Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits

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Abstract

Proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) is a relatively recently described form of glomerulonephritis that mimics immune-complex-type glomerulonephritis on light microscopy and electron microscopy. However, by immunofluorescence, the glomerular deposits are monotypic, staining for a single light chain isotype and a single gamma heavy chain subclass, most commonly IgG3 kappa. PGNMID is classified as a monoclonal gammopathy of renal significance – lesion characterized by non-organized deposits in patients who do not have systemic lymphoma or multiple myeloma. Despite the monotypic nature of glomerular deposits, only a small subset of patients has a detectable serum monoclonal immunoglobulin, and hematologic malignancy is rare. Furthermore, PGNMID does not appear to represent a premyelomatous condition in most patients. The disease mainly affects adults and is slightly more common in females. Most patients present with nephrotic-range proteinuria and hematuria with or without renal insufficiency. Prognosis is variable, with nearly a quarter of patients progressing to ESRD within 2.5 years despite immunomodulatory therapy. Early recurrence in the renal allograft is observed in most patients. The pathogenesis of PGNMID remains elusive.

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Introduction

Glomerular diseases caused by monoclonal immunoglobulin deposition include light and heavy chain deposition disease, type 1 cryoglobulinemic glomerulonephritis, immunotactoid glomerulonephritis, light and heavy chain amyloidosis, and monoclonal fibrillary glomerulonephritis (Bridoux et al. 2015). In 2004, a novel form of glomerular injury related to monoclonal IgG deposition that could not be assigned to any of the above conditions was described and termed "proliferative glomerulonephritis with monoclonal IgG deposits" (PGNMID) (Nasr et al. 2004). On immunofluorescence (IF), the glomerular deposits were monotypic, staining for a single light chain isotype and a single gamma heavy chain subclass. However, light microscopy (LM) exhibited endocapillary proliferative or membranoproliferative glomerulonephritis, and electron microscopy (EM) revealed mostly granular electron-dense deposits, mimicking immune-complex glomerulonephritis. Since then, there have been two reported large series on PGNMID, one from Columbia University of 37 patients (Nasr et al. 2009) and one from the Mayo Clinic of 54 patients (Bhutani et al. 2015) and over 25 case reports or small series. The reported renal biopsy incidence of PGNMID ranged from 0.17% to 3.7% (Gowda et al. 2015; Nasr et al. 2009). It is eightfold rarer than AL amyloidosis and twice as rare as Randall type monoclonal immunoglobulin deposition disease, but more common than type 1 cryoglobulinemic glomerulonephritis and immunotactoid glomerulonephritis. In this chapter we will review the clinical renal and hematologic characteristics, pathologic features, diagnostic criteria, treatment, outcome, recurrence in the allograft, and potential pathogenesis of PGNMID. Of note, rare cases of proliferative glomerulonephritis with non-organized monoclonal IgM, IgA, or lambda light chain deposits have been reported (Bhutani et al. 2015) which will not be addressed in this chapter.

Demographic and Clinical Characteristics of PGNMID

PGNMID appears to be a glomerular-limited condition as no extraglomerular or extrarenal deposits have been described thus far in this form of glomerulonephritis. Patients with PGNMID typically present in their sixth to seventh decade of life with a median age of 56 years. Two thirds of patients are >50 years old and 17% are >70 years old at diagnosis. Rarely, PGNMID can affect children. There is a slight female predominance (female-to-male ratio of 1.2:1). The vast majority of reported patients were Caucasian. Most patients do not have clinical evidence of underlying infectious, autoimmune, or other systemic disease, although there have been few reported patients who had a history of carcinoma (of colon, anus, bladder, breast), infection (recent upper respiratory tract, HCV, HIV, parvovirus B19), or autoimmune disease (Sjogren's syndrome, autoimmune hemolytic anemia) (Nasr et al. 2009; Bhutani et al. 2015). Chronic hypertension and diabetes mellitus are present in 38% and 14% of patients, respectively.

