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CASE REPORT

Granulomatosis with polyangiitis associated with IgA nephropathy

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Abstract Granulomatosis with polyangiitis (GPA), previously referred to as Wegener's granulomatosis, is a rare necrotizing granulomatous vasculitis, especially in children. GPA affects small- to medium-sized vessels, leading to involvement of multiple organs, including the upper and lower respiratory tracts and kidneys. Glomerular lesions associated with GPA typically present as crescentic glomerulonephritis with necrotizing lesions, with little or no staining for immunoglobulins and complement proteins. We report a unique pediatric case of GPA associated with IgA nephropathy, a representative immune-mediated glomerular disease. The initial renal biopsy specimen revealed fibrous sclerosis and mild mesangial proliferation without deposition of IgA. However, after clinical remission of GPA by treatment, the serum IgA level continued to be significantly higher than normal, and her paranasal sinusitis was poorly controlled. An acute upper respiratory infection resulted in worsened urinary findings without any systemic signs of GPA. The second renal biopsy specimen revealed deposition of IgA and C3 in the mesangium. The patient was treated with oral prednisolone alone, which led to complete remission of proteinuria within 1 month. IgA nephropathy is possibly associated with GPA during remission stage, and serum IgA level may be a valuable indicator to predict its association.

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Introduction

Granulomatosis with polyangiitis (GPA), previously referred to as Wegener's granulomatosis (WG) [1], is a rare necrotizing granulomatous vasculitis, especially in children [2]. GPA affects small- to medium-sized vessels, leading to involvement of multiple organs, including the upper and lower respiratory tracts and kidneys. Serum anti-neutrophil cytoplasmic antibody directed against proteinase 3 (PR3-ANCA) is known to be involved in the pathophysiology of GPA; however, the precise pathomechanism related to PR3-ANCA remains elusive. Glomerular lesions associated with GPA typically present as crescentic glomerulonephritis with necrotizing lesions, with little or no staining for immunoglobulins and complement proteins. This condition is referred to as pauci-immune glomerulonephritis [3]. Here, we present a unique pediatric case of GPA associated with IgA nephropathy, a representative immune-mediated glomerular disease. To the best of our knowledge, this is the first pediatric case of GPA in which IgA nephropathy was associated with the remission stage.

Case report

Our patient was a 13-year-old girl who had been admitted to a previous hospital because of bilateral ankle joint pain. Several recurrent red and purple palpable purpura were observed mainly on the upper and lower extremities but not on the buttocks. No colicky intermittent abdominal pain occurred. She also had had microscopic hematuria with

