



Hemato-Renal Profile of Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits

Abstract

Background: Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is a rare entity classified under the umbrella of monoclonal gammopathy of renal significance. The clinical implications of circulating monoclonal immunoglobulin (MIg), light chain restriction on immunofluorescence (IF) microscopy, histopathological pattern, and type of therapy on renal outcomes are not clearly defined. **Materials and Methods:** Sixteen patients of PGNMID diagnosed between 2013 and 2020 were included from a biopsy registry of 11,459 patients at a single center. Follow-up data was collected from electronic medical records until June 2021. **Results:** The mean age of the cohort was 41.7 ± 13.5 years. Forty-four (7/16) percent showed monoclonal protein on serum or urine electrophoresis, 25% (3/12) had IgG kappa by serum immunofixation electrophoresis (IFE) and 38% (5/13) had abnormal kappa: lambda free light chain (FLC) ratio. The predominant light microscopy pattern, membranoproliferative glomerulonephritis (MPGN) was seen in 7/16 (43.7%) patients. The predominant heavy chain detected by IF microscopy was IgG (13/16, 81.3%). Kappa and lambda light chain restriction were seen in 56.3 (9/16) and 43.8 (7/16) percent of patients respectively. Circulating monoclonal kappa light chains were detected in 50 and 29% of kappa-PGNMID patients by IFE and FLC assay respectively. None of the lambda-PGNMID patients had detectable circulating monoclonal lambda light chains. Patients with circulating MIg had more proteinuria, lower estimated glomerular filtration rate, and a higher percentage of plasma cells on bone marrow biopsy. Thirty-eight percent of our cohort (5/13) progressed to kidney failure over a median (range) period of 3 (IQR, 1-7) months. Of these, 4/5 received immunosuppression, and 1/5 were treated with plasma cell-targeted chemotherapy. **Conclusion:** PGNMID is a rare disease with a biopsy incidence of 0.1%. Only a quarter of patients with PGNMID have circulating MIg. Presence of circulating MIg, type of monoclonal light chain restriction in kidney biopsy, and type of therapy did not predict renal outcomes. Patients with MPGN had favorable renal outcomes despite a higher degree of proteinuria at presentation.

Keywords: Electrophoresis, Glomerulonephritis, Immunoglobulin, Nephrotic syndrome, Plasma cells

Introduction

Proliferative glomerulonephritis with monoclonal immune deposits (PGNMID) is an immune complex glomerulonephritis with monoclonal immunoglobulin deposits within glomeruli.¹ These deposits are characterized by electron microscopy (EM) as nonorganized and electron-dense located in subendothelial, mesangial, or subepithelial regions.² A quarter to one-third of patients progress to kidney failure despite immunosuppression.³ A circulating monoclonal immunoglobulin detected by immunofixation electrophoresis (IFE) or serum free light chain (FLC) assay

or a nephropathic clone detected by flowcytometry is seen in only 25–30% of cases.^{3,4} This study reports the hemato-renal profile of PGNMID patients at a tertiary care center and aims to determine the clinical implications of circulating monoclonal immunoglobulin (MIg), histopathological pattern and type of monoclonal light chain restriction in kidney biopsy, and type of therapy on renal outcomes.

Materials and Methods

This was an observational retrospective biopsy registry cohort [Glomerular Research and Clinical Experiments—Proliferative

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Glomerulonephritis with Monoclonal Immunoglobulin Deposits (GRACE-PGNMID)] done among out- and inpatient services of the Department of Nephrology at Christian Medical College, Vellore. Consent was waived as it was retrospective data collection from electronic medical records. In total, 11,459 native adult kidney biopsies were performed between January 2013 and December 2020, of which 16 cases met the following diagnostic criteria of PGNMID (biopsy incidence of 0.1%) [Supplemental Figure 1]:

1. Light microscopy (LM) showing a proliferative pattern like membranoproliferative or endocapillary proliferative or mesangioproliferative glomerulonephritis.
2. Immunofluorescence (IF) staining for a single light chain (kappa or lambda) and heavy chain (gamma, alpha or mu) isotype indicating monoclonality.
3. Granular electron-dense deposits with no substructure in mesangial, subendothelial, and/or subepithelial locations by EM.
4. Absence of clinical and laboratory evidence of cryoglobulinemia.

