Proliferative glomerulonephritis with monoclonal IgM- κ deposits in chronic lymphocytic leukemia/small lymphocytic leukemia: case report and review of the literature

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Abstract A 48-year-old man with chronic lymphocytic leukemia presented with nephrotic syndrome, hematuria, and mild deterioration of renal function. Further analysis using serum immunofixation electrophoresis detected monoclonal immunoglobulin (Ig) M- κ and IgG- κ M-protein. Testing for cryoglobulin in serum was negative. Light microscopy of a renal biopsy specimen showed membranoproliferative glomerulonephritis features with marked mononuclear cell infiltration in the interstitium. On immunofluorescence study, the deposition of IgM heavy chain was predominantly observed with the same distribution of κ light chain, whereas no λ light chain was found. Electron microscopy revealed fine granular deposits in the mesangial, subendothelial, and subepithelial areas, mimicking those observed in the immune complex-mediated glomerulonephritis. These pathological findings were consistent with recently described cases of proliferative

glomerulonephritis with monoclonal IgG deposits. Thus, monoclonal IgM deposition can also cause proliferative glomerulonephritis.

Keywords Membranoproliferative glomerulonephritis · Monoclonal IgM- κ · Lymphoproliferative disorder · Nephrotic syndrome

Introduction

Renal involvement in chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL) is relatively uncommon. In cases with these conditions, nephrotic syndrome is frequently observed [1]. Although the etiology varies, the most frequent lesion found on kidney biopsy is membranoproliferative glomerulonephritis (MPGN) feature, which is caused by the deposition of abnormal immunoglobulin (Ig) secreted by leukemia B cells [1, 2].

Abnormal monoclonal Ig deposition can cause various glomerular lesions. Of these, proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID), recently described by Nasr et al., was characterized by diffuse endocapillary proliferative or membranoproliferative-like glomerulonephritis with fine granular deposits, mimicking immune complex-type deposits on electron microscopy [3]. This new concept of the glomerular disease has expanded the disease spectrum. Some rare cases were associated with hematological disorders, such as multiple myeloma, amyloid light chain (AL) amyloidosis, or CLL/SLL [4, 5]. Moreover, monoclonal IgA deposition may also develop into the new form of proliferative glomerulonephritis [6].

Herein, we describe a rare case of CLL/SLL showing MPGN with monoclonal IgM- κ deposition. The analysis of ultrastructural features revealed non-organized deposits in

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the mesangial, subendothelial, and subepithelial areas. These findings led us to label the disorder as proliferative glomerulonephritis with monoclonal IgM deposits (PGNMIMD).

Case report

A 48-year-old man with no significant medical history was admitted to our hospital because of legs edema with heavy proteinuria and hematuria. On admission, physical examination revealed marked edema in bilateral lower legs. Urinalysis showed a proteinuria level of 4.8 g/24 h and more than 100 red blood cells/high-power field. Laboratory tests found an elevated serum creatinine level of 1.34 mg/dL, total serum protein level of 4.7 g/dL, and serum albumin level of 2.4 g/dL. The serum C3 level was slightly decreased to 78 mg/dL (normal range 85–160 mg/dL), although the serum C4 level and total serum hemolytic activity were within normal ranges. Other laboratory findings were as follows: leukocyte count, $9.65 \times 10^3/\mu\text{L}$ with 30.7 % lymphocyte; erythrocyte count, $6.29 \times 10^6/\mu\text{L}$; hemoglobin, 17.8 g/dL; hematocrit, 55.1 %; platelet count, $269 \times 10^3/\mu\text{L}$; blood urea nitrogen, 23 mg/dL; uric acid, 7.0 mg/dL; total cholesterol, 289 mg/dL; triglycerides, 243 mg/dL; C-reactive protein, 0.39 mg/dL; serum IgG, 311 mg/dL; serum IgA, 164 mg/dL; and serum IgM, 147 mg/dL. Hepatobiliary function was normal, and blood glucose was within the normal range. Tests for hepatitis B and C, antinuclear antibody, anti-double-stranded DNA antibody, cryoglobulin, myeloperoxidase antineutrophil cytoplasmic antibody (ANCA), protease-3 ANCA, and rheumatoid factor were all negative. The soluble interleukin-2 receptor level was elevated to 4370 U/mL (normal range 145–519 U/mL). Serum immunofixation electrophoresis (IFE) revealed a band positive for IgM- κ and IgG- κ M-protein. Urinary IFE also showed weak bands of IgG- κ and κ -type Bence Jones protein. Computed tomography revealed no evidence of lymph node swelling. Renal biopsy was performed for accurate diagnosis.

