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BRIEF REPORT

Long-term follow-up of juvenile acute nonproliferative glomerulitis (JANG)

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Abstract This report concerns a 9-year-old boy who was diagnosed with atypical type II membranoproliferative glomerulonephritis and later proved to have juvenile acute nonproliferative glomerulitis (JANG). To the best of our knowledge, this is the first report on the long-term clinical and pathological follow-up of JANG.

Keywords Juvenile acute nonproliferative glomerulitis (JANG) · Rapidly progressive crescentic glomerulonephritis · Dense deposit disease (DDD)

Introduction

Juvenile acute nonproliferative glomerulitis (JANG) is a newly established clinicopathological entity in childhood rapidly progressive crescentic glomerulonephritis, and it was first reported by West et al. as a subtype of dense deposit disease (DDD) [1]. Clinically, JANG is characterized by gross hematuria, rapidly declining renal function, and a serum C3 level at the lower normal limit or slightly depressed at the disease onset. Pathologically, the disease may resemble rapidly progressive type II membranoproliferative glomerulonephritis (MPGN) but can be distinguished both morphologically and clinically.

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Case report

In December 1988, a 9-year-old boy developed gross hematuria triggered by a common cold. Many red blood cells in urinary sediment as well as proteinuria (14.6 g urinary protein excretion per day) were detected. He showed signs of mild hypocomplementemia with a serum C3 level of 42 mg/dl at presentation (normal range: 65–135 mg/dl), while antistreptolysin O (ASO) titer was within normal range. He was clinically asymptomatic, with normal blood pressure, normal renal function (serum creatinine 0.5 mg/dl), and no edema. We observed him without any treatment for 2 months to exclude the possibility of poststreptococcal acute glomerulonephritis (PSAGN), because the C3 level has been reported to return to normal after less than 8 weeks in the regular course of PSAGN [1, 2]. As his serum C3 level remained depressed for more than 2 months and his clinical course was not typical of PSAGN, the first renal biopsy was performed in February 1989. Light microscopy showed focal segmental mesangial proliferation, but there was no increase in mesangial matrix as visualized by periodic acid-Schiff (PAS) stain (Fig. 1a). The capillary walls were not thickened, and cellular crescents were observed in two of 18 glomeruli.

Immunofluorescent stains were positive for C3 along the capillary walls of the glomeruli (Fig. 1b), but no immunoglobulins were observed. Electron microscopy of uranyl acetate and lead citrate-stained preparations showed intra-

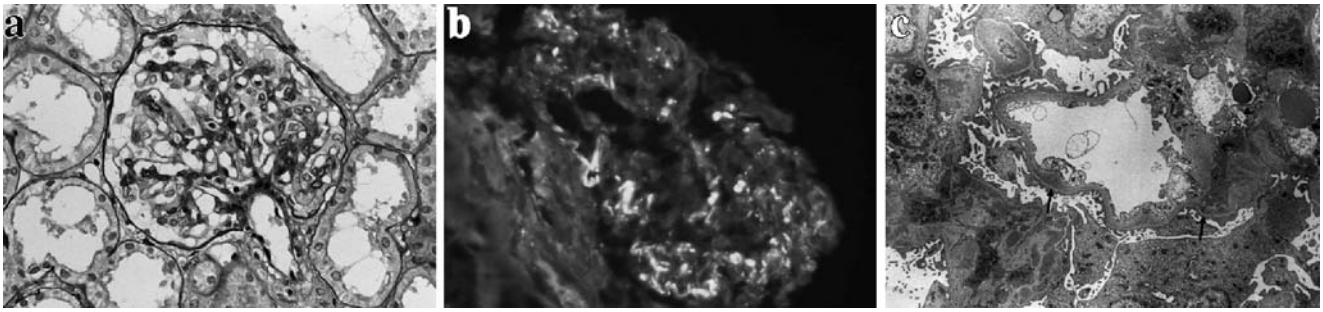

Fig. 1 **a** First renal biopsy findings. The glomerulus showing mild increase of mesangial cells (periodic acid-Schiff ×400). **b** Immunofluorescence showing deposits of C3 along the capillary walls. **c** In this electron micrograph of a glomerulus, the *arrows* indicate intramembranous electron-dense deposits

membranous electron-dense deposits along the glomerular basement membrane (GBM) as well as mesangial and subepithelial deposits (Fig. 1c). We diagnosed our patient with atypical dense deposit disease (DDD), because his pathological findings did not meet the criteria for any other type of glomerulonephritis. Treatment with 3 mg/kg per day of dipyridamole was started after the renal biopsy, and proteinuria had disappeared 3 months after the onset.

