Clinical Case Report

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Mixed cryoglobulinemic membranoproliferative glomerulonephritis due to monoclonal gammopathy of undetermined significance

A case report

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Abstract

Rationale: Membranoproliferative glomerulonephritis (MPGN) can be induced by autoimmune diseases, chronic infection, chronic hepatitis, and paraproteins (including cryoglobulinemia). In addition, the mixed cryoglobulinemic MPGN is reported to be highly correlated with hepatitis C virus (HCV) infection.

Patient concerns: We reported a rare case of a 61-year-old woman without a history of viral hepatitis infection; she presented with bilateral leg edema and proteinuria. Renal pathology revealed MPGN with multiple positive immunofluorescent staining. The consequent serum survey revealed positive cryoglobulin and monoclonal gammopathy of kappa type of immunoglobulin M. However, bone marrow study showed no obvious plasma cell proliferation, indicating that multiple myeloma was less likely.

Diagnoses: This patient's cryoglobulinemic MPGN could be related to monoclonal gammopathy of undetermined significance.

Interventions: Oral immunosuppressant.

Outcomes: After steroid treatment, her renal function normalized and proteinuria kept in low level.

Lessons: We demonstrated a rare cause of cryoglobulinemic MPGN without HCV infection, which led to a favorable prognosis after receiving steroid therapy. Moreover, the diagnosis of monoclonal gammopathy should be considered when facing such case and aggressive steroid therapy might be beneficial.

Abbreviations: HCV = hepatitis C virus, Ig = immunoglobulin, MGUS = monoclonal gammopathy of undetermined significance, MPGN = membranoproliferative glomerulonephritis.

Keywords: cryoglobulins, hepatitis C virus infection, membranoproliferative glomerulonephritis, monoclonal gammopathy, renal failure, renal pathology

1. Introduction

Membranoproliferative glomerulonephritis (MPGN) is characterized by the presence of mesangial hypercellularity, subendothelial deposition of immune complexes, and duplication of glomerular basement membrane.[1] Currently, MPGN is classified as immune-complex-mediated and complement-mediated MPGN; immune-complex-mediated MPGN is secondary to chronic infection, autoimmune disorders, and paraproteinemia (monoclonal gammopathy or cryoglobulinemia).[2–4] Mixed cryoglobulinemic MPGN, meaning that the cryoglobulins comprise more than 2 classes of immunoglobulin (Ig), has been mainly correlated with hepatitis C virus (HCV) infection.[5,6]

However, in this report, we presented a rare case of mixed cryoglobulinemic MPGN with contributions from monoclonal gammopathy of undetermined significance (MGUS) but not HCV infection.

2. Case presentation

A 61-year-old Taiwanese woman was admitted to the hospital because of bilateral leg edema, dizziness, and refractory hypertension. Her medical history was unremarkable, and there was no particular personal or family history of illness.

On admission in our hospital, a physical examination revealed cognition to be within normal limits, temperature of 36.2°C, heart rate of 92 beats/min, and a blood pressure of 190/100 mm Hg. Significant laboratory test findings included renal impairment (creatinine: 1.7 mg/dL), severe anemia (hemoglobin: 7.0 g/dL), hypoalbuminemia (albumin: 3.1 g/dL), and heavy proteinuria (2625 mg/24 h) (Table 1). Renal sonography showed bilateral kidneys of normal size (the right kidney was 12 cm and

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Ethic approval was waived by the ethics committee at the Shin Kong Wu Ho-Su Memorial Hospital because our case study was based on chart review. However, the written informed consent was obtained from patient for publishing the related images and laboratory data.

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Table 1

Laboratory data at admission.

