Wegener’s Granulomatosis

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Cover Illustration by Christine Schaar
I. INTRODUCTION

Wegener’s granulomatosis (WG) is a serious idiopathic systemic necrotizing granulomatous vasculitis characterized by inflammation of the upper and lower respiratory tracts and often associated with glomerulonephritis. The other idiopathic vasculitides affecting lungs are Churg-Strauss syndrome and necrotizing sarcoid granulomatosis. Secondary pulmonary vasculitides, such as bronchocentric granulomatosis (bronchial and bronchiolar granulomatous inflammation related to allergic bronchopulmonary aspergillosis), lymphomatoid granulomatosis (angiocentric lymphoproliferative disorder), and diffuse pulmonary hemorrhage are included in a broader differential diagnosis.

II. EPIDEMIOLOGY

The estimated annual incidence of WG is 8.5 cases per million population. Its incidence peaks in the fourth to fifth decades of life, but it has also been found in children as young as 3 months. Men are slightly more commonly affected than women. It has been reported in all races, but individuals of northern European descent have a higher incidence. Seasonal peak has been seen in the winters. A gradual increase in the incidence may be the result of improved diagnostic techniques and increased awareness of the disease.

II. PATHOGENESIS

The etiology of WG has not been determined. However, hypersensitivity reactions to infection with Staphylococcus aureus and parvovirus B-19 have been postulated to stimulate production of cytokines. Antineutrophil cytoplasmic antibodies (ANCAs) activate cytokine-primed neutrophils expressing proteinase 3 (PR3) and myeloperoxidase (MPO) on their cell membrane. This induces an oxygen radical burst, contributing to endothelial and tissue damage. In animal models, the presence of ANCAs has been indirectly linked with the pathogenesis of WG.

II. CLINICAL PRESENTATION AND EVALUATION

CASE 1 PRESENTATION

Patient 1 is a 54-year-old white woman who is admitted to the hospital with a 4-week history of progressive dyspnea on exertion, recurrent bouts of hemoptysis, right pleuritic chest pains, and a low-grade fever. She has had a left temporal headache for 1 week with blurring of vision and a red, painful right eye. Other symptoms include generalized body aches, painful mouth ulcers, and tiredness. She is anorexic and has lost 12 lb.

She has a 45-pack-year history of smoking but does not use alcohol or recreational drugs. Six years ago she...
was diagnosed with giant cell arteritis (GCA) and polymyalgia rheumatica, which were associated with sudden blindness in her left eye. She was treated with prednisone for 2 years. Most of her symptoms resolved, but the visual loss persisted. Over the ensuing 4 years, she had recurrent attacks of otitis media on the left side, requiring frequent courses of antibiotics and eventually ear surgery, leaving her with a sensory-neural hearing deficit in her left ear (80% hearing loss). She also has a history of chronic sinusitis and has experienced occasional bouts of wheezing and dyspnea over this period. She has had no recurrence of her presumed GCA and has not required steroids since her initial course of steroid therapy.

On examination, she is dyspneic and appears ill. She is in atrial fibrillation, with a heart rate of 110 bpm. Blood pressure is 145/80 mm Hg. Respiration rate is 16 breaths/min and temperature is 99.2°F. Her right eye is painful and red, with a dilated but reactive pupil. She is blind in the left eye; funduscopic examination shows optic atrophy. She has superficial mouth ulcers and her nares are erythematous. Bronchial breathing is evident over the apex of the left lung, and a few crackles can be heard at the base of the right lung. Small vasculitic lesions (approximately 5 mm) are present on her shins.

A computed tomographic (CT) scan of the thorax shows bilateral hilar and mediastinal adenopathy with multiple lung nodules. Two of the nodules are cavitat ed. Laboratory data for patient 1 are shown in Table 1. The differential diagnosis in this patient includes GCA, WG, tuberculosis, malignancy, sarcoidosis, and fungal infection.

The presence of cytoplasmic (c) ANCA and microscopic hematuria warrants a histopathologic examination to characterize the vasculitic process in this patient. A right temporal artery biopsy and an open lung biopsy are performed and confirm the diagnosis of WG.

- What clinical manifestations frequently occur in WG? Does this case describe a typical presentation?
- What is the role of ANCA serology in the diagnosis of WG?
- What is the characteristic histopathologic lesion of WG?

**DISCUSSION**

WG affecting the temporal artery masqueraded as GCA on patient 1’s initial presentation. The earlier presumed diagnosis of GCA (temporal artery biopsy was not performed initially) was incorrect. Vasculitis sometimes presents as an overlap syndrome, and other vasculitides may be mistaken for WG. However, serology and a temporal artery biopsy may be helpful in establishing the correct diagnosis. Increasingly diverse presentations of WG are being reported in the literature.

