IgA Nephropathy with Complement Deficiency

Eiichiro Kanda, Haruko Shimamura, Hiroyuki Tamura, Shinichi Uchida, Yoshio Terada, Hisato Sakamoto, Michio Kuwabara, Takashi Akiba, Takashi Ida, Sei Sasaki and Fumiaki Marumo

Abstract

We treated a female patient suffering from immunoglobulin A (IgA) nephropathy and congenital deficiency of the ninth component of the complement system (C9). She was admitted with hematuria and proteinuria, and the C9 deficiency was diagnosed based on the low hemolytic activity of 50% of the hemolytic unit of the complements (CH50) and the normal C3 level in the plasma. Renal biopsy revealed mild mesangial proliferation, and immunofluorescence examination revealed mild mesangial deposits of IgA and C3 with the same distribution. We discuss the pathogenesis of IgA nephropathy and the role of the complements in its progression.

(Key words: membrane attack complex (MAC), complement, glomerulonephritis, C9)

Introduction

IgA nephropathy is among the most common forms of glomerulonephritis (1). Patients with IgA nephropathy typically present microscopic hematuria. Optical microscopic examination of renal biopsy specimens typically shows mesangial expansion with an increased matrix size and numbers of cells. The diagnostic finding is the presence of mesangial deposits of IgA, which are detected by immunofluorescence microscopy. The IgA deposits in the glomerular mesangium have been suggested to act as antibodies against viral, bacterial, or dietary agents (2–9). The antibodies are probably produced as part of the specific host immune response to various environmental antigens.

The C5b-9 terminal complement complex, also referred to as the membrane attack complex (MAC), is known to have cytotoxic activity (10). Immunofluorescence studies on nephritic tissue obtained from humans with IgA nephropathy have shown the presence of MAC in glomerular immune deposits (11, 12). MAC is considered to be one of the factors contributing to the severity and progression of the disease (13).

We report here the case of a patient with IgA nephropathy and congenital C9 deficiency, and consider the mechanisms underlying the development of IgA nephropathy.

Case Report

A 40-year-old woman presenting with hematuria and proteinuria was admitted to our hospital in October 1997. She had been asymptomatic and was discovered to have proteinuria in 1974 and hematuria in 1994 in urinary screening tests. She was referred to our hospital for evaluation of urinary abnormality. A low hemolytic activity of CH50 was found in our outpatient clinic in August 1997. The family history was non-contributory.

On examination, the pulse was regular at 72 beats/min, and the blood pressure was 118/74 mmHg. The lungs, heart, abdomen, and musculoskeletal system were normal. Urinary tests revealed proteinuria and hematuria. Microscopical observation of the urine sediment showed 5–7 erythrocytes, 0–1 leukocytes and 1–2 hyaline casts per high-power field. The 24-hour urinary protein excretion was 250 mg. The creatinine clearance was calculated to be 101 ml/min/1.48 m². The electrocardiogram was normal, and radiographs of the chest and abdomen revealed no abnormalities.

Hematological and biochemical findings are shown in Table 1, which were all within normal limits. Tests for the presence of hepatitis B and C viruses using serological markers were negative. Immunological test results are presented in Table 2. The concentration of IgA was 390 mg/dl, and the patient was negative for the presence of anti-nuclear antibody (ANA), anti-DNA antibody and cryoglobulin. The CH50 activity was 17.5 units/ml. The serum concentration of each complement is shown in Table 3. The concentrations of C1q, C3, C4, C5, C6, C7 and C8 were all within normal limits. The concentration of C9 was less than 0.5 mg/ml.

In the ethylenediaminetetraacetic acid (EDTA) test, the CH50 activity was decreased to 24.1 units/ml, and the concentration of C9 was less than 0.5 mg/ml. Consequently, the pos-
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Because of the possibility of the presence of autoimmune diseases, e.g., systemic lupus erythematosus, which consume complements, was excluded, and it was suggested that the low hemolytic activity of the complement system was due to the decreased production of complements. The serum transaminase level was within normal limits, and there was no evidence of liver disease. Laboratory data were thus strongly suggestive of congenital C9 deficiency.

Analysis of a percutaneous biopsy specimen of the kidney showed mild expansion of the mesangium with an increased matrix size, by periodic acid-methenamine silver (PAS) staining (Figs. 1 and 2). No glomerular crescents or necrotic glomeruli were apparent, and the small arteries showed no abnormalities. There was no interstitial fibrosis. Immunofluorescence staining revealed apparently segmental IgA deposits in the