Baseline assessments and treatment

Data on demographic profiles, clinical features, histopathological variables, treatment details, morbidity, and mortality were retrieved from electronic patient records. Proteinuria was assessed from 24-hour timed collection. Estimated glomerular filtration rate (eGFR) was calculated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

All kidney biopsy specimens were processed for LM, IF, and EM. Serial 3- μ m-thick sections were stained for hematoxylin and eosin, periodic acid Schiff reagent, Masson's trichrome, and Jones' methenamine silver for LM. Four-micrometer cryostat sections were stained with fluorescein-tagged polyclonal rabbit anti-human antisera specific to IgG, IgA, and IgM; complement factors C3, C4, and C1q; and kappa and lambda light chains (Dako, Carpinteria) for IF. The IF staining intensity was semi-quantitatively evaluated and graded from 0 to 3+. Ultrastructural examination was done with Tecnai T12 Spirit electron microscope.

Bone involvement was assessed by skeletal survey (X-rays) of skull, pelvis, and spine in all patients. Magnetic resonance imaging (MRI) and positron emission tomography and computed tomography (PET-CT) scans were not done in any patients. Bone marrow aspiration and biopsy was done in 14 out of 16 patients. Immunohistochemistry (IHC) of marrow plasma cells for kappa and lambda light chains was done in 12 out of 14 patients who underwent bone marrow biopsy. All patients underwent both serum and urine electrophoresis. Serum IFE and FLC assays were done in 12 out of 16 and 13 out of 16 patients, respectively. Circulating MIg was defined as presence of monoclonal heavy and/or light chain by IFE. Following cut-offs for kappa: lambda FLC ratio was used: 0.26–1.65 (eGFR >60 mL/min/1.73 m²), 0.46–2.62

(eGFR 45–60 mL/min/1.73 m²), 0.48–3.38 (eGFR 30–44 mL/min/1.73 m²) and 0.54–3.30 (eGFR <30 mL/min/1.73 m²).⁵

Follow-up

Follow-up data was collected until June 2021. Complete remission (CR) was defined as proteinuria \leq 0.5 g/day and last visit eGFR >90 mL/min/1.73 m² or return to pre-morbid eGFR level. Partial remission (PR) was defined as a reduction in proteinuria by at least 50% and to <2 g/day with stable renal function (decrease in eGFR not exceeding 25% from biopsy time and last visit eGFR >15 mL/min/1.73 m²). Kidney failure was defined as last visit eGFR \leq 15 mL/min/1.73 m² or initiation of renal replacement therapy (RRT). Persistent renal dysfunction (PRD) was defined as failure to meet either CR, PR, or kidney failure.⁴

Statistical analysis

Data was presented as mean \pm standard deviation (SD) or median (inter-quartile range [IQR]) or frequency (percentages) according to types and distribution of variables. 'Likewise or case deletion' approach was used to handle missing data. Differences among groups of normally distributed variables were analyzed by t-test. Differences among groups of nonparametric variables were analyzed by Mann-Whitney U test or the Kruskal-Wallis test. Categorical variables were compared using Pearson's chi-squared test or Fisher's exact test. Statistical analysis was performed using Statistical Package for Social Sciences software for Windows version 21.0 (SPSS Inc., Chicago, IL). A p-value of <0.05 was taken as significant.

Results

Baseline demographic and clinical characteristics

The mean age of the cohort was 42 \pm 13.5 years with a male: female ratio of 1:1 [Table 1]. Three-fourths of the cohort had hypertension at presentation. The most common renal symptom was peripheral edema (94%). None of the patients had any extra-renal manifestations. Non-visible hematuria and nephrotic range proteinuria were seen in 87.5% (14/16) and 81.3% (13/16) of patients, respectively. The median eGFR at the time of kidney biopsy was 35.5 (IQR, 24–74.6) mL/min/1.73 m² with one patient (6.3%) requiring RRT. Hypocomplementemia (low C3) was seen in 37.5% (6/16) of patients.

