Microscopic Polyangiitis Associated with Diffuse Panbronchiolitis

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Abstract

There are several case reports of systemic vasculitis associated with chronic suppurative lung diseases. We describe a 46-year-old female, previously diagnosed as having diffuse panbronchiolitis (DPB), presenting with hemosputum and dyspnea. Her serum titer of MPO-ANCA was positive together with a high titer of BPI-ANCA. Chest X-ray and chest CT scan showed pulmonary hemorrhage, and the renal biopsy specimen revealed necrotizing, crescentic glomerulonephritis. She was diagnosed as having ANCA-associated vasculitis, and more specifically, microscopic polyangiitis accompanied by DPB. She was treated with methylprednisolone pulse therapy, followed by intravenous cyclophosphamide. This case suggested a possible association with chronic bacterial infection, which may play a role in the pathogenesis of ANCA-associated vasculitis.

Key words: microscopic polyangiitis, ANCA-associated vasculitis, BPI-ANCA, diffuse panbronchiolitis, chronic suppurative lung disease

Introduction

Antineutrophil cytoplasmic antibody (ANCA) is acknowledged to be commonly associated with systemic small-sized vessel vasculitis, and circulating ANCA against myeloperoxidase (MPO-ANCA) is often used as a serological marker for ANCA-associated vasculitis syndrome, especially microscopic polyangiitis (1, 2). Microscopic polyangiitis with MPO-ANCA is considered to be frequently associated with necrotizing glomerulonephritis and pulmonary hemorrhage. There are several reports of the coexistence of systemic vasculitis and chronic suppurative lung diseases, including diffuse panbronchiolitis (DPB), bronchiectasis, and cystic fibrosis (3–8). Chronic respiratory infection may play a role in the pathogenesis of ANCA-associated vasculitis syndrome. In addition, in gram-negative bacterial infections, bactericidal/permeability-increasing (BPI) protein has been identified in the azurophilic granules in neutrophils. The ANCA against BPI, known as BPI-ANCA, identified by Zhao et al (9), was suggested to have an association with chronic infectious lung diseases. Herein, we report a case of microscopic polyangiitis associated with a long history of DPB, whose serum was positive for both MPO-ANCA and BPI-ANCA.

Case Report

A 46-year-old Japanese woman, a non-smoker, had complained of purulent sputum with recurrent pneumonia accompanied by chronic sinusitis since 1987. Her cold hemagglutinin titer was increased 64-fold (normal <32-fold). She possessed the human leukocyte antigen (HLA)-A11, which is positively associated with DPB in Korean patients, but she did not have HLA-B54, which has a significant positive association in Japanese patients (10). A chest CT scan revealed diffuse reticulonodular shadows and bronchial structures with bronchiectasis in both lung fields (Fig. 1A). She had been diagnosed as having DPB, and was treated with clarithromycin (CAM) since 1996.

In August 2000, she presented with hemosputum and dyspnea. Her chest X-ray and CT scan showed diffuse patchy opacities with centrilobular nodular lesions in bilateral lung fields. Urinalysis was positive for protein. The enzyme-linked immunosorbent assay (ELISA) titer of MPO-ANCA revealed an elevation of 108 EU (normal <10 EU), while the PR-3 ANCA was normal. These findings suggested
a diagnosis of ANCA-associated vasculitis. She was treated with methylprednisolone (m-PSL) pulse (1 g/day, 3 days), followed by a PSL at 30 mg/day. In January 2001, she suffered recurrence, and m-PSL pulse therapy was administered, followed by an initial high dose of PSL at 60 mg/day, together with intravenous cyclophosphamide (IVCY) at 300 mg/body biweekly. These treatments were effective, and her symptoms improved along with a reduction in the MPO-ANCA titer. A renal biopsy was performed in March 2001, which showed crescentic necrotizing glomerulonephritis (Fig. 2). On August 28, 2001, she complained of hemoptysis and dyspnea again, having completed a course of PSL administration at 15 mg/day, and she was admitted to our hospital.