Thirty-one glomeruli were microscopically examined, eight of which showed global sclerosis. The remaining glomeruli exhibited a diffuse increase of mesangial cells and focal endocapillary proliferation accompanying periodic acid-Schiff-positive intracapillary thrombi. Most of the basement membrane in the glomeruli became thickened with the formation of double contours (Fig. 1a). In one glomerulus, cellular crescent was observed. Prominent infiltration of lymphocytes with focal and clustered distribution was also observed in the interstitium. Marked intensity for IgM heavy chain (3+) and C3 (2+), and weak intensity for C1q (+) in both the mesangium and capillary walls were demonstrated by immunofluorescence (IF) study

(Fig. 1b). In contrast, the IF test was negative for IgG (–) and showed weak intensity for IgA (+) (Fig. 1c). The IF test for κ light chains was positive (2+) in the mesangium and along the capillary walls without staining for λ light chain (–) (Fig. 1d, e). Electron microscopy revealed diffuse, finely granular but not fibrillary electron-dense deposits resembling immune complex deposits in the mesangial, subendothelial, and subepithelial areas (Fig. 2a, b).

Further immunohistochemical analyses using paraffin-embedded sections of renal biopsy specimens showed that the infiltrated lymphocytes were positive for CD20, CD79a, and CD5 (Fig. 3a). The same immunophenotyping B cell population was also detected in blood by flow cytometry. More importantly, fluorescence in situ hybridization analysis of paraffin-embedded sections (PS-FISH) of the renal biopsy specimen detected Ig heavy chain rearrangement (Fig. 3b). Cytological evaluation of aspirated bone marrow showed 40.8 % mature leukemic lymphocytes without plasma cell proliferation.

Therefore, the present case was diagnosed as CLL/SLL concomitant with type III MPGN secondary to monoclonal IgM- κ deposition. Monthly combination therapy of rituximab (500 mg/m² on day 1), fludarabine (30 mg/m² on days 1–3), and cyclophosphamide (750 mg/m² on days 1–3) was administered. Four courses of this regimen resulted in hematological remission, together with a reduction in the protein/creatinine ratio of 2 g/g. Serum creatinine was 1.5 mg/dL, indicating no significant change in renal function.

Discussion

We described a case of CLL/SLL presenting with nephrotic syndrome. Renal biopsy findings showed an MPGN lesion that was consistent with the profile of PGNMID. More interestingly, proliferative glomerulonephritis was caused by monoclonal IgM secretion and deposition, which is rare.

CLL/SLL rarely exhibits various glomerular lesions, including MPGN, minimal change disease, amyloidosis, focal segmental sclerosis, and crescentic glomerulonephritis associated with ANCA [1, 2, 5, 7–12]. Of them, we identified sixteen cases of secondary MPGN associated with CLL/SLL [1, 2, 5, 7–10]. Cryoglobulinemia was found in six of these cases, of which two cases were type I (IgG1 λ and IgG κ), two cases were type II (IgG-IgM and IgG-IgA), one case was type III (IgG-IgM), and one case was undetermined. Of the other cases, one case was diagnosed with fibrillary/immunotactoid glomerulopathy (IgG) and two cases were diagnosed with proliferative glomerulonephritis with monoclonal IgG deposits (IgG1 λ and IgG1 κ). In contrast, the present case showed unique pathological findings, monoclonal IgM deposition mediated

Fig. 1 **a** Proliferation of mesangial and endocapillary cells with thickening of the basement membrane and double contour formation are observed [periodic acid-Schiff (PAS) stain, original magnification $\times 400$]. **b** Immunoglobulin (Ig) M heavy chain is strongly positive.

