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The Uncertainty Puzzle of Monoclonal Gammopathy of Renal Significance Without Detectable Clones

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Although the nephrotoxic potential of the light chains was demonstrated in a report by Smithline *et al.*[1] as early as 1976 in a patient who did not meet the criteria for malignancy. It was not until recently when the international kidney and monoclonal gammopathy research group officially designated the term monoclonal gammopathy of renal significance (MGRS) and defined it as any clonal disorder (plasma cell or B cell) that does not fulfill the criteria for cancer yet produces a nephrotoxic monoclonal immunoglobulin that directly or indirectly results in kidney disease or injury.[2] The treatment of MGRS-related renal disorders primarily revolves around identifying and treating involved clones responsible for producing nephrotoxic monoclonal immunoglobulin using clone-directed therapy.[3] However, in certain instances, a pathologic clone or even monoclonal protein cannot be detected, creating a clinical dilemma for clinicians.

Among all the MGRS-related renal disorders, proliferative glomerulonephritis with monoclonal Immunoglobulin deposits (PGNMIDs) is distinctively associated with the inability to identify nephropathic clone. The previously reported data suggests very high monoclonal protein detection rates with immunoglobulin-related amyloidosis (99%), Randall-type monoclonal Immunoglobulin Deposition Disease (100%), and light chain proximal tubulopathy (97%), while only 30% with PGNMID.[2] In line with previous data, the authors identified 29 patients with MGRS with undetectable clones and monoclonal protein in this single-center, retrospective cohort study.[4] All but one of these patients were diagnosed with PGNMID, while one with heavy chain deposition disease.

Considering the rarity of this condition, minimal data exists to date. Nasr *et al.*,[5] the same group that initially described PGNMID in 2004, reported 27 of 37 patients (70%) of PGNMID with no identifiable dysproteinemia. Bhutani *et al.*[S1] reported 30 of 40 (75%) PGNMID patients without detectable clone. Recently, Zhou *et al.*[6] described 64 patients with PGNMID, of which 45 (70%) were with undetectable clone. Other reports were even smaller (Guiard *et al.*[7] $n = 13$, Gumber *et al.*[8] $n = 10$, Gowda *et al.*[9] $n = 6$, and Kousios *et al.*[S2] $n = 6$). None of these studies were primarily focused on patients with undetectable clone. The current study by Terashita *et al.*[4] is an extensive report, including 29 patients with MGRS with undetectable clone, and uniquely focused on identifying outcomes based on different novel clone-directed therapies (i.e., Rituximab-based vs. Bortezomib-based regimens). The authors sought to investigate the correlations between treatment regimens and kidney outcomes, defined by proteinuria and estimated glomerular filtration rate, and the impact of repeat kidney biopsy.

The authors have commendably divided the groups into conservative therapy, plasma cell clone (PC)-directed therapy, lymphocytic clone (LC)-directed therapy, and non-clone-directed therapy. The rationale being many nephrologists, when faced with the dilemma of MGRS with an undetectable clone, are not certain whether to attempt conservative therapy versus attempt to treat themselves (Rituximab-based therapy) versus insist hematologists to initiate treatment (plasma cell-directed therapy). Hence, this study can significantly help make such a decision.

"Conservative therapy" referred to the absence of any specific treatment for MGRS and included renin-angiotensin-aldosterone

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system inhibitors. Overall, patients chosen for conservative therapy had significantly lower median proteinuria than those who received clone-directed therapy. Of 8 patients initially assigned to conservative therapy, 2 patients were switched to PC-clone directed therapy after 1 year and 6 patients were followed to report the outcomes. Of these, 2 patients had initial proteinuria < 0.5 g/g Cr, 2 achieved complete response (CR), and 2 were non-responders. These findings are similar to previously reported data by Nasr *et al.*[5] that of 9 patients, 2 had CR, 2 had partial response, and 5 had progressive renal dysfunction, including 1 progressing to end-stage renal disease. Here, it is vital to know that if left untreated, most patients progress to end-stage renal disease. However, it is also essential to note that spontaneous remission of proteinuria is possible, even in patients with nephrotic range proteinuria, as seen in one patient in this study who achieved CR. As PGNMID is a kidney-limited disease and considering the potential toxicity associated with clone-directed therapy, it may be reasonable to evaluate which patients can be considered for a trial of conservative therapy (i.e., stable renal function) prior to initiating empiric clone-directed therapy.

