPO. Accordingly, specific ELISAs have been developed to determine the presence of anti-PR3 and anti-MPO antibodies.

As with any test, the predictive value of these assays depends on (1) the prevalence of the disease in the patient population tested, and (2) the sensitivity and specificity of the test. Conventionally, c-ANCAs and anti-PR3 ELISA are said to have an 85 to 90% sensitivity and 95% specificity for generalized active WG with lower sensitivity for limited disease (approximately 60%) and disease in remission (approximately 40%).[40–46] p-ANCA or anti-MPO testing is less sensitive, with sensitivities of approximately 35 to 75% for MPA and 35 to 50% for CSS.[43,46–50] False-positive testing may occur with other systemic autoimmune diseases (*ie*, rheumatoid arthritis and SLE), inflammatory bowel disease, subacute bacterial endocarditis, and other infections among others. It should also be remembered that if these tests are not applied selectively to high-risk patient populations, then the positive predictive value of the testing declines. A revealing study by Mandl et al[51] demonstrated that when clinical guidelines were used to identify patients who were at risk for a small-vessel vasculitis, the positive predictive value of the test increased without reducing sensitivity. While ANCA testing alone or PR3 and MPO ELISAs alone are used by many centers as their initial screening test for ANCA-associated vasculitis, the combination of ANCA testing plus the use of ELISAs maximizes sensitivity in identifying patients with ANCA-associated vasculitis.[43,47,51–53] Given that a definitive diagnosis ultimately must be based on the accumulated data and not on ANCA/PR3/MPO testing alone, combination testing offers the clinician a better opportunity to avoid missing a potential case of ANCA-associated vasculitis.

ANCA testing has also been proposed as a surrogate marker to predict disease relapse in patients who are currently in remission.[54–56] While it is true that a rise in ANCA titers often precedes or accompanies a disease flare, a rise in ANCA titers alone is insufficiently sensitive and specific to accurately predict disease relapse, such that the diagnosis of disease flare remains a clinical diagnosis at the present time.[41,55,57,58]

Imaging Studies

Imaging studies can be very helpful in the diagnosis. Chest radiographs and, particularly, CT scans of the chest may identify pulmonary disease even when clinically occult. Other imaging studies such as CT scans of the sinuses or abdomen, echocardiography, angiography, and MRI of the brain may be of use depending on the clinical scenario and extent of the organ involvement.

Bronchoscopy

The utility of bronchoscopy in the diagnosis and management of ANCA-associated vasculitis is limited to the evaluation of alveolar hemorrhage and infection, and endobronchial lesions such as those seen in patients with WG or sarcoidosis. Transbronchial biopsy specimens are, by and large, insufficient to make a diagnosis of vasculitis.[59]

Skin, Sinus, or Airway Biopsy

Although the biopsy of extrarenal and extrapulmonary sites in general carries a lower likelihood of making a definitive diagnosis,[60] the accessibility of the site and the low morbidity of these procedures makes performing a biopsy at these sites desirable when they are clinically involved.

Renal Biopsy

Percutaneous renal biopsy is commonly performed in the setting of acute glomerulonephritis. While features specific for vasculitis such as granulomatous inflammation or necrotic vessels are rarely seen, the finding of a segmental necrotizing glomerulonephritis without immune deposits (*ie*, pauci-immune glomerulonephritis) reflects a systemic vasculitis in most cases.[16,61–63] It is very important that in addition to conventional histopathology, immunofluorescence (and electron microscopic) studies be performed on these samples as other conditions can be ruled out by the absence of characteristic immunofluorescence patterns, such as IgA deposition in patients with Henoch-Schönlein purpura, linear IgG deposition in patients with Goodpasture syndrome, and irregular Ig and complement deposition in patients with SLE.

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Surgical Lung Biopsy

When the lung is clinically involved, surgical lung biopsy gives a definitive diagnosis in the clear majority of cases. Moreover, the use of video-assisted thoracoscopic surgery has significantly reduced its morbidity and mortality.[8,64] At the time of surgery, some tissue should be frozen (for immunofluorescence studies), fixed in formalin (for hematoxylin-eosin and special stains), and placed in a saline solution for culture. Because of the variety of testing performed on the samples, the processing should be closely coordinated among the physicians and surgeons involved, and the pathologist should be alerted that vasculitis is in the differential diagnosis.

