Rapidly progressive IgA vasculitis-associated nephritis successfully treated with immunosuppressive therapy in an adolescent with chronic granulomatous disease

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Abstract

Chronic granulomatous disease (CGD) is a rare immunodeficiency disorder with genetic defects in the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex in phagocytes, leading to recurrent severe infections and granuloma formation. Genitourinary involvement, including obstructive granulomas, infections, nephrotoxicity of anti-infective agents, and amyloidosis, is frequently observed in patients with CGD, whereas the clinical and pathological details of the less commonly reported glomerular disease remain obscure. Here, we report the case of a patient with CGD who developed rapidly progressive IgA vasculitis-associated nephritis (IgAVN) and review the literature on biopsy-proven glomerular diseases in patients with CGD. A 22-year-old male patient with CGD developed rapidly progressive glomerulonephritis (RPGN) following peripheral purpura and was diagnosed with crescentic IgAVN based on the renal biopsy evaluation. There was no evidence of active infections, and he received pulse intravenous methylprednisolone followed by oral prednisolone. His renal function returned to normal within 4 weeks, and his proteinuria and microhematuria finally resolved. The present case and literature review indicate that IgAVN and IgA nephropathy with RPGN are the most common causes of glomerular disease in patients with CGD. Clinicians should be aware of the possibility of these diseases as causes of RPGN in CGD, because delays in diagnosis and appropriate treatment may affect renal outcomes.

Keywords Chronic granulomatous disease (CGD) · Kidney biopsy · Autoimmune disease · Immunoglobulin A (IgA) · Glomerulonephritis · Treatment

Introduction

Chronic granulomatous disease (CGD) is a rare primary immunodeficiency disorder, with an estimated prevalence of 1 in 290,000 live births in Japan [1]. CGD is caused by mutations in genes encoding nicotinamide adenine dinucleotide phosphate (NADPH) oxidase subunits in phagocytes [2]. NADPH oxidase is responsible for killing catalase-positive microorganisms through the generation of reactive oxygen species; therefore, starting in early childhood, patients

with CGD are highly susceptible to recurrent bacterial and fungal infections [2].

Noninfectious complications of CGD include granuloma formation and autoimmune diseases [3]. Granuloma formation, a classical finding of CGD that occurs as a result of uncontrolled inflammatory response, is identified in nearly 70% of patients and commonly affects the gastrointestinal tract, lungs, and urogenital tract [4]. In recent years, it has become evident that patients with CGD are at a higher risk of autoimmune diseases, including discoid and systemic lupus erythematosus, juvenile idiopathic arthritis, autoimmune thrombocytopenia, and antiphospholipid syndrome [5–7]. Although the mechanisms underlying the increased risk of autoimmune diseases associated with CGD are not fully understood, defects in phagocytic function are suggested to result in repeated antigen stimulation and hypergammaglobulinemia, leading to autoantibody production [8]. IgA nephropathy has also been reported in a case series

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of autoimmune diseases in patients with CGD [5]; however, whether IgA nephropathy is associated with CGD remains unclear. Here, we describe the case of rapidly progressive IgA vasculitis-associated nephritis (IgAVN) in a patient with CGD who was successfully treated with immunosuppressive therapy. We also summarize previous cases of biopsy-proven glomerulonephritis in patients with CGD.

Case report

A 22-year-old Japanese male patient with CGD was referred to our hospital for evaluation of worsening kidney function for 3 months. Three months before admission, he developed palpable purpura in the lower extremities, which resolved spontaneously within weeks. He had no history of kidney disease and no signs of preceding infection. At 7 months of age, he was diagnosed with gp91^{phox}-deficient CGD because of severe perianal abscess. Following prophylactic treatment with itraconazole and trimethoprim-sulfamethoxazole, he had been free from serious infections until the present admission. At 7 years of age, he developed inflammatory bowel disease-like symptoms. Colon biopsies revealed non-caseating granulomas in the lamina propria with no evidence of infectious microorganisms, supporting the diagnosis of CGD-associated colitis. After the initiation of treatment with 5-aminosalicylic acid, the patient had sustained remission of the colitis symptoms. He had no family history of CGD. His regular medications were itraconazole 200 mg/day, trimethoprim-sulfamethoxazole 400/2000 mg/day, and 5-aminosalicylic acid 500 mg three times daily.