Non-clone-directed therapy included glucocorticoids, oral cyclophosphamide, and mycophenolate mofetil. Of 8 patients initially assigned to non-clone-directed therapy, 6 were switched to clone-directed therapy during follow-up because of failure to respond, and only 2 patients remained in this category and achieved complete remission using a steroid/cyclophosphamide-based regimen. These findings of poorer response with non-clone directed therapy were also shown in the report of 64 patients with PGNMID by Zhou *et al.*,[6] where they noticed the lowest response rate in the steroid group (25 of 26 patients had undetectable clone) compared to the groups receiving clone directed therapy, even when patients assigned to steroids had lower mean proteinuria and serum creatinine compared to the other groups.[6] Based on the currently available data and understanding of the pathophysiology, clone-directed therapy remains the cornerstone of the treatment of MGRS with undetectable clone.

Clone-directed therapy included PC- and LC-directed therapy. Both the groups had almost similar degrees of renal dysfunction and proteinuria. Interestingly, an almost equal proportion of patients achieved partial or better renal response in each group, 7 of 13 (53%) in PC-directed therapy and 4 of 8 (50%) in the LC-directed therapy group with a median duration of follow-up of 55 months. In the previous report by Gumber *et al.*[8] with 10 patients with undetectable clone, 8 received LC-directed therapy of which 6 (75%) achieved partial or better renal response in comparison to 1 patient who received PC-directed therapy achieved partial response. The overall partial or better renal response rate to clone-directed therapy (Bortezomib/Rituximab group) was almost 60% in the study by Zhou *et al.*.[6] In a recent open-label phase 2 trial using 6 months of daratumumab in 10 patients with PGNMID (All without detectable clones in bone marrow biopsy), 4 had CR and 6 had partial response within one year (an overall response rate of 100%).[S3] This may suggest daratumumab may be a promising single-agent option when it comes to choosing an empiric clone-directed therapy. However, it should be noted that the degree of interstitial fibrosis and tubular atrophy (IFTA) was very low (mean 12.5%). In developing countries where cost may be a limiting factor for using bortezomib or daratumumab, immunomodulatory drugs (i.e., thalidomide or lenalidomide) in combination with dexamethasone may be acceptable alternatives with close attention to adverse events and renal dose adjustments.[6]

Due to a limited number of patients and lack of data on individual patients with IFTA, it is difficult to conclude if one regimen is preferable over the other when it comes to choosing an empiric clone-directed therapy in patients with MGRS without detectable clone. The rationale for why some patients are started on LC-directed therapy versus PC-directed therapy derives from previous observations from Gumber *et al.*[8] and Bhutani *et al.*[S1] Both the groups witnessed almost 50% chances of detecting either a PC or LC among the patients where clones were identified in bone marrow examination of patients with PGNMID ($n = 3$ with PC clone vs. $n = 3$ with LC clone in Gumber *et al.*[8] and $n = 6$ with PC clone versus $n = 4$ with LC clone in Bhutani *et al.*[S1]). Among the patients with IgM monoclonal protein in the blood, urine, or IgM deposit in the kidney without detectable clone, a Rituximab-based regimen may be preferred as most IgM-producing cells are CD20 positive. Clone-directed therapy in patients without detectable clones is guided by renal parameters such as proteinuria and kidney function instead of the hematologic response. If no favorable response is seen after 2 or 3 cycles, therapy should be changed to target a different clone.[3] The overall treatment of PGNMID without detectable can be approached by the proposed algorithm in Figure 1.

