

Proliferative Glomerulonephritis with Monoclonal IgG Deposits Associated with Membrano-Proliferative Features: Case Report

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Abstract

Proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) is a recently described entity. It is featured by glomerular nonorganized monoclonal immunoglobulin G deposits. Monoclonal IgG deposits are associated with glomerular proliferative lesions, mimicking different types of immune-complex glomerulonephritis. We report two classic cases of PGNMID which fulfilled all criteria of this disease. We conclude that recognition of proliferative glomerulonephritis with monoclonal IgG deposits requires routine immunostaining for light chain and IgG isotype.

Keywords: Proliferative glomerulonephritis; Monoclonal IgG deposits; PGNMID

Introduction

Proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) is a recently described entity [1,2]. The etiology of PGNMID is not fully understood. Patients with PGNMID present nephrotic-range proteinuria or nephrotic syndrome, hematuria and renal failure without clinical evidence of multiple myeloma or B-cell lymphoproliferative disorders [3,4]. Renal diseases caused by monoclonal IgG include light and heavy deposition disease, type 1 cryoglobulinemic disease, immunotactoid glomerulopathy, light and heavy amyloidosis, and fibrillary glomerulonephritis [5]. PGNMID is featured by glomerular nonorganized monoclonal immunoglobulin G deposits. Monoclonal IgG deposits are associated with glomerular proliferative lesions, mimicking different types of immune-complex glomerulonephritis [6-15]. Diagnostic criteria of PGNMID include the presence of glomerular monoclonal IgG deposits restricted to a single IgG subclass and a single light-chain isotype, the presence of granular deposits by electron microscopy and the absence of clinical and laboratory evidence of cryoglobulin. The immune deposits in glomeruli are composed mostly of IgG3 kappa type. Human IgG is divided into four subclasses. Of the four subclasses, IgG3 has several properties that allow being “nephritogenic”. The prognosis of PGNMID is variable; about 22% patients progressed to end stage renal disease (ESRD). The disease can recur in the transplanted kidney [16,17]. Administration of immunosuppressive therapy including rituximab has been found to successfully ameliorate impaired renal function in patients with PGNMID [18].

Case Report

We report two cases of PGNMID with IgG3 monoclonal deposits in two females: 44-years-old (Case 1) and 61-years-old (Case 2). At presentation both patients had nephrotic syndrome. Renal failure was seen in an older woman.

Case 1

On admission to the Nephrology Department her blood pressure was 130/80 mmHg, her pulse rate was 74 beats per minute and her body temperature was 36.6°C. Physical examination showed edema of the lower limbs. Examination of the lungs, heart, abdomen, and central, and peripheral nervous systems showed no abnormalities. Complete blood counts revealed: white blood cells 4,400/mcL, red blood cells 3.8 million/mcL, hemoglobin 11.5 g/dL. Serum biochemical analysis showed: total protein 4.5 g/dL, serum albumin 2.5 g/dL, serum creatine 0.79 mg/dL

(eGFR 84.4 mL/min). Urinalysis revealed proteinuria and hematuria. Urinary protein excretion was 4.7 g/24 h.

Case 2

On admission, the patient's blood pressure was 130/80 mmHg. Her pulse rate was 76 beats per minute, and her body temperature was 36.3°C. Physical examination showed edema of the lower limbs. Examination of the lungs, heart, abdomen, central and peripheral nervous systems showed no abnormalities. Complete blood counts revealed: white blood cells 3,500/mcL, red blood cells 3.1 million/mcL, hemoglobin 8.5 g/dL. Serum biochemical analysis revealed: total protein 4.3 g/dL, serum albumin 2.3 g/dL, serum creatine 2,73 mg/dL (eGFR 19 mL/min). Urinalysis revealed proteinuria. Urinary protein excretion was 6.7 g/24 h.

None of these patients had detectable levels of serum monoclonal IgG or overt multiple myeloma. None of them had paraproteinemia. Serum cryoglobulins titers and complement levels were normally in both patients. Antinuclear antibody, hepatitis B surface antigen, anti-hepatitis B virus antibody and rheumatoid factor were negative.

The renal biopsy was undergone in both patients. The samples of renal biopsy specimens were embedded in paraffin and sectioned at 2 µm, followed by H and E, Masson's trichrome, periodic acid-Schiff, methenamine-silver, and Congo red staining. Congo red staining was completely negative in both cases. For immunofluorescence study (IF), the samples were sectioned in frozen conditions, followed by a direct staining for IgG, IgG1, IgG2, IgG3, IgG4, IgA, IgM, C3, C1q, kappa and lambda light chain. The electron microscopy (EM) examination was done with JEM 1011 electron microscopy after routine staining.