However, severe proteinuria and gross hematuria were triggered by a common cold 11 months after the first onset. Many red blood cells were detected in urinary sediment, and proteinuria (6.4–20.5 g urinary protein excretion per day) was confirmed. On admission, no edema, hypertension, oliguria, or anemia was present. Blood urea nitrogen (BUN) was 11 mg/dl and serum creatinine 0.7 mg/dl. ASO titer was within normal range, and serum C3 level (58 mg/dl) was slightly below the lower limit of the normal range. Antinuclear antibody (ANA) was negative. Test for antineutrophil cytoplasm antibody (ANCA) was not performed. Two weeks after admission, the disease had not been resolved and the BUN had risen to 29 mg/dl and the serum creatinine to 1.3 mg/dl. A second renal biopsy was therefore performed in December 1989.

Light microscopy showed cellular or cellulofibrous crescents in 20 of 22 glomeruli (90.9%) (Fig. 2a), and a mild increase in mesangial cell proliferation was observed in areas not associated with crescents (Fig. 2b). There were large numbers of neutrophils within glomeruli as well as of interstitial inflammatory cell infiltrates. Both tubular atrophy and interstitial fibrosis were noted. There was no

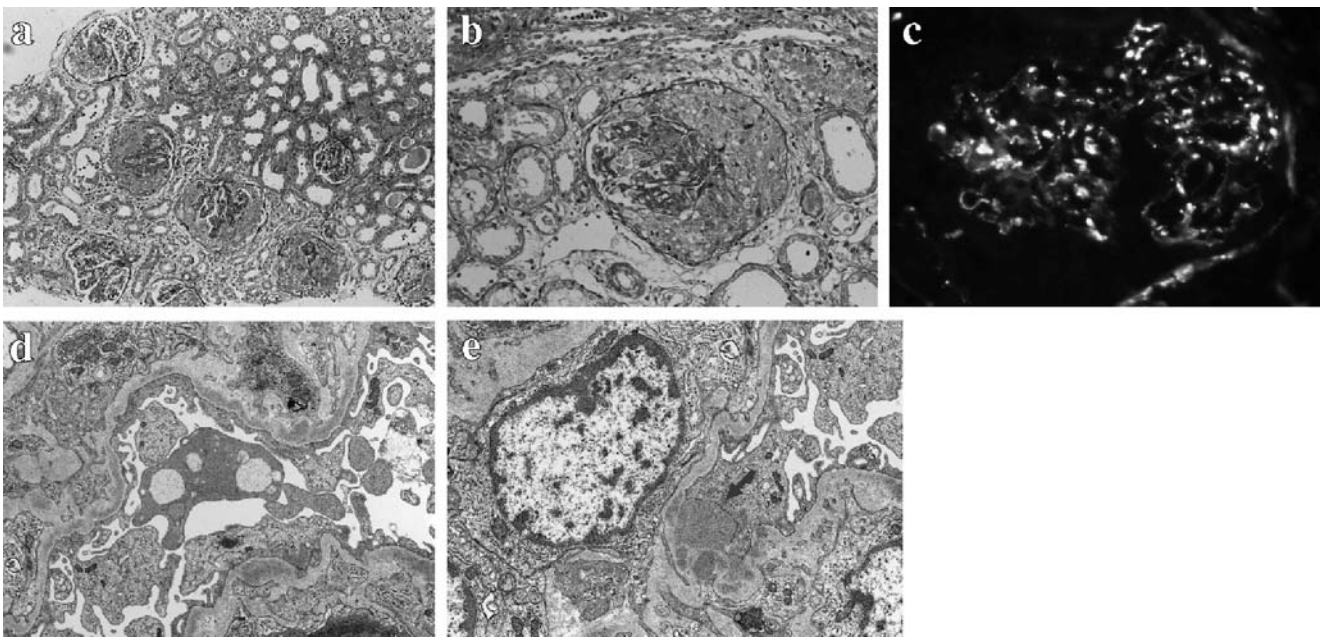

Fig. 2 Renal biopsy findings of the second biopsy. **a** Light-microscopic findings of glomeruli revealed cellular or cellulofibrous crescents [periodic acid-Schiff (PAS ×100)]. **b** There were a mild increase in mesangial cell proliferation in areas not associated with crescents (PAS ×200). **c** Immunofluorescence showing large, discrete deposits of C3 in the mesangial areas. **d** Electron micrograph of a glomerular capillary, still showing strong intramembranous electron-dense deposits. **e** Electron micrograph of a glomerulus; the *arrow* indicates a typical subepithelial paramesangial deposit

Table 1 Pathological findings of renal biopsies

No. of biopsy	Period to biopsy (years)	Light microscopy					Immunofluorescence	Electron microscopy			
		No. of glomeruli	No. of crescents (%)	No. of GS (%)	TA	IF	C3	Deposit			Mesangial interposition
							Capillary/ mesangium	Subendothelial	Intramembranous	Subepithelial	Mesangial	
1st	0.2	18	2 (11.1%)	0	–	–	1 g/-	–	2+	1+	2–3+	–
2nd	1	22	20 (90.9%)	0	1+	2+	-/2 g	–	2+	1+	3+	–
3rd	1.3	20	6 (30.0%)	0	1–	1–	-/2 g	1+	–	–	2+	–
					2+	2+						
4th	3	22	0	1 (4.5%)	1+	1+	-/1 g	–	2+	–	2+	–
5th	9.2	27	0	9	1–	1+	1 s/1 s	1+	–	–	1+	–
				(33.3%)	2+							

- absent, *1+* slight, *2+* moderate, *3+* intense, *g* global, *s* segmental, *GS* global sclerosis, *TA* tubular atrophy, *IF* interstitial fibrosis

