CASE REPORT

New-onset haematoproteinuria in a 63-year-old man with intraperitoneal lymph node enlargement

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SUMMARY

A 63-year-old man was referred to our hospital because of renal dysfunction with haematoproteinuria. Intraperitoneal lymph node enlargement was also noted. M protein was not detected by electrophoresis of his serum and urine; however, an increase in the κ/λ ratio was detected by free light-chain assay. Percutaneous kidney biopsy was performed, and the patient was diagnosed with proliferative glomerulonephritis with monoclonal immunoglobulin deposits. Lymph node biopsy showed follicular lymphoma. Urinalysis findings improved after treatment of the lymphoma. Proliferative glomerulonephritis with monoclonal immunoglobulin deposits is rarely considered to be associated with haematological disease. We report a case of lymphoma-associated proliferative glomerulonephritis with monoclonal immunoglobulin deposits with light-chain abnormality detected by free light-chain assay, but not by electrophoresis.

CASE PRESENTATION

The patient was a 63-year-old man with abnormal urinalysis findings. Hypertension and oedema had developed 3 months earlier. Progression of renal dysfunction (creatinine: 1.38 mg/dL), new-onset proteinuria (3.25 g/g creatinine) and haematuria had been observed 1 month earlier, at which time the patient was referred to our hospital. He had a medical history of urolithiasis, and was also being followed up with CT every 6 months by a haematologist at another hospital, for intraperitoneal lymph node enlargement. Treatment with antihypertensive and diuretic drugs was initiated before admission to our hospital.

INVESTIGATIONS

The patient's blood pressure was 148/86 mm Hg, pulse was 72 bpm and body temperature was 36.3°C (97.3°F). Submandibular lymph node enlargement was noted on physical examination. His peripheral oedema had disappeared with diuretic treatment, and no other notable physical findings were observed. Urinalysis revealed microscopic haematuria (10–19 red blood cells/high-power field) and granular casts. His 24 h urine protein excretion was 2.08 g/day. Blood tests revealed renal dysfunction (creatinine, 1.20 mg/dL; estimated glomerular filtration calculated using the Cockcroft-Gault equation, 45.1 mL/min), hypoproteinaemia (total protein, 5.9 g/dL; albumin, 3.5 g/dL), complement levels 32.2 U/mL CH₅₀ (reference range 25.0–48.0), 89 mg/dL C₃ (reference range 86–160), 15 mg/dL C₄ (reference range 17–45) and soluble interleukin (IL) 2 receptor titre 1960 U/mL.

BACKGROUND

The development of renal lesions in patients with haematological disease is not uncommon. Classically, renal lesions may be caused by the accumulation of high levels of immunoglobulin produced by abnormal B-cell tumours, such as kidney myeloma.¹ Even low levels of immunoglobulin may induce renal lesions if the immunoglobulin is nephrotoxic.^{2,3} We encountered a patient with lymphoproliferative disease complicated by glomerular deposition disease. We provide a report of this case and a literature review.

Figure 1 Light microscopic findings. (A) Periodic acid–Schiff stain. (B) Periodic acid–methenamine–silver (PAM) stain. Mesangial cell proliferation and mesangial matrix expansion were observed in both sections. Cellular interposition and duplication were noted in the PAM-stained section.

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Figure 2 Electron microscopic findings. (A) Low magnification of glomerulus. (B) High magnification of deposits. Amorphous electron-dense deposits were present in the mesangial and subendothelial space, and cellular interposition was noted. The deposits showed no organised structure.

