

Systemic Vasculitis in a Patient With Atopic Dermatitis, Eosinophilia, Pulmonary-Renal Syndrome, and Positive Myeloperoxidase Antibody

A Classification Conundrum

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The antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) consist of Wegener granulomatosis (WG), microscopic polyangiitis (MPA), and Churg-Strauss syndrome (CSS).¹ There often is an overlap of features in AAV patients, making the exact diagnosis challenging despite the American College of Rheumatology classification criteria and the Chapel Hill Consensus Definitions.^{2,3} We report an atypical case of AAV in a patient with chronic atopic dermatitis and eosinophilia but without a history of asthma, complicated by diffuse alveolar hemorrhage, renal insufficiency, cardiac failure, and positive myeloperoxidase (MPO) ANCA.

CASE REPORT

A 71-year-old white woman was admitted to the hospital with fatigue, dyspnea, and cough for 3 weeks. She had a history of chronic atopic dermatitis involving the hands, forearms, and face; eosinophilia since childhood; atrial fibrillation on warfarin; and nonobstructive coronary artery disease stable on metoprolol and candesartan. There was no history of asthma, drug-induced eosinophilia, parasitic infection, or nicotine use. A year before admission, computed tomographic (CT) scans showed intermittent migratory pulmonary nodules with ground-glass opacities. That year, a bronchoscopy with transbronchial biopsies of the right upper lobe showed chronic inflammation without eosinophils. Initial pulmonary function tests revealed an FEV₁ (forced expiratory volume in 1 second) of 1.54 L (62% of predicted) and FVC (forced vital capacity) of 2.15 L (66% of predicted) with an FEV₁/FVC ratio of 72% of predicted, and the DLCO (diffusing capacity of lung for carbon monoxide) was normal (84%). Laboratory evaluation revealed normal inflammatory markers, negative MPO and proteinase 3 (PR3) ANCAs, but the eosinophil count was elevated to 6600/μL and a serum immunoglobulin E (IgE) level of 3249 kU/L (0–114 kU/L). The pulmonary nodules resolved without therapy or specific diagnosis. The patient was subsequently lost to follow-up for 6 months when she presented with increasing dyspnea, recurrence of the pulmonary nodules, and ground-glass opacities on CT scan. Laboratory and infectious workup again was nondiagnostic. The patient was followed up

clinically for 4 months and finally hospitalized with apparent fulminant systemic vasculitis.

Her admission laboratory values showed a hemoglobin of 7.3 g/dL; leukocyte count of 10,170/μL with 8000 eosinophils/μL; international normalized ratio of 4.7; serum creatinine of 1.8 mg/dL (baseline, 1.1 mg/dL), which rose to 3.2 mg/dL on hospital day 3; urinalysis with 2+ proteinuria; 3+ hemoglobin; and dysmorphic red blood cells. The erythrocyte sedimentation rate was 104 mm/hr; the CRP was 5.6 mg/dL; MPO ANCA was positive at 1.36 (>1.2 positive); PR3 ANCA was negative at 0.16 (<0.80); and a serum IgE level of 4072 IU/mL (0–100 IU/mL). Her presenting chest x-ray showed numerous bilateral ill-defined nodular opacities, and a chest CT scan demonstrated diffuse ground-glass opacities and consolidation with peribronchovascular predominance (Fig.). A sinus CT scan was normal. Bronchoscopy revealed no endobronchial abnormalities but bronchoalveolar lavage showed increasing hemorrhagic aliquots. Further analysis revealed hemosiderin-laden macrophages, 60% macrophages, 39% neutrophils, and 1% lymphocytes. Bacterial, fungal, and viral stains/cultures were negative. On hospital day 4, she developed hypoxic respiratory failure and an elevation in pro-brain natriuretic peptide of 2980 pg/mL (0–400 pg/mL) requiring treatment with noninvasive positive pressure ventilation and intravenous furosemide. Infectious etiologies were excluded with negative acid fast and fungal smears and blood and sputum cultures.

