CEN Case Rep (2014) 3:139–144
DOI 10.1007/s13730-013-0104-z

CASE REPORT

Recurrent proliferative glomerulonephritis with monoclonal immunoglobulin G deposits leads to rapid graft loss after kidney transplantation: a case report

Kunio Kawanishi · Kazuho Honda · Shigeru Horita · Junki Koike · Tomokazu Shimizu · Kazunari Tanabe · Yutaka Yamaguchi · Kosaku Nitta

Received: 28 August 2013 / Accepted: 31 October 2013 / Published online: 8 December 2013

Abstract We present a case of recurrent proliferative glomerulonephritis with monoclonal immunoglobulin G (IgG) deposits (PGNMID) that progressed rapidly to allograft failure. A 56-year-old man had progressed to end-stage renal failure within 1 year after the diagnosis of membranoproliferative glomerulonephritis (MPGN) by kidney biopsy. He underwent living donor kidney transplantation from his brother 6 months later. Serial allograft biopsies revealed early glomerular deposition of IgG, C1q, and C3 at post-operative day 26, and gradual progression of the glomerular deposition and histology of glomerulonephritis. Several immunosuppressive therapies did not prevent proteinuria, microhematuria, and graft dysfunction, and the patient returned to hemodialysis at 7 months after transplantation. Retrospectively, we demonstrated monoclonal IgG3κ deposition in the native and allograft kidney, and the patient was diagnosed with recurrent PGNMID. The serial graft biopsies revealed the pathological details of the progression of PGNMID. This is a rare case of PGNMID that recurred and progressed rapidly to graft failure after kidney transplantation.

Keywords Proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) · Kidney transplantation · Recurrent glomerular disease

K. Kawanishi (✉) · K. Nitta
Department of Medicine, Kidney Center, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan
e-mail: KKawa@kc.twmu.ac.jp

K. Kawanishi · K. Honda
Department of Pathology, Tokyo Women's Medical University, Tokyo, Japan

S. Horita
Division of Pathology, Kidney Center, Tokyo Women's Medical University, Tokyo, Japan

J. Koike
Department of Pathology, Kawasaki Municipal Tama Hospital, Kawasaki, Kanagawa, Japan

T. Shimizu · K. Tanabe
Department of Urology, Kidney Center, Tokyo Women's Medical University, Tokyo, Japan

Y. Yamaguchi
Yamaguchi's Pathology Laboratory, Matsudo, Chiba, Japan

Introduction

Proliferative glomerulonephritis with monoclonal immunoglobulin G (IgG) deposits (PGNMID) has been recently described by Nasr et al. [1, 2], and is characterized by immunofluorescence findings indicating monoclonal IgG deposits and electron-dense deposits (EDDs) localized to glomeruli. Most patients present with nephrotic proteinuria, hematuria, and variable degrees of kidney dysfunction. The most common light microscopic pattern is membranoproliferative glomerulonephritis (MPGN). The prevalence of PGNMID is still uncertain, but Nasr et al. [2] reported 34 cases, with biopsy incidence 0.17 %, at Columbia University Medical Center from 1999 through 2008. And it should be distinguished from MPGN caused by various etiologies (Table 1) [3]. Immunofluorescence staining has revealed that most patients show IgG3κ deposits (53.1 %) with C3 (97.3 %) and C1q (63.9 %), and subendothelial and mesangial EDDs are commonly detected by electron microscopy [2]. PGNMID is distinguished by the pattern or structure of deposits from monoclonal immunoglobulin deposition disease, including amyloidosis,

Table 1 Etiological classification of membranoproliferative glomerulonephritis (MPGN) [3]

Infections
Hepatitis B, hepatitis C, HIV
Infections endocarditis, shunt nephritis
Mycoplasma, brucellosis, malaria, schistosomiasis
Immunologic disease
Systemic lupus erythematosus
Antiphospholipid antibody syndrome
Mixed connective tissue disease
Rheumatoid arthritis
Dysproteinemia
Light-chain deposition disease (LCDD)
Heavy-chain deposition disease (HCDD)
Waldenström macroglobulinemia
Fibrillary glomerulonephritis
Cryoglobulinemia
Immunotactoid
Proliferative glomerulonephritis with monoclonal immunoglobulin G deposition (PGNMID)
Complement disorder
Dense deposit disease (DDD)
C3 glomerulonephritis (C3GN)
CFHR5 nephropathy
Partial lipodystrophy
Malignancies
Leukemia, lymphoma, myeloma
Others
Transplant glomerulopathy, thrombotic microangiopathies, hemolytic-uremic syndrome, radiation nephritis, sickle cell anemia, alpha-1 antitrypsin deficiency