Physical examination revealed a body temperature of 36.8 °C, and blood pressure of 150/90 mmHg. On auscultation, course crackles were audible at the bilateral lung bases. A sputum culture later grew Stenotrophomonas (Pseudomonas) maltophilia (gram-negative bacillus). The chest X-ray and chest CT scan showed diffuse patchy lesions, small nodular shadows around bronchioles in both lung fields, and ground-glass opacities around the pulmonary arteries (Fig. 1B). The laboratory findings revealed a white blood cell count of 12.2×10³/μl (83.6% neutrophils, 13.9% lymphocytes, 2.3% monocytes, 0.2% eosinophils). The C-reactive protein (CRP) was positive at 2.5 mg/dl. The ELISA titer of MPO-ANCA was positive at 28 EU (normal <10 EU), and the BPI-ANCA titer was elevated at 240 EU (normal <10 EU). Anti-glomerular basement membrane antibody and fluorescein antinuclear antibody were negative (Table 1). The patient suffered from respiratory failure, and resting arterial blood gases at room air showed a PaO₂ 58.1 Torr, PaCO₂ 41.4 Torr, and HCO₃⁻ 30.6 mEq/l. She was diagnosed as having a
recurrence of ANCA-associated vasculitis, and specifically, microscopic polyangiitis. She was treated again with m-PSL pulse therapy (1 g/day, 3 days), followed by IVCY (500 mg/body, biweekly). Then, PSL at 40 mg/day was administered, and the dose was tapered slowly. This treatment improved the clinical symptoms and laboratory findings. CRP decreased, testing negative a one week after initiation of this treatment, and a negative test for proteinuria was obtained on day 16. The titer of MPO-ANCA decreased with administration of methotrexate and IVCY (Fig. 3). In January 2003, her microscopic polyangiitis was stable with a negative titer for MPO-ANCA, although BPI-ANCA showed a high titer of over 400 EU.

Discussion

Several reports have indicated a possible correlation between ANCA-associated vasculitis and chronic airway infection. Among thirty patients with DPB, four patients were found to have serum MPO-ANCA, however it was absent in other pulmonary disease patients (11). Including this case, seven systemic vasculitis cases were previously reported, specifically, microscopic polyangiitis associated with chronic airway infectious diseases (3–8) (Table 2). Interestingly, five of the cases were Japanese patients. Over the course of 10 years, these seven cases of chronic suppurative lung diseases such as DPB, bronchiectasis or chronic bronchitis, were accompanied by systemic vasculitis and were treated by PSL, with or without cyclophosphamide. Most cases were non-smokers with a history of chronic sinusitis. Serum P-ANCA or MPO-ANCA was found in six of seven cases. The causes of chronic suppurative lung diseases were found to be gram-negative bacilli, such as *Pseudomonas aeruginosa* or *Haemophilus influenzae*, which were detected in most cases as the presumed pathogenic agent.

In the present case of chronic airway infection recurring over 13 years, *Stenotrophomonas (Pseudomonas) maltophilia* was detected as a gram-negative bacterial infection. She was diagnosed as having microscopic polyangiitis with pulmonary hemorrhage and crescentic glomerulonephritis with an increasing serum titer of MPO-ANCA, 4 years after being diagnosed with DPB. Interestingly, she had a very high titer of BPI-ANCA together with a remarkable increase in MPO-ANCA.

The cause of the ANCA-associated vasculitis including microscopic polyangiitis remains unknown, and the ANCA-cytokine sequence theory was proposed to explain the development of vasculitis. MPO-ANCA leads to an activation of neutrophils and a degradation by inflammatory cytokines, resulting in vascular endothelial damage. Recently, there was a case report of a Japanese woman with bronchiectasis, in whom both serum MPO-ANCA and BPI-ANCA were positive with persistent *Pseudomonas aeruginosa* found in her sputum. Although she was not shown to have vasculitis, both ANCA titers decreased after lung resection (12). To our knowledge, other than for the present case, there have been no case reports demonstrating microscopic polyangiitis coexisting with both BPI-ANCA and MPO-ANCA.
In a gram-negative bacterial infection, BPI-ANCA may play an important role in the autoimmune mechanism. BPI possesses 44% homology with the amino acid sequence of lipopolysaccharide (LPS) protein, and is thought to be suppressed by the LPS activity in gram-negative bacteria. BPI is also a target antigen of ANCA. Serum BPI-ANCA is frequently expressed in cystic fibrosis, chronic airway infection, and chronic inflammatory bowel disease (13). BPI-ANCA was detected in one (9%) of 11 patients with Wegener’s granulomatosis, and in 2 (29%) cases with microscopic polyangiitis. In all 3 cases, it was unclear whether MPO-ANCA was detected together with BPI-ANCA (14).

