REVIEW

The Antineutrophil Cytoplasmic Antibody–Associated Vasculitides

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Wegener's granulomatosis, microscopic polyangiitis, and Churg-Strauss syndrome are small- to medium-vessel vasculitides linked by overlapping pathology and the presence of antineutrophil cytoplasmic antibodies (ANCA). Commonly referred to as the ANCA-associated vasculitides, these diseases are challenging to diagnose and to treat. Distinguishing the ANCA-associated vasculitides from other forms of vasculitis or nonvasculitic processes (such as infection) can be particularly difficult. This review describes the clinical and pathologic hallmarks of the ANCA-associated vasculitides, discusses the role of ANCA assays in diagnosis and treatment, and outlines an approach to the evaluation and management of these diseases. **Am J Med. 2004;117:39–50.** ©2004 by Elsevier Inc.

Anticytoplasmic antibodies directed against neutrophils (or antineutrophil cytoplasmic antibodies [ANCA]) were reported in association with segmental necrotizing glomerulonephritis in the early 1980s. In 1985, van der Woude and others (1) reported the presence of diffuse cytoplasmic staining of neutrophils in patients with Wegener's granulomatosis. In studies of patients with Wegener's granulomatosis, microscopic polyangiitis, or renal-limited vasculitis, Falk and Jennette (2) noted another pattern of immunostaining—perinuclear fluorescence of alcohol-fixed neutrophils. Today, Wegener's granulomatosis, microscopic polyangiitis, and the Churg-Strauss syndrome are commonly referred to as the ANCA-associated vasculitides.

The 1990 American College of Rheumatology classification criteria for Wegener's granulomatosis and the Churg-Strauss syndrome (Table 1) (3,4) were developed to ensure the inclusion of uniform disease populations in research studies (5). These criteria did not address the utility of ANCA for classification or the difference between polyarteritis nodosa and microscopic polyangiitis. These limitations were addressed by the Chapel Hill Consensus Conference (Table 2) (6). To date, widely accepted diagnostic criteria for these diseases have not been developed.

A population-based study from Norfolk, England, reported incidences of 8.5 cases per million for Wegener's granulomatosis, 3.6 cases per million for microscopic polyangiitis, and 2.4 cases per million for the Churg-Strauss syndrome (7). In two large U.S. cohorts of patients with Wegener's granulomatosis (8,9), whites comprised more than 90% of all cases, whereas African Americans, Hispanics, and Asians together represented 1% to 4% of cases. The mean age at diagnosis is about 55 years, but cases involving octogenarians are not unusual.

CLINICAL FEATURES

There is substantial overlap in many of the clinical features of the ANCA-associated vasculitides. In some cases, distinguishing between two or more of these diseases on the basis of clinical features alone is difficult (Table 3).

Upper Respiratory Tract and Ears

Although patients with the Churg-Strauss syndrome or microscopic polyangiitis may experience substantial ear, nose, or sinus disease, this pattern of involvement is most characteristic of Wegener's granulomatosis. More than 90% of patients with Wegener's granulomatosis eventually develop upper airway or ear abnormalities (8,9). The nasal symptoms of Wegener's granulomatosis include nasal pain and stuffiness, rhinitis, epistaxis, and brown or bloody crusts. Nasal inflammation may lead to septal erosions, septal perforation, or, in many cases, nasal bridge collapse—the "saddle-nose deformity" (Figure 1). Because damage to the sinuses increases susceptibility to infections, the distinction between active Wegener's granulomatosis and secondary infections in the sinuses may be challenging.

Two principal categories of ear disease—conductive and sensorineural hearing loss—are typical of Wegener's granulomatosis (10–12). The most common cause of conductive hearing loss may be Eustachian tube dysfunction due to nasopharyngeal disease. Inner ear disease in

Table 1. The 1990 American College of Rheumatology Classification Criteria for Wegener's Granulomatosis and Churg-Strauss Syndrome

Wegener's Granulomatosis	Churg-Strauss Syndrome

Nasal or oral inflammation
  Painful or painless oral ulcers or purulent or
    bloody nasal discharge
	Asthma
	  Wheezing or high-pitched rales

Abnormal chest radiograph
  Nodules, fixed infiltrates, or cavities
	Eosinophilia
	  >10% of white blood cell differential

Urinary sediment
  Microhematuria or red cell casts
	Mononeuropathy or polyneuropathy
	  Mononeuropathy, multiple mononeuropathies, or
	    polyneuropathy attributable to vasculitis

Granulomatous inflammation on biopsy specimen
  Granulomatous inflammation within the wall of
    an artery or in the perivascular area
	Pulmonary infiltrates, nonfixed
	  Migratory or transitory pulmonary infiltrates

	Paranasal sinus abnormality
	  Acute or chronic paranasal sinus pain, tenderness, or
	    radiographic opacification

	Extravascular eosinophils
	  Biopsy of artery, arteriole, or venule showing accumulations
	    of eosinophils in extravascular areas

From references 3 and 4.