light-chain deposition disease (LCDD), light- and heavy-chain deposition disease (LHCDD), type 1 cryoglobulinemic glomerulonephritis, immunotactoid glomerulonephropathy (IT), and fibrillary glomerulonephritis (FGN). The deposits are negative for Congo red staining and usually show a granular texture without substructures, as observed in IT or FGN localized to glomeruli [1, 2].

Although most patients have no detectable monoclonal IgG (M-peak) in their serum or urine, the glomerular deposits of PGNMID are thought to be derived from circulating monoclonal IgG. Thus, PGNMID in kidney allografts can recur frequently [4–6], although its recurrence rate is uncertain due to its rarity. The recurrence of PGNMID is usually detected at 3–5 months after transplantation using episode biopsies [4–6], whereas the timing of recurrence of MPGN varies from 1 week to several years after transplantation [7–9]. The renal prognosis is usually favorable, with the exception of cases with concurrent infection [5]. Here, we report a rare case of PGNMID that recurred on post-operative day (POD) 26 and progressed to graft failure within 7 months after kidney transplantation. The serial graft biopsies revealed the pathological details of the progression of PGNMID.

Case report

A 56-year-old man with nephrotic syndrome was diagnosed with MPGN by kidney biopsy in December 1993 (Fig. 1). He had no monoclonal IgG (M-peak) in his serum or urine. There was no evidence of cryoglobulinemia, hepatitis virus infection, or any other cause of secondary MPGN from his laboratory data (Table 2). Oral prednisolone (1 mg per kg body weight) therapy combined with renin–angiotensin system (RAS) blockade and antiplatelet drugs, followed by cyclophosphamide (50 mg per day), was administered. However, microhematuria (20–100/high-power field), proteinuria (2.5–9.2 g per day), and hypocomplementemia (C3 0.34–0.48 g/L; C4 0.11–0.17 g/L; CH50 27–48 kU/L) persisted, and his renal function deteriorated gradually. He started hemodialysis (HD) therapy 1 year after the diagnosis, in November 1994 (Fig. 2a). Six months later, he received a living donor kidney transplant [ABO compatible and two human leukocyte antigen (HLA) mismatches] from his 56-year-old brother in June 1995 (Fig. 2a). The initial immunosuppressive therapy comprised cyclosporine (CYA), methylprednisolone, and mycophenolate mofetil (MMF). Cyclosporine was started at 6 mg per kg body weight and was adjusted to maintain a trough level in whole blood of 2–3 $\times$ 10^{-4} g/L. MMF was started and maintained at 2 g per day according to the number of white blood cells. The clinical course after transplantation was unremarkable, and he was discharged from the hospital with a serum creatinine (sCr) level of 132.6 μmol/L. At his first visit to the outpatient clinic, a slight elevation of the sCr level (167.9 μmol/L) and microhematuria without proteinuria were detected, and an allograft biopsy was performed on POD 26, which revealed no significant tubulointerstitial or vascular rejection without significant glomerular morphology. However, by immunofluorescence analysis, slight mesangial deposition of IgG, C3, and C1q was detected, suggesting the possibility of early recurrence of MPGN. Intravenous steroid pulse therapy (0.5 g per day for 2 days) and subsequent muromonab-CD3 (Orthoclone OKT3®) were administered for the treatment of presumed vascular rejection. Subsequently, his sCr temporally declined to 123.76 μmol/L; however, microhematuria persisted. During the subsequent 3 weeks, his sCr level gradually elevated to 185.6 μmol/L, and allograft biopsy was performed on POD 57. Histological analysis showed similar minimal tubulointerstitial lesions with no sign of vascular rejection. Next, the other episodes of sCr elevation occurred on PODs 74 and 90. Because of the persistent increase in the sCr