Parameters, unit	Value	Normal reference
Blood		
White blood cell, $\times 10^3/\mu L$	9.1	3.8–10
Hemoglobin, g/dL	7.0	13–18
MCV, fl	86.1	81–98
Platelet, $\times 10^3/\mu L$	100	140–450
Blood nitrogen, mg/dL	43	7–25
Creatinine, mg/dL	1.7	0.5–1.3
Sodium, meq/dL	135	133–145
Potassium, meq/dL	4.1	3.3–5.1
Total protein, g/dL	6.0	6.4–8.9
Albumin, g/dL	3.1	3.5–5.7
Total cholesterol, mg/dL	224	<200
Triglyceride, mg/dL	145	50–130
Immunoglobulin A, mg/dL	379	82–453
Immunoglobulin G, mg/dL	441	751–1560
Immunoglobulin M, mg/dL	745	46–304
Complement 3, mg/dL	69.2	79–152
Complement 4, mg/dL	4.57	16–38
Urine		
Occult blood	3+	Negative
24 hours total protein, mg	2625	<150

MCV = mean corpuscular volume.

left kidney was 11 cm) but with increased echogenicity. Under the impression of acute renal failure due to glomerulonephritis, serum immunological markers were checked; they revealed elevated IgM and decreased complements levels. The serological test results for hepatitis B surface antigen, hepatitis C antibody, human immunodeficiency virus screens, antinuclear antibody, and antineutrophil cytoplasmic antibodies were all negative. However, serum immunoelectrophoresis was positive for the kappa type of monoclonal IgM and for the cryoglobulin (Table 1).

Therefore, diagnostic renal biopsy was performed, and it showed lobulated, diffuse mesangial, and endocapillary proliferation with double-contour of the glomerular basement membrane (Fig. 1) and positive immunofluorescent staining of IgG, IgM, kappa, lambda, and C3 deposition (Fig. 2), which was compatible with the diagnosis of MPGN. Electron microscopy revealed a duplication of glomerular capillary walls with dense deposits in the subendothelial zone (Fig. 3). Further bone marrow examination was performed for monoclonal gammopathy, and it showed hypocellular marrow (cellularity: 30%) without an increased number of plasma cells, indicating the diagnosis of multiple myeloma was not favored.

Based on clinicopathologic correlation, cryoglobulinemic MPGN secondary to MGUS was impressed. Oral immunosuppressant therapy was adopted, including cyclosporine (25 mg daily for 3 months and then reduced to 25 mg every day for another 3 months) and prednisolone (20 mg daily for 3 months and then gradually tapered to 5 mg daily). She has continued the low-dose prednisolone therapy (5 mg daily) for approximately 4 years, and her renal function remained in the normal range with mild proteinuria (urine protein–creatinine ratio: 0.79 mg/mg).

3. Discussion

A majority of patients with MPGN are children, but the condition can occur at any age and the clinical presentation and course are variable. The proportions of males and females are nearly equal.[7] In general, one-third of patients with MPGN will have spontaneous remission, one-third will have progressive disease, and one-third will have disease processes that will undergo alternate increases and decreases but never completely disappear.[8]

Cryoglobulins precipitate at temperatures lower than normal body temperature (37°C) and are categorized as types I to III.[9] Type I cryoglobulinemia, in which the monoclonal Ig composes the cryoglobulin and most often due to underlying multiple myeloma or Waldenström macroglobulinemia.[10] Type II cryoglobulinemia, in which the cryoglobulin contains both a polyclonal IgG and a monoclonal IgM rheumatoid factor directed against the IgG, is most often due to chronic infection with HCV. Type III cryoglobulinemia, in which both IgG and IgM are polyclonal, is often seen in patients with chronic inflammatory and autoimmune diseases (such as systemic lupus erythematosus and Sjögren syndrome), lymphoproliferative malignancies, and HCV infection.[11–13] Types II and III were termed as the mixed cryoglobulinemia. In our case, the immunoelectrophoresis was not performed for his cryoglobulinemia, of which the type classification would be limited. However, according to the positive immunofluorescent staining of IgG, IgM, kappa, lambda, and C3 deposition in renal

