Proliferative glomerulonephritis with monoclonal IgG deposits

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Introduction

Glomerular diseases caused by monoclonal IgG deposition include light and heavy chain deposition disease (LHCDD) (1), type 1 cryoglobulinemic glomerulonephritis (2), immunotactoid glomerulonephritis (IT) (3), and rarely fibrillary glomerulonephritis (FGN) (3) (Table 1). LHCDD is characterized by the presence of nodular sclerosing glomerulopathy by light microscopy (LM), diffuse, linear staining of glomerular basement membranes (GBM) and tubular basement membranes (TBM) for a single heavy chain and a single light chain by immunofluorescence (IF), and nonfibrillar, “powdery”, continuous electron dense deposits in GBM and TBM by electron microscopy (EM) (1). Type 1 cryoglobulinemic glomerulonephritis exhibits a membranoproliferative or diffuse proliferative glomerulonephritis pattern on LM, usually with prominent intracapillary infiltrating monocytes and distinctive large, glassy intraluminal immune deposits (2). Ultrastructurally, the deposits commonly show an annular-tubular or fibrillar substructure. The glomerular deposits in IT are composed of microtubular structures with a diameter of 30-50 nm and a tendency for parallel alignment, whereas in FGN they are composed of Congo red-negative, randomly-oriented fibrils measuring 16-24 nm in diameter (3).

Table 1: Causes of glomerular monoclonal IgG deposition

1- Light and heavy chain deposition disease
2- Type 1 cryoglobulinemic glomerulonephritis
3- Immunotactoid glomerulonephritis
4- Fibrillary glomerulonephritis
5- Light and heavy chain amyloidosis
Recently, we and others have encountered patients with a novel form of glomerular injury related to monoclonal IgG deposition that could not be assigned to any of the above conditions, which we termed “proliferative glomerulonephritis with monoclonal IgG deposits” (PGNMID) (4-10). On IF, the glomerular deposits were monoclonal, staining for a single light chain isotype and a single gamma heavy chain subclass. However, LM exhibited endocapillary proliferative or membranoproliferative glomerulonephritis and EM revealed mostly granular electron dense deposits, mimicking ordinary immune-complex glomerulonephritis (4). Here, we present the clinical and pathologic characteristics of 37 patients with PGNMID, representing the largest series to date.

**Diagnostic criteria for PGNMID**

The following criteria are required for the diagnosis of PGNMID (4):

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

**Clinical features**

The biopsy incidence of PGNMID was 0.17%. The disease was eight-fold rarer than AL amyloidosis and approximately twice as rare as Randall type monoclonal immunoglobulin deposition disease. The mean age at presentation was 54.5 years (range 20-81) and close to 2/3 of patients were >50 years old. There was a female predominance (female-to-male ratio of 2:1). Only 27% of patients had a monoclonal (M)-spike on
standard serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP), and immunofixation electrophoresis (IFE), whereas multiple myeloma (MM) was rare affecting 3% of patients. None of the patients had lymphadenopathy, hepatosplenomegaly, or lymphoma. One patient had primary renal amyloidosis of the lambda type affecting blood vessels diagnosed concomitantly with PGNMID of the IgG2 lambda type on renal biopsy. Four patients had history of carcinoma. One patient who had detectable IgGλ M-spike in serum had an upper respiratory tract infection 5 days prior to presentation with renal failure. Another patient had a history of HIV infection. None of the remaining 35 patients had a history of recent or chronic infection. One patient carried a diagnosis of autoimmune hemolytic anemia. None of the patients had a history of SLE, rheumatoid arthritis, mixed connective tissue disease, or Sjogren’s syndrome.

Serum cryoglobulin titers were negative in all patients (performed repeatedly in many patients) and none of the patients had any systemic manifestation of cryoglobulinemia. Hypocomplementemia was present in a quarter of patients (low C3, low C4, or low C3 and C4). Rheumatoid factor, tested in 18 patients, was negative in 17 and positive in 1. Hepatitis C antibody, tested in 30 patients, was negative in 29 and positive in 1 (who had MM and normal serum complements).

