

Case Report

Proliferative Glomerulonephritis with Monoclonal Immunoglobulin G Lambda Deposits: Report of the First Pediatric Case

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Abstract

Proliferative glomerulonephritis with monoclonal immunoglobulin G deposits (PGNMID) is a recently described, uncommon renal disorder which is considered a monoclonal gammopathy of renal significance. Although some patients will have a detectable monoclonal spike, overt hematologic malignancy is found in only a minority. Most patients with PGNMID are over the age of 50 years, and to our knowledge no cases have been reported in children or adolescents. Renal biopsy shows variable histologic patterns by light microscopy, with membranoproliferative and membranous patterns being most common. Immunofluorescence microscopy demonstrates restriction to a single immunoglobulin G heavy chain isotype and a single light chain subtype. Electron microscopy reveals granular, unorganized deposits. We report a rare pediatric case which occurred in a 17-year-old female. The rarity of this entity in the adult population has not permitted a standard treatment regimen to be established. Our adolescent patient was treated with multiple treatment regimens including prednisone, mycophenolate mofetil, rituximab, bortezomib, and daratumumab. Our case demonstrates that awareness of this disorder by pediatric nephrologists and pathologists is vital to guide accurate disease classification, prognosis, and treatment.

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Introduction

Proliferative glomerulonephritis with monoclonal immunoglobulin G deposits (PGN-MID) is a recently described, uncommon entity which mimics immune-complex-type glomerulonephritis (GN). Deposition of monoclonal immunoglobulins is found in a variety of other diseases affecting the kidneys, including monoclonal immunoglobulin deposition disease (MIDD), immunotactoid GN, type 1 cryoglobulinemia, and amyloidosis. Renal biopsy can aid in the distinction of PGNMID from these other entities [1–3]. By light microscopy, the most commonly reported patterns include membranoproliferative GN followed by membranous nephropathy and endocapillary proliferative GN. Immunofluorescence (IF) microscopy demonstrates restriction to a single immunoglobulin G (IgG) heavy chain subtype (usually IgG3) and a single light chain isotype (kappa more common than lambda). Electron microscopy (EM) shows granular, unorganized deposits in subepithelial, subendothelial, and mesangial locations which varies according to the histologic pattern [3, 4].

Clinically, the majority of patients present with renal insufficiency and nephrotic-range proteinuria, and approximately half of patients have nephrotic syndrome. Only about 30% of patients have a detectable monoclonal spike (M-spike) by serum protein electrophoresis and urine protein electrophoresis with immunofixation. The majority do not have hematologic malignancy. Most patients are Caucasian, and the majority are female. Nearly all patients with PGNMID are over the age of 40 years [3, 4].

To our knowledge, this is the first reported pediatric case of this entity. Our case broadens the epidemiologic understanding of the disease and presents it as a diagnostic consideration for pediatric nephrologists and renal pathologists in the appropriate clinical setting. The description of our experience in managing this exceedingly rare case also adds to the body of knowledge regarding clinical response to various treatments.

Case Presentation

A 17-year-old female with an unremarkable past medical history developed sudden-onset right-sided abdominal pain, gross hematuria, lower extremity edema, and nephrotic-range proteinuria following a mild upper respiratory infection. She presented to the emergency department with a fever of 39° C and complained of sharp flank pain, headaches, and fatigue. Laboratory results were notable for hypoalbuminemia (serum albumin 1.2 g/dL), low complement C3 of 63 mg/dL (range 82–163 mg/dL), low complement C4 of 10.6 mg/dL (range 14–41 mg/dL), elevated C-reactive protein (2.71 mg/dL), normal blood urea nitrogen, and normal serum creatinine (0.7 mg/dL). Antistreptolysin O titer was normal. Initial timed 24-h urine collection revealed nephrotic-range proteinuria of 3,679 mg/day with a protein creatinine ratio of 3.7.

The protein to creatinine ratio increased to 9.5 three weeks after presentation and a renal biopsy was performed. Under light microscopy, glomeruli had a membranoproliferative pattern with hyperlobulated glomeruli, diffuse endocapillary hypercellularity, diffuse glomerular basement membrane duplication, and mild mesangial matrix expansion with hypercellularity (Fig. 1a). No segmental sclerosis, crescents, or fibrinoid necrosis were seen. There was mild interstitial edema associated with a multifocal mild mononuclear leukocytic infiltrate, but no significant interstitial fibrosis or tubular atrophy. Small numbers of intratubular red blood cell casts were present.

