Glomerular Diseases

Clinical Nephrology

Glomerular Dis 2025;5:142–150
DOI: 10.1159/000544864

Received: December 16, 2024
Accepted: February 9, 2025
Published online: February 20, 2025

The Clinical and Pathological Characteristics of Patients with Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits

Tariku T. Gudura[a] Hanny Sawaf[a] Randy Ogbenna[b] Ali Mehdi[a]
Leal Herlitz[c] Surafel K. Gebreselassie[d] Shane A. Bobart[d, e]

[a]Department of Kidney Medicine, Cleveland Clinic Foundation, Cleveland, OH, USA; [b]Department of Medicine, Cleveland Clinic Foundation, Cleveland, OH, USA; [c]Department of Pathology, Cleveland Clinic Foundation, Cleveland, OH, USA; [d]Department of Kidney Medicine, Cleveland Clinic Florida, Weston, FL, USA; [e]Division of Nephrology, Hypertension and Transplantation, Department of Medicine, Weill Cornell Medical College, Houston Methodist Hospital, Houston, TX, USA

Keywords
Kidney biopsy · Proliferative glomerulonephritis with monoclonal immunoglobulin deposits

Abstract
Introduction: Proliferative glomerulonephritis with monoclonal immunoglobin (Ig) deposits (PGNMID) is a rare form of kidney disease associated with low monoclonal protein detection rates and poor renal outcomes. The lack of effective therapy is partly due to limited data and understanding of its pathogenesis. ***Methods:*** We conducted a retrospective analysis of 18 patients with PGNMID from the Cleveland Clinic Kidney Biopsy Epidemiology Project from January 2015 to March 2023. ***Results:*** PGNMID was more predominant among males (67%), and whites (78%), with median age of 60 years. Over 2/3rd of patients presented with hypertension, renal insufficiency, and hematuria, while 26% of patients had nephrotic syndrome. Mean serum creatinine and proteinuria at biopsy were 3.2 mg/dL and 4.3 g/g, respectively. A detectable monoclonal (M) protein was detected in 28% of cases; however, only 3 patients had underlying hematologic disorders (multiple myeloma, CLL, and B-cell lymphoma). An endocapillary hypercellularity/membranoproliferative pattern (72%), IgG/kappa (83%), and IgG3 (56%) were predominant findings on kidney pathology. Eight patients (44%) progressed to end-stage kidney disease (ESKD), with a median onset of 7.5 months after the initial kidney biopsy. While 6 patients achieved complete remission primarily with clone-directed therapy. ***Conclusion:*** Despite monoclonal protein deposition on kidney biopsy, 28% patients with PGNMID had a detectable monoclonal protein. Unlike other forms of paraproteinemic kidney diseases, renal outcomes for patients with PGNMID are poor, with 44% progressing to ESKD (median time 7.5 months) after kidney biopsy in our cohort. Clone-directed therapy to improve outcomes remains the mainstay of treatment, despite the absence of detectable clone in most cases. Thus, further investigation into the pathogenesis of PGNMID is warranted to guide future treatment discovery and clinical trials.

Introduction

Proliferative glomerulonephritis with monoclonal immunoglobin (Ig) deposits (PGNMID) is a rare and poorly understood cause of kidney disease [1]. Based on multiple

karger@karger.com
www.karger.com/gdz

Correspondence to:
Shane A. Bobart, sbobart@houstonmethodist.org

retrospective data reports, the incidence of PGNMID accounts for 0.17–3.7% of native kidney biopsies [2, 3]. PGNMID typically affects whites over the age of 50 years old, with common presentations including kidney dysfunction, hypertension, hematuria, and non-nephrotic to nephrotic range proteinuria [4]. A membranoproliferative pattern of glomerular injury is the most common histologic finding on light microscopy followed by endocapillary, mesangial, and diffuse proliferative patterns [5]. On immunofluorescence (IF), most cases exhibit monotypic IgG3 and kappa; however, other monotypic deposits of IgA, IgM, and lambda light-chain PGNMID are also reported in literature [1]. On electron microscopy, granular deposits without substructure are the most predominant finding.