At presentation, all patients had proteinuria, which was in the nephrotic range in 69% of patients, and close to a half of patients had full nephrotic syndrome. Microhematuria was documented in 77% of patients, whereas gross hematuria was present in <3% of patients. Two thirds of patients had renal insufficiency, including 3 who were on hemodialysis. The mean serum creatinine was 2.77 mg/dl (range, 0.7-17). Peripheral edema was present in 62% of patients.

**Pathologic features**

On LM, the glomerular alterations were heterogeneous, with the majority of biopsies displaying variable degrees of endocapillary hypercellularity and duplication of the GBM. The most common pattern of glomerular injury, seen in 57% of cases was membranoproliferative glomerulonephritis characterized by diffuse and global duplication of the GBM with mesangial cell interposition and mesangial expansion by increased mesangial cell number and matrix. Most of these cases also showed
endocapillary hypercellularity and some exhibited segmental membranous features. The second most common pattern, seen in 35% of cases, was endocapillary proliferative glomerulonephritis, characterized by endocapillary hypercellularity and leukocyte infiltration causing luminal occlusion. Some of these cases had associated segmental membranoproliferative features, neutrophil infiltration, or segmental membranous features. The third histological pattern, seen in 5% of cases only, was predominantly membranous glomerulonephritis characterized by GBM thickening and global subepithelial deposits. The fourth and rarest pattern, observed in 3% of cases, was pure mesangial proliferative glomerulonephritis. Crescents were present in 1/3 of cases, affecting a mean of 20% of glomeruli; in 5% of cases crescents involved ≥ 50% of glomeruli.

By IF, deposits were seen exclusively in the glomeruli, localized mainly to the glomerular capillary wall and mesangium, and generally had a granular texture. IgG was the only immunoglobulin deposited. There was light chain isotype restriction, with sole positivity for kappa in 73% of cases and sole positivity for lambda in 27% of cases. There was glomerular co-deposition of C3 in almost all cases and C1q in 2/3 of cases. Staining for IgG1-4 subclasses showed monotypic deposits, including IgG1 (29% of cases), IgG2 (3% of cases), and IgG3 (68% of cases). No case showed positivity for IgG4.

On EM, the deposits were confined to the glomerular compartment, present primarily in the mesangium and subendothelial space. Subepithelial deposits were less frequent, seen in 57% of patients, and were segmental in most cases.

In 70% of cases, the electron dense deposits had a finely granular texture throughout, without substructure, resembling immune-complex type glomerulonephritis. In the remaining 30% of cases, the deposits were mostly granular, but with focally variegated texture. Rarely, ill-defined fibrils measuring <12 nm in diameter and focal organization into lattice-like arrays with a periodicity of 15 nm were seen involving a portion of otherwise granular deposits.

**Treatment and outcome**

Most patients were treated with steroids alone or in combination with other immunosuppressive agents, whereas some were treated with renin angiotensin system
blockade alone. Prognosis was variable. Follow-up (mean 30.3 months) was available in 32 patients, of whom 37.5% had complete or partial recovery, 37.5% had persistent renal dysfunction, and 21.9% progressed to ESRD. Five patients (4 with ESRD and 1 with partial recovery) died. None of the patients lacking M-spikes on SPEP/UPEP at presentation subsequently developed M-spike or MM during the follow-up period (up to 114 months), and none of those with M-spikes at presentation subsequently developed MM or lymphoma.

**Etiology and pathogenesis**

The pathogenesis of PGNMID remains elusive. The absence of underlying infectious, autoimmune, or other systemic disease in the vast majority of 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 as a free, noncomplexed immunoglobulin, which has the ability to aggregate to form definable dense deposits. Because up to 2/3 of patients have no detectable M protein (by standard SPEP/UPEP/IFE) even after long follow-up, in these cases we propose that this unique glomerulonephritis may arise in the course of normal immune responses. It is possible that during an immune response (to extrinsic or intrinsic antigens), a clone of B-cells proliferates and produces a monoclonal IgG molecule (particularly IgG3) with 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 in by SPEP/UPEP/IFE due to its high avidity for the glomeruli and rapid aggregability favored by its intrinsic physical properties and glomerular sieving itself.

