

Clinical Report

Relapsing proliferative glomerulonephritis with monoclonal IgG deposits showing circumferential crescentic glomerulonephritis

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Abstract

Several types of glomerulonephritis associated with dysproteinemia, such as AL-amyloidosis, light- and heavy-chain deposition disease, and type 1 cryoglobulinemic glomerulopathy, demonstrate monoclonal immunoglobulin deposition. Progressive glomerulonephritis with monoclonal IgG deposits (PGNMID) is also known to feature monoclonal glomerular deposits, but most of these cases occur without underlying disease. We here report a case of recurrent PGNMID that developed as diffuse cellular crescentic glomerulonephritis 8 years after an initial diagnosis of membranoproliferative glomerulonephritis (MPGN). Determination of the monoclonality of the deposited immunoglobulin is vital to make the correct diagnosis and enable an early administration of aggressive immunosuppressive therapy.

Keywords: crescentic glomerulonephritis; hypocomplementemia; monoclonal IgG deposits; proliferative glomerulonephritis

Background

The term ‘progressive glomerulonephritis with monoclonal IgG deposits (PGNMIDs)’ was coined by Nasr to reflect a disorder that typically presented with nephrotic or nephritic syndrome [1, 2]. While membranoproliferative and endocapillary proliferative patterns are the most commonly observed in PGNMID, a few cases of crescent formation have also been noted [2]. IgG3 κ is the major subtype of monoclonal deposition, but PGNMID is generally not associated with hematological malignancies such as multiple myeloma or lymphoma, and is differentiated from light- and heavy-chain deposition disease and type 1 cryoglobulinemic glomerulopathy by the absence of any characteristic organized deposition as detected by electron microscopy. In our current report, we describe a case of recurrent PGNMID as diffuse cellular crescentic glomerulonephritis 8 years after the initial development of membranoproliferative glomerulonephritis (MPGN) in this patient. We performed immunofluorescence studies using initial biopsied specimens to confirm the same monoclonal IgG depositions on the glomeruli.

Case report

Clinical history and laboratory data

A 41-year-old man presented at our hospital with gross hematuria and pretibial edema 3 weeks after developing upper airway inflammation. Eight years prior to this episode,

he had undergone a renal biopsy at another hospital due to acute nephritic syndrome and was diagnosed with MPGN at that time. He had then been administered prednisolone for around 3 years, but discontinued this medication on his own volition.

A physical examination of this patient at our hospital revealed a blood pressure of 154/84 mmHg, and a weight of 92.4 kg, representing a 3.4 kg gain in his ordinal weight. Urinalysis revealed 3+ proteinuria and 1+ hematuria, and a 24-h protein excretion of 1.2 g/day. Further laboratory tests revealed chronic renal failure associated with hypogammaglobulinemia and slight hypocomplementemia (Table 1). We detected no anti-DNA, anti-glomerular basement membrane or anti-neutrophil cytoplasmic antibodies, and no hepatitis B, hepatitis C nor HIV. Cryoglobulins were not detected, and protein electrophoresis of serum and urine did not show a paraprotein. The results of a chest X-ray were unremarkable and abdominal computed tomography showed bilateral kidney enlargement but no tumor lesion was detected. Given the rapid increase in his serum creatinine level, we performed a second renal biopsy for this patient at our hospital.

A second kidney biopsy for the patient at our hospital

The kidney biopsy sample obtained from this patient at our hospital showed 26 glomeruli under light microscopy, none of which were sclerosed. All of these glomeruli showed cellular crescents, and circumferential global crescents, so-called full-moon changes, were also obvious. Capillary tufts were found to be compressed by the crescents, and focal