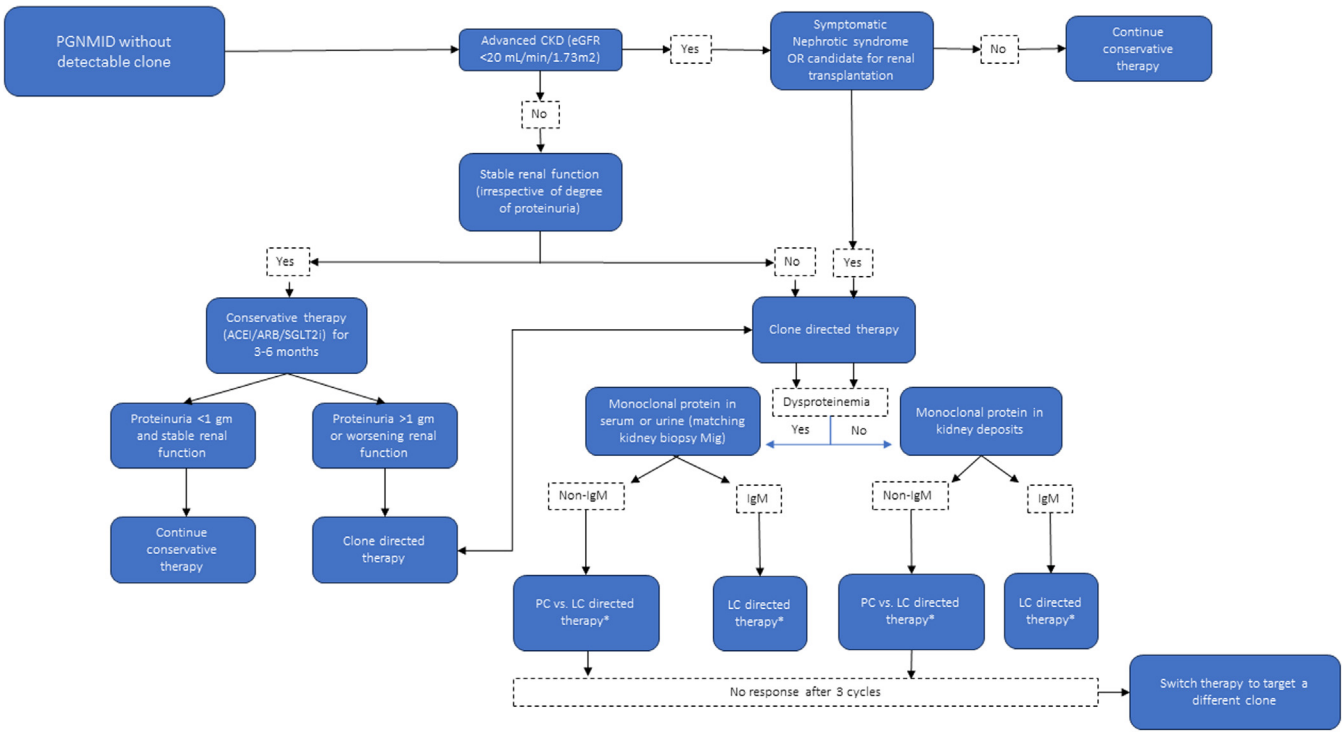

Figure 1. Treatment of proliferative glomerulonephritis with monoclonal Immunoglobulin deposits (PGNMID) without detectable clone. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; IgM, immunoglobulin M; LC, Lymphocytic clone; Mig, monoclonal immunoglobulin; PC, plasma cell clone; SGLT2i, sodium glucose cotransporter 2 inhibitor. *Plasma cell clone directed therapy can include single agent daratumumab versus bortezomib based regimen. Lymphocytic clone directed therapy includes Rituximab. In developing countries where cost may be a limiting factor for using bortezomib or daratumumab, immunomodulatory drugs (i.e., thalidomide, lenalidomide) in combination with dexamethasone may be acceptable alternative. Treatment should be selected and administered in consultation with a hematologist or oncologist experienced in the use of antimyeloma and antilymphoma agents.

Importance of IFTA

Among the patients with low IFTA (<25%), partial or better renal response was seen in almost 60% (10 of 17) of the patients, whereas a higher degree of IFTA was associated with worse outcomes. Notably, 2 patients who achieved CR with conservative therapy had a low IFTA.

Role of Repeat Kidney Biopsy

Regarding the role of repeat biopsies, the authors noticed that 7 of 29 patients had received repeat kidney biopsies. Repeat kidney biopsies may be helpful as they may demonstrate the disappearance of deposits (response to treatment), worsening activity (indication to change to a different clone-directed therapy), and increased IFTA (consideration to withdraw treatment).

