Proliferative glomerulonephritis with monoclonal IgG2κ deposit successfully treated with steroids: a case report and review of the literature

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Abstract A novel form of glomerular injury with monoclonal immunoglobulin (Ig) IgG deposition, termed “proliferative glomerulonephritis (GN) with monoclonal IgG deposits” (PGNMID), is a recently described entity. PGNMID presents with various histological patterns, such as membranoproliferative GN, endocapillary proliferative GN and membranous nephropathy (MN). The deposits are composed of monoclonal immunoglobulin, most commonly IgG3 and occasionally IgG2. At present, the clinical significance of each IgG subclass and the morphological patterns of glomerular injury have not been fully investigated due to the limited number of PGNMID cases reported. The patient was a 27-year-old woman presenting with a mild degree of proteinuria and no other physical or serological abnormalities. Monoclonal Ig could not be identified in her serum or urine. Renal biopsy found features of MN with deposition of monoclonal IgG2κ. Electron microscopy examination revealed non-organised electron-dense deposits predominantly in subepithelial

locations. Based on a diagnosis of PGNMID, she was treated with prednisolone and proteinuria significantly decreased in less than 4 weeks. Although the clinical outcomes of PGNMID remain to be defined, MN features may possibly be a sign of favourable prognosis—a hypothesis supported by recent reports. The absence of advanced chronic damage in the kidney, such as glomerulosclerosis or tubulointerstitial fibrosis, may also have contributed to the favourable outcome in the present case. Further studies on additional PGNMID cases that allow the correlation of morphological features and IgG subclasses with clinical outcomes are needed in order to confirm our findings and further solidify the clinical aspects of this new disease entity.

Keywords Proliferative glomerulonephritis · Monoclonal IgG · Membranous nephropathy · Steroid

Introduction

Monoclonal immunoglobulin (Ig) G deposition can cause several types of glomerular injury, such as light- and heavy-chain deposition disease [1, 2], cryoglobulinaemic glomerulonephritis (GN) [3, 4], immunotactoid glomerulopathy and, occasionally, fibrillary GN [5, 6]. Ultrastructurally, electron-dense deposits (EDD) in these glomerular diseases can be categorised into 2 distinct patterns: one with organised EDD formation, as seen in amyloidosis, immunotactoid glomerulopathy and fibrillary GN, and the other with non-organised powdery EDD, often seen in light- and heavy-chain deposition disease. Recently, a novel form of glomerular injury associated with monoclonal IgG deposition that did not belong to any of the previously defined categories, termed “proliferative GN

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with monoclonal IgG deposits” (PGNMID), was described as a new disease entity [7, 8].

PGNMID usually presents with light microscopic features of membranoproliferative GN (MPGN) or endocapillary proliferative GN, in which granular, non-organised deposits are typically seen in the subendothelial and mesangial regions [8]. A pattern of membranous nephropathy (MN) with subepithelial deposits without significant endocapillary proliferative changes has also been reported [9]. The glomerular deposits are composed of monoclonal single light- or heavy-chain immunoglobulin, most commonly IgG3 kappa (κ). IgG1 is the second most common immunoglobulin subclass, while the occurrence of IgG2 is relatively rare [10]. The majority of PGNMID patients have no background diseases. A small number of PGNMID cases may be associated with underlying diseases, such as haematologic neoplasms or viral infection, and the exact aetiologies of PGNMID remain obscure [10–13].

Although patients with PGNMID typically present with nephritic or nephrotic syndrome, the prognosis is variable. One report showed that the majority of PGNMID cases had persistent renal dysfunction or progressed to end-stage renal disease (ESRD), while a few cases exhibited complete remission (CR) [7]. In accordance with these variable outcomes, treatment regimens are empirical and inconsistent, depending on the case or institution, and final consensus on the best treatment protocol has not been achieved. Therefore, study of the clinicopathological aspects of PGNMID is needed in order to characterise the morphological features that are associated with prognosis.

Herein, we report a case of PGNMID with no background medical history. The patient was initially found to have proteinuria during a routine medical check-up. After 5 years, she underwent renal biopsy due to increasing proteinuria. The biopsy revealed PGNMID with features of MN, characterised by the presence of monoclonal IgG2 κ and non-organised, EDD in the subepithelial regions. Immunosuppressant treatment with steroid monotherapy was effective, leading to CR in less than a month. We compare the clinical and histopathological aspects of our case with that of other reported cases and conduct a brief review of the literature.

Case report

Clinical history

The patient was a 27-year-old Japanese woman. She was initially found to have mild proteinuria for the first time during a routine medical check-up in April 2005. Until then, her medical history had been unremarkable. She had no complaints or significant physical abnormalities at that

time. Her family medical history was also unremarkable. She reported social alcohol consumption and did not smoke. She was followed up at that hospital without any medication, but her proteinuria began to increase, reaching approximately 1.0 g/creatinine in June 2011. She was referred to our hospital in July 2011 for further examination and treatment.