Patients typically present with proteinuria, hematuria, and renal insufficiency. All patients have proteinuria (median 3.8 g/day, interquartile range 2–8.2), which is in the nephrotic range in 69% of patients, and about half have full nephrotic syndrome. Microhematuria is present in 77% of patients, whereas gross hematuria is rare, reported in <3% of patients. Two thirds of patients have renal insufficiency at presentation (median eGFR 36 mL/min/1.73 m^2 (interquartile range 20–50)), including 8% who require dialysis at the time of diagnosis. The mean serum albumin is 3.1 g/dL (range 1.1–4.9). Peripheral edema is present in 62% of patients. Serum cryoglobulin and rheumatoid factor are typically negative, without systemic manifestations of cryoglobulinemia. Hypocomplementemia is present in 21–27% of

patients (low C3 alone, low C4 alone, or low C3 and C4, with equal frequencies).

Hematologic Characteristics of PGNMID

Overall, only 19% to 27% of patients with PGNMID have a detectable circulating monoclonal immunoglobulin (MIg) by serum immunofixation (SIFE), which is more sensitive than serum protein electrophoresis (SPEP). In these patients, the MIg is detectable at presentation although rare patients with an initial negative SIFE develop positive SIFE on repeat testing as late as 3 years after presentation. Using the standard serum free light chain ratio (sFLCR) (range 0.26–1.65), sFLCR has comparable sensitivity to SIFE for the detection of MIg. Patients with abnormal sFLCR and those with positive SIFE for MIg do not overlap completely. In the abovementioned cohort by Bhutani et al. (2015), 50 patients were tested by sFLCR; 11 (22%) had abnormal sFLCR; and two thirds of these had negative SIFE. Together, SIFE and sFLCR detected MIg in 30% of patients. However, using the extended renal range of sFLCR (0.3–3.1), only one patient had abnormal sFLCR. Urine protein electrophoresis (UPEP) with immunofixation (UIFE) is less sensitive than the serum monoclonal protein studies in detecting the nephropathic MIg (detection rate 8–9%), and they are typically negative when the serum studies are negative.

The clone detection rate on bone marrow (BM) examination (including testing by immunohistochemistry and flow cytometry) is 19%, and it correlates with the results of SIFE and sFLCR. The nephropathic clone is detected in 100% of patients with positive SIFE and abnormal sFLCR, in 75% of patients with positive SIFE and normal sFLCR, in 17% of patients with abnormal sFLCR and negative SIFE, and in 0% in those with negative SIFE and normal sFLCR (Bhutani et al. 2015). The nephropathic clone is most commonly a plasma cell clone, and the percentage of monoclonal plasma cells is usually <10% of the BM cellularity. CD20-positive B-cell clones are less common and are most commonly chronic lymphocytic leukemia (CLL) clones. The above data suggests that BM biopsy is not informative in PGNMID patients with negative SIFE and normal sFLCR. Hematologic malignancy is rare in PGNMID, reported in 3–4% of patients, and includes CLL and multiple myeloma (Barbour et al. 2011; Nasr et al. 2009). One patient with concurrent AL amyloidosis involving the renal vessels with sparing of glomeruli has also been reported (Nasr et al. 2004).

Pathologic Features of PGNMID

The diagnostic criteria for PGNMID are listed in Table 1. On LM, the glomerular alterations are heterogeneous, with the majority of cases showing variable degrees of endocapillary hypercellularity and duplication of the glomerular basement membranes (GBM). The most frequent pattern of glomerular injury, seen in 55–68% of cases, is membranoproliferative glomerulonephritis (MPGN) characterized by diffuse and global duplication of the GBM with cellular interposition and mesangial expansion by increased mesangial cell number and matrix (Fig. 1a). Most of these cases also exhibit endocapillary hypercellularity, and some show segmental membranous features. The second most

Table 1 Diagnostic criteria for PGNMID

Immune deposit staining positive for gamma heavy chain (IgG), with negativity for alpha (IgA) and mu (IgM) heavy chains, indicating restriction to a single immunoglobulin class
Positive staining for a single gamma (IgG) subclass (IgG1, IgG2, IgG3, or IgG4), indicating restriction to a single IgG subclass
Positive staining for a single light chain isotype (kappa or lambda), indicating that the deposits are monotypic
Predominantly granular electron-dense deposits in mesangial, subendothelial, and/or subepithelial locations by EM, resembling immune complex type deposits
Absence of clinical or laboratory evidence of cryoglobulinemia