Direct IF demonstrated diffuse, global, chunky granular glomerular capillary wall and mesangial positive staining by IgG (4+ on a scale of 0–4), C1q (4+), C3 (4+), and lambda (4+) (Fig. 1b). IgA, IgM, and kappa were negative. Restriction to IgG and monoclonal lambda raised the suspicion of PGNMID, necessitating IgG subclass staining. The glomeruli showed diffuse global staining by IgG3 (4+) (Fig. 1c). IgG1, IgG2, and IgG4 were all negative.

EM showed extensive (>80%) podocyte foot process effacement and segmental duplication of glomerular basement membranes. There were numerous subendothelial and mesangial electron-dense deposits with a few scattered subepithelial deposits. These deposits were granular with focally variegated texture (Fig. 1d). No organized substructures or fibrillar deposits were present. There were no tubuloreticular inclusions and no deposits within the tubular basement membranes.

The renal biopsy findings prompted additional laboratory studies. Serological testing for cryoglobulins was negative, as was rheumatoid factor. Serum and urine protein electrophoresis did not reveal a monoclonal immunoglobulin. IgG levels were low with normal IgA and IgM levels. Immunofixation electrophoresis showed a normal pattern with no monoclonal proteins. An alternative complement pathway functional assay was low at 3% (normal 50–130%), and alternative complement pathway soluble membrane attack complex was elevated at 0.48 mg/L (normal <0.3 mg/L).

The patient was initially treated with prednisone (40 mg b.i.d.) and lisinopril with no resolution of proteinuria or intermittent gross hematuria. Mycophenolate mofetil (1,000 mg b.i.d.) was initiated 3 weeks after presentation, and steroids were tapered to 30 mg every other day. After 3 months of this treatment there was improvement of serum albumin to 3 g/dL and protein creatinine ratio to 1.4. Complement C3 and C4 levels returned to normal. There was persistent intermittent gross hematuria and proteinuria. Rituximab therapy (four doses at 375 mg/m²/dose) was begun 4 months after diagnosis. After rituximab therapy, her albumin consistently stayed around 3–3.4 mg/dL, with her urine protein creatinine ratio at 1.1–1.2. Both alternative complement pathway functional assay and soluble membrane attack complex had normalized approximately 2 months after completion of the rituximab course. Two months after rituximab, due to a decrease in serum albumin to 2.8, she received intermittent high-dose steroids for 4 months which improved her serum albumin to 3.2–3.8. Mycophenolate mofetil was stopped due to myelosuppression 7 months after starting treatment. Ten months after initial presentation, the patient relapsed with nephrotic-range proteinuria (5 g/24 h), low serum albumin (2.7 mg/dL), and increase in serum creatinine from baseline (0.7 mg/dL) to 0.9 mg/dL. A bone marrow biopsy was performed to detect possible hematologic abnormalities, but it was not adequate for evaluation. At another institution, lambda light chains were detected in the patient's serum using a research test called monoclonal immunoglobulin rapid accurate mass measurement. The decision was made to treat with bortezomib (Velcade®) plus dexamethasone as per the multiple myeloma protocol at that institution. She received the regimen of Velcade/dexamethasone for 4 months, but due to persistent proteinuria, the anti-CD38 monoclonal antibody daratumumab was added to her regimen. She received the combined Velcade/dexamethasone/daratumumab regimen for approximately 4 months at another institution. With this regimen, her serum albumin improved to 3.3–3.6 and her urine protein creatinine ratio remained at 1–1.4. Five months after completion of her Velcade/dexamethasone/daratumumab regimen, she had another relapse, with her serum albumin decreasing to 2.9 and her urine protein creatinine ratio increasing to 2.4. The same regimen was restarted, and at the time of writing the patient is receiving this therapy with improvement in her serum albumin to 3.3 and her urine protein creatinine ratio at 1.4.

