Rapidly Progressive Glomerulonephritis Associated with PR3-ANCA Positive Subacute Bacterial Endocarditis

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Abstract

Patients with bacterial endocarditis often have renal complications. This report presents the case of an elderly man with rapidly progressive glomerulonephritis (RPGN) associated with subacute bacterial endocarditis (SBE) due to Enterococcus faecalis infection. The patient was positive for anti-protease 3-antineutrophil cytoplasmic antibody (PR3-ANCA) and rheumatoid factor (RF) with hypocomplementemia. Treatment for SBE with antibiotics and the surgical replacement of the affected valves resulted in an improvement of RPGN, the disappearance of PR3-ANCA and RF, and the normalization of hypocomplementemia. This rare case suggests the importance of recognizing the cause of positive PR3-ANCA, because SBE could be an occult cause of RPGN mimicking ANCA-associated vasculitis.

Key words: antineutrophil cytoplasmic antibody (ANCA), rapidly progressive glomerulonephritis (RPGN), subacute bacterial endocarditis (SBE)

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Introduction

Antineutrophil cytoplasmic antibody (ANCA) is associated with a wide spectrum of vasculitis including Wegener’s granulomatosis, microscopic polyangiitis and Churg-Strauss syndrome (1). ANCA is also detected in some patients with infectious diseases (2, 3). The appearance of anti-proteinase 3-antineutrophil cytoplasmic antibody (PR3-ANCA) in patients with bacterial endocarditis is rare, but 7 cases of PR3-ANCA positive bacterial endocarditis complicated with renal failure (defined as a serum creatinine of 2 mg/dL or above) have been reported (4-8). These patients were confirmed to have bacterial infections such as Streptococcal species, whereas no case due to Enterococcus faecalis has so far been reported.

This report presents the first case of rapidly progressive glomerulonephritis (RPGN) associated with PR3-ANCA positive subacute bacterial endocarditis (SBE) due to an Enterococcus faecalis infection. Surgical replacement of the affected valves in combination with antibiotic treatment led to eradication of the infection followed by an improvement of the renal failure, the disappearance of PR3-ANCA and rheumatoid factor (RF), and the normalization of hypocomplementemia. This case suggests that serum PR3-ANCA could be positive in patients with SBE.

Case Report

An 83-year-old man was admitted with a 7-month history of sustained weight loss (-12 kg), general malaise without a fever and renal dysfunction. His renal function had been normal until 4 months before admission. He had been treated for diabetes mellitus for 7 years. He had no history of any recent dental work.

A physical examination at the time of admission revealed a body temperature of 36.8°C, a pulse rate of 88 beats/min and blood pressure of 120/73 mmHg. Bilateral pulmonary crackles and II/VI diastolic murmur were audible. Otorhinolaryngological tests showed no abnormalities. Laboratory studies revealed a white blood cell count of 7,200/mm3, blood urea nitrogen (BUN) of 50 mg/dL, serum

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creatinine of 3.86 mg/dL, C-reactive protein (CRP) of 12.5 mg/dL, C3 of 35 mg/dL (normal range 86-160 mg/dL), C4 of 15 mg/dL (normal range 17-45 mg/dL), CH50 of 16 U/mL (normal range 32-60 U/mL). Antinuclear antibody (ANA) was weakly positive (1:40; speckled, normal range < 40) and RF was also positive (87 IU/mL, normal range 0-26 IU/mL). The PR3-ANCA test was positive at a low titer of 11 EU (normal range <10 EU), although the myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA) test was negative. Uriminalysis gave results of 2+ for protein and 3+ for occult blood in a dipstick examination, and a microscopic examination detected more than 100 red blood cells per high-power field (Table).

Cardiac ultrasonography and serial blood cultures were performed to determine the origin of the inflammation, and prominent lesions were observed on the mitral and tricuspid valves (Fig. 1). Enterococcus faecalis was serially detected in the blood cultures. The patient was diagnosed with SBE, because he fulfilled Duke’s criteria for bacterial endocarditis (9). The patient was treated with 12 g per day intravenous ABPC (ampicillin) and 120 mg per day GM (gentamicin sulfate) for 5 weeks followed by 1,000 mg VCM (vancomycin) three times per week for 3 weeks (Fig. 2), based on the guidelines for the treatment of infective endocarditis (JCS 2008) and the results of antimicrobial susceptibility. However, his renal function declined and intermittent hemodialysis (HD) was therefore started on the 10th day of hospitalization.

The aortic, mitral and tricuspid valves were surgically resected on the 26th day of hospitalization, because inflammatory signs such as CRP did not improve and his cardiac condition worsened. The valvular cultures were sterile, probably due to the antimicrobial treatment. His physical status recovered after the operation. His renal function gradually improved and HD was finally discontinued 3 months later. Furthermore, PR3-ANCA and RF became negative, and the hypocomplementemia was resolved (Fig. 2). There has been no recurrence of SBE, no signs of systemic vasculitis and no deterioration of renal function over a 1-year follow-up.

