A case report of proliferative glomerulonephritis with monoclonal immunoglobulin M-kappa deposits without associated lymphoproliferative disorder or detectable paraproteinemia

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Abstract

A 53-year-old man presented with proteinuria and hematuria. No significant abnormality was detected in his physical examination or laboratory tests, including evidence of paraprotein in serum and urine. Renal biopsy revealed mesangial proliferation, thickened glomerular basement membranes, and spike formation. Immunofluorescence revealed deposition of immunoglobulin (Ig) M heavy chain, kappa (κ) light chain, and complement component C3 along capillary walls in the glomeruli. Light chain staining indicated significant restriction, because only κ chain, not lambda chain, was present in glomeruli. Aggregated electron dense deposits were observed in the subepithelial area and within the lamina densa on electron-microscopic examination. Cryoglobulinemia and amyloidosis were ruled out. Clinically, steroid therapy was not initiated due to patient preference, and the only prescribed medication was an angiotensin II receptor blocker. At the approximately 3-year follow-up, estimated glomerular filtration rate had decreased very mildly. The present case demonstrates that deposition of monoclonal IgM- κ may be associated with membranoproliferative glomerulonephritis-like changes in the glomeruli. Although no underlying hematological abnormality or paraproteinemia was observed in this case within the range of limited clinical examination, the patient's condition is consistent with proliferative glomerulonephritis with monoclonal IgM deposits, similar to the recently established proliferative glomerulonephritis with monoclonal IgG deposits. Further elucidation of the pathophysiology and effective treatments of the disorder should be expected in the future through the accumulation of similar cases.

Keywords PGNMID · PGNMIMD · Monoclonal · IgM · MPGN

Introduction

Syndromes involving deposition of monoclonal immunoglobulin or paraprotein in the glomeruli include proliferative glomerulonephritis with monoclonal IgG deposits (PGN-MID), reported by Nasr et al. [1, 2], as well as amyloidosis, cryoglobulinemic glomerulonephritis, immunotactoid glomerulopathy, and Randall-type monoclonal immunoglobulin

deposition disease (MIDD). PGNMID is characterized histopathologically by diffuse endocapillary proliferative or membranoproliferative glomerulonephritis (MPGN)—such as glomerular lesion with fine granular deposits, mimicking immune complex-type deposits on electron microscopy. In addition, PGNMID involves glomerular deposition of monoclonal IgG, consisting of one of the gamma heavy chain subclasses and a restricted light chain. PGNMID differs from MIDD in that 29–65% of MIDD cases are associated with multiple myeloma, whereas PGNMID is neither associated with multiple myeloma nor the related lymphoproliferative disorders in general, even though 30% of PGNMID cases are complicated with monoclonal gammopathy of undetermined significance (MGUS) [3]. In recent years, several cases with clinical characteristics and histopathological features resembling PGNMID, as originally reported by Nasr et al. [1], but involving glomerular IgM deposition rather than IgG have been described [4–10]. Most of these cases were

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associated with macroglobulinemia, MGUS, or other hematological disorders in addition to PGNMID; therefore, there are inconsistencies in the reports characterizing conditions with a similar disease background to that of PGNMID as originally described by Nasr et al. but involving IgM rather than IgG.

Here, we present the case of a patient who developed MPGN-like glomerular lesion with monoclonal IgM-kappa (κ) deposits and non-organized immune complex-type granular electron-dense deposits, without any underlying hematological abnormality in the range of limited clinical examination. The present case may contribute to the extension of the disease spectrum of PGNMID and related disorders.

Case presentation

The patient was a 53-year-old Japanese man who was found to have asymptomatic mild proteinuria (1+) on routine physical examination, beginning about 10 years prior to admission and detected continuously from that time onward. Hypertension and hematuria had also been observed within the last 5 years. 4 months before admission, the patient was referred to our hospital for a more detailed examination of his proteinuria and hematuria. He had no significant family history. The patient's past medical history included hypertension and dyslipidemia, and he had been taking losartan, benidipine hydrochloride, hydrochlorothiazide, and rosuvastatin orally. He had smoked 20 cigarettes per a day between the ages of 20 and 52 years and was a social drinker.