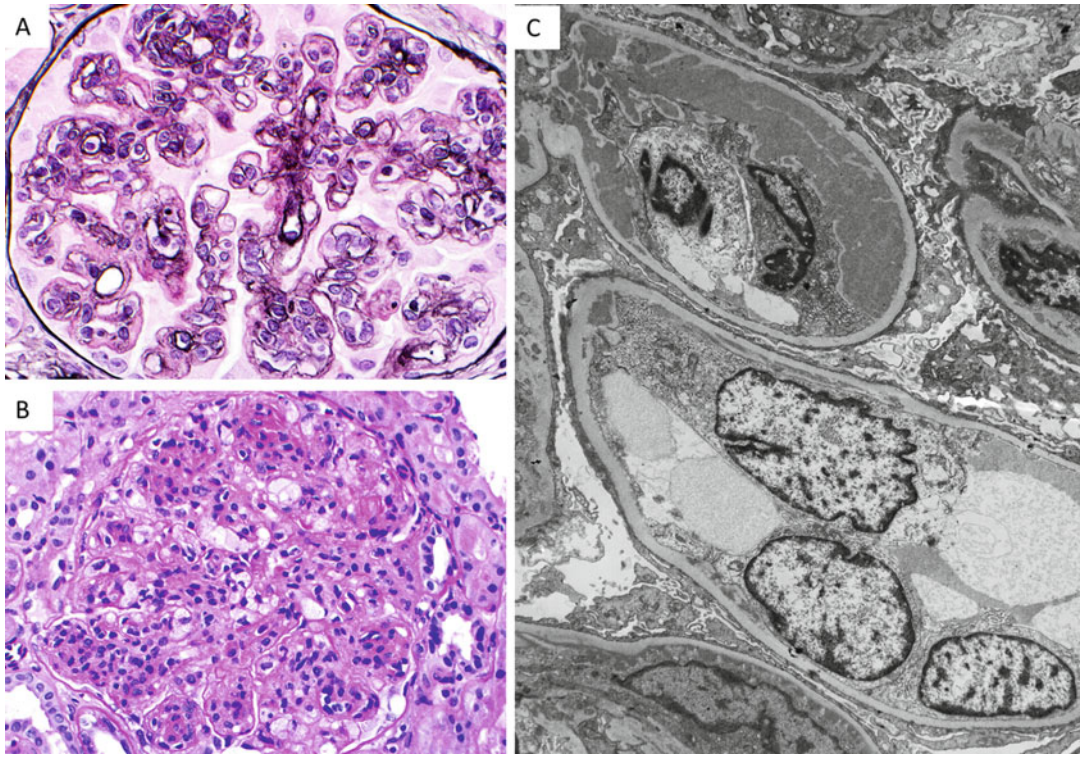

Fig. 1 (**a**) Membranoproliferative pattern of PGNMID. There is widespread duplication of the glomerular basement membrane associated with cellular interposition. The glomerulus also shows global mesangial and segmental endocapillary hypercellularity (silver stain). (**b**) Endocapillary proliferative pattern of PGNMID. The glomerulus shows global mesangial hypercellularity and endocapillary hypercellularity which segmentally occludes the glomerular capillary lumina (periodic acid-Schiff stain). (**c**) Electron microscopy in PGNMID. There are large granular subendothelial and mesangial electron-dense deposits without substructure. Podocytes display global foot process effacement

common pattern, seen in 20–35% of cases, is endocapillary proliferative glomerulonephritis, characterized by endocapillary hypercellularity and leukocyte infiltration causing luminal occlusion (Fig. 1b). Some of these cases have associated segmental membranoproliferative features, neutrophil infiltration, or segmental membranous features. A pure mesangial proliferative glomerulonephritis pattern, characterized by mesangial hypercellularity without endocapillary proliferative or membranoproliferative features, occurs in 3–13% of cases. A fourth histological pattern, encountered in 5% of cases, is predominantly membranous glomerulonephritis characterized by GBM thickening and global subepithelial deposits (Komatsuda et al. 2008; Guiard et al. 2011). Crescents are present in 18–32% of patients and are typically focal affecting <50% of glomeruli. Crescentic transformation of PGNMID has been reported after upper respiratory tract infection or treatment with filgrastim (Batal et al. 2016).

