Seeing the light (chains): a paradigm shift in PGNMID

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Proliferative glomerulonephritis with monoclonal Ig deposits was originally defined by glomerular immunostaining with single Ig heavy and light chain subclasses; however, its true monoclonality has been challenged because of low detection of monoclonal paraproteins. Using highly sensitive and specific methods, investigators now provide strong evidence against monoclonality in most proliferative glomerulonephritis with monoclonal Ig deposits cases, findings that challenge inclusion of this disorder as a monoclonal gammopathy of renal significance and have potentially important therapeutic implications.

Kidney International (2025) **108,** 996–998; https://doi.org/10.1016/j.kint.2025.09.018

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Proliferative glomerulonephritis with monoclonal Ig deposits (PGNMID) is a rare immune-complex–mediated glomerulonephritis with heterogeneous light microscopic features, but unified by a common pattern of immunofluorescence (IF) staining originally defined as monoclonal Ig deposits, most commonly IgG, and a single light chain (LC) subclass.[1] Although PGNMID is currently included as an entity of monoclonal gammopathy of renal significance (MGRS),[2] detection rates of a circulating paraprotein are universally and surprisingly low, and identification of the originating clonal disorder is even rarer.[3] For these reasons, and reports of PGNMID in pediatric populations,[4] the true monoclonal nature of the glomerular deposits in PGNMID has been challenged for some time.

In this issue of *Kidney International*, investigators from France and the Mayo Clinic set out to meet this challenge, reporting on a large, well-characterized cohort of patients with PGNMID with detailed clinical and demographic data and thorough conventional hematologic evaluation.[5] Unique to this study, however, was their ability to perform a more comprehensive evaluation using their growing arsenal of highly sophisticated and specialized assays, which, in addition to laser-capture microdissection and mass spectroscopy, now includes highly sensitive high-throughput Ig repertoire sequencing assay from bone marrow mRNA (rapid amplification of cDNA ends repertoire sequencing [RACE-Rep-Seq]) and new IF techniques to query the monoclonality of the glomerular deposits.

Despite its heterogeneity of pathologic features, the diagnosis of PGNMID is relatively straightforward. Diagnosis hinges on IF or immunohistochemical staining, which demonstrates a monotypic Ig (usually an IgG and most frequently IgG3), and a single LC isotype, although less common PGNMID subtypes, including IgM, IgA, and LC only, have also been reported.[3] The seemingly monoclonal nature of the deposits would imply the presence of a circulating paraprotein originating from a clonal disorder, and yet routine hematologic evaluation is positive in only up to 30% of cases.[3] The likelihood of identifying a circulating monoclonal Ig reportedly varies with PGNMID subtype, but the rarity of the disease and small case numbers in previous studies likely affect the statistical significance of these observations. In the current study of Javaugue *et al.*,[5] a large, multicenter cohort of 56 patients allowed the investigators to examine the hematologic characteristics of the different PGNMID subtypes and reveal any relative differences in monoclonal Ig detection rates. Most importantly, this identified a subset of confirmed clone-negative PGNMID cases that could then be further characterized, to determine if the glomerular deposits were truly monoclonal or not, thus providing clues to pathogenic mechanisms.

Not surprisingly, 73% (41 of 56) of PGNMID cases were PGNMID-IgG3, of which 80% (33 of 41) were κ LC isotype and 20% were λ. This equated to approximately 60% (31 of 56) of all cases exhibiting IgG3-κ staining. Sixteen of the patients with IgG3-κ PGNMID underwent serologic testing for IgG subtype levels and were all normal, suggesting that the IgG3 was selectively being deposited in the glomeruli, and none met hematological or clinical criteria for multiple myeloma or lymphoma. Blood flow cytometry was negative in all 16 patients, whereas bone marrow flow cytometry detected plasma cell clones in only 2 of these IgG3-κ cases. Interestingly, one of the latter showed discordant λ production despite the glomerular κ deposits, whereas the other was concordant. RACE-Rep-Seq analysis on bone marrow aspirates was performed and shown to be more sensitive than flow cytometry for detecting pathogenic clones (13 of 56 vs. 7 of 56; $P = 0.2$) in the full cohort of patients with PGNMID. Nonetheless, using the former technique detection of a clone matching the glomerular deposits was found in only 9.8% (4 of 41) of the PGNMID-IgG3 cases (6% [2 of 33] in PGNMID-IgG3κ and 25% [2 of 8] in PGNMID-IgG3λ), compared with 60% (9 of 15) positive clone detection in all

