Fatal Pulmonary-renal Syndrome Manifested with Immune Complex Crescentic Glomerulonephritis in a Patient with MPO-ANCA Seropositivity

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Recent reports have indicated that a significant number of immune complex glomerulonephritis (GN) cases are associated with antineutrophilic cytoplasmic antibody (ANCA). However, most of the reported cases were associated with underlying primary glomerular diseases. When primary glomerular diseases were not found, immune deposits tended to be non-specific and the level of ANCA is usually borderline. We report here upon a case of life-threatening pulmonary-renal syndrome manifested simultaneously with immune complex GN and myeloperoxidase (MPO)-ANCA seropositivity. A 29-year-old man was admitted with pulmonary hemorrhage and rapidly progressing renal dysfunction. On admission, ANCA revealed perinuclear staining with a titer of 1:160. The MPO-ANCA level was 59 IU by ELISA. Other serologic markers including ANA, anti-DNA, and anti-GBM Ab were negative. Renal biopsy showed cellular crescents in eight of 18 glomeruli. Immunofluorescence staining showed strong granular deposits of C3, C1q, IgG and IgM in the capillary loop and the mesangium. Electron microscopy showed multifocal electron dense deposits scattered in the mesangium, paramesangium, and the subendothelial and subepithelial areas. The patient initially responded to steroid and cyclophosphamide. MPO-ANCA decreased to less than 10 IU. Twenty-three days after hospital discharge, the patient was re-admitted urgently with fever, generalized papulonodular skin lesions, and a recurrence of massive pulmonary hemorrhage and renal dysfunction. He died from uncontrolled pulmonary hemorrhage and respiratory insufficiency. P-ANCA titer and MPO-ANCA level at the second admission were 1:320 and 82 U/ml respectively. Interestingly, relapse was shown to be triggered by varicella zoster infection.

Key Words: Pulmonary-renal syndrome, Immune complex glomerulonephritis, MPO-ANCA

INTRODUCTION

Although antineutrophilic cytoplasmic antibody (ANCA)-associated glomerulonephritis (GN) is generally known to be a pauci-immune disease, it has become increasingly evident that a significant number of immune complex GN cases are associated with ANCA. Recent results have shown that as many as 11% of immune complex GN cases are positive for myeloperoxidase (MPO)-ANCA. In the literature, the majority of these cases have been reported to be secondary to or superimposed on underlying primary glomerular diseases, such as antiglomerular basement membrane antibody (anti-GBM Ab) nephritis, lupus nephritis, IgA nephropathy, postinfectious GN or membranous GN. When it occurs in the absence of these primary glomerular diseases, the immune deposits are generally non-specific and weakly positive and the serum MPO-ANCA level is borderline. If confined to those in which serum MPO-ANCA level is significant, glomerular immune deposits are strongly positive (at least more than 2+) and there is no underlying primary glomerular disease, the actual frequency of simultaneous occurrence of immune complex GN and ANCA seropositivity is still unknown. In particular, cases associated with severe extrarenal manifestations have been rarely reported. We report here upon a case of pulmonary-renal syndrome, which manifested simultaneously with immune complex GN and MPO-ANCA seroposi-
tivity. The pulmonary hemorrhage was life threatening. A kidney biopsy demonstrated strong granular immune deposits and crescents in the glomeruli. The MPO-ANCA level was elevated and paralleled disease activity occurred during the clinical course.

CASE REPORT

A 29-year-old man was admitted in June 1999 with hemoptysis, fever and general weakness of four days duration. He has visited a local clinic five months before, where routine urinalysis and blood biochemistry had been found normal. He had no previous medication history and was a non-smoker. On admission, foamy urine, nocturia and hemoptysis with fresh blood of more than two-tea spoons in quantity were noted. Neither peripheral numbness nor arthralgia was found. On physical examination, his blood pressure was 160/90 mmHg, heart rate 84/min, respiratory rate 20/min and his body temperature was 37.8°C. Inspiratory crackles were heard on the whole lung fields. Ear, nose and throat were unremarkable. No skin lesions were found. Laboratory findings included hemoglobin 9.0 g/dL (normal range 14-18), white blood cell count 8,100/μL (4,800-10,800), platelet count 276,000/μL (130,000-400,000), eosinophil count 206/μL (<200), C-reactive protein 0.8 mg/dL (<0.5) and erythrocyte sediment rate 85 mm/hr (0-10). Blood urea nitrogen was 18.5 mg/dL (8-20) and serum creatinine was 2.0 mg/dL (0.5-1.4). Routine urinalysis showed a pH of 6.0, a specific gravity of 1.020, protein 3+, and blood 3+. Dysmorphic red blood cells and granular cast were found upon high-power field microscopic examination. His 24-hour urine protein amount was 14,604 mg/day.