On admission, he was afebrile with a body temperature of 36.4 °C, and his blood pressure was 112/75 mmHg. His height and weight were 154.4 cm and 44.0 kg, respectively. Cardiovascular, respiratory, and abdominal examinations were normal. No purpura or peripheral edema was noted. He had no arthralgia or abdominal pain. Urinalysis revealed 3+ proteinuria and 30–49 red blood cells/high-power field with red blood cell casts. Spot urine protein-to-creatinine ratio was 2.14 g/gCr and the 24 h urine protein excretion was 0.63 g. His serum creatinine level had increased from the baseline value of 0.76 to 1.33 mg/dL over 3 months. Complete blood count showed the following values: white blood cell count, 7,500/μL with a normal differential cell count (60.5% neutrophils, 5.0% eosinophils, 0.3% basophils, 28.7% lymphocytes, and 5.5% monocytes); hemoglobin, 11.6 g/dL; and platelet count, 272,000/μL. The C-reactive protein level was 0.67 mg/dL (reference, ≤ 0.14 mg/dL), and the procalcitonin and beta-D-glucan levels were negative. His serum IgA level was elevated to 617 mg/dL (reference, 93–393 mg/dL), with normal IgG and IgM levels. The antistreptolysin O antibody titer and serum complement levels were within the normal limits. Connective tissue disease screening for

anti-nuclear and anti-neutrophil cytoplasmic antibodies and cryoglobulins revealed negative results. Renal ultrasonography revealed normal-sized kidneys.

Kidney biopsy was performed for the evaluation of rapidly progressive glomerulonephritis (RPGN). Light microscopy revealed diffuse mesangioproliferative glomerulonephritis with crescent formation (Fig. 1a, b). Sixty-nine glomeruli were identified, with cellular and fibrocellular crescents in thirteen glomeruli, fibrous crescents in twenty-one glomeruli, and global sclerosis in seven glomeruli. Segmental fibrinoid tuft necrosis was observed in two glomeruli (Fig. 1b). No endocapillary proliferative lesions were observed. There was patchy interstitial infiltration of predominantly mononuclear inflammatory cells. Interlobular arteries and arterioles were unremarkable. Immunofluorescence microscopy showed mesangial IgA and weak C3 depositions, which were confirmed by electron microscopy (Fig. 1c–e). No subepithelial humps were observed (Fig. 1f). The histological findings and purpuric episode suggested crescentic glomerulonephritis due to IgA vasculitis.

Detailed workup revealed no evidence of active infections, and blood and urine cultures were negative. Chest computed tomography revealed multiple small pulmonary nodules (Fig. 2a). No *Aspergillus* or *Cryptococcus* antigens were detected in the serological assays. Interferon-gamma releasing assay was negative for *Mycobacterium tuberculosis* (*M. tuberculosis*). Transbronchial biopsy of the pulmonary nodules revealed nonspecific infiltration of inflammatory cells but no findings of granulomas, vasculitis, or infection. Bronchial wash cultures showed no bacterial, fungal, or *M. tuberculosis* growth. Transthoracic echocardiography showed no vegetations.

The patient received intravenous methylprednisolone 500 mg for 3 days, followed by oral prednisolone 35 mg (0.8 mg/kg) daily for the RPGN. Four weeks after the initiation of prednisolone, his creatinine level returned to normal (0.96 mg/dL) and the pulmonary nodules decreased in size (Fig. 2b). Six months after the initiation of steroid treatment, he developed *Salmonella* bacteremia, while under treatment with 10 mg prednisolone and required inpatient antibiotic treatment for 2 weeks. No other adverse events were noted. Prednisolone was tapered off over a period of 15 months. At the 2.5 year follow-up after prednisolone discontinuation, the patient's serum creatinine level was stable at 0.85 mg/dL, with remission of microhematuria and proteinuria. His clinical course is shown in Fig. 3.

Discussion

The present patient developed RPGN following peripheral purpura during the course of CGD. His renal biopsy showed crescentic glomerulonephritis with mesangial IgA

Fig. 1 Kidney biopsy findings. **a** The glomeruli exhibit cellular and fibrocellular crescents with mesangial proliferation (periodic acid-Schiff stain, original magnification $\times 200$). **b** Glomerular fibrinoid necrosis with cellular crescent is shown (Masson's trichrome staining, original magnification $\times 400$). **c**, **d** Immunofluorescent staining showing mesangial IgA (**c**) and weak C3 (**d**) depositions (original magnification $\times 400$). **e** An electron micrograph showing mesangial electron-dense deposits (original magnification $\times 1,500$). **f** There are no subepithelial deposits, i.e., humps (original magnification $\times 4,000$)

