CASE REPORT

A case of post-pneumococcal acute glomerulonephritis with glomerular depositions of nephritis-associated plasmin receptor

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Abstract We report the case of a 12-year-old girl who was referred to our hospital with anuria associated with pneumonia. On admission, the patient's blood test results revealed severe renal failure, hypoproteinemia, and hypocomplementemia. Her urinalysis results revealed hematuria, proteinuria, and a positive titer for *Streptococcus pneumoniae*. *S. pneumoniae* was also detected in her sputum and blood cultures. The patient was diagnosed with post-pneumococcal acute glomerulonephritis (AGN) with acute renal failure. A renal biopsy demonstrated the infiltration of neutrophils and mononuclear cells into capillary loops. Immunofluorescence studies showed dominant-positive deposition of C3c along the capillary loops and nephritis-associated plasmin receptor (NAPlr) depositions in the mesangial area and capillary loops. Electron microscopy revealed dense deposits in the glomerular basement membrane without a hump in the subepithelial area. These findings were consistent with endocapillary proliferative glomerulonephritis. AGN associated with pneumococcal infection is very rare. This case suggests that NAPlr is the causative antigen not only of post-

streptococcal AGN, but also of post-pneumococcal AGN. To our knowledge, this is the first report that shows a relationship between post-pneumococcal AGN and NAPlr depositions in the glomeruli.

Keywords Acute glomerulonephritis · Nephritis-associated plasmin receptor (NAPlr) · *Streptococcus pneumoniae*

Introduction

Post-streptococcal acute glomerulonephritis (AGN) accounts for more than 80 % of childhood AGN cases. In contrast, AGN associated with pneumococcal infection is very rare. The nephritis-associated plasmin receptor (NAPlr) is presumed to be a virulence factor associated with post-streptococcal AGN [1]. To our knowledge, this is the first report that shows a relationship between AGN secondary to pneumococcal infection and glomerular depositions of NAPlr.

Case report

A 12-year-old girl was referred to our hospital because of anuria. The patient had not experienced proteinuria, hematuria, or urinary tract infection previously. She had no family history of renal disease. She had not presented previous cutaneous or pharyngeal symptoms in the several months before the onset, suggesting *Streptococcus pyogenes* infection. She had cough 1 week prior to hospital admission, which was followed by fever, vomiting, and severe diarrhea. On Day 6 after the onset of these symptoms, the patient had visited the municipal hospital because

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of persistent cough, fever, and severe diarrhea. Laboratory examination findings indicated an elevated serum creatinine level of 7.4 mg/dL and a urea nitrogen level of 78 mg/dL. The patient's white blood cell (WBC) count and serum C-reactive protein (CRP) levels were elevated: 27,000/ μ L and 27 mg/dL, respectively. After admission, antibiotic therapy was administered for the bacterial infection. Although fluid replacement therapy was initiated owing to suspicion of pre-renal acute renal failure, the patient's renal function did not improve, and her anuria was persistent. Therefore, she was transferred to our hospital on Day 7 after the onset of symptoms.

Upon admission to our hospital, the patient's height was 162 cm, and her weight was 55.2 kg (it was 58 kg before symptom onset). Her body temperature, heart rate, respiratory rate, blood pressure, and percutaneous oxygen saturation were 36.6 °C, 72 beats per minute, 28 breaths per minute, 108/60 mmHg, and 96 %, respectively. The patient's pharynx was slightly injected, and the palatine tonsils were hypertrophied (Mackenzie grade 1) without pus secretion. Respiratory sounds were decreased in the left lower lobe, and wheezing was heard. The blood test results revealed severe renal failure, hypoproteinemia, and hypocomplementemia (Table 1). Serum anti-streptolysin O antibody (ASO) and anti-streptokinase antibody (ASK) levels were elevated to 903 IU/mL and 1:10,240, respectively. WBC count and serum CRP level were elevated at 16,700/ μ L and 27.8 mg/dL, respectively. Both sputum and blood culture tests performed prior to the start of antibiotic therapy in the municipal hospital

indicated infection by *Streptococcus pneumoniae*. Urinalysis results were positive for *S. pneumoniae* antigen and revealed macrohematuria and pyuria. The urine protein-to-creatinine ratio (uP/uCr) increased to 2.2 g/g Cr. Ultrasonography revealed enlargement of the both kidneys and increased brightness of both kidney cortices. Chest computed tomography scan showed an infiltrative shadow on the left lower lobe and slight pleural effusion on both sides.

