Proliferative glomerulonephritis with monoclonal IgG deposits in a young female: a rare case misdiagnosed and immunosuppressive-treated for over four years

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Case Report

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Abstract

BACKGROUND

Proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) is a newly recognized rare disease. The renal pathology is characterized by prominent manifestations of membranous hyperplasia, which is easy to misdiagnose. Clinical symptoms are severe. Massive proteinuria and hypoproteinemia are conspicuous, and most patients have renal insufficiency and microscopic hematuria.

CASE PRESENTATION

A 27-year-old female was admitted to a hospital for macroscopic hematuria and proteinuria 4 years prior, and renal biopsy in the hospital suggested moderate-to-severe mesangial proliferating glomerulonephritis (MsPGN). She had taken glucocorticoid, cyclophosphamide (CTX), mycophenolate mofetil (MMF) and other treatments, and achieved brief partial remission. Recently, she visited our hospital due to massive proteinuria. Repeated renal biopsy and anatomic slice re-evaluation 4 years previous revealed monoclonal immunoglobulin deposition in the glomerulus. Bone marrow examination was performed to exclude hematologic malignancy, and the diagnosis was PGNMID. The patient showed remission after 4 cycles of bortezomib (B) + cyclophosphamide (C) + dexamethasone scheme (D).

CONCLUSION

PGNMID is usually misdiagnosed as MsPGN or membranoproliferative glomerulonephritis (MPGN). Although it often occurs in middle-aged and elderly individuals, it cannot be readily excluded in young people, even when serum immunofixation electrophoresis (IFE) is negative. IgG subtype and light chain staining are necessary in the presence of high suspicion of this disease. An accurate diagnosis at the earliest stage may avoid overuse of glucocorticoids and immunosuppressants.

Background

PGNMID, first reported by Nasr et al.[1] in 2004, is a newly recognized disease characterized by glomerular monoclonal IgG deposition, and histopathological manifestations of renal biopsy show glomerular proliferative lesions. A total of 56.8% of PGNMID patients have been diagnosed with MPGN base on light microscopy, with prominent manifestations of membranous hyperplasia[2]. Due to its complexity, the pathogenesis is not fully understood.

The disease is commonly seen in middle-aged and elderly people, among which 65% are over 50 years old[2]. The incidence of PGNMID by autologous kidney biopsy is approximately 0.07% ~ 0.17%[2, 3]. The main clinical manifestations of PGNMID include proteinuria, hematuria and renal insufficiency.

We report a young female patient who was diagnosed with MsPGN due to proteinuria in another hospital, with poor therapeutic effects. She was recently admitted to our hospital, and repeated renal biopsy suggested PGNMID.
Case Presentation

Chief complaints

A 27-year-old Chinese woman with hematuria and albuminuria for over 4 years was admitted to our nephrology department on December 15.

History of present illness

After a month of gross hematuria and frothy urine, the patient visited her local hospital for treatment in June 2015. Laboratory examinations showed the following: 24-h urine protein (UP) 3.09 g/d; serum albumin, 24.6 g/L; serum creatinine (Scr), 120 µmol/L; IFE, serum protein electrophoresis (SPEP) and autoimmune markers including anti-neutrophil cytoplasmic antibody, antinuclear antibody, anti-double stranded DNA and anti-glomerular basement membrane antibody, were negative. Histological examination of the renal biopsy at that time revealed moderate-to-severe MsPGN with crescent formation. She was given methylprednisolone injection (500 mg/d, 3 days in total, then 40 mg/d). A few days later, she was discharged and stopped taking the drugs on her own and then went to a private clinic in Hong Kong for further treatment. She had taken prednisone and CTX for 3 mouths; CTX was then replaced by MMF (the doses were unknown). This treatment was applied for 2 years, after which MMF was substituted with tacrolimus. The dosages were gradually reduced and then withdrawn on August 28, 2018, as prescribed. During this time, her 24-h UP fluctuated between 2 and 3 g/d, and Scr was in the 80 to 110 µmol/L range. The nephritic syndrome relapsed in January 2019, and the previous specialist treated her with prednisone (500 mg/d, 3 days in total) and CTX (100 mg/d). CTX was replaced by MMF (1 g/d) one month later because of severe hair loss and irregular menstruation. Prednisone was reduced gradually and then withdrawn completely in October 2019. She went for a checkup on December 15, 2019, and the laboratory data were as follows: Scr, 92 µmol/L; serum albumin, 38.3 g/L; UP, 3+; urine occult blood, 3+.