Baseline hematological parameters

Hypercalcemia, renal dysfunction, anemia, and lytic bone lesions were seen in 7.6% (1/13), 37.5% (6/16), 50% (8/16), and 0% (none of 16) of patients, respectively [Table 1]. Forty-four percent (7/16) of patients had a detectable monoclonal (M) protein by either serum or urine protein electrophoresis. However, only one of these seven (14.3%) patients had M protein quantification >30 g/L. IgG kappa was detected in serum by IFE in 3/12 (25%) patients. Thirty-eight percent (5/13) of patients had an elevated kappa: lambda FLC ratio. Bone marrow plasmacytosis >10% occurred in only one of

Table 1: Baseline clinical and hematological characteristics of GRACE-PGNMID cohort

Baseline characteristics at kidney biopsy	Entire cohort (N = 16)	Baseline characteristics at kidney biopsy	Entire cohort (N = 16)
Baseline demographic and clinical characteristics		Serology (n, %)	
Age, years	41.7 ± 13.5	Low C3	6 (37.5)
Gender (n, %)		Low C4	0
Males	8 (50)	ANA [†]	1 (6.3)
Females	8 (50)	dsDNA	0
Body mass index, kg/m ²	23.9 ± 4.7	Cryoglobulin	0
Comorbidities		HBsAg	0
Diabetes mellitus (n, %)	2 (12.5)	Anti-HCV antibody	0
Hypertension (n, %)	12 (75)	HIV	0
Systolic BP, mmHg	137.8 ± 16.5	MPO-ANCA [†]	0
Diastolic BP, mmHg	85 ± 11.1	PR3-ANCA [†]	0
Hypothyroidism (n, %)	5 (31.3%)	Baseline hematological parameters	
Renal manifestations (n, %)		Hemoglobin, g/dL	10.3 ± 1.7
Edema	15 (93.8)	Lytic bone lesions (n, %)	0
Oligo-anuria	1 (6.3)	Hypercalcemia (n, %) [†]	1 (7.7)
Dyspnea	3 (18.8)	Protein electrophoresis	
Visible hematuria	0	Serum protein electrophoresis	
Systemic manifestations (n, %)		M protein, yes (n, %)	
Fever	1 (6.3)	Quantification of M protein, g/L [median (IQR)]	
Bone pain	0	Urine protein electrophoresis (n, %)	
Urine abnormalities (n, %)		M protein, yes (n, %)	
Non-visible hematuria	14 (87.5)	Serum or urine protein electrophoresis (%)	
Leucocyturia	8 (50)	M protein, yes (n, %)	
Casts	6 (37.5)	Serum immunofixation electrophoresis (n, %) [†]	
Serum albumin, g/dL	2.6 ± 0.6	Normal	
24-hour urine protein, g/day [Median (IQR)]	5.6 (3.9–8.9)	IgG kappa	
Kidney function		Serum free light chain assay [†]	
Baseline creatinine, mg/dL [Median (IQR)]	1.3 (0.9–1.6)	Serum kappa FLC, mg/dL [median (IQR)]	
Serum creatinine at biopsy, mg/dL [Median (IQR)]	1.9 (1–2.9)	Serum lambda FLC, mg/dL [median (IQR)]	
eGFR CKD-EPI at biopsy, mL/min/1.73 m ² [Median (IQR)]	35.5 (24–74.6)	Serum kappa: lambda FLC ratio [median (IQR)]	
Renal replacement therapy at biopsy, yes (n, %)	1 (6.3)	Abnormal kappa: lambda FLC ratio ^{††} (n, %)	
		Bone marrow examination [†]	
		Plasma cells, % [median (IQR)]	
		Plasma cells > 10%	
		Immunohistochemistry [†]	
		No restriction	
		Kappa restriction	
		Lambda restriction	

ANA: Antinuclear antibody, BP: Blood pressure, IQR: Inter-quartile range, CKD-EPI: Chronic kidney disease epidemiology, dsDNA: Double stranded DNA, eGFR: Estimated glomerular filtration rate, GRACE-PGNMID, Glomerular research and clinical experiments-proliferative Glomerulonephritis with monoclonal immunoglobulin deposits, FLC: Free light chain, HBsAg: Hepatitis B surface antigen, HCV, Hepatitis C virus, HIV: Human immunodeficiency virus, MPO-ANCA: Myeloperoxidase-antineutrophil cytoplasmic antibody, PR3-ANCA: Proteinase 3-antineutrophil cytoplasmic antibody. [†]Evaluable patients (N) for ANA = 15, ANCA serology = 14, hypercalcemia = 13, serum immunofixation electrophoresis = 12, serum free light chain assay = 13, bone marrow examination = 13, bone marrow immunohistochemistry = 12. ^{††}Normal kappa: lambda FLC ratio: 0.26–1.65 (eGFR > 60 mL/min/1.73 m²), 0.46–2.62 (eGFR 45–60 mL/min/1.73 m²), 0.48–3.38 (eGFR 30–44 mL/min/1.73 m²) and 0.54–3.30 (eGFR <30 mL/min/1.73 m²)