Wegener's granulomatosis may be associated with sensorineural hearing loss, vestibular dysfunction, or both. In contrast to middle ear disease, the mechanism of inner ear disturbances in Wegener's granulomatosis is poorly understood (13).

In 60% to 70% of patients with the Churg-Strauss syndrome, allergic rhinitis is the earliest disease manifestation, typically appearing years before the development of full-blown systemic vasculitis (14,15). Rhinitis may be severe and may require serial polypectomies to relieve obstruction and sinusitis. Nasal polyps in the Churg-Strauss syndrome are usually histologically identical to those seen in patients without the disease. Nasal crusting and conductive hearing loss (due to serous otitis or granulomatous middle ear inflammation) may also occur in the Churg-Strauss syndrome.

Trachea
Subglottic stenosis and, less commonly, stenotic lesions of the bronchi are serious and potentially fatal complications of Wegener's granulomatosis. Subglottic involvement is often asymptomatic initially, but becomes apparent as hoarseness, pain, cough, wheezing, or stridor. Thin-cut computed tomographic scans are often useful, but the most accurate means of assessing tracheal stenosis is by direct laryngoscopy.

Eyes
Orbital masses termed pseudotumors, which are characteristic of Wegener's granulomatosis, typically occur in a retrobulbar location, causing proptosis, diplopia, or visual loss. Scleritis may lead to necrotizing anterior scleritis and blindness. Peripheral ulcerative keratitis may also threaten vision in any of the ANCA-associated vasculitides. Other ocular manifestations include conjunctivitis, episcleritis, keratitis, and uveitis. Nasolacrimal duct obstruction is most typical of Wegener's granulomatosis.

Lungs
In Wegener's granulomatosis, the pulmonary manifestations range from asymptomatic lung nodules and fleeting (or fixed) pulmonary infiltrates to fulminant alveolar hemorrhage. The nodules are usually multiple and bilateral (Figure 2), are often cavitary, and may be confused with mycobacterial or fungal infections. The infiltrates are often misdiagnosed initially as pneumonia. Hilar and

Table 2. The Chapel Hill Consensus Conference Definitions of the Antineutrophil Cytoplasmic Antibody–Associated Vasculitides

Wegener's granulomatosis
  Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small- to medium-sized vessels (e.g., capillaries, venules, arterioles, and arteries). Necrotizing glomerulonephritis is common.

Microscopic polyangiitis
  Necrotizing vasculitis, with few or no immune deposits, affecting small vessels (i.e., capillaries, venules, or arterioles). Necrotizing arteritis involving small- and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs.

Churg-Strauss syndrome
  Eosinophil-rich and granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small- to medium-sized vessels, associated with asthma and eosinophilia.

From Jennette (6).

Table 3. Clinical Features of the Primary Antineutrophil Cytoplasmic Antibody–Associated Vasculitides

Feature	Wegener's Granulomatosis	Microscopic Polyangiitis	Churg-Strauss Syndrome
ANCA positivity	80%–90%	70%	50%
ANCA antigen specificity	PR3 ≫ MPO	MPO > PR3	MPO > PR3
Fundamental histology	Leukocytoclastic vasculitis; necrotizing, granulomatous inflammation (rarely seen in renal biopsy specimens)	Leukocytoclastic vasculitis; no granulomatous inflammation	Eosinophilic tissue infiltrates and vasculitis; granulomas have eosinophilic necrosis
Ear/nose/throat	Nasal septal perforation, saddle-nose deformity, conductive or sensorineural hearing loss, subglottic stenosis	Absent or mild	Nasal polyps, allergic rhinitis, conductive hearing loss
Eye	Orbital pseudotumor, scleritis (risk of scleromalacia perforans), episcleritis, uveitis	Occasional eye disease: scleritis, episcleritis, uveitis	Occasional eye disease: scleritis, episcleritis, uveitis
Lung	Nodules, infiltrates, or cavitary lesions; alveolar hemorrhage	Alveolar hemorrhage	Asthma, fleeting infiltrates, alveolar hemorrhage
Kidney	Segmental necrotizing glomerulonephritis, rare granulomatous features	Segmental necrotizing glomerulonephritis	Segmental necrotizing glomerulonephritis
Heart	Occasional valvular lesions	Rare	Heart failure
Peripheral nerve	Vasculitic neuropathy (10%)	Vasculitic neuropathy (58%)	Vasculitic neuropathy (78%)
Eosinophilia	Mild eosinophilia occasionally	None	All

ANCA = antineutrophil cytoplasmic antibody; MPO = myeloperoxidase; PR3 = proteinase 3.

mediastinal adenopathy occur rarely in Wegener's granulomatosis (16).