Despite its establishment as a distinct pattern of injury in the kidney by Nasr et al. [6] in 2004, the pathogenesis of PGNMID remains unclear. It can occur in both the young and elderly, in the setting of malignancy, infection, and is also considered part of the spectrum of monoclonal gammopathy of renal significance (MGRS) [4]. As part of MGRS, PGNMID is thought to arise from the deposition of nephrotoxic monoclonal protein in the glomeruli leading to direct injury. However, only one-third of cases will have detectable monoclonal protein in serum, urine, or bone marrow samples [6, 7]. Clone-directed therapy such as rituximab for CD20 expressing cells or daratumumab for plasma cells-directed therapy may slow the progression of renal disease [8–11].

Overall, there is a paucity of data on this rare condition with poor understanding of the pathogenesis with varying treatment regimens. As a result, renal outcomes for patients with PGNMID remain poor, with 30–40% of patients progressing to end-stage kidney disease (ESKD) in months to a few years [12, 13], highlighting the need for prompt diagnosis and treatment. Given its uncommon nature, we aimed to utilize a large cohort of biopsy proven kidney disease [14], to identify patients with PGNMID and describe their clinical and pathological data, with a goal of adding valuable data to improve the overall understanding of this challenging condition.

Methods

Study Design

This retrospective study was approved with waiver of consent by the Cleveland Clinic Institutional Review Board (IRB# 22-1093). We utilized the Cleveland Clinic Kidney Biopsy Epidemiology Project (CCKBEP) to obtain our cohort of patients with a biopsy proven diagnosis of PGNMID. The CCKBEP is a catalogue of the biopsy diagnoses and clinical and demographic data of all patients who had a kidney biopsy performed/reviewed at the Cleveland Clinic from January 2015 and onward [14].

Kidney Biopsy

All biopsy reports were reviewed by a renal pathologist at the Cleveland Clinic and processed according to the standardized protocol for light microscopy (hematoxylin and eosin, periodic acid-Schiff, trichrome, and Jones stains) and IF (IgG, IgA, IgM, C3, C1q, kappa, lambda, and fibrinogen) and IgG subtyping. Pronase digestion was used when necessary to uncover masked immunoglobulins. The presence of interstitial fibrosis and tubular atrophy were graded using the total renal chronicity score (TRCS) based on the amount of renal cortex involved as absent/insignificant (<10%), mild (10%–25%), moderate (26%–50%), or severe (>50%) [15].

For the purposes of this study, the definition of PGNMID on biopsy included positive glomerular staining for monotypic immunoglobulins, positive staining for a single light chain isotype; kappa or lambda by routine IF evaluation with IgG subclass typing when available; EM with granular electron dense deposits, and the pattern on LM was noted if endocapillary proliferative/membranoproliferative, mesangial or other. A typical lesion included in this cohort is seen in Figure 1.

Clinical Parameters

Eighteen patients met pathology criteria and had sufficient data for further analysis. We abstracted demographic, clinical, and laboratory data via retrospective chart review. The following variables were queried and obtained at biopsy: age, race, self-reported sex, presence or absence of hypertension, diabetes, tobacco use, hematuria, anemia, nephrotic syndrome, detectable monoclonal protein, presence of cryoglobulinemia, hepatitis serology, hypocomplementemia, acute kidney injury (using baseline creatinine and creatinine at biopsy), proteinuria (protein creatinine ratio and 24 h urine collection when available), time to ESKD, treatment regimen used. We assessed the presence of the following outcomes at last follow-up: complete remission (CR: proteinuria ≤0.5 g/day with stable/improved renal function), partial remission (PR: >30% reduction in proteinuria, proteinuria ≤3.0 g/day, stable/improved renal function), persistent renal disease (>20% renal function decline/persistence of proteinuria), or progression to ESKD.

Statistical Analysis

Patient characteristics were presented using descriptive statistics, including mean ± SD for continuous variables and percentages for categorical variables.

