Case Report

Antineutrophil Cytoplasmic Antibody Vasculitis Associated with *Mycobacterium avium intracellulare* Infection

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ABSTRACT. A variety of possible associations between infection and antineutrophil cytoplasmic antibody (ANCA) associated vasculitis have been reported. We describe a 75-year-old woman who presented with chronic nonproductive cough, migratory polyarthralgias, and microscopic hematuria. She had an elevated perinuclear ANCA and antimyeloperoxidase antibody. She had a positive PPD test and a cavitary lesion in the right upper lung lobe; biopsy of the lung lesion showed granulomatous vasculitis, but the culture grew *Mycobacterium avium intracellulare* (MAI). There are clinical and histiologic similarities between ANCA vasculitis and pulmonary MAI infection. Treatment of vasculitis with immunosuppressive agents could be detrimental in patients with MAI infection. Thus, when ANCA associated vasculitis is considered, mycobacterium infection should be excluded before starting immunosuppressive therapy. (J Rheumatol 2005;32:1610–2)

Key Indexing Terms:
ANTINEUTROPHIL CYTOPLASMIC ANTIBODY VASCULITIS
MYCOBACTERIUM AVIUM INTRACELLULARE INFECTION

According to the Chapel Hill international consensus definitions, which use the vessel size as the determinant for classification of vasculitides, Wegener's granulomatosis (WG), microscopic polyangiitis, and Churg-Strauss syndrome are described as small-vessel vasculitides and are commonly associated with antineutrophil cytoplasmic antibodies (ANCA). They are acknowledged as ANCA associated vasculitis syndromes[1]. The association of infections and ANCA vasculitis has been noted by various authors, especially in WG[2]. Recently we encountered a patient with ANCA associated vasculitis and pulmonary *Mycobacterium avium intracellulare* (MAI) infection, suggesting a possible association between ANCA associated vasculitis and MAI infections. We emphasize the clinical similarities between ANCA associated vasculitis and MAI infection, since treatment of vasculitis with immunosuppressive agents could be devastating in patients with MAI infection.

CASE REPORT

A 75-year-old woman was referred by her primary physician for evaluation of chronic nonproductive cough, migratory polyarthralgias, and microscopic hematuria. She had these symptoms intermittently for 5 years, but they had worsened in the past 2–3 months. Her history included hypertension and chronic kidney disease with a baseline serum creatinine of 1.4 mg/dl. Pertinent data included an elevated erythrocyte sedimentation rate (ESR; 110 mm/h), perinuclear ANCA (pANCA) 1:640 (normal < 1:20), and antimyeloperoxidase antibody (MPO) 29 (normal < 6). She also had a positive PPD test (20 mm erythema and induration) and a cavitary lesion in the right upper lung field.

She underwent a right thoracoscopic wedge resection. The histology revealed granulomatous vasculitis with focally abundant eosinophils (Figure 1). The culture of the tissue was positive for MAI (identified by DNA probe). She was treated with ciprofloxacin, azithromycin, and ethambutol for 18 months. After surgical resection and MAI treatment, she felt better and had no cough or arthralgia. ESR decreased (53 mm/h). However, hematuria was still present.

Two months after discontinuation of MAI treatment, she had episodes of hemoptysis, dyspnea, migratory polyarthritis, and new purpuric skin lesions at the second, third and fourth finger pulps and the left calf. She had worsening renal function (creatinine 2.1 mg/dl). A radiograph showed chronic fibrotic changes in both lower lung fields. A computer tomographic scan of the chest showed diffuse airspace disease in the right lower lung field with bronchiectatic change in the right upper lung field. pANCA and MPO were elevated (1:320 and 29, respectively). Cytoplasmic ANCA (cANCA) and antiproteinase 3 antibody were negative. A urinalysis revealed 1+ proteinuria and 194 red blood cells per high power field; no cast was noted. A skin biopsy from the left calf showed necrotizing vasculitis of medium and small arteries with occasional eosinophils (Figure 2). The most likely cause of the hemoptysis was felt to be alveolar hemorrhage secondary to alveolar vasculitis. However, recurrent infection could not be excluded. Bronchoscopy showed bloody secretions from the left lingular lobe with airway abnormality. No acid-fast organism was seen in bronchoalveolar lavage fluid after AFB stain. She was treated with intravenous methylprednisone (1 g/day for 3 days), followed by oral prednisone 60 mg/day and oral cyclophosphamide 2 mg/kg/day. In addition, MAI treatment was prescribed for 8 weeks until the result of the bronchoalveolar lavage culture was negative for any bacteria, mycobacteria, or fungus. She was improved, with decreased cough, no arthralgia, resolution of micro-