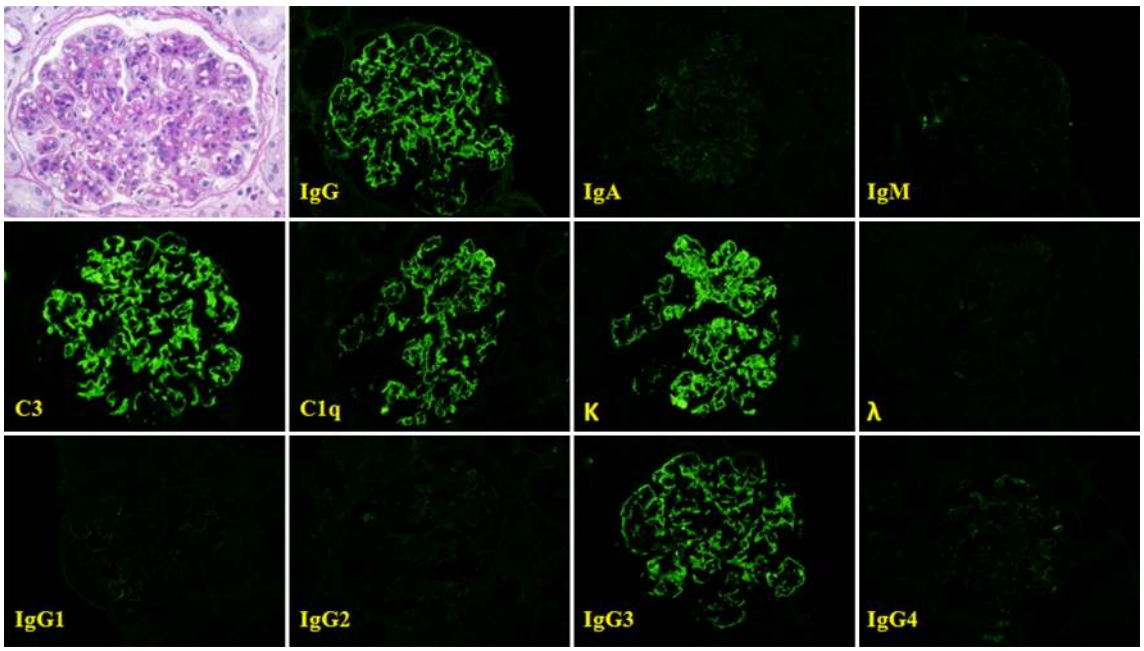

Fig. 1 Light microscopy and immunofluorescence findings in a native kidney biopsy. The glomerulus showed a lobular appearance with mesangial and endocapillary hypercellularity, and the diagnosis was membranoproliferative glomerulonephritis (MPGN). IgG, C1q, and C3 were massively deposited in both the mesangium and glomerular capillaries. Subsequent immunostaining revealed monoclonal IgG3κ deposition, and the patient was diagnosed with proliferative glomerulonephritis with monoclonal immunoglobulin G (IgG) deposits (PGNMID) retrospectively

level, we strongly suspected severe acute rejection involving large vessels which could not be detected by the biopsy. Several courses of intravenous steroid pulse therapy and intravenous administration of 15-deoxyspergualin (DSG; 0.3 g per day) were performed between PODs 75 and 78. Despite these antirejection therapies, allograft biopsies on PODs 76 and 164 revealed a progression of mesangial proliferation and an increase in glomerular IgG and C3 deposition (Fig. 2b). In addition to microhematuria, proteinuria (0.2–0.4 g per day) was detected after POD 90 and became markedly high (3.6 g per day) in October 1995. Thus, we added azathioprine (0.1 g per day); however, his sCr level finally reached the level of end-stage renal disease (ESRD), and HD was restarted in December 1995 (Fig. 2a).

Because the concept of PGNMID had not been established when the patient was treated in the 1990s, he was diagnosed with MPGN. After establishment of the PGNMID concept, we retrospectively confirmed the monoclonality of glomerular IgG deposits using immunofluorescence analyses for IgG subclasses, as well as the κ and λ light chains, and recognized that glomerular IgG was composed of monoclonal IgG3κ in both the native kidney biopsy (Fig. 1) and allograft kidney biopsies (Fig. 2b). Therefore, we concluded that his original kidney disease was PGNMID (IgG3κ type), which recurred in the kidney allograft.