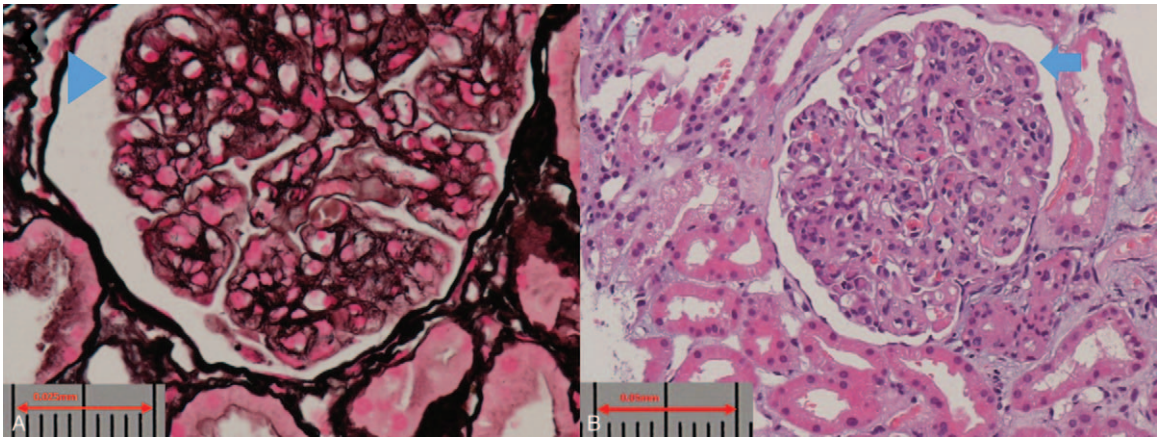

Figure 1. Light microscopy. (A) Silver stain, revealing double-contour of the glomerular basement membrane (arrow head). (B) Hematoxylin and eosin stain, showing lobulated, diffused mesangial and endocapillary proliferation (arrow).

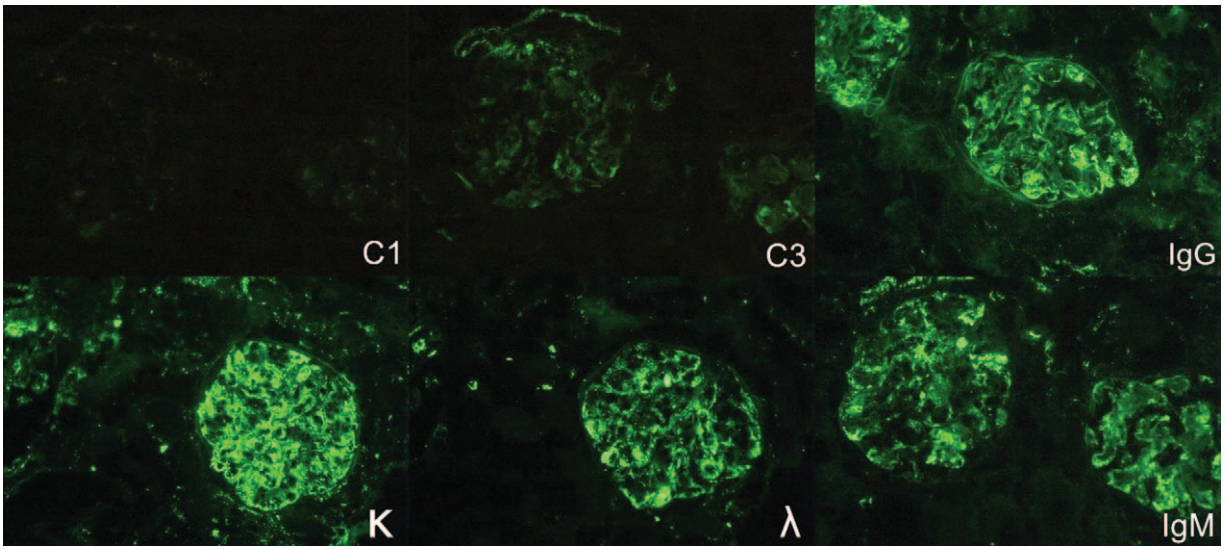

Figure 2. Immunofluorescence microscopy. The result shows a positive deposition of IgG, IgM, C3, κ, and λ.