On admission to our hospital, her blood pressure was 100/60 mmHg, pulse rate was 76 beats per minute and body temperature was 36.0 °C. Physical examination revealed no significant systolic heart murmur on auscultation and no pretibial oedema. Examination of the lungs, heart, abdomen, and central and peripheral nervous

Table 1 Laboratory findings of the patient on admission to hospital

CBC		Urinalysis	
RBC ($\times 10^4/\mu\text{L}$)	417	Proteinuria	1+
Hb (g/ μL)	12.6	Protein (g/day)	0.5
WBC (μL)	5860	Occult blood	+/-
PLT ($\times 10^3/\mu\text{L}$)	214	RBC (cells/HPF)	20–29
Biochemistry		WBC (cells/HPF)	20–29
CRP (mg/dL)	0.1	Bence Jones protein	—
BUN (mg/dL)	12.1		
Cre (mg/dL)	0.41		
T-Prot (mg/dL)	6		
Alb (mg/dL)	3.5		
T-Chol (mg/dL)	170		
C3 (mg/dL)	92.8		
C4 (mg/dL)	20.9		
CH50 (U/mL)	31.4		
ANA	40		
Anti-dsDNA (IU/mL)	10		
RA (IU/mL)	<5		
Cryoglobulin	—		
IgG (mg/dL)	792		
IgA (mg/dL)	98		
IgM (mg/dL)	187		
HPB19 IgM	—		
HPB19 IgG	7.75		
HBs-Ag	—		
HCV-Ab	—		
HIV-Ab	—		
SPEP	Normal		

Abbreviations (normal range): *CBC* complete blood count, *RBC* red blood cell count, *Hb* haemoglobin, *WBC* white blood cell count, *PLT* platelet count, *CRP* C-reactive protein (<0.3 mg/dL), *BUN* blood urea nitrogen (9–21 mg/dL), *Cre* creatinine (0.8–1.4 mg/dL), *T-Prot* total serum protein (6–8.5 g/dL), *Alb* albumin (3.5–5.5 g/dL), *T-Chol* total cholesterol (130–220 mg/dL), *C3* (80–150 mg/dL), *C4* (15–40 mg/dL), *CH50* (32–44 U/mL), *ANA* antinuclear antibody (< $\times 40$), *Anti-dsDNA* anti-double stranded DNA (<20 IU/mL), *RA* rheumatoid factor (<15 IU/mL), *IgG* (870–1700 mg/dL); *IgA* (110–410 mg/dL); *IgM* (35–220 mg/dL); *HPB*, anti-parvovirus B19 IgM (<1.1 U); *HPB19 IgG* (<1.1 U), *SPEP* serum protein electrophoresis

systems found no abnormalities. The patient's laboratory data on admission are summarised in Table 1. Renal function tests were normal; serum creatinine level was 0.41 mg/dL and blood urea nitrogen level was 12.1 mg/dL. Peripheral blood counts and electrolytes were all within normal limits. Autoimmune and viral serological tests showed no significant abnormalities. Neither monoclonal gammopathy nor Bence Jones proteinuria was detected by immunoelectrophoresis. Serum complement levels were normal (C3, 92.8 mg/dL; C4, 20.9 mg/dL; CH50, 31.4 U/mL). Urinalysis showed proteinuria (0.5 g/day) but no obvious haematuria (erythrocytes, 20–29/high-power field).

Renal pathology

Based on the above clinical findings, percutaneous renal biopsy was performed to determine the pathological characteristics of the renal disorder. The biopsied sample consisted of a renal cortex containing 38 glomeruli, of which no glomeruli were segmentally or globally sclerosed. All the glomeruli exhibited diffuse thickening of the peripheral capillary walls (Fig. 1). Periodic acid methenamine silver (PAM) staining revealed variable basement abnormalities such as diffuse spike formation and focal double contour, probably associated with intramembranous

and subepithelial deposits (Fig. 1a–c). Masson trichrome staining showed subepithelial and intramembranous deposits and mild mesangial expansion, together with a few mesangial deposits (Fig. 1d, e). No tubulointerstitial or arteriolar lesions were evident (Fig. 1f). Congo red staining revealed no amyloid deposition (data not shown).

Immunofluorescence (IF) staining produced strong glomerular staining of IgG and C3 globally in the peripheral capillary loops and segmentally in the mesangial areas (Fig. 2). Weak staining of IgM, C1q and C4 was noted in the segmental peripheral capillary tufts and mesangial areas. Interestingly, the deposited IgG was composed only of subclass IgG2 κ light chain.