Treatment

General Principles

Therapy for the vasculitides relies on aggressive immunosuppression, and, as such, complications of therapy are common and may be severe. Therefore, the degree of immunosuppression is generally titrated to reflect the severity of the disease so that disease control is obtained while minimizing the potential for adverse side effects. To this end, the accurate and frequent assessment of disease severity such as that proposed by the European Vasculitis Study Group (EUVAS) is recommended. Moreover, vasculitis therapy is often divided into a two-part model, an initial "remission-induction" phase, in which more intensive immunosuppressive therapy is used to control active disease, and a "maintenance" phase, in which less intensive therapy is used, minimizing the adverse side effects while still maintaining disease remission. Regardless of the phase of therapy, close drug-specific and disease-specific monitoring is necessary to identify any disease flare, infection, or drug toxicity as early as possible. Clinicians should have a formalized protocol for the prospective monitoring of drug-related side effects of therapy during initiation, dose escalation, and maintenance therapy, and should be familiar with the toxicities associated with each pharmacologic approach. Finally, measures such as vaccination, physical and occupational therapy, nutrition, oxygen therapy, the treatment of comorbid diseases, and psychosocial support should not be overlooked and greatly help in minimizing the morbidity associated with these diseases.

Treatment recommendations depend critically on an accurate determination of disease severity. EUVAS has devised a clinically useful grading system in which the patient's disease is categorized as (1) limited, (2) early, generalized, (3) active, generalized, (4) severe, and (5) refractory. Clinical criteria and first-line treatment recommendations appear in Table 2.[67,83,86,97,116,121–127]

Remission-Induction

Limited Disease

Limited disease refers to localized disease of the upper airways. By definition, these patients have no systemic symptoms, end-organ function is not threatened, and there is no renal involvement. As such, therapy can often be limited to a single agent such as corticosteroids, azathioprine, or methotrexate. Some authors have even advocated the use of trimethoprim/sulfamethoxazole (T/S) alone for this group of patients,[65] although it is not clear whether T/S alone represents effective therapy (see below). That said, for more aggressive limited disease, therapy may need to be escalated along the lines outlined for early generalized or active generalized disease.

Early, Generalized Disease

Early, generalized disease is distinguished from active, generalized disease by whether or not organ

Table 2—*EUVAS Grading of Disease Severity and First-Line Treatment Options for Induction Therapy**

Disease Classification	Constitutional Symptoms	Renal Function	Threatened Organ Function	Treatment Options for Induction
Limited	No	Serum creatinine < 120 μmol/L (1.4 mg/dL)	No	Corticosteroids OR methotrexate OR azathioprine
Early, generalized	Yes	Serum creatinine < 120 μmol/L (1.4 mg/dL)	No	Cyclophosphamide + corticosteroids or methotrexate + corticosteroids
Active, generalized	Yes	Serum creatinine < 500 μmol/L (5.7 mg/dL)	Yes	Cyclophosphamide + corticosteroids
Severe	Yes	Serum creatinine > 500 μmol/L (5.7 mg/dL)	Yes	Cyclophosphamide + corticosteroids + plasma exchange
Refractory	Yes	Any	Yes	Consider investigational or compassionate use agents (see text)

*Data are from references 67, 83, 86, 97, 116, and 121–127.

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function is threatened. Nevertheless, treatment recommendations for these two classes of disease severity have traditionally been similar in that the use of cyclophosphamide plus corticosteroids has remained the first-line therapy for both early and active generalized disease. However, the Methotrexate vs Cyclophosphamide for "Early Systemic Disease" trial[66] appears to corroborate the findings of smaller studies[67–69] that have suggested that methotrexate is as equally efficacious as cyclophosphamide in the induction of disease remission in patients with early generalized disease. Thus, both agents now represent acceptable first-line therapy for this group of patients and, given the more favorable side-effect profile of methotrexate relative to cyclophosphamide, therapy with methotrexate plus corticosteroids is finding increasing favor.