**Table. Laboratory Data at the Time of Admission**

<table>
<thead>
<tr>
<th>WBC</th>
<th>7,200 /mm³</th>
<th>BUN</th>
<th>50 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>lym</td>
<td>3%</td>
<td>Cre</td>
<td>3.86 mg/dL</td>
</tr>
<tr>
<td>mono</td>
<td>2%</td>
<td>UA</td>
<td>6.6 mg/dL</td>
</tr>
<tr>
<td>stab</td>
<td>9%</td>
<td>Na</td>
<td>131 mEq/L</td>
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<tr>
<td>seg</td>
<td>85%</td>
<td>K</td>
<td>3.8 mEq/L</td>
</tr>
<tr>
<td>eos</td>
<td>0%</td>
<td>Cl</td>
<td>101 mEq/L</td>
</tr>
<tr>
<td>baso</td>
<td>0%</td>
<td>Ca</td>
<td>7.7 mg/dL</td>
</tr>
<tr>
<td>Hb</td>
<td>7.2 g/dL</td>
<td>IgG</td>
<td>3468 mg/dL</td>
</tr>
<tr>
<td>Hct</td>
<td>21.8%</td>
<td>IgA</td>
<td>330 mg/dL</td>
</tr>
<tr>
<td>Plt</td>
<td>8.9 x 10⁹ /mm³</td>
<td>IgM</td>
<td>246 mg/dL</td>
</tr>
<tr>
<td>RBC</td>
<td>275 x 10⁹ /mm³</td>
<td>ANA</td>
<td>1:40, speckled</td>
</tr>
<tr>
<td>Hb</td>
<td>7.2 g/dL</td>
<td>C3</td>
<td>35 mg/dL</td>
</tr>
<tr>
<td>Alb</td>
<td>2.1 g/dL</td>
<td>C4</td>
<td>15 mg/dL</td>
</tr>
<tr>
<td>ALT</td>
<td>22 IU</td>
<td>CH50</td>
<td>16 U/mL</td>
</tr>
<tr>
<td>AST</td>
<td>30 IU</td>
<td>RF</td>
<td>87 IU/mL</td>
</tr>
<tr>
<td>LDH</td>
<td>324 IU</td>
<td>MPO-ANCA</td>
<td>&lt;10 EU</td>
</tr>
<tr>
<td>CRP</td>
<td>12.5 mg/dL</td>
<td>PR3-ANCA</td>
<td>11 EU</td>
</tr>
</tbody>
</table>

**Discussion**

The detection of PR3-ANCA is highly specific for Wegener’s granulomatosis (10). However, a variety of infections, such as invasive Amebiasis, Legionnaire’s diseases, Leptospirosis and Human Immunodeficiency Virus (HIV) have been reported to cause weakly positive results for PR3-ANCA (2, 3). Wagner et al. also described an association between bacterial endocarditis and PR3-ANCA (11). To date, seven cases of PR3-ANCA positive bacterial endocarditis complicated with renal failure have been reported (4-8). Those patients were mainly confirmed to have bacterial infections such as Streptococcus species (e.g., Streptococcus viridans, Streptococcus bovis and Streptococcus morbillorum), whereas no case due to Enterococcus faecalis has ever been reported. This is the first case of RPGN associated with PR3-ANCA positive SBE due to Enterococcus faecalis infection.

The implication of the presence of PR3-ANCA in bacterial endocarditis remains unclear. However, the infectious process may induce the production of PR3-ANCA, possibly through polyclonal B-cell activation. Persistent vascular injury by a bacterial antigen may activate endothelial cells, induce the expression of cytoplasmic enzymes by polymor-
It is clinically difficult to achieve a differential diagnosis between the ANCA-positive bacterial endocarditis and non-bacterial endocarditis due to ANCA-associated vasculitis. However, it is likely that hypocomplementemia and the presence of at least one other species of autoantibodies such as RF, ANA and cryoglobulin are useful markers of ANCA-positive bacterial endocarditis. Most cases of ANCA-positive bacterial endocarditis disclose a subacute course with Strep-tococcus viridans bacteremia (12). In addition, the titers of PR3-ANCA are generally low and normalize following the resolution of bacterial endocarditis (4, 7, 8). Physicians mainly treat ANCA-positive bacterial endocarditis with antibiotics and/or surgical procedures (4, 8). Immunosuppressive therapy remains controversial, because immunosuppressive therapy may worsen the infection. The current case showed a subacute course and distinct immunological findings such as hypocomplementemia, positive RF and a low titer of PR3-ANCA. The SBE improved with antibiotics and the surgical replacement of the affected valves, the hypocomplementemia recovered, and both RF and PR3-ANCA became negative. However, non-bacterial endocarditis due to ANCA-associated vasculitis shows normal to high complement levels without other autoantibodies (13, 14) and requires long-term immunosuppressive therapy to control the disease activity (13-15).

About 30% of bacterial endocarditis is complicated by renal failure and renal failure is a significant predictor of mortality (16). Several renal lesions have been reported in patients with PR3-ANCA positive bacterial endocarditis and the most common lesion is diffuse proliferative and exudative glomerulonephritis (4-7, 11, 17). Those patients show glomerular immune deposits, thus suggesting a pathogenesis compatible with immune complex-mediated glomerulonephritis, but incompatible with pauci-immune glomerulonephritis. Treatment usually leads to recovery of renal function, but irreversible renal failure can also occur, if treatment is delayed (18). Treatment successfully led to recovery of SBE followed by improvement of renal function in the current patient, although no renal biopsy could be obtained because of his poor condition.

In summary, this report presented the first case of RPGN associated with PR3-ANCA positive SBE due to an Enterococcus faecalis infection. This case suggests that clinicians should keep in mind SBE as PR3-ANCA associated diseases with kidney injury, particularly RPGN.

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

References
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