No definitive laboratory tests are available for the diagnosis of WG. However, laboratory data are helpful in classification and further evaluation of the disease extent. Commonly performed tests include ANCA testing, complete blood count, erythrocyte sedimentation rate, C-reactive protein level, and a comprehensive metabolic profile and urinary analysis (Table 1).

**CLASSIFICATION**

WG can be classified based on organ involvement or ANCA serology.

**Limited Versus Classic Disease**

Classic (generalized) WG affects lungs, kidneys, ears, nose, upper airways, and other organs. Limited WG involves the respiratory system without affecting...
the kidneys. Kidney biopsy in asymptomatic patients with limited WG may still show characteristic changes of focal glomerulonephritis, and many patients with limited disease do eventually develop kidney involvement during the course of their disease.

ELK Classification

This system is based on organ system involvement, occurring either singly or in combination (E = ear, nose, throat, sinuses; L = lungs; K = kidneys). This classification has helped in understanding the course of the disease and has prognostic and therapeutic implications. Based on this classification, a disease extent index has been postulated (see Monitoring of Disease).

ANCA Serology Classification

Disease may be classified as ANCA-positive (up to 90% of generalized WG cases) or ANCA-negative. ANCA-positive cases may be further classified based on whether the cytoplasmic (c-ANCA) or the perinuclear (p-ANCA) staining pattern is evident.

CLINICAL FEATURES

WG is a multifaceted disease with protean clinical and diagnostic features (Table 2). It is often misdiagnosed or diagnosed late with serious consequences. Physicians should have a high index of suspicion to facilitate a diagnosis of WG. Constitutional symptoms (eg, fever, malaise, night sweats, weight loss) are prominent in patients with generalized WG.

### Table 2. Clinical Features of Wegener’s Granulomatosis

<table>
<thead>
<tr>
<th>Organ (percent involvement)</th>
<th>Symptoms and Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lungs, pleura (85%)</td>
<td>Solitary or multiple nodules, cavitation, infiltrates, atelectasis, collapse, alveolar hemorrhage, pleural effusion, inflammatory pseudotumor</td>
</tr>
<tr>
<td>Kidney (77%)</td>
<td>Proteinuria, microscopic hematuria, focal segmental necrotizing glomerulonephritis, rapidly progressive glomerulonephritis, renal insufficiency, renal failure</td>
</tr>
<tr>
<td>Nose (60%-80%)</td>
<td>Epistaxis, nasal crusting, chondritis, septal perforation, saddle nose deformity</td>
</tr>
<tr>
<td>Sinuses (60%-80%)</td>
<td>Mucosal thickening, pansinusitis, bone destruction</td>
</tr>
<tr>
<td>Ear (60%)</td>
<td>Serous otitis, sensory-neural deafness, mastoiditis</td>
</tr>
<tr>
<td>Trachea, bronchi (60%)</td>
<td>Subglottic stenosis, mucosal ulceration, inflammatory pseudotumor, bronchomalacia, dyspnea, stridor, wheezing</td>
</tr>
<tr>
<td>Skin (50%)</td>
<td>Urticaria, papules, vesicles, erythema, petaechiae, pyoderma gangrenosum, palpable purpura</td>
</tr>
<tr>
<td>Orbit (40%-70%)</td>
<td>Conjunctivitis, episcleritis, corneoscleral ulceration, uveitis, retinal vasculitis, ophthalmoplegia, optic neuropathy, central artery occlusion, orbital pseudotumor, dacryocystitis, lacrimal duct stenosis</td>
</tr>
<tr>
<td>Central nervous system (33%)</td>
<td>Multiple mononeuropathy, cranial nerve palsies, peripheral neuropathies, cerebral infarcts, seizures, transverse myelitis</td>
</tr>
<tr>
<td>Joints (30%)</td>
<td>Arthralgia, symmetric polyarthritis of small and large joints</td>
</tr>
<tr>
<td>Oral cavity (30%)</td>
<td>Jaw pain, hyperplastic gingivitis, ulcerations</td>
</tr>
<tr>
<td>Gastrointestinal tract (&lt; 10%)</td>
<td>Erosive esophagitis, bowel perforation</td>
</tr>
<tr>
<td>Genital tract (&lt; 10%)</td>
<td>Orchitis, epididymitis, prostatitis</td>
</tr>
<tr>
<td>Heart (&lt; 10%)</td>
<td>Coronary arteritis, myocardial infarction, aortic/mitral valvulitis, pericarditis, pancarditis</td>
</tr>
<tr>
<td>Salivary glands (&lt; 10%)</td>
<td>Swelling</td>
</tr>
<tr>
<td>Spleen (&lt; 10%)</td>
<td>Splenomegaly, splenic infarcts</td>
</tr>
<tr>
<td>Breast (rare)</td>
<td>Inflammatory pseudotumor mimicking breast cancer</td>
</tr>
<tr>
<td>Pituitary gland (rare)</td>
<td>Diabetes insipidus</td>
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</tbody>
</table>

Respiratory System Involvement

Common clinical manifestations of respiratory system involvement are listed in Table 2. Parenchymal involvement may manifest as multiple nodules that may cavitate. Healing usually occurs without scarring.