Active, Generalized Disease

The outcomes of patients with vasculitis were dismal prior to the landmark National Institutes of Health-sponsored study of Fauci et al,[15] which demonstrated the effectiveness of therapy with oral cyclophosphamide plus oral corticosteroids for the treatment of WG. Since that time, the use of cyclophosphamide plus corticosteroids has become and remains the principle first-line therapy for the treatment of generalized active vasculitis. There is now evidence that therapy with pulsed IV cyclophosphamide may be as effective as therapy with oral cyclophosphamide and is associated with fewer side effects[70,71]; however, the Daily Oral Vs Pulse Cyclophosphamide for Renal Vasculitis trial undertaken by EUVAS comparing the efficacy of therapy with pulsed IV cyclophosphamide and oral continuous cyclophosphamide has not yet been published, and the question remains unanswered.

Severe Disease

Severe disease is defined by the presence of severe renal involvement (creatinine concentration, > 5.7 mg/dL), DAH, or other life-threatening disease. Although the management of patients with severe disease had previously been the subject of some debate, recent studies[72–77] have suggested that such patients should receive a combination therapy consisting of cyclophosphamide, corticosteroids, and plasma exchange. The addition of plasma exchange therapy to the standard cyclophosphamide-plus-corticosteroid regimen has been shown to be superior to therapy with high-dose, pulsed IV steroids in restoring renal function in patients with severe renal impairment.[72–78] Based on several case reports and a case series of 20 patients published by Klemmer et al,[77] this strategy also appears to be effective for the treatment of DAH. Additional therapies for patients with DAH may include activated human factor VII, which has been used to induce hemostasis with success at the case report level.[79,80] Extracorporeal membrane oxygenation has also been used at the case report level to "buy time" in patients with severe DAH until other interventions have had a chance to work, although the use of extracorporeal membrane oxygenation in adults remains controversial.[81]

Refractory Disease

Patients who have not responded to cytotoxic agents, high-dose corticosteroids, or plasma exchange are deemed to have refractory disease. For this small but severely ill group of patients, one must consider the use of novel agents. Therapies with agents such as infliximab, rituximab, and antithymocyte globulin have all been suggested for the treatment of refractory vasculitis, and are discussed in detail in later sections. Similarly, IV Ig has also been used for the treatment of refractory vasculitis and represents another potential alternative.

Maintenance

Conceptually, maintenance therapy for vasculitis is less aggressive than induction therapy with the idea that a lesser degree of immunosuppression is required to maintain disease remission than to induce it, and should be associated with fewer and less severe adverse effects. Hence, following the induction of remission with an agent such as cyclophosphamide, patients are generally converted to receive therapy with azathioprine or methotrexate. In addition, patients often receive a low dosage of corticosteroids along with the cytotoxic agent as part of their maintenance regimen. As with all cytotoxic agents, these agents must be introduced with dose escalation over time and with close drug-specific monitoring to identify any adverse side effects as early as possible. Second-line agents that may be considered if patients are unable to receive therapy with azathioprine or methotrexate include cyclophosphamide, mycophenolate mofetil (MMF), leflunomide, or cyclosporine.[67,68,82–85]

The timing of the transition from the induction agent to the maintenance therapy has been a subject of debate, with some physicians suggesting that patients should have an empiric 12-month course of induction therapy and others supporting clinical criteria as the chief determinant of when to transition. However, the results of the Cyclophosphamide vs Azathioprine for Remission in Generalized Vasculitis trial[86] demonstrated that patients with active generalized vasculitis may be transitioned from oral cyclophosphamide to azathioprine once a clinical re-

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mission has occurred (generally within 3 to 6 months) with no increase in the rate of relapse, no increase in disease activity scores, and no decrease in the glomerular filtration rate.

Another point of controversy has centered on the use of T/S[87,88] or the reduction of nasal *Staphylococcus aureus* carriage as therapy for patients with ANCA-associated vasculitis.[89,90] Studies[88] have demonstrated a reduced rate of disease relapse in patients who are maintained on T/S compared to those without, and additional work has suggested that this phenomena is related to *S aureus* nasal carriage.[89,90] Although T/S has been recommended by some authors for isolated, limited upper airways disease,[65] T/S cannot be considered as a substitute for immunosuppressive therapy in patients who have generalized disease.[91–93] The EUVAS-sponsored Placebo-Controlled Trial of Nasal Mupirocin for the Prevention of Relapse trial in which patients were randomized to the eradication of nasal *S aureus* with topical mupirocin or to placebo should provide additional data to help answer the question as to whether disease relapse is indeed related to *S aureus* nasal carriage. Nevertheless, T/S therapy should be considered for *Pneumocystis carinii* prophylaxis in patients who are receiving therapy with cyclophosphamide or other aggressive immunosuppression regimens, barring an allergy to sulfa drugs or other contraindications.