30–49 red blood cells (RBC)/high-power field and thus had been diagnosed with Henoch–Schönlein purpura (HSP). Her symptoms, including the hematuria, improved rapidly upon treatment with oral prednisolone at initial dosage of 1 mg/kg/day. However, these symptoms reappeared and subsided depending on the prednisolone dosage over the 4-week hospitalization. Eventually, she was also found to have hoarseness and mild proteinuria, and therefore she was transferred to our hospital. On admission to our hospital, she was treated with prednisolone at dosage of 1 mg/kg/day. The pertinent physical examination findings included blood pressure of 112/60 mmHg, respiratory rate of 20/min, and nasal obstruction, but she was afebrile. There were several areas of purpura on the bilateral upper and lower extremities. Her knees, ankles, and wrist joints exhibited no swelling and no tenderness. Admission laboratory studies revealed the following values: hemoglobin: 12.8 g/dl; white blood cells: 16,700/ml; platelet count: 30.8×10^4/ml; C-reactive protein: 1.3 mg/dl; erythrocyte sedimentation rate: 55 mm in 60 min; blood urea nitrogen: 5.9 mg/dl; and serum creatinine: 0.5 mg/dl (estimated GFR: 109 %). Serum complement 3 and 4, and CH50 were normal. The serum immunoglobulin A level was high, at 437 mg/dl (mean ± 2 SD in our hospital: 29–325 mg/dl), but the levels of other immunoglobulins, including the G, M, and D isotypes, were normal. Anti-nuclear antibody and anti-double stranded DNA antibody tests were negative. An enzyme-linked immunosorbent assay (ELISA) yielded negative results for anti-myeloperoxidase ANCA but detected an extremely high titer of PR3-ANCA [400 ELISA units (EU)/ml; normal value: <10 EU/ml]. Urinalysis of first morning urine revealed proteinuria 1+ (protein:creatinine ratio 0.3 g/g) and 5–9 (RBC)/high-power field. Skin biopsy of a purpura lesion showed nonspecific lymphocyte infiltration surrounding the vessels. Laryngoscopy did not reveal any apparent granulomatous lesions in the upper airway, including the vocal cords; however, computed tomography (CT) scan of the paranasal sinuses revealed prominent thickening of the inner lining of the maxillary and frontal sinuses. CT scan of the chest revealed no pathologic findings. An initial renal biopsy was performed. Light microscopic examination revealed 8 glomeruli. There were signs of fibrous sclerosis in 1 glomerulus and signs of mild mesangial proliferation in the other 7 glomeruli. Immunofluorescence microscopy and electron microscopy demonstrated no immune deposits or electron-dense deposits, respectively. Thus, the patient was eventually diagnosed with GPA and then treated with intravenous methylprednisolone pulse therapy at dosage of 1,000 mg/day for 3 consecutive days, followed by oral prednisolone (1 mg/kg/day) and oral cyclophosphamide (2 mg/kg/day) for 12 weeks. This combined immunosuppressive therapy led to complete clinical remission together with normalization of the altered laboratory values, including the PR3-ANCA level (Fig. 1a). The patient's condition, including urinalysis results, remained stable despite tapering off the prednisolone to 1 mg/day over a period of 44 months. However, the serum IgA level continued to be significantly higher than normal (Fig. 1a), and her paranasal sinusitis was poorly controlled despite prophylactic treatment with trimethoprim + sulfamethoxazole. Eventually, an acute upper respiratory infection resulted in worsened urinary findings [protein:creatinine ratio 1.1 g/g and 10–19 (RBC)/high-power field]. A second renal biopsy was performed to evaluate the renal pathology and determine the appropriate approach for further management. Light microscopic examination of 18 glomeruli revealed segmental sclerosis in 1 and fibrous crescent in 1. The other glomeruli showed mild to moderate mesangial matrix expansion and cell proliferation (Fig. 1b). Immunofluorescence microscopy demonstrated predominant deposition of 2+ IgA (Fig. 1c), 2+ IgG and 2+ C3 (Fig. 1d) in a granular pattern in the mesangium. Electron-dense deposits were observed in the paramesangial region (Fig. 1e). Thus, we concluded that the IgA nephropathy was associated with the remission stage of GPA. Treatment with oral prednisolone (30 mg/day) was again initiated. Thereafter, although the clinical course of paranasal sinusitis was not improved, the proteinuria remitted completely within 1 month.

Discussion

Pauci-immune extracapillary necrotizing glomerulonephritis is a characteristic feature of renal involvement in patients with GPA. However, there is a detailed pathological report showing that, in an analysis of 73 GPA patients, a mean of 40 % of the glomeruli in a biopsy sample were normal, 42 % had crescents, 16 % exhibited signs of glomerulosclerosis, and 23 % exhibited signs of fibrinoid necrosis of the glomerular tufts [4]. On the other hand, the initial renal biopsy specimen from our case included only 8 glomeruli, where there was no typical necrotizing glomerular findings; instead, only fibrous sclerosis was found in 1 glomerulus. Therefore, the diagnosis for GPA in this case based on the renal histology was limited. However, the abnormal urinary findings, the extremely high titer of serum PR3-ANCA, and the existence of severe sinusitis distinctly indicated that our patient could be diagnosed as having GPA based on the definition by the European League Against Rheumatism/Paediatric Rheumatology International Trials Organisation/Paediatric Rheumatology European Society (EULAR/PRINTO/PRES) criteria [5]. Although the initial onset of purpura observed in the previous hospital was first diagnosed due to

