A Case of Sinobronchial Syndrome Complicated with Myeloperoxidase Antineutrophil Cytoplasmic Antibody Associated Vasculitis: Review of the Literature

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Abstract

We report a case of long-standing sinobronchial syndrome complicated by microscopic polyangiitis (MPA) during the clinical course. The patient showed a mild elevation of myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA) 17 months prior to the diagnosis of MPA. Subsequently, her MPO-ANCA level gradually became more elevated, and finally her MPO-ANCA level peaked when purpura appeared. Histologic examination of the skin biopsy was consistent with leukocytoclastic vasculitis. Based on the pathological and clinical findings, a diagnosis of MPA was made. Corticosteroid therapy finally led to a remission of MPA with normalized MPO-ANCA titers.

Key words: sinobronchial syndrome (SBS), myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA), chronic airway diseases (CAD), microscopic polyangiitis (MPA)


Introduction

Myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA) is used as a serologic marker for the most common type of crescentic glomerulonephritis and for microscopic polyangiitis (MPA) (1). An association between chronic airway diseases (CAD) such as bronchiectasis (BE), diffuse panbronchiolitis (DPB) and sinobronchial syndrome (SBS), and vasculitis has been reported. To our knowledge, there have been 22 reported cases of CAD complicating systemic vasculitis (2-14). In these reported cases, CAD preceded the onset of vasculitis.

We report herein a case of SBS complicated by MPA during the clinical course. We were able to observe the development of MPA with the elevation of MPO-ANCA level in a patient with SBS. In addition, we reviewed the reported cases of systemic vasculitis complicated by CAD.

Case Report

A 70-year-old woman was admitted to our hospital in mid-January 2009 for the treatment of acute exacerbation of BE. BE was diagnosed when the patient was in her fifties, and she had received follow-up care at our hospital. Recently, SBS was diagnosed because BE was complicated by chronic sinusitis, but there was no evidence of immunologic abnormality. Chest X-ray and computed tomography of the chest showed cylindrical and cystic BE in bilateral lungs, predominantly in the left lower lobe (Fig. 1). Six months prior to admission, MPO-ANCA was elevated to 24 EU (normal <20 EU) without elevation of proteinase-3 antineutrophil cytoplasmic antibody. Based on the elevated MPO-ANCA level, vasculitic syndrome was suspected. However, the clinical symptoms and results of physical examination and laboratory tests did not meet the criteria for a diagnosis...
of any vasculitic syndrome at that time. Laboratory tests on admission revealed that the white blood cell count and C-reactive protein (CRP) level were elevated to 8,900/μL and 9.03 mg/dL, respectively. Sputum culture revealed the presence of Pseudomonas aeruginosa. Antibiotic therapy was effective, and the infection was resolved. However, the patient’s MPO-ANCA level was markedly elevated to 109 EU without any clinical symptoms of vasculitic syndrome.

Three months after admission, in mid-April 2009, she coughed up massive blood of 200 ml, and was emergently admitted to our hospital. Hemostatics and antibiotics effectively resolved her symptom. MPO-ANCA level at that time was still high (101 EU). Renal biopsy was done to diagnose her disease, and the findings were consistent with IgA nephropathy. Serum creatinine level was 0.80 mg/dL, and the urine gave a ++ test for blood and a + test for protein. Aspergillus antigen was positive so antifungal therapy (voriconazole) was started after this episode. After a year of the administration of voriconazole, aspergillus antigen turned to be negative. Consequently, she was followed as a patient with MPO-ANCA positive SBS.

Purpura suddenly appeared on her lower limbs three months after the second admission and was associated with a further elevation of MPO-ANCA level (146 EU) (Fig. 2). At that time proteinuria and hematuria also developed. The onset of ANCA-associated vasculitis was highly suspected, therefore a skin biopsy of the lower limb has been performed. Histology of the skin biopsy showed an infiltration of neutrophils and lymphocytes around the small arterioles and capillaries in the dermis and fragmentation of nuclei of these inflammatory cells, leading to the diagnosis of leukocytoclastic vasculitis (Fig. 3). According to pathological and clinical findings, a diagnosis of MPA was made. Prednisolone (1 mg/kg) was started and tapered down as the purpura...
and MPO-ANCA levels were gradually resolved. After the administration of corticosteroids, her hematuria and proteinuria were also ameliorated. Moreover, her occasional hemoptysis was resolved and the MPO-ANCA level normalized after 8 months of administration of prednisolone (Fig. 2).