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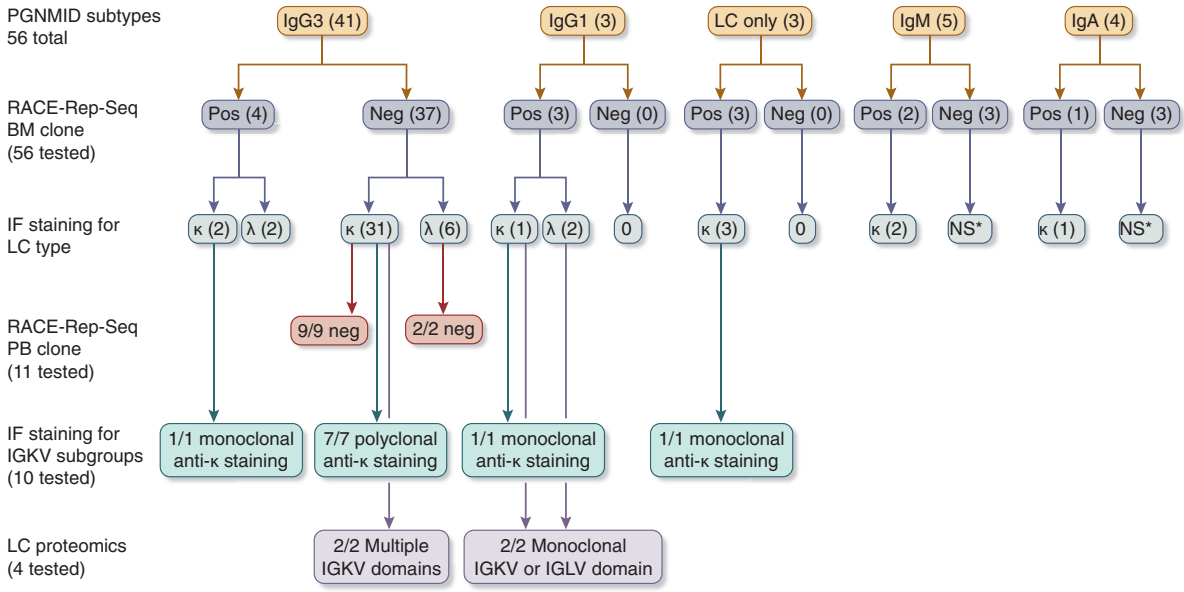

Figure 1 | Summary of clonal sequencing analysis, light chain (LC) clonality, and proteomic studies in patients with proliferative glomerulonephritis with monoclonal Ig deposits (PGNMID). IgG3 was the most abundant Ig subtype found in patients with PGNMID (73%), most of which contained the κ LC isotype (80%). Rapid amplification of cDNA ends repertoire sequencing (RACE-Rep-Seq) analysis of bone marrow (BM) failed to reveal a matching clone in 90% of the patients with PGNMID IgG3, all of whom were also negative (Neg) for circulating peripheral blood clones (PB) by RACE-Rep-Seq. Immunofluorescence (IF) staining in the kidney biopsies demonstrated monoclonality for either κ or λ LC in selected cases that were clone positive (Pos) by RACE-Rep-Seq but demonstrated LC polyclonality in all tested patients with clone-negative IgG3-κ. Proteomic studies using laser capture microdissection and mass spectroscopy confirmed the presence of peptides from a single LC variable region in the 2 clone-positive IgG1-κ and IgG1-λ cases tested, whereas both clone-negative IgG3-κ cases demonstrated peptides from multiple LC variable regions. IGKV, κ light chain variable region; IGLV, λ light chain variable region.

remaining, non-IgG3 PGNMID cases. Notably, RACE-Rep-Seq analysis failed to detect a pathogenic clone from the peripheral blood in all of the PGNMID-IgG3 cases. These findings, summarized in Figure 1, suggest that the low incidence of clonal disorders that is widely reported in PGNMID can be largely explained by the prevalence of IgG3-κ and IgG3-λ, and that most PGNMID cases may not be MGRS lesions at all.