Table 2 Data profile of the proliferative glomerulonephritis with monoclonal immunoglobulin G (IgG) deposits (PGNMID) patient

At the first admission (in 1993)	
Total protein (g/L)	47 (67–83)
Albumin (g/L)	26 (38–52)
Urinary protein (g/day)	5.7 (0.03–0.12)
Hematuria (/high power field)	>100
Blood urea nitrogen (mmol/L)	7.6 (2.85–7.85)
Serum creatinine (μmol/L)	88.4 (53.9–91.9)
CH50 (kU/L)	27 (25–48)
C3 (g/L)	0.34 (0.86–1.60)
C4 (g/L)	0.13 (0.17–0.45)
Antinuclear antibody test	<1:40
Serum cryoglobulin	Negative
M protein[a]	Not detected
Anti-HBV antibody	Negative
Anti-HCV antibody	Negative
Anti-HIV antibody	Negative
After diagnosis of PGNMID (in 2012)	
IgG (g/L)	8.79 (8.70–17.0)
IgG1 (g/L)	3.97 (3.20–7.48)
IgG2 (g/L)	4.00 (2.08–7.54)
IgG3 (g/L)	0.434 (0.066–0.883)
IgG4 (g/L)	0.472 (0.048–1.05)
κ (g/L)[b]	0.233 (0.033–0.194)
λ (g/L)[c]	0.652 (0.057–0.263)
κ/λ ratio	3.57 (0.37–3.1 in CKD)