**Discussion**

The possibility of the development of vasculitis should be considered during the management of patients with a long-standing CAD. The present case was clinically significant in that we could observe the development of MPA with the elevation of MPO-ANCA in a patient with SBS. Mild elevation of MPO-ANCA has been reported in patients with chronic bronchial suppuration (12, 15, 16). In one such study, 4 of 30 patients with DPB were positive for MPO-ANCA (12). Three of the four patients with DPB but without vasculitis showed a low titer of MPO-ANCA (10-60 EU) (12). The other DPB patient who had vasculitis showed a high titer of MPO-ANCA (442 EU). Indeed, the present case had shown a mild elevation of MPO-ANCA (24 EU) 17 months prior to the diagnosis of MPA. Then, the MPO-ANCA level became gradually elevated, and finally the MPO-ANCA level peaked (146 EU) simultaneously with the appearance of purpura. To date, 22 cases of vasculitis with preceding CAD have been reported (Table 1) (2-14), however, all of the cases were found to be elevated ANCA on the onset of vasculitis.

Thus, long-standing CAD followed by onset of ANCA-associated vasculitis strongly supports the “ANCA-cytokine sequence hypothesis” (6). CAD could cause the neutrophil destruction, which is followed by ANCA elevation (3). Moreover, ANCA leads to activation of neutrophils and degranulation by inducing inflammatory cytokines and this finally results in vascular damage. To date, there have been 22 reported cases of vasculitis following a long-standing history of CAD: 18 as BE, 3 as DPB, and 1 as SBS (Table 1) (2-14). In 15 patients for whom ANCA was measured, 11 patients showed positive p-ANCA or MPO-ANCA whereas only 2 patients showed positive c-ANCA. One possible explanation for these findings is the causative pathogens of chronic airway suppuration. Bacterial infections also have been associated with the initiation and relapse of Wegener’s granulomatosis (WG). Among these bacteria, *Staphylococcus aureus* seems to have the strongest association with WG (17). On the other hand, according to the review of the 22 reported cases, Gram-negative bacilli such as *Haemophilus influenzae* and *Pseudomonas aeruginosa* were the common causative pathogens (Table 1). Kain et al recently found that 93% of patients with active ANCA associated necrotizing glomerulonephritis, which often shows positive MPO-ANCA, had autoantibodies to human lysosomal membrane protein 2 (LAMP-2), and a major epitope of LAMP-2 is homologous to the bacterial adhesion protein FimH, which is found in Gram-negative bacteria. Actually, rats immunized with FimH developed pauci-immune necrotizing crescentic glomerulonephritis in conjunction with antibodies to rat LAMP-2 and human LAMP-2 (17). In patients with preceding CAD followed by ANCA associated vasculitis, Gram-negative bacilli are the most common causative pathogens. Consequently, long-standing airway infection might associate with the onset of p-ANCA (MPO-ANCA) associated vasculitis. Recently, Takahashi et al reported a radiologic review of 26 patients with MPA. This review revealed the presence of BE in 9 patients (35%), 4 of whom had long-standing histories (from 13 to 31 years) prior to the onset of MPA (13). Accordingly, in patients with a long-standing history of CAD or bronchiectatic changes in chest radiographic examination, careful attention should be paid for the development of vasculitis in future.

Balancing the efficacy of immunosuppression with its adverse effects is very important for the treatment of vasculitis complicated by CAD. In 86% (12 of 14) of reported cases that were treated for vasculitis, cyclophosphamide (CPA) or azathioprine was used in combination with corticosteroids (CS) (Table 1). Most of these patients improved after the induction of immunosuppressive therapy. In one case, however, CPA was discontinued due to the exacerbation of BE (8). In the present case, the clinical subtype was considered to be early systemic, and in such a condition, CS in combination with daily oral CPA is reported to be effective (17). Because the patient had taken voriconazole for pulmonary aspergillosis and sputum culture had consistently revealed the presence of *Pseudomonas aeruginosa*, we initiated therapy with prednisolone (1 mg/kg) but without CPA to avoid extreme immunosuppression. CS monotherapy finally led to a remission of MPA. Reported cases showed good prognosis for treatment of systemic vasculitis with CAD (Table 1). Likewise, Takahashi et al suggested a better prognosis in patients with MPA with CAD than in those without CAD (13). In that study, only one patient (10%) with CAD died within 90 days of the onset of MPA, while...
7 patients (43.8%) without CAD died. Avoiding an exacerbation of CAD with immunosuppressive therapy remains a therapeutic challenge in these patients. It is unknown whether CS monotherapy or CS combined with CPA is more efficacious for the treatment of systemic vasculitis with CAD. Further accumulation of cases will be necessary to clarify this point.

The authors state that they have no Conflict of Interest (COI).

References


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