Differential diagnosis includes primary or metastatic malignancy, lymphomatoid granulomatosis, necrotizing sarcoid granulomatosis, and fungal or Nocardia infection. Airway lesions may heal by scarring, leading to subglottic, tracheal, or bronchial stenosis. Flow-volume loops may be helpful in detecting early obstructive changes in major airways.

Although uncommon, hilar adenopathy and mediastinal masses have been described in 2% of patients with WG, and a diagnosis of WG should not be dismissed because of hilar or mediastinal lymphadenopathy. Enlarged lymph nodes associated with WG may regress in size after 3 months of therapy. Endobronchial disease resulting in atelectasis of either a lobe or the whole lung and pleural effusions/thickening are other uncommon radiologic features of WG.

Renal Involvement

Kidneys are classically affected in the generalized form of WG (Table 2). Some patients with the c-ANCA staining pattern have nongranulomatous pulmonary renal syndrome with alveolar capillaritis; some have polyarteritis nodosa without respiratory tract involvement, and others may have glomerulonephritis only.

Patients with the p-ANCA staining pattern have a higher frequency of renal-limited disease. Occasionally, lungs are also involved but there is no associated granulomatous vasculitis.

Ocular Involvement

Ocular involvement is common in both localized and classic WG. Orbital lesions are usually bilateral and are irreversible if not treated promptly. Scleral involvement can lead to staphyloma. Only 60% of patients with localized orbital involvement have c-ANCAs.

Imaging studies, including CT scan and magnetic resonance imaging, are very useful in assessing orbital involvement in WG. Orbital biopsy is invaluable in patients whose disease is undiagnosed. Radiation therapy may be needed in advanced cases of proptosis.

LABORATORY FEATURES

Histopathology

Histopathologic presence of necrotizing granulomatous lesions is the most specific indicator in establishing a diagnosis of WG. Characteristic features include vasculitis, necrosis, and background inflammation. Vasculitis involves medium-sized blood vessels; large vessels are usually spared. Necrotizing granulomata are replete with multinucleate giant cells and are typically suppurative with numerous neutrophils. Demonstration of classic lesions is less common and depends on the biopsy (site and size) and use of immunosuppressive therapy.

ANCA Serology

ANCA evaluation requires both (1) an indirect immunofluorescence assay of the patient's serum on ethanol-fixed neutrophils, and (2) enzyme-linked immunosorbent assays (ELISAs) for the presence of antibodies to the 2 principal ANCA targets: MPO and PR3. The c-ANCA staining pattern results from antibodies to PR3, and the p-ANCA staining pattern (actually an artifact of ethanol fixation) is produced by antibodies to MPO and several other antigens. Table 3 shows various vasculitides with positive ANCA serology.

Although ANCA testing is an essential step in the diagnosis of WG, a negative test result does not rule out the diagnosis, because of the low specificity of the test. The usefulness of ANCA testing in the diagnosis of WG varies with the clinical setting and the experience of the laboratory in conducting such tests. Most patients with WG have c-ANCAs, but a small number of WG patients have p-ANCAs. c-ANCAs are present in only 50% of WG patients in whom vasculitis is absent.

A positive c-ANCA result does not obviate a tissue diagnosis. ANCA positivity may be detected in several disorders, including infections (eg, AIDS, tuberculosis, bacterial endocarditis, pneumonia), inflammatory diseases (eg, inflammatory bowel disease, connective tissue disorders, autoimmune hepatitis), and malignant tumors (eg, carcinoma of the lung, lymphoma, renal cell carcinoma, atrial myxoma). The predictive value of a positive ANCA test result for the diagnosis of WG increases with the presence of c-ANCAs, the presence of a high titer of anti-PR3, and the absence of antinuclear antibodies.

DIAGNOSTIC CRITERIA

Classic necrotizing granulomatous lesions are present in fewer than 50% of WG cases. In the absence of obvious vasculitis, a correlation of clinical, pathologic, and serologic findings may facilitate early recognition of the disease.