[a] Immunofixation in his serum and urine

[b, c] Polyacrylamide gel analysis of his serum

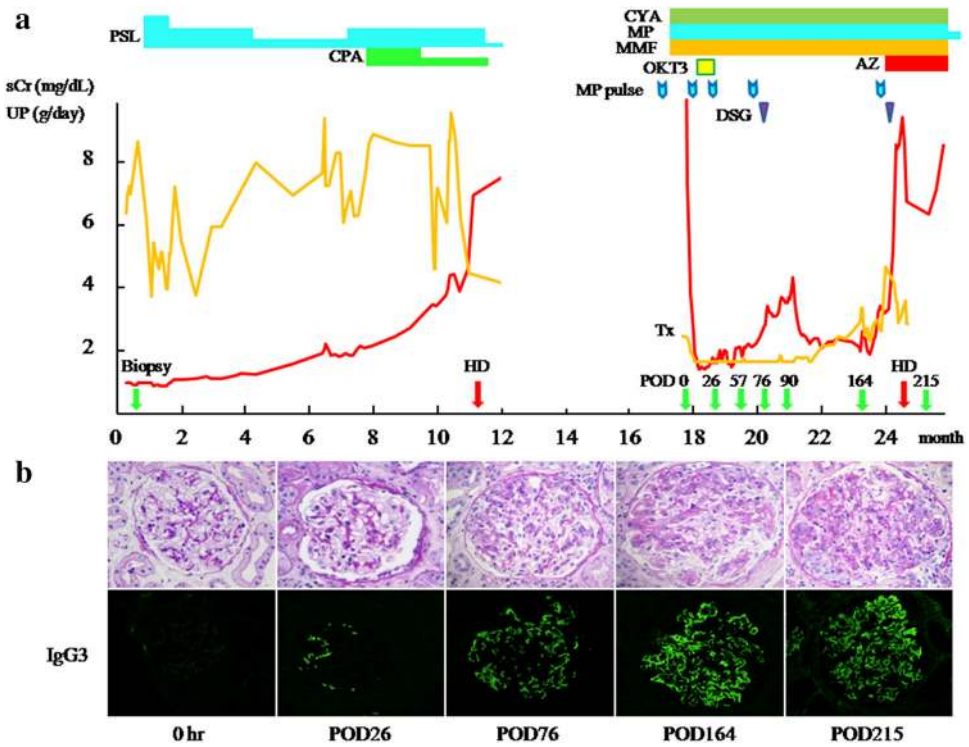

Fig. 2 Clinical course of recurrent PGNMID before and after kidney transplantation (**a**) and serial progression of glomerular proliferative changes and IgG3 deposition in the allograft kidney (**b**). **a** Clinical course demonstrating urinary abnormalities, renal function, and the treatments performed. Treatment-resistant microhematuria and proteinuria persisted. Renal function of the patient deteriorated gradually and hemodialysis (HD) therapy was started 1 year after the biopsy. Half a year later, he was transplanted the allograft kidney from his brother. PGNMID recurred within at least post-operative day (POD) 26 and his renal graft failure after 7 months in spite of several immunosuppressive therapies. The *vertical bi-axis* shows serum Cr (*red*) and urinary protein (*yellow*) levels.Biopsy (*green arrow*), *HD* hemodialysis (*red arrow*), *Tx* transplantation, *PSL* prednisolone, *CPA* cyclophosphamide, *CYA* cyclosporine, *MP* methylprednisolone, *MMF* mycophenolate mofetil, *OKT3* muromonab-CD3, *DSG* 15-deoxyspergualin, *AZ* azathioprine. **b** Glomerular morphology showed minor abnormalities at transplantation (0 h) and POD 26, mild mesangial proliferative at POD 76, and membranoproliferative at PODs 164 and 215. IgG3 deposition appeared at POD 26 when glomerular changes were minimal and concomitantly progressed from the mesangial pattern (POD76) to mesangial and capillary patterns (PODs 164 and 215)

By electron microscopy, a small amount of EDDs was first detected in the mesangium in the allograft biopsy on POD 26, and these EDDs were more clearly detected on POD 57 (Fig. 3a). In the subsequent allograft biopsy on POD 90, deposits were observed in both mesangial and subendothelial areas accompanying mesangial interposition (Fig. 3b). Endocapillary proliferation with inflammatory cells was found on POD 164 (Fig. 3c). Under high magnification, the deposits had a granular texture without organized microstructures such as microtubules or fibrils (Fig. 3d). After obtaining informed consent from the patient, we evaluated his serum IgG subclass content: total IgG, 8.79 (8.70–17) g/L; IgG1, 3.97 (3.20–7.48) g/L; IgG2, 4.00 (2.08–7.54) g/L; IgG3, 0.43 (0.066–0.883) g/L; and IgG4, 0.472 (0.048–1.05) g/L (normal ranges). M protein was negative again in serum by immunofixation. We also performed a serum-free light-chain (FLC) assay and found that he had κ-dominant monoclonal gammopathy [$\kappa = 0.233$ (0.0033–0.0194) g/L; $\lambda = 0.0652$ (0.0057–0.0263) g/L; κ/λ ratio = 3.57 (0.26–1.65 in non-CKD; 0.37–3.1 in CKD)] [10]. The patient was maintained on regular HD during the following 18 years and showed no clinical evidence of multiple myeloma or lymphoma.

Discussion

Here, we present a case of PGNMID that rapidly progressed to renal failure in both the native and allograft kidney. The original diagnosis was MPGN; however, we retrospectively diagnosed the present case with PGNMID by IgG heavy-chain subclass and light-chain analysis of the glomerular deposits. Recurrent glomerular diseases usually develop within the first 2 years after allograft transplantation [11]. Seven cases of recurrent PGNMID have been reported to date; these were histologically diagnosed 3–22 months after transplantation [3–5]. In the present case, monoclonal IgG and complement deposition were