Table 2: Baseline histopathological characteristics of GRACE-PGNMID cohort

Baseline histopathological characteristics	Entire cohort
Light microscopy (N = 16)	
Number of glomeruli	14.4 ± 6.4
Globally sclerosed glomeruli [median (IQR)]	22.2 (7.7-33.3)
Glomerular lesions (n, %)	
Light microscopy pattern	
Membranoproliferative glomerulonephritis	7 (43.8)
Mesangial proliferation	5 (31.3)
Diffuse endocapillary proliferation	2 (12.5)
Focal endocapillary proliferation	2 (12.5)
Crescents	
Focal (<50%)	3 (18.7)
Diffuse (>50%)	1 (6.2)
Tuft necrosis	
Glomerular neutrophil infiltration	6 (37.5)
Diabetic glomerulosclerosis	
Tubular lesions (n, %)	0
Acute tubular injury	5 (31.3)
Interstitial (n, %)	
Interstitial inflammation (focal, diffuse) (n, %)	13, 2 (81.3, 12.5)
IFTA moderate-severe (n, %)	14 (87.5)
Vascular lesions (n, %)	
Arterio(lar)sclerosis	14 (87.5)
Immunofluorescence staining (N = 16)	
Predominant immunoglobulin (n, %)	
IgG	13 (81.3)
IgM	2 (12.5)
IgA	1 (6.3)
Light chain restriction (n, %)	
Kappa	9 (56.3)
Lambda	7 (43.8)
Mean staining intensity	
IgG	2.2 ± 1.4
IgM	0.5 ± 0.9
C3	1.6 ± 1
C1q	0.4 ± 0.6
C4	0.2 ± 0.6
Biclonality or mismatch between serum IFE and tissue immunofluorescence	
Site of immunofluorescence staining	1 (7.7)
Glomerular capillary wall	7 (43.8)
Mesangium	2 (12.5)
Glomerular capillary wall + mesangium	7 (43.8)
Texture of immunofluorescence deposits	
Granular	16 (100)
Smudgy	0
Semi-linear	0
Electron microscopy (N = 16)	
Site of deposits (n, %)	
Mesangial deposits	10 (62.5)
Subendothelial deposits	13 (81.3)
Subepithelial deposits	4 (25)
Type of deposits (n, %)	
Granular	16 (100)
Focal variegated	0
Foot process effacement (focal, diffuse) (n, %)	
Rare microtubules	4, 10 (25, 62.5)
Rare microtubules	1 (6.7)

GRACE-PGNMID: Glomerular research and clinical experiments-Proliferative glomerulonephritis with monoclonal immunoglobulin deposits, IFE: Immunofixation electrophoresis, IFTA: Interstitial fibrosis and tubular atrophy, IQR: Inter-quartile range, N: Total number, n: Pathology present.

