Pulmonary Opacities and Glomerulonephritis in a 15-Year-Old Boy*

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A 15-year-old boy was referred for evaluation of hemoptysis and worsening dyspnea on exertion. His medical illness began 4 years previously with the onset of nausea, vomiting, arthralgia, and flu-like symptoms. A truncal rash was also noted but resolved prior to biopsy. The BUN value was 23 mg/dL, and the creatinine was 1.0 mg/dL. Urinalysis revealed an active urinary sediment, and renal biopsy demonstrated crescentic glomerulonephritis with negative immunofluorescence. Serum IgA and complement levels were within normal limits. A diagnosis of Henoch-Schönlein purpura was made, and corticosteroid therapy was initiated.

Over the next 4 years, several relapses occurred as the corticosteroid dosage was reduced. The relapses were characterized by nausea, vomiting, hypertension, and worsening renal function. On each occasion, the patient’s symptoms improved with reinstitution of high-dose corticosteroid therapy.

On current evaluation, the patient complained of the subacute onset of dyspnea on exertion, hemoptysis, sore throat, arthralgia, abdominal pain, and a rash on the lower extremities. He also complained of worsening sinus congestion and rhinorrhea. He did not have a fever or night sweats.

Physical Examination

Vital signs included temperature, 37.4°C; pulse, 86 beats per minute; respirations, 26 breaths per minute; BP, 90/50 mm Hg. The patient appeared to be moderately ill. Skin signs disclosed a purpuric rash on lower extremities. Results of examination of head, eyes, ears, nose, and throat were normal. Lung examination showed diffuse expiratory wheezing and bibasilar crackles on auscultation. Cardiac examination disclosed a regular rhythm without murmurs or gallops. Results of examination of the abdomen were normal. Extremities showed no clubbing, cyanosis, or edema.

Laboratory Findings

The WBC count was 8,200/mL with normal differential cell count; hemoglobin value, 8.8 g/dL; hematocrit, 28%; platelet count, 335,000/mL. The sodium value was 140 mEq/dL; potassium level, 6.0 mEq/dL; chloride value, 107 mEq/dL; bicarbonate value, 19 mEq/dL; BUN, 52 mg/dL; creatinine level, 3.2 mg/dL. Urinalysis disclosed a specific gravity of 1.020; pH, 5.0; blood, 2+; protein, 2+; numerous granular casts. The chest roentgenogram is shown in Figure 1.

Hospital Course

High-dose corticosteroid therapy was initiated, and bronchoscopy with transbronchial biopsies was performed. A diagnosis was established.

What is the most likely diagnosis?

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Diagnosis: Wegener’s granulomatosis (WG).

Transbronchial biopsy specimens revealed alveolar hemorrhage, granulomatous inflammation with giant cells, and capillaritis (Fig 2). The combination of these pathologic findings and a positive cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA) value of 1:500 are diagnostic of WG.

WG is a systemic granulomatous vasculitis of small arteries and veins involving the upper and lower respiratory tracts with associated glomerulonephritis. The true incidence of the disease is unknown. A limited form of WG involving only the upper and lower respiratory tracts occurs in 28% of patients. The male-female ratio is 1:1, and the mean age of presentation is 40 years with approximately 15% of patients presenting prior to the age of 19 years.

The typical clinical presentation is characterized by upper respiratory tract signs and symptoms including recurrent epistaxis, mucosal ulcerations, and septal perforation. Lower respiratory tract involvement is characterized by cough, dyspnea, hemoptysis, and pleuritis. Upon initial presentation, signs and symptoms of upper and lower respiratory involvement are present in approximately 90% of patients. The presence of tracheobronchial involvement including subglottic stenosis occurs in approximately 15% of individuals and results in long-term morbidity. Comparing childhood-onset WG with adult-onset disease, subglottic stenosis was noted to be five times more prevalent in the pediatric population with most other aspects of the disease occurring with a similar frequency.

The presence of renal involvement at initial presentation is infrequent, occurring in 18% of the cases. However, 75% of patients eventually develop signs of glomerulonephritis, usually within the first 2 years of presentation. Skin involvement varies and includes palpable purpura, ulcers, vesicles, papules, and subcutaneous nodules. Other nonspecific findings include fever, malaise, and weight loss.

