Proliferative glomerulonephritis with unusual microlamellar organized deposits related to monoclonal immunoglobulin G3 (IgG3) kappa

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Abstract

A 71-year-old woman presented with massive proteinuria and microhematuria. Renal biopsy showed diffuse global membranoproliferative and endocapillary proliferative lesions with leukocytic infiltration and an irregular duplication of the glomerular basement membrane on light microscopy. Immunofluorescence study showed granular deposits of monoclonal immunoglobulin G3 (IgG3) kappa, C3, and C1q in the glomeruli. Electron microscopy revealed unique structurally organized microlamellar electron-dense deposits. There was no evidence of systemic diseases such as paraproteinemia, cryoglobulinemia, or systemic lupus erythematosus. Following renal biopsy, the oral administration of mizoribine in addition to prednisolone gradually improved the patient's clinical status. So far, partial remission has continued for a year, and she has not been affected with hematopoietic or lymphoproliferative disorders. We report a case of proliferative glomerulonephritis with unusual microlamellar organized deposits related to monoclonal IgG3 kappa. Our case was immunologically identical to proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID). Therefore, we concluded that our case should be categorized as an atypical form of PGNMID, though it was difficult to diagnose using the usual diagnostic approach to glomerular diseases with organized deposits.

Keywords Proliferative glomerulonephritis · Monoclonal · IgG subclass restriction · IgG3 kappa · Microlamellar organized electron dense deposits

Introduction

Glomerular diseases with organized deposits are relatively uncommon. They are typically classified into several entities according to the characteristics of the deposits [1–3]. With the exception of amyloidosis, systemic lupus erythematosus, and non-immunoglobulin-derived diseases (including diabetic glomerulosclerosis,

collagenofibrotic glomerulopathy, and fibronectin glomerulopathy), they are divided into four categories: (1) monoclonal immunoglobulin deposition diseases (MIDD), (2) cryoglobulinemic glomerulonephritis (CG), (3) immunotactoid glomerulopathy (ITG), and (4) fibrillary glomerulonephritis (FGN). Common ultrastructural features of MIDD are nonfibrillary, powdery, and punctate electron-dense deposits (EDD) with monoclonal immunoglobulins. Cryoglobulinemia is characterized by the presence of cryoglobulins in serum and is associated with various systemic conditions including hepatitis C infection, lymphoproliferative disorders, and systemic lupus erythematosus [4]. CG occurs in about 20–30% of patients with cryoglobulinemia and exhibits variable ultrastructural features. The most characteristic findings are paired, curved, microtubular structures that may mimic those seen in ITG. In particular, type I CG resembles ITG in both morphological and immunological conditions. Glomerular deposits in type I CG and ITG have similar ultrastructural microtubular deposits and are

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mainly composed of monoclonal immunoglobulins in patients with hematopoietic or lymphoproliferative disorders [5, 6]. On the other hand, FGN is commonly characterized by polyclonal but subclass-restricted organized deposits without concomitant hematopoietic disorders. In addition, electron microscopy features of FGN deposits are characterized by randomly arranged nonbranching microfibrils [7]. Since the “typical structures” that are present in these diseases can only be found in limited cases, it is often difficult to diagnose glomerular diseases using only this approach. In other cases, ultrastructural findings may vary depending on the biochemical properties of immunoglobulins and the conditions of the deposited sites.

Recently, proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) was proposed as a new disease entity, characterized by the deposition of monoclonal immunoglobulin, restricted to a single subclass of IgG and a single light-chain isotype [8, 9]. PGNMID cases also present non-organized EDD in contrast to aforementioned diseases.

In this manuscript, we report a case of membranoproliferative and endocapillary proliferative glomerulonephritis (GN) with unusual microlamellar EDD related to monoclonal immunoglobulin G (IgG3 kappa). The glomerular deposits in our case did not clearly correspond to conventional structural patterns; however, we concluded that our case should be categorized as an atypical form of PGNMID based on immunological mechanisms.