The patient was diagnosed with post-pneumococcal AGN with acute renal failure. On the day of admission, she began acute blood purification therapy. She underwent hemodialysis therapy intermittently seven times for 12 days after admission. The patient was also administered intravenous antibiotics for pneumonia and sepsis. On Day 13 of the patient's hospital stay, her blood urea nitrogen stabilized at 30–40 mg/dL and her serum creatinine level stabilized at 4–5 mg/dL without hemodialysis therapy; both eventually improved as urine volume increased.

A renal biopsy was performed on Day 16 of the hospital stay because massive proteinuria persisted despite improved renal function. Eighteen glomeruli were observed on light microscopy. Seven of 18 glomeruli exhibited cellular crescent formation (Fig. 1a), and four exhibited adhesion to the Bowman capsule. The glomerulus was distended without mesangial expansion or mesangial cell proliferation (Fig. 1b). Endocapillary hypercellularity (mainly of neutrophils and mononuclear cells) was prominent (Fig. 1b). Focal infiltration of neutrophils into the tubulointerstitium and dilation of tubules were observed. Immunofluorescence

Table 1 Laboratory data of the patient on admission to our hospital

WBC 16,700/ μ L	CRP 27.8 mg/dL	ASO 903 IU/mL	(Urinalysis)
Hb 11.9 g/dL	TP 5.5 g/dL	ASK 1:10,240	RBC >100/HPF
Ht 35.1 %	Alb 2.0 g/dL	Anti-ds DNA Ab 1.7 IU/mL	WBC >100/HPF
Plt 25.4×10^4 / μ L	BUN 104 mg/dL	MPO-ANCA <1.3 IU/mL	NAG 14.5 IU/g Cr
PT% 66.7 %	Cr 9.03 mg/dL	PR3-ANCA <3.5 IU/mL	β_2 MG 1,282 μ g/L
APTT 33.1 s	UA 15.4 mg/dL	Anti-GBM Ab <10 IU/mL	uP/uCr ratio 2.2 g/g Cr
FDP 38.2 μ g/dL	Na 130 mmol/L	(Venous blood gas test)	FENa 0.34 %
Fibrinogen 734 mg/dL	K 4.5 mmol/L	pH 7.310	
D-dimer 21.1 μ g/mL	Cl 94 mmol/L	PCO ₂ 32.7 mmHg	
	Ca 8.3 mg/dL	HCO ₃ ⁻ 16.0 mmol/L	
	P 7.5 mg/dL	BE -8.9 mmol/L	
	C3 10 mg/dL		
	C4 33 mg/dL		

WBC white blood cell, Hb hemoglobin, Ht hematocrit, Plt platelet, PT% prothrombin time %, APTT activated partial thromboplastin time, FDP fibrinogen degradation product, CRP C-reactive protein, TP total protein, Alb albumin, BUN blood urea nitrogen, Cr creatinine, UA uric acid, Na sodium, K potassium, Cl chlorine, Ca calcium, P phosphorus, C3 complement 3, C4 complement 4, ASO anti-streptolysin O antibody, ASK anti-streptokinase antibody, Anti-ds DNA Ab anti-double stranded DNA antibody, MPO-ANCA myeloperoxidase-antineutrophil cytoplasmic antibody, PR3-ANCA proteinase 3-antineutrophil cytoplasmic antibody, Anti-GBM Ab anti-glomerular basement membrane antibody, PCO₂ partial pressure of carbon dioxide, HCO₃⁻ bicarbonate ion, BE base excess, RBC red blood cell, NAG N-acetyl- β -D-glucosaminase, β_2 MG β_2 microglobulin, uP/uCr ratio urine protein-to-creatinine ratio, FENa fractional excretion of sodium

Fig. 1 **a** The glomerulus exhibiting cellular crescent formation (periodic acid silver-methenamine-Masson stain). **b** Prominent endocapillary hypercellularity, mainly of neutrophils and mononuclear cells, without mesangial expansion or mesangial cell proliferation (periodic acid silver-methenamine-Masson stain)

staining revealed dominant-positive deposition of C3c in the capillary loops (Fig. 2). Furthermore, glomerular deposition of NAP1r (Fig. 3a) and up-regulated plasmin activity (Fig. 3b) were observed by immunofluorescence staining and in situ zymography, respectively. Electron microscopic examination revealed dense deposits in the glomerular basement membrane without a hump in the subepithelial area. These findings were consistent with endocapillary proliferative glomerulonephritis.