Novel Agents/Biological Agents

Tumor Necrosis Factor-α Inhibitors

Tumor necrosis factor (TNF)-α is a pluripotent proinflammatory cytokine that has been implicated in the pathogenesis of autoimmune and inflammatory diseases, including vasculitis. The TNF-α inhibitors represent a major advance in the treatment of rheumatoid arthritis, and it has been hypothesized that these agents may be effective (1) for the induction of disease remission in patients with refractory disease and (2) as a potential candidate for maintenance therapy in patients in whom a remission has already been achieved. Despite these theoretic benefits, the Wegener Granulomatosis Etanercept Trial (WGET) demonstrated that etanercept (Enbrel; Immunex Corporation; Thousand Oaks, CA) was not effective for the maintenance of disease remission in patients with WG and did not enhance the effects of standard therapy.[94] The trial was stopped early when no differences were seen between experimental and control groups when comparing the rates of sustained remission, periods of low-level disease activity, the time required to achieve remission, and the rate of disease flare. Interestingly, six of the patients who received cyclophosphamide plus etanercept developed solid cancers, raising the question as to whether etanercept can potentiate carcinogenesis when given concurrently with cyclophosphamide. Another interesting finding of the WGET trial was an elevated incidence of deep venous thrombosis, equally distributed between the etanercept and control groups (20 total events among 180 patients with a mean follow-up period of 27 months), suggesting a possible increased incidence of venous thrombosis in patients with ANCA-associated vasculitis.

With regard to the induction of disease remission by other TNF-α inhibitors, several small studies, case series, and case reports[95–99] have examined the efficacy of infliximab (Remicade; Centocor; Horsham, PA) in inducing disease remission in patients with ANCA-associated vasculitis. The largest study to date was performed by Booth et al,[95] in which the authors found that infliximab was effective at inducing remission in 88% of patients. However, the authors also found high rates of severe infection (21%) and disease relapse (20%) in the infliximab-treated group, limiting enthusiasm for this treatment strategy. A larger, randomized treatment trial will be necessary to determine whether or not there is a role for infliximab in the induction of disease remission in patients with refractory disease. Whether the differences seen among the TNF-α studies relate to the differing properties of etanercept and infliximab or to the complex role of TNF-α in the pathogenesis of the ANCA-associated vasculitides remains unclear.

B-Cell Depletion

Rituximab (Rituxan; Genentech; South San Francisco, CA) is a monoclonal anti-CD20 antibody that targets a subset of B lymphocytes and represents an effective treatment modality for non-Hodgkin (B-cell) lymphomas. Interest in using rituximab for the treatment of rheumatologic diseases, most notably in patients with refractory SLE and rheumatoid arthritis, but also other autoimmune diseases including vasculitis, has been increasing.[100–103] The results of a series of 11 patients[100] with active ANCA-associated vasculitis, who had either received maximal doses of cyclophosphamide or had other contraindications to cyclophosphamide and who were treated with rituximab on a compassionate-use basis, were recently published. The authors found that they were able to induce remission in all 11 patients and that ANCA titers became undetectable in 8 of 11 patients. While there are other case reports and case series in the literature that also suggest that rituximab may be useful in treating patients with refractory vasculitis,[104–106] no randomized, controlled trials have yet been performed.