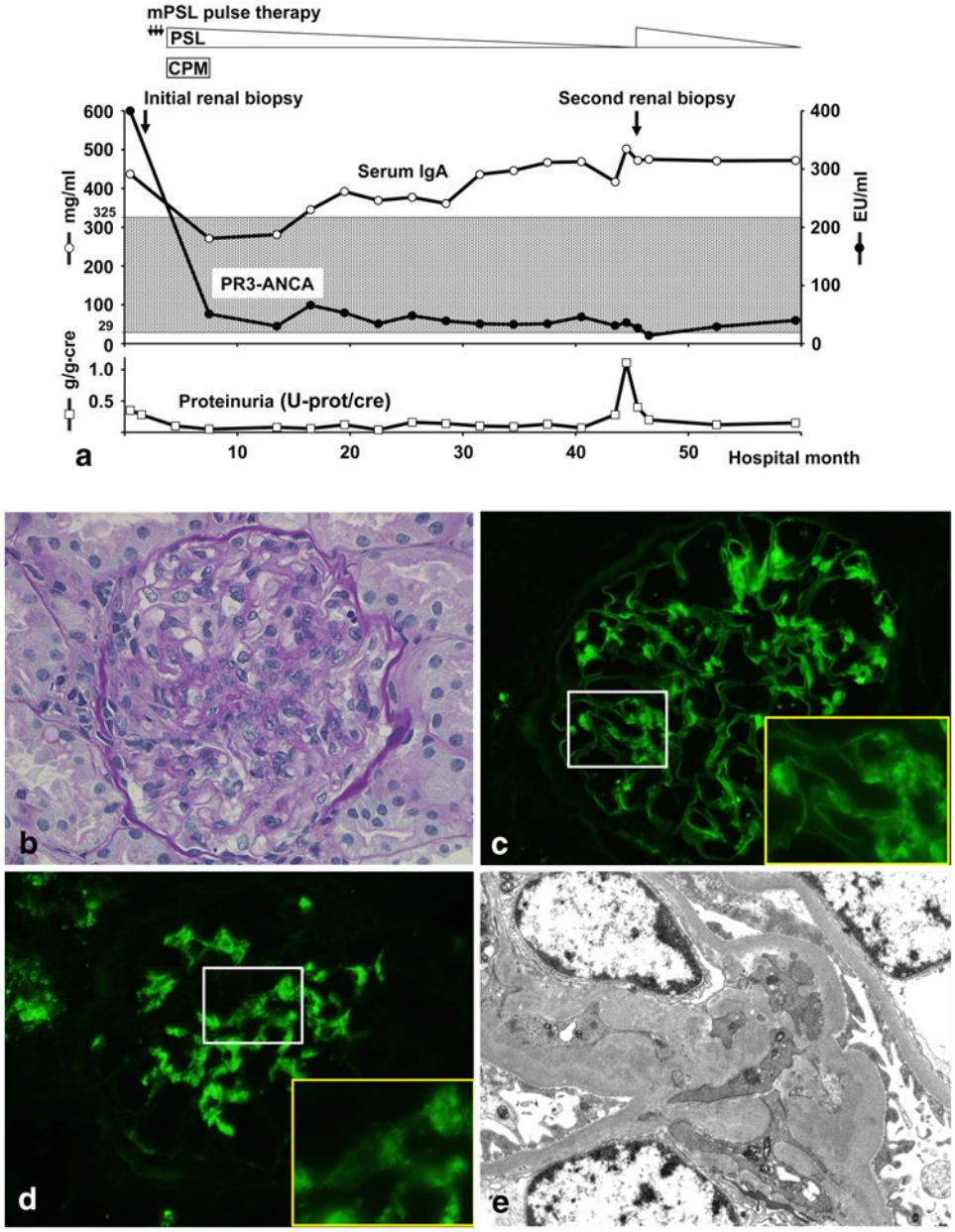

Fig. 1 **a** Clinical course. *PR3* proteinase 3, *ANCA* anti-neutrophil cytoplasmic antibody, *IgA* immunoglobulin A, *mPSL* methylprednisolone, *PSL* prednisolone, *CPM* cyclophosphamide, *U-prot/cre* urinary protein:creatinine ratio. A half-tone dot meshing shows the range of mean value ± 2 SD revealing the serum IgA level of 90 children aged from 13 to 15 years in our hospital. **b–e** Renal biopsy findings of the second renal biopsy specimen. **b** Glomeruli with mesangial matrix expansion and mild hypercellularity (periodic–acid Schiff staining ×400). **c**, **d** Immunofluorescence microscopy of the renal biopsy specimen demonstrated mesangial IgA (**c**) and C3 (**d**) deposition (×400). *Insets* in panels **c** and **d** show high magnification to clearly visualize granular pattern (×1,000). **e** Electron microscopic view showed that electron-dense deposits were present in the paramesangial region (×4,600)

