Kidney Medicine

Relapsing and Remitting Proliferative Glomerulonephritis With Monoclonal Immunoglobulin Deposits in Association With Infection and Vaccination: A Case Report

Simon Moubarak, Loren P. Herrera Hernandez, Lynn D. Cornell, Tiffany Caza, and Ladan Zand

Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is the second most common monoclonal gammopathy of renal significance. Rates of progression to kidney failure as well as rates of recurrence after kidney transplantation are high, especially in the absence of treatment. Treatment is usually targeted toward the abnormal clone, but even in the absence of an identifiable clone, empiric treatment is still recommended to avoid worsening prognosis. In this report, we present an unusual course of a PGNMID case with a relapsing and remitting pattern of illness, likely triggered by infection and vaccination. The patient in this case showed subsequent improvement after each episode, with stable kidney function over the years. This case report highlights the importance of investigating possible recent infectious exposures or vaccinations as potential triggers for this disease. This association should be considered for future patients with PGNMID, especially when there is no identifiable clone to help guide therapy.

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INTRODUCTION

Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is a glomerulonephritis that results from injury related to monoclonal immunoglobulins and is the second most common form of monoclonal gammopathy of renal significance after amyloid light chain amyloidosis.[1] Patients present with varying degrees of proteinuria, microscopic hematuria, and decreased kidney function. On kidney biopsy, light microscopic findings can be variable and include mesangial proliferative, endocapillary proliferative, membranoproliferative, or a membranous pattern of injury. Immunofluorescence shows monotypic immunoglobulin deposits with light chain restriction. The most common monoclonal immunoglobulin identified is IgG3 kappa.[2] Electron microscopy shows nonorganized electron-dense deposits. The immunoglobulins are produced by either a nonmalignant B-cell or plasma cell clone. Treatment is directed toward the abnormal clone.[3,4] However, in up to 70% of patients, an abnormal clone cannot be identified.[3] Even in the absence of an identifiable clone, empiric therapy is still recommended as studies have suggested high rate of progression to kidney failure with high rate of recurrence after kidney transplantation in the absence of therapy.[5] The optimal choice of therapy, however, has been debated. More recently, a report of 2 cases of PGNMID was published showing relatively stable kidney function in the absence of any therapy directed at monoclonal proteins, suggesting that immunosuppression may not be required in all patients and that the clinical course may be more heterogeneous than once thought.[6] Here, we present an unusual case of PGNMID with a relapsing and remitting course triggered by infection and vaccination with subsequent improvement and stable kidney function over the years.

CASE REPORT

A woman in her forties with no significant medical history originally presented 13 years prior with an episode of gross hematuria, proteinuria, and an elevated creatinine level of 1.7 mg/dL (from baseline of 0.9 mg/dL) after an episode of upper respiratory infection. A kidney biopsy was performed and was interpreted as postinfectious glomerulonephritis. She was treated conservatively and had complete resolution of hematuria and proteinuria with normalization of her creatinine back to baseline. She went on to have a normal pregnancy 2 years after this episode with no complications. She remained in her usual state of health until 13 years later when she developed an episode of viral gastroenteritis. A week after the infection, she noted a significant increase in her blood pressure up to 178/102 mm Hg, evidence of gross hematuria, and foamy urine with preserved kidney function. Further evaluation revealed 24-hour urine protein of 6.8 g, and urinalysis with microscopy showed > 100 red blood cells per high power field. Serum creatinine remained at baseline of 0.9 mg/dL. Additional serological work up revealed normal C3 and C4 levels, negative antineutrophil cytoplasmic antibody panel, and negative hepatitis B and C serology. A computed tomography scan of the chest, abdomen, and pelvis was performed and was unremarkable. Serum protein electrophoresis showed hypogammaglobulinemia and serum immunofixation was negative. Serum free light chain ratio was normal, and urine protein electrophoresis with urinary immunofixation were