c IgG heavy chain is negative. **d** Stain of κ light chain is positive. **e** λ light chain is entirely negative [immunofluorescence (IF) study, original magnification $\times 400$, respectively]

Fig. 2 **a** Electron microscopy shows finely granular electron-dense deposits in the paramesangial and subendothelial areas resembling immunocomplex glomerulonephritis (original magnification $\times 3000$). **b** Subepithelial deposits (arrows) are also observed (original magnification $\times 5000$)

Fig. 3 **a** Specific staining for CD20 is positive (original magnification $\times 200$). **b** Fluorescence in situ hybridization analysis of paraffin-embedded sections (PS-FISH) demonstrates split signal for Ig heavy chain (IgH). The arrows show distinct red (centromere site) and green (telomere site) split signals in nuclei, suggesting IgH gene rearrangement

Table 1 Summary of proliferative glomerulonephritis with monoclonal IgM deposits (PGNMIMD)

Author, reference	Age (years)/sex	sCr (mg/dL)	UP (g/24 h)	SIEP	UIEP	Cryoglobulin	LM	IF	EM	Hematological disorder
Tsuji et al. [20]	83/M	1.0	2.0	IgMκ	NA	NA	MPGN, SS	μ	Intramembra	WM
Lima et al. [21]	76/M	2.6	6	IgMκ	IgMκ	Negative	Endo, extra	μ	NA	BMG
Veltman et al. [22]	53/M	1.8	0.63–0.83	IgMκ	κLC	Negative	MPGN	μ, κ	No deposits	WM
Ramos et al. [23]	48/M	2.9	4–5	IgMκ	IgMκ	Negative	MPGN	μ, κ, C3	No glomeruli	
Audard et al. [15]	63/M	2.0	2.0	IgMκ	κLC	Negative	MPGN	μ, κ	NA	WM
Audard et al. [15]	66/M	2.1	6.0	IgMκ	κLC	Negative	MPGN	μ, κ, C3	NA	SBNHL
Audard et al. [15]	69/M	1.3	5.5	IgMκ	κLC	Negative	MPGN	μ, κ, C3	NA	IgM RD
Sethi et al. [10]	77/F	2.0	2.4	λLC	λLC	Negative	MPGN	μ, λ	Non-organized	MGUS
Sethi et al. [10]	54/F	3.1	4.3	IgMκ	IgMκ	Negative	MPGN	μ, κ	Non-organized	MGUS
Sethi et al. [10]	66/M	3.6	1.4	IgGκ	IgGκ	ND	MPGN	μ, κ	Non-organized	MGUS
Sethi et al. [10]	48/F	3.1	4.6	IgMκ	IgMκ	Negative	MPGN	μ, κ	Non-organized	MGUS
Sethi et al. [10]	64/M	3.7	1.5	IgMκ	IgMκ	Negative	MPGN	μ, κ	Non-organized	MGUS
Sethi et al. [10]	60/M	3.0	3.0	IgMκ	Negative	Negative	MPGN	μ, κ	Non-organized	MGUS
Sethi et al. [10]	56/F	1.8	0.55	IgMκ	IgMκ	Negative	MPGN	μ, κ	Non-organized	MGUS
Sethi et al. [10]	58/M	1.7	2.5	IgMκ	Negative	Negative	MPGN	μ, κ	No glomeruli	MGUS
Sethi et al. [10]	70/M	5.6	5.3	IgMκ, IgMλ	Negative	Negative	MPGN	μ, κ	ND	CLL
Sethi et al. [10]	82/M	1.9	10.2	IgMκ, IgGλ	IgGλ	Negative	MPGN	μ, κ	Non-organized	LGBCL
Sethi et al. [10]	71/M	1.5	1.815	IgMκ	κLC	Negative	MPGN	μ, κ	Non-organized	LPL
Yahata et al. [14]	38/M	1.5	6.5	None	None	Negative	MPGN	μ, κ, C3	Non-organized	
Present case	48/M	1.3	4.8	IgMκ, IgGκ	IgGκ, κLC	Negative	MPGN	μ, κ, C3	Non-organized	CLL