With the previously suspected association to MGRS now in question, the investigators sought to further challenge the concept that the glomerular deposits in PGNMID are truly monoclonal. They compared the deposits of RACE-Rep-Seq clone-negative cases with the deposits in cases with detectable clones, including the 1 clone-positive IgG3-κ specimen with concordant glomerular deposits. Using noncommercially available monoclonal antibodies against 4 different κ light chain variable (IGKV) regions, IGKV1, IGKV2, IGKV3, and IGKV4, indirect immunofluorescence revealed positive staining for all 4 antibodies in the deposits from all of the clone-negative IgG3-κ cases, compared with subgroup restriction in the clone-positive cases that largely matched the clonotypes from the sequencing data derived from the RACE-Rep-Seq assays. Similarly, subgroup-restricted glomerular staining and sequence concordance was confirmed from all true MGRS cases tested, whereas polyclonal glomerulonephritis cases displayed pan-positive staining with all 4 κ LC subgroups. Proteomic analysis of glomeruli using laser-capture mass spectroscopy from isolated cases also identified increased peptides corresponding to a single IGKV domain or λ light chain variable region (IGLV) domain, which matched the RACE-Rep-Seq sequences from clone-positive cases, whereas clone-negative IgG3-κ cases failed to show increased peptide isolation. These studies, also summarized in Figure 1, provide solid evidence that the glomerular deposits in the clone-negative PGNMID-IgG3κ cases are not monoclonal, but rather monotypic, in nature.

These data challenge the previously held belief that PGNMID cases should be considered lesions within the spectrum of MGRS. Although concern for a paraprotein-mediated process may justifiably arise when routine IF demonstrates glomerular staining for a single Ig heavy chain and/or single LC, this finding does not necessarily indicate clonality. Routine IF studies for κ and λ LCs may not be sufficiently sensitive to detect oligoclonality or polyclonality, which may be uncovered using specialized methods, such as the IF studies for different κ LC variable regions noted above or high-resolution confocal IF microscopy, which routinely found the presence of κ LCs in cases of IgA nephropathy showing only IgA-λ staining by routine IF.[6] Indeed, as stated by Javaugue *et al.*,[5] "monotypic

deposits do not always indicate monoclonality," and the clinical implications from this body of work are profound.

A diagnosis of PGNMID should prompt a thorough hematologic evaluation, but the data from this study of Javaugue *et al.*[5] show that conventional investigational methods, such as flow cytometry, serum and urine protein electrophoresis and immunofixation, and even pathologic evaluation of bone marrow biopsies, may lack the sensitivity to detect a low-level clone. Moreover, routine IF staining showing LC restriction coupled with immunostaining demonstrating a single heavy chain subclass may lack the specificity to distinguish a monoclonal from an oligoclonal or subtle polyclonal process, leading to misdiagnosis as an MGRS disease and potential exposure to toxic chemotherapy or immunosuppressive regimens that hold their own infectious and malignant risks. Although the investigators were able to use the highly specialized assays presented in their article,[5] many centers do not currently have access to such methods, and the investigational antibodies used for their IF studies are not yet commercially available, raising the question as to how this will affect future kidney biopsy-based diagnosis and even standard of care for patients. This is of particular concern in pediatric patients with PGNMID, in whom an MGRS diagnosis would seem unlikely, and complete characterization of the glomerular deposits would be of great interest.