In the presence of vasculitis, the American College of Rheumatology (ACR) diagnostic criteria help to differentiate WG from other forms of vasculitis (Table 4). However, these criteria do not definitively establish a diagnosis of WG in a given patient. Additionally, these criteria were derived before ANCA testing was widely available.

In 1992, the Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis (CHC-1992) defined...
WG as “granulomatous inflammation involving the respiratory tract, with necrotizing vasculitis affecting small- to medium-sized vessels” commonly associated with necrotizing glomerulonephritis and the presence of ANCAs. When the CHC-1992 definition is used, histopathologic documentation of granulomatous involvement of the respiratory tract is not mandatory. Radiographic or clinical evidence that is highly suggestive of a granulomatous pathology may be sufficient to make a diagnosis of WG.

Neither the ACR criteria nor the CHC-1992 definition addresses the problem of incomplete presentations of the disease.

DIFFERENTIAL DIAGNOSIS

Giant Cell Arteritis

GCA, or cranial arteritis, is a vasculitic inflammatory condition involving mainly the large- and medium-sized arteries. GCA typically affects white people older than 50 years. Blindness in GCA is uncommon, occurring only in 10% of the cases; it is usually subacute. Sudden blindness should raise the possibility of a thromboembolic phenomenon.

Vasculitis affecting the temporal artery can be the initial presenting symptom in WG. Nodular lesions that are occasionally identified on chest radiograph in patients diagnosed with GCA are probably signs of a missed diagnosis of WG. Pulmonary symptoms in GCA, occasionally the presenting features, respond quickly to prednisone.

Churg-Strauss Syndrome

This is a primary systemic vasculitic disease characterized by severe asthma, fever, and eosinophilia. Patients with Churg-Strauss syndrome may have rhinitis, pericarditis, and neuritis. Skin biopsy of the vasculitic lesion typically shows eosinophilic infiltration. Eosinophilia is an uncommon feature of WG.

Microscopic Polyangiitis

Microscopic polyangiitis is a necrotizing vasculitis of the small vessels. It is a variant of polyarteritis nodosa (PAN) and is usually associated with necrotizing glomerulonephritis, pulmonary capillaritis, and hemorrhage. Asthma and hypertension are typically absent in microscopic polyangiitis, and neuropathy is less common than in PAN. Microscopic polyangiitis is more common in people of southern European and Mediterranean descent.

Patients with microscopic polyangiitis often test positive for p-ANCAs and for antibodies directed against MPO. Antibodies to MPO have also been reported in patients with hydralazine-induced glomerulonephritis, anti-glomerular basement membrane disease, and in some patients with systemic lupus erythematosus. Differentiating WG from microscopic polyangiitis may be difficult at the time of initial presentation. However, a diagnosis of WG can usually be confirmed histologically by demonstration of necrotizing granulomata.

III. TREATMENT

Before effective treatments were available, WG was associated with an 80% mortality in the first year after the diagnosis. The use of immunosuppressive agents,
and cyclophosphamide in particular, has reduced the mortality rate during the first year to 13\%.5

STANDARD REGIMEN

The “standard regimen” consists of cyclophosphamide (2 mg/kg) and prednisone (1 mg/kg) for 1 month. The prednisone is tapered as the patient shows improvement. The cyclophosphamide is continued for 6 months to 1 year after remission of the clinical symptoms; it is then gradually tapered over several months before stopping. Side effects of cyclophosphamide include myelodysplasia, opportunistic infections, hemorrhagic cystitis, and gonadal dysfunction.

Drawbacks to the standard regimen include considerable treatment-associated morbidity. Also, although the remission rate under the regimen is 90\%, the relapse rate is high. The variable course of the disease warrants a stage- and activity-dependent treatment regimen, necessitating a high degree of patient monitoring.

ALTERNATIVE TREATMENTS

Because of the potentially serious side effects of cyclophosphamide and its failure in controlling the disease in some cases, several other agents have been evaluated for treatment of WG. Use of cyclosporin-A, methotrexate, or azathioprine has not been shown to be superior to the standard regimen. Intravenous immunoglobulins have been used in dialysis-dependent individuals who were resistant to immunosuppressive therapy. The role of trimethoprim/sulfamethoxazole in the treatment of WG is unclear.

MONITORING OF DISEASE

Because of the diverse disease patterns and course, treatment for WG must be individualized. A multidisciplinary team approach is required to assess the severity and extent of the disease. At this time, a combination of clinical, radiologic, and histopathologic manifestations is the most important determinant of the overall assessment of the disease.