(reference range 145–519). No abnormality was noted on electrophoresis of serum or urine, and neither antinuclear nor antineutrophil antibodies were detected. However, the results of free light-chain (FLC) assay were abnormal: κ 88.7 mg/L; λ 31.9 mg/L; κ/λ ratio 2.78 (see discussion of reference range below). On imaging, simple cysts were present in the bilateral kidneys, but no atrophy was observed. In addition, multiple abdominal intraperitoneal lymph nodes were enlarged. Percutaneous kidney biopsy was performed. Periodic acid–Schiff staining revealed 34 glomeruli in one preparation, among which three demonstrated global sclerosis (figure 1). Diffuse global mesangial cell proliferation was observed, and partial nodular outgrowth of the mesangial matrix was also noted. The glomerular basement membrane was thickened, with partial cellular interposition and duplication. Electron microscopy revealed amorphous electron-dense deposits in the mesangial and subendothelial regions, and cellular interposition (figure 2). The results of an immunofluorescence study showed granular deposition of IgG, C3, C1q and κ (figure 3), and subsequent immunoenzyme staining was positive for IgG3 subclass (figure 4).

DIFFERENTIAL DIAGNOSIS

The patient was diagnosed with proliferative glomerulonephritis with monoclonal immunoglobulin deposits.

TREATMENT

We started Losartan treatment and informed the haematologist of a possible case of haematological disease-associated glomerular deposition. Cervical lymph node biopsy was performed, and the patient was pathologically diagnosed with follicular

lymphoma. Flow cytometry demonstrated an increase in the κ -positive cell count. Bone marrow biopsy revealed lymphoma cell invasion. Six courses of R-CHOP therapy (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) were administered, and the patient remained under maintenance therapy with rituximab at the time of this writing.

OUTCOME AND FOLLOW-UP

During a 2-year follow-up, the patient's enlarged lymph nodes decreased in size on CT, and soluble IL-2 receptor titre, which reflects lymphoma activity, decreased to 462 U/mL. His renal function had not worsened and urinalysis showed improved urine protein (to 0.20 g/g creatinine), and his haematuria had almost disappeared.

DISCUSSION

Proliferative glomerulonephritis with monoclonal immunoglobulin deposits is a relatively new type of monoclonal IgG deposition-associated glomerulonephritis, first proposed by Nasr *et al*⁴ in 2004. The diagnostic criteria for proliferative glomerulonephritis with monoclonal immunoglobulin deposits are: (1) the presence of glomerular monoclonal IgG deposits restricted to a single IgG subclass and a single light-chain isotype, associated with endocapillary proliferative, membranoproliferative, or membranous features; (2) the presence of granular deposits by electron microscopy and (3) the absence of clinical and laboratory evidence of cryoglobulinaemia.

Immunofluorescence revealed that IgG3 was the most common IgG subtype in patients with proliferative glomerulonephritis with monoclonal immunoglobulin deposits, despite accounting for only 8% of circulating IgG. IgG3 is the most positively charged IgG and has the highest molecular weight. It thus tends to become trapped by the glomerular capillary wall and is 'nephritogenic', as a result of its self-aggregation and complement-fixing capacities.⁵ Proliferative glomerulonephritis with monoclonal immunoglobulin deposits may thus be triggered by relatively low levels of abnormal globulin. Bridoux *et al*¹ also proposed that the development of kidney disease in patients with mild lymphoproliferative disease was determined by the structural characteristics, rather than the rate of monoclonal IgG production.

Nasr *et al*⁵ suggested that proliferative glomerulonephritis with monoclonal immunoglobulin deposits might arise in the course of the normal immune response, given that two-thirds of patients had no detectable M protein, even after long follow-up

Figure 3 Immunofluorescence results. (A) C1q, (B) C3, (C) IgG, (D) IgM, (E) κ chain and (F) λ chain. IgG, κ chain, C3 and C1q were positive in the mesangial and capillary walls. IgA and C4 were negative.

