□ CASE REPORT □

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.
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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 noncontributory.

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. Microsopical 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/1.48m². 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-

Table 1. Laboratory Data on Admission

Peripheral blood

White cell count	6,600/mm³
Red cell count	4,500,000/mm³
Hemoglobin	13.5 g/dl
Hematocrit	39.8%
Platelet count	229,000/mm³

Blood chemical examination

C reactive protein	0.3 mg/dl
total protein	7.1 g/dl
albumin	4.1 g/dl
blood urea nitrogen	10 mg/dl
creatinine	0.6 mg/dl
uric acid	4.9 mg/dl
sodium	138 mEq/l
potassium	3.5 mEq/l
chloride	100 mEq/l
calcium	10.2 mg/dl
phosphate	4.0 mg/dl
lactate dehydrogenase	145 U/l
aspartate aminotransferase	16 U/l
alanine aminotransferase	6 U/l
γ-glutamyl-transpeptidase	13 U/dl
alkaline phosphatase	115 U/l
total bilirubin	0.7 mg/dl
direct bilirubin	0.1 mg/dl
total cholesterol	205 mg/dl
triglyceride	92 mg/dl
glucose	107 mg/dl
creatine phosphokinase	46 U/l
thymol turbidity test	2.4 U
zinc sulfate turbidity test	8 U
cholinesterase	278 U/l

Table 2. Immunological Test

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rheumatoid factor	3 IU/ml
anti streptolysin-O	42 IU/ml
immunoglobulin G	1,731 mg/dl
immunoglobulin A	390 mg/dl
immunoglobulin M	182 mg/dl
anti nuclear antigen	×40
anti DNA antibody	(−)
anti smooth muscle antibody	(−)
anti mitochondrial antibody	(−)
anti sm antibody	(−)
anti RNP antibody	(−)
anti SS-A antibody	(−)
anti SS-B antibody	(−)
anti scl-70 antibody	(−)
cytoplasmic anti neutorophil antibody	(−)
anti cardiolipin β2GP1 antibody	(−)
cryogloblinemia	(−)

sibility 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

Table 3. Protein Concentration of Complements

		without EDTA*	in EDTA†	
CH50	(U/ml)	17.5	24.1	(30.0–40.0)
C1q	(mg/dl)	15.4	11.9	(8.8–15.3)
C3	(mg/dl)	109	104	(84–151)
C4	(mg/dl)	36	36	(17–40)
C5	(mg/dl)	16.8	13.6	(8.0–15.0)
C6	(mg/dl)	5.7	5.8	(2.5–4.5)
C7	(mg/dl)	6.5	6.5	(2.4–4.6)
C8	(mg/dl)	8.9	10.3	(5.5–8.9)
C9	(mg/dl)	0.5	0.5	(2.7–7.3)

EDTA: ethylenediaminetetraacetic acid. *The concentration of each complement was measured without EDTA. †The concentration of each complement was measured in EDTA.
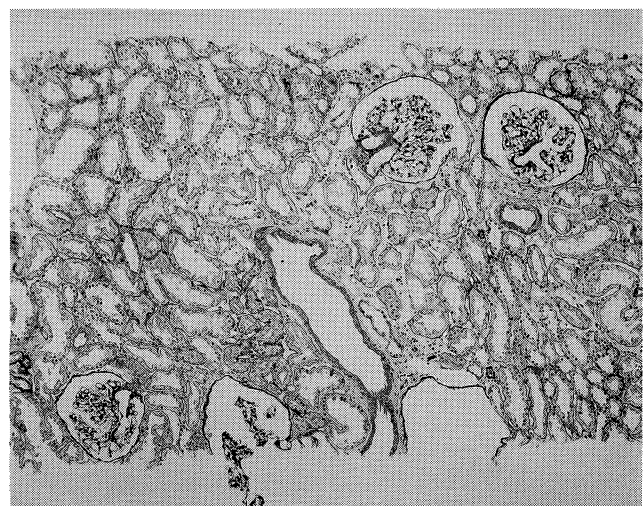
Figure 1. Three glomeruli showing mild mesangial proliferation. Neither a tubular nor vascular lesion was observed (PAS staining, ×84).
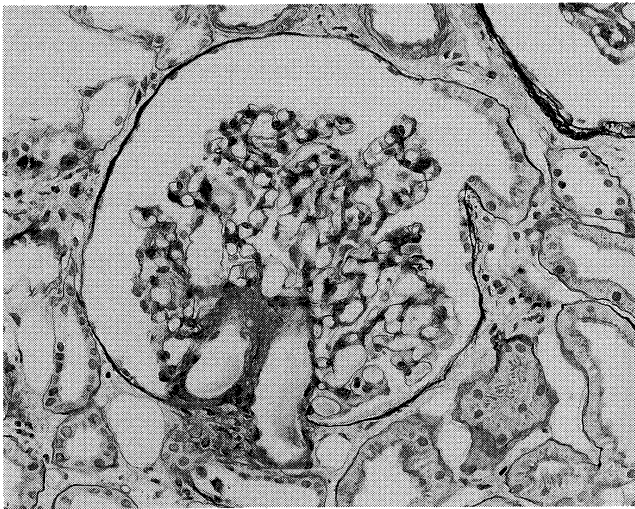
Figure 2. Mild mesangial proliferation was observed. Neither glomerular crescent formation nor capsular adhesion was observed (PAS staining, ×320).

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 purpula 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.

Immunoflourescence 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
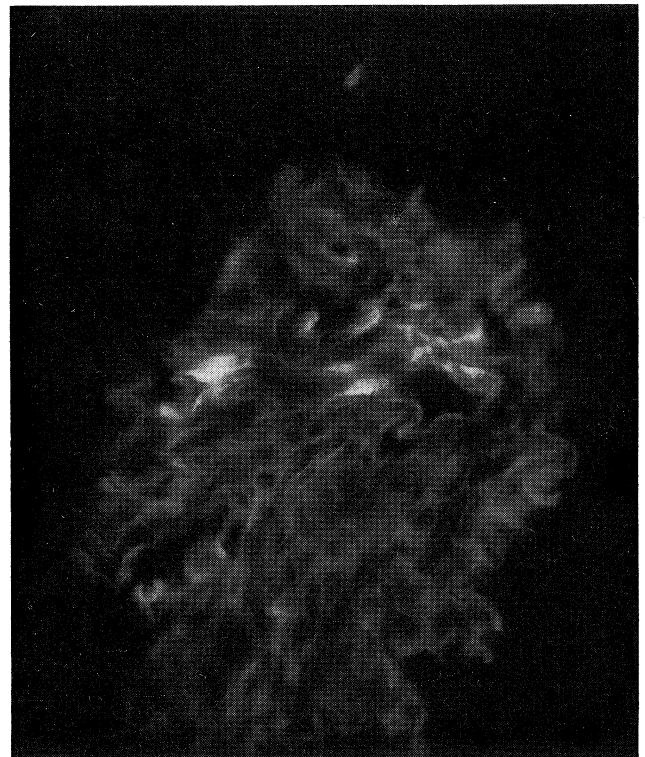
Figure 3. IgA immunostaining was mainly observed in the mesangial area (stained by goat anti-human IgA antibody).

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 unkown.

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 depositon 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 C1q, C3, C4a, C4b or C9 deficiency have been reported (32–36). C1q 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 complements.

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.

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