In terms of initial serologic findings, ASO, rheumatoid factor, antinuclear antibody, anti-DSP-DNA, cryoglobulin, Coombs test, HBs antigen, HBs antibody, HCV antibody, VDRL and anti-HIV antibody were all negative. Tests for complement activation included: C3 106 mg/dL (88-201), C4 26 mg/dL (16-47), CH50 91 mg/dL (51-150). Immunoglobulin (Ig) G, Ig A and Ig M were 1,050 mg/dL (694-1618), 264 mg/dL (68-378) and 150 mg/dL (60-263), respectively. In subsequent serologic testing, ANCA was positive with a perinuclear pattern of staining by indirect immunofluorescence (IF) on ethanol-fixed human neutrophils. MPO-ANCA level was 591U (<10) by enzyme-linked immunosorbent assay (ELISA) using human MPO (Calbiochem, La Jolla, CA, USA). PR3-ANCA antibody and anti-GBM Ab were negative. Chest radiography showed ill-defined mottled densities (Fig. 1A) and high-resolution chest computed tomography showed ground-glass opacities distributed in both whole

Fig. 1. (A)Chest radiograph shows ill-defined mottled densities and (B) High-resolution computed tomograph shows ground-glass opacities in both lung fields suggesting diffuse pulmonary hemorrhage.
lungs suggesting diffuse pulmonary hemorrhage (Fig. 1B). By fiberoptic bronchoscopic examination, only fresh blood clots in right bronchus were found. Transbronchial lung biopsy revealed only nonspecific chronic inflammation. On the fourth hospital day, his serum creatinine increased to 3.9 mg/dL.

Renal biopsy was performed on the fifth day. Under light microscopy, cellular crescents presented in eight of 18 glomeruli (Fig. 2). The number of mesangial cells had increased and focal segmental mesangial widenings were noted. The interstitium showed mild inflammatory cell infiltrations, which were composed of neutrophils, lymphocytes and a small number of eosinophils. IF stains showed granular deposits of C3(2+), Clq(2+), IgG(3+) and IgM(2+) in the capillary loop and mesangium (Fig. 3A). Electron microscopy showed multifocal electron dense deposits most prominently in subendothelial layer but also in mesangium, paramesangium and subepithelial layers (Fig. 3B).

After renal biopsy, the patient received methylprednisolone pulse therapy, 500 mg intravenously on three consecutive days, followed by daily oral administration of 60 mg of prednisolone. Oral cyclophosphamide was added at a dose of 100 mg daily. Four days after treatment, hemoptysis and fever disappeared and serum creatinine began to decrease. Eleven days after treatment, he was discharged with a serum creatinine level of 1.9 mg/dL and a cleared chest radiograph. During weekly outpatient follow-up, no remarkable symptoms were noted, serum creatinine had decreased to 1.6 mg/dL and MPO-ANCA levels measured at outpatient office were less than 10 IU.

During July 1999, 23 days after his hospital discharge, he visited the emergency room with fever and sudden chest pain. On physical examination, throat injection and dark papulonodular skin lesions were found on the face and chest. Careful history taking disclosed that he contacted with a cousin with varicella zoster. Under the diagnosis of varicella zoster, cyclophosphamide was discontinued and intravenous acyclovir was immediately started. On the second day of admission his serum creatinine increased to 3.3 mg/dL. On the third day, sudden massive pulmonary

![Fig. 2](image1.png)

Fig. 2. Light microscopy shows a cellular crescent in a glomeruli located in central area. Eight of 18 glomeruli are filled with the similar cellular crescents. Increased number of mesangial cells and focal segmental mesangial widenings are also noted (PAS, × 200).

![Fig. 3](image2.png)

Fig. 3. (A) This IF shows granular deposits of IgG, mainly in the capillary loops and the mesangium. C3, Clq and IgM are also stained strongly with a similar pattern (× 400). (B) Electron microscopic image shows multifocal electron dense deposits scattered in the mesangium, paramesangium, subendothelial and subepithelial layers (× 7,500).
hemorrhage and subsequent respiratory arrest occurred. Despite of intensive resuscitation, he expired seven hours after arrest. Methylprednisone pulse therapy could not be performed. P-ANCA titer and MPO-ANCA as measured at the second admission, were 1:320 and 82 U/ml respectively.