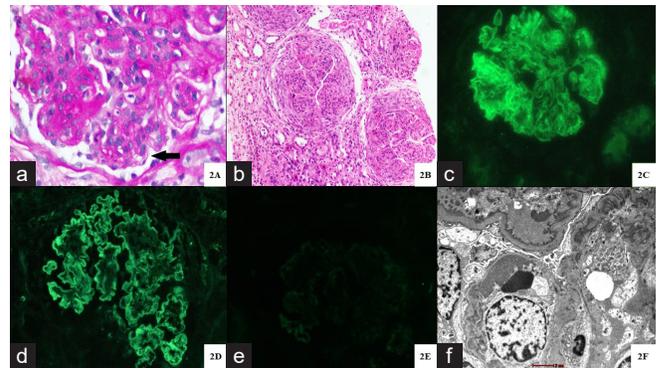


Figure 1: Histopathology of proliferative glomerulonephritis with monoclonal immunoglobulin deposits. (a) Glomerulus with marked mesangial expansion, mesangial hypercellularity, segmental endocapillary hypercellularity and segments of irregular capillary wall thickening with reduplication (bold black arrow) (Periodic acid schiff stain; original magnification X 400). (b) Three glomeruli with circumferential cellular crescents with underlying glomerular capillary tuft showing global endocapillary hypercellularity with lobular accentuation. Adjacent interstitium shows edema with severe acute tubular injury. (Hematoxylin and eosin stain; original magnification X 100). (c-e) Immunofluorescence microscopy displaying global, granular capillary wall, along with mesangial staining for IgG (4+ intensity) (c) and kappa light chain (4+ intensity) (d). There is no staining for lambda light chain (e). (original magnification X 400). (f) Ultrastructural examination displaying abundant large subendothelial electron dense immune complex type deposits along with concomitant mesangial deposits. Podocytes show global effacement. A diagnostic substructure is not evident. (Transmission electron microscopy, original magnification X 6000).

14 patients (7.1%). Light chain restriction of marrow plasma cells was not seen in any of the tested patients.

Baseline histopathological parameters

The mean ± SD number of glomeruli was 14.4 ± 6.4 [Table 2]. The predominant light microscopy pattern was membranoproliferative glomerulonephritis (MPGN) (7/16, 43.7%) [Figure 1a]. Twenty five percent patients (4/16) had crescents, though only one patient had crescents in >50% of glomeruli [Figure 1b]. Chronic lesions like arteriosclerosis and moderate-to-severe interstitial fibrosis and tubular atrophy (IFTA) were present in the majority of patients (14/16, 87.5%).

The predominant monoclonal immunoglobulin was IgG (13/16, 81.2%) with a mean staining intensity (MSI) of 2.2 ± 1.4 [Figure 1c]. Kappa and lambda light chain restriction were seen in 56.3% (9/16) and 43.8% (7/16) of patients, respectively [Figure 1d and 1e]. C3 staining was positive in 50% (8/16) of patients with MSI of 1.6 ± 1. C1q staining was positive in 37.5% (6/16) of patients with MSI of 0.2 ± 0.6. Ultrastructural examination was characterized by classical granular electron-dense deposits predominantly in sub-endothelial location (13/16, 81.3%) [Figure 1f]. Diffuse foot process effacement was seen in 62.5% of patients (10/16).

Treatment

Renin-angiotensin-aldosterone system inhibitors were started in 25% (4/16) of patients immediately after kidney biopsy [Supplemental Table 1]. Nineteen (3/16), sixty-nine (11/16) and twelve (2/16) percent of patients received conservative

treatment, immunosuppression as per glomerulonephritis (GN) protocol, and plasma cell targeted chemotherapy, respectively. All 11 patients on GN immunosuppressive protocol regimen received oral glucocorticoid for a median (range) duration of 4 (IQR, 3–6) months. Thirty-six percent (4/11) in addition received a second immunosuppressant (mycophenolate mofetil in 3/4 and oral cyclophosphamide in 1/4 patients). Cyclophosphamide, bortezomib, and dexamethasone (CyBorD) induction regimen was given to 2/16 (16%) patients.

Outcomes

Eighty-one percent (13/16) of patients had longitudinal follow-up records of >3 months, with a median (range) duration of follow-up of 6 (3–27) months [Supplemental

Table 1]. Fifteen (2/13), thirty-eight (5/13) and eight (1/13) percent patients attained CR, PR, and PRD, respectively during the follow-up period. Thirty-eight percent (5/13) of patients progressed to kidney failure over a median (range) period of 3 (IQR, 1–7) months. Of the 10 patients who received immunosuppression (with follow-up details >3 months), one (10%) attained CR, four (40%) PR, one (10%) had PRD and four (40%) progressed to kidney failure. Of the two patients who were treated with CyBorD regimen, one attained PR and the other progressed to kidney failure. Though, only one patient (8%) developed multiple myeloma during the follow-up period, 75% (3/4) of tested patients had persistence of M protein on serum

Table 3: Classification of PGNMID based on presence or absence of circulating monoclonal immunoglobulin by serum immunofixation electrophoresis