Electron microscopy analysis revealed diffuse thickening of glomerular capillary basement membranes associated with the presence of irregularly sized EDD predominantly in the intramembranous regions (Fig. 3a, b). Some of these deposits could represent old subepithelial deposits covered by newly formed membranous material. EDD were occasionally noted in mesangial locations (Fig. 3a). No organised structures could readily be identified within the EDD (Fig. 3c, d). No EDD were detected in the tubulointerstitium and arterial walls (data not shown).

Based on the above histological and immunohistological findings, we diagnosed this case as PGNMID with monoclonal IgG2 κ deposits exhibiting MN features.

Fig. 1 Light microscopy findings (a–c PAM stain, d–f Masson trichrome stain; a $\times 200$, b, c $\times 800$, d, e $\times 1600$, f $\times 400$). The glomeruli were slightly enlarged (arrows in a), with segmental to global mild thickening of the peripheral capillary walls. Note the segmental to diffuse distribution of irregular spike formations (arrows in b and c), with variably sized subepithelial deposits (arrows in d and

e). Double contour of the glomerular basement membranes with intramembranous deposits was noted focally (arrowhead in c). Mesangial deposits were also present in some mesangial areas (arrowheads in d and e). Tubulointerstitial and arterial alterations were not evident (f)

Fig. 2 Immunofluorescence findings. Immunofluorescence analysis was performed using fluorescein isothiocyanate (FITC)-conjugated antibodies against IgG, IgA, IgM, C3, C1q and C4 (MBL, Nagoya, Japan), and IgG1, IgG2, IgG3 and IgG4 (Binding Site Limited, Birmingham, UK), as well as kappa (κ) and lambda (λ) light chains (Dako). Fine granular staining of IgG (3+) and C3 (3+) was identified, mainly along the glomerular capillary walls and segmentally in the mesangial areas. Of all the IgG subclasses, only IgG2 was

significantly positive (3+), while the other IgG subclasses (IgG1, IgG3, IgG4) were all negative. κ light chain was positive (3+) in a manner similar to IgG2, whereas λ light chain was negative. These findings indicate the presence of IgG2 κ monoclonal immunoglobulin deposition in the glomeruli. The deposition of IgM (1+), C1q (1+) and C4 (1+) was also noted in segmental peripheral and mesangial areas

Clinical course after renal biopsy

The oral administration of prednisolone (PSL) was initiated at a dosage of 35 mg/day after the diagnosis of PGNMID. After 26 days, CR of proteinuria was achieved. The PSL dosage was reduced to 30 mg/day; urinalysis remained negative for the next 4 weeks and the patient was discharged. As of the last follow-up (10 months after discharge), no significant proteinuria has been detected. No other abnormalities have been detected by laboratory examinations.

Discussion

We report a case of PGNMID discovered during a routine medical check-up. Renal biopsy revealed MN characterised by thickening of the capillary walls. IF study revealed monoclonal IgG2 κ deposits within the glomeruli, which was suggestive of PGNMID. Electron microscopy analysis showed non-organised EDD predominantly in the intramembranous regions. Treatment with steroid monotherapy led to CR without recurrence of the disease. Our case is unique in that (1) PGNMID exhibited IgG2 κ deposits and (2) the patient had no apparent serological data abnormalities and responded well to therapy.

Antibodies of the IgG isotype activate a wide range of effector functions. Four subclasses of IgG are defined

based on the antigenic uniqueness of their heavy chains, which are products of distinct genes [14, 15]. The subclasses are designated IgG1, IgG2, IgG3 and IgG4 in order of their proportions in serum. Although the heavy chains exhibit more than 95 % sequence homology, each IgG subclass has a unique profile of effector activities [16, 17]. To date, 3 subtypes of IgG, IgG1, IgG2 and IgG3, with either κ or lambda (λ) heavy chains have been reported to cause PGNMID [7, 10]. Of these subtypes, IgG3 is thought to be particularly nephritogenic because of its ability to self-aggregate and fix complement via Fc–Fc interactions, resulting in the influx of inflammatory cells and subsequent proliferative GN [18]. With regard to IgG2, only a few cases have been reported in the literature [10]. In our case, PGNMID was associated with IgG2 κ deposition, with a good response to steroid treatment, resulting in CR. However, the associations between the deposition of each IgG subtype, the morphological phenotype and the clinical features such as prognosis and response to treatment have not been fully investigated. Further comparative studies investigating the associations between IgG subclasses and prognosis should be performed to explore the clinical significance of the IgG subtype in PGNMID.