Discussion

PGNMID is an uncommon type of monoclonal gammopathy of renal significance (MGRS), which mimics immune complex-mediated GN. MGRS refers to renal diseases which are caused by the secretion of monoclonal immunoglobulin secreted by B-cell clones which do not meet criteria for hematologic malignancies such as multiple myeloma or lymphoma. Multiple other renal lesions can fall within the category of MGRS. A combination of morphologic findings seen by light microscopy, staining patterns by IF, and ultrastructural features seen by EM is required to arrive at a precise pathologic diagnosis. MGRS can result in tubular lesions such as cast nephropathy and light chain proximal tubulopathy. In addition to PGNMID, glomerular disorders include immunotactoid glomerulopathy, type 1 cryoglobulinemic GN, and fibrillary GN. Immunoglobulin-related amyloidosis (predominantly light chain) and MIDD can result in glomerular, tubular, and vascular lesions. Some lesions can be readily recognized by their morphologic appearance. For example, cast nephropathy has fractured casts which are very pale by periodic acid-Schiff stain, and amyloid is Congo-red positive. EM is informative in many cases. Fibrillar deposits are present in amyloidosis and fibrillary GN, which can be distinguished by their size. Microtubules are seen with immunotactoid GN and cryoglobulinemic GN, and crystals can be seen in light-chain proximal tubulopathy. MIDD has punctate, powdery, granular deposits. IF is essential in all cases to demonstrate monoclonality [1]. In PGNMID, renal biopsy demonstrates monoclonality for a single light-chain isotype (kappa more commonly) and a single gamma heavy-chain subclass (most commonly IgG3, as in our case) [3, 4]. Our case showed a membranoproliferative pattern by light microscopy along with predominantly subendothelial and mesangial deposits by EM.

Despite the monoclonality seen by renal biopsy, only 11/37 patients in an expanded case series reported by Nasr et al. [3] had a detectable M-spike and only 1 patient had myeloma. When a patient did have an M-spike, the monoclonal proteins had the same heavy- and light-chain isotypes as those deposited in the kidney. The authors concluded that PGNMID does not seem to precede multiple myeloma in most patients. As with our patient, 49% had full nephrotic syndrome. Approximately 11% of their patients had low complement C3 and C4, as our patient did initially. The majority of the patients in that study were female, and the mean age was 54.5 years (range 20–81 years). No standard treatment regimens were used. Patients received a variety of immunomodulatory therapies including steroids, alkylating agents, mycophenolate mofetil, rituximab, and bortezomib. Out of 32 patients with available follow-up data, 38% had partial to complete recovery, 38% had persistent renal dysfunction, and 22% progressed to end-stage renal disease.

In a series of 26 patients with PGNMID described by Guiard et al. [4], 31% had a detectable M-spike. Again, no pediatric cases were reported, with a mean age of 52 years (range 29–77 years). However, in contrast to the study by Nasr et al. [3], a hematologic malignancy (myeloma, lymphoma) was identified in 9 out of the 22 patients who underwent bone marrow biopsy. The most common pattern seen by renal biopsy was membranous nephropathy (14 patients), followed by membranoproliferative GN (12 patients). IgG subclass staining was performed in 21 of the cases. The authors pointed out that there was a correspondence between the histologic pattern of disease and the subclass of the monoclonal IgG seen in deposits. Membranous nephropathy was associated with IgG1 deposits in 64% of patients, whereas membranoproliferative GN was associated with IgG3 in 80% (as in our patient). Seven of the patients received rituximab as either first- or second-line therapy, 5 of whom did not

have malignancy. Good response was achieved with 5 patients having complete remission of nephrotic syndrome and 2 having partial remission.

PGNMID has been described in association with hematologic malignancies in isolated case reports as well. Noto et al. [5] described a patient with nephrotic syndrome and a renal biopsy showing endocapillary proliferative GN with monoclonal IgG1 kappa deposits. Serum protein electrophoresis and urine protein electrophoresis showed M-spikes of IgG kappa, and bone marrow biopsy confirmed multiple myeloma. The patient was successfully treated with bortezomib and dexamethasone. Barbour et al. [6] described 2 patients with preexisting chronic lymphocytic leukemia who developed hypertension, increased serum creatinine, microhematuria, and nephrotic-range proteinuria. Renal biopsies from both patients showed endocapillary proliferative GN with monoclonal IgG1 deposits. Both were treated with rituximab plus cyclophosphamide in one case and fludarabine in the other, and both showed significant improvement.