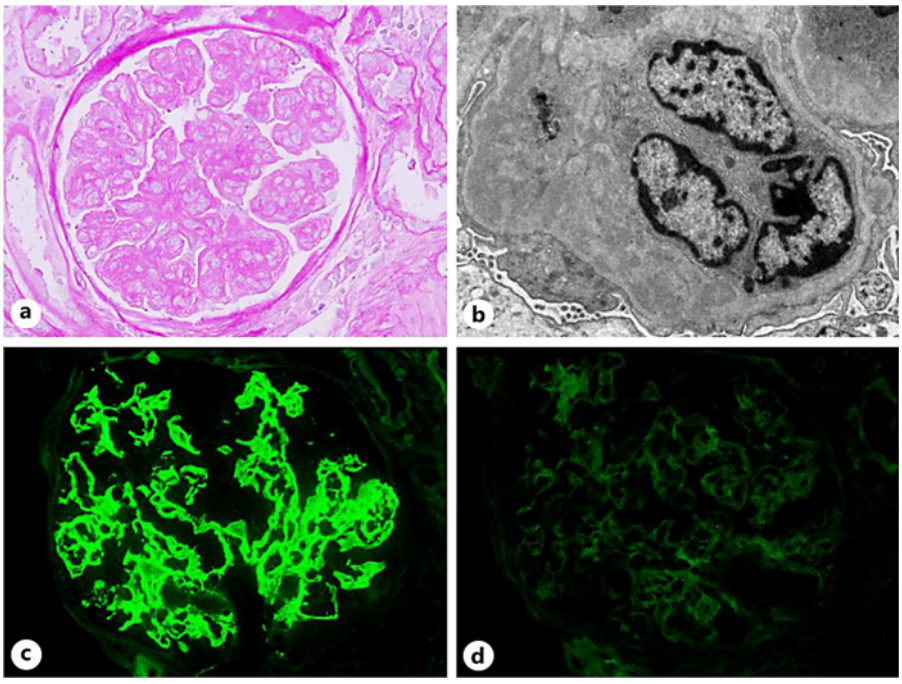

Fig. 1. Characteristic morphologic findings of PGNMID. **a** Periodic Acid Schiff (×400) shows a glomerulus with global endocapillary hypercellularity and extensive double contours of glomerular basement membranes characteristic of a membranoproliferative pattern of injury. **b** Transmission electron microscopy (×4,800 magnification) shows a glomerular capillary with moderately electron dense subendothelial immune-type deposits without evident substructure. IF staining showed strong staining for IgG and kappa (kappa is pictured in (**c**) at ×400) with negative staining for lambda (**d**, ×400). IgG subclass staining was performed and showed strong IgG3 staining (similar to what is pictured in (**c**)), with negative staining for IgG1, IgG2, and IgG4.

Univariate Cox model was performed to explore the potential factors for the event of complete/partial remission. All statistical analyses were conducted using SPSS version 28.0.11.

Results

Clinical Features

Of 4,126 patients with native kidney biopsies in the CCKBEP, a lesion consistent with PGMNID was detected in 34 patients accounting for an incidence of 0.8%. A total of 18 patients are described in the final cohort after excluding those with incomplete data. Males accounted for about 67% of cases while 78% of patients self-reported as white. The median age was 60 years old, with 22% of patients younger than 50 years. The mean serum creatinine and proteinuria at biopsy were 3.2 mg/dL (0.64–9.0) and 4.3 g/g (0–14 g), respectively. Clinical features at kidney biopsy were hypertension (81%), acute kidney injury (72%), hematuria (78%), nephrotic syndrome (26%), and hypocomplementemia (23%). No patient had active hepatitis or positive cryoglobulins at the time of biopsy. A monoclonal protein was detected in 28%, with an underlying malignancy identified in only 17% (3/18) of cases (MM, CLL, and B cell lymphoma) (Table 1). Of the 15 patients who underwent bone marrow biopsy, 12 were negative (online suppl. Table 1; for all online suppl. material, see https://doi.org/10.1159/000544864).

Univariate Cox model revealed that there were only two factors being significantly associated with the event of complete/partial remission, patients with age of greater than 60 were less likely to have complete/partial remission compared to patients with age of equal or less than 60 (HR = 0.13, 95% CI = [0.03–0.68], p value = 0.0156), patients without anemia were more likely to get complete/partial remission compared to patients with anemia (HR = 7.51, 95% CI = [1.47–38.45], p value = 0.0156). There were no other demographic, clinical, and pathological factors being significantly associated with the event of complete/partial remission.