Pulmonary capillaritis, which is equally likely to occur in Wegener's granulomatosis and microscopic polyangiitis, may lead to lung hemorrhage, hemoptysis, and rapidly changing alveolar infiltrates (Figure 3). A subset of patients with ANCA-associated vasculitis, particularly those with microscopic polyangiitis, may have pulmonary interstitial fibrosis (17).
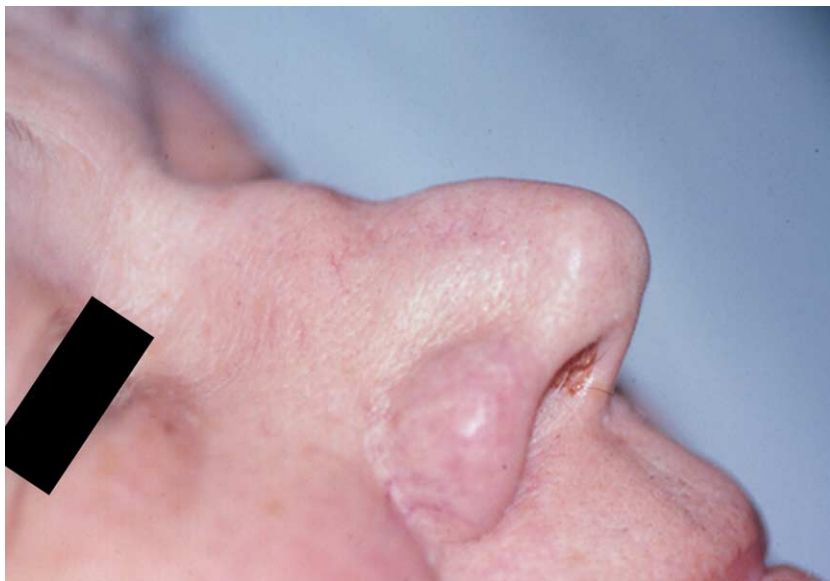
Obstructive airway disease and fleeting pulmonary in-

Figure 1. Saddle-nose deformity in Wegener's granulomatosis.

Figure 2. Multifocal cavitary nodules in Wegener's granulomatosis.

filtrates are the hallmarks of the Churg-Strauss syndrome. The majority of patients report the new onset of asthma months to years before the appearance of overt vasculitis. Chest radiographs are abnormal, however, in only one third of patients (14).

Kidneys

The most feared clinical presentation of renal disease among the ANCA-associated vasculitides is rapidly progressive glomerulonephritis. More than 75% of patients with Wegener's granulomatosis will eventually develop renal involvement (8,9). The progression of the disease often appears to accelerate once kidney involvement is obvious. Thus, the appearance of an active urine sediment or a rise in serum creatinine level in Wegener's granulomatosis signals the need for an immediate full evaluation, prompt treatment, and careful monitoring. A

Figure 3. Alveolar hemorrhage in microscopic polyangiitis.

more indolent form of renal involvement, which is more likely to occur in microscopic polyangiitis or the Churg-Strauss syndrome, has also been described (18). Renal disease associated with microscopic polyangiitis is typically detected well after onset of the disease. This is reflected in renal biopsy specimens that typically demonstrate more sclerosis and fibrosis than do specimens from patients with Wegener's granulomatosis.

There is also a form of pauci-immune vasculitis in which the inflammation is confined to the kidneys, with no overt disease in other organ systems. Such cases are referred to as "renal-limited vasculitis". In general, the renal presentation and course of patients with renal-limited vasculitis are similar to those of other forms of ANCA-associated vasculitis. Most such cases are associated with myeloperoxidase-ANCA.

The kidney is typically the organ that is slowest to respond to therapy in ANCA-associated vasculitis. Whereas most eye, joint, lung, skin, and other manifestations of active disease begin to improve quickly upon the start of appropriate therapy, renal function may continue to worsen even after the start of intensive immunosuppression, sometimes taking several weeks to establish a new baseline. Glomerulonephritis may lead to fibrotic crescents and other scarring within the kidney, leading to long-term concerns about progression to end-stage renal disease through hyperfiltration.

Arthritis/Arthralgias

Prominent musculoskeletal symptoms occur in at least 60% of patients with ANCA-associated vasculitis and are frequently the presenting complaint. The combination of joint complaints, cutaneous nodules (frequently mistaken for rheumatoid nodules), and the high frequency of rheumatoid factor positivity among patients with ANCA-associated vasculitis (around one third are rheumatoid factor positive) often lead to the misdiagnosis of rheumatoid arthritis early in the disease course. Arthralgias are more common than frank arthritis. The recurrence of musculoskeletal complaints in a patient in remission often marks the start of a disease flare.

Skin

In both the Churg-Strauss syndrome and Wegener's granulomatosis, cutaneous nodules may occur at sites that are also common locations for rheumatoid nodules, particularly the olecranon region (9,19). Skin findings in the ANCA-associated vasculitides also include all of the potential manifestations of cutaneous vasculitis: palpable purpura (Figure 4), vesiculobullous lesions, papules, ulcers, digital infarctions, and splinter hemorrhages.

Nervous System

Sensory neuropathy is commonly associated with the ANCA-associated vasculitides. At its worst, vasculitic neuropathy may lead to a devastating mononeuritis mul-

Figure 4. Purpura in microscopic polyangiitis.

