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NEPHROLOGY ROUNDS

Two Cases of Proliferative Glomerulonephritis With Monoclonal IgG Deposits Treated With Renin Angiotensin Inhibition Alone With Long-term Follow-up

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Received 7 March 2021; revised 29 April 2021; accepted 10 May 2021; published online 17 May 2021

Kidney Int Rep (2021) **6,** 2218–2222; https://doi.org/10.1016/j.ekir.2021.05.011

INTRODUCTION

Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is a recently recognized form of monoclonal gammopathy of renal significance (MGRS). It is characterized by a glomerulonephritis with exclusively glomerular monotypic Ig deposits, typically IgG and less commonly IgM or IgA. The glomerular deposits are nonorganized with granular amorphous texture and contain a complete Ig molecule with light-chain restriction and heavy-chain subclass restriction. A rare variant with deposits of light chain only also has recently been described.[1] The light microscopic pattern is typically membranoproliferative but can also have membranous features. Despite the presence of glomerular monotypic immunoglobulin deposits on biopsy, a monoclonal (M)-protein is detected in the serum or urine in only a minority of patients with PGNMID.[2–5] The prevalence of M-protein and a detectable clone appears to vary depending on the subtype of IgG and the Ig class, with higher prevalences reported for IgG1 than IgG3[3,6] and for IgM and IgA than the IgG forms of PGNMID.[1,7,8]

The optimal treatment of this disease is controversial. It has been suggested that all patients should be treated with immunosuppressive therapy, even if no monoclonal gammopathy or clone of neoplastic plasma cells or B cells is found on workup.[9] We describe 2 patients with PGNMID without M-spike or identified clone who had stable renal disease without immunosuppressive therapy after 11 and 6 years of follow-up, respectively.

CASE PRESENTATION

Patient 1

Patient 1 was a 41-year-old White woman without significant past medical history, on oral contraceptives alone, who was noted to have proteinuria on urinalyses over the previous year. A recent urinalysis had 3+ protein with no blood. The 24-hour urine collection contained 2.3 g of protein. Serum creatinine was 0.6 mg/dl and serum albumin was 3.2 g/dl. Her physical examination was unremarkable.

A kidney biopsy was performed (Figure 1). The portion for light microscopy contained 2 glomeruli, 1 of which was globally sclerotic, with 3 additional glomeruli present for immunofluorescence and 3 for electron microscopy. The 7 open glomeruli all exhibited a membranoproliferative pattern with mesangial hypercellularity, cellular interposition, and duplication of glomerular basement membranes. Tubular atrophy and interstitial fibrosis were mild and focal. Vessels were unremarkable. By immunofluorescence on frozen tissue, there were granular global glomerular capillary wall and mesangial deposits of IgG (1+) with kappa light chain restriction (1+), accompanied by 1–2+ C3 and trace C1q. Staining for the IgG subtypes revealed restricted positivity for IgG1 (1+). There were no glomeruli remaining in the paraffin block to perform pronase immunofluorescence. Electron microscopy showed granular electron-dense deposits involving the mesangium and subendothelial regions with more segmentally distributed subepithelial and intramembranous deposits. Most of the deposits had amorphous, granular texture with the exception of