HSP, we eventually concluded this to be one of the vasculitis symptoms with GPA, because the extremely high titer of PR3-ANCA was already apparent at our hospital. The pathogenesis of GPA is currently understood to involve cellular immunity via interleukin-17-producing T cells and microbial factors, in particular *Staphylococcus aureus* and Gram-negative bacteria [6]. However, there has been no evidence provided to date showing that immunocomplexes directly underlie the development of the vasculitis associated with GPA. A previous study using immunofluorescence microscopy of 93 biopsy samples with GPA revealed that 26 patients (28.0 %) had some glomerular positivity for one or more immunoglobulins or complement proteins [7]. However, the distribution patterns of these proteins were primarily focal and segmental with a partly linear and granular pattern. Moreover, their staining intensity was weak, suggesting that most of these proteins were passively trapped in the lesions. According to our literature search using PubMed, we found a total of 21 cases with GPA showing IgA deposition in the glomerular mesangial region [7–15] (Table 1), among which there were only 10 cases that revealed predominant deposition with diffuse pattern and more than 2+ intensity [7–10]. Among these cases, 8 reports showed kidney samples that were evaluated at the acute stage due to acute renal failure and rapidly progressive renal failure, and 2 cases were diagnosed during a remission period. There was only one pediatric case: a 12-year-old girl who developed

Table 1 Reports in the literature of patients with GPA showing mesangial IgA deposition

Author	Number	Sex	Age (years)	IgA (mg/dl)	ANCA (U/ml)
Aasarod et al. [7]	2	2M	46–48	NR	57–66
Andrassy et al. [8]	4	4M	49–70	153–529	Positive
Vrtovsnik et al. [9]	1	1M	32	NR	32
Haasetal [10]	5	2M, 3F	12–73	NR	80–463
Ronco et al. [11]	1	NR	NR	NR	NR
Rollino et al. [12]	1	1M	49	307	27
Bantis et al. [13]	3	3M	43–53	NR	Positive
Neumann et al. [14]	3	2M, IF	20–80	NR	Positive
Joerg et al. [15]	1	1M	58	NR	143

PR3 proteinase 3, *ANCA* anti-neutrophil cytoplasmic antibody *IgA* immunoglobulin A, *NR* not reported

acute renal failure. Her kidney glomeruli were revealed to contain 100 % crescents and diffuse IgA 2+ staining in the mesangium in addition to a diffuse mesangial pattern of 1+ C3 and 1–2+ IgG staining [10]. Therefore, our case is the first pediatric case of GPA at the remission stage associated with IgA nephropathy.

The pathophysiology of the association of IgA nephropathy with our GPA case remains unclear. However, although the first renal biopsy specimen did not reveal any evidence of immunodeposits, the second one clearly displayed immune complex deposition consisting of IgA, IgG, and C3 in mesangial area, supporting association of de novo IgA nephropathy with GPA. If so, what was the trigger to lead to an association of de novo IgA nephropathy in this case? There is general agreement that serum levels of IgA are increased by 50–70 % in patients with IgA nephropathy [16]. It is speculated that B cells that respond to mucosal infections might produce the nephritogenic IgA1 molecules [17]. Thus, substantial mucosal involvement via the airway may trigger IgA production in GPA patients. Indeed, some GPA patients were found to have high serum IgA levels [8]. In our case, the etiology of continuous high titer of serum IgA was most likely due to the poorly controlled parasinusitis. In the whole clinical course, paranasal sinusitis was not remitted, being recurrently exacerbated depending on antibiotic therapy and local treatment. Thus, a high titer of serum IgA in GPA patients could be a valuable indicator of the existence of poorly controlled respiratory infections, including paranasal sinusitis, and could predict an association with IgA nephropathy.

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

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