Human IgG is divided into four subclasses that differ in their heavy chain structure, molecular weight, concentration in the serum, isoelectric point (pI), and immunogenicity. Of the 4 subclasses, IgG3, which comprises only 8% of IgG in the circulation, has several properties that allow it to be intrinsically “nephritogenic” (11, 12). (1) It is the most positively charged subclass (pI, 8.2-9.0), favoring affinity for
intrinsic anionic sites in the glomerular capillary wall. (2) It has the highest molecular weight (170,000 Dalton), making it more size-restricted by the glomerular filtration barrier. Thus, in the course of filtration, the intracapillary concentration of circulating IgG3 would be predicted to rise, promoting the potential for intraglomerular aggregation. (3) In fact, IgG3 has the unique physicochemical property of self-aggregability via Fc-Fc interactions and is known to be selectively enriched in murine and human cryoglobulinemia, murine lupus nephritis (13, 14, 2) and human IgG myeloma hyperviscosity syndrome (12). (4) It has the greatest complement fixing capacity, which in turn could activate downstream inflammatory mediators that promote glomerular leukocyte infiltration and proliferation, leading to glomerulonephritis.

These special properties of IgG3 may explain the predominance of this relatively uncommon serum subtype in patients with PGNMID. Monoclonal IgG3 was identified in the glomeruli of two-thirds of patients, particularly those without detectable M-spikes, and was accompanied by co-deposition of C3 in all patients and by hypocomplementemia in one-third of patients. Glomerular C3 activation and resultant hypocomplementemia are also known to occur in other glomerular diseases associated with monoclonal IgG3 deposition such as type 1 cryoglobulinemic glomerulonephritis and IT (2, 3), attesting to its ability to activate complement even in the absence of circulating immune complexes.

In contrast to heavy chain deposition disease in which the CH1 constant domain is deleted, using monoclonal antibodies to epitopes of the constant domains of IgG heavy chains, we found no detectable deletion in any of the constant domains in PGNMID (4). The intact CH2 domain is essential for complement fixation. Amino acid sequencing of glomerular deposits in PGNMID is needed to determine whether there are unique amino acid substitutions in the heavy or light chains that may increase the pI or hydrophobicity of IgG molecules, which could promote the propensity for self-aggregation and glomerular deposition, as has been reported in Randall-type light chain deposition disease (15).

**Conclusions**
PGNMID is a novel form of glomerulonephritis that mimics immune-complex type glomerulonephritis on LM and EM. However, by IF, the glomerular deposits are monoclonal, staining for a single light chain isotype and a single gamma heavy chain subclass, most commonly IgG3 kappa. Despite the monoclonality, few patients have a detectable serum M-spike, and hematologic malignancy is rare. Furthermore, PGNMID does not appear to represent a premalignant condition. The disease affects adults and is 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.

References:


**PGNMID: Brief bullet points (Renal #3 – Nasr)**

1- PGNMID is a novel form of glomerular injury related to monoclonal IgG deposition, most commonly IgG3κ.

2- It affects adults and is more common in females. Only a quarter of patients have detectable M spike and hematologic malignancy is rare. Renal presentation includes nephrotic-range proteinuria and hematuria with or without renal insufficiency.

3- On IF, the glomerular deposits are monoclonal, staining for a single light chain isotype and a single gamma heavy chain subclass. However, LM exhibits endocapillary proliferative or membranoproliferative GN and EM reveals mostly granular electron dense deposits, mimicking ordinary immune-complex GN.

4- Prognosis is variable with close to a fourth of patients progressing to ESRD.

5- Pathogenesis remains elusive. Deposition of monoclonal IgG as a free, noncomplexed immunoglobulin, which has the ability to aggregate to form definable dense deposits is favored.
Key words Renal #2 - Nasr

PGNMID
Proliferative glomerulonephritis
Membranoproliferative glomerulonephritis
Monoclonal IgG deposits
IgG3