evidence of vasculitis. Immunofluorescent stains showed large, discrete mesangial deposits containing C3 (Fig. 2c), but no immunoglobulins were observed. Electron microscopy showed continuous electron-dense deposits along the GBM (Fig. 2d) and in some mesangial areas, while similar electron dense material in the form of hump-like deposits was present in subepithelial paramesangial areas (Fig. 2e). We diagnosed our patient with acute exacerbation of atypical DDD, and treatment with multiple combined therapy consisting of prednisolone (1 mg/kg per day), cyclophosphamide, heparin/warfarin, and dipyridamole was initiated. In addition, intravenous methylprednisolone (mPSL) pulse and plasma exchange therapies were administered. Proteinuria gradually decreased, and the third renal biopsy was performed 3 months after the start of the multiple combined therapy.

Light microscopy showed fibrous crescents in six of 20 glomeruli (30.0%). Focal mesangial cell proliferation was observed in areas not associated with crescents. The multiple combined therapy was continued for 12 weeks and replaced with 30 mg of alternate-day prednisolone and the Chinese herbal medicine Saire-to. After the alternate-day prednisolone treatment had been continued for 24 months, the fourth renal biopsy was performed in December 1991. Again, light microscopy showed focal mesangial proliferation, but cellular or cellulofibrous crescents were absent. Global sclerosis was observed in only one of 22 glomeruli (4.5%). The alternate-day prednisolone was discontinued after the fourth renal biopsy, and the fifth renal biopsy was performed in February 1998. Light-microscopic findings showed global sclerosis in nine of

Table 2 Comparisons of characteristics of rapidly progressive dense deposit disease (DDD) and of juvenile acute nonproliferative glomerulitis (JANG) with those of the reported patient

	Rapidly progressive DDD	JANG	Reported patient
Intramembranous dense deposits	Present by definition	Present 3/13	Present
Hypertension	Present	Absent	Absent
Nephrotic syndrome	Often present	Absent	Absent
Serum C3	Moderately to severely depressed	Normal in 6/13	Lower limit of normal or slightly depressed
Response to steroid therapy	Poor	Excellent	Excellent
Subepithelial paramesangial deposits	Absent when C3 level normal [10]	Abundant in all	Abundant
Mesangial cell proliferation	Increased	Normal	Slightly increased

27 glomeruli (33.3%), and cellular or cellulofibrous crescents remained absent. A slight increase in mesangial cell proliferation was observed in areas not associated with global sclerosis. After the fifth renal biopsy, treatment with angiotensin-converting enzyme (ACE) inhibitor was started.