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<tr>
<th>Table 1. Laboratory Data on Admission</th>
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<tr>
<td><strong>Peripheral blood</strong></td>
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<td>White cell count</td>
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<td>Hemoglobin</td>
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<td>Hematocrit</td>
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<td><strong>Blood chemical examination</strong></td>
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<td>C reactive protein</td>
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<td>Lactate dehydrogenase</td>
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<td>Aspartate aminotransferase</td>
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<td>Alanine aminotransferase</td>
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<td>γ-glutamyl-transpeptidase</td>
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<td>Alkaline phosphatase</td>
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<td>Total cholesterol</td>
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<td>Glucose</td>
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<td>Creatine phosphokinase</td>
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<td>Thymol turbidity test</td>
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<td>Zinc sulfate turbidity test</td>
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<td>Cholinesterase</td>
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<th>Table 2. Immunological Test</th>
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<td>Rheumatoid factor</td>
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<td>Anti streptolysin-O</td>
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<td>Immunoglobulin G</td>
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<td>Immunoglobulin A</td>
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<td>Anti RNP antibody</td>
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<td>Anti SS-A antibody</td>
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<td>Anti SS-B antibody</td>
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<td>Anti Scl-70 antibody</td>
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<td>Cytoplasmic anti neutrophil antibody</td>
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<td>Anti cardiolipin B2GP1 antibody</td>
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<td>Cryoglobulinemia</td>
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<th>Table 3. Protein Concentration of Complements</th>
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<tr>
<td><strong>without EDTA</strong></td>
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<tr>
<td>CH50 (U/ml)</td>
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<tr>
<td>C1q (mg/dl)</td>
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<td>C3 (mg/dl)</td>
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<td>C9 (mg/dl)</td>
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EDTA: ethylenediaminetetraacetic acid. *The concentration of each complement was measured without EDTA. †The concentration of each complement was measured in EDTA.

Figure 1. Three glomeruli showing mild mesangial proliferation. Neither a tubular nor vascular lesion was observed (PAS staining, ×84).
mesangial area and along the capillary walls (Fig. 3). IgG and C3 deposits were observed in the same area. The intensity of IgA immunostaining was moderate and codominant compared with those of IgG and C3 immunostaining. There was no evidence for the presence of known associated diseases which show IgA mesangial deposits, such as Henoch-Schönlein purpura or systemic lupus erythematosus. The diagnosis of IgA nephropathy with congenital C9 deficiency was thus established.

**Discussion**

IgA nephropathy is characterized by the presence of mesangial proliferative glomerulonephritis and IgA deposits in the mesangial area. Fifty percent of the patients have an increased serum IgA level, mainly in the polymeric form, at some time in the course of the disease, with a shift towards the predominance of subclass IgA1 (14). IgA antibodies against dietary components (8, 9) and infectious agents, such as herpes viruses, H. parainfluenzae and adenoviruses, may be found in some patients with IgA nephropathy (2-7). Abnormalities in the production and catabolism of IgA are thought to play an important role in the etiology and pathogenesis of IgA nephropathy (15). Circulating IgA or IgG antibodies react either with the mesangial matrix in some patients with IgA nephropathy, or with a cytoplasmic antigen in cultured human mesangial cells in others (16, 17). This suggests the possibility of an autoimmune reaction to a mesangial antigen.

Immunofluorescence studies on tissues from humans with IgA nephropathy have shown the presence of MAC in the glomerular immune deposits (11, 12, 18). IgA nephropathy frequently displays a high intensity of immunostaining for alternative pathway complement components (e.g., properdin and C3) and terminal complement components (e.g., C5, C9 and MAC). In contrast, the immunostaining for the early classical pathway complement components (e.g., C1q and C4) is often absent or low in intensity (11). However, the importance of immune deposits and the role of the complement system in renal injury remain unknown.

MAC has a hydrophobic external face and a hydrophilic internal channel. Disruption of the lipid bilayer leads to the destruction of the pathogens. It is thought that MAC mediates glomerular injury in several models of experimental nephritis (19). MAC is also considered to be a noninflammatory mediator of glomerular injury in some models (19-21). In support of this view, MAC has been shown in cultured mesangial cells to release such cytokines as interleukin 1 (IL-1), tumor necrosis factor, basic fibroblast growth factor (bFGF), and platelet-derived growth factor (PDGF) (22-26).

The clinical significance of glomerular MAC deposition is questionable. It is thought that the intensity and distribution of immunostaining for S protein and the terminal complement components may contribute to the pathological and clinical severity (27, 28). In congenitally C9 deficient patients, it is thought that defects in local MAC formation may be associated with a rather mild course of IgA nephropathy. However, Tagami et al reported a Japanese patient with IgA nephropathy and congenital C9 deficiency, whose clinical features were severe (29). A retrospective study of renal biopsies from patients
with IgA nephropathy did not show a relationship between the severity of glomerular MAC deposition and any of the clinical parameters including proteinuria, hematuria, or plasma creatinine at the time of biopsy (30). It is suggested that MAC is not necessary for the development of hematuria and IgA nephropathy (29, 31). It is thus debatable whether MAC is related to the progression of IgA nephropathy.

Some cases of IgA nephropathy with a congenital Clq, C3, C4a, C4b or C9 deficiency have been reported (32–36). Clq binds to antibody molecules to trigger the classical pathway of complement activation. C3b is a large cleavage fragment of C3, and initiates the activation of complement-mediated lysis via an alternative pathway. The existence of such cases suggests that there may be an unknown complement activation mechanism that does not require these components.

In the present case, the histological features such as diffuse proliferative glomerular lesions, focal and segmental glomerular sclerosis or tubular atrophy, arteriolar sclerosis, and interstitial fibrosis were not apparent, indicating a favorable prognosis. It is currently unknown whether the lack of C9 contributes to these mild histological changes. However, if MAC were in any way related to the progression of IgA nephropathy, we would have to monitor the patient more carefully.

In summary, we report the case of a middle-aged woman with IgA nephropathy and congenital C9 deficiency, and show that the formation of MAC is not essential for the induction of IgA nephropathy. The precise interplay among mechanisms underlying IgA nephropathy remains unclear. Further accumulation of case studies is necessary to resolve this issue.

References