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MMF

MMF (Cellcept; Roche Pharmaceuticals; Nutley, NJ) is primarily used for immunosuppression in transplant patients, and suppresses both T and B lymphocytes. Given its relatively favorable side-effect profile and clinical potency, MMF is finding increased use in the management of systemic connective tissue diseases, even though trials for these indications lag behind clinical practice. Similarly, MMF has been proposed as a potential therapy for the ANCA-associated vasculitides. A 2004 study of MMF for remission maintenance after induction by cyclophosphamide plus prednisone was conducted at the National Institutes of Health,[107] and while the drug was relatively well-tolerated, the authors found a relapse rate of 43% (6 of 14 patients.) This was in contrast to an earlier study[108] of MMF for remission maintenance, which identified only a 9% relapse rate (1 of 11 patients). The much larger International Mycophenolate mofetil Protocol to Reduce Outbreaks of Vasculitides (IMPROVE) trial currently being conducted by EUVAS will directly compare the efficacy of MMF to azathioprine for remission maintenance and hopefully will provide a convincing answer regarding the role of MMF as a remittive agent.[66]

Leflunomide

Leflunomide (Arava; Sanofi-Aventis; Bridgewater, NJ) is a new immunosuppressive agent that primarily targets T cells and has been used increasingly in the treatment of rheumatoid arthritis. A phase II study[109] of 20 patients found the drug to be relatively well-tolerated in patients with WG when used for remission maintenance with one major and eight minor disease relapses over the course of the study (mean follow-up period, 1.75 years). Again, larger, randomized, controlled trials will be necessary to clarify the role of leflunomide in patients with vasculitis.

Antithymocyte Globulin

Anti-T-cell therapy had been proposed for the treatment of refractory vasculitis. A EUVAS-sponsored open-label study[110] of 15 patients with refractory WG who were treated with antithymocyte globulin (ATG) found that 13 of 15 patients achieved either a partial disease remission (9 of 15 patients) or complete disease remission (4 of 15 patients), but 2 patients died (from pulmonary hemorrhage and infection) following administration of the first dose of ATG. Additional, nonfatal complications were also seen, most notably infection and serum sickness reactions. Still, given the poor prognosis of patients with severe, refractory ANCA-associated vasculitis, consideration should be given to ATG despite the morbidity, mortality, and costs involved.

Monitoring for Complications

Careful monitoring for complications is absolutely necessary to minimize the morbidity and mortality of the disease and its therapies. Patients with clinical deterioration raise a differential diagnosis of (1) infection, (2) drug toxicity, (3) disease relapse. or (4) a new, unrelated disease.

Infection is a major contributor to morbidity and mortality in patients with vasculitis and often mimics a disease flare or presents with atypical features. A study by Bradley et al[111] found that 10% of vasculitis patients who had been treated with cyclophosphamide developed clinically important infections (*ie*, sepsis and pneumonia) even when patients with drug-induced leukopenia were excluded. Patients who were maintained using high-dose glucocorticoids and intensive immunosuppressive/cytotoxic therapy were at especially high risk for fatal infections. Gayraud et al[21] found similar results with infectious complications representing 12.9% of deaths among a sample of treated vasculitis patients. Likewise, drug toxicity is a relatively frequent and clinically important problem. In a study by Reinhold-Keller et al,[112] in which WG patients were treated with cyclophosphamide, there was a 12% incidence of cystitis, an 8% incidence of myelodysplastic syndrome, and a 5% incidence of solid malignancy.

Approximately 50% of patients with ANCA-associated vasculitis will experience one or more disease flares despite receiving therapy, with relapse being more common among patients with WG (40 to 65%) and less common among patients with CSS (15 to 25%.)[21,113] Such flares may present with clinical manifestations similar to those seen at the time of the original diagnosis or with new signs and symptoms, or the involvement of previously unaffected organs. In general, disease relapse requires reinduction therapy with an escalation of a patient's immunosuppressive regimen. While disease relapse remains a clinical diagnosis, the WGET study group recently published a study[114] applying a serum proteomic approach to gauging the state of remission in patients with WG, raising the hope that sensitive serum markers may one day permit accurate discrimination between quiescent and active disease.

Summary

Considerable advances have been made in the management of and therapy for the small-vessel vasculitides. The recent completion of a number of critical, randomized, controlled trials has led to evidence-based recommendations regarding the management of these devastating diseases. The introduction of novel therapeutic approaches, combined with increased clinical awareness of the complex and competing consider-

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ations in the management of these patients, allows us to anticipate further improvements in the outcomes of patients with these severe diseases.

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