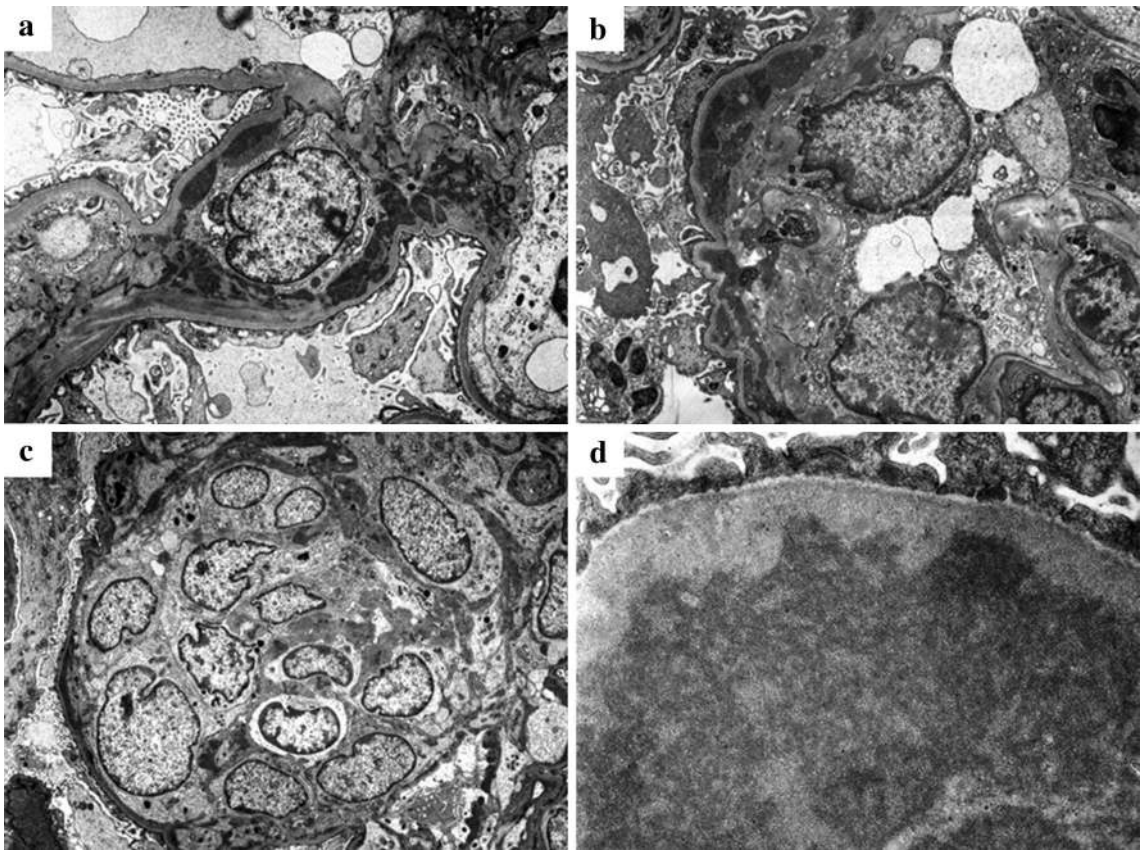

Fig. 3 Electron microscopic findings in the allograft kidney. Electron-dense deposits (EDDs) were found in the mesangial area at POD 57 (**a**), and in both the mesangial and subendothelial areas accompanying mesangial interposition at POD 90 (**b**) (×3,000). Endocapillary proliferation with inflammatory cells was found at POD 164 (×3000). Under high magnification, the deposits displayed a granular texture without organized microstructures such as microtubules or fibrils (×15000) (**d**)

detected at POD 26, which is the earliest case among the previous cases.

The clinical outcomes of PGNMID are various, and Nasr et al. [2] reported that 7/32 (21.9 %) patients with PGNMID progressed to renal failure. The authors suggested that the favorable outcome was attributable to disease stabilization by early immunosuppressive therapy that included a regimen of high-dose prednisolone and rituximab [4]. However, Masai et al. [12] reported a patient with PGNMID (IgG3κ type) who showed resistance to steroids and cytotoxic agents, and progressed to kidney failure. These reports and our case indicate that the outcome of PGNMID is not always favorable. Especially in the recurrent cases, sufficient immunosuppressive therapy, such as high-dose prednisolone combined with rituximab or plus cyclophosphamide, should be selected for the treatment of PGNMID according to recent recommendations [4].

The most common type of deposit in unfavorable cases of primary and recurrent PGNMID remains unclear due to the small numbers of patients in previous studies [4–6]. Nasr et al. [2] reported that the most common subtype of primary PGNMID was IgG3κ (53.1 %), followed by IgG1κ (21.9 %). In the recurrent cases with PGNMID, the IgG subtypes was IgG3κ in five cases and IgG3λ and IgG2λ in one case, respectively [4–6]. The IgG3 subtype possesses the following unique physicochemical properties: self-aggregation via Fc–Fc interactions, the highest molecular weight, the greatest complement-fixing ability, and the most positive charge, making this subtype intrinsically "nephritogenic" [13, 14].

On the other hand, Debiec et al. [15] reported a patient with recurrent membranous nephropathy 13 days after kidney transplantation whose graft biopsy specimen showed granular staining monoclonal IgG3κ and corresponding PLA2R antigen expressed on donor podocytes. Treatment with rituximab stabilized both proteinuria and serum creatinine, and circulating anti-PLA2R became undetectable. This case also suggested that a presence of circulating monoclonal immunoglobulin, especially the IgG3 subclass, could deposit in the allograft soon after the transplantation and cause the recurrent glomerular disease through complement activation. Further research is

required to clarify the pathogenesis and progression of PGNMID in relation to the IgG subclass.