By IF, the monotypic deposits are seen exclusively in the glomeruli, localized mainly to the glomerular capillary wall and mesangium and generally have a granular texture. IgG is the only immunoglobulin deposited (Fig. 2). There is light chain isotype restriction, with sole positivity for kappa in 70–73% of cases and sole positivity for lambda in 27–30% of cases (Fig. 2). There is glomerular co-deposition of C3 in almost all cases and C1q in 55–64% of cases (Fig. 2). Staining for IgG1–4 subclasses shows monotypic deposits: IgG3 only in 60–68% of

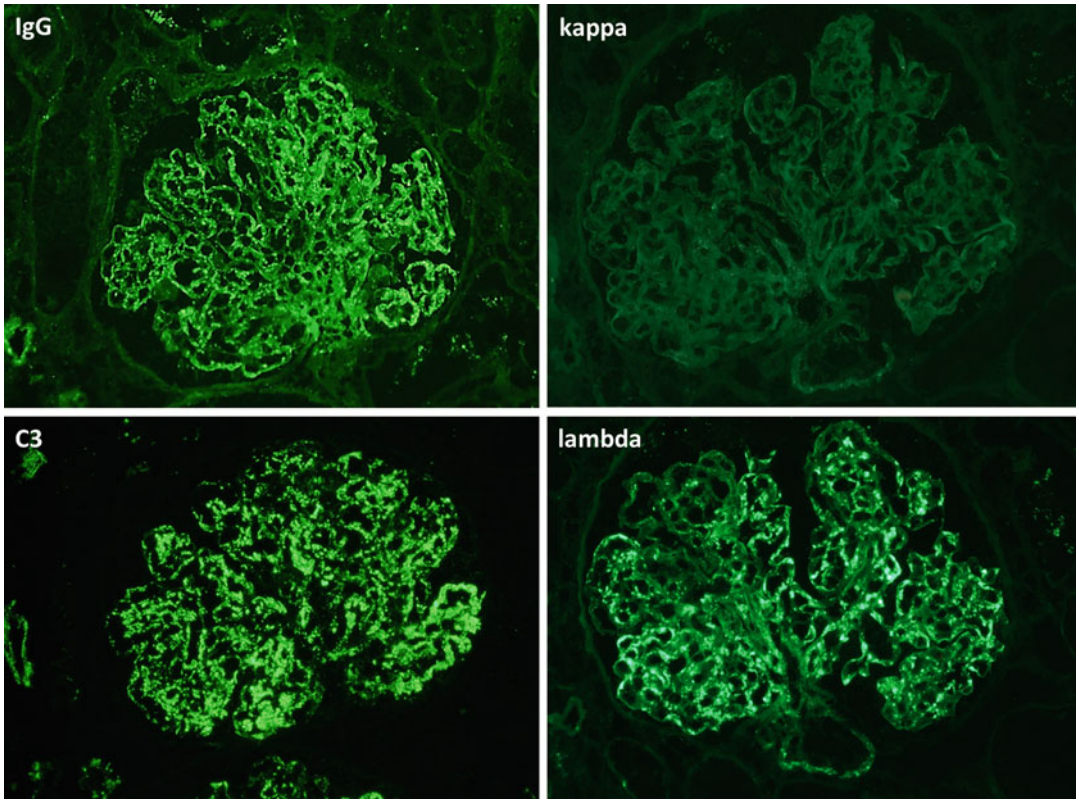

Fig. 2 Immunofluorescence in this case of PGNMID shows bright granular global mesangial and glomerular capillary wall positivity for IgG, C3, and lambda. The glomerulus is negative for kappa

cases, IgG1 only in 24–29% of cases, and IgG2 only in 3–16% of cases (Fig. 3). No case of PGNMID with monotypic IgG4 deposits has been reported so far.

On EM, the deposits are confined to the glomerular compartment, present primarily in the mesangium and subendothelial space (Fig. 1c). Subepithelial deposits are less frequent, seen in 17–57% of patients, and are segmental in most cases. In 70–81% of cases, the electron-dense deposits have a finely granular texture throughout, without substructure, resembling immune-complex-type deposits. In the remaining cases, the deposits are mostly granular, but with focally variegated texture. In a small subset of cases, ill-defined fibrils, microtubules, lattice-like arrays, or paracrystalline substructure can be seen involving a portion of otherwise granular deposits.