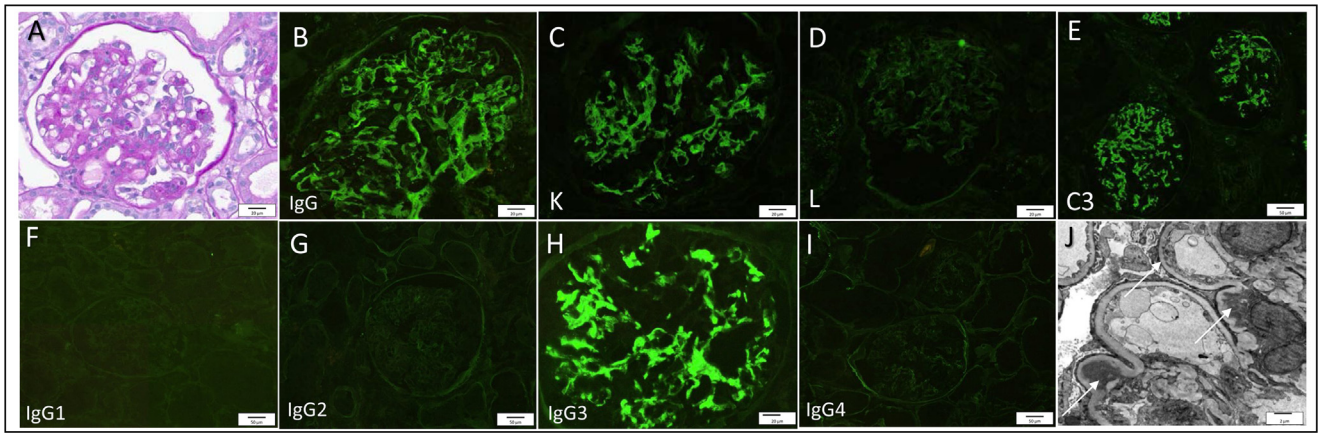

Figure 1. Second kidney biopsy. (A) Glomerulus with mesangial proliferation (periodic acid–Schiff). (B-E) Granular mesangial and capillary wall staining with IgG kappa and C3 and negative lambda. (F-I) IgG subtype staining with IgG3 showing positive staining similar to IgG and kappa and negative IgG1, IgG2, and IgG4. (J) Electron microscopy image showing electron-dense deposits in the mesangial and subendothelial areas (arrows).

negative for any monoclonal gammopathy. A second kidney biopsy was performed after this episode (Fig 1). The biopsy was consistent with PGNMID with IgG3 kappa deposits. She subsequently underwent a bone marrow biopsy that was normal with no evidence of an abnormal clone.

Given the new diagnosis of PGNMID on her current biopsy, her kidney biopsy from 13 years prior was re-evaluated as shown in Figure 2. Light microscopy showed focal mesangial and endocapillary proliferation, and pronase immunofluorescence confirmed the presence of kappa restriction. Electron microscopy images showed electron-dense deposits in the mesangium with few subendothelial deposits. There was no substructure present. These findings were consistent with the findings of her second biopsy of PGNMID with IgG3 kappa deposits. Given her prior episode of spontaneous remission, the decision was made to treat conservatively. She began antihypertensive therapy with losartan and furosemide. A month after her kidney biopsy, her proteinuria improved to 2.1 g/d. At 3 months' follow-up, her proteinuria improved to 0.4 g/d, hematuria improved to 20 red blood cells per high power field, and serum creatinine remained stable at 0.9 mg/dL. A month later, she received her third dose of the coronavirus disease 2019 (COVID-19) Pfizer vaccine. Two days after the vaccination she developed fever and chills. A severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction test was negative. Five days later, she started feeling unwell with body aches, significant fatigue, a significant increase in her blood pressure to 178/102 mm Hg, and development of lower extremity edema. Urinalysis with microscopy showed > 100 red blood cells per high power field and 24-hour urine studies showed 26 g/d of proteinuria. Serum creatinine was up to 1.2 mg/dL. Given the severity of proteinuria and worsening kidney function, the decision was made to start with a course of corticosteroids first and assess response before proceeding with additional therapy (such as anti-CD20 or anti-plasma cell). She was initiated on prednisone 60 mg daily with taper over 5 months. On her last follow-up while on 2.5 mg daily of prednisone, her serum creatinine returned to baseline of 0.85 mg/dL, serum albumin returned to normal at 4.4 g/dL, 24-hour urinary protein decreased to 108 mg, and urinalysis showed hematuria down to 3-10 red blood cells per high power field.

DISCUSSION

This is the first reported case of a patient with PGNMID with IgG3 kappa deposits who had a relapsing and remitting course that was triggered by an infection or immune response to a vaccine over a span of a decade. This contrasts with previous reported cases of PGNMID that tend to have a progressive course over time. There is now growing evidence that PGNMID may be more diverse than previously realized. This is substantiated by recent case reports of patients with PGNMID who have had a stable course despite conservative therapy for many years.[6] In addition, there are also reported cases of PGNMID that were triggered by known infections including coronavirus disease 2019 (COVID-19) infection and parvovirus B19 infection.[2,7] There is also a report of 2 patients in the form of an abstract with a diagnosis of PGNMID who presented after an episode of infection (upper respiratory infection and cholangitis). What is unique in our case is the long duration of follow-up in the patient and evidence of repeated relapses with infection/vaccination and subsequent remission.[8]