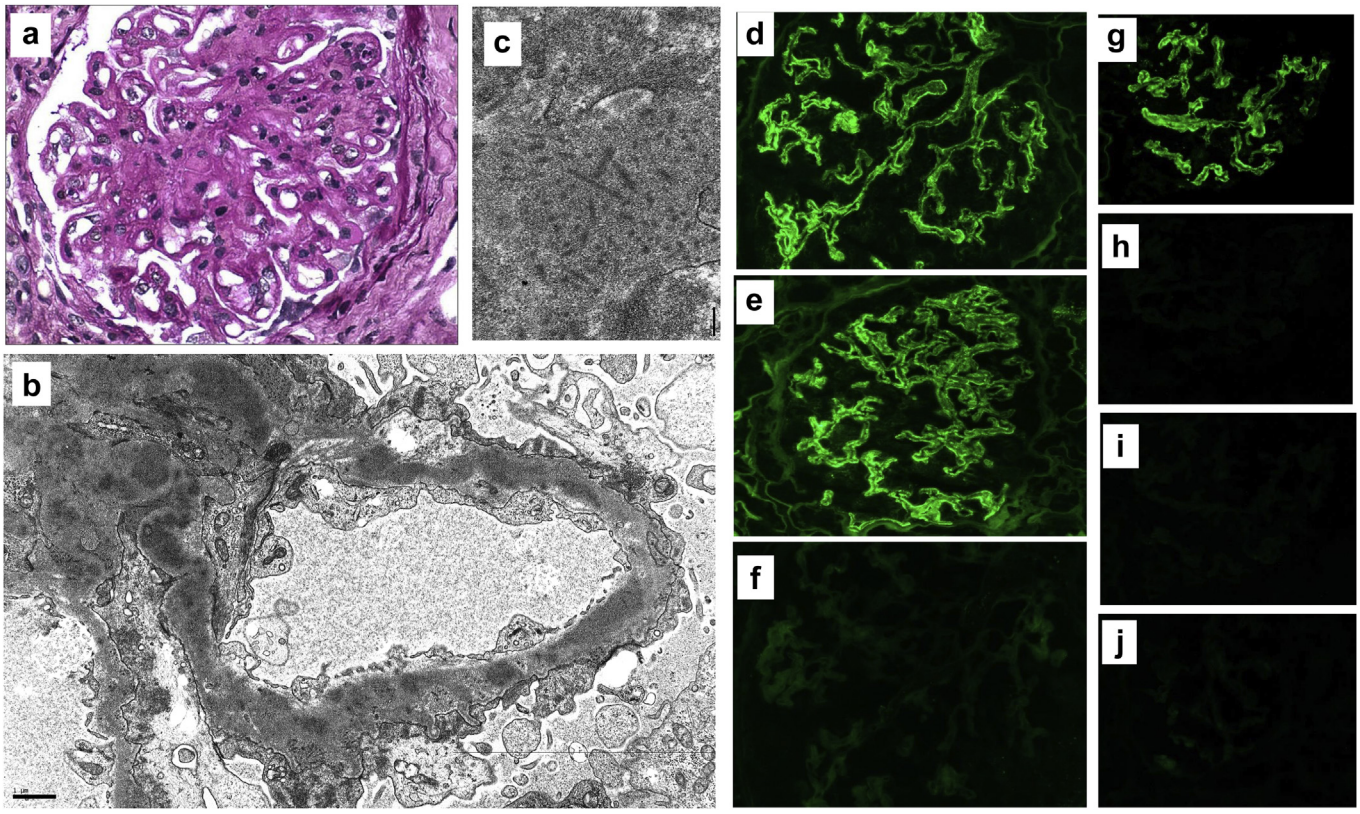

Figure 1. Renal biopsy findings from patient 1. (a) The glomeruli display mesangial hypercellularity, peripheral mesangial interposition, and double contours enclosing subendothelial deposits, producing a membranoproliferative pattern (periodic acid–Schiff, original magnification × 600). (b) By electron microscopy, granular amorphous deposits are seen within the mesangial matrix and in a subendothelial distribution, with rare small subepithelial deposits. The podocyte foot processes are markedly effaced (electron micrograph, original magnification × 12,000). (c) On high-power examination, a minority of the granular deposits are admixed with thick irregular fibrils ranging from 30 to 60 nm in diameter without hollow cores (electron micrograph, original magnification × 80,000). By immunofluorescence, there is granular global glomerular capillary wall and mesangial staining for (d) IgG (original magnification × 600) and (e) kappa (original magnification × 600), with negative staining for (f) lambda (original magnification × 600). Staining for the IgG subtypes shows restricted reactivity for (g) IgG subtype 1 (original magnification × 600), with negativity for (h) subtype 2, (i) subtype 3, and (j) subtype 4. These staining results are consistent with monotypic IgG1-kappa deposits.

approximately 20% of deposits showing ill-defined fibrillar substructure ranging from 30 to 60 nm without hollow cores. Foot process effacement involved approximately 80% of the glomerular capillary surface area.

Following biopsy, protein electrophoresis and immunofixation of serum and urine were obtained and were negative for M-protein. Cryoglobulins were negative and serum complements (C3 and C4) were within normal range. Enalapril was initiated at 2.5 mg daily followed by a decrease in proteinuria. On follow-up 11 years post biopsy, proteinuria is 243 mg/g by urine protein-creatinine ratio. Urinalysis shows trace protein and no RBC. Serum creatinine is 0.6 mg/dl. The serum free light-chain ratio remains normal.

