Membranous Glomerulopathy Induced by Myeloperoxidase-anti-neutrophil Cytoplasmic Antibody-related Crescentic Glomerulonephritis

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Abstract

A 68-year-old woman was referred for evaluation of nephrotic-range proteinuria and a course suggesting rapidly progressive glomerulonephritis. Serum anti-neutrophil cytoplasmic antibody against myeloperoxidase (MPO) was 204 U/ml. A renal biopsy specimen revealed necrotizing glomerulonephritis with crescent formation. However, immunofluorescence showed staining with IgG and C3 along capillary walls. IgG positivity included both IgG1 and IgG4. Electron microscopic examination disclosed both paramesangial and subepithelial deposits. This case suggests that rarely, MPO-ANCA-related crescentic glomerulonephritis may present nephrotic-range proteinuria and show immune deposits along capillary walls.

Case Report

A 68-year-old woman with marked edema in the lower extremities and rapidly progressive renal dysfunction was referred to our institution on April 14, 2003. In July 2002, urinalysis and renal function tests performed as part of routine medical check-up had shown normal results. Epigastric pain and nausea began to occur in February 2003. On March 31, 2003, during another medical check-up at a community outpatient clinic, renal function test results were abnormal, serum creatinine, 2.4 mg/dl; urea nitrogen, 45 mg/dl; as were results of a urinalysis, 4+ for proteins; 3+ for occult blood. She was referred to our hospital for more extensive studies.

On admission the patient was 156 cm tall and weighed 61 kg. Blood pressure was 158/92 mm Hg. Body temperature was 36.9°C. The palpebral conjunctivae showed pallor, and marked edema was present in the lower extremities. No respiratory and neurologic abnormalities were apparent. Chest X-ray was normal.

Key words: myeloperoxidase-anti-neutrophil cytoplasmic antibody, MPO-ANCA, rapidly progressive glomerulonephritis, crescentic glomerulonephritis, secondary membranous nephropathy, pauci-immune type

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-related glomerulonephritis has been classified as a pauci-immune type of crescentic glomerulonephritis since glomerular immune complex deposits are not demonstrable by immunofluorescence microscopy or electron microscopy (1–3). Clinically this disease usually is associated with proteinuria in the non-nephrotic range. When immunoglobulin and complement can be detected on renal biopsy specimens from patients with myeloperoxidase (MPO) ANCA-related nephritis, an additional primary glomerular disease such as membranous nephropathy (MN) (4–9) may be present, although such overlap is rare.

We report a patient with MPO-ANCA-related nephritis accompanied by MN showing nephrotic-range proteinuria. Evaluation of IgG subclass in staining of glomerular capillaries and localization of electron-dense deposits showed a close relationship between these two diseases in our patient.

For editorial comment, see p 779.
Laboratory findings on admission (Table 1). The erythrocyte count was 2.58×10^6/μl; hemoglobin, 7.9 g/dl; hematocrit, 22.9%; leukocyte count, 7,400/μl; and platelet count, 25.1×10^4/μl. In serum, the total protein concentration was 5.3 g/dl; albumin, 2.5 g/dl; urea nitrogen, 53 mg/dl; creatinine, 3.0 mg/dl; and C-reactive protein, 1.4 mg/dl. The erythrocyte sedimentation rate was 97 mm/h.

IgM-rheumatoid factor was 52 U/ml (normal range <2); anti-proteinase-3 (PR-3) ANCA, less than 10 U/ml (normal range, <10); MPO-ANCA, 204 U/ml (normal range, <10). In a urinalysis, dipstick readings were pH, 5.5; glucose, negative; protein, 4+; and occult blood, 3+. The urinary sediment contained 11 to 30 erythrocytes per high-power field (HPF). No Bence-Jones protein was detected in the urine. A 24-h urine collection contained 6.97 g of protein and 14,206 μg of beta 2 microglobulin (MG). Creatinine clearance was 22.7 ml/min. On April 15, 2003, a renal biopsy was performed.