PGNMID has been reported to recur in kidney allografts. Nasr et al. [7] described 4 cases which recurred in the allografts at a mean of 3.8 months after transplantation. The monoclonal IgG deposits in the transplants and in the native kidneys had identical heavy- and light-chain isotypes. Albawardi et al. [8] reported that out of 21 renal biopsy specimens with PGNMID in their files, 2 were recurrent cases in allografts, and 2 more were described as de novo cases in allografts. One case recurred approximately 13 months after transplantation, and 1 recurred at about 22 months.

In conclusion, we describe PGNMID in a 17-year-old patient, who to our knowledge is the first pediatric case reported. This expands the age range for PGNMID and proves that it is not confined to the adult population. At the present time, there is no standardized treatment for this rare disease. Although a small number of patients have experienced complete response using immunomodulatory drugs, including rituximab and bortezomib, our patient achieved partial response and is still undergoing treatment. Awareness that PGNMID is part of the differential diagnosis for renal diseases caused by deposition of monoclonal IgG in pediatric patients is necessary to guide correct disease classification, prognosis, and potential therapeutic options.

Statement of Ethics

The authors have no ethical conflicts to declare.

Disclosure Statement

The authors declare no conflict of interest.

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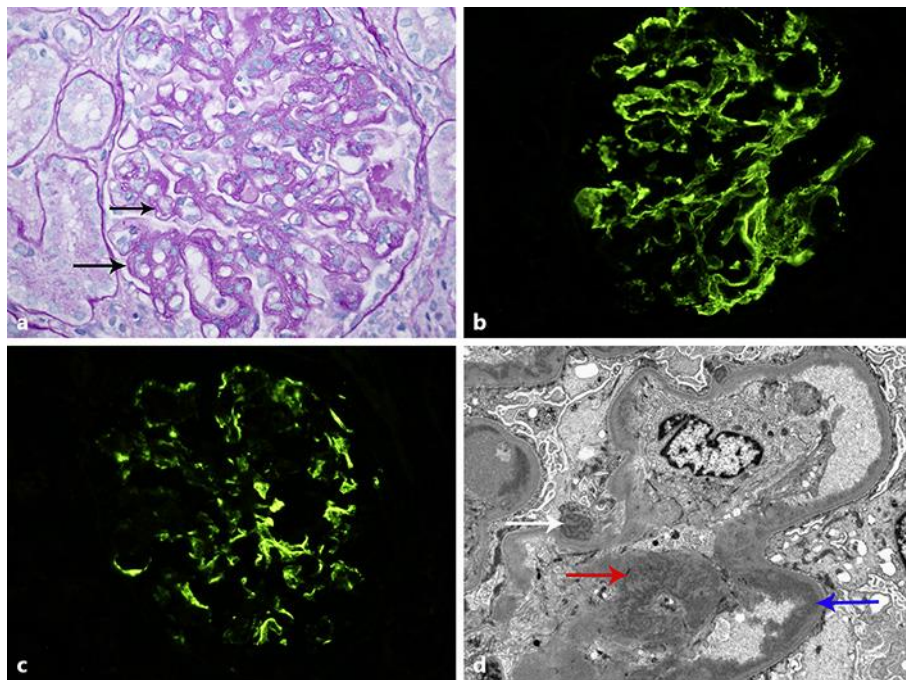


Fig. 1. Kidney biopsy findings. **a** Light microscopy shows a glomerulus with basement membrane double contours (arrows) and endocapillary hypercellularity. Periodic acid-Schiff stain; original magnification $\times 400$. **b** Immunofluorescence microscopy shows strong (4+), granular glomerular capillary wall and mesangial staining by lambda. Original magnification $\times 400$. **c** Immunofluorescence microscopy shows strong (4+), granular glomerular capillary wall and mesangial staining by IgG3. Original magnification $\times 400$. **d** Electron microscopy shows subepithelial (white arrow), subendothelial (blue arrow), and mesangial (red arrow) granular electron-dense deposits, some with a variegated appearance. Original magnification $\times 1,500$.