Table 1. Laboratory data for the PGNMID subject

	At presentation	After plasmapheresis	Reference range
Total protein (g/L)	48	37	65–80
Serum urea nitrogen (mmol/L)	21.5	15.6	2.9–7.1
Serum creatinine ($\mu\text{mol/L}$)	864	450	35.4–88.4
eGFR ($\text{mL}/\text{min}/1.73 \text{ m}^2$)	5.9	N/A	≥ 90
Urinary protein/24 h (g/24 h)	1.2	8.7	< 0.2
IgG (g/L)	4.28	N/A	8.7–17.0
Complement C3 (mg/dL)	78	N/A	86–160
Complement C4 (mg/dL)	31	N/A	17–45

endocapillary proliferative changes were noted. Foci of tubulointerstitial nephritis with neutrophilia were detected, but no arteritis was identified. Immunofluorescence studies revealed IgG3 κ monoclonal deposits in the glomeruli, as well as a mild positivity of C1q and C3, but IgA and IgM were both negative. Electron microscopy analysis revealed mesangial dense deposits, and subendothelial deposits with mesangial interposition were also noted, but no subepithelial deposit was evident. No organized structure was observed in the deposits at higher magnification under electron microscopy (Figure 1).

Re-evaluation of the patient's first biopsy

The clinicians who previously treated our patient kindly provided us with glass slides of his first renal biopsy specimens. This first biopsy was an open wedge procedure and the sample submitted for light microscopy contained over 100 glomeruli, none of which were sclerosed. Light microscopy revealed glomerular lobulation with marked mesangial proliferation of the glomeruli, consistent with MPGN. To determine the monoclonality of the deposits, cryosections were freshly prepared for staining of IgG subclasses and immunofluorescence analyses of these samples subsequently confirmed monoclonal deposition of IgG3 κ of the glomeruli (Figure 2).

Diagnosis

The patient was diagnosed with recurrent PGNMID in accordance with the monoclonal pattern of IgG3 κ deposition found in both the first and second renal biopsy specimens.

Clinical follow-up

The patient underwent hemodialysis the day after his first presentation at our hospital due to a severely worsening kidney function. Although steroid half-pulse therapy (prednisolone 500 mg daily for 3 days) and subsequent oral administration of 40 mg/day of prednisolone were performed, no improvement in his renal function was observed after 2 weeks. Intravenous cyclophosphamide and 6 days of plasmapheresis treatment were additionally performed, but severe proteinuria persisted and his serum creatinine level remained high. We thus decided to continue hemodialysis.

Discussion

PGNMID is a quite rare disease with a reported biopsy incidence of only 0.17% [2]. Immunofluorescence analysis of