Patient 2

The patient was a 25-year-old Black woman with a history of obesity, who presented for an elevated serum creatinine. She had been diagnosed with hypertension 10 months previously and was noted to have a serum creatinine of 1.4 mg/dl. A urinalysis was unremarkable. The 24-hour urine collection contained 296 mg of protein. She was taking losartan-HCTZ and aspirin. Physical examination was notable for body mass index of 31, normal blood pressure, and no other physical findings. A renal biopsy was performed primarily because of the finding of positive antiphospholipid antibodies. Table 1 provides a summary of the immunologic workup.

A kidney biopsy (Figure 2) contained 41 glomeruli for light microscopy, of which 20 were globally sclerotic. Three glomeruli contained segmental scars with overlying segmental fibrous crescents. The remaining glomeruli were hypertrophied with mild diffuse mesangial hypercellularity accompanied by mesangial expansion by eosinophilic deposits. The glomerular capillary lumina were patent, and the glomerular basement membranes were normal in thickness. There was no evidence of a thrombotic microangiopathy.

Table 1. Immunologic workup for patient 2

Test	2013	2014 (biopsy)	Normal range
C3	86	82	90–180 mg/dL
C4	28	23	16–47 mg/dL
ANA	1:160	Negative	<1:40
Anti-dsDNA	6		5–9 IU/ml borderline positive
Rheumatoid factor		8	<14 IU/ml
ANCA	Negative		
Anticardiolipin IgG	24	20	≤14 GPL
β2-glycoprotein	IgG 48 IgA 29	IgG 41 IgA 46	≤20 SGU ≤20 SGA
Lupus anticoagulant	50	40	≤40 s
SPEP/ UPEP	No M spike	No M spike	0.60–1.60 gm/dL
Immunofixation	Faint band in Lambda (serum)	Not detected	
Serum free light-chain ratio		1.2	0.26–1.65
HBsAg	Negative		
HCV antibody	Negative		
HIV	Negative		
RPR	1:4		Nonreactive titer
FTA-AB	Reactive minimal		Nonreactive

ANA, antinuclear antibody; ANCA, anti–neutrophil cytoplasmic antibodies; anti-dsDNA, anti–double stranded DNA; C3/C4, complement 3 and 4; FTA-AB, fluorescent treponemal antibody absorption; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; RPR, rapid plasma reagin; SPEP, serum protein electrophoresis; UPEP , urine protein electrophoresis.

Tubular atrophy and interstitial fibrosis occupied approximately 30% of the cortex. There was mild arteriosclerosis. Immunofluorescence on frozen tissue showed mesangial deposits staining for IgG (2+) with kappa light-chain restriction (2+), accompanied by 1–2+ C3 and trace C1q. Stains for the IgG subclasses revealed restricted 2+ mesangial staining for IgG1. Immunofluorescence performed on pronase-digested paraffin sections confirmed these results and identified no masked deposits. By electron microscopy, there were abundant granular mesangial electron deposits without organized substructure.

A bone marrow biopsy with flow cytometry on bone marrow cells was unremarkable. The losartan dose was increased to 50 mg/d. She was not treated with immunosuppression. Approximately 1.5 years after kidney biopsy, she developed hyperthyroidism due to Graves disease, for which methimazole was given for 3 years followed by remission of thyroiditis. Six years after the biopsy, serum creatinine is 1.5 mg/dl and urine protein-creatinine ratio is 600 mg/g. Urinalysis shows no microhematuria. A recent serum free light-chain ratio is normal.

DISCUSSION

PGNMID is relatively unique in the spectrum of MGRS, in that despite monotypic IgG kidney deposits, no monoclonal gammopathy or hematologic malignancy is identified in the majority of cases, making the

