Acute Post-streptococcal Glomerulonephritis with Acute Kidney Injury in Nephrotic Syndrome with the Glomerular Deposition of Nephritis-associated Plasmin Receptor Antigen

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Abstract

We herein report the case of a 17-year-old man who developed an increased plasma creatinine level (11.1 mg/dL) and oliguria with massive proteinuria (27.3 g/day) four weeks after an abraded wound to his right knee. The histology of the renal biopsy specimens showed diffuse endocapillary proliferative glomerulonephritis with the deposition of nephritis-associated plasmin receptor in the glomerulus. A case of acute kidney injury due to nephrotic syndrome caused by acute post-streptococcal glomerulonephritis was diagnosed. His renal function and proteinuria were improved with supportive care, including hemodialysis, without the administration of immunosuppressive agents.

Key words: acute post-streptococcal glomerulonephritis, acute kidney injury, nephrotic syndrome, nephritis-associated plasmin receptor (NAPr)

(Intern Med 52: 2087-2091, 2013)
(DOI: 10.2169/internalmedicine.52.0103)

Introduction

Acute post-streptococcal glomerulonephritis (APSGN) may develop as a result of a streptococcal infection. The renal pathological change of APSGN is characterized by diffuse endocapillary proliferative glomerulonephritis (1). APSGN has been considered to have a generally good prognosis (2, 3). However, a small percentage of APSGN patients have reportedly developed an acute kidney injury (AKI) or nephrotic syndrome (2, 4-6). These atypical cases of APSGN are not easy to diagnose even when a renal biopsy is performed because several types of glomerular nephritis, such as lupus nephritis and membranoproliferative glomerulonephritis (MPGN), also at times show AKI or nephrotic syndrome due to endocapillary proliferative glomerulonephritis (7, 8).

Recently, the deposition of the nephritis-associated plasmin receptor (NAPr), which is universally present in hemolytic streptococcus and is considered to be homologous to the group A streptococcus plasmin receptor in the glomeruli, was detected as a nephritogenic antigen in APSGN patients (9, 10). Since NAPr deposition in the glomeruli is believed to trigger glomerular impairment both directly and indirectly in APSGN, it is a useful marker for the diagnosis of APSGN (10, 11). We herein describe a case of APSGN with AKI due to nephrotic syndrome with the glomerular deposition of NAPr.

Case Report

A 17-year-old Japanese man suffered an abraded wound on his right knee during a sporting activity in early August 2011. He consulted a clinic, complaining of pain, rubefac-
tion and swelling of his right knee 5 days after developing the wound. He was diagnosed with cellulitis of the right knee and treated with antibiotics (cefazolin and levofloxacin). Although a blood analysis showed that his C-reactive protein (CRP) level had increased to 3.0 mg/dL, his renal function and urinalysis showed no abnormalities at that point. His previous urinalysis that had been conducted for a school physical examination had also shown no abnormalities. Although his cellulitis improved, he experienced general fatigue, headache, palpebral edema, nausea and oliguria starting approximately 5 weeks after receiving his knee wound. He then consulted a different hospital and was transferred to our nephrology center for diagnosis and treatment. Table shows his other blood and urinalysis results upon admission. He was diagnosed to have AKI with nephrotic syndrome on the basis of these results. A renal biopsy was performed to investigate the pathology of his AKI with nephrotic syndrome. Light microscopic analysis of a renal biopsy specimen revealed glomeruli that were large and cellular with an infiltration of polymorphonuclear leukocytes and lymphocytes, and a focally and segmentally increased mesangial matrix as well as the proliferation of mesangial cells (Fig. 1A). Immunofluorescence analysis showed a garland type deposition of IgG and C3c in the glomerular capillary (Fig. 1B). Electron microscopy analysis showed hump-like subepithelial deposits (Fig. 1C, arrow). On the basis of his clinical history, laboratory data and renal histological analysis, we suspected a diagnosis of diffuse endocapillary proliferative glomerulonephritis due to APSGN. However, neither MPGN nor lupus nephritis could be definitively ruled out because these conditions can also show these same renal pathological changes with AKI and nephrotic syndrome that are rare in APSGN. Therefore, we performed NPAlr staining on the renal specimens. NPAlr deposition was observed in the neutrophils as well as in the mesangial and endothelial cells in all of the glomeruli with plasmn activity (Fig. 2). Thus, we diagnosed his condition as APSGN. He was treated using supportive care including multiple courses of hemodialysis as well as the administra-
Figure 1. Renal biopsy findings showing the histopathological features of diffuse endocapillary proliferative glomerular nephritis. (A) Light microscopy, periodic acid-Schiff (PAS) staining (×400) shows the presence of diffuse, large and cellular glomerulus with an infiltration of polymorphonuclear leukocytes and lymphocytes, as well as a focal and segmental increase of the mesangial matrix and a proliferation of the mesangial cells. (B) Immunofluorescence analysis (×400) shows the deposition of C3c in the glomerular capillary. (C) Electron microscopy (×6,000) shows the dense hump-like subepithelial deposits.