Pathological Findings

On light microscopy, the mean number of glomeruli was 18 (4–58). The most predominant finding on light microscopy was endocapillary hypercellularity/membranoproliferative pattern (72.2%) followed by pure mesangial (28%) and membrano-proliferative lesions/pattern of injury (16%). Two-thirds of patients had a mild total renal chronicity index while only 1 case had a crescent. On IF, 17 patients showed capillary wall granular IgG staining with a mean IgG stain of 2.6 (trace to 3+). IgM was positive in 1 case. Sixteen of 18 cases showed positive C3 on routine IF, with similar intensity of IgG staining. No IgA staining

Table 1. Patient characteristics at biopsy

Patient characteristics	Value (n = 18)
Age, years	60.3±12.8
Race, white	14 (77.8)
Sex, male	12 (66.7)
Hypertension	14 (77.8)
Diabetes	1 (5.6)
Acute kidney injury	13 (72.2)
Hematuria (n = 16)	14 (87.5)
Anemia (n = 18)	11 (61.1)
Nephrotic syndrome	4 (22.2)
Detectable serum monoclonal (M) protein (n = 18)	5 (27.8)
Lymphoma	2 (11.2)
Multiple myeloma	1 (5.6)
Hypocomplementemia (n = 17)	4 (23.5)
History of smoking or tobacco use	9 (50)
Serum creatinine at baseline, mg/dL (n = 17)	2.4±1.6
Serum creatinine at biopsy, mg/dL (n = 17)	3.2±2.6
Baseline eGFR, mL/min per 1.73 m^2 (n = 14)	50.5±27.6
Urine protein to creatinine ratio at biopsy, g/g (n = 14)	4.3±3.7
24-h urine protein at biopsy, g (n = 5)	5.0±5.1
Median time (range) to ESKD from initial biopsy, months	7.5 (1–156)

was present. Kappa light chain restriction was present in 17 of 18 cases while lambda light chain restriction was detected only in 1 case. Among the 13 cases with IgG subclass staining, 10 (77%) had positive staining for IgG3 while 1 case each had IgG1, IgG2, and IgG4 staining (7.7% each) (Table 2). Table 3 outlines the clinical presentation and key characteristics of the patients who had non-IgG3 subtype staining on biopsy.

Treatment and Outcomes

Cyclophosphamide, bortezomib, and dexamethasone (CyBorD) with (n = 6) or without daratumumab (n = 6) were the most common chemotherapy regimens used for treatment. Rituximab monotherapy was used (n = 2) with 1 patient each achieving complete and partial remission. Two patients received cyclophosphamide and prednisone, and both progressed to ESKD. The remaining patients (n = 2) progressed to ESKD (no treatment, n = 1) and persistent renal disease (acalabrutinib, n = 1) (Table 4).

Of the patients treated with the CyBorD with daratumumab, 66% (4 of 6) had complete remission, while among those treated with CyBorD without daratumumab, 50% (3 of 6) progressed to ESKD while one achieved complete remission, and two achieved partial remission. Of the 2 patients treated with rituximab, one had complete remission of proteinuria while the other had partial remission without renal disease progression. Overall, of 18 patients included in the final analysis, 8 (44%) progressed to ESKD after kidney biopsy with a mean duration of 7.8 months (0–13), 6 (33.3%) had complete remission and the remaining patients had partial remission (n = 3) and persistent disease (n = 1). The characteristics of the 6 patients who achieved complete remission are outlined in Table 5. Both univariate Cox model and Fisher's exact test failed to reveal therapy being significantly associated with the event of complete/partial remission (Univariate Cox Model p value = 0.8950, and Fisher's test p value = 0.2225) and failed to show the presence of a monoclonal protein being associated with the event of complete/partial remission (Univariate Cox Model p value = 0.2699, and Fisher's test p value = 0.6380).