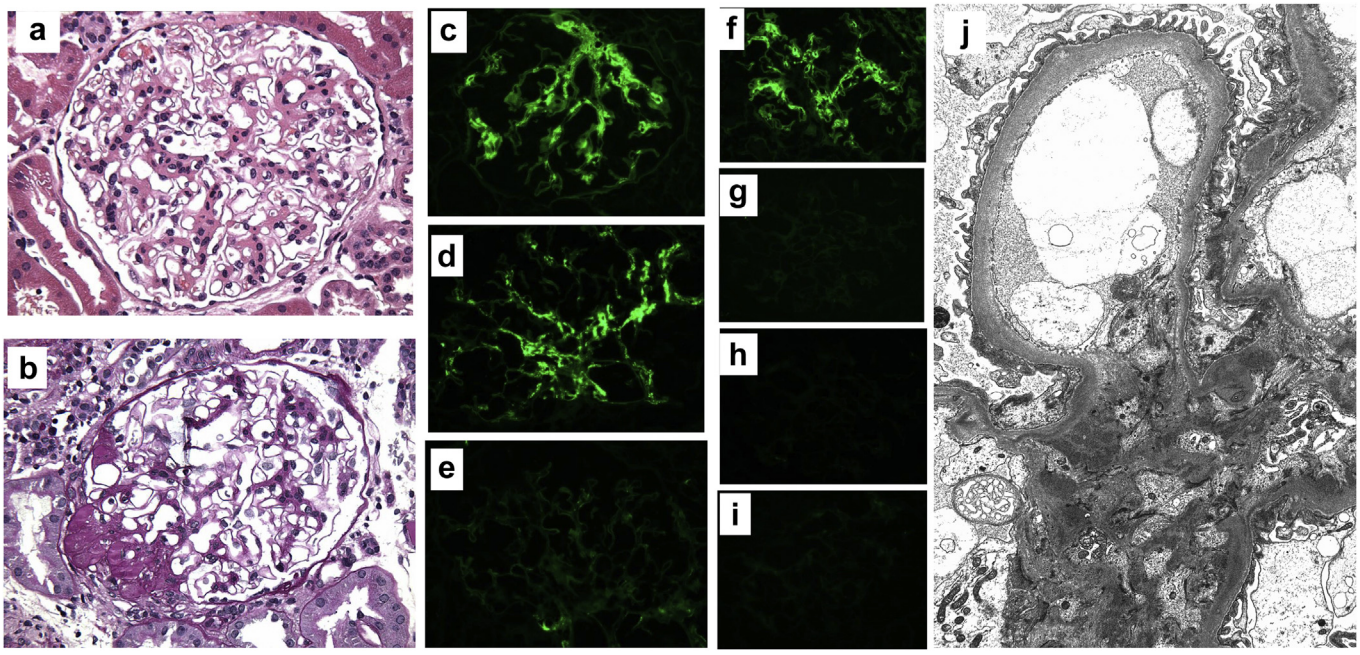

Figure 2. Renal biopsy findings from patient 2. (a) The glomeruli display diffuse and global, mild to moderate mesangial hypercellularity with patent capillaries (hematoxylin and eosin, original magnification × 400). (b) Several glomeruli contain segmental scars with overlying small segmental fibrous crescents associated with disruption of Bowman capsule (periodic acid–Schiff, original magnification × 400). Immunofluorescence reveals a granular mesangial pattern of staining for (c) IgG (original magnification × 600) and (d) kappa light chain (original magnification × 600), with negativity for (e) lambda light chain (original magnification × 600). IgG subtypes show restricted mesangial staining for (f) IgG subtype 1 (original magnification × 600) with negativity for (g) IgG subtype 2, (h) subtype 3, and (i) subtype 4. These staining results are consistent with monotypic IgG1-kappa deposits. Electron microscopy shows granular, nonorganized mesangial electron-dense deposits. (j) No deposits are seen involving the peripheral glomerular capillary wall, and podocyte foot processes are well preserved (electron micrograph, original magnification × 8000).

management uncertain. In an important observational study by Gumber *et al.*,[9] a subgroup of 10 patients with PGNMID and no pathologic clone detected by bone marrow biopsy who were treated with immunosuppression (primarily rituximab, often accompanied by steroids, and cyclophosphamide) appeared to have better outcomes than three untreated patients who progressed to end-stage kidney disease. Based primarily on this experience, the authors suggested not only to deliver clone-targeted therapy when a clone is identified but also to implement empirical immunosuppression targeting a "hypothesized underlying clone" when no clone is found after extensive hematologic workup using therapies directed against plasma cells (such as bortezomib) or CD20-positive B lymphocytes (such as rituximab).[9] However, it is not certain whether the data support such a universal recommendation. The 3 patients who progressed to end-stage kidney disease all had moderate to severe interstitial fibrosis and tubular atrophy on biopsy, which portends a poor prognosis irrespective of treatment.

Furthermore, In the largest series of PGNMID to date of 37 patients by Nasr *et al.*,[3] there was a broad spectrum of outcomes. Twenty-five percent of patients progressed to end-stage kidney disease, whereas 38% had complete or partial recovery. These included 9 patients treated with renin-angiotensin system blockade alone, of whom 4 (44%) had a complete or partial remission. One of these patients was in complete remission with a follow-up of 114 months, or almost 10 years. This favorable outcome occurred despite presentation with nearly 4 g of proteinuria and the presence of crescents on biopsy. Our current report adds 2 more cases where the disease did not appear to require immunosuppressive therapy.