Fig. 2 **a** Chest computed tomography showing bilateral lung nodules. **b** The nodules have disappeared or decreased in size on follow-up chest computed tomography 1 month after the initiation of steroid therapy

deposition. Based on the renal pathological findings, the differential diagnosis included IgA nephropathy, IgAVN,

and IgA-dominant infection-related glomerulonephritis (IRGN). Differential diagnosis of these conditions is

Fig. 3 Clinical course of the patient

important, because they require different treatment strategies; however, a definitive distinction is often difficult. IgA-dominant IRGN, first defined by Nasr et al. in 2013, usually occurs in the setting of an ongoing infection most likely due to *Staphylococcus aureus* (*S. aureus*) [9]. The mainstay of treatment in IgA-dominant IRGN is antibiotic treatment with appropriate surgical drainage [9]. The clinical and histological features that favor IgA-dominant IRGN over IgA nephropathy and IgAVN are old age, diabetes mellitus, concurrent staphylococcal infection, hypocomplementemia, prominent endocapillary proliferation in glomeruli, stronger staining for C3 than for IgA, and epithelial humps on electron microscopy [9]. The present patient did not exhibit any of these features. The detailed workup for infections did not reveal any evidence of concurrent infections. In addition, the patient fully recovered with steroid therapy, further suggesting the absence of underlying active infections. The multiple pulmonary nodules resolved after steroid initiation and thus were considered as granulomas. Taken together, the diagnosis of IgA-dominant IRGN was unlikely and the patient was diagnosed with IgAVN with consideration of the preceding purpura.

Genitourinary tract involvement frequently occurs in CGD and progresses to end-stage renal disease in approximately 3% of affected patients [10]. The common manifestations include urinary tract obstruction due to granulomas, urinary tract infections, nephrotoxicity of anti-infective agents, and amyloidosis associated chronic inflammation [10–12]. Glomerular diseases are less commonly observed in CGD; we have identified nine cases of biopsy-proven glomerulonephritis in patients with CGD. The clinical features of these cases and the present case are summarized in Table 1 [5, 13–18]. IgAVN and IgA nephropathy were the most common glomerular diseases, reported in 2 patients each. Interestingly, all four patients presented with RPGN.

In one patient with IgA nephropathy, the presence of active concurrent *S. aureus* infection raised the possibility of IgA-dominant IRGN, whereas the remaining three patients had no evidence of active infections. One of the three patients already had advanced glomerulosclerosis at the time of biopsy and rapidly progressed to end-stage renal disease. The other two patients, including the present case, had crescentic glomerulonephritis and received steroid treatment; both patients successfully achieved complete remission of RPGN, with no life-threatening infectious adverse events.

IgA vasculitis is an autoimmune disease that causes systemic small-vessel vasculitis, typically involving the skin, gastrointestinal tract, and kidneys [19]. In the kidney, IgA vasculitis and IgA nephropathy are considered to share key pathogenic mechanisms on the basis of their similar histological and immunological features [20–22]. Although the exact underlying mechanisms have not been fully elucidated, galactose-deficient IgA1 (Gd-IgA1) is considered to be a critical molecule in the pathogenesis of both IgAVN and IgA nephropathy [20–22]. Gd-IgA1 can act as an autoantigen. Specifically, defects in the galactosylation of the IgA1 hinge region exposes N-acetylgalactosamine residues, and autoantibodies are induced in susceptible individuals [20, 23]. The immune complexes comprising Gd-IgA1 and its autoantibodies are thought to deposit in the mesangium and induce kidney injury [20, 23]. In both IgAVN and IgA nephropathy, serum Gd-IgA1 levels are elevated and immune complexes containing Gd-IgA1 are detected in glomeruli [21, 22]. Factors promoting Gd-IgA1 production are unknown; however, several studies have shown that genetic predisposition, mucosal infection, abnormal mucosal immune response, and certain cytokines may enhance Gd-IgA1 production [21, 24]. Therefore, we speculate that the development of IgAVN or IgA nephropathy in patients with CGD reflects a complex interplay among impaired elimination of pathogens,