Having a flare of an underlying glomerulonephritis with an infection is not new. This association has been well established in certain glomerulonephritides such as IgA nephropathy and C3 glomerulonephritis. Infections can carry specific cell surface antigens, which in turn

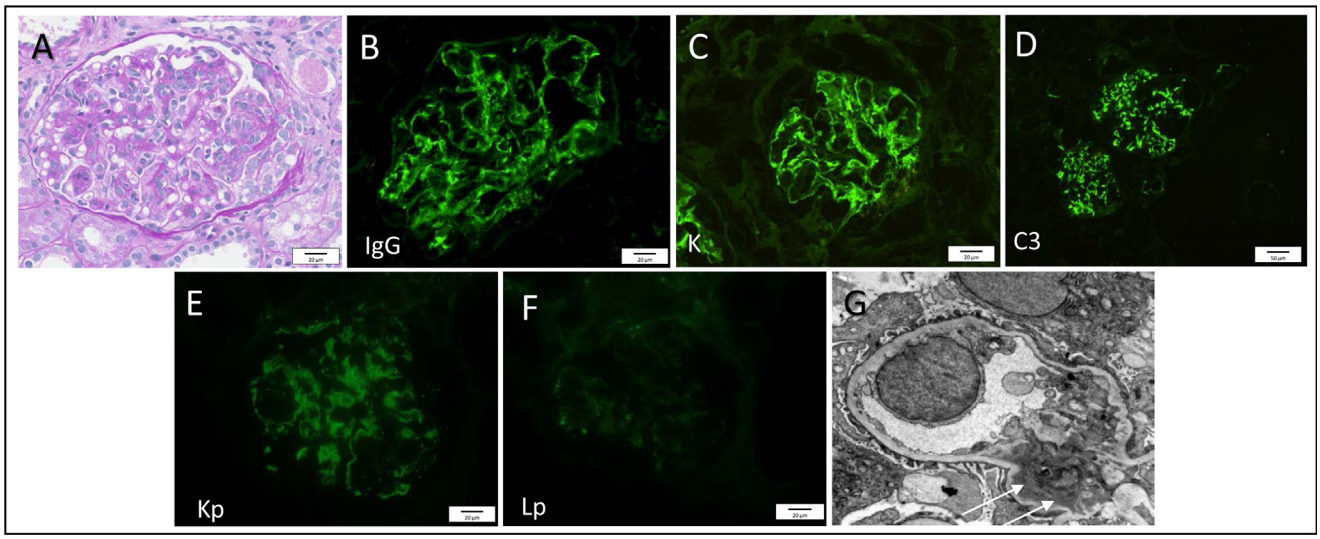

Figure 2. First kidney biopsy. (A) Glomerulus with mesangial and endocapillary proliferation and early crescent formation (periodic acid–Schiff). (B-D) Granular mesangial and capillary wall staining with IgG, kappa, and C3. (E-F) Pronase immunofluorescence with kappa and lambda light chains demonstrate kappa restriction. (G) Electron microscopy image showing mesangial deposits (arrows).

promote the production of antibodies that are implicated in the pathogenesis of these diseases.[9,10] The mechanism by which an infection may prompt the development of PGNMID is not entirely clear. It is likely that the infection triggers proliferation of an abnormal B-cell or plasma cell clone that results in production of IgG3 kappa (as in this case, and as described with parvovirus B19 infection), which then subsequently resolves. Development of an abnormal clone after chronic infection and antigenic stimulation (eg, hepatitis C) has been well described, but perhaps in some individuals, even a short exposure to infection can result in proliferation of an abnormal clone.[11] What is notable in our patient is that with each repeated episode related to infection or vaccination, the disease severity was more pronounced, with the last infection resulting in significant proteinuria (over 26 g) and gross hematuria requiring initiation of steroid therapy. Despite the severe presentation, however, the patient responded well to a course of steroids alone.

This case report highlights the importance of taking a proper history and asking about possible recent infectious exposures or vaccination and considering infections and immune stimulation as potential triggers for this disease. In such cases, a close and brief duration of monitoring may be indicated before proceeding with therapy, especially knowing that there are no definitive therapies available, and that they all carry risks of side effects.

In conclusion, we report the first case to our knowledge of PGNMID that exhibited a relapsing-remitting pattern triggered by infection and immunization. This association should be considered for future patients with PGNMID, especially when no clone in the bone marrow or monoclonal spike in blood and urine can be detected.

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