The histological features of PGNMID are heterogeneous [7]. The most common histological pattern is MPGN, characterised by diffuse and global double-contoured glomerular capillary walls with mesangial deposits. This type

Fig. 3 Electron microscopy findings (**a** $\times 7000$, **b** $\times 12000$, **c**, **d** $\times 40000$). Electron microscopy revealed irregularly sized EDD predominantly in the intramembranous (arrowheads in **a**) and subepithelial regions covered by newly formed membranous material

(arrowheads in **b**), and occasionally in mesangial (arrow in **a**) locations. **c**, **d** are high-magnification images of **b**. No apparent organised structures were noted within these deposits (**c**, **d**)

of GN occasionally presents with endocapillary hypercellularity, including focal leukocyte infiltration. The second most common type is endocapillary proliferative GN, characterised by endocapillary hypercellularity and active inflammatory cell infiltration. The third histological pattern is MN, characterised by thickening of the capillary walls and subepithelial deposits. Although the clinical significance of each histological subtype remains unclear, it has been shown that IgG3 is the most common in cases with the histological pattern of MPGN [10]. On the other hand, IgG1, the second most common subtype, is strongly associated with the MN pattern. Our case exhibited membranous features with IgG2 κ deposition. There are only 2 cases with the same combination (MN + IgG2) in the literature, one of which had CR, while the other patient died (probably because of underlying haematological malignancy) [10]. Due to the limited clinical information, we could not evaluate the clinical significance of MN with IgG2 κ further. The collection of data from more cases is needed in order to characterise the clinical aspects of this pathological phenotype.

Although PGNMID is becoming universally accepted as a new disease entity, its clinical outcome remains variable. In particular, the efficacy of immunomodulatory agents such as steroids or cyclosporine for treating PGNMID has not been established. Nasr et al. [7] reported that, out of 32 PGNMID cases (approximately 92 % of them had either MPGN or endocapillary PGN features), only 4 patients (12.5 %) achieved CR (defined as proteinuria <0.5 g/day), while the remaining patients, including 7 ESRD cases (21.9 %), did not exhibit significant recovery after a variety of therapies were administered. Of the 6 cases treated with corticosteroid alone, only 1 had CR, while the others had incomplete remission, persistent renal dysfunction or ESRD [7]. Moreover, Masai et al. [19] showed that 3 PGNMID cases with MPGN features exhibited progressive renal failure or persistent proteinuria refractory to steroid and cytotoxic agents. On the other hand, 62.5 % of PGNMID cases with MN features (10 out of 16 cases, including ours) reported so far have achieved CR with a good response to therapy, regardless of the aetiology (Table 2). Taken together, it is likely that MN features of PGNMID

Table 2 Outcomes and response to steroid therapy in proliferative glomerulonephritis with monoclonal IgG deposits exhibiting membranous features

Author	Number of cases	Deposited immunoglobulin	Aetiology (number of cases)	CR (+)	CR (–)
Komatsuda et al. [9]	2	IgG3κ	Idiopathic (2)	1	1
	1	IgG1κ	Idiopathic (1)	1	0
Guiard et al. [10]	4	IgG1κ	CLL (1), unknown (3)	3	1
	3	IgG1λ	MM (1), CLL (1), unknown (1)	2	1
	2	IgG2κ	CLL (1), unknown (1)	1	1
	2	IgG3κ	Unknown (2)	1	1
Yamada et al. [13]	1	IgG1λ	HCV (1)	0	1
Present case	1	IgG2κ	Idiopathic (1)	1	0
Total	16			10	6

Complete remission (CR) is defined as remission of proteinuria to <0.5 g/day, with normal renal function

may be associated with a favourable outcome compared with PGNMID with non-MN features. Furthermore, Nasr et al. [7] also reported that increased serum creatinine levels and the degree of chronic lesions such as tubular atrophy, interstitial fibrosis or global glomerulosclerosis can be correlated with unfavourable outcomes in PGNMID. In our case, the patient presented with normal renal function, and renal histology revealed membranous features without significant chronic damage in both the glomeruli and the tubulointerstitium. Therefore, it was reasonable to expect that our patient would respond well to steroid therapy.

In summary, we have presented a case of PGNMID discovered during a routine medical check-up. The patient had a mild degree of proteinuria, but her laboratory data were within normal limits. Renal biopsy revealed MN with deposition of monoclonal IgG2κ, suggestive of PGNMID. She was treated with steroid monotherapy, and proteinuria significantly decreased and the patient achieved CR. Although the clinical outcomes of PGNMID are variable, MN features may be a sign of favourable prognosis, an idea supported by other recent reports. Further studies on a larger number of PGNMID cases that seek to correlate the morphological features and IgG subclasses to clinical

outcomes are needed in order to confirm our findings and to further solidify the clinical aspects of this new disease entity.

Conflict of interest All the authors have declared that no conflict of interest exists.

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