Case Report

Anti-GBM-associated crescentic glomerulonephritis with discrete IgG deposition, but with no electron-dense material in glomeruli


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Key words: anti-GBM antibody; crescentic glomerulonephritis; discrete IgG deposit

Introduction

Crescentic glomerulonephritis is characterized by extracapillary proliferation resulting from severe inflammatory injury of various aetiologies. It is usually rapidly progressive. Meanwhile, anti-glomerular basement membrane (GBM) antibody-mediated glomerular lesions induce crescentic glomerulonephritis. When associated with pulmonary haemorrhage, it is given the eponym 'Goodpasture's syndrome'. However, anti-GBM glomerulonephritis without evidence of pulmonary purpura occurs in about 30% of patients with crescentic glomerulonephritis [1].

On the other hand, anti-GBM glomerulonephritis is also characterized by linear deposition of IgG in the GBM. Some patients with anti-GBM glomerulonephritis exhibit granular or non-linear IgG deposits indicating the involvement of an immune complex-mediated event [2].

We present a case of anti-GBM glomerulonephritis with non-linear IgG deposits in the glomerular capillary wall without evidence of subepithelial or subendothelial deposits of immune complexes.

Case report

A 30-year-old Japanese male was seen at our outpatient clinic because of proteinuria that was detected during a routine health examination. Urinalysis at the outpatient clinic showed 2+ proteinuria and 2+ haematuria. The serum creatinine and BUN were normal. About 1 month later he came to the hospital with a high fever that lasted for about a week. Laboratory tests showed elevation of creatinine (470 μmol/l) and BUN (20.6 mmol/l urea), and he was hospitalized for further examination. At admission, his blood pressure was 82/40 mmHg and his pulse rate was 70/min and regular. A cardiac examination was normal. The lungs were clear on auscultation. No neurological abnormalities were noted except for hearing loss, which was present since childhood. There was no family history of renal abnormalities nor any evidence of a congenital renal disturbance, including Alport's syndrome. He was not a smoker.

Laboratory tests on admission showed the following values: serum creatinine, 6.72 μmol/l; BUN, 30.9 mmol/l urea; uric acid, 463.7 μmol/l; Na, 137 mmol/l; K, 5.7 μmol/l; Cl, 103 mmol/l; Ca, 2.15 mmol/l; P, 1.0 mmol/l. The results of blood analysis were as follows: Hb, 8.3 g/dl; platelets, 21.6 x 10⁹/l; WBC, 5.7 x 10⁹/l, with a normal haemogram. His CRP level was 15.2 mg/dl, ASO, 232.7 U/ml; CH₅₀, 45 U; C₅, 84 mg/dl; C₆, 54 mg/dl; IgG, 1574 mg/dl; IgA, 744 mg/dl; IgM, 413 mg/dl; RF < 19.5 U/ml; ANA 320 x; anti-DNA < 5.0 IU/ml; P-ANCA < 10 EU; C-ANCA < 9 EU. The anti-glomerular basement membrane (GBM) antibody was as high as 3706 U when measured by ELISA using anti-GBM detection kit (Euro-Diagnostica, Malmö, Sweden; < 10 U, negative; 10–20 U, undetermined; > 20 U, positive for anti-Goodpasture's antigen). Urinalysis revealed 2+ proteinuria and 3+ haematuria. His Ccr was 5.6 l/day. After treatment with 100 mg furosemide given intravenously, the patient voided about 900 ml/day of urine, but creatinine rose to 884 μmol/l. Haemodialysis (HD) was then instituted. After several courses of HD alone, plasma exchange therapy was initiated with 3.2 l plasma. He underwent five consecutive courses of plasma exchange therapy in combination with HD.

After plasma exchange therapy, the patient received 1000 mg methylprednisolone administered intravenously for 3 days followed by 30 mg daily oral prednisolone for 7 days. The drug was tapered off because the patient's serum creatinine and BUN levels failed to decrease. A regular regimen of HD was instituted.

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Anti-GBM antibody level measured at the end of plasma exchange therapy was 2189 U and gradually decreased to 350 U and 72 U 2 and 3 months thereafter, respectively.

**Western blotting**

Western blotting analysis was carried out by transferring onto the pore membrane electrophoresed NCI fraction of bovine GBM, which was prepared as described elsewhere [3]. The membrane was cut into strips, each incubated with patient's serum and monoclonal antibody to \( \alpha_3 \) chain of type IV collagen of GBM. The results confirmed the serum antibody to \( \alpha_3 \) chain, recognized as Goodpasture's antigen (Fig. 1).