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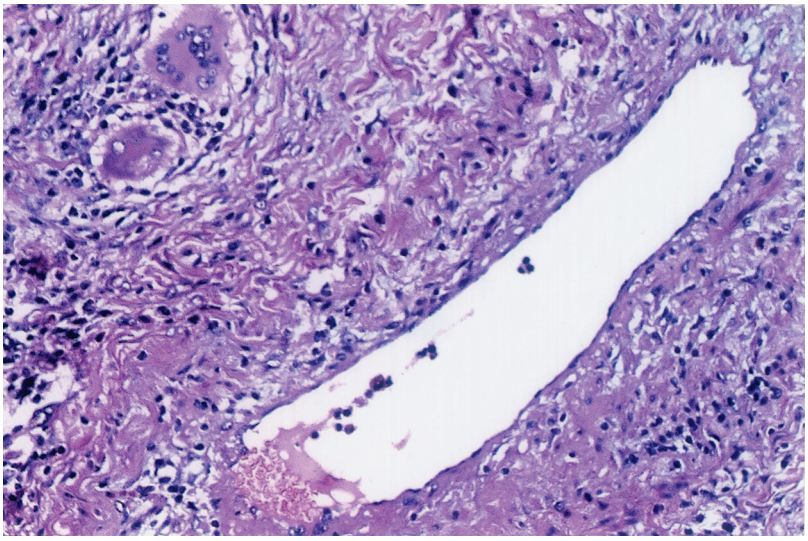

Figure 1. Lung biopsy revealed granulomatous vasculitis with focally abundant eosinophils at the time of identification of the MAI infection (original magnification × 200).

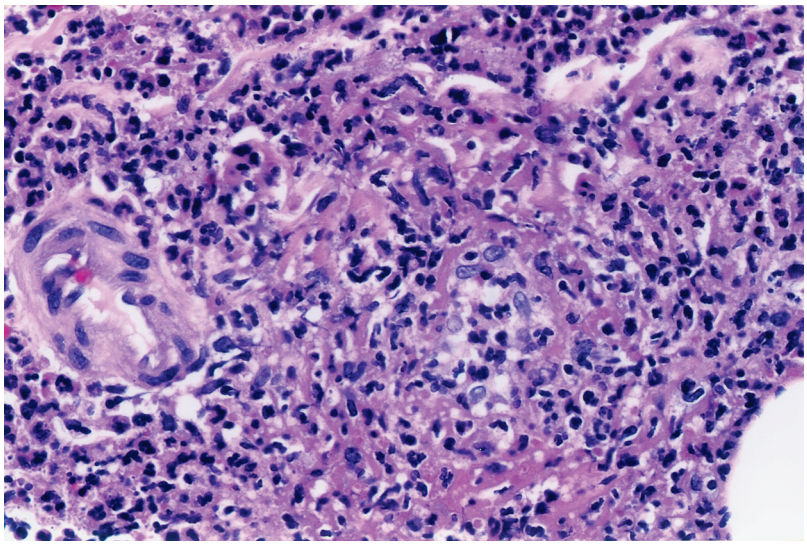

Figure 2. Skin biopsy revealed necrotizing vasculitis of medium and small arteries with occasional eosinophils (original magnification × 400).

scopic hematuria, and improvement of renal function. ANCA testing was not repeated. Prednisone was tapered and continued at 5 mg/day, and finally discontinued in 2 years. Oral cyclophosphamide was continued at 50 mg and 25 mg every other day for 2 years and then switched to azathioprine 50 mg daily.