Table 2. Summary of histopathological findings

Characteristics	Value (n = 18)
Glomerular injury pattern	
Endocapillary hypercellularity/membranoproliferative	13 (72.2)
Mesangial	5 (27.8)
Total renal chronicity score	
Minimal	3 (16.6)
Mild	9 (50)
Moderate	4 (22.2)
Severe	2 (11.1)
IF	
IgG	17 (94.4)
IgM	1 (5.6)
C3	16 (88.9)
Kappa light chain restriction	17 (94.4)
Lambda light chain restriction	1 (5.6)
IgG subclass type	
IgG3	10/13 (77)
IgG1	1/13 (7.7)
IgG2	1/13 (7.7)
IgG4	1/13 (7.7)

Table 3. Clinical presentation of patients with non-IgG3 class staining on IgG subclass typing staining

Patient characteristics	IgG subclass 1	IgG subclass 2	IgG subclass 4
Race	Black	White	White
Gender	Male	Male	Male
Creatinine at biopsy	1.5	2.3	3.8
Proteinuria at biopsy	0.8	4	2.8
Complement level	Normal	Normal	Normal
M protein	No	No	No
Hypercellularity on LM	Mesangial	Mesangial	Endocapillary
Treatment	CyBorD + Dara	CyBorD + Dara	CyBorD + Dara
Outcome	Complete remission	ESKD	ESKD

Discussion

We report the clinical and pathological characteristics of a large cohort of patients with PGNMID from a multicenter, tertiary institution in the USA. Overall, the prevailing theme of the study is that patients with PGNMID present with significant renal dysfunction, rates of clonal detection are low; however, clone-directed therapy is promising to improve outcomes. To date, there have been 6 other case series published in the literature. Compared to prior studies, key similarities in our study include age, gender, prevalence of hypertension, microscopic hematuria, pattern of injury on biopsy, creatinine and proteinuria at presentation, and detection rate of an M-protein. Key differences include higher rate of hypocomplementemia, tobacco use, less nephrotic syndrome, with greater progression to ESKD even in the presence of mild chronicity compared to prior works.

Historically, early reports of single light chain subclass (kappa chain) immunoglobulin deposition causing glomerulonephritis date back to 1985, when 11 patients were reported with findings of mesangio-capillary glomerulonephritis and deposition of monoclonal Ig light chains and only 1 patient had a detected monoclonal gammopathy [16]. It was not until 2004 that Nasr et al. [6], coined the term proliferative glomerulonephritis with

Table 4. Treatment regimens and outcomes

Chemotherapy regimen	Treatment outcome				Total
	ESKD	complete remission	partial remission	persistent renal disease	
CyBorD	3	1	2	0	6
Rituximab	0	1	1	0	2
CyBorD + Dara	2	4	0	0	6
Cyc/Pred	2	0	0	0	2
Others	1	0	0	1	2
Total	7	6	3	1	18

CyBorD + Dara, cytotoxin, bortezomib, dexamethasone, and daratumumab; Cyc/Prednisone, cyclophosphamide and prednisone.

Table 5. Characteristics of patients with complete remission at the end of follow-up

Patient characteristics	Patient 4	Patient 6	Patient 7	Patient 10	Patient 13	Patient 17
Creatinine at biopsy, mg/dL	1.0	1.5	5.9	3.1	0.8	0.7
Proteinuria at biopsy, g/g	2.8	0.8	8.2	6.8	2.6	1.5
Proteinuria, last follow-up, g/g	0.1	0.2	0.1	0.5	0.2	0.2
M protein	No	No	Yes	No	No	No
Autoimmune disease	Yes	No	No	Yes	Yes	No
Renal chronicity index	Mild	Mild	Minimal	Severe	Mild	Minimal
IgG subclass	IgG3	IgG1	IgG3	IgG3	–	IgG3
Type of treatment	CyBorD	CyBord + Dara	CyBord + Dara	CyBorD + Dara	Rituximab	CyBorD + Dara

monoclonal immunoglobulin deposits (PGNMID), using 10 cases to describe what was previously considered "unclassifiable monoclonal immunoglobulin forming granular electron-dense deposits in mesangial, subendothelial, and subepithelial sites mimicking immune complex-mediated glomerulonephritis." Two decades later, much is still left to be known about this condition. The incidence and prevalence of PGNMID remain unknown, due to a lack of pathognomonic clinical presentation and heterogeneity of findings of kidney biopsies with a prevalence of 0.17–0.21% of kidney biopsies [3, 6]. In our cohort, PGNMID was detected in 0.8% of patients who underwent native kidney biopsies, excluding kidney donors, with this higher rate likely due to the ability to better recognize this pattern of glomerular disease using Nasr et al.'s [6] criteria.

