Garland-pattern postinfectious glomerulonephritis with IgA-dominant deposition

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Abstract A histological subtype of acute postinfectious glomerulonephritis (APIGN), the garland pattern, is identified not only by characteristic histological findings, but also by severe clinical course as compared with typical APIGN. However, since the morbidity of APIGN has decreased globally, there have been few reports on this disease form in developed countries during the last two decades. Herein, we report a case of adolescent garland-pattern APIGN with IgA-dominant deposits, presenting with severe nephrotic syndrome and protracted hematuria and proteinuria. We also review the clinical and histological features of 13 previously reported cases in Japan and compare them with our present case. In our review, we confirmed IgA deposition in at least three of these patients, in whom urinary protein excretion tended to be greater than those patients without IgA. Greater awareness of this condition is necessary to ensure appropriate follow-up of the clinical course of patients with garland-pattern APIGN with IgA deposition.

Keywords Postinfectious glomerulonephritis · Garland pattern · IgA-dominant · Nephrotic syndrome · Hypocomplementemia · Corticosteroid

Introduction

Acute postinfectious glomerulonephritis (APIGN) is a representative disease of acute nephritic syndrome, characterized by hematuria, edema, and hypertension. Most cases in young people recover with only conservative treatment, indicating an excellent prognosis of typical APIGN [1, 2]. However, some patients with garland-pattern APIGN present with nephrotic syndrome (NS) and/or acute renal failure (ARF) [3]. Moreover, although relatively uncommon, some cases progress to chronic nephritis or end-stage renal disease [4, 5]. Nowadays, the morbidity of APIGN has decreased globally, especially in developed countries, and there has been a dearth of reports of garland-pattern APIGN during the last two decades [6, 7]. Here, we report a case of adolescent garland-pattern APIGN with IgA-dominant deposits.

Case report

A 16-year-old girl with no significant past medical history noticed generalized edema approximately 2 weeks after suffering from a fever of 38 °C. She had no symptoms suggestive of upper respiratory tract or skin infection, and the flu test was negative. She had a rapid weight gain of 5 kg within a month, and was, thus, referred to our hospital for admission. On admission, there was bilateral pitting edema of the legs. Her blood pressure was 109/65 mmHg. Laboratory findings were as follows: blood urea nitrogen 21 mg/dl, serum creatinine 0.76 mg/dl, total protein 4.4 g/dl, serum albumin 1.5 g/dl, antistreptolysin O (ASO) titer 188 IU/ml (normal 0–244 IU/ml), C3 84 mg/dl (normal 65–135 mg/dl), C4 15 mg/dl (normal 13–35 mg/dl), CH50 33 U/ml (normal 30–45 U/ml), IgA 284 mg/dl (normal

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110–410 mg/dl), cryoglobulin (+), antinuclear antibody (–), antineutrophil cytoplasmic antibody (–), rheumatoid factor (–), hepatitis B surface antigen (–), and hepatitis C antibody (–). Urinalysis showed macrohematuria, with the

sediment containing more than 100 red blood cells (RBCs), 30–49 leukocytes, and a few granular casts per high-power field (HPF); spot urinary protein excretion was 14.5 g/g creatinine, all of which suggested NS. Chest X-ray

Fig. 1 Renal biopsy findings. **a** Light microscopic findings of the first renal biopsy showing endocapillary proliferative glomerulonephritis with infiltrating neutrophils (arrows) by periodic acid-Schiff staining ($\times 400$). **b, c** Immunofluorescence showing tight deposits of C3 (**b**) and IgA (**c**) along the capillary walls and parts of the mesangium, indicating the garland pattern, as well as IgA-dominant acute postinfectious glomerulonephritis (APIGN). **d, e** Electron microscopic findings of the first renal biopsy showing subepithelial deposits (**d** $\times 2,000$, **e** $\times 6,500$). **f** Light microscopic findings of the second renal biopsy: endocapillary proliferation of the glomeruli had disappeared, although diffuse mesangial proliferation persisted on periodic acid-Schiff staining ($\times 400$). **g, h** Immunofluorescence showing deposits of C3 (**g**) and IgA (**h**) in the mesangial region, indicating mesangial-pattern APIGN. **i** Electron microscopic findings of the second renal biopsy showing a small amount of deposits in the subepithelial, subendothelial, and paramesangial areas ($\times 2,000$)

demonstrated neither cardiac enlargement nor pleural effusion. Ultrasonography showed normal kidney shape.