Figure 2. Immunofluorescence analysis shows the distribution of NAPlr (FITC, green) and C3 (Alexa Four 594, red) in a glomerulus (top panels) as well as plasmin activity in the glomerulus (in situ zymography) (bottom panels). NAPlr: nephritis-associated plasmin receptor

tion of anti-platelet agents, but was not treated with any immunosuppressive agents. Subsequent to the treatments, his urine volume increased, his plasma Cr level markedly decreased to 0.9 mg/dL and his plasma C3 level increased into the normal range on hospital day 20. The proteinuria and hematuria each followed a protracted course; however, these conditions recovered to normal ranges within 8 months of the initial renal biopsy.
We herein described a case of APSGN with AKI and nephrotic syndrome. The renal histology of APSGN has reportedly shown diffuse endocapillary proliferative glomerulonephritis. In addition, the existence of a preceding streptococcus infection, a decrease in the plasma C3 level and increases in the plasma ASO and ASK levels were helpful for the diagnosis of APSGN. Although APSGN shows a decreased glomerular filtration rate as well as some degree of proteinuria and hematuria, only a few cases cause AKI and nephrotic syndrome. It has been reported that the frequencies at which AKI and nephrotic syndrome are exhibited in APSGN are 9-27% and 20-25%, respectively (2, 6). In the present case, the renal pathological changes, the existence of a pre-infection, the increased ASO and ASK levels, and the decreased C3 level were consistent with APSGN (12). However, we could not initially rule out any other types of glomerular nephritis that can show diffuse endocapillary proliferative glomerulonephritis, such as MPGN or lupus nephritis, because the present case developed AKI in nephrotic syndrome. Therefore, we performed NAPlr staining on the glomeruli to confirm the diagnosis of APSGN. NAPlr is an antigen that is universally present in hemolytic streptococcus, and is considered to be homologous to the group A streptococcus plasmin receptor known as glyceraldehyde-3-phosphate dehydrogenase (9-11). The deposition of NAPlr in the glomeruli was reportedly observed in all patients for up to two weeks following the onset of APSGN, and it is considered to be a nephritis-induced antigen (9-11). NAPlr has been reported to damage the glomeruli by binding with the plasmin in the glomeruli. The binding action maintains the proteolytic activity of the plasmin, which in turn engages in fibrinolysis, extracellular matrix turnovers and inflammation by the activation of immune cells (11). It can also develop antibodies that form immune complexes that can be deposited in the glomeruli, accompanied by both complement and immune cells (11, 13). In the present case, NAPlr was positively stained in the neutrophils as well as in the mesangial and endothelial cells in all of the glomeruli. Plasmin activity was also observed. These findings contributed to the diagnosis of APSGN in the present case. However, a correlation between the intensity of the NAPlr staining and the severity of the clinical and pathological changes of APSGN has not yet been determined, and should therefore be elucidated in future studies. It is worthy to note that the distribution of NAPlr was different from that of C3c and the IgG that was detected as hump-like subepithelial deposits in the present case. This difference was consistent with the previous reports of APSGN. Although the mechanisms of this difference are not yet fully understood, Oda et al. suggested the following mechanism of the development of APSGN by NAPlr: First, the immunodetectable free NAPlr that are not fully saturated and can therefore interact with an anti-NAPlr antibody induce glomerular damage by binding with plasmin to maintain its proteolytic activity in the early stages of APSGN (10, 11, 14). Next, the host develops an immune reaction against NAPlr, and the circulating antibody forms an immune complex, either in situ or in circulation, that can pass through the damaged glomerular basement membrane and accumulate in the subepithelial space as humps (10, 11, 14). These latent steps of immune cell accumulation and immune complex deposition are accompanied by the activation of the complement (10, 11, 14). Further studies are needed to confirm the mechanisms of the development of APSGN based on the localizations of NAPlr at each stage.

The present case developed AKI and nephrotic syndrome which is rare in APSGN. Ferrario et al. reported that the severity of endocapillary proliferation, the deposition of an immune complex in the endothelial and mesangial cells and the severity of the interstitial damage were associated with AKI in APSGN (15). Sorger et al. reported that the deposition of IgG and C3 into the garland type rather than into the starry sky or mesangial types in the glomerular capillary showed severe proteinuria (16, 17). The severe endocapillary proliferation and the IgG and C3 deposition into the garland type in the glomeruli that was seen in the present case may contribute to the development of AKI with nephrotic syndrome. Although this patient initially presented with palpebral edema, he had a normal blood pressure with no apparent edema upon his admission to our department. A reduction in the body fluid levels owing to a loss of appetite caused by general fatigue and nausea may have contributed to the normal blood pressure and the lack of edema upon admission for the present case.

Although it has been reported that the administration of corticosteroids was effective in a few severe cases of APSGN that developed into nephrotic syndrome (18), this treatment course has not yet been well established. In the present case, we did not use any immunosuppressive agents, such as corticosteroids, since the patient’s renal function and proteinuria improved following admission. In addition, the patient’s renal function recovered to the normal range on hospital day 20. A urinalysis also revealed normal ranges for

![Renal biopsy](image-url)
all analytes within 8 months of the initial renal biopsy.

In conclusion, NAPlr staining of the glomeruli is thus considered to be a useful tool in the confirmation of the diagnosis of APSGN in AKI with nephrotic syndrome.

The authors state that they have no Conflict of Interest (COI).

References