As reported in previous case reports, it predominantly affects Caucasians, adults, and males. In our case series of 18 patients, whites accounted for about 78% while Blacks and Asians accounted for 11.1% and 5.5%, respectively. Although the disease is more prevalent among adults aged over 20 years there have been PGNMID cases among young adults aged 10–19 years [17]. In our study, the mean age of detection was 60 years (32–84), and 20% of affected patients were younger than 50 years. This suggests that one should consider PGNMID as a possible cause of kidney disease for patients presenting with acute kidney failure of unclear cause, irrespective of the age and race and supports the low clonal detection rate as an M-Protein is more likely among older individuals. This can be highlighted in the case of 1 patient in our cohort, a 32-year-old black male who had no detectable clone but was treated with CyBorD and daratumumab with good remission. Interestingly, on biopsy he had IgG1 subtype staining versus the more common IgG3 subtype staining

(Table 3). Thus, more insight into this complex disease that can affect all age groups and ethnicities is needed.

Regarding common clinical presentations: acute kidney injury, hypertension, hematuria, and nephrotic syndrome were the predominant findings reported by previous case series [4]. Similarly, our cohort of patients also presented with hypertension (81%), acute kidney injury (72%), hematuria (78%), nephrotic syndrome (26%), and hypocomplementemia (23%). Additionally, the serum creatinine and proteinuria at biopsy were clinically high at 3.2 mg/dL (0.64–9.0) and 4.3 g/g (0–14.0 g), respectively, and 2 patients required dialysis at presentation. To corelate with the high creatinine at presentation, 33% of patients presented with moderate to severe total renal chronicity score on biopsy. This highlights the ongoing dilemma of patients presenting with advanced kidney dysfunction, which often may not respond to the limited treatment options available. Thus, clinician awareness and vigilance are needed to allow for earlier diagnosis to potentially find disease that may respond to treatment.

Regarding histopathological findings, historically, the light microscopy pattern is heterogeneous ranging from predominantly membranoproliferative glomerulonephritis to mesangial and endocapillary hypercellularity and crescent formation is often rare. In our case series, only 1 patient had crescents on biopsy while the predominant patterns of injury were endocapillary hypercellularity/membranoproliferative (72.2%) followed by pure mesangial (28%) and membrano-proliferative lesions (16%) which is similar to other studies.

Regarding outcomes, 44% of patients (n = 8) progressed to ESKD, with median time to ESKD of 7.5 (1–156) months suggesting poor renal survival. Interestingly, the TRCS score for these 8 patients were 4 mild, 3 moderate, and 1 severe chronicity. Thus, even with mild chronicity patients progressed rapidly to ESKD. However, 33.3% (n = 6) had complete remission defined as proteinuria less than 0.5 g per day with stable renal function. Of these 6 patients, 3 had mild, 2 had moderate, and 1 had severe TRCS scores, respectively. Finally, 3 patients achieved partial remission and 1 with persistent disease during follow-up. Unlike slowly progressive diseases with higher total chronicity scores and poor renal outcomes, over 65% of our patients had a mild total chronicity score, suggesting an acute occurrence of disease but despite this, even those with mild to moderate TRCS progressed to ESKD, highlighting the need for effective treatments. Being younger and less anemic was statistically associated with the event of complete or partial remission. One could speculate this could be due to milder underlying hematological issues, but the overall clinical significance of this finding needs additional exploration and study. While none of the attempted treatment regimens, the presence of a monoclonal protein were also not associated with complete or partial remission. However, statistical analysis is limited by the size of this retrospective study.

Despite PGNMID being recognized as a distinct entity for two decades at this point, there is still no consensus on a preferred therapeutic approach. For patients with detectable circulating paraprotein clone, clone-directed therapy is used but for those without detectable paraprotein, either B cell-directed or plasma cell-directed therapy is used. In our cohort, the clone detection rate was 28% (5/18 patients). There have been some favorable findings for PGNMID treated with clone-directed therapy for patients with detectable underlying clone or hypothesized clone-directed therapy for undetectable clone [11]. In addition, daratumumab, a monoclonal anti-CD38 antibody, showed a promising result by reducing proteinuria and stabilizing kidney function in a small sample size phase two open label clinical trial of 11 patients [10]. However, our study showed high rates of progression to ESKD despite use of plasma cell-directed therapy with CyBorD with or without daratumumab. Meanwhile, of 2 patients treated with rituximab, 1 had complete remission and other had partial remission of proteinuria. Therefore, targeting B-cells remains a good strategy, but more insight into the pathogenesis is needed.