On Day 23 of the hospital stay, three courses of methyl prednisolone pulse therapy were started for crescentic glomerulonephritis. For each course, intravenous methyl prednisolone (500 mg/dose) was administered consecutively for 3 days/week, followed by prednisolone (30 mg/day). Afterwards, oral prednisolone was started at 30 mg/day and then tapered gradually. The levels of uP/uCr, serum albumin, serum Cr, and serum C3 all improved gradually after steroid therapy was initiated, and returned

Fig. 2 Immunofluorescence staining depicts dominant-positive deposition of C3c in the capillary loops

to the normal range at the time of discharge, on Day 54 of the hospital stay. Serum ASO and ASK levels peaked upon admission and decreased to 780 IU/mL and 1:2,560, respectively, at Day 43 of admission. The patient's laboratory values have remained normal since she was discharged from the hospital.

Discussion

Acute glomerulonephritis associated with pneumococcal infection is very rare. To our knowledge, no study has reported the causative antigen of AGN associated with pneumococcal infection. In the present case, our patient developed AGN after pneumococcal infection and had NAP1r deposition in the glomeruli. This case may suggest that NAP1r is the causative antigen not only of post-streptococcal AGN, but also of post-pneumococcal AGN.

Some pediatric cases of AGN associated with pneumococcal infection have been reported [2, 3]. The time interval between pneumococcal infection and AGN is reportedly between 1 and 10 days [2, 3]. This is consistent with the clinical course of our case. The presence of pneumonia and the identification of *S. pneumoniae* in the blood and sputum cultures at the time of presentation suggested that *S. pneumoniae* was the causative agent of AGN. However, the following findings confused the final diagnosis of post-pneumococcal AGN with post-streptococcal AGN: (1) immunofluorescence staining revealed NAP1r deposition in the glomeruli, and (2) serum ASO and ASK levels were high at the time of presentation.

Fig. 3 **a** Immunofluorescence staining depicted nephritis-associated plasmin receptor (NAPlr) depositions (arrow) in the glomeruli. **b** Up-regulated plasmin activity (arrow) was observed by in situ zymography. The distribution of plasmin activity was similar to that of NAPlr deposition

NAPlr was previously isolated as the causative antigen of AGN after group A *Streptococcus* infection and was known to be identical to streptococcal glyceraldehyde-3-phosphate dehydrogenase (GAPDH) [1]. The sequences of pneumococcal GAPDH share 89.0 % identity with those of GAPDH of *S. pyogenes* (streptococcal GAPDH: NAPlr) [4]. Moreover, the C-terminal sequences of pneumococcal GAPDH, which are most likely associated with plasmin-binding activity, are 100 % identical to those of streptococcal GAPDH (NAPlr) [4]. It is assumed that up-regulated plasmin activity associated with streptococcal GAPDH (NAPlr) mediates glomerular damage in post-streptococcal AGN [1, 4]. Therefore, it seems highly plausible that the pneumococcal GAPDH shares similar function with streptococcal GAPDH (NAPlr) and induce plasmin-related glomerular damage in post-pneumococcal AGN. Thus, we suspected that glomerular deposition detected by anti-NAPlr antibody in this patient was not

exactly the streptococcal GAPDH (NAPlr) but was the pneumococcal GAPDH, which might play important roles similarly in the induction of post-pneumococcal AGN.

Serum ASO level often increases non-specifically in the absence of streptococcal infection. Cases of post-pneumococcal AGN with non-specific increases in serum ASO levels have been reported [2, 3, 5]. A retrospective study of six patients with AGN secondary to pneumonia reported that a non-specific increase of serum ASO levels was observed in five cases in the absence of streptococcal infection [6]. A study showed that the streptococcal streptokinase and the fragment generated by the plasmin (Pm) digestion of fibronectin (FN), the main component of the extracellular matrix, share a common epitope that is recognized by a human anti-streptokinase antibody (ASK) [7]. This finding suggests that the Pm-generated FN fragment could react with circulating ASKs elicited by previous streptococcal infection. Therefore, we think that the elevation of serum ASK level in the present case was caused by the following mechanism. The high level of plasma fibrinogen degradation product and D-dimer in the present case suggested that coagulation and fibrinolytic pathways were activated during *S. pneumoniae* sepsis. Pm, activated in association with the activated fibrinolytic pathways, digested FN and promoted the production of the FN fragment. The FN fragment may have promoted the production of ASK in the present case.

It is difficult to prove that there was no involvement of group A *Streptococcus* infection in the present case. However, the patient had not presented previous cutaneous or pharyngeal symptoms in the several months before the onset, suggesting *S. pyogenes* infection. In addition, we believe that it is also difficult to deny any causal relationship between severe *S. pneumoniae* infection and acute glomerulonephritis in the present case. Based on these considerations, we finally diagnosed our patient with post-pneumococcal AGN. This case suggests that bacterial GAPDH (which includes NAPlr) is the causative antigen of post-pneumococcal AGN, as well as post-streptococcal AGN.

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

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