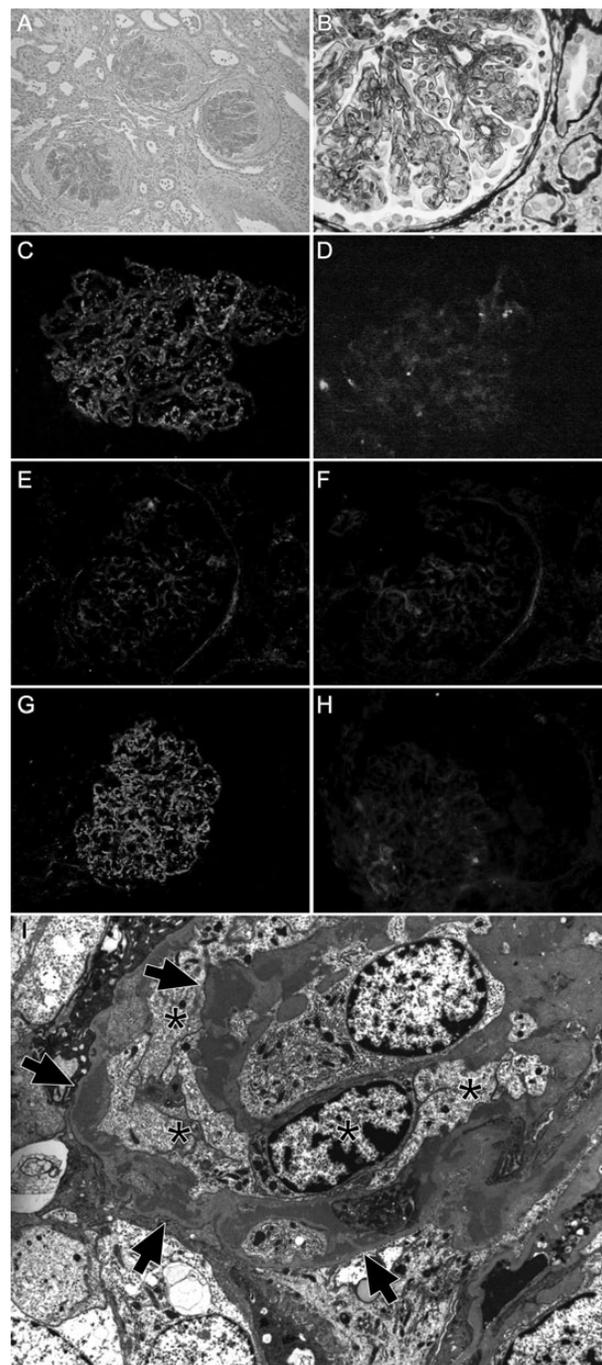


Fig. 1. Microscopic analysis of renal biopsy specimens of our PGNMID case prepared at our hospital. Circumferential cellular crescents with endocapillary proliferation were clearly detectable (A, periodic acid-Schiff; B, periodic acid-Schiff-methenamine silver). An immunofluorescence photomicrograph showing monoclonal IgG3 κ deposition of the mesangium and glomerular basement membrane is shown (C, κ ; D, λ ; E, IgG1; F, IgG2; G, IgG3; H, IgG4). (I) Electron microscopy showing marked subendothelial dense deposits (arrows) with a mesangial interposition (asterisks).

our current patient led us to conclude that it was a PGNMID case with IgG3 κ deposition since this patient initially developed renal dysfunction 8 years prior to his presentation at our hospital. Our current case first developed MPGN as revealed by light microscopy, and a second biopsy performed at our hospital revealed diffuse global crescent formation,