The patient's condition at admission was as follows: blood pressure 131/78 mmHg, pulse rate 67 beats per minute, and no abnormal findings on physical examination. His blood test (Table 1) indicated serum creatinine of 0.95 mg/dl and estimated glomerular filtration rate (eGFR) of 65.7 ml/min/1.73 m² (according to the modification of the CKD Epidemiology Collaboration Equation for Japanese). No monoclonal paraprotein (gammopathy) was detected on serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP), or immunofixation electrophoresis (IFE). In addition, serum free light chain (FLC) ratio (1.22) was within the normal range (reference range: 0.26–1.65). Cryoglobulin was negative, and soluble interleukin-2 receptor level (448 U/ml) was within normal limits. In the antinuclear antibody test, the titer was 1:80 for nucleolar type antibody, whereas anti-dsDNA, anti-SS A, and anti-SS B antibodies were negative. With regard to infectious agents, hepatitis B surface antigen/antibody, hepatitis B virus DNA, and hepatitis C virus antibody were all negative. The patient's urine test indicated proteinuria (urine protein/creatinine ratio of 4.93 g/g Cr) and microscopic hematuria.

Renal biopsy histopathology

Renal biopsy was performed for histopathological diagnosis. Among the 16 glomeruli sampled for light microscopy (Fig. 1), one globally sclerotic glomerulus, 2 segmentally sclerotic glomeruli, and 3 glomeruli with adhesion were observed. The remaining glomeruli appeared enlarged (approximately 250 μ m in diameter), and marked diffuse thickening of glomerular basement membranes (GBM) and

Table 1 Laboratory findings on admission

Urinalysis		Biochemistry	
Red blood cell count	1–4/high-power field	Total protein	6.0 g/dl
Hyaline cast	20–29/wide field	Albumin	3.8 g/dl
Fatty cast	5–9/wide field	Urea nitrogen	15 mg/dl
Protein creatinine ratio	4.93 g/gCr	Creatinine	0.95 mg/dl
Protein	5.29 g/day	Total cholesterol	224 mg/dl
Peripheral blood		Triglycerides	179 mg/dl
White blood cell count	5600/ μ l	Low-density lipoprotein cholesterol	109 mg/dl
Red blood cell count	4.82×10^6 / μ l	Hemoglobin A1c	6%
Hemoglobin	14.9 g/dl	C-reactive protein	0.16 mg/dl
Hematocrit	44.2%	Serology	
Platelets	24.5×10^4 / μ l	C3 complement	124.5 mg/dl
		C4 complement	37.6 mg/dl
		IgG	709 mg/dl
		IgA	147 mg/dl
		IgM	46 mg/dl
		Free κ chain	19.9 mg/dl
		Free λ chain	16.3 mg/dl
		Free κ/λ ratio	1.22

Fig. 1 Microphotographs showing light microscopic findings of a renal biopsy specimen of the present case. **a** Low-power view of periodic acid-Schiff (PAS)-stained section demonstrates thickening of the basement membrane and proliferation of mesangial cells in the glomeruli. **b, c** High-power view of periodic acid methenamine silver-stained section demonstrates marked thickening of the basement membrane with spike formation and moth-eaten appearance, subepi-

thelial deposits (arrows), and subendothelial deposits (arrowheads). **d** High-power view of acid fuchsin orange G-stained section demonstrates widespread thickening of the glomerular capillary walls, subepithelial deposits (arrows) and subendothelial deposits (arrowheads). **e** PAS-stained section demonstrates tubulo-interstitial nephritis with marked tubular atrophy, inflammatory cell infiltration, and foamy cell appearance

mesangial cell proliferation were noted, particularly in 7 glomeruli. Periodic acid methenamine silver staining revealed spike formation and moth-eaten appearance in the thickened GBM. Mesangial interposition and/or duplication of the capillary wall were not obvious in these glomeruli, and neither endocapillary hypercellularity nor crescent formation was noted. With trichrome staining, fuchsinophilic depositions were identified in both subepithelial and subendothelial locations. Congo red staining for amyloid was negative.

Moderate degrees of tubular atrophy and interstitial fibrosis were observed. Inflammatory cells including exclusively mature lymphocytes infiltrated focally in the interstitium. Neither atypical nor transformed lymphocytes were observed among these inflammatory cells. Scattered foamy cells also infiltrated the interstitium, while infiltration of neutrophils, plasma cells, and eosinophils was less noticeable. Tubulitis was not noted. The significant pathological change was not identified in the blood vessels, except for the alteration that was suitable for his age.