Recurrence of WG is monitored by following ANCA levels, imaging studies, and biopsy of the involved tissues. Relapse of intrathoracic manifestations of WG is common after the drug therapy is tapered off or stopped. A delay in radiographic resolution of more than a week after reinitiation of therapy is suggestive of inadequate immunotherapy or a superimposed infection. Incidence of Staphylococcus aureus infection and Pneumocystis carinii pneumonia (PCP) are increased in patients on immunosuppressive therapy.

On CT scan, a response to immunotherapy is reflected by decreasing size and number of pulmonary nodules, thickening of cavity walls, and increased spiculation of the outer margins of pulmonary lesions. An expanding area of consolidation or the presence of an air-fluid level suggests worsening of WG. A patchy, ground-glass appearance may signify PCP or cyclophosphamide-induced alveolitis. The presence of this sign may warrant an open lung biopsy for diagnosis.

Microscopic nonglomerular hematuria in an individual on cyclophosphamide is an early sign of hemorrhagic cystitis caused by the drug.

c-ANCA Monitoring

c-ANCA titers parallel disease activity, but this is not always a reliable indicator for predicting relapse. A rise in c-ANCA titers may reflect a relapse, but such a rise may predate clinical changes by several months. Changes in titers of at least 2 dilutions are required to indicate a meaningful change in the levels of autoantibodies.

Not all c-ANCA titer increases are followed by clinical deterioration. Thus, instituting immunosuppressive therapy based solely on a rising c-ANCA titer could be unwise. Nonetheless, a rising titer is an ominous sign and patients should be monitored closely. Interestingly, the progression from limited to generalized disease, or a clinical relapse in a patient with generalized disease, is extremely unusual in the absence of c-ANCAs.

Disease Extent Index

Recently, an index has been proposed to assess the severity and the extent of the disease.6 Every organ system

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Table 4. American College of Rheumatology 1990 Criteria for the Classification of Wegener’s Granulomatosis

<table>
<thead>
<tr>
<th>Criterion*</th>
<th>Description</th>
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<tbody>
<tr>
<td>Nasal or oral inflammation</td>
<td>Painful nasal or oral ulcers or purulent or bloody nasal discharge</td>
</tr>
<tr>
<td>Abnormal chest radiograph</td>
<td>Nodules, fixed infiltrates, or cavities</td>
</tr>
<tr>
<td>Urinary sediment</td>
<td>Microscopic hematuria (&gt;5 erythrocytes/high-power field) or erythrocyte casts</td>
</tr>
<tr>
<td>Granulomatous inflammation on biopsy</td>
<td>Granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area</td>
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</table>

*The presence of 2 or more of these criteria in a patient with vasculitis supports a diagnosis of Wegener’s granulomatosis.

affected by active WG is assigned 2 points. Constitutional symptoms are allocated 1 point, with a maximum score of 21 points (Table 5). This index has been shown to have predictive value in therapeutic trials.

Another scoring system that has been validated and computerized is the Birmingham Vasculitis Activity Score (BVAS), which is based on clinical evaluation of vasculitic symptoms in the involved organs on an “intention-to-treat” basis. However, the time it takes to perform the BVAS evaluation limits its usefulness.

TREATMENT OF PREGNANT PATIENTS

Experience with WG in pregnancy is limited. However, cyclophosphamide and methotrexate have been used in the treatment of WG in the second and third trimesters without any evidence of congenital anomalies in the fetus. Trimethoprim/sulfamethoxazole should be avoided because it can cause congenital abnormalities, hemolytic anemia, and jaundice.

OUTCOMES OF TREATMENT

In a National Institutes of Health long-term follow-up study of patients treated for WG, 91% had marked improvement in their symptoms. Complete remission occurred in 75% of cases, but 50% of the remissions were associated with 1 or more relapses. Fewer than 50% of patients remained in remission over a 5-year period. Mortality rate was 13%, and almost all patients had serious morbidity, either from their disease or from side effects associated with the therapy.

IV. SUMMARY POINTS

- Wegener’s granulomatosis (WG) is a rare disease with serious consequences if it is misdiagnosed or the diagnosis is delayed. Physicians from all specialties should be familiar with the protean manifestations of WG.
- Initial localized disease may eventually involve multiple organs over time. Antineutrophil cytoplasmic antibody (ANCA)–negative localized disease is less likely to relapse and carries a better prognosis.
- Recurrent sinus or ear infections that are resistant to antibiotics should raise suspicion of WG.
- There are no unique features of WG in elderly patients or in pregnant women. Fetal abnormalities related to cyclophosphamide are less likely to occur after the first trimester of pregnancy.
Positive ANCA serology is helpful in diagnosing WG only in the presence of vasculitis. Clinical, radiographic, and histologic correlation is important in establishing the diagnosis.