The first renal biopsy was done on the fourth day of hospitalization (Fig. 1a–e). Light microscopy (LM) showed proliferative endocapillary glomerulonephritis, accompanied by diffuse proliferation of mesangial cells, swelling of endothelial cells, infiltration with neutrophils, and partial lobulation of the glomeruli. Immunofluorescent microscopic examination (IF) revealed tight C3 and IgA deposits along the capillary walls, which is typical of garland-pattern APIGN. C4, C1q, IgG, and IgM were negative. Electron microscopy (EM) showed massive subepithelial deposits, although subendothelial or mesangial deposits were not detected. Besides, there were no electron-dense deposits with a “fingerprint”-like appearance, to indicate the presence of cryoglobulins. Based on these renal biopsy findings and the clinical course and findings, she was diagnosed with garland-pattern APIGN. We measured the levels of antibodies to parvovirus, herpes simplex virus, varicella zoster virus, cytomegalovirus, measles virus, rubella virus, mumps virus, Epstein–Barr virus, and mycoplasma and *Legionella* urinary antigens, which have been reported as the other responsible microorganisms of APIGN, apart from group A *Streptococcus*

(GAS). However, no causative microorganism of the preceding infection could be identified.

At first, minimal change disease was highly suspected based on her age, rapidity of onset, and laboratory findings. Since it was speculated that the macrohematuria resulted from menstruation as urinalysis showed few signs of glomerular hematuria, we initiated oral prednisolone at 50 mg/day from the second hospital day (Fig. 2). However, microscopic hematuria and severe proteinuria persisted after completion of her menstrual period, even 2 weeks after the initiation of treatment. Based on the renal biopsy findings and clinical course, we added methylprednisolone pulse therapy at 500 mg/day for 3 consecutive days from the fifteenth day of hospitalization, followed by 50 mg of oral prednisolone for 6 weeks in total, after which prednisolone was tapered. On the eighteenth hospital day, she complained of sudden pain in the left lower extremity and was examined for deep vein thrombosis by means of contrast-enhanced computed tomography, which demonstrated no thrombus; her pain disappeared soon thereafter. Subsequently, her serum creatinine increased to 3.5 mg/dl, which suggested the presence of contrast nephropathy rather than worsening of the glomerulonephritis. However, she did not present with any symptoms associated with ARF and her renal function gradually normalized with only conservative treatment. Macroscopic hematuria disappeared soon after the initiation of therapy, although NS continued for 3 months. She showed a curious lack of hypertension, hypocomplementemia, and elevation of ASO titer during hospitalization. She also consistently demonstrated no purpura, and cryoglobulin was negative, except at the time of admission.

A second renal biopsy 9 months after her initial illness (Fig. 1f–i) demonstrated that the endocapillary proliferation and partial lobulation of the glomeruli had disappeared, although diffuse mesangial proliferation remained. IF showed C3, IgA, and IgG deposits in the mesangial region, indicative of mesangial-pattern glomerulonephritis.

Fig. 2 Clinical course during the first 4 months

Table 1 Summary of garland-pattern acute postinfectious glomerulonephritis (APIGN) cases in Japan