Table 1 Case reports of biopsy-proven glomerulonephritis in patients with CGD

Case	Age/sex	Genotype	Histological diagnosis of kidney biopsy	Concurrent infection	Renal manifestation	Treatment/Outcome
Present case 2020	22/M	gp91phox	Necrotizing crescentic GN with IgA deposits (IgAVN)	None	RPGN	mPSL 500 mg×3 days and PSL 35 mg daily/S-Cre improved from 1.43 to 0.96 mg/dL within 1 month
2013 [13]	44/F	p47phox	MN	NA	Proteinuria	NA/NA
	27/M	p47phox	FSGS	NA	NA	NA/NA
	15/M	p47phox	FSGS, TIN	NA	Nephrotic syndrome	NA/Progressed to ESRD at the age of 19 years
2008 [5]	13/M	gp91phox	Severe nephrocalcinosis necrotizing crescentic GN with IgA deposits (IgA nephropathy)	None	RPGN	PSL 30 mg twice daily/S-Cre improved from 1.9 to 0.8 mg/dL after 2 months
2002 [14]	22/M	gp91phox	Crescentic GN with IgA deposits (IgA nephropathy)	Liver abscess Intramuscular abscess (<i>S. aureus</i>)	RPGN	NA/NA
1991 [15]	8/F	p47phox	Sclerosing GN with IgA deposits (IgAVN)	None	RPGN	Renal supportive care/ Progressed to ESRD within 6 months
1991 [16]	4/M	gp91phox	Lupus nephritis Subendothelial deposits of IgG, IgM, C3, C1q	None	Proteinuria Microhematuria	PSL 30 mg every other day/ Renal function remained stable
1985 [17]	14/M	Autosomal recessive	Mes proliferative GN IF study was not done EM revealed Mes EDD	Prolonged fever	Proteinuria	Penicillin therapy for 9 months. PSL and CPA therapy for 2 weeks resulted in pneumonia/Progressed to ESRD at the age of 16
1979 [18]	18/F	unknown	Sclerosing GN with crescents No deposits in glomeruli	Subcutaneous abscess (<i>S. aureus</i>)	RPGN	Antibiotics therapy and temporary hemodialysis/S-Cre improved from 6.0 to 2.9 mg/dL

Abbreviations: CGD chronic granulomatous disease, GN glomerulonephritis, RPGN rapidly progressive glomerulonephritis, mPSL, methylprednisolone, PSL prednisolone S-Cre serum creatinine, IgAVN IgA vasculitis-associated nephritis, MN membranous nephropathy, FSGS focal segmental glomerulosclerosis, TIN tubulointerstitial nephritis, ESRD end-stage renal disease, *S. aureus* *Staphylococcus aureus*, Mes mesangial, IF immunofluorescence, EM electron microscopy, EDD electron dense deposit, CPA cyclophosphamide, NA not available

dysregulated IgA production, elevated cytokines in response to inflammatory stimuli, and increased susceptibility to autoimmune disease. In the present case, subclinical intestinal mucosal inflammation (CGD-associated colitis) also could potentially contribute to the development of IgAVN through the alteration of mucosal immune responses. Additional studies of serum levels or glomerular deposition of Gd-IgA1 are warranted in this patient population, and further studies are needed to better understand the underlying mechanisms.

Treatment of autoimmune diseases in patients with CGD remains challenging, because immunosuppressive therapy can increase the risk of infectious complications in these immune-compromised patients. The number of reported patients with CGD and autoimmune diseases remains low, and information on treatment and outcomes is still limited. In general, crescentic IgAVN with RPGN has poor renal prognosis; thus, the commonly accepted treatment is high-dose oral prednisolone (1–2 mg/kg/day) with or without pulse methylprednisolone (10–30 mg/kg, maximum 1 g/day) and additional immunosuppressive agents [19, 25]. In the present case, the initial corticosteroid dose was reduced to pulse methylprednisolone 11 mg/kg followed by prednisolone 0.8 mg/kg daily. This treatment was effective in achieving remission of the rapidly progressive IgAVN; however, one infectious event requiring hospitalization occurred during the treatment. More studies are warranted to evaluate optimal immunosuppressive therapy regimens in patients with CGD.

In summary, IgAVN and IgA nephropathy with RPGN are the most common causes of glomerulonephritis in patients with CGD. Clinicians should be aware of the possibility of IgAVN and IgA nephropathy as potential causes of RPGN in patients with CGD and should consider kidney biopsy as delays in diagnosis and appropriate treatment may affect renal outcomes.

Compliance with ethical standards

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

Ethical statement This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Written informed consent was obtained from the patient for the publication of his clinical data.

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