Case report

A 71-year-old Japanese woman with bilateral lower thigh edema was admitted to our hospital. Nephrotic range proteinuria and renal insufficiency recurred repeatedly during the past year and a half. Although she remained in stable condition via dietary treatment and antihypertensive therapy over a period of time, she was eventually admitted to our hospital because of marked proteinuria and deterioration of renal function.

Upon admission, the patient was alert and clear. Her blood pressure was 130/80 mmHg. There was no swelling of the superficial lymph nodes and no skin eruption. Pitting edema was noted on the bilateral lower thighs. Over the past 6 years, she had been diagnosed with dyslipidemia and treated with oral medications at a local clinic. Urinary protein excretion was 4.86 g/day. Serum total protein, albumin, and total cholesterol values were 6.5, 3.3 g/dl, and 245 mg/dl, respectively. Reduced renal function was noted (Table 1).

A renal biopsy was performed. On light microscopy, 24 glomeruli were observed, of which three were sclerotic. The biopsy specimen revealed diffuse global membranoproliferative and endocapillary proliferative lesions with macrophage infiltration and irregular duplication of the glomerular basement membrane (GBM) (Fig. 1). Three glomeruli showed fibrous or fibro-cellular crescent formations. Interstitial fibrosis was observed, mainly

Table 1 Laboratory test

WBC	6400/ μ l	Glucose	169 mg/dl	Cryoglobulin	(–)
RBC	339×10^4 / μ l	HbA1c	5.5%	IEP	WNL
Hb	10.2 g/dl	CRP	0.21 mg/dl	IgG subclass	
Ht	30.8%			IgG1 (423–1080)	588 mg/dl
Platelets	23.2×10^4 / μ l	ANA	(–)	IgG2 (265–931)	245 mg/dl
		IC-C1q	≤ 1.5 μ g/ml	IgG3 (5–121)	169 mg/dl
AST	29 IU/l	C3	93 mg/dl	IgG4 (4–108)	10 mg/dl
ALT	13 IU/l	C4	36 mg/dl		
T-Cho	245 mg/dl	CH50	54.5 U/ml	Urinalysis	
LDL-C	124 mg/dl	IgG	970 mg/dl	pH	5.0
TG	97 mg/dl	IgA	426 mg/dl	SG	1.022
TP	6.5 g/dl	IgM	207 mg/dl	Protein	(3+)
Albumin	3.3 g/dl				4.86 g/gCre
BUN	35.2 mg/dl	MPO-ANCA	< 10EU	Occult blood	(3+)
Creatinine	2.95 mg/dl	PR3-ANCA	< 10EU	RBC	> 100/HPF
Uric acid	9.3 mg/dl	Anti-GBM Ab	< 10EU	NAG	14.9 U/l
Na	142 mEq/l			β_2 MG	15,840 μ g/l
Cl	99 mEq/l	HCV Ab	(–)	BJP	(–)
K	3.5 mEq/l	HBs Ag	(–)	Selectivity index	0.45

WBC white blood cell, RBC red blood cell, Hb hemoglobin, Ht hematocrit, TG triglycerides, TP total protein, BUN blood urea nitrogen, ANA anti-nuclear antibody, HCV Ab hepatitis C virus antibody, HBs Ag hepatitis B virus surface antigen, IEP immunoelectrophoresis, BJP Bence–Jones protein

Fig. 1 Light microscopic findings of glomerular proliferative lesions (**a** PAM stain, **b** Masson trichrome stain, magnification $\times 400$). Light microscopy showed diffuse global membranoproliferative and endo-

capillary proliferative lesions with macrophage infiltration and irregular duplication of the GBM. Arrowheads indicated subendothelial deposits

around sclerotic glomeruli, with lymphocytic infiltration. On immunofluorescence study, granular staining for IgG and C3 was seen mainly in the periphery of glomerular lobes (Fig. 2). Only IgG3 through four subclasses of

IgG was seen in the pattern of IgG. Furthermore, only a kappa light-chain was positive (Fig. 2). Electron microscopy showed unique structurally organized microlamellar EDD, mainly in the subendothelial areas and occasionally