Treatment and Prognosis of PGNMID

In the absence of prospective, controlled studies, the optimal therapeutic regimen has not been established. Renin angiotensin system blockade and immunomodulatory (IM) therapy with steroids alone or in combination with other immunosuppressive agents, such as cyclophosphamide, mycophenolate mofetil, cyclosporine, rituximab, and bortezomib, have been used in PGNMID with variable results. In patients with stages 1 and 2 CKD, mild proteinuria (<1 g/day), and no histologic evidence of progression (glomerulosclerosis, crescents, interstitial fibrosis), symptomatic therapy only is advised (Fermand et al. 2013; Nasr et al. 2009). In patients with higher CKD stages, nephrotic range proteinuria, and/or histologic evidence of progression, IM is indicated. Clone-directed chemotherapy (such as cyclophosphamide

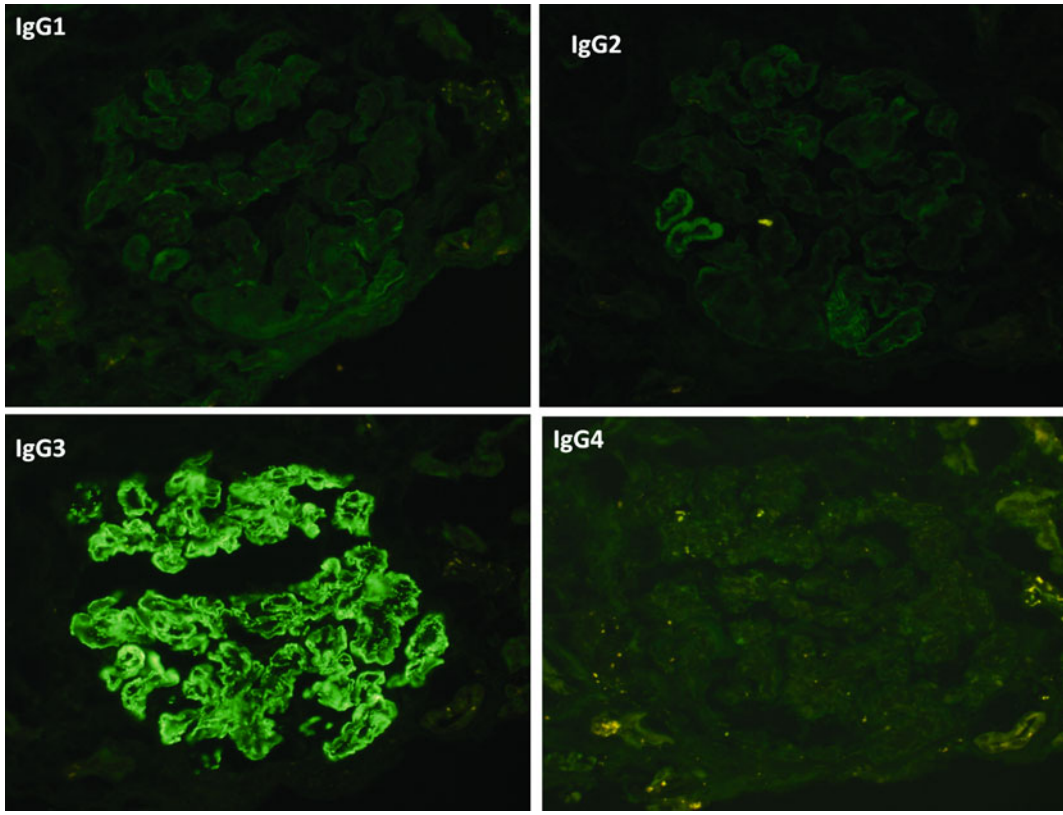

Fig. 3 Immunofluorescence staining for IgG subtypes in this case of PGNMID shows bright glomerular positivity for IgG3. The glomerulus is negative for IgG1, IgG2, and IgG4

and bortezomib or CyBorD (cyclophosphamide/bortezomib/dexamethasone)) should be the first line of treatment in the subset of PGNMID patients with a detectable BM nephropathic clone. In patients without a detectable nephropathic clone, the first line of therapy has not been established, but treatment with cyclophosphamide is a reasonable choice (Fermand et al. 2013; Bhutani et al. 2015). Anecdotal reports found rituximab to be effective, particularly in CLL-associated PGNMID in which the nephropathic clone is a CD20+ B cell (Barbour et al. 2011; Guiard et al. 2011).