History of past illness

She had no diagnosed history of metabolic disease, coronary heart disease or liver disease.

Physical examination upon admission

There was slight pitting edema in both lower extremities. A mild anemic appearance was the other physical features. No swelling of surface lymph nodes was found.

Laboratory examinations

On admission, laboratory data revealed the following values: hemoglobin (Hb), 71 g/L; Scr, 94 µmol/L; serum uric acid, 528 µmol/L; serum albumin, 24.6 g/L; globulin, 19.7 g/L; calcium, 1.97 mmol/L; complement C3, 0.84 g/L; C4 0.19 g/L; UP, 2+; urine occult blood, 2+; 24-h UP, 1.1 g/d. Liver function was normal. We detected no anti-DNA, anti-glomerular basement membrane or anti-neutrophil cytoplasmic antibodies and no hepatitis B, hepatitis C or HIV. IFE and SPEP did not show any paraproteins, though the
ratio of urine free light chain (κ/λ) was as high as 6.7974. Computed tomography of the chest, abdomen and pelvis detected no enlarged lymph nodes.

**Second renal biopsy**

To ascertain any new pathologic changes in her kidneys, we performed a second renal biopsy for this patient at our hospital. The histological examination of the renal biopsy showed 27 glomeruli, 11 of which were globally sclerotic and 3 of which were segmentally sclerotic; no crescent was found. Marked mesangial cells and matrix proliferation were observed in the remaining glomeruli, with glomerular lobulation and focal endothelial hyperplasia. Segmental basement membrane thickening, mesangial interposition and tram track signs were visible. Endocapillary proliferative changes were noted by electron microscopy. The glomerular capillary loops were compressed, and the lumen was stenotic. Segmental mesangial matrix interposition was found. Furthermore, electron-dense deposits were observed in the subendothelial and mesangial areas; at the ultrastructural level, the deposits were not fibrillar or microtubular structures. Part of the interstitial region was infiltrated by inflammatory cells (Fig. 1).

Immunohistology revealed positive petaloid deposition of IgG(3+), C3(2+), IgM(1+) and C1q (+/-) along the capillary loops; IgA and Fib were negative. According to additional tests, IgG3(3+), Kappa(3+), Lambda(1+), IgG1, IgG2, IgG4, PLA2R, THSD7A, AA, HCV, HBsAg, HBeAg, HBcAg, Congo red and oxide Congo red staining were positive (Fig. 2).

Figure 2 (a-b). IF staining revealed positive petaloid deposition of IgG (a) and C3 (b). (c-f) Immunofluorescence staining for IgG subclass showed intense positivity for IgG3 (e) and negative staining for IgG1 (c), IgG2 (d), and IgG4 (f). (g-h) There was strong glomerular staining for κ light chain (g) and weak staining for λ light chain (h). original magnification × 400 (a-h).

**Re-evaluation of the patient’s first biopsy**

The clinicians who previously treated this patient kindly provided us with glass slides of her first renal biopsy specimens. To determine the nature of the deposits, cryosections were freshly prepared for light chain and IgG subclass staining, and subsequent immunofluorescence analyses of these samples confirmed monoclonal deposition of IgG3κ in the glomeruli (Fig. 3).

**Hematologic examinations**

To further define the diagnosis, the patient underwent a series of bone marrow examinations. Bone marrow smears showed hyperplasia of the granulocyte series, erythron series and megakaryocytic series. Biopsy revealed active bone marrow proliferation, without any obvious mutant cells. A bone marrow flow cytometry immunofluorescence assay indicated no immunophenotypic abnormal evidence of multiple myeloma, acute leukemia, plasma cells, non-Hodgkin's lymphoma, or high-risk myelodysplastic syndrome. Multiple myeloma-associated gene mutation analysis, karyotype analysis of bone marrow chromosomes, and fluorescence in situ hybridization (FISH), including Vysis TP53/CEP 17, cytocell RB1(13q14), Vysis IGH, cytocell CKS1B/CDKN2C(P18), and were all negative.
Final diagnosis

The patient was diagnosed with PGNMID in accordance with the monoclonal pattern of IgG3κ deposition found in both the first and second renal biopsy specimens.