At the most recent follow-up (17 years and 5 months after the onset), the patient had only mild proteinuria (urinary protein-to-creatinine ratio 0.20 mg/mg), which continues to be treated with the ACE inhibitors. Renal function (serum creatinine 0.7 mg/dl) and blood pressure continue to be normal, and no adverse effects attributable to his medications have been noted.

The pathological findings of renal biopsy specimens are shown in Table 1.

Discussion

Our diagnosis of this patient as having acute exacerbation of atypical DDD has been reported by us previously [3]. However, the reason he developed acute crescenteric glomerulonephritis was not clear at that time.

In 2000, West et al. first reported 13 children with a disease entity that leads to rapidly progressive crescentic glomerulonephritis [4]. The disease onset was characterized by gross hematuria, rapidly declining renal function, and a serum C3 level at the lower limit of normal or slightly depressed. None had an elevated blood pressure or a nephrotic syndrome. Light microscopy of the first biopsies showed that up to 80% of the glomeruli were involved in crescent formation. The glomeruli not involved in crescent formation were often hypercellular with infiltrating neutrophils, but there was no mesangial proliferation. Blood vessels were normal. The distinctive abnormality detected by immunofluorescence was the absence of deposits reactive to anti-immunoglobulin (Ig) G and the presence of mesangial deposits containing C3, which were reminiscent of those seen in biopsies of hypocomplementemic patients with DDD. Electron microscopy showed the presence of waist basement-membrane-related deposits in addition to the paramesangial deposits in eight patients. Three patients presented dense deposit alteration of the lamina densa of the GBM, similar to that seen in DDD. Because of this characteristic and because the disease in their experience was seen only in children up to the age of 12 years and had not been reported in adults, they gave it the name juvenile acute nonproliferative glomerulitis (JANG). They showed that in all patients treated with aggressive steroid treatment alone (i.e. no cytotoxic agents), JANG responded, with complete reversal to normal renal function. They also reported that JANG exceeded in frequency more than any other entity as a cause of rapidly progressive glomerulonephritis in children. During a 31-year period in which the 13 JANG patients were seen in their clinic, seven were diagnosed as rapidly progressive IgA nephropathy [5] and only four as rapidly progressive DDD. It is thus possible that the frequency of JANG may be more common as a cause of rapidly progressive glomerulonephritis than generally thought.

Although distinguishing patients with JANG accompanied by intramembranous dense deposits from those with DDD presents difficulties, the two diseases do show clinical differences. The rapidly progressive crescentic glomerulonephritis and gross hematuria in DDD is accompanied by a hypocomplementemia, which is usually severe [6, 7] and is often associated with hypertension and a nephrotic syndrome. The two diseases also differ in details of glomerular morphology and in their response to steroid therapy. As seen in the Table 2, clinical and pathological characteristics of our patient were similar to those described by West et al. [4, 8]. We therefore diagnosed our patient as a case of JANG.

Factor H is a plasma protein that plays a key role in the control of the alternative complement pathway. Interestingly, it has recently been shown that mice with factor H deficiency and uncontrolled C3 activation develop membranoproliferative glomerulonephritis [9]. It is known that factor H dysfunction is also present in DDD [10] and produces severe hypocomplementemia. However, there is no clear evidence of factor H dysfunction in patients with JANG. In our case, we could not measure the serum levels of factor H at that time. Therefore, further examinations of the complement system are needed to distinguish both diseases.

In conclusion, we suggest that it is important to distinguish JANG in the early stage from other forms of rapidly progressive glomerulonephritis in childhood to avoid overtreatment, because it seems that a favorable clinical course can be attained for JANG if treated with only high-dose corticosteroids. Further complement analysis, including factor H, may provide additional insight into the pathophysiology of this condition.

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