Figure 5. Fibrinoid necrosis occurring in the renal biopsy specimen of a patient with Churg-Strauss syndrome. Note the segmental localization of the necrosis to a single quadrant of the glomerulus.

tiplex or a disabling sensory polyneuropathy. Mononeuritis multiplex occurs more commonly in the Churg-Strauss syndrome (up to 78% of patients [20]) and microscopic polyangiitis (up to 58% [14]) than in Wegener's granulomatosis.

Central nervous system abnormalities occur in approximately 8% of patients with Wegener's granulomatosis, usually in the form of cranial neuropathies, mass lesions, or pachymeningitis. Parenchymal brain involvement by vasculitis is uncommon in the ANCA-associated vasculitides (9,21–23).

Heart

The Churg-Strauss syndrome is the form of ANCA-associated vasculitis that is most likely to involve the heart, usually in the form of rapid-onset heart failure (20). Cardiac complications in Wegener's granulomatosis and microscopic polyangiitis are both less common and more difficult to attribute with certainty to the underlying disease. Focal cardiac valvular lesions, valvular insufficiency, pericarditis, and coronary arteritis have been described in Wegener's granulomatosis (24–26).

Gastrointestinal Tract

Eosinophilic gastroenteritis often precedes the frank vasculitic phase of the Churg-Strauss syndrome. Among patients with either the Churg-Strauss syndrome or microscopic polyangiitis, unexplained abdominal pain occurs in up to one third of patients and may lead to ischemic bowel. Gastrointestinal involvement is less common in Wegener's granulomatosis. Asymptomatic elevations of hepatic aminotransferase levels may be observed in patients with ANCA-associated vasculitis.

Blood

Eosinophilia (before treatment) is a *sine qua non* of the Churg-Strauss syndrome. Eosinophil counts are usually sensitive markers of disease flares, but respond very quickly (within 24 hours) to treatment with high doses of glucocorticoids. Tissue infiltration by eosinophils, how-
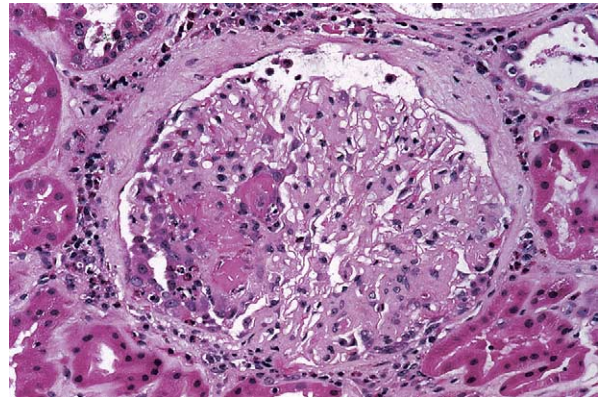
ever, may remain. Mild eosinophilia (up to 15% of the total white blood cell count) may also occur in Wegener's granulomatosis. Most patients with Churg-Strauss syndrome also have elevated serum immunoglobulin E levels. In addition to ANCA, nonspecific autoantibodies, such as antinuclear antibodies and rheumatoid factor, also occur in high percentages of patients with ANCA-associated vasculitis.

Other

ANCA-associated vasculitides rarely affect the parotid gland, pulmonary artery, breast, or genitourinary organs (9,10,27,28). When there is involvement of these organs, comorbid processes must be excluded.

PATHOLOGY

Fibrinoid necrosis (Figure 5) has been referred to as the "ANCA-associated lesion" (29), but it may be found in a variety of vasculitic (and nonvasculitic) conditions, such as polyarteritis nodosa, scleroderma renal crisis, systemic lupus erythematosus, and malignant hypertension.

The histologic features of pulmonary Wegener's granulomatosis are similar to those found in specimens from other tissues, but the large amounts of tissue obtained at open or thoracoscopic lung biopsies often capture the full pathologic spectrum. Both vasculitic and necrotizing granulomatous features, which do not invariably coexist, may be confirmed in lung biopsy specimens. In addition, pulmonary Wegener's granulomatosis frequently demonstrates an extensive, nonspecific inflammatory background (30). Coalescence of such neutrophilic microabscesses leads to extensive regions of "geographic" necrosis. The range of granulomatous inflammation found in Wegener's granulomatosis may include palisading granulomas, scattered giant cells, and poorly formed granulomas.

Renal disease in the ANCA-associated vasculitides is associated with focal, segmental lysis of glomerular tufts, disruption of the basement membrane, and accumulation of fibrinoid material (i.e., fibrinoid necrosis). Crescents in Bowman's space develop as a result of spillage of inflammatory mediators across the ruptured glomerular capillaries, accumulation of macrophages, and epithelial cell proliferation.

