A man with immunoglobulin A nephropathy complicated by infection-related glomerulonephritis with glomerular depositions of nephritis-associated plasmin receptor

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Abstract

A 27-year-old man who developed heavy proteinuria with hematuria and acute kidney injury 2 weeks after a fever was referred to our hospital. Because he had low complements without autoantibodies, we clinically diagnosed him with infection-related glomerulonephritis. The proliferation of mesangial cells and endothelial cells with glomerular deposits of immunoglobulin A and complement 3 was found. Deposition of glomerular nephritis-associated plasmin receptor, a marker of infection-related glomerulonephritis, was also found. In addition, the distribution of nephritis-associated plasmin receptor deposition almost perfectly matched the plasmin activity-positive region. Over 3 months later, his symptoms were resolved, although moderate proteinuria and active urine sediment were persistent. He underwent a second renal biopsy, and the histological findings revealed that he had immunoglobulin A nephropathy. Therefore, we diagnosed him with infection-related glomerulonephritis superimposed on immunoglobulin A nephropathy at the first renal biopsy. The glomerular deposition of nephritis-associated plasmin receptor is a useful marker and may cause worsening urinalysis findings after bacterial infection in cases of chronic glomerulonephritis.

Keywords Infection · Glomerulonephritis · Nephritis-associated plasmin receptor · Chronic glomerulonephritis

Introduction

Immunoglobulin A nephropathy (IgAN) is recognized as the most common form of glomerulonephritis in the world [1]. As a major primary disease of end-stage kidney disease (ESKD) in Japan is chronic glomerulonephritis (CGN) [2], the prevention of progression of IgAN is crucial. Some patients with IgAN have worsening clinical symptoms with macroscopic hematuria and/or heavy proteinuria after bacterial infection [3]. While macroscopic hematuria or heavy

proteinuria usually resolves spontaneously within a week, in rare cases, the exacerbated urinary findings are prolonged, and acute kidney injury (AKI) develops [3]. In a majority of IgAN patients who develop AKI, the kidney function returns to baseline, but incomplete recovery of the kidney function has been reported in long-term follow-up studies [4].

Infection-related glomerulonephritis (IRGN) is an immune-mediated glomerulonephritis caused by non-renal bacterial infections and has a poor renal prognosis in adults [5]. In patients with CGN, it is difficult to distinguish flare-up of the original CGN from IRGN. Nephritis-associated plasmin receptor (NAPlr) was isolated from the cytoplasmic fraction of group A streptococcus (GAS), and its deposition was reported to be observed in the glomeruli of patients with post-streptococcal acute glomerulonephritis (PSAGN) [6, 7]. In addition, recently, glomerular NAPlr deposition was reported to be observed in not only patients with PSAGN but also those with other glomerular diseases, in whom a preceding bacterial infection had been suggested [8]. These findings indicate that glomerular NAPlr deposition can aid

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in making a diagnosis and reveal the pathogenesis of IRGN in patients with CGN.

We herein report a man in his 20 s who developed IRGN during a course of IgA nephropathy and received a repeat renal biopsy.

Case report

A 27-year-old man was admitted to our hospital with bilateral leg edema heavy proteinuria, and an elevated serum creatinine level. Three days before this admission, he had visited a local hospital with edema and found to have proteinuria and hematuria. Because his symptoms worsened, he was referred to our hospital. He had been found to have micro-hematuria with proteinuria at a health checkup for the last several years. He had been in his usual state of health until 2 weeks before admission, when he had developed a fever with a temperature of up to 40 °C. He did not have a sore throat or abdominal pain. He was treated with NSAIDs and oral antibiotics, and his fever went down after 3 days.

He gained 8 kg over 2 weeks and had strong symmetric edema, mainly on his lower legs. His blood pressure was 139/96 mmHg. Laboratory findings included the following:

hemoglobin, 13.3 g/dL; white blood cell count, 8830/ μ L; platelet count $28.6 \times 10^4/\mu$ L; total serum protein, 5.1 g/dL; serum albumin, 2.3 g/dL; urea nitrogen, 17 mg/dL; serum creatinine, 1.34 mg/dL [estimated glomerular filtration rate (eGFR), 54.7 mL/min/1.73 m²]; elevated ASO level (497 U/mL); and hypocomplementemia (C3 18 mg/dL, C4 23 mg/dL). All classes of immunoglobulins were within normal ranges, and the antinuclear antibody titer was negative. He had heavy proteinuria (13.4 g/g creatinine) and high numbers of red blood cells (50–99/high-powered field), and granular casts were found in the urine sediment. His urine volume was 600–700 mL/day (0.4–0.5 mL/kg/h), which met the diagnostic criteria for AKI. These findings and the episode of prior infection indicated that he had IRGN. In contrast, sustained hematuria with proteinuria suspected that he had CGN and his GN had flared up, so we performed a renal biopsy on hospital day 5.

There were 30 glomeruli in the specimens. Mesangial cell proliferation and mesangial matrix increasing were found, and endocapillary proliferation was also observed (Fig. 1a). On immunofluorescence, mild diffuse mesangial staining was found in IgA (Fig. 1b) and C3.