Table 2. Systemic Vasculitis Associated with Suppurative Lung Diseases

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Smoker/Non-smoker</th>
<th>Duration at onset of vasculitis</th>
<th>Chronic respiratory disease</th>
<th>Chronic sinusitis</th>
<th>Isolated bacteria</th>
<th>ANCA detected</th>
<th>Symptom</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>57</td>
<td>Female</td>
<td>ND</td>
<td>12 years</td>
<td>Bronchiectasis</td>
<td>ND</td>
<td>ND</td>
<td>P-ANCA</td>
<td>Peripheral neuropathy</td>
<td>(3)</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
<td>Male</td>
<td>non-smoker</td>
<td>17 years</td>
<td>Bronchiectasis</td>
<td>ND</td>
<td>P. aeruginosa</td>
<td>negative</td>
<td>Peripheral neuropathy</td>
<td>(4)</td>
</tr>
<tr>
<td>3</td>
<td>47</td>
<td>Female</td>
<td>ND</td>
<td>37 years</td>
<td>Bronchiectasis</td>
<td>ND</td>
<td>ND</td>
<td>P-ANCA</td>
<td>Crescentic glomerulonephritis</td>
<td>(5)</td>
</tr>
<tr>
<td>4</td>
<td>53</td>
<td>Male</td>
<td>Nd</td>
<td>11 years</td>
<td>DPB</td>
<td>+</td>
<td>S. pneumoniae H. influenzae</td>
<td>P-ANCA</td>
<td>Necrotizing glomerulonephritis</td>
<td>(6)</td>
</tr>
<tr>
<td>5</td>
<td>46</td>
<td>Female</td>
<td>non-smoker</td>
<td>18 years</td>
<td>DPB</td>
<td>+</td>
<td>P. aeruginosa</td>
<td>MPO-ANCA</td>
<td>Peripheral neuropathy</td>
<td>(7)</td>
</tr>
<tr>
<td>6</td>
<td>65</td>
<td>Female</td>
<td>non-smoker</td>
<td>36 years</td>
<td>Chronic bronchiitis</td>
<td>+</td>
<td>H. influenzae P. aeruginosa</td>
<td>MPO-ANCA</td>
<td>Renovascular hypertension</td>
<td>(8)</td>
</tr>
<tr>
<td>Present Case</td>
<td>46</td>
<td>Female</td>
<td>non-smoker</td>
<td>13 years</td>
<td>DPB</td>
<td>+</td>
<td>S. maltophilia</td>
<td>MPO-ANCA</td>
<td>Necrotizing glomerulonephritis</td>
<td>Pulmonary hemorrhage</td>
</tr>
</tbody>
</table>

ND: not determined, DPB: diffuse panbronchiolitis, MPO-ANCA: myeloperoxidase ANCA; P-ANCA: perinuclear ANCA.
Kobayashi (13) reported high serum BPI-ANCA titers in patients with DPB and bronchiectasis. In addition, the serum BPI-ANCA titer was significantly higher in patients with prolonged colonization of gram-negative bacteria. BPI-ANCA is thought to inhibit the bacterial activity of neutrophils and to prolong bacterial colonization (15). BPI-ANCA may only reflect the influences of long-term chronic airway infection. In the present case, the high titer of BPI-ANCA was unchanged, and showed a high titer throughout the active and remission clinical periods of microscopic polyangiitis, although the MPO-ANCA titer reflected her disease activity as microscopic polyangiitis. It is unclear whether BPI-ANCA plays an important role in the autoimmune phenomenon of ANCA-associated vasculitis, which may be triggered by a gram-negative bacterial infection in chronic suppurative lung disease, and resembles the deterioration of Wegener’s granulomatosis, which is triggered by a Staphylococcus aureus infection.

References