The laboratory evaluation usually includes an elevated erythrocyte sedimentation rate (range, 17 to 140 mm/h), normochromic and normocytic anemia, leukocytosis, and thrombocytosis. Urinalysis typically demonstrates hematuria, proteinuria, and RBC casts. Antineutrophil cytoplasmic antibody has emerged as an important tool in the evaluation of patients with suspected vasculitis. c-ANCA is an autoantibody directed against proteinase-3 (a serine proteinase present within neutrophil azurophilic granules). Perinuclear-ANCA is mainly directed against myeloperoxidase and is associated with microscopic polyangiitis as well as other systemic vasculitides. c-ANCA is present in the majority of patients with active disease, with a sensitivity of 88% and a specificity of 98%. However, in patients with inactive disease, the sensitivity of c-ANCA decreases to as low as 65 to 70%. The c-ANCA titers rise again before a relapse.

The most common roentgenographic findings are single or multiple pulmonary nodules which have a tendency to cavitate. These nodules typically have well-defined margins and range in size from a few millimeters to 9 cm in diameter. Other less common abnormalities include pleural effusions, bilateral alveolar infiltrates (usually associated with alveolar hemorrhage), hilar adenopathy, and the presence of an aspergilloma in a preexisting cavity.

Histologically, WG is characterized by the presence of parenchymal necrosis, vasculitis, and granulomatous inflammation accompanied by a mixed infiltrate of neutrophils, lymphocytes, histiocytes, and eosinophils. The vasculitic component involves pulmonary arteries, pulmonary veins, and capillaries, and the necrotizing granulomas vary from punctate microabscesses to large geographic zones of necrosis with surrounding palisading histiocytes. Renal histologic findings in WG demonstrate focal segmental necrotizing glomerulonephritis with minimal evidence of immune complex deposition. This histologic lesion is nonspecific, but in the context of a consistent clinical picture and a positive c-ANCA value, it is highly suggestive of WG.

Diffuse alveolar hemorrhage (DAH) is an uncommon manifestation of WG, and it occurs in approximately 5% of patients. The histologic correlate of diffuse alveolar hemorrhage in WG is capillaritis. Even though the frequency of DAH in WG is low, capillaritis was observed in 35% of typical granulomatous lesions, always being focal and located adjacent to the granulomatous process. Capillaritis is
characterized by the presence of (1) fibrin thrombi occluding capillaries in the alveolar septa, (2) fibrin clots attached to alveolar septa in a sessile fashion, (3) neutrophils and nuclear dust in the interstitium and adjacent blood vessels, and (4) interstitial RBCs. However, the presence of capillaritis is not diagnostic of WG. The differential diagnosis of capillaritis can be divided into three broad categories depending upon the presence of (1) anti-basement membrane antibodies (eg, Goodpasture’s syndrome), (2) immune complexes (eg, systemic lupus erythematosus, Henoch-Schönlein purpura, and mixed cryoglobulinemia), and (3) antineutrophil cytoplasmic antibody (eg, WG, polyarteritis nodosa, and microscopic polyarteritis). The presence of DAH and a positive c-ANCA value strongly suggest the diagnosis of WG.

The standard therapy consists of low-dose cyclophosphamide (2 mg/kg/d) and prednisone (1 mg/kg/d). With this regimen, marked improvement or partial remission occurs in 90% of patients; a complete remission occurs in 70% of individuals. This regimen is continued for 12 months, and approximately 50% of the patients with complete remissions suffer at least one relapse. Treatment with 800 mg of sulfamethoxazole and 160 mg of trimethoprim twice daily appears to reduce the relapses in patients with WG in remission.

The present patient progressed to end-stage renal disease and subsequently underwent kidney transplantation. The pulmonary involvement resolved and has not recurred.

**Clinical Pearls**

1. Although the mean age of presentation is 40 years, approximately 15% of cases are diagnosed in patients prior to 19 years of age.

2. The presence of renal dysfunction at presentation is uncommon, occurring in 18% of patients, and usually is asymptomatic.

3. Renal histologic findings in WG reveal focal, segmental necrotizing glomerulonephritis, which is a nonspecific lesion.

4. Transbronchial biopsy of alveolar tissue has a low diagnostic yield in WG. If 4 to 8 biopsies are obtained with fluoroscopic guidance in sites of grossly abnormal regions of the lung, the diagnostic yield improves slightly. Ulcerative, exophytic, or stenotic tracheobronchial lesions have a higher yield of histopathologic abnormalities suggestive of the diagnosis.

5. The combination of DAH and a positive c-ANCA value is virtually diagnostic of WG.

6. The histologic correlate of DAH in WG is capillaritis.

**Suggested Readings**