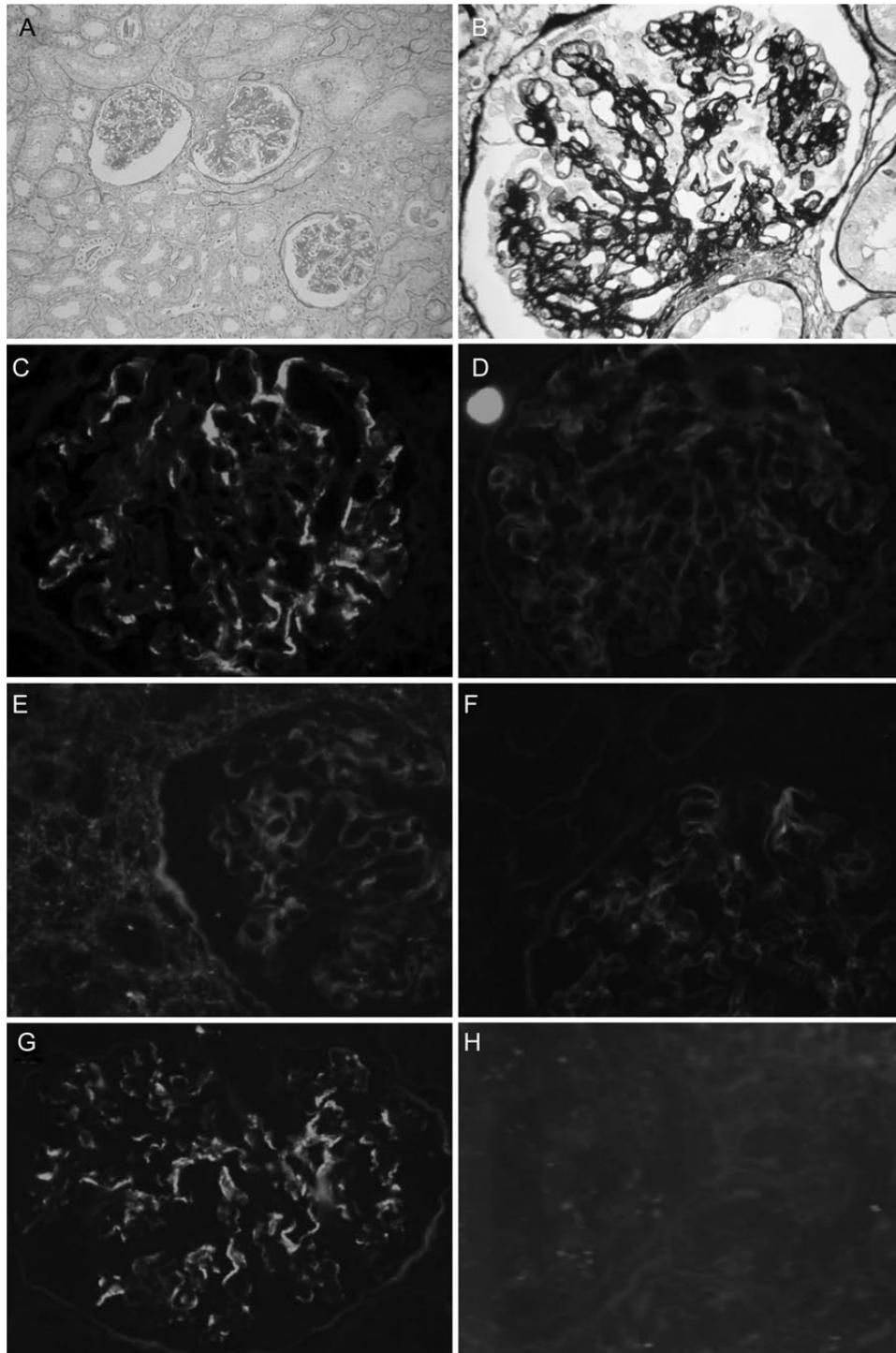


Fig. 2. Re-evaluation of previous renal biopsy specimens from our PGNMID case which were prepared 8 years before at a different hospital. Light microscopy revealed membranoproliferative changes of the glomeruli with occasional double contours (A, periodic acid-Schiff; B, periodic acid-Schiff-methenamine silver). Immunofluorescence analyses revealed monoclonal IgG κ deposits of the glomerulus (C, κ ; D, λ ; E, IgG1; F, IgG2; G, IgG3; H, IgG4).

indicating histological transformation of his PGNMID. Nasr *et al.* [3] have reported four previous cases of recurrent PGNMID in renal allografts, two of which recurred in the native kidney before transplantation. Of note in this regard, both of these cases developed crescent formation in biopsy specimens taken 4 or 8 months prior to hemodialysis. Crescents would thus seem to indicate a severely

poor prognosis for the patient's kidney function. Indeed, a higher percentage of crescents has been found to correlate with the rate of progression to end-stage renal disease (ESRD) in a univariate analysis by Cox regression [2].

Although the pathogenesis of PGNMID remains elusive, our current case study suggests that some infection causing upper airway inflammation exacerbates this condition to

result in crescentic glomerulonephritis. Ranghino *et al.* [4] have reported the development of PGNMID with crescent formation 1 month after upper airway infection, and Nasr *et al.* [2] have also described a case of PGNMID with an upper respiratory tract infection 5 days prior to a presentation of renal failure, although the underlying histological pattern was not detailed. Hence, PGNMID should be differentiated from bacterial infection-related glomerulonephritis since both PGNMID and IRGN share several unique clinicopathological features such as hypocomplementemia and endocapillary proliferative change [5].

Nasr *et al.* [2] have reported that 7 out of a cohort of 32 (21.9%) patients with PGNMID progressed to ESRD, indicating an aggressive course in at least a sub-population of PGNMID. Although Ranghino *et al.* [4] have reported a case of PGNMID that was successfully treated with plasmapheresis, an intervention with intravenous cyclophosphamide and plasmapheresis in our current case did not enable a withdrawal from dialysis. Moreover, in previous allograft cases, aggressive immunosuppressive administration including rituximab has been found to successfully ameliorate impaired renal function [3]. Prompt administration of such therapeutic options at an early stage thus appears to be necessary to induce a complete remission of PGNMID. Although infection is a risk factor for a poor prognosis in this disease, long-term and careful follow-up examinations of additional PGNMID patients will be required to develop more optimal treatment options. With this aim in mind, immunofluorescence studies, especially for κ , λ , and IgG subclasses, will be invaluable for specimens with dominant or co-dominant IgG deposition to collect definitively established cases of PGNMIDs.

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Conflict of interest statement. None declared.

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