Although patient 1 had a full renal remission, patient 2 would be better described as having stable renal disease with persistent renal dysfunction and low-grade proteinuria. This is not surprising considering the degree of glomerulosclerosis, relatively inactive glomerular lesions, and moderate interstitial fibrosis and tubular atrophy on biopsy. It seems unlikely her course would have been improved by addition of immunosuppression. Arguably, had the glomerulonephritis been detected during a more active phase, the choice of optimal therapy may have been different.

It should be emphasized that "clonal" immunosuppressive therapy is not without risks. Bortezomib is known to have significant neurotoxicity as well as myelosuppression. Although rituximab is generally considered more benign, it has potential adverse effects, particularly infusion-related reactions, including anaphylactoid reactions, as well as subsequent immunocompromised state.[S1] In Gumber *et al.*, rituximab was generally given together with other immunosuppressive agents, which could increase this risk.[9]

Table 2. Teaching points

Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is a form of monoclonal gammopathy of renal significance (MGRS) characterized by a glomerulonephritis with exclusively glomerular monotypic immunoglobulin deposits.
PGNMID is distinctive among causes of MGRS in that most cases have no monoclonal protein detected in blood or urine and normal findings on bone marrow biopsy.
The optimal treatment of PGNMID in such cases remains uncertain.
It has been suggested that all PGNMID patients, regardless of whether there is a monoclonal gammopathy, should be treated with immunosuppression directed at a hypothetical B cell or plasma cell clone.
We describe 2 PGNMID patients without detected clones who were treated successfully with renin-angiotensin system (RAS) inhibition alone for 11 and 6 years, respectively.
These cases illustrate that RAS inhibition alone can be considered a viable treatment option for selected PGNMID patients with nonaggressive disease.

Patient 1 had focally organized fibrillar deposits on electron microscopy. These lacked the microtubular substructure seen in immunotactoid glomerulonephritis or cryoglobulinemia. Although the deposits of PGNMID are typically nonorganized, a minority of cases in the series by Nasr *et al.* also had focally organized deposits of various types.[3] Differential diagnosis of these biopsy findings would include unusual monotypic fibrillary glomerulonephritis. Unfortunately, no glomeruli or renal cortical parenchyma currently remain in the paraffin block to perform DNAJB9 immunostain,[S2] a diagnostic test for fibrillary glomerulonephritis that was not available in 2009. Nonetheless, the absence of characteristic fibrils in the range of 16 to 24 nm favors PGNMID with focally organized thick fibrillar deposits.

Patient 1 had a negative serologic workup, whereas patient 2 had evidence of systemic immune activation, including low serum C3, positive antiphospholipid antibodies, borderline positive anti–double stranded DNA, transiently positive antinuclear antibodies, and subsequent development of autoimmune thyroiditis. Although typically considered a renal limited disorder,[5] PGNMID can be associated with hypocomplementemia (as frequently as 36% in one series),[4] and rarely is associated with autoimmune conditions including ankylosing spondylitis, Graves disease, rheumatoid arthritis, positive antinuclear antibody, and hemolytic anemia.[S3,S4] To our knowledge, borderline positive syphilis serologies, as seen in our patient, have not been reported previously.

A limitation of our report is the incomplete hematologic evaluation performed to exclude neoplastic clones. Patient 1 did not undergo bone marrow biopsy nor was flow cytometry performed on peripheral cells. Although patient 2 did have a bone marrow biopsy with flow cytometry, peripheral blood was not analyzed by flow

cytometry. Nonetheless, the fact that the serum free light-chain ratio remained normal after prolonged follow-up in both patients makes it less likely that a clone was missed. In practice, all PGNMID patients should have a thorough evaluation for a clonal disorder, including bone marrow biopsy and flow cytometry on peripheral blood, and possibly even more sensitive molecular studies on bone marrow and circulating lymphocytes to detect subtle clonal populations.[5]

In conclusion, our cases show that some patients with PGNMID and no detectable pathologic clone can have stable renal disease and prolonged remission for years with renin-angiotensin system blockade alone. This should be considered a viable treatment option for selected patients without evidence of aggressive disease (Table 2).

DISCLOSURE

All the authors declared no competing interests.

PATIENT CONSENT

The authors declare that they have obtained consent from the patients discussed in the report.

SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Supplementary References.

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