**Biopsy specimen findings**

Light microscopic examination of a renal specimen containing 29 glomeruli revealed global sclerosis in 9 and cellular or fibrocellular crescents in 20 (Fig. 1A). Bowman’s capsule showed marked destruction reflecting increased proliferation of epithelial cells, and thrombi were seen in capillary lumina (Fig. 1B). Necrotizing crescentic glomerulonephritis was diagnosed. However, close examination of sections stained with periodic acid-Schiff methenamine silver (PAM) demonstrated only very limited few spike formations along glomerular basement membranes (Fig. 2). Mononuclear cell infiltration and fibrosis were observed in most of the interstitium, and severe tubular atrophy was apparent. Interlobular arteries were mildly to moderately sclerotic, while no hyaline sclerosis or findings of vasculitis were detected in arterioles. Immunofluorescence microscopy revealed granular deposition of IgG and C3 along glomerular capillary walls (Fig. 3A, B); IgG subclass analysis showed that the former included IgG1 as well as IgG4. (Fig. 3C, D) No staining was present for IgA, IgM, C1q, or C4. Electron microscopy showed prominent wrinkling of the glomerular basement membrane. Electron-dense deposits were present in the paramegglomerular region as well as in the subepithelial region in relation to glomerular capillary walls (Fig. 4).

**Clinical course**

Our final diagnosis was atypical membranous nephritis (MN) accompanied by ANCA-related crescentic glomerulonephritis. Treatment was started with prednisolone (30 mg/day) together with intravenous cyclophosphamide (500 mg/day for only 1 day) on April 18. Serum CRP was normalized 6 days after initiation of treatment and mild fever disappeared at the same period. MPO-ANCA became negative 66 days after initiation of treatment. Beginning in February 2004, prednisolone was tapered gradually to 5 mg/day alternately. Serum creatinine fell to 1.8 mg/dl, and proteinuria
decreased to 0.5 g/day. The urinary sediment contained 6 to 10 erythrocytes per high-power field (HPF).

**Discussion**

Rapidly progressive glomerulonephritis (RPGN) is characterized by deterioration of renal function over weeks or months. Its histologic appearance is mainly that of crescentic glomerulonephritis. Most cases of idiopathic RPGN have been considered pauci-immune, in nature and type, since immune complex deposits could not be detected by immunofluorescence microscopy or by electron microscopy. However, after ANCA was found to be present in most of these patients, the disease was named microscopic polyangitis (1–3). Wegener’s granulomatosis and Churg-Strauss syndrome are well-known as types of ANCA-positive pauci-immune RPGN accompanied by involvement of other organs. By clinical urinalysis, proteinuria is small or absent in this disease, but the urinary sediment contains many red cells. If deposits of immunoglobulin are detected in kidney specimens from patients with ANCA-linked RPGN, other accompanying primary glomerular diseases such as MN should be considered; although this concurrence is infrequent, it has been reported recently. Gaber et al reported a case of MN superimposed on ANCA-positive Wegener’s granulomatosis in 1993 (4). Light microscopy revealed crescentic necrotizing glomerulonephritis. However, granular IgG was demonstrated along the peripheral glomerular capillaries by immunofluorescence, and many subepithelial electron-dense deposits were detected by electron microscopy. They concluded that as a result of MN; proteinuria continued even after renal failure was treated successfully by immunosuppressive therapy. Marshall et al reported two cases in which MN associated with ANCA-positive crescentic glomerulonephritis had features consistent with lupus nephritis (5). Subsequently, more instances of MN associated with ANCA-associated microscopic polyangiitis have been reported (Table 2) (6–9). The authors maintained that when the clinical course of MN was much more aggressive than usual, such an overlap should be considered. Typical pathologic
features of MN were present in these cases, and the combination of these two diseases was considered coincidental.

However, the present case showed differences from the usual primary MN. Spike formation along the basement membrane was slight, and electron dense-deposits were present in the paramesangial region as well as in the subepithelial region of the glomerular basement membrane. IgG1 as well as IgG4 was present in glomeruli.