Thrombotic changes in the glomerular capillary loops are among the earliest histologic changes. Acute tubular necrosis and tubulointerstitial nephritis also are seen commonly. Immunofluorescence studies of renal biopsy specimens demonstrate scant deposition of immunoglobulin and complement, giving rise to the term pauci-immune glomerulonephritis. Although renal biopsy findings alone are not diagnostic of the ANCA-associated vasculitides, they may confirm the diagnosis when other clinical, radiologic, and serologic data are compatible with one of these diagnoses.

In most cases, the glomerulonephritis that occurs in Wegener's granulomatosis is indistinguishable from that of the other ANCA-associated vasculitides. Granulomas are observed only occasionally in renal biopsy specimens from patients with Wegener's granulomatosis. The presence of eosinophils on biopsy specimens, although characteristic of the Churg-Strauss syndrome, may also be seen in Wegener's granulomatosis and microscopic polyangiitis. Overwhelming numbers of eosinophils, however, are typical of the Churg-Strauss syndrome.

In contrast to biopsy specimens from the kidney and lung, tissue samples from involved areas of the upper respiratory tract (nose, sinuses, and subglottic region) are nondiagnostic in up to 50% of specimens (31). In such cases, nonspecific acute and chronic inflammation are the usual findings.

ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES

The Antigens
Proteinase 3 (PR3), a 29-kd serine protease, is found in the azurophilic granules of neutrophils and peroxidase-positive lysosomes of monocytes (32). Whether endothelial cells express PR3 on their surfaces in vivo is still a matter of debate (33–40). Myeloperoxidase, which constitutes nearly 5% of the total protein content of the neutrophil, is localized to the same cellular compartments as PR3. The protein is a covalently linked dimer with a molecular weight of 140 kd.

Proteinase 3, in contrast to myeloperoxidase, is also found on the plasma membrane of resting neutrophils and monocytes in many patients. Some patients have little to no PR3 expression on neutrophils, others have high PR3 expression, and some have bimodal populations of neutrophils in which one population of cells expresses PR3 and another population does not (41). Expression of PR3 on the neutrophil membrane appears to be a risk factor for disease flare in the ANCA-associated vasculitides (42,43). Proteinase 3 is also overexpressed in a variety of acute and chronic myeloid leukemia cells (44).

The autoantibodies directed against PR3 and myeloperoxidase are directed against multiple epitopes. Sera from different patients may recognize different epitopes. All ANCA, however, recognize restricted epitopes of PR3 involving its catalytic site (45).

Clinical Testing for ANCA
Two types of assays for ANCA—immunofluorescence and enzyme immunoassay—are now in common use. Capture enzyme immunoassay techniques (46), which may offer some advantages in test characteristics over the more widely available assays, are currently performed only in specialty centers.

With immunofluorescence, three principal patterns of fluorescence are recognized: the cytoplasmic (C-ANCA), perinuclear (P-ANCA), and "atypical" patterns. In patients with vasculitis, the C-ANCA pattern usually corresponds to the detection of PR3-ANCA by enzyme immunoassay. The combination of a C-ANCA pattern on immunofluorescence testing and PR3-ANCA is associated with Wegener's granulomatosis (47). The P-ANCA pattern, which usually corresponds to the presence of myeloperoxidase-ANCA in vasculitis patients, occurs in approximately 10% of patients with Wegener's granulomatosis, but is more typical of microscopic polyangiitis, the Churg-Strauss syndrome, and renal-limited vasculitis. The great majority of patients with drug-induced ANCA-associated vasculitides are P-ANCA positive, often with very high titers of myeloperoxidase-ANCA.

Atypical ANCA patterns on immunofluorescence testing are found in a wide variety of disorders, including inflammatory bowel disease, systemic immune-mediated diseases, and infections. These atypical patterns, which are frequently difficult to distinguish from the P-ANCA pattern, result from the presence of antibodies with a wide range of specificities, including specificities for lactoferrin, elastase, and bactericidal permeability–inhibiting protein (48). Regardless of the immunofluorescence pattern, positive immunofluorescence assays should be confirmed by the performance of enzyme immunoassays for the specific antibodies associated with vasculitis. Even for C-ANCA, the positive predictive value for Wegener's granulomatosis is only in the range of 45% to 50% (16,49).

Clinical Utility of ANCA Serologies
Despite advances in ANCA testing techniques, the cornerstone of diagnosis in Wegener's granulomatosis remains the rigorous interpretation of histopathological specimens within the overall clinical context. When bi-

Table 4. Clinical Utility of Antineutrophil Cytoplasmic Antibody Testing

- Positive ANCA serologies are extremely useful in suggesting the diagnosis in the proper clinical setting.
- Positive immunofluorescence assays without confirmatory enzyme immunoassays for anti-PR3 or antimyeloperoxidase antibodies are of limited utility.
- Histopathology remains the gold standard for diagnosis in most cases.
- Negative ANCA assays do not exclude ANCA-associated vasculitis because between 10% of 50% of patients with ANCA-associated vasculitis (depending on the particular disease) may be ANCA negative.
- Persistence of ANCA in the absence of clinical indications of active disease does not indicate a need for continued treatment.
- In a patient who was ANCA positive during active disease, persistent ANCA negativity provides reassurance—but no guarantee—that the disease is not active. If disease flares occur in such patients, they are usually limited.
- A patient who becomes ANCA positive again following a period of clinical quiescence associated with negative ANCA assays is at risk of a flare. The temporal correlation between the return of ANCA and a disease flare, however, is poor.