Outcomes in Kidney Transplants

The authors described 2 patients with renal transplants, both diagnosed almost 7 years after the transplantation. Although one patient died from a simultaneous diagnosis of Merkel cell cancer, the second patient with PGNMID without detectable clone was treated conservatively without any change in immunosuppression and ended up developing end-stage renal disease, requiring a second renal transplant 8 years after initial transplantation.

Conclusion

1. PGNMID is distinctively associated with the inability to identify nephropathic clone.
2. Most patients, if left untreated, progress to end-stage renal disease.
3. Spontaneous remission of proteinuria is possible, even in patients with nephrotic range proteinuria. Trial of conservative therapy can be considered for selected patients (i.e., stable renal function, low IFTA).
4. Clone-directed therapy remains the cornerstone of MGRS with undetectable clone.
5. The selection of empiric lymphocytic versus plasma cell clone-directed therapy may have a similar response probability. However, Rituximab-based regimen may be preferred for patients with IgM dysproteinemia or IgM deposit in the kidney.
6. If feasible, single-agent daratumumab may be a promising agent for treating PGNMID without a detectable clone. Further data about the effect of daratumumab in PGNMID are desperately needed.

7. IMiD may be a reasonable alternative in developing countries where bortezomib or daratumumab are unavailable due to cost.
8. A lower degree of IFTA is associated with better renal outcomes, while repeat kidney biopsy may help determine change or withdrawal of clone-directed therapy.

DISCLOSURE

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SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Supplementary References.

REFERENCES

1. Smithline N, Kassirer JP, Cohen JJ. Light-chain nephropathy. Renal tubular dysfunction associated with light-chain proteinuria. *N Engl J Med*. 1976;294:71–74. https://doi.org/10.1056/NEJM197601082940202
2. Leung N, Bridoux F, Batuman V, et al. The evaluation of monoclonal gammopathy of renal significance: a consensus report of the International Kidney and Monoclonal Gammopathy Research Group. *Nat Rev Nephrol*. 2019;15:45–59. https://doi.org/10.1038/s41581-018-0077-4
3. Leung N, Bridoux F, Nasr SH. Monoclonal gammopathy of renal significance. *N Engl J Med*. 2021;384:1931–1941. https://doi.org/10.1056/NEJMra1810907
4. Terashita M, Selamet U, Midha S, et al. Clinical outcomes of monoclonal gammopathy of renal significance without detectable clones. *Kidney Int Rep*. 2023;8:2765–2777. https://doi.org/10.1016/j.ekir.2023.09.022
5. Nasr SH, Satoskar A, Markowitz GS, et al. Proliferative glomerulonephritis with monoclonal IgG deposits. *J Am Soc Nephrol*. 2009;20:2055–2064. https://doi.org/10.1681/ASN.2009010110
6. Zhou H, Li M, Zeng C, Chen Z, Zhang T, Cheng Z. Efficacy of immunomodulatory drugs in combination with dexamethasone in proliferative glomerulonephritis with monoclonal immunoglobulin deposits. *Kidney Int Rep*. 2022;7:2166–2175. https://doi.org/10.1016/j.ekir.2022.07.009
7. Guiard E, Karras A, Plaisier E, et al. Patterns of noncryoglobulinemic glomerulonephritis with monoclonal Ig deposits: correlation with IgG subclass and response to rituximab. *Clin J Am Soc Nephrol*. 2011;6:1609–1616. https://doi.org/10.2215/CJN.10611110
8. Gumber R, Cohen JB, Palmer MB, et al. A clone-directed approach may improve diagnosis and treatment of proliferative glomerulonephritis with monoclonal immunoglobulin deposits. *Kidney Int*. 2018;94:199–205. https://doi.org/10.1016/j.kint.2018.02.020
9. Gowda KK, Nada R, Ramachandran R, et al. Proliferative glomerulonephritis with monoclonal immunoglobulin deposition disease: the utility of routine staining with immunoglobulin light chains. *Indian J Nephrol*. 2015;25:344–348. https://doi.org/10.4103/0971