Direct immunofluorescent staining performed on cryostat sections revealed finely granular reactivity for IgM and κ light chain along the glomerular capillary loops and faint reactivity for complement component C3 in the same area (Fig. 2). Similar results were confirmed through

immunoperoxidase staining of formalin-fixed paraffin-embedded (FFPE) sections. Other immunohistochemical analyses (Fig. 3) indicated that a majority of lymphocytes infiltrating in the interstitium were CD3-positive cells (T lymphocytes), with only scattered CD20-positive cells (B lymphocytes). Only a few plasma cells containing cytoplasmic IgM were recognized among them.

Aggregated electron-dense deposits (EDDs) were observed in the subepithelial area and within the lamina densa on electron microscopic examination (Fig. 4). A subset of EDDs were washed out or resorbed and displayed an electron-lucent appearance. A few similar punctate EDDs were present in the subendothelial area and the mesangial matrix but without nodule formation. Foot process effacement involved approximately 75% of the glomerular capillary surface area.

Clinical course

Although bone marrow aspiration was not performed due to the patient's lack of consent, clinical signs suggestive of possible hematological abnormality were not observed. As the patient did not wish to undergo adrenocorticosteroid therapy, he was treated exclusively with an angiotensin II

Fig. 2 Microphotographs showing immunofluorescence findings. Immunofluorescent observation revealed definitive granular staining for IgM heavy chain and kappa light chain along the capillary walls

in the glomerulus and faint reactivity complement component C3, but negative staining for other antibodies

Fig. 3 Microphotographs showing immunohistochemical staining for CD3 (a), CD20 (b), and IgM (c) on formalin-fixed paraffin-embedded sections. Focal infiltration of mainly CD3-positive lymphocytes is evident (a), but CD20-positive cells (b) and IgM-positive sells (c) are rare

receptor blocker (ARB). Over approximately 3 years of observation, eGFR decreased very mildly from 65.7 ml/

min/1.73 m² at the initial visit to 64.2 ml/min/1.73 m², and protein levels in the urine ranged from 3.5 to 3.8 g/g Cr.

Fig. 4 Electron micrographs showing glomerular alteration. **a** Aggregated electron-dense deposits are apparent in the subepithelium (arrows). **b** Occasionally, electron-lucent deposits, which are regarded

as washed out or resorbed deposits, are also observed in the intramembranous (lamina densa) area (arrowheads)

Discussion

Nasr et al. [1] summarized the clinicopathological features of PGNMID, which has been recently recognized as a distinct glomerulopathic entity associated with monoclonal immunoglobulin deposition, as follows: (1) nephrotic-range proteinuria manifested in 70% of cases of PGNMID, hematuria in 77%, and deterioration of renal function in 68%; (2) all cases negative for amyloid deposition and association of cryoglobulin; (3) light microscopy showing MPGN commonly present (56.8%), most frequently MPGN type 1 and occasionally MPGN type 3, followed by endocapillary proliferative glomerulonephritis (35.1%); and (4) electron microscopy showing electron-dense non-organized deposits in subendothelial locations in all cases as well as in the mesangial area (94.6%), the subepithelial layer (56.8%), and within the basement membrane (13.5%), resembling immune-complex-type glomerulonephritis. Based on these features, the present case appeared to fit the clinicopathological characteristics of PGNMID because the patient demonstrated the above-mentioned characteristics, especially with regard to histological and electron-microscopic features.

PGNMID is defined as a glomerulopathy with deposition consisting of a single IgG subclass and restricted light chain, especially IgG3- κ [1]. In addition, some recent case reports have described glomerular alterations similar to PGNMID with the deposition of monoclonal IgA (PGNM IgA deposits) [11] or monoclonal IgM deposits (PGNMIMD) [4] instead of monoclonal IgG. The present case should also be categorized as PGNMIMD, because immunofluorescence analysis using cryostat sections and immunoperoxidase labeling of FFPE sections in this case exhibited specific deposition of IgM- κ chain and not IgG in glomeruli. At the

moment, however, it is still uncertain whether PGNMID and proliferative glomerulonephritis with IgM or IgA deposits should be recognized as distinct disease entities or not. Further accumulation of cases such as the present one should be required to address this question.