ANCA = antineutrophil cytoplasmic antibody; PR3 = proteinase 3.

opsy specimens are nondiagnostic, ANCA assays provide an important adjunct to diagnosis (Table 4).

In the proper clinical setting, a positive ANCA assay greatly increases the likelihood that a form of ANCA-associated vasculitis is present. Most series indicate that up to 10% to 20% of patients with active, untreated Wegener's granulomatosis are ANCA negative (50). For patients with limited Wegener's granulomatosis (9), 30% or more of patients lack ANCA. Approximately 70% of patients with microscopic polyangiitis and 50% of those with Churg-Strauss syndrome (higher in some series) have ANCA.

Utility of ANCA Assay following Disease Activity and in Predicting Flares

In general, ANCA titers have imperfect correlations with disease activity. The positive predictive value of a rise in ANCA titer as measured by immunofluorescence was only 57% in a prospective study, compared with 71% for enzyme immunoassay (51). Moreover, among patients with an elevation of ANCA titer measured by enzyme immunoassay, only 39% suffered disease flares within 6 months. A rise in ANCA titer, therefore, is a risk factor for a flare, but the adjustment of immunosuppressive medications based solely on the rise or fall of ANCA titers is rarely justified (48,52–54).

ANCA serologies may provide valuable information about disease activity in some settings. In one prospective study of 33 patients who suffered disease relapses (55),

only 2 patients showed no preceding rise in ANCA titer (and both of those had persistently high ANCA levels, even in remission).

PATHOPHYSIOLOGY

The ANCA-associated vasculitides are complex disorders mediated by the immune system in which tissue injury results from the interplay between an initiating inflammatory event and a highly specific pathogenic immune response (i.e., the production of ANCA) to previously shielded epitopes of neutrophil granule proteins. ANCA produce tissue damage via interactions with primed neutrophils and endothelial cells (56).

There is now substantial evidence that ANCA are directly involved in the widespread tissue damage that is the hallmark of the ANCA-associated vasculitides. Recombinant activating gene 2 (RAG-2)–deficient mice that receive antimyeloperoxidase antibodies develop clinical features consistent with ANCA-associated vasculitis, including crescentic glomerulonephritis and systemic necrotizing vasculitis (57). In humans, the evidence is indirect. Propylthiouracil is known to accumulate within neutrophil granules, and may lead to a drug-induced ANCA-associated vasculitis, possibly by increasing the immunogenicity of myeloperoxidase (leading to the characteristically high titers of antimyeloperoxidase antibodies seen in this disease) (58).

With regard to the specific role of ANCA, the general hypothesis is that the antibodies induce a necrotizing vasculitis by inciting a respiratory burst and degranulation of leukocytes (neutrophils and monocytes), leading to endothelial injury. The initial events in the process require the priming of leukocytes by cytokines and perhaps other stimuli, leading to the expression of PR3 and myeloperoxidase on the cell surface.

The effects of ANCA are determined by the state of neutrophil activation. ANCA may constitutively activate primed neutrophils and promote binding of the primed neutrophils to the vascular endothelium, degranulation, and the release of neutrophil chemoattractants, hence creating an auto-amplifying loop.

In addition to ANCA, multiple other elements of the immune system participate in the pathophysiology of these diseases. The autoantibody response that produces ANCA probably follows the exposure of a cryptic epitope. The antibody response may then generalize to the rest of the molecule by epitope spread. This hypothesis implies a prominent role for the T cell in the pathogenesis of the ANCA-associated vasculitides. Moreover, most patients with ANCA-associated vasculitides produce isotype-switched immunoglobulin G ANCA, implying a secondary immune response driven by T cells. The number of activated B cells, however, correlates with the Birming-

ham Vasculitis Activity Score and the extent of disease (59), which supports the hypothesis that B lymphocytes are involved in the generation of pathogenic ANCA.

Proteinase 3 and myeloperoxidase have been observed within glomeruli in renal disorders associated with neutrophilic infiltrates, but not in normal kidneys, implying that changes in the local environment may play an important role in determining the distribution of organ involvement in these diseases.

ANCA are only a piece of a much larger puzzle. In the Churg-Strauss syndrome, for example, the special role played by the eosinophil has not been elucidated adequately. Moreover, the presence of ANCA does not inevitably lead to vasculitis (60). The recent advances in this field are impressive, but highlight the need for further research on the basic pathogenetic mechanisms of these diseases.