Rising ANCA levels parallel the disease activity but may predate clinical deterioration by several months. Sometimes, there is no clinical worsening in spite of elevated levels. Therapy should not be guided by the ANCA levels alone.

Imaging studies are useful in establishing the diagnosis and in monitoring disease activity and recurrence.

Cyclophosphamide/ corticosteroid combination therapy is the treatment of choice. Close monitoring is important to reduce both disease- and treatment-related morbidity. Immunosuppressive therapy increases the incidence of opportunistic infection, commonly Pneumocystis carinii pneumonia and Staphylococcus aureus infection.

Long-term outcome with treatment continues to improve with better understanding of the disease.

**Board Review Questions**

1. **All of the following statements regarding giant cell arteritis (GCA) are correct EXCEPT:**
   - A) Respiratory symptoms are present in up to 25% of cases.
   - B) Cough, throat pain, and hoarseness may be the initial presenting symptoms.
   - C) Wegener’s granulomatosis (WG) can present as headache, thereby mimicking GCA.
   - D) Headache with sudden blindness is a typical initial presentation.
   - E) Chest radiograph is usually normal.

2. **Hilar adenopathy has been described in all of the following conditions EXCEPT:**
   - A) WG
   - B) Microscopic polyangiitis
   - C) Phenytoin (Dilantin) therapy
   - D) Mycoplasma pneumonia
   - E) Churg-Strauss syndrome

3. **Which one of the following conditions is LEAST likely to present with cavitating lung lesions?**
   - A) Pulmonary infarction
   - B) Churg-Strauss syndrome
   - C) WG
   - D) Sarcoidosis
   - E) Rheumatoid nodule

4. **All of the following statements concerning involvement of the major airways in WG are correct EXCEPT:**
   - A) Subglottic stenosis tends to occur in younger patients.
   - B) Tracheal stenosis of less than 9 mm can compromise airflow, requiring stent placement or operative intervention.
   - C) Tracheal cartilage is typically involved in WG.
   - D) Biopsy of the involved airways is diagnostic in only 20% of cases.
   - E) Tracheobronchial involvement may be mistaken for asthma.

5. **All of the following statements regarding antineutrophil cytoplasmic antibodies (ANCAs) are correct EXCEPT:**
   - A) ANCAs with cytoplasmic staining pattern (c-ANCAs) are present in only 50% of WG patients in whom vasculitis is absent.
   - B) c-ANCA is specifically targeted against proteinase 3.
   - C) In patients with limited WG, a positive serology for c-ANCA carries a worse prognosis.
   - D) The specificity of c-ANCA testing is laboratory dependent.
   - E) c-ANCA tests may be positive in patients with systemic lupus erythematosus and alveolar hemorrhage.

6. **Patient 2 is a 54-year-old Greek woman who is evaluated because of poorly controlled asthma requiring frequent courses of prednisone. She also reports numbness and tingling in the left thigh in a lateral cutaneous nerve distribution (meralgia paresthetica). For the past week, she has had several vasculitic lesions on her shins. She has had rhinitis all her life but has had asthma for only the past 4 years. Three months ago, she was found to have a pericardial effusion, the etiology of which was undetermined. The effusion resolved on antibiotics and the steroids that were prescribed for her worsened asthma. Her leukocyte count is 14,000/ mm³ (5400 eosinophils) and her chest radiograph shows bilateral infiltrates. She tests positive for ANCAs with the perinuclear staining pattern (p-ANCAs), with a significant rise in anti-myeloperoxidase (MPO) titers. Which of the following diseases is most likely to present with this picture?**
   - A) Microscopic polyangiitis
   - B) WG
   - C) Churg-Strauss syndrome
   - D) Henoch-Schönlein purpura
   - E) Allergic bronchopulmonary aspergillosis
7. All of the following statements regarding microscopic polyangiitis are correct EXCEPT:
   A) Presence of p-ANCAs and antibodies to MPO is a common feature.
   B) Microaneurysms are not usually seen.
   C) Necrosis of small vessels is not associated with granulomata.
   D) It is more common in individuals of southern European and Mediterranean descent.
   E) Asthma and systemic hypertension are common.