Renal prognosis of PGNMID is variable. In the study by Nasr et al. (2009) in which follow-up (mean 30 months) was available on 32 patients, 38% had complete or partial recovery (reduction in proteinuria by at least 50% and to <2 g/d with stable renal function), 38% had persistent renal dysfunction, and 22% progressed to ESRD. Predictors of ESRD on univariate analysis were creatinine at biopsy, percentage of global glomerulosclerosis, and the degree of interstitial fibrosis, but not IM treatment or detection of circulating MIg. On multivariate analysis, higher percentage of glomerulosclerosis was the only independent predictor of ESRD. Only a single patient with negative SIFE at presentation subsequently had positive SIFE, and none of the patients with positive SIFE at presentation subsequently developed MM on follow-up, suggesting that PGNMID is not a precursor of myeloma in most patients (Nasr et al. 2009).

PGNMID in the Renal Allograft

Ten case reports or small series addressing recurrent PGNMID in the renal allograft have been recently reported (Albawardi et al. 2011;

Al-Rabadi et al. 2015; Nasr et al. 2011). The recurrence rate appears to be as high as 80% (Bhutani et al. 2015). Recurrent PGNMID in most patients develops in the first-year post transplant with an average time from transplant to recurrence of 4 months (range 3–13 months). Early detection is enhanced by the use of protocol surveillance biopsies. The recurrent disease manifests clinically with proteinuria, hematuria, and variable degrees of renal insufficiency. The monotypic deposits in the glomeruli of renal allograft and native kidneys are identical with regard to the IgG light and heavy chain isotype restriction (most commonly IgG3, rarely IgG1). As in PGNMID in the native kidneys, most patients do not have a detectable circulating MIg or hematologic malignancy. PGNMID may also develop de novo in the renal allograft (Albawardi et al. 2011). PGNMID in the allograft responds to early aggressive IM therapy including high-dose prednisone, cyclophosphamide, and rituximab, but disease relapse may occur after discontinuation of therapy. The impact of recurrence on the long-term graft survival remains to be determined.

Pathogenesis of PGNMID

The pathogenesis of PGNMID remains elusive. The absence of the underlying infectious, autoimmune, or other systemic disease in most patients and the light chain and heavy chain subclass restriction argue against antigen-antibody immune complex deposition and, instead, favor that monoclonal IgG is deposited in glomeruli as a free, noncomplexed immunoglobulin. Since the majority of patients do not have a detectable circulating MIg or underlying clonal cell population, in these cases PGNMID could arise in the course of normal immune responses. One hypothesis is that during an immune response, a clone of B cells or plasma cells proliferates and produces a monoclonal IgG molecule (particularly IgG3) with the ability to self-aggregate and rapidly deposit in glomeruli through entrapment and/or interaction with negatively charged glomerular constituents. The small quantity of this monoclonal IgG may elude detection by our standard SPEP/SIFE owing to its high avidity for the glomeruli and rapid aggregability favored by its intrinsic physical properties and glomerular sieving itself. In contrast to heavy chain deposition disease in which the CH1 constant domain is deleted, there is no detectable deletion in any of the constant domains in PGNMID (Nasr et al. 2004). The intact CH2 domain is essential for complement fixation.

IgG3, which comprises only 8% of IgG in the circulation, has several properties that allow it to be intrinsically "nephritogenic." IgG3 has the highest molecular weight among the IgG subclasses, making it more size restricted by the glomerular filtration barrier, has the unique physicochemical property of self-aggregability via Fc-Fc interactions, and has the greatest complement-fixing capacity, which could activate downstream inflammatory mediators that promote glomerular leukocyte infiltration and proliferation, leading to glomerulonephritis. These special properties of IgG3 may explain the overrepresentation of this uncommon serum subtype in patients with PGNMID and the universal glomerular co-deposition of C3.

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