Treatment

We corrected the previous diagnosis result to PGNMID and immediately initiated 4 cycles of the BCD scheme within 5 months. The specific formula was: B (1.3 mg/m$^2$) d1, d4, d8, d11 + C (0.3 g) d1, d2, d3, d4 + D (20 mg) d1, d2, d4, d5, d8, d9, d11, d12. Losartan potassium (50 mg/d) was given since the diagnosis was clear.

Outcome and follow-up

The patient was followed up for 220 days to date. There was no specific discomfort during the period. Her condition improved after BCD treatment. At the last follow-up, the urine protein-to-creatinine ratio was 1.4 g/g, Scr was stable at 111 µmol/L, complement was normal, and the urine free light chain ratio decreased from 8.0097 to 6.1111. In addition, Hb was stable at 112 g/L, and serum albumin rose to 38.3 g/L (Fig. 4).

Discussion

As illustrated in our patient, PGNMID is an important phenotype of monoclonal gammopathy of renal significance. Because of the complexity of its pathogenesis, the exact causes of PGNMID are still not fully understood. It is believed that the disease is caused by the deposition of intact immunoglobulins produced by clonally proliferating plasma cells or B cells in the glomerulus[4]. For a definitive diagnosis, complete examination including serum and urine immunofixation, protein electrophoresis, free light chain assay, and complete renal pathology is necessary. In 2009, Nasr SH et al.[2] retrospectively identified 37 patients; according to IFE, 7 patients had a monoclonal spike (M-spike) in both serum and urine, and 4 patients had an M-spike detectable in the serum only, but no patient had an M-spike detectable in the urine only. Our case is the first report of a PGNMID patient who had monoclonal protein in the urine only. The mechanism needs to be studied further.

Bortezomib is a proteasome inhibitor that is regarded as the first-line drug for the treatment of plasma cell disease. It induces apoptosis of monoclonal plasma cells and inhibits renal fibrosis[5]. The detection rate of circulating monoclonal immunoglobulin in PGNMID patients is low. Nasr et al.[2] reported that monoclonal immunoglobulins can be detected in only 30% of patients and that abnormal plasma cells in bone marrow usually comprise less than 10%. Bhutani et al.[6] found that 60% of kidney-related monoclonal diseases originate from plasma cell clones. Therefore, in the absence of circulating or bone marrow monoclonal evidence, bortezomib based treatment is acceptable. The BCD scheme is one of the treatments for PGNMID. However, due to the limited number of cases, no randomized clinical trial has been published. Our patient received BCD chemotherapy, and remission was achieved during follow-up,
suggesting that the BCD scheme may be an appropriate option for PGNMID. Nonetheless, further evidence-based research is still needed.

**Conclusion**

Although PGNMID is a rare disease that often occurs in middle-aged and elderly individuals, it cannot be easily excluded in young people, especially in those whose pathological type is MPGN or MsPGN, even when serum IFE is negative. Renal biopsy should be repeated if necessary. An accurate diagnosis at the earliest stage may avoid the overuse of glucocorticoids and immunosuppressants as well as any subsequent serious side effects.

**Abbreviations**

PGNMID: Proliferative glomerulonephritis with monoclonal IgG deposits; MsPGN: Mesangial proliferating glomerulonephritis; CTX: Cyclophosphamide; MMF: Mycophenolate mofetil; MPGN: Membranoproliferative glomerulonephritis; IFE: Immunofixation electrophoresis; UP: Urine protein; Scr: Serum creatinine; SPEP: Serum protein electrophoresis; Hb: Hemoglobin; FISH: Fluorescence in situ hybridization

**Declarations**

**Author contributions**

Zi-Gan Xu reviewed the literature and contributed to manuscript drafting. Wei-Long Li, Xi Wang, Shu-Yuan Zhang, Ying-Wei Zhang, Chun-Di Li, Ping Zeng collected the information from patients. Xing Wei, Shao-Dong Luan were surgeons for biopsy and revised the manuscript. Shao-Dong Luan supervised the study. All authors read and approved the final manuscript.

**Informed consent statement**

Written informed consent was obtained from the patient for publication of this report and any accompanying images.

**Conflict-of-interest statement**

The authors declare that they have no conflict of interest.

**CARE Checklist (2016) statement**

The authors have read the CARE Checklist (2013), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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Availability of data and materials

The datasets used and / or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

Not applicable.

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