Case	Age (years)	Sex	Max UP (g/day)	Alb (g/dl)	Cre (mg/dl)	Hypertension	Hypocomplementemia	IgA deposition	Responsible microorganism	Therapy	Time to disappearance of proteinuria (months)	Year
1	2	F	5.5 ^a	1.3	1.1	(−)	(+)	(−)	N/A	Supportive	N/A (>2.5)	1992
2	35	M	15–20	2.4	1	(−)	(−)	(+)	GAS	CTC	6	1992
3	7	F	12	3	5.2	(+)	(+)	(+)	GAS	HD, CTC (pulse), CPA, MZR	4–6	1994
4	8	M	8 ^a	3.6	3.7	(+)	(+)	(−)	GAS	CVVH, CAPD, PE, CTC (pulse)	<15	1997
5	17	M	7.1 ^a	2.6	3.5	N/A	(+)	(−)	GAS	CTC (pulse)	18	1997
6	8	M	14	3.5	0.6	(+)	(+)	(+)	N/A	CTC (pulse), CPA	4	1999
7	24	M	(4+)	2.4	12.3	(+)	(+)	(−)	GAS	HD, CTC (pulse)	N/A	1999
8	13	M	6.5 ^a	2.8	N/A	N/A	(+)	(−)	N/A	CTC	N/A (<8?)	2003
9	8	F	N/A	N/A	2.3	N/A	N/A	(−)	GAS	HD	N/A	2005
10	6	M	>300 mg/dl	2.8	3.2	(+)	(+)	N/A	GAS	HD, CTC (pulse)	N/A	2007
11	6	F	>10	N/A	1.6	(+)	(+)	(−)	GAS	PE, CTC (pulse)	6	2007
12	32	F	11.5 ^a	N/A	1.1	(−)	(+)	N/A	N/A	CTC (pulse)	1	2007
13	N/A	N/A	23	2.3	17.3	N/A	(+)	N/A	GAS	HD, CTC (pulse)	N/A (>9)	2009
14	16	F	14.6	1.5	0.76	(−)	(−)	(+)	Not identified	CTC (pulse)	Persisted (>36)	Current case

Max UP maximum urinary protein excretion, Alb serum albumin on admission, Cre serum creatinine on admission, N/A not available, GAS group A *Streptococcus*, CTC corticosteroid, HD hemodialysis, CPA cyclophosphamide, MZR mizoribine, CVVH continuous veno-venous hemofiltration, CAPD continuous ambulatory peritoneal dialysis, PE plasma exchange

^a Urinary protein excretion on admission

EM showed a small amount of deposits in the subepithelial, subendothelial, and paramesangial areas. These results indicated that the glomerulonephritis, though on its way to recovery, was still histologically active. After prednisolone was completely tapered off, supportive therapy was administered on an outpatient basis. To date, more than 3 years after disease onset, the moderate to severe glomerular hematuria with proteinuria (0.5–1.0 g/g creatinine) has remained unchanged.

Discussion

Sorger et al. [3] classified acute poststreptococcal glomerulonephritis (APSGN) into three subtypes, starry sky pattern, garland pattern, and mesangial pattern, based on immunofluorescent studies. The garland pattern is characterized by the presence of densely packed C3 and immunoglobulin deposits along the capillary walls. LM often shows distinctive histopathological findings similar to membranoproliferative glomerulonephritis. Reportedly, garland-pattern APIGN more frequently presents with NS and/or ARF compared to the other two types, with some patients progressing to chronic nephritis or end-stage renal disease [4, 5].

Table 1 shows a summary of the 14 reported cases of garland-pattern APIGN in Japan, including our case. Thirteen cases were reported to the Japana Centra Revuo Medicina between 1992 and 2009. All of the patients were young people without any comorbidities (male:female ratio 7:6; age range 2–35 years old; average age 14 years old; $n = 13$). Complications of hypertension and hypocomplementemia were seen in 60 and 85 % of the patients, respectively. Only Cases 2 and 14 (our case) showed neither hypertension nor hypocomplementemia. 64 % were caused by GAS, and no responsible microorganisms other than GAS were reported in the other cases. At least 9 cases developed both severe proteinuria (more than 5.5 g/day) and ARF, and 6 of 10 cases complicated by ARF required dialysis therapy [hemodialysis in 5 cases, continuous venovenous hemofiltration (CVVH) and continuous ambulatory peritoneal dialysis (CAPD) in 1 case]. Corticosteroids were administered in 12 cases (86 %), while supportive therapy was required in only 1 patient (Case 1), who developed both NS and ARF, and presented with protracted severe proteinuria and renal dysfunction for more than 2.5 months. The time to disappearance of proteinuria varied in each case, although it took several months or more in most cases. Although in 5 of the previously reported cases it was not stated whether proteinuria finally disappeared or not, the abnormal urinalysis seen in our patient seems prolonged compared to the other cases.