Also unknown are the pathogenic mechanisms that are driving cases of PGNMID in which an injurious paraprotein is not detectable. For example, despite the fact that IgG3 is the most abundant isotype in such cases and is known to be a strong activator of the classic pathway of complement, clone-negative patients in the cohort of Javaugue *et al.*,[5] many of whom had IgG3 glomerular deposits, were most often not hypocomplementemic, with one-third of biopsies being negative for glomerular C1q staining. It has been postulated that there may be specific physiochemical properties of IgG3 that may predispose this to deposit and accumulate in glomeruli, although the precise mechanism is unknown.[1] Moreover, exposure to a specific viral or bacterial antigen may trigger an *oligoclonal* amplification of one/few isolated IgG3 clonotypes, resulting in a robust overrepresentation of these few clones as part of the immune response, and may explain why many PGNMID cases have been associated with a preceding infection.[1,3] A similar mechanism has been described in other diseases, such as neurologic autoimmune and inflammatory diseases, where oligoclonal bands can be observed in the cerebrospinal fluid.[7] Changing patterns of oligoclonal expansion are a normal part in the evolution of immune responses and may result in the emergence of new clones in response to different antigenic triggers or underlying autoimmune diseases, for example.[8] This may, in part, explain the fluidity of glomerular IF patterns over time, including shifts between polyclonal and monoclonal, reported from consecutive biopsies from the same patient.[9]

Paradigm shifts have occurred in our understanding of other glomerular diseases (namely, with the association of alternative complement pathway abnormalities in C3 glomerulopathy and specific antigen-driven triggers in membranous nephropathy). The study of Javaugue *et al.*[5] provides the basis for a new paradigm shift in our understanding of the pathogenesis of PGNMID, revealing the existence of likely non-MGRS PGNMID cases that may be better described as "proliferative glomerulonephritis with *monotypic* (rather than monoclonal) deposits."

DISCLOSURE

All the authors declared no competing interests.

REFERENCES

1. Nasr SH, Satoskar A, Markowitz GS, et al. Proliferative glomerulonephritis with monoclonal IgG deposits. *J Am Soc Nephrol*. 2009;20:2055–2064.
2. Nasr SH, Royal V, Best Rocha A, et al. Renal Pathology Society/International Kidney and Monoclonal Gammopathy Research Group consensus on pathologic definitions and terminology of monoclonal gammopathy-associated kidney lesions. *Kidney Int*. 2025;108:184–193.
3. Gudura TT, Sawaf H, Ogbenna R, et al. The clinical and pathological characteristics of patients with proliferative glomerulonephritis with monoclonal immunoglobulin deposits. *Glomerular Dis*. 2025;5:142–150.
4. Miller P, Xiao AY, Kung VL, et al. Progression of proliferative glomerulonephritis with monoclonal IgG deposits in pediatric patients. *Pediatr Nephrol*. 2021;36:927–937.
5. Javaugue V, Pascal V, Nasr SH, et al. Revisiting proliferative glomerulonephritis with monoclonal immunoglobulin deposits through immunoglobulin repertoire sequencing. *Kidney Int*. 2025;108:1146–1157.
6. Rizk DV, Novak L, Hall SD, et al. Colocalization of IgG and IgA heavy chains with kappa and lambda light chains in glomerular deposits of IgA nephropathy patients using high-resolution confocal microscopy and correlation with Oxford MEST-C scores. *J Clin Med*. 2023;12:7361.
7. Ren J, Wang J, Liu R, et al. CSF oligoclonal bands in neurological diseases besides CNS inflammatory demyelinating disorders. *BMJ Neurol Open*. 2025;7:e000912.
8. Kolovou K, Laskari K, Roumelioti M, et al. B-cell oligoclonal expansions in renal tissue of patients with immune-mediated glomerular disease. *Clin Immunol*. 2020;217:108488.
9. Satoskar AA, Ibrahim DY, Brodsky SV, et al. Membranoproliferative glomerulonephritis with changing immunofluorescence pattern. *Kidney Int Rep*. 2022;7:1123–1127.