Renal tissue in Case 1 (a younger women) consisted of 21 glomeruli with 1 sclerosed, and renal tissue obtained from an older woman

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(case 2) consisted of 15 glomeruli with 2 sclerosed. The renal biopsy in both patients showed accentuated glomerular lobularity, mesangial hypercellularity and matrix expansion, segmental endocapillary proliferation, and glomerular basement membrane duplication (Figure 1). Interstitial fibrosis and tubular atrophy was seen in biopsy specimen in an older woman (Case 2).

By immunofluorescence, granular deposits were identified along capillary loop and focally in mesangium. IgG was the only immunoglobulin deposited. In a similar distribution to the IgG deposits, glomerular granular deposition of IgG3 (Figure 2), C3 and C1q was detected. Both cases showed light-chain isotype restriction: sole positivity for lambda (Case 1) (Figure 3) or kappa chain (Case 2). Immunostaining for IgG1, IgG2 and IgG4 was negative in both biopsy specimens.

Electron microscopy revealed nonorganized electron-dense subendothelial and mesangial deposits in both renal biopsy specimens (Figure 4).

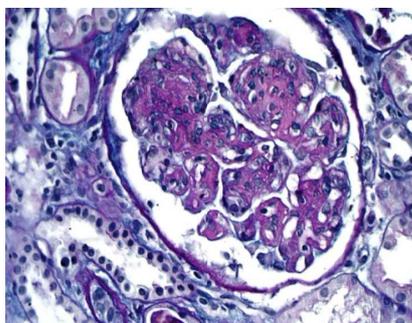


Figure 1: Focal endocapillary proliferation, matrix expansion and thickening of the peripheral capillary walls. PAS stain, magn 200x.

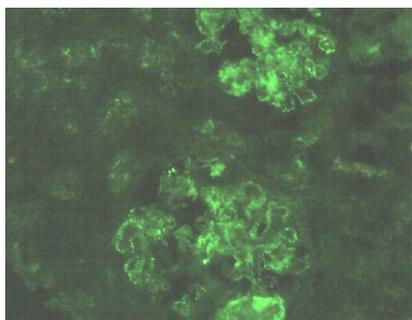


Figure 2: Direct IF for IgG3. Glomerular positivity for IgG3 along the peripheral capillary walls and in mesangium, magn 200x.

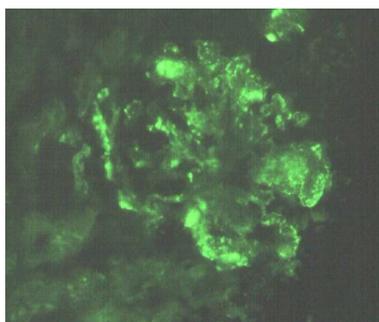


Figure 3: Direct IF for λ light chain (case 1). Lambda light chains stain strongly positive along the peripheral capillary walls and mesangial areas, magn 200x.

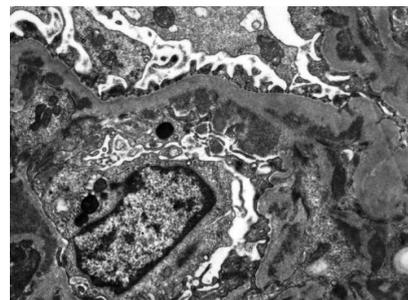


Figure 4: Electron microscopy demonstrates dense deposits without any organized substructural features located within endothelial space and in the mesangial areas, magn 10000x.

Discussion

Proliferative glomerulonephritis with monoclonal IgG deposits, which was first described in 2004 by Nasr et al. [1], has been a recently reported renal disease accounting for 0.07% of the diagnoses by renal biopsy [6,19]. As was mentioned earlier, the diagnosis of PNGMID is based on several restricted criteria as renal biopsy findings of glomerulonephritis with glomerular immune deposits staining positive for heavy chain IgG, negativity for IgA and IgM heavy chains and positive staining for a single IgG subclass (IgG1, IgG2, IgG3 or IgG4) [20]. Moreover, positive staining for a single light chain isotype indicating monoclonality should be noticed and predominantly granular dense deposits in mesangial, subendothelial or subepithelial location by electron microscopy. The cases with clinical or laboratory evidence of cryoglobulinemia should be excluded [2,3]. Only two of our 2153 immunofluorescence and electron-microscopy diagnoses of proliferative glomerulonephritides met all these very restricted criteria indicating that classic form of PGNMID is really very rare renal disease. This is noteworthy that not all reported up to now cases of proliferative glomerulonephritis with monoclonal IgG deposits fulfilled mentioned above criteria [3].

Conclusion

In summary, the presented cases demonstrate that recognition of PGNMID requires routine immunostaining for light chain and IgG isotype.

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