Our study has several strengths, including it being drawn from a large multicenter cohort reviewing all cases of native PGNMID within an 8-year period via a consistent pathology review process. Limitations include lack of IgG subtyping in all biopsies, and the inherent limitations involved with carrying out retrospective studies including heterogeneity of data as well as treatment regimens. Taken together, our findings show that this rare entity continues to have poor outcomes, yet a clone-based approach may currently be the most optimal way to manage these patients. Hence these findings help us in advocating for the development of more multidisciplinary clinics, with joint evaluation by nephrology and hematology being essential. Treatment with clone-based therapy remains the best approach and should be considered even in the absence of a detectable clone given the favorable outcomes described when used.

Conclusion

Our study adds to the growing evidence of low clonal detection and poor outcomes for patients with PGNMID. Early diagnosis and attempts to treat are crucial. Patients

may respond to clone-directed therapy despite the absence of a clone. Therefore, a multidisciplinary approach and additional studies are needed to better understand the true pathogenesis of this disease to guide targeted therapeutic interventions and future clinical trials.

Acknowledgments

The authors would like to thank Dr. Kurt Spindler and Elizabeth Sosic for their administrative support and Hong Liang for statistical support.

Statement of Ethics

This retrospective study was approved with waiver of consent by the Cleveland Clinic, Institutional Review Board (IRB# 22-1093).

Conflict of Interest Statement

S.A. Bobart reports having an honorarium from Travere Therapeutics and other interests or relationships as Faculty for the GlomCon fellowship. L. Herlitz reports having consultancy agreements with Novartis, Travere, Kezar Life Sciences and reports having an advisory or leadership role on the ASN Kidney360 Editorial Board. All remaining authors have nothing to disclose.

Funding Sources

Cleveland Clinic Florida Regional Grant: which had no role in the study design, execution and analysis, manuscript conception, planning, writing nor decision to publish.

Author Contributions

S.A. Bobart and H. Sawaf conceptualized the study. T.T. Gudura, S.A. Bobart, L. Herlitz, H. Sawaf, were responsible for the data curation. T.T. Gudura was responsible for formal analysis and software. S.A. Bobart and S.K. Gebreselassie were responsible for the funding acquisition, project administration, and resources. S.A. Bobart, S.K. Gebreselassie, T.T. Gudura, and H. Sawaf were responsible for investigation. S.A. Bobart, A. Mehdi, T.T. Gudura, and H. Sawaf were responsible for methodology. S.A. Bobart, S.K. Gebreselassie, A. Mehdi, and H. Sawaf provided supervision. S.A. Bobart, T.T. Gudura wrote the original draft. T.T. Gudura, R. Ogbenna, S.A. Bobart, S.K. Gebreselassie, L. Herlitz, A. Mehdi, and H. Sawaf reviewed and edited the manuscript. All authors contributed to the writing of the manuscript and have read and approved the manuscript.

Data Availability Statement

The full data that support the findings of this study are not publicly available due to the Cleveland Clinic IRB requiring a Data Use Agreement but are available from the Cleveland Clinic IRB (irb@ccf.org) upon reasonable request.

References

1 Bridoux F, Javaugue V, Nasr SH, Leung N. Proliferative glomerulonephritis with monoclonal immunoglobulin deposits: a nephrologist perspective. Nephrol Dial Transplant. 2021;36(2):208–15. https://doi.org/10.1093/ndt/gfz176

2 Xing G, Gillespie R, Bedri B, Quan A, Zhang P, Zhou XJ. Proliferative glomerulonephritis with monoclonal IgG deposits in children and young adults. Pediatr Nephrol. 2018;33(9):1531–8. https://doi.org/10.1007/s00467-018-3949-8

3 Nasr SH, Satoskar A, Markowitz GS, Valeri AM, Appel GB, Stokes MB, et al. Proliferative glomerulonephritis with monoclonal IgG deposits. J Am Soc Nephrol. 2009;20(9):2055–64. https://doi.org/10.1681/ASN.2009010110