Treatment with intravenous methylprednisolone (1 mg/kg per day) was initiated for 3 days for presumed AAV manifested by pulmonary-renal syndrome and congestive heart failure. Nephrology and cardiothoracic consultants both declined to perform renal and/or lung biopsy because the patient was too unstable with severe anemia and multiorgan failure on warfarin therapy. She had dramatic improvement in her multiorgan failure and was discharged

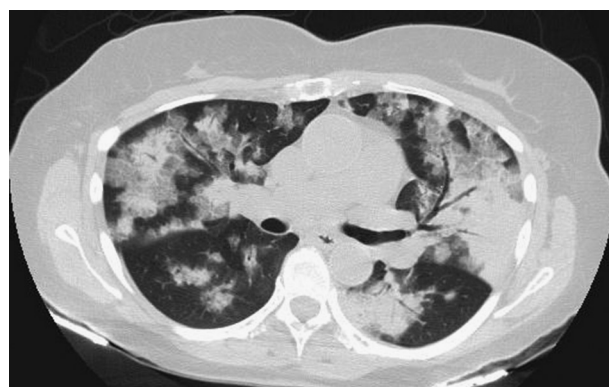


FIGURE. High Resolution Computed Tomography of the lung showing diffuse areas of consolidation with ground-glass opacification in a peribronchovascular distribution.

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on 60 mg of prednisone daily. Monthly intravenous pulse cyclophosphamide was initiated because of poor prognostic features with a 5-factor score of 3 (azotemia, proteinuria, and cardiomyopathy).⁴ A second chest CT scan, 4 months after the initiation of therapy, showed complete resolution of the ground-glass opacities and consolidation. The patient returned to work full-time. After 6 months of intravenous cyclophosphamide, she was transitioned to azathioprine and low-dose prednisone and remains in clinical remission.

DISCUSSION

Godman and Churg⁵ originally described WG, MPA, and CSS to have overlapping pathologic features despite having some unique clinical characteristics. These AAV continue to challenge clinicians because the clinical presentations and PR3 and MPO ANCA are not always predictive of the histopathologic findings on a diagnostic biopsy. Our unstable patient had clinical features suggesting CSS, WG, and MPA with a high risk of mortality based on her age and 5-factor score, resulting in the need for aggressive treatment without a tissue diagnosis.⁶

The AAV have an incidence of 8.5 cases per million in WG, 3.6 cases per million in MPA, and 2.4 cases per million for CSS.⁷ The primary clinical features in our patient that may overlap with the AAV include alveolar hemorrhage, renal insufficiency with active urinary sediment, and positive PR3 or MPO ANCA. Cardiac involvement is very rare in WG typically with valvular lesions, whereas CSS tends to be associated with cardiomyopathy and congestive heart failure. Eosinophilia is very common with CSS and asthma, but CSS has never been described with atopic dermatitis in the absence of asthma. Although uncommon, severe eosinophilia has been reported with WG but is typically associated with a positive PR3 ANCA.⁸ Speculation could suggest that the chronic eosinophilia in our patient was associated with atopic dermatitis, and the diagnosis may be MPA or WG. Eosinophilia, IgE levels, and serum eosinophil cationic protein have been useful to monitor disease activity in CSS, but they also correlate with disease activity in atopic dermatitis.⁹ The bronchoscopy findings in our patient on 2 separate occasions did not reveal the presence of eosinophils, so their elevation may not be pathogenic for AAV. Another consideration could be hypereosinophilic syndrome and malignancy, but diffuse alveolar hemorrhage or glomerulonephritis does not occur, and the eosinophilia does not respond to corticosteroid therapy.¹⁰

The American College of Rheumatology classification criteria and the Chapel Hill Consensus Definitions both emphasize the diagnostic value of tissue diagnosis, and our case illustrates this point.^{2,3} In this patient, a renal biopsy showing segmental necrotizing glomerulonephritis would support only an AAV. A lung biopsy would have been optimal to discriminate between WG, CSS, or MPA. We can only conclude clinically that our patient had an AAV with a high risk of mortality. She was treated with aggressive immunosuppressive therapy analogous to CSS with pulmonary-renal syndrome and cardiomyopathy.

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