**Biopsy findings**

Light microscopy showed crescentic glomerulonephritis in all 20 glomeruli. The crescent formation was cellular and mostly circumferential. Capillary tufts compressed by the crescents were hyalinized in a few glomeruli (Fig. 2), and Bowman's capsules were ruptured, resulting in protrusion of crescent components into the interstitial space in some. Immunofluorescence microscopy identified granular deposition of C3 along the capillary wall.

In some glomeruli IgG deposits were present in only small segments and deposits were not visible along the capillary wall. In the remaining glomeruli, non-linear IgG staining was observed along the capillary wall (Fig. 3). No IgA or IgM staining was observed.

*Fig. 1. Western blotting analysis. Electrophoresed NCI fraction of bovine GBM was blotted into the strips, which were incubated with monoclonal antibody to \( \alpha_3 \) chain of type IV collagen and with patient's serum. Particularly of note is the reaction of the serum with \( \alpha_3 \) chain known as Goodpasture's antigen.*

**Discussion**

Crescentic glomerulonephritis is defined as a morphological lesion in the renal glomeruli in which various types of cells, basement membrane material, fibrin and collagen are present. Renal function often deteriorates rapidly in patients with crescentic glomerulonephritis [5]. Anti-GBM antibody and anti-neutrophil antibodies (ANCA) can cause crescentic glomerulonephritis [1], and the coexistence of these autoantibodies has been detected in some of these patients [6]. In the present case only anti-GBM antibody was detected.

The present case showed no evidence of pulmonary haemorrhage. Although anti-GBM antibody-mediated disease is well known for accompanying pulmonary haemorrhage, pulmonary lesions are actually present in only 70% of anti-GBM-positive cases [1], possibly because of differences in the endothelial structure of glomerular and pulmonary capillaries [1]. Unlike endothelial cells in the lung, those in glomeruli are fenestrated. Thus, anti-GBM in the circulation gains access more easily to the GBM than to the alveolar basement membrane. When the patient's serum was applied to a normal lung section in the present study, linear binding to the alveolar wall was observed in the section pretreated with 6 M urea (pH 3.5), suggesting that the antigen may reside at the basement membrane of the alveolar wall [4].

Our patient was not a smoker, which may also explain absence of lung purpura [6]. However, it is not clear how the anti-GBM antibody was generated in our patient.

Anti-GBM-mediated glomerulonephritis is characterized by linear deposition of IgG along the capillary wall of glomeruli [1], but the present case showed discrete IgG deposits along the glomerular capillary wall. Discrete IgG deposits have also been observed in previous cases positive for circulating anti-GBM anti-
Fig. 2. Rupture of Bowman’s capsule and protrusion of cellular components of the crescent. A compressed glomerular tuft was hyalinized. PASM. ×400.

Fig. 3. Immunofluorescence showed non-linear IgG staining ×400.

Fig. 4. Indirect immunofluorescence. The patient’s serum was applied to a normal renal section which was stained for human IgG by the indirect method. Linear IgG deposition was observed. ×400.

Fig. 5. Immunofluorescence of a lung section treated with the patient’s serum and stained by the indirect method. The section was pretreated with 6 M urea (pH 3.5). Sections without urea pretreatment were negative for IgG. ×400.

Body [2,7–9]. In these previous cases, electron microscopy revealed local immune complex deposits, suggesting the presence of other forms of immune complex-mediated glomerulonephritis, such as membranous nephritis [2,8,9] or infectious glomerulonephritis [7].

Richman et al. have suggested that membranous glomerulonephritis may evolve into anti-GBM crescentic glomerulonephritis [9].

In the present case, no electron-dense deposits were observed by electron microscopy. We could not rule out, however, the possibility of subepithelial/subendothelial immune complex deposition because only a few glomeruli, and not the entire area of the glomerulus, were studied by electron microscopy.

When the patient’s serum was applied to a normal
kidney section, linear immunofluorescence along the glomerular capillary was observed, suggesting that the IgG of the patient bound diffusely to normal GBM, but not to the patient’s GBM. Therefore, it may be, as Tomaszewski et al. have suggested, that deposition of IgG in the GBM appears continuous or discrete depending on the severity of the GBM lesion caused by the disease [8]. This theory is supported by the study of Schiffer et al. [10] who studied the distribution of Goodpasture’s antigen in the various types of glomerular lesions. The presence of GBM gaps on the ultrastructural level or local loss of antigenic sites induced by cytokines or other mediators of inflammation may provide an explanation. Therefore, in some cases of anti-GBM-mediated disease, one may not necessarily need to consider the two different mechanisms to explain the discrete IgG deposition of anti-GBM glomerulonephritis.

References

Received for publication: 2.1.96
Accepted in revised form: 29.5.96