**DISCUSSION**

We experienced an interesting case of pulmonary renal syndrome. The patient showed a significant serum MPO-ANCA level simultaneously with the presence of strong positive granular immune deposits in the glomerulus. Previously, pulmonary-renal syndrome has been described only in three immunopathogenic situations: anti-GBM diseases, ANCA-associated systemic vasculitis, and immune complex-mediated GNs.

Anti-GBM diseases are known to be frequently associated with ANCA seropositivity up to 30%. Some authors have observed that manifestations of ANCA preceded before anti-GBM nephritis manifested and suggested that anti-GBM Ab may occur subsequently to ANCA-induced glomerular damage. Lupus nephritis is another common cause of concurrent manifestation of ANCA and immune complex GN. Jennette et al. reported MPO-ANCA was detected in 26% of lupus nephritis patients. Other studies have reported that P-ANCA, specifically anti-MPO or lactoferrin antibodies, are frequently detected among drug-induced SLE or SLE with severe cutaneous vasculitis and/or crescentic GN. A number of cases have been reported on overlaps of ANCA-associated crescentic GN in IgA nephropathy or membranous GN. Some manifested as concomitant occurrences of immune deposit crescentic GN in patients with ANCA seropositivity, whereas others showed pauci-immune crescentic GN followed by IgA nephropathy or membranous GN, or vice versa. There also was a case of MPO-ANCA-associated immune deposit rapid progressive GN and pulmonary hemorrhage in a patient with hepatitis C viral hepatitis. Even though a definite relationship was not confirmed, these workers suggested that viral-induced immunologic abnormalities, such as MPO-ANCA seropositivity, cryoglobulinemia or hypocomplementemia, play an important role in the pathogenesis.

When encountered a patient showing pulmonary-renal syndrome manifested with both positive serum ANCA and immune deposit GN, and believe it was reasonable to suspect anti-GBM diseases initially. However, our case was some distance removed from anti-GBM diseases in that the pattern of immune deposits was granular and because anti-GBM Ab was absent. We had also considered the possibility of SLE during the first evaluation, but serologic markers including antinuclear antibody and anti-DNA antibody were repeatedly negative and neither cutaneous nor articular manifestation suggesting SLE was noted. There were no clinical findings that suggested autoimmune diseases, such as rheumatoid arthritis, ulcerative colitis or Crohn disease, which may also show MPO-ANCA positivity. Wegener’s granulomatosis, microscopic polyarteritis and Churg-Strauss syndrome could be excluded in our patient by the findings of no granulomatous lesion in the nose, throat or chest, the absence of asthma history, no eosinophilia, and no leukocytoclastic reactions in the renal pathologic specimen. In a survey upon kidney biopsies by Bajema et al., only 25 of 135 patients with ANCA associated systemic vasculitis showed completely negative immune deposits in the glomerulus. However, immune stains were not scored as strongly positive in almost all patients showing immune deposits, and it was suggested that the incidences of immune deposits in the glomerulus of the patients with ANCA seropositivity depend on the definition of pauci-immune. Others also suggested that there are some overlaps in the amount of immune deposits between pauci-immune and immune complex GNs. The present case is removed from this situation because the immune deposits were sufficiently significant.

It is still unclear whether ANCA contributes to pathogenesis or simply reflects the glomerular damage in ANCA-associated immune complex GN. Considering the clinical course, it seems that the ANCA has a leading pathogenic role in our case. Some studies have suggested that the initial
ANCA associated vasculitic insult may trigger the secondary immunopathogenic processes. Verburgh et al.\textsuperscript{12} and Jayne et al.\textsuperscript{13} observed that ANCA preceded anti-GBM nephritis in patients with ANCA associated anti-GBM GN. They hypothesized ANCA associated damage to the glomerular basement membrane uncovers hidden antigen from GBM and induces the formation of antibodies. Some experimental animal models\textsuperscript{23,24} support this hypothesis, and showed that immune complex GN was induced by the infusion of ANCA. At least, ANCA-associated cellular responses and immune complex-mediated humoral responses may not be exclusively independent and occur dependently or subsequently.

We present here a case of pulmonary-renal syndrome manifested simultaneously with immune complex GN and MPO-ANCA seropositivity. It is interesting that systemic symptoms were severe enough to be life-threatening, glomerular immune deposits were strongly positive, serum MPO-ANCA levels were significantly high and, furthermore, all these occurred simultaneously. Serum MPO-ANCA levels were correlated with clinical disease activity.

REFERENCES