4 Li M, Xu G. An update of proliferative glomerulonephritis with monoclonal immunoglobulin deposits. Clin Kidney J. 2022;15(6):1041–8. https://doi.org/10.1093/ckj/sfab269

5 Motwani SS, Herlitz L, Monga D, Jhaveri KD, Lam AQ; American Society of Nephrology Onco-Nephrology Forum. Paraprotein-related kidney disease: glomerular diseases associated with paraproteinemias. Clin J Am Soc Nephrol. 2016;11(12):2260–72. https://doi.org/10.2215/CJN.02980316

6 Nasr SH, Markowitz GS, Stokes MB, Seshan SV, Valderrama E, Appel GB, et al. Proliferative glomerulonephritis with monoclonal IgG deposits: a distinct entity mimicking immune-complex glomerulonephritis. Kidney Int. 2004;65(1):85–96. https://doi.org/10.1111/j.1523-1755.2004.00365.x

7 Leung N, Bridoux F, Hutchison CA, Nasr SH, Cockwell P, Fermand JP, et al. Monoclonal gammopathy of renal significance: when MGUS is no longer undetermined or insignificant. Blood. 2012;120(22):4292–5. https://doi.org/10.1182/blood-2012-07-445304

8 Lee H, Duggan P, Neri P, Tay J, Jimenez-Zepeda VH. Bortezomib maintenance for the treatment of monoclonal gammopathy of renal significance. Mediterr J Hematol Infect Dis. 2019;11(1):e2019007. https://doi.org/10.4084/MJHID.2019.007

9 Rahbari E, Barreca A, Nicolino B, Ciochetto C, Piraina V, Maroni S, et al. PGNMID and anti-CD38 monoclonal antibody: a therapeutic challenge. G Ital Nefrol. 2022;39(1):2022-vol1.

10 Zand L, Rajkumar SV, Leung N, Sethi S, El Ters M, Fervenza FC. Safety and efficacy of daratumumab in patients with proliferative GN with monoclonal immunoglobulin deposits. J Am Soc Nephrol. 2021;32(5):1163–73. https://doi.org/10.1681/ASN.2020101541

11 Gumber R, Cohen JB, Palmer MB, Kobrin SM, Vogl DT, Wasserstein AG, et al. A clone-directed approach may improve diagnosis and treatment of proliferative glomerulonephritis with monoclonal immunoglobulin deposits. Kidney Int. 2018;94(1):199–205. https://doi.org/10.1016/j.kint.2018.02.020

12 Albawardi A, Satoskar A, Von Visger J, Brodsky S, Nadasdy G, Nadasdy T. Proliferative glomerulonephritis with monoclonal IgG deposits recurs or may develop de novo in kidney allografts. Am J Kidney Dis. 2011;58(2):276–81. https://doi.org/10.1053/j.ajkd.2011.05.003

13 Leung N, Bridoux F, Batuman V, Chaidos A, Cockwell P, D'Agati VD, 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(1):45–59. https://doi.org/10.1038/s41581-018-0077-4

14 Bobart SA, Portalatin G, Sawaf H, Shettigar S, Carrion-Rodriguez A, Liang H, et al. The Cleveland Clinic kidney biopsy epidemiological project. Kidney360. 2022;3(12):2077–85. https://doi.org/10.34067/KID.0005882022
15 Sethi S, D'Agati VD, Nast CC, Fogo AB, De Vriese AS, Markowitz GS, et al. A proposal for standardized grading of chronic changes in native kidney biopsy specimens. Kidney Int. 2017;91(4):787–9. https://doi.org/10.1016/j.kint.2017.01.002
16 Alpers CE, Tu WH, Hopper J, Biava CG. Single light chain subclass (kappa chain) immunoglobulin deposition in glomerulonephritis. Hum Pathol. 1985;16(3):294–304. https://doi.org/10.1016/s0046-8177(85)80017-4
17 Gowda KK, Nada R, Ramachandran R, Joshi K, Tewari R, Kohli HS, et al. Proliferative glomerulonephritis with monoclonal immunoglobulin deposition disease: the utility of routine staining with immunoglobulin light chains. Indian J Nephrol. 2015;25(6):344–8. https://doi.org/10.4103/0971-4065.151354