Figure 4 Immunoenzyme analysis results. (A) IgG1, (B) IgG2, (C) IgG3 and (D) IgG4. Only the IgG3 subclass was positive in the mesangial and capillary walls.

periods, and underlying haematological disease was very rare. However, proliferative glomerulonephritis with monoclonal immunoglobulin deposits is thought to be included in monoclonal gammopathy of renal significance, a term used by Leung *et al*² for nephritogenic monoclonal gammopathies associated with B-cell proliferation, not meeting the criteria for multiple myeloma and lymphoma. Two previous case reports described concomitant haematological disease with proliferative glomerulonephritis with monoclonal immunoglobulin deposits.^{6,7}

In our case, although the expression of IgG3 in the patient's lymphoma cells was not proven, we considered the patient to have monoclonal gammopathy derived from follicular lymphoma, causing proliferative glomerulonephritis with monoclonal immunoglobulin deposits, on the basis that the patient's urinary abnormalities improved as a result of lymphoma treatment, and because the same light chain was detected in lymphoma cells by flow cytometry and in the glomerulus by immunofluorescence.

Nasr *et al*⁵ evaluated the presence of monoclonal gammopathy by protein electrophoresis and immunofixation electrophoresis. However, because proliferative glomerulonephritis with monoclonal immunoglobulin deposits may be caused by even low levels of abnormal globulin, a more sensitive method to detect monoclonal gammopathy may be needed. The FLC assay is a latex agglutination-based immunonephelometric method for detecting κ and λ chains. Charafeddine *et al*⁸ reported that the assay showed high sensitivity for FLC antibodies, reacting with FLC-labelled cells up to a dilution of 1:16 000, while Bradwell *et al*⁹ reported on an assay that used the same mechanism, but with detection limits >50-fold lower than protein electrophoresis and perhaps 20-fold lower than immunofixation electrophoresis. On the contrary, Hutchison *et al*¹⁰ reported that the κ/λ ratio increased in line with chronic kidney disease stage and described the relationship between renal function and FLC as follows: κ chains are produced twice as fast as λ chains; however, λ chains more frequently form dimers, which slows their renal clearance, resulting in a lower concentration of κ compared with λ chain in normal serum. As the renal clearance of FLC is reduced, the reticuloendothelial system becomes an

important route for its clearance. Because this system is not influenced by molecular weight, the serum half-lives of the κ and λ chains become more similar as renal function worsens. They proposed a reference range for the κ/λ ratio in patients with severe renal failure including haemodialysis and in peritoneal dialysis patient was 0.37–3.1, compared with a normal range of 0.26–1.65. However, the mean glomerular filtration rate was 29.4 mL/min in the Hutchison *et al*'s study, compared with 45.1 mL/min in the current case. Indeed, they described a mean κ/λ ratio in chronic kidney disease stage 3 of 1.04 (0.45–2.3), and we therefore considered the ratio of 2.78 in our case to be elevated. The results of FLC assays in patients with renal insufficiency thus need to be evaluated carefully.

In conclusion, we experienced a patient with probable proliferative glomerulonephritis with monoclonal immunoglobulin deposits and associated monoclonal gammopathy complicating haematological disease. Confirmation of this association requires the identity of IgGs in lymphoma cells and glomeruli to be confirmed, highlighting the need for careful use of FLC assays in patients with proliferative glomerulonephritis with monoclonal immunoglobulin deposits.

Learning points

- ▶ Proliferative glomerulonephritis with monoclonal immunoglobulin deposits is a new type of monoclonal IgG deposition-associated glomerulonephritis.
- ▶ Two-thirds of cases do not have identifiable circulating monoclonal protein.
- ▶ One-third of cases are associated with circulating monoclonal protein, and investigations of haematological disease are warranted in these patients.
- ▶ Free light-chain assay may help to detect low levels of monoclonal gammopathy, but careful evaluation is needed in patients with renal insufficiency.

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Contributors AM and the other authors examined the patient together, and contributed to diagnose this case as PGNMID with follicular lymphoma. AM conceived of this manuscript mainly, and SH, YS and SF contributed to its refinement. All the authors approved the final manuscript.

Competing interests None declared.

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