sCr serum creatinine, UP urinary protein, SIEP serum immune or immunofixation electrophoresis, UIEP urinary immune or immunofixation electrophoresis, LM light microscopy, IF immunofluorescence, EM electron microscopy, LC light chain, MPGN membranoproliferative glomerulonephritis, SS segmental sclerosis, Endo, extra endo- and extracapillary glomerulonephritis, intramembra intramembranous deposits, WM Waldenström's macroglobulinemia, BMG benign monoclonal gammopathy, SBNHL small B cell non-Hodgkin lymphoma, IgM RD IgM-related disease, MGUS monoclonal gammopathy of undetermined significance, CLL chronic lymphocytic leukemia, LGBCL low-grade B cell lymphoma, LPL lymphoplasmacytic lymphoma, ND not done, NA not available

glomerulonephritis, with the absence of clinical and laboratory findings of cryoglobulin. Only one similar case has been reported previously, in the study by Sethi et al. [10].

The deposition of monoclonal Ig containing light and heavy chains with non-organized deposits usually occurs in light and heavy chain deposition disease (LHCDD), which

is characterized by nodular mesangial glomerulosclerosis resembling Kimmelstiel–Wilson nodules and the continuous deposition of fine granular electron-dense materials along the inner aspect of glomerular or tubular basement membranes [13]. These findings are entirely different from those observed in the present case. Thus, LHCDD was

ruled out in the present case. On the other hand, PGNMID was proposed by Nasr et al. [3] as a new type of renal disorder that showed depositions of both light and IgG heavy chains. These monoclonal light and IgG heavy chains are not free, but consist of whole (intact) monoclonal IgG. Histologically, PGNMID shows diffuse endocapillary proliferation or membranoproliferative-like glomerulonephritis with monoclonal IgG deposition and granular electron-dense deposits mimicking immune complex-type deposits on electron microscopy. Interestingly, Yahata et al. [14] recently described a similar case of MPGN secondary to monoclonal IgM- κ deposition without Waldenström's macroglobulinemia or other hematological disorders. They proposed the use of the term proliferative glomerulonephritis with monoclonal IgM deposits (PGNMIMD) in addition to the term PGNMID proposed by Nasr et al. to describe the essential features of a case of PGNMID. The characteristics of the present case were consistent with the case described by Yahata et al. on the basis of light microscopic, immunopathologic, and electron microscopic findings.

Waldenström's macroglobulinemia is well known as an IgM-secreting hematological disorder. In addition, B cell lymphoma, CLL, or multiple myeloma also show the same hematological property [15]. Although glomerulopathy secondary to monoclonal IgM deposition is rare, the most characteristic lesion is intracapillary deposits of IgM with or without cryoglobulinemia and AL amyloidosis [15, 16]. Otherwise, immunotactoid/fibrillary glomerulopathy, cryoglobulinemia-related glomerulopathy, and light chain deposition disease were also reported [10, 17–19]. Furthermore, we could identify 19 cases suitable for the concept of PGNMIMD in the literature [10, 14, 15, 20–23].

Features of PGNMIMD are summarized in Table 1. The mean age of patients was 62.5 years (range 38–83 years) and 16 out of 20 (80 %) were males. The average serum creatinine level at presentation was 2.37 mg/dL (range 1–5.6 mg/dL), and more than half of the patients (11/20, 55 %) showed nephrotic-range proteinuria (>3.0 g/24 h). Predominant deposition of IgM- κ was significant. The most common entity was monoclonal gammopathy of undetermined significance. Waldenström's macroglobulinemia was present in three cases, B cell lymphoma in two cases, and CLL in two cases, including our case. Further accumulation of data is needed in order to adequately describe PGNMIMD. Careful evaluation by electron microscopy is essential for accurate diagnosis and categorization in paraproteinemia-associated nephropathy.

In conclusion, we described a case of PGNMIMD with CLL/SLL. This condition is relatively rare, but this case provides important information for classifying renal disorders in patients with plasma cell dyscrasia. PGNMID may not be restricted to cases with monoclonal IgG deposition. Therefore, expansion of the disease spectrum is

required. The more accurate term of diagnosis in the present case was proliferative glomerulonephritis with monoclonal IgM deposits (PGNMIMD).

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

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