Parameter	Circulating monoclonal immunoglobulin		p value
	Present (N = 3)	Absent (N = 9)	
Baseline demographic and clinical characteristics (N = 12)			
Age (years)	51.3 ± 6.6	42.1 ± 14.4	0.320
Sex (n, %)			
Males	2 (66.7)	5 (55.6)	0.505
Females	1 (33.3)	4 (44.4)	
Body mass index, kg/m ²	23.4 ± 2.7	24.1 ± 6.1	0.861
Comorbidities			
Diabetes mellitus (n, %)	1 (33.3)	1 (11.1)	0.455
Hypertension (n, %)	3 (100)	6 (66.7)	0.509
Systolic BP, mmHg	142.7 ± 6.4	130 ± 15	0.196
Diastolic BP, mmHg	91.7 ± 2.9	79.4 ± 10.7	0.086
Renal manifestations (n, %)			
Edema	3 (100)	8 (88.9)	0.546
Oligo-anuria	0	1 (11.1)	0.546
Dyspnea	0	2 (22.2)	0.550
Visible hematuria	0	0	
Systemic manifestations (n, %)			
Fever	1 (11.1)	0	0.546
Bone pain	0	0	
Urine abnormalities (n, %)			
Non-visible hematuria	2 (66.7)	8 (88.9)	0.455
Leucocyturia	1 (33.3)	3 (33.3)	0.764
Casts	1 (33.3)	4 (44.4)	0.636
Serum albumin, g/dL	2.3 ± 0.7	2.8 ± 0.6	0.284
24-hour urine protein, g/day [median (range)]	9.1 (7.9–15)	4.3 (0.3–6)	0.013
Kidney function			
Baseline creatinine, mg/dL [median (range)]	1.6 (1.5–1.65)	1.1 (0.5–2.5)	0.451
Serum creatinine at biopsy, mg/dL [median (range)]	2.5 (1.9–3.7)	1.2 (0.5–4.7)	0.229
eGFR CKD-EPI at biopsy, mL/min/1.73 m ² [median (range)]	29 (17.5–29.4)	61 (13.4–130)	0.229
Renal replacement therapy at biopsy, yes (n, %)	0	1 (11.1)	0.750
Serology (n, %)			
Low C3	3 (100)	3 (100)	0.182
Low C4	0	0	

(Continued)

Table 3: Continued

Parameter	Circulating monoclonal immunoglobulin		p value
	Present (N = 3)	Absent (N = 9)	
Baseline hematological parameters			
Hemoglobin, g/dL	9.5 ± 1.9	10.7 ± 1.9	0.358
Lytic bone lesions (n, %)	0	0	
Hypercalcemia (n, %) [†]	0	1 (11.1)	0.692
M protein detection by protein electrophoresis (n, %)			
Serum protein electrophoresis, yes	1 (33.3)	3 (33.3)	0.764
Urine protein electrophoresis, yes	2 (66.7)	0	0.045
Serum or urine protein electrophoresis, yes	3 (100)	3 (33.3)	0.046
Immunofixation electrophoresis			
Normal	0	9 (100)	
IgG kappa	3 (100)	0	
Serum free light chain assay			
Serum kappa FLC, mg/dL [median (range)]	469 (98–705)	100 (19–136)	0.115
Serum lambda FLC, mg/dL [median (range)]	49 (38–246)	50 (17.4–100)	0.644
Serum kappa: lambda FLC ratio [median (range)]	2.9 (2–12)	1.1 (0.9–2.9)	0.051
Abnormal kappa: lambda FLC ratio (n, %)	3 (100)	2 (22.2)	0.045
Bone marrow examination (n, %) [†]	6 (5–14)	1 (0–4)	0.013
Plasma cells, % [median (range)]			
Plasma cells > 10%	1 (33.3)	0	0.273
Immunohistochemistry [†]			
No restriction	3 (100)	7 (100)	
Kappa restriction	0	0	
Lambda restriction	0	0	
Baseline histopathological parameters (N = 12)			
Light microscopy (N = 12)			
Number of glomeruli	13.3 ± 6.1	16.4 ± 7.5	0.313
Globally sclerosed glomeruli [median (range)]	27.8 (10-33.3)	10.5 (0-71.4)	0.459
Glomerular lesions (n, %)			
Light microscopy patterns			
Membranoproliferative pattern	2 (66.7)	3 (33.3)	
Mesangial proliferation	0	4 (44.4)	
Diffuse endocapillary proliferation	0	1 (11.1)	
Focal endocapillary proliferation	1 (33.3)	1 (11.1)	
Crescents	1 (33.3)	2 (22.2)	0.618
Tuft necrosis	1 (11.1)	0	0.750
Glomerular neutrophil infiltration	0	4 (44.4)	0.491
Tubular Lesions (n, %)			
Acute tubular injury	2 (66.7)	2 (22.2)	0.236
Interstitial (n, %)			
Interstitial inflammation (focal, diffuse) (n, %)	3, 0 (100, 0)	7, 1 (77.8, 11.1)	0.670
IFTA moderate-severe (n, %)	2 (66.7)	8 (88.9)	0.455
Vascular lesions (n, %)			
Arterio(lar)sclerosis	3 (100)	7 (77.8)	0.545