DISCUSSION

Despite the presence of ANCA and vasculitis on biopsy, our patient was initially diagnosed with pulmonary MAI infection and was apparently successfully treated with ciprofloxacin, azithromycin, and ethambutol. Once MAI treatment was stopped, she developed symptoms of cough, hemoptysis, arthralgia, and purpuric rash. She was subsequently diagnosed with ANCA associated vasculitis, most likely WG, on the basis of increasing ESR, ANCA, and MPO, and skin biopsy that showed vasculitis with necrotizing granulomas. We review the possible associations of MAI infection with ANCA associated vasculitis.

The first possibility is that MAI infection might have an etiologic or precipitating role in development of ANCA with or without associated vasculitis. In several studies, respiratory tract infections or other infections were associated with increases in ANCA titers, clinical illness, or both. Pinching, *et al*[3] showed that 9/20 relapses among WG patients followed infectious episodes and 10/18 patients studied had a history of chronic suppurative infection of the respiratory tract, long predating the onset of the WG. Similar observations were made by Sitara, *et al* in the study of 4 ANCA-positive patients with necrotizing vasculitis; 2/4 patients had history of chronic bronchial suppuration antedating the vasculitis[4].

Stegeman, *et al* found that chronic nasal carriage of

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Staphylococcus aureus among 57 patients with WG was associated with relapses of the disease[5]. Subsequently, Stegeman, *et al* conducted a randomized, placebo controlled study comparing the incidence of relapse in WG between patients who took cotrimoxazole versus placebo and followed them for 24 months. Patients who took cotrimoxazole remained in remission (82%) more often compared to those who took placebo (60%). There were fewer respiratory tract infections and nonrespiratory tract infections in the cotrimoxazole group[6].

Toyoshima, *et al* reported a patient with WG who responded to antituberculous drugs. The patient presented with multiple pulmonary nodules and a positive PPD test. Lung biopsy showed caseous granulomas with no evidence of any pathogens. The patient was treated with antituberculous drugs, with complete resolution of pulmonary nodules. Relapse occurred after cessation of the drugs. ANCA was positive and repeat lung biopsy showed necrotizing granulomas and vasculitis consistent with WG. There were no pathogenic organisms. The patient was successfully treated with cotrimoxazole[7].

The second possibility is that patients with ANCA associated vasculitis may be predisposed to mycobacterium infection. Nakayama, *et al*[8] describe a case of MPO-ANCA vasculitis causing stenosis of the main pulmonary artery associated with pulmonary MAI infection. Several reported cases of pulmonary vascular disease in patients with congenital heart disease were associated with mycobacterium infection. Reduced recruitment of lymphocytes and macrophages from the blood to the inflammatory lesion as a result of reduced perfusion could be a predisposing factor for mycobacterium infection[8].

The third possibility is that mycobacterium infection might be mimicking a clinical presentation of ANCA associated vasculitis. Mycobacterium infections may not only cause increasing ANCA titers, but may also share similar histological features with ANCA vasculitis. De Clerck, *et al*[9] reported a case in which a patient presented with fever, a pulmonary infiltrate, and positive ANCA. The patient was initially treated with immunosuppressive therapy; a few days later, sputum cultures and a bronchial aspirate became positive for *M. tuberculosis*. Antituberculous agents were started and the patient clinically improved[9]. Harrison, *et al* reported a case of nasopharynx tuberculosis misdiagnosed as WG, and subsequently inappropriately treated with immunosuppressive drugs, which led to the development of miliary tuberculosis[10].

Although positive ANCA titers have been a valuable diagnostic marker for ANCA associated vasculitis, the result must be interpreted very cautiously. The diagnostic accuracy of ANCA was evaluated in a multicenter European collaborative study. Both cytoplasmic ANCA and perinuclear ANCA were detected by indirect immunofluorescence testing. The sensitivity of cANCA and pANCA in WG was reported as 64% and 21%, respectively. From the same study, the sensitivity of cANCA and pANCA in microscopic polyarteritis was reported as 23% and 58%[11]. ANCA could also be elevated in nonvasculitic rheumatic diseases, chronic suppurative respiratory tract infection, and lymphomas and as a result of use of medications such as hydralazine, minocycline, and propylthiouracil[4,12-15].

MAI infection may not only cause an elevated ANCA titer, but also may be associated with development of clinical systemic vasculitis. When the diagnosis of ANCA associated vasculitis is considered, mycobacterium infection should be excluded before starting immunosuppressive therapy.

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