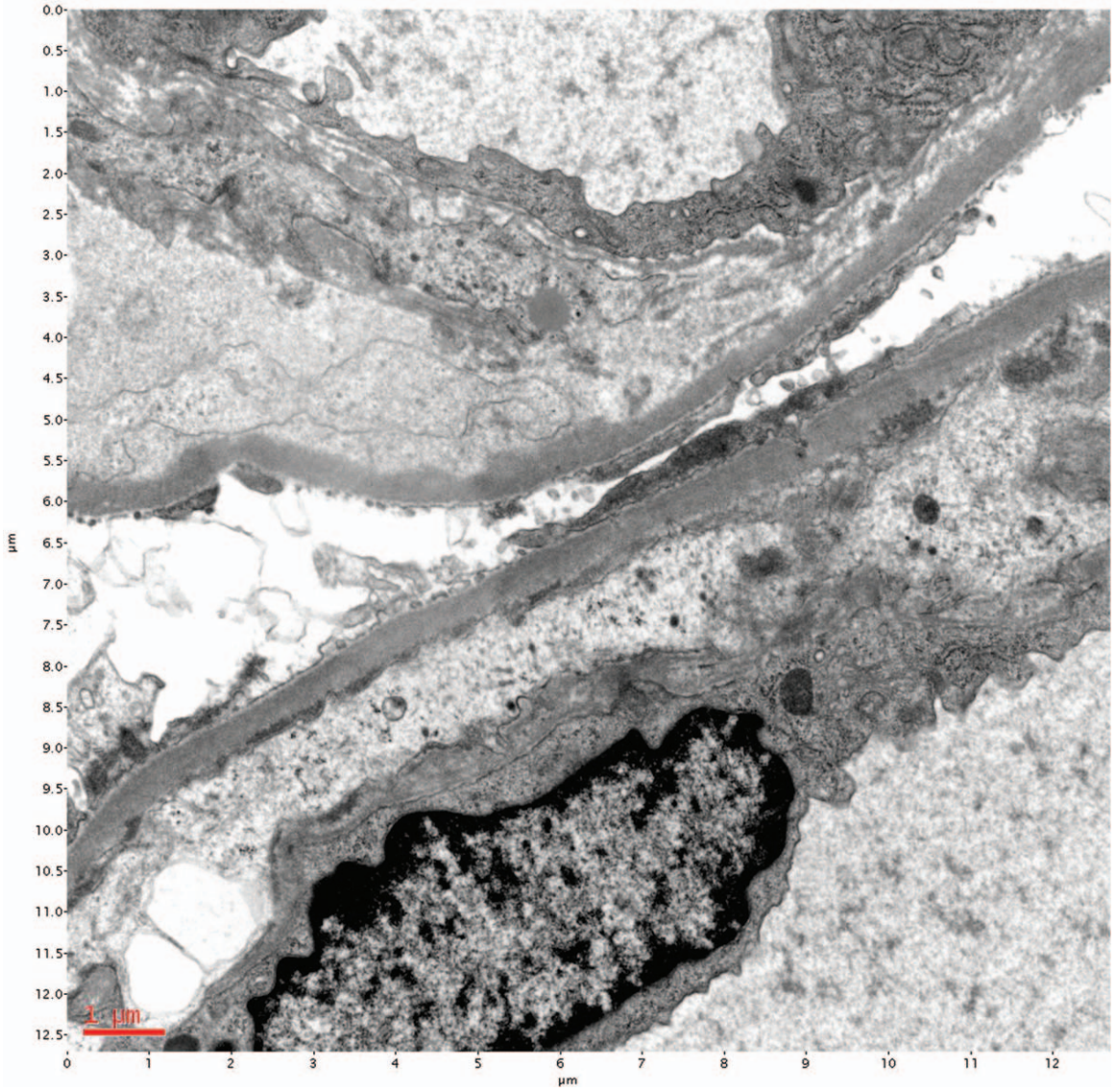

Figure 3. Electron microscopy. Duplication of glomerular capillary walls with dense deposits in the subendothelial zone.

Table 2

Patients with mixed cryoglobulinemic membranoproliferative glomerulonephritis and negative hepatitis C virus infection.