8. Patient 3 is an 86-year-old white man who is admitted for acute renal failure and epistaxis. Three months ago, he presented with a 1-week history of blood-stained white sputum and painful elbows, knees, and small joints of the hands. He had experienced malaise and anorexia for 4 weeks. There was no clinical evidence of synovitis or joint deformity. Chest radiograph, chest computed tomographic (CT) scan, and bronchoscopic studies were unremarkable. Urinalysis and renal function testing results were unremarkable. Erythrocyte sedimentation rate (ESR) was elevated (86 mm/h). In his current presentation, his c-ANCA test is positive with significantly raised proteinase-3 titers. A renal biopsy confirms a diagnosis of WG. All of the following statements concerning WG and renal disease are correct EXCEPT:
   A) Proteinuria is often the earliest abnormality detected.
   B) Focal segmental necrotizing glomerulonephritis is common but not diagnostic.
   C) Microaneurysms are characteristically seen on renal angiography.
   D) Hypertension is not common.
   E) Plasma exchange is beneficial only in dialysis-dependent cases that are refractory to immunosuppressive therapy.

9. Patient 4 is a 21-year-old man who presents with a 1-year history of recurrent progressive, bilateral eyelid swelling associated with circumcorneal injection and proptosis and persistent nasal obstruction. Head CT scan demonstrates bilateral orbital infiltration replacing the usual fat, and proptosis and swelling of the middle and inferior turbinates. A diagnosis of nonspecific sclerosing inflammation is made on orbital biopsy. Nasal biopsy shows nonspecific inflammation. ANCA testing is inconclusive and a diagnosis of WG cannot be confirmed. He is started on prednisone and his symptoms improve. The steroids are tapered over a 10-month period. Four years later, patient 4 develops nasal obstruction, dyspnea, and sore throat. Chest radiograph shows 2 parenchymal nodules at the left base of the lung. A subglottic mass is visualized and biopsied, showing only nonspecific inflammation. c-ANCA testing is strongly positive, supporting a diagnosis of WG. Patient 4 is empirically treated with prednisone and cyclophosphamide with good results. All of the following statements concerning WG involving the eye are correct EXCEPT:
   A) Ocular involvement is common in both localized and classic disease.
   B) c-ANCAs may be present in 60% of cases with localized orbital involvement.
   C) Radiation therapy may be required to treat advanced cases of proptosis.
   D) Scleral involvement can lead to staphyloma.
   E) Orbital biopsy is nondiagnostic in most cases.

10. Patient 5 is a 78-year-old white man who presents with a 7-month history of unsteadiness, right-sided tinnitus, and right-sided temporal, maxillary, and nasal pain. His ESR is elevated (90 mm/h). Biopsy of the right temporal artery shows no evidence of vasculitis. The patient is put on prednisone 40 mg/day with good response. Three months later, he develops rightsided peripheral facial hemiparesis and dysarthria. A CT scan of the temporal bones reveals a soft-tissue mass with bony destruction. His urinalysis is normal but his ESR has risen to 100 mm/h. Analysis for p-ANCA is positive, with an anti-MPO titer of 6 U. Nasal biopsy reveals necrotizing granulomatous vasculitis, confirming the diagnosis of WG. All of the following statements regarding WG in the elderly population are correct EXCEPT:
   A) Incidence of the disease increases above 60 years of age.
   B) Elderly patients with low serum albumin levels require smaller doses of prednisone.
   C) Mononeuritis multiplex is more common than in younger patients.
   D) Lung parenchymal infiltrates are more common than in younger patients.
   E) Hemoptysis as an initial presentation is less common than in younger patients.

11. Patient 6 is a 34-year-old man with WG with pulmonary and renal involvement. He responded to cyclophosphamide and steroids with good results. After 6 months, tapering of his treatment is begun. Two weeks after the taper is initiated, he presents with dyspnea and an interstitial infiltrate on chest radiograph. All of the following statements regarding diagnosis in this patient are correct EXCEPT:
A) Pneumocystis carinii pneumonia (PCP) should be considered.
B) This picture is compatible with diffuse alveolar hemorrhage.
C) The change in this patient’s condition is likely due to a recurrence of WG.
D) The incidence of pneumococcal infection is increased in patients with WG.

12. All of the following statements regarding the histopathologic evaluation of WG are correct EXCEPT:
A) Eosinophilic infiltration is characteristic.
B) Vasculitis typically involves the small- and medium-sized vessels.
C) There is an absence of sarcoid-like, non-necrotizing granulomata.
D) Biopsies of the lung and upper respiratory tract have the highest sensitivity and specificity.
E) Biopsy is far more diagnostic than serum ANCA testing.

ANSWERS

EXPLANATIONS
1. **D** Blindness in GCA is uncommon, occurring in only 10% of the cases; it is usually subacute. Sudden blindness should raise the possibility of a thromboembolic phenomenon. Vasculitis affecting the temporal artery can be the initial presenting symptom in WG. Nodular lesions that are occasionally identified on chest radiograph in patients diagnosed with GCA are probably signs of a missed diagnosis of WG.