On electron microscopy (EM), electron dense deposits (EDDs) were observed in the mesangial region without any

Fig. 1 Microscopic findings of the first renal biopsy specimens. **a** Light microscopy showed mesangial proliferation and intraductal proliferation. (PAS $\times$ 400). **b** Immunofluorescence microscopy demonstrating mesangial deposits of IgA ($\times$ 400). **c** Electron microscopy reveals high electron-density deposits, mainly in the mesangial

region. Mesangial interposition was also found. **d** Immunofluorescence microscopy showed positive staining for NAP1r in the glomeruli ($\times$ 100). **e** Plasmin activity was distributed almost the same as in “d” in the glomeruli ($\times$ 100)

hump-shaped subepithelial EDDs (Fig. 1c). As it was difficult to determine whether the cause was IRGN or IgAN flare-up, we performed immunofluorescence staining of the biopsy tissues with anti-NAPlr antibody. NAPlr deposition was found in the glomeruli (Fig. 1d) with a distribution almost identical to the plasmin activity-positive region (Fig. 1e). These findings indicated that the patient had IRGN. He was treated with salt restriction and did not receive any drug therapies. On the 14th hospital day, his edema had disappeared, and his systolic blood pressure had decreased to 110 mmHg. Urinary protein excretion decreased to 2.5 g/day. One month after admission, he was discharged from our hospital.

Three months later, his serum creatine level had decreased (1.08 mg/dL, eGFR 68.5 mL/min/1.73 m²), and complements were normalized. However, moderate proteinuria (> 1 g/g creatinine) and active urine sediment (microscopic hematuria with granular casts) were persistent. He was suspected of having CGN IgA nephropathy and received a renal biopsy again. In the second biopsy, mesangial cell proliferation and an increase in the mesangial matrix were found, but intraductal proliferation was not noted (Fig. 2a). On an immune-histological analysis, glomerular staining of IgA (Fig. 2b) and C3 were also found. On EM, EDDs were also observed in the mesangial region (Fig. 1c). The results of

the second biopsy suggested mildly active IgAN, and unlike the previous biopsy, no NAPlr deposits were detected. We diagnosed him with IgAN, and he underwent tonsillectomy with steroid pulse therapy.

Discussion

Glomerular IgA-dominant deposition in the setting of proliferative glomerulonephritis usually indicates IgAN, IgA vasculitis, lupus nephritis or, less often, IRGN [1, 3]. To determine the treatment strategy and avoid inappropriately administering immunosuppressive medications, including high-dose corticosteroids, it is important to differentiate IRGN and other diseases.

In the present case, the presence of persistent hematuria and proteinuria without purpura over 1 year before admission, negative autoantibody tests and glomerular positive staining for IgA (both first and second biopsies) indicated that he had IgAN. In contrast, the presence of hypocomplementemia and glomerular positive staining of NAPlr, a marker for IRGN, which was found in the first biopsy indicated that he had IRGN. In addition, the clinical presentation of low serum complement 3 levels, substantial proteinuria and AKI, which were found at the first renal biopsy, are

Fig. 2 Microscopic findings of the second renal biopsy specimens. **a** Light microscopy showed mesangial proliferation. (PAS $\times 400$) (**a**). **b** Immunofluorescence microscopy demonstrating mesangial deposits of IgA ($\times 400$). **c** Electron microscopy reveals high electron-density

deposits in the mesangial region. **d** Immunofluorescence microscopy showed negative staining for NAPlr in the glomeruli ($\times 100$). **e** Plasmin activity was not detected in the glomeruli ($\times 100$). PAS periodic acid-schiff staining

reported to be more common in cases of IRGN than in IgAN flare-up [9, 10]. Therefore, he was diagnosed with IRGN superimposed on IgAN rather than IgA-dominant IRGN or IgAN flare-up. The findings of glomerular staining of IgA but not NAPlr in the second biopsy specimen also supported our diagnosis.

Hump-shaped subepithelial EDDs were not observed in our case. Nasr et al. defined the diagnostic criteria for IRGN as having at least three of the following five criteria: (1) clinical or laboratory evidence of infection preceding the onset of GN; (2) depressed serum complement; (3) endocapillary proliferative and exudative GN on light microscopy (LM); (4) C3-dominant or codominant glomerular staining on immunofluorescence (IF); and (5) “hump-shaped” subepithelial deposits on electron microscopy (EM) [5, 11]. They reported that subepithelial humps were not found in 8 of 83 patients with IRGN [11], and the present case met four of these criteria.

NAPlr is a nephritis-inducing antigen isolated from the intracellular component GAS depending on the affinity for IgG of PSAGN patients and is the same molecule as streptococcal glyceraldehyde-3-phosphate dehydrogenase (GAPDH) [7, 8]. Therefore, NAPlr was originally considered a nephritogenic protein for PSAGN [12]. Subsequently, because the presence of glomerular NAPlr deposits was reported in patients with glomerular diseases other than PSAGN, NAPlr is now considered a marker of IRGN [8].

GAPDH from bacteria has been shown to have plasmin-binding activity. NAPlr as well as GAPDH bind plasmin and maintain the plasmin activity, which has been reported to cause glomerular damage by protecting it from physiological inhibitors [12, 13]. In fact, the distribution of NAPlr deposition was almost identical to the plasmin activity-positive region in our first biopsy specimen. These findings suggested that the worsening urinalysis findings after bacterial infection in IgAN were related to glomerular damage caused by elevated plasmin activity induced by NAPlr deposition.

In conclusion, the glomerular deposition of NAPlr is a useful clinical marker for distinguishing IRGN in CGN from CGN flare-up. NAPlr deposition in the glomeruli may cause worsening urinalysis findings after bacterial infection in IgAN.

Declarations

Conflict of interest The authors have declared that no conflict of interest exists.

Ethical approval All of the procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional and/or National Research Committee at which the studies were conducted (number 2020-071, Nippon Life Hospital IRB)

and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the participant included in this article.

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