No	Reference	Age/ gender	BP, mm Hg	Serum Cr, mg/dL	CrCl, mL/min	Proteinuria, g/24 h	SIFE	Cryo	Clinical diagnosis	Therapy	Prognosis
1	Sethi et al[4]	59/Male	143/87	1.6	57	1.5	IgMκ	Type I	MGUS	N/A	N/A
2	Sethi et al[4]	75/Male	150/60	2.4	25	4.1	IgM, IgG κ	Type I	CLL	N/A	N/A
3	Sethi et al[4]	77/Female	155/81	1.3	42	8.3	IgMκ	Type II	LGBCL	N/A	N/A
4	Okura et al[15]	81/Male	166/80	1.4	39	4.3	IgMκ	Type II	MGUS	Steroid	Good
5	Our patient	61/Female	190/100	1.7	31	2.6	IgMκ	Type II	MGUS	Steroid	Good

BP = blood pressure, CLL = chronic lymphocytic leukemia, Cr = creatinine, CrCl = creatinine clearance, Cryo = cryoglobulin, LGBCL = low grade B cell lymphoma, MGUS = monoclonal gammopathy of undetermined significance, N/A = not applicable, SIFE = serum immunofixation electrophoresis.

pathology and the evidence of serum monoclonal IgM, the type II cryoglobulinemic MPGN was impressed.

In patients with HCV infection, the immune complex consists of anti-HCV IgG and IgM anti-IgG (rheumatoid factor). The HCV may serve as the inciting agent because it has been found in high concentrations in the cryoprecipitate.[12,14] In addition to the increased production, a decreased clearance of the circulating immune complexes due to hepatic dysfunction may promote circulatory cryoglobulin accumulation and subsequent tissue deposition. This is supported by the known association between circulating cryoglobulins and prolonged liver disease and cirrhosis.[14]

In a report from the Mayo Clinic,[4] which included 68 patients with MPGN who were not infected with HCV, 28 patients (41%) presented with monoclonal and/or biclonal gammopathy, 24 were positive for monoclonal gammopathies, and 4 were positive for biclonal gammopathies. Out of 24 monoclonal gammopathies, 10 were positive for IgM κ, 9 were positive for IgG κ, 4 were positive for IgG λ, and 1 had only "light chains." Out of 28 patients, 16 had MGUS, which was revealed on performing bone marrow biopsy. Cryoglobulin was positive in only 3 cases among the 28 patients. Two patients showed type I cryoglobulin, and 1 patient showed type II cryoglobulin. Moreover, Okura et al[15] had reported 81-year-old male with mixed cryoglobulinemic MPGN without HCV infection, who led a favorable outcome after a steroid therapy. Table 2 shows the published cases with cryoglobulinemic MPGN but without HCV infection in the literature, which just 4 cases have been reported. Our case was similar to the one reported by Okura et al,[15] who both had favorable response after steroid therapy.

Our patient was positive for cryoglobulinemia. Therefore, a careful follow-up is required because cryoglobulinemia is usually associated with lymphoproliferative disease (Waldenström macroglobulinemia or multiple myeloma). No standard treatment for monoclonal gammopathy-associated MPGN treatment was suggested and decisions will be made purely on the basis of clinical experience. Thereafter, there is a need for prospective, controlled studies in a larger cohort of patients with MPGN with monoclonal gammopathy to determine the optimal therapy.[16]

4. Conclusion

We reported a rare case of mixed cryoglobulinemic MPGN associated with underlying monoclonal gammopathy but not with HCV infection. Moreover, cryoglobulinemic MPGN seems to be associated with a favorable prognosis. Therefore, early diagnosis and treatment are essential. The aggressive steroid therapy may be beneficial for such case.

Author contributions

Conceptualization: Yu-Wei Fang, An-Hung Yang.
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Investigation: Ming-Hsein Tsai.
Supervision: Ming-Hsein Tsai.
Writing – original draft: Jung-Hui Hsu.
Writing – review & editing: Yu-Wei Fang, Ming-Hsein Tsai.

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