Recently, a morphologic variant of APIGN, IgA-dominant APIGN, has been recognized. To date, 85 such cases

have been reported in the English literature [8]. This variant is characterized by intense deposits of IgA along the peripheral capillary walls and/or in mesangial regions, as the dominant or co-dominant immunoglobulin on IF, along with diffuse endocapillary proliferative glomerulonephritis on LM and subepithelial electron-dense deposits on EM [9]. IgA-dominant APIGN typically occurs in association with staphylococcal infection in the elderly, especially those with some predisposing factors such as diabetes mellitus, and frequently presents with severe proteinuria and ARF, resulting in a poor prognosis compared to classic APIGN [8, 9]. The first renal biopsy in our patient revealed tight dense deposits of C3 and IgA along the capillary walls, indicating both garland-pattern APIGN as well as IgA-dominant APIGN. However, she showed a curious lack of hypertension, hypocomplementemia, and specific preceding infectious episodes. In addition, she was an adolescent with no significant past medical history. These findings indicate an atypical clinical course and findings of garland-pattern APIGN, as well as of IgA-dominant APIGN. Including our present case, at least 4 cases of garland-pattern APIGN accompanied by IgA deposition have been reported in Japan (Table 1). There are no obvious differences in age, sex, and serological findings in patients with and without IgA deposition. However, the maximum urinary protein excretion in patients with IgA deposition tends to be greater than in those patients without IgA deposits. Although only a small number of patients have been reported at this time, these cases might require more careful attention.

Clinically, our patient presented with higher creatinine levels and severe NS, suggesting a poor prognosis [10–14]. Hence, we administered corticosteroid treatment combined with methylprednisolone pulse therapy. However, the efficacy of immunosuppressive therapy for severe cases of APIGN, including garland-pattern or IgA-dominant APIGN, is still controversial. Roy et al. [15] reported that treatment with prednisone, azathioprine, cyclophosphamide, dipyridamol, and heparin offered no advantage in patients with rapidly progressive crescentic APIGN. Conversely, there are some reports that methylprednisolone pulse therapy or oral prednisolone treatment is effective for APIGN complicated by NS, ARF, or crescent formation in renal biopsy specimens [10, 16–19]. This needs further investigation.

Regarding the causative microorganisms of APIGN, more diverse organisms, such as *Staphylococcus* and Gram-negative bacteria, have been increasingly linked [11]. Nasr et al. [4] examined four recent studies, including 242 patients of APIGN, conducted in developed countries and reported that the responsible bacterium was *Streptococcus* in 68 patients (28 %), *Staphylococcus* in 44 patients (17 %), and Gram-negative bacteria in 25 patients (10 %). They also reported that 7–16 % of patients had no clinical

evidence of infection preceding the renal disease, and the offending microorganism was not identified in more than a quarter of the patients. Some previous reports also indicate no infectious histories in patients with IgA-dominant APIGN [14, 20, 21]. These may indicate that the background of APIGN is changing in modern times. Srisawat et al. [22] examined the clinicopathological features of post non-streptococcal glomerulonephritis in adults and reported that a low level of C3 was detected in only 26.3 % of patients, which was statistically significantly different from APSGN ($p < 0.01$). They also reported that there was no significant difference in the intensity of IgA on IF between these two types of glomerulonephritis. Therefore, it is speculated that streptococcal pyrogenic exotoxin B (SPEB) and nephritis-associated plasmin receptor (NAPlr), which are major putative nephritogenic antigens of GAS, directly activate alternative pathways and lower the C3 level, indicating that the pathogenesis of hypocomplementemia in APIGN is mainly linked to GAS infection [23, 24]. Our patient had a fever of 38 °C approximately 2 weeks before the disease onset. However, she did not show hypocomplementemia, preceding specific infectious episodes, or any detectable causative microorganisms as far as we could investigate. An elevation of ASO titer was not seen during hospitalization. Considering all of these facts and the presence of IgA deposition, *Staphylococcus* might have caused subclinical infection and the subsequent renal disease.

In conclusion, we report a case of adolescent garland-pattern APIGN with IgA-dominant deposition. Our review of the literature in Japan shows that garland-pattern APIGN is commonly caused by GAS infection and frequently occurs with hypocomplementemia complicated by NS and/or ARF. Some patients show IgA deposition along with C3 on IF and tend to have greater proteinuria than patients without IgA. Therefore, greater awareness of this disease form and follow-up of the clinical course of garland-pattern APIGN with IgA-dominant deposition is required.

Conflict of interest All the authors have declared no competing interest.

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