DIFFERENTIAL DIAGNOSIS

Because of the multiorgan system nature of the ANCA-associated vasculitides, the differential diagnosis of these diseases is lengthy. One frequently challenging task is the differentiation of these diseases from other forms of vasculitis. Indeed, clear distinctions are often impossible between Wegener's granulomatosis and microscopic polyangiitis, since granulomatous inflammation is not detected on all biopsy specimens from patients with Wegener's granulomatosis. Distinguishing the ANCA-associated vasculitides from other forms of vasculitis is often more critical because the specific treatments differ.

In addition, the ANCA-associated vasculitides must be distinguished from a host of other disorders associated with inflammation and multiorgan system dysfunction (Table 5), including diseases that have a similarly protean ability to affect numerous organs. Numerous disorders may mimic the destructive upper airway disease seen in Wegener's granulomatosis. Infection (mycobacteria, fungi, actinomycosis, and syphilis), malignancy (squamous cell carcinoma and extranodal lymphoma), or illicit drug use (intranasal cocaine or the smoking of crack) may all create diagnostic dilemmas. Because granulomatous infections of the lung (e.g., mycobacteria or fungi) may also cause vasculitis and necrosis, the diagnosis of Wegener's granulomatosis should not be based on lung biopsy specimens until special stains and cultures for infection are negative.

The Churg-Strauss syndrome has an additional major branch of its differential diagnosis because of the eosinophilia associated with the disease. Allergic bronchopulmonary aspergillosis, chronic eosinophilic pneumonia, eosinophilic gastroenteritis, the hypereosinophil syndrome, and eosinophilic leukemias must all be excluded.

Table 5. Differential Diagnosis of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis

Another form of ANCA-associated vasculitis
    Wegener's granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis, drug-induced ANCA-associated vasculitis, or renal-limited vasculitis
Another form of vasculitis. Typical vasculitic mimickers:
    Polyarteritis nodosa, Henoch-Schönlein purpura, cryoglobulinemia, antiglomerular basement membrane disease
Systemic inflammatory disorders associated with autoimmunity
    Systemic lupus erythematosus, sarcoidosis, inflammatory bowel disease, relapsing polychondritis
Infection
    Endocarditis, sepsis, deep fungal infections, mycobacteria (*Mycobacterium tuberculosis* and *Mycobacterium avium-intracellulare*), actinomycosis, syphilis
Malignancy
    Lymphomatoid granulomatosis, lymphoma, Castleman's disease, lung tumors
Hypereosinophilic disorders
    Allergic bronchopulmonary aspergillosis, chronic eosinophilic pneumonia, eosinophilic gastroenteritis, hypereosinophil syndrome, eosinophilic leukemia
Miscellaneous
    Idiopathic pulmonary alveolar hemorrhage, illicit drug use (intranasal cocaine, smoking of crack)

ANCA = antineutrophil cytoplasmic antibody.

Finally, after patients have begun treatment for an ANCA-associated vasculitis, the recurrence of symptoms suggesting an ongoing or recurrent inflammatory process indicates a careful search for an opportunistic infection, including repeat tissue biopsies in some cases.

TREATMENT

Current choices for treatment in Wegener's granulomatosis are based on the classification of patients into the categories of either severe or limited disease. Severe Wegener's granulomatosis constitutes an immediate threat either to the function of a vital organ or to the patient's life. Conversely, limited Wegener's granulomatosis consists of disease manifestations that do not pose such threats.

Severe Wegener's granulomatosis requires urgent treatment with cyclophosphamide and high doses of glucocorticoids. A longitudinal study from the National Institutes of Health (NIH) employed a combination of cyclophosphamide (2 mg/kg/d, with doses reduced for patients with renal dysfunction) and glucocorticoids (1 mg/kg/d, tapered over an average of 1 year) (8). More than 90% of patients improved substantially on this regimen, and 75% achieved disease remissions, many of

which lasted a minimum of several years. Approximately 40% of the patients had no disease flares during a mean follow-up of more than 6 years. Unfortunately, because of the prolonged courses of cyclophosphamide used in that series, long-term morbidity from the treatment (as well as the disease) was substantial. Because of its tendency to involve such major organs as the kidneys, lungs, and peripheral nerves in a severe fashion, microscopic polyangiitis (like Wegener's granulomatosis) usually requires both glucocorticoids and a cytotoxic agent from the outset of therapy for disease control.

Clinical practice regarding the use of either daily or intermittent (e.g., monthly intravenous) cyclophosphamide varies from center to center. In Wegener's granulomatosis, daily cyclophosphamide may be more likely to result in durable remissions (20,61), but is also associated with a greater number of side effects (62). Consequently, meticulous monitoring, particularly of the white blood cell count, is essential. Measuring complete blood counts every 2 weeks is appropriate for patients treated daily with cyclophosphamide. The induction of neutropenia is not required to achieve a therapeutic effect. Cyclophosphamide should be withheld temporarily if the white blood cell count falls below 4.0 x 10^9/L. Treatment may be reinstituted at a lower dose after the resolution of neutropenia.