Fig. 2 Deposits of monoclonal immunoglobulin (IgG3 kappa) and complements (magnification $\times 400$). Immunofluorescence staining showed strongly positive for IgG, especially IgG3, kappa light chain,

and C3, in the periphery of glomeruli. C1q and C4 were weakly positive in the pattern of C3

in the paramesangial and subepithelial areas of the glomeruli, which were microlamellar rather than microtubular (Fig. 3). The specimen was negative for Congo-red staining. Repeated tests for cryoglobulin were also negative. We diagnosed the patient with proliferative GN with unusual microlamellar organized glomerular deposits related to monoclonal IgG3 kappa. We considered that the pathogenesis of glomerular injury in our case was identical to PGNMID immunologically.

Following renal biopsy, oral administration of prednisolone (0.8 mg/kg/day) was initiated. However, clinical findings and urinary abnormalities did not improve. Therefore, we administered mizoribine (MZR), an oral immunosuppressant, in addition to prednisolone. Following the initiation of therapy, the clinical symptom and urinary abnormalities gradually improved. So far, partial remission has continued for a year, and she has not been affected with hematopoietic or lymphoproliferative disorders.

Discussion

We described a case of membranoproliferative and endocapillary proliferative GN with unique microlamellar structural EDD related to monoclonal IgG3 kappa. GN associated with monoclonal IgG deposits can be seen in type I CG, ITG, and PGNMID [10, 11]. The first two generally show

characteristic organized EDD. On the other hand, the pathology of PGNMID is typically defined by non-organized EDD. Our case and PGNMID cases shared a common immunological condition, which is monoclonal immunoglobulin positive and complement activation in glomeruli. The inclusion criteria for PGNMID are glomerular deposits with granular EDD resembling immune complex GN. Meanwhile, the first reported cases of PGNMID included a patient with glomerular organized EDD with a lattice-like structure [8]. Notably, the patient in that case was unique because of the presence of amyloidosis. Morphologically, our case differed from typical PGNMID cases because EM revealed unusual and structural EDD. Furthermore, the structural pattern of our case was a rare occurrence for previously described glomerular diseases with organized deposits. Joh et al. reported a similar structural and immunological pattern of glomerular lesions in a 49-year-old woman who presented with nephrotic syndrome and microhematuria [12]. The microlamellar deposits in the case presented by Joh et al. were 25 nm in width and had a periodicity of 50 nm. Morphological findings of the deposits were quite similar to those observed in our case. However, the patient in the study by Joh et al. had paraproteinemia and exhibited both serological and pathological monoclonality.

The formation of organized structures is due to various factors, including circulating factors and the nature of deposited sites. The former factors include abnormal production of monoclonal immunoglobulins. ITG and PGNMID are

Fig. 3 Unusual microlamellar organized deposits. Electron microscopy (EM) showed unique structural electron-dense deposits in glomerular subendothelial and subepithelial areas (**a**). High-mag-

nification EM image revealed microlamellar but not microtubular deposits (**b, c**). Lamellar structures were 10–25 nm in width and were arranged in a nearly parallel style, with a periodicity of 25 nm

sometimes accompanied by M-spike protein and plasma cell dyscrasia. No serological evidence of monoclonality was detected in our patient. As there is often a discrepancy between the pathological and serological findings in glomerular deposition diseases, they can be difficult to diagnose on the basis of the pattern of organized structures. We speculate that glomerular diseases with organized deposits should be distinguished based on immunological rather than structural findings.

In conclusion, we report a case of proliferative GN with unusual microlamellar organized deposits related to monoclonal IgG3 kappa. Our case is unique in that it could not be classified clearly using conventional criteria for glomerular diseases with organized deposits. However, we concluded that our case should be diagnosed as an atypical form of PGNMID based on immunological mechanisms.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Human and animal rights All procedures performed in this case report were in accordance with the ethical standards of the institutional committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Written informed consent was obtained from the patient for publication of this case report and any accompanying images. This study does not contain any studies with animals performed by any of the authors.

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