(Continued)

Table 3: Continued

Parameter	Circulating monoclonal immunoglobulin		p value
	Present (N = 3)	Absent (N = 9)	
Immunofluorescence staining (N = 12)			
Heavy chain (n, %)			0.750
IgG	3 (100)	8 (88.9)	
IgM	0	1 (11.1)	
IgA	0	0	
Light chain restriction (n, %)			0.636
Kappa	2 (66.7)	5 (55.6)	
Lambda	1 (33.3)	4 (44.4)	
Site of IF staining			0.036
Glomerular capillary wall	1 (33.3)	3 (33.3)	
Mesangium	2 (66.7)	0	
Glomerular capillary wall + mesangium	0	6 (66.7)	
Electron microscopy (N = 12)			
Site of deposits (n, %)			
Mesangial deposits	2 (66.7)	7 (77.8)	0.618
Sub-endothelial deposits	2 (66.7)	8 (88.9)	0.455
Sub-epithelial deposits	0	3 (33.3)	0.509
Foot process effacement (focal diffuse) (n, %)	0, 2 (0, 66.7)	3, 6 (33.3, 66.7)	0.364
Treatment characteristics (N = 12)			
Renin-angiotensin system inhibitors (n, %)	1 (33.3)	3 (33.3)	0.764
Type of therapy (n, %)			
Conservative therapy	0	2 (22.2)	0.368
Immunosuppression	3 (100)	5 (55.6)	
Plasma cell targeted chemotherapy	0	2 (22.2)	
Outcome at last follow-up (N = 11)			
>3 months of follow-up (n, %)	3 (100)	8 (88.9)	
Duration of follow-up, months [median (range)]	6.5 (3-27)	30 (4-35)	0.182
Renal outcomes (n, %)			0.821
Complete remission	1 (33.3)	1 (12.5)	
Partial remission	1 (33.3)	3 (37.5)	
Persistent renal dysfunction	0	1 (12.5)	
Kidney failure	1 (33.3)	3 (37.5)	
Other outcomes (n, %)			
Infections	2 (33.3)	1 (12.5)	0.667
Death	1 (33.3)	0	0.273

BP: Blood pressure, CKD-EPI: Chronic kidney disease-epidemiology collaboration, eGFR, eGFR: Estimated glomerular filtration rate, FLC: Free light chain, IF: Immunofluorescence, IFTA: Interstitial fibrosis and tubular atrophy, IQR: Inter-quartile range, PGNMID: Proliferative glomerulonephritis with monoclonal immunoglobulin deposits. † Evaluable patients (N) for hypercalcemia (13), bone marrow examination = 11, bone marrow immunohistochemistry = 10, N= total number, n=pathology present.

electrophoresis. One patient (8%) died during the follow-up period due to infection.

PGNMID with or without circulating MIg

Patients with circulating MIg had more proteinuria [9.1 (IQR, 7.9–15) vs. 4.3 (IQR, 0.36) g/day, p = 0.013] and lower eGFR [29 (range, 17.5–29.4) v. 61 (13.4–130) mL/min/1.73 m², p = 0.229] at kidney biopsy [Table 3]. All the three patients with circulating MIg had either

positive serum or urine electrophoresis as compared to 3 out of 9 (33.3%) patients without circulating MIg (p = 0.046). Kappa: lambda FLC ratio was higher in patients with circulating MIg [2.9 (range, 2–12) v. 1.1 (range, 0.9–2.9), p = 0.051]. Patients with a circulating MIg also had a higher median percentage of plasma cells on bone marrow biopsy [6% (range, 5–14) vs. 1% (range, 0–4), p = 0.013]; and one of these three (33.3%) patients had bone marrow plasmacytosis >10%. However, renal outcomes did

not differ between the two groups (kidney failure: With circulating MIg 1/3, 33.3% v. without circulating MIg 3/8, 37.5%).