The Current Approach

In recent years, a new standard of care for the treatment of the ANCA-associated vasculitides has emerged (63). Many centers now employ shorter courses of induction treatment with cyclophosphamide (e.g., 3 to 6 months), followed by longer periods of treatment with either azathioprine (64) or methotrexate (65) to maintain disease remission. The optimal length of treatment with methotrexate or azathioprine is not clear, but continuation of these medications for at least 1 year after remission is reasonable in most patients. For patients who demonstrate propensities to flare, long-term use of the least toxic drug for the maintenance of remission may be appropriate. This may include methotrexate or azathioprine, and perhaps a low dose of prednisone (e.g., 5 mg/d).

Not all patients need to be treated with cyclophosphamide. Among patients with limited Wegener's granulomatosis, for example, remission is induced in approximately three fourths of patients with the use of methotrexate (up to 25 mg/wk) and glucocorticoids alone. Moreover, many patients with Churg-Strauss syndrome may be treated effectively with glucocorticoids alone, although cyclophosphamide or other cytotoxic agents should be considered for severe cases resulting in mononeuritis multiplex or cardiac dysfunction. In all cases, the choice of therapy should reflect the severity of the disease manifestations.

Other Potential Medical Treatments in ANCA-Associated Vasculitis

The use of trimethoprim-sulfamethoxazole as a treatment for Wegener's granulomatosis is controversial. Although it may have some role in maintaining disease remission in patients with histories of upper respiratory tract involvement (66), the use of trimethoprim-sulfamethoxazole alone is not appropriate.

A wide array of other therapies, such as plasmapheresis, intravenous immunoglobulin, mycophenolate mofetil, and leflunomide, have been employed in small numbers of patients, but so far there are insufficient data to judge their efficacy. Preliminary studies of tumor necrosis factor inhibitors have shown some promising results (67–69), but the results of more definitive studies are expected (70).

Nonmedical Interventions

Once scarring and fibrosis are well established in the subglottic region, airway narrowing may be due to the progression of scar tissue rather than to Wegener's granulomatosis–related inflammation. In such cases, subglottic stenosis responds poorly to immunosuppressive therapy, and the most effective therapeutic approach to this problem is laryngoscopic dilatations of the airway, augmented by intralesional corticosteroid injections (71). Serial procedures are often required. If severe subglottic stenosis precludes a safe dilatation procedure, a patent airway should first be secured by a tracheostomy. Wegener's granulomatosis often leads to chronic naso-sinus dysfunction. Regardless of disease activity, most patients require multiple daily saline irrigations to minimize the accumulation of secretions and crusts, and to reduce the incidence of secondary infections. Persistent or recurrent infections may require surgical drainage. Distinguishing between worsening sinus disease caused by active Wegener's granulomatosis and superinfection may be difficult. In the absence of a prompt response to antibiotics, surgical drainage and biopsy are often required for a more definitive diagnosis.

COURSE AND PROGNOSIS

In contrast to the situation in the first 40 years following the descriptions of the ANCA-associated vasculitides, these diseases are now highly treatable. Unfortunately, disease relapses are a major threat. Microscopic polyangiitis and the Churg-Strauss syndrome are somewhat less likely than Wegener's granulomatosis to flare after the achievement of remission. The percentages of patients with those diseases who suffer disease flares after appropriate courses of treatment have been estimated to be about 25% to 40%.

Even with therapy, mortality and morbidity are substantial. In a cohort of 158 patients followed at the NIH

from the late 1960s through the early 1990s (72), 12% of deaths were due to either the disease or complications of treatment, and 86% suffered permanent disease-related morbidity, including chronic renal insufficiency (42%), end-stage renal disease requiring dialysis (10%), hearing loss (35%), nasal deformity (28%), tracheal stenosis (13%), and visual loss (8%). Many patients incurred more than one type of permanent morbidity. In a more recent retrospective study of 246 patients with ANCA-associated renal vasculitis (73), cumulative patient survival at 5 years was 76%. There was an 18% mortality rate at 1 year, however, with infections as a major cause of death. In this cohort, mortality was associated with age older than 60 years, the development of end-stage renal failure, and an initial serum creatinine level greater than 2.26 mg/dL.

Much of the morbidity in the ANCA-associated vasculitides relates to prolonged courses of immunosuppression, particularly the need to re-treat patients who suffer multiple relapses. In the 1229 patient-years of follow-up in the NIH series, only 46% of these years were spent in remission. Serious infections occurred in 46%. Other morbidities included drug-induced cystitis caused by cyclophosphamide (43%), increased risk of malignancy (particularly bladder cancer, leukemia, and lymphoma), infertility (57% of women with childbearing potential), and a host of side effects related to the use of glucocorticoids.

THE FUTURE

The ANCA-associated vasculitides remain challenging in both diagnosis and treatment. Their many clinical nuances and the potential toxicities of current therapies require considerable expertise for successful management. Multicenter collaborations, such as those that have been conducted in both North America and Europe in recent years, have yielded important new insights. Such collaborations, combined with translational research occurring between clinical investigators and basic scientists, offer substantial hope for the development of safer and more effective therapies for these conditions.

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