2. **B** Though uncommon, hilar adenopathy and mediastinal masses have been described in 2% of patients with WG.

3. **B** Infections and neoplasms are important causes of cavitary lesions in the lungs. Bilateral nodules with cavitation occur in 33% of patients with WG. Patients with congesive heart failure are at a higher risk of developing cavitation following pulmonary infarction. Pulmonary cavitation in Churg-Strauss syndrome is so rare that one should rather consider infection.

4. **C** WG commonly affects the tracheobronchial tree; however, cartilage involvement is more typical of relapsing polychondritis. Flow-volume loops may be helpful in diagnosing fixed airway obstruction. Biopsy may show only nonspecific changes. Rigid bronchoscopy may be required for resection of endobronchial pseudotumors, dilatation of stenoses, and stent placement.

5. **E** Although ANCA testing is an essential step in the diagnosis of WG, a negative test result does not rule out the diagnosis, because of the low specificity of the test. The usefulness of ANCA testing in the diagnosis of WG varies with the clinical setting and the experience of the laboratory in conducting such tests. Most patients with WG have c-ANCAs, but a small number of WG patients have p-ANCAs. c-ANCAs are present in only 50% of WG patients in whom vasculitis is absent. ANCAs may be detected in several disorders, including infections (eg, AIDS, tuberculosis, bacterial endocarditis, pneumonia), inflammatory diseases (eg, inflammatory bowel disease, connective tissue disorders, autoimmune hepatitis), and malignant tumors (eg, carcinoma of the lung, lymphoma, renal cell carcinoma, atrial myxoma). Presence of c-ANCAs has not been reported in cases of lupus-associated alveolar hemorrhage.

6. **C** Asthma is not a feature of microscopic polyangiitis or Henoch-Schönlein purpura. Eosinophilia is an uncommon feature of WG. Rhinitis, pericarditis, neuritis, eosinophilia, and presence of p-ANCAs with antibodies to MPO support a diagnosis of Churg-Strauss syndrome. Skin biopsy of the vasculitic lesion in Churg-Strauss syndrome typically exhibits eosinophilic infiltration.

7. **E** Microscopic polyangiitis is a necrotizing vasculitis of the small vessels. It is a variant of polyarteritis nodosa (PAN) and is usually associated with necrotizing glomerulonephritis, pulmonary capillaritis, and hemorrhage. Asthma and hypertension are typically absent in microscopic polyangiitis, and neuropathy is less common than in PAN. Patients with microscopic polyangiitis often test positive for p-ANCAs and for antibodies directed against MPO. A small number of patients with WG are positive for p-ANCA. Differentiating WG from microscopic polyangiitis may be difficult at the time of initial presentation. However, a diagnosis of WG can usually be confirmed histologically by demonstration of necrotizing granulomata.

8. **C** This case represents insidious onset of WG rapidly developing into acute renal failure over a 3-month period. Because patient 3’s lungs and lower airways demonstrated no abnormalities on the initial bronchoscopy and chest CT scan, his blood-tinged sputum
probably resulted from upper airways involvement. Interestingly, patient 3 gave no history suggestive of upper airways involvement. Microaneurysms are typically associated with PAN rather than with WG.

9. (E) Orbital lesions are usually bilateral and are irreversible if not treated promptly. Imaging studies including CT scan and magnetic resonance imaging are very useful in assessing the orbital involvement in WG. Orbital biopsy can be valuable in patients with undiagnosed disease. Although classic necrotizing granuloma are only rarely seen, nonspecific orbital inflammation with positive ANCA serology supports a diagnosis of WG.

10. (A) No clinical features of WG are unique to the elderly, although central nervous system involvement is more common in elderly patients. The incidence of serious infection is no higher than that in younger patients with WG; however, elderly patients with WG have a higher incidence of serious infections as compared with elderly patients with other vasculitides.

11. (D) Incidences of Staphylococcus aureus infection and PCP are increased in patients with WG, but incidence of pneumococcal infection is not. Relapse of intrathoracic manifestations of WG is common after drug therapy is tapered or discontinued. A delay in radiographic resolution of more than a week after reinstitution of therapy is suggestive of either inadequate immunotherapy or a superimposed infection. A patchy ground-glass appearance may be caused by PCP or cyclophosphamide-induced alveolitis.

12. (A) Eosinophilic infiltration is classically seen in Churg-Strauss syndrome and is not a characteristic of WG. Histopathologic presence of necrotizing granuloma is the most specific lesion in establishing the diagnosis of WG. A positive c-ANCA test result is indicative of WG but does not obviate a tissue diagnosis.

REFERENCES


SUGGESTED READINGS