Figure 3. Immunofluorescence microscopy of a renal biopsy specimen. A. Granular deposition of IgG was revealed along glomerular capillary walls. B. Granular deposition of C3 was revealed along glomerular capillary walls. C. Granular deposition of IgG1 was revealed along glomerular capillary walls. D. Granular deposition of IgG4 was revealed along glomerular capillary walls. A, B, C, D: (respectively ×40 objectives).
MN has been classified into a primary form and other forms secondary to various causes. IgG subclass has been reported to be important in making this distinction (10). Although the primary form is positive for only IgG4 in most cases (11), the secondary forms are varied and are often positive for multiple IgG subclasses including IgG1. Cancer, antirheumatic agents such as bucillamine, and lupus are known causes of secondary MN (12–14). Localization of electron dense deposits has also been reported to be a discriminant feature (13). Deposits are located only in the subepithelial region of the glomerular capillary wall in the usual case of primary MN. On the other hand, electron-dense deposits also are visible in the paramesangial region in secondary MN (13). In this case, both IgG1 and IgG4 are positive, in addition, IgG1 is more remarkable than IgG4. Paramesangial electron dense deposits are seen. For these reasons, it is reasonable to consider this case to be secondary MN. However, this patient had not had any specific diseases such as cancer and hepatitis which cause secondary MN. As a result, we speculated that MPO-ANCA-related RPGN may have caused a secondary form of MN in this patient.

Table 2. Case Reports of MPO-ANCA Related Crescentic Glomerulonephritis Combined with Membranous Nephropathy

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age/Sex</th>
<th>Presentation</th>
<th>Initial urine protein (g/day)</th>
<th>Initial Scr</th>
<th>MPO-ANCA</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kanahara (6)</td>
<td>47/F</td>
<td>Pulmonary hemorrhage</td>
<td>5.76</td>
<td>1.1 mg/dl</td>
<td>297 EU</td>
<td>MP, PC</td>
<td>Recovery</td>
</tr>
<tr>
<td>Tse (7)</td>
<td>64/M</td>
<td>Nephrotic syndrome</td>
<td>10</td>
<td>509 µmol/l</td>
<td>1 : 100</td>
<td>None</td>
<td>Dialysis</td>
</tr>
<tr>
<td>Taniguchi (8)</td>
<td>65/M</td>
<td>Hematuria</td>
<td>2.4</td>
<td>154 µmol/l</td>
<td>1 : 100</td>
<td>PC</td>
<td>Recovery</td>
</tr>
<tr>
<td>Dwyer (9)</td>
<td>68/F</td>
<td>Renal dysfunction</td>
<td>1.26</td>
<td>1.45 mg/dl</td>
<td>350 EU</td>
<td>P</td>
<td>Recovery</td>
</tr>
<tr>
<td></td>
<td>67/M</td>
<td>Renal failure</td>
<td>7.16</td>
<td>0.69 mmol/l</td>
<td>7,100 U/ml</td>
<td>PA</td>
<td>Dialysis</td>
</tr>
<tr>
<td></td>
<td>69/M</td>
<td>Lethargy</td>
<td>0.56</td>
<td>0.13 mmol/l</td>
<td>78 U/ml</td>
<td>PC</td>
<td>Recovery</td>
</tr>
</tbody>
</table>


Figure 4. Electron microscopy of a renal biopsy specimen. Electron microscopy showed prominent wrinkling of the glomerular basement membrane. Electron-dense deposits were present in the paramesangial region (*) as well as in the subepithelial region (Ӧ) in relation to the glomerular capillary walls at high magnification (×9,000).

The pattern of immuno deposits in our case is similar to that of lupus nephritis. Lupus nephritis shows electron deposits in various regions such as mesangial regions and GBM (15). Two mechanisms are suggested in lupus nephritis. First, autoantibody deposition from circulation as complexes. Second, in situ immune complex formation in which antibody reacts with an intrinsic GBM antigen or an exogenous planted antigen. The first mechanism leads mainly to subendothelial or mesangial deposits which cause diffuse proliferative glomerulonephritis. The second mechanism leads mainly to subepithelial deposits seen in membranous nephropathy. The mechanism in the present case might be similar to the first mechanism, since diffuse immune deposits including paramesangial deposits are seen. However, a decrease of complement is not observed in our case. Therefore, the immune complex in our case might be different from that in lupus nephritis. The reason that immune complex deposits are seen despite the MPO-ANCA-related nephritis that should be pauci-immune is still uncertain.

In conclusion, when immune deposits are seen in the capillary walls, MPO-ANCA-related crescentic glomerulonephritis may become nephrotic. Since coexistent IgG1 and paramesangial electron dense deposits are not seen in primary MN, MPO-ANCA-related RPGN may sometimes cause a secondary form of MN. Effects of MPO-ANCA-related glomerulonephritis may have caused membranous nephropathy secondarily in this patient with rapidly progressive glomerulonephritis.

References