The glomerular morphology of PGNMID is various: membranoproliferative (56.8 %), endocapillary proliferative (35.1 %), mesangioproliferative (2.7 %), membranous (5.4 %), and crescentic (32.4 %) [2]. Moreover, the locations of EDDs are also various: mesangial (94.6 %), subendothelial (100 %), subepithelial (56.8), and intramembranous (13.5 %) [2]. In the present case, light microscopic glomerular change was minimal at PODs 26 and 57, mesangial proliferation and intracapillary macrophage infiltration were subsequently evident at POD 76, and capillary involvement of glomerular inflammation (membranoproliferative lesion) became apparent at PODs 94, 164, and 215. EDDs were first detected in the mesangial region (at POD 26), and subsequently appeared in the subendothelial region (POD 57 and later). The morphological transition of the present case, therefore, indicates that the various glomerular morphologies of PGNMID may be influenced by the stage of the disease progression.

In conclusion, we retrospectively diagnosed and evaluated a case of recurrent PGNMID that progressed rapidly to allograft failure. Sufficient immunosuppressive therapy, such as high-dose prednisolone combined with rituximab or plus cyclophosphamide, is recommended for the treatment of PGNMID in general, but our case indicated that the outcome of PGNMID in the kidney allograft is not always favorable.

Acknowledgments We thank Hideki Nakayama and Mayuko Ohno for their technical support.

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

References

1. Nasr SH, Markowitz GS, Stokes MB, et al. Proliferative glomerulonephritis with monoclonal IgG deposits: a distinct entity mimicking immune-complex glomerulonephritis. Kidney Int. 2004;65:85–96.
2. Nasr SH, Satoskar A, Markowitz GS, et al. Proliferative glomerulonephritis with monoclonal IgG deposits. J Am Soc Nephrol. 2009;20:2055–64.
3. Rogers TE, Rakheja D, Zhou XJ. Glomerular diseases associated with nephritic syndrome and/or rapidly progressive glomerulonephritis. In: Zhou XJ, Laszik Z, Nadasdy T, D'Agati VD, Silva FG, editors. Silva's diagnostic renal pathology. Cambridge: Cambridge University Press; 2009.
4. Nasr SH, Sethi S, Cornell LD, et al. Proliferative glomerulonephritis with monoclonal IgG deposits recurs in the allograft. Clin J Am Soc Nephrol. 2011;6:122–32.
5. Albawardi A, Satoskar A, Von Visger J, et al. Proliferative glomerulonephritis with monoclonal IgG deposits recurs or may develop de novo in kidney allografts. Am J Kidney Dis. 2011;58:276–81.
6. Sumida K, Ubara Y, Marui Y, et al. Recurrent proliferative glomerulonephritis with monoclonal IgG deposits of IgG2λ subtype in a transplanted kidney: a case report. Am J Kidney Dis. 2013;62:587–90. doi:10.1053/j.ajkd.2013.01.013.
7. Canaud G, Audard V, Kofman T, et al. Recurrence from primary and secondary glomerulopathy after renal transplant. Transpl Int. 2012;25:812–4.
8. Lien YH, Scott K. Long-term cyclophosphamide treatment for recurrent type I membranoproliferative glomerulonephritis after transplantation. Am J Kidney Dis. 2000;35:539–43.
9. Lorenz EC, Sethi S, Leung N, et al. Recurrent membranoproliferative glomerulonephritis after kidney transplantation. Kidney Int. 2010;77:721–8.
10. Hutchison CA, Harding S, Hewins P, et al. Quantitative assessment of serum and urinary polyclonal free light chains in patients with chronic kidney disease. Clin J Am Soc Nephrol. 2008;3:1684–90.
11. Ivanyi B. A primer on recurrent and de novo glomerulonephritis in renal allografts. Nat Clin Pract Nephrol. 2008;4:446–57.
12. Masai R, Wakui H, Komatsuda A, et al. Characteristics of proliferative glomerulo-nephritis with monoclonal IgG deposits associated with membranoproliferative features. Clin Nephrol. 2009;72:46–54.
13. Grey HM, Hirst JW, Cohn M. A new mouse immunoglobulin: IgG3. J Exp Med. 1971;133:289–304.
14. Capra JD, Kunkel HG. Aggregation of γG3 proteins: relevance to the hyperviscosity syndrome. J Clin Invest. 1970;49:610–21.
15. Debiec H, Hanoy M, Francois A, et al. Recurrent membranous nephropathy in an allograft caused by IgG3κ targeting the PLA2 receptor. J Am Soc Nephrol. 2012;23:1949–54.