The pathogenesis of PGNMID is not fully understood. The majority of PGNMID patients have no background disorder, whereas a subset of PGNMID cases may be associated with underlying disease, such as hematological neoplasms. Indeed, synchronous or metachronous combination of multiple myeloma and related disorders has not been described, although an association with MGUS has been recognized in approximately 30% of PGNMID patients [1]. In the remaining 70% of PGNMID cases, causative serum protein abnormalities including M-protein have not been identified. In contrast, according to Oe et al. [4], of 20 patients with PGNMIMD, 8 cases were associated with MGUS; 6 with lymphoproliferative disorders, especially chronic lymphocytic leukemia; and 3 with Waldenström's macroglobulinemia. Without exception, other previous reports also indicated underlying lymphoproliferative disorders in PGNMIMD [5–9]. The present patient had no detectable abnormality in serum protein: (1) an increase of IgM was not serologically observed; (2) M-protein was not identified through any means of laboratory testing including SPEP, UPEP, and IFE; (3) FLC ratio was within the normal range; and (4) neither cryoglobulin nor autoantibodies were detected. Unfortunately, bone marrow examination was not performed; however, the patient's physical findings and laboratory data suggested no evidence of underlying hematological disease. Moreover, to determine whether clonal proliferation of lymphocytes was present, careful histological and immunohistochemical analyses were performed on the patient's kidney

biopsy specimen because relatively dense lymphocytic infiltration was recognized in the interstitium of the kidney. However, these cells exhibited mature lymphocyte morphology, did not include atypical or transformed cells, and most expressed T-cell phenotype with only a subset expressing B-cell markers. The infiltrating lymphocytes, therefore, were considered to be non-neoplastic inflammatory cells, and underlying lymphoma or related disorders was not detected as far as we examined.

It appears that the present case may be categorized as “idiopathic” PGNMIMD because the patient did not present any evidence of underlying hematological abnormality as far as examined. Yahata et al. [10] presented the case similar to the present one in that the patient demonstrated PGNMID-like glomerulopathy with deposition of monoclonal IgM in a renal biopsy (PGNMIMD) but no evidence of serological monoclonality. However, although serological tests were negative for cryoglobulin and no typical organized deposition (microtubular/annular structures or microfibrils) was recognized on electron microscopy, Yahata et al. suggested the possibility of cryoglobulinemic glomerulonephritis with latent existence of cryoglobulin because renal biopsy findings indicated intracapillary protein thrombi and globular electron-dense deposits, which likely represent phagocytosed immune deposits in cryoglobulinemic glomerulonephritis. Therefore, these authors concluded that they cannot completely rule out the possibility of cryoglobulin nephropathy. In the present case, serological and pathological findings did not suggest latent cryoglobulin nephropathy or related conditions and, therefore, the clinical background in our case might differ from that in the case reported by Yahata et al.

The etiology of PGNMID has not been fully elucidated, but cases of post-transplant relapse suggest a possible etiology [12–16]. It has been suggested that certain potent factors that could contribute to the pathogenesis of renal lesions might continuously exist in the blood, even if M-protein is not detected using SPEP, UPEP, or IFE and the FLC ratio is normal. Therefore, extremely low levels of monoclonal immunoglobulins may be present in the blood, and they are likely to be produced by monoclonally proliferated B-lymphocytes in the process of normal immune response [12]. Two types of PGNMID have been reported in post-transplant relapse, IgG deposits [12–15] and IgA deposits [16], but post-transplant relapse of PGNMIMD has not been reported to date. If such a case should be reported, a mechanism similar to that mentioned above may be supported.

There have been few reports concerning the treatment of PGNMID and related disorders, and there is not yet a well-established therapeutic regimen. According to the report by Nasr et al. [1], approximately 56% of PGNMID patients received steroid or immunosuppressant drugs, and approximately 30% received renin-angiotensin system (RAS) inhibitor monotherapy. Among 32 patients with a follow-up period

of 30.3 months, 37.5% achieved complete or incomplete remission, another 37.5% experienced continuous deterioration of renal function, and 21.9% progressed to end-stage renal failure. In our case, the patient has been treated with an ARB, and no obvious progression of renal function impairment has been identified as of approximately 3 years after the initial visit. In PGNMIMD, although there has been no report on RAS inhibitor monotherapy follow-up, it is necessary to further consider therapeutic measures based on the accumulation of similar cases in the future.

Conclusion

We experienced a case of PGNMIMD with no background disease including lymphoproliferative disorders, MGUS, and cryoglobulinemia, as far as we examined. We observed a change in eGFR over the course of treatment with ARB for approximately 3 years, but progression of renal failure was extremely slow. Since no similar cases have been reported in the literature, the further clarification of related pathological conditions and treatments through further accumulation of cases is expected in the future.

Compliance with ethical standards

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

Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent Informed consent was obtained from the patient included in this article.

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