Light microscopy patterns of PGNMID

As compared to other patterns, patients with MPGN pattern had more proteinuria (7.9 (IQR, 5.8–9) g vs. 4.2

(IQR, 3.1–8.5) g, p = 0.071) and hypocomplementemia (4/7, 57.1% vs. 2/9, 22.2%, p = 0.302) at kidney biopsy [Table 4]. However, all patients with MPGN patterns attained either complete or partial remission during the follow-up period. As compared to this, 71.4% (5/7) of patients with other patterns progressed to kidney failure (p = 0.003).

Table 4: Light microscopy patterns of PGNMID

Parameter	MPGN pattern (N = 7)	Other LM patterns (N = 9)	p value
Baseline demographic and clinical characteristics (N = 16)			
Age (years)	47.3 ± 12.6	37.3 ± 13.2	0.589
Sex (n, %)			
Males	3 (42.9)	5 (55.6)	0.614
Females	4 (57.1)	4 (44.4)	
Body mass index, kg/m ²	24 ± 5.2	23.9 ± 4.7	0.948
Comorbidities			
Diabetes mellitus (n, %)	1 (14.3)	1 (11.1)	0.849
Hypertension (n, %)	6 (85.7)	6 (66.7)	0.585
Systolic BP, mmHg	142.6 ± 18.1	134.1 ± 15.2	0.326
Diastolic BP, mmHg	86.1 ± 10.8	84.1 ± 11.8	0.729
Renal manifestations (n, %)			
Edema	7 (100)	8 (88.9)	0.362
Oligo-anuria	1 (14.3)	0	0.438
Dyspnea	2 (28.6)	1 (11.1)	0.550
Visible hematuria	0	0	
Systemic manifestations (n, %)			
Fever	1 (14.3)	0	0.438
Bone pain	0	0	
Urine abnormalities (n, %)			
Non-visible hematuria	7 (100)	7 (77.8)	0.475
Leucocyturia	4 (57.1)	4 (44.4)	0.614
Casts	1 (14.3)	5 (55.6)	0.145
Serum albumin, g/dL	2.4 ± 0.4	2.8 ± 0.8	0.261
24-hour urine protein, g/day [median (IQR)]	7.9 (5.8–9)	4.2 (3.1–8.5)	0.071
Kidney function			
Baseline creatinine, mg/dL [median (IQR)]	1.2 (0.8–1.6)	1.4 (1–1.7)	0.451
Serum creatinine at biopsy, mg/dL [median (IQR)]	1.9 (0.8–2.5)	2 (1.1–3.4)	0.337
eGFR CKD-EPI at biopsy, mL/min/1.73 m ² [median (IQR)]	41 (29–74.8)	33 (20.5–70.5)	0.606
Renal replacement therapy at biopsy, yes (n, %)	1 (14.3)	0	0.438
Serology (n, %)			
Low C3	4 (57.1)	2 (22.2)	0.302
Low C4	0	0	
Baseline hematological parameters			
Hemoglobin, g/dL	9.8 ± 1.7	10.6 ± 1.7	0.340
Lytic bone lesions (n, %)	0	0	
Hypercalcemia (n, %) †	0	1 (11.1)	0.692
M protein detection by protein electrophoresis (n, %)			
Serum protein electrophoresis, yes	3 (42.9)	3 (33.3)	0.696
Urine protein electrophoresis, yes	3 (42.9)	0	0.063
Serum or urine protein electrophoresis, yes	4 (57.1)	3 (33.3)	0.615

(Continued)

Table 4: Continued

Parameter	MPGN pattern (N = 7)	Other LM patterns (N = 9)	p value
Serum immunofixation electrophoresis (n, %) [†]			
Normal	3 (60)	6 (85.7)	0.523
IgG kappa	2 (40)	1 (14.3)	
Serum free light chain assay [†]			
Serum kappa FLC, mg/dL [median (IQR)]	98 (36–289)	100 (51.3–28.5)	0.913
Serum lambda FLC, mg/dL [median (IQR)]	49 (29–58)	55 (38.8–90.8)	0.546
Serum kappa: lambda FLC ratio [median (IQR)]	1.6 (1–7)	1.6 (1–2.7)	0.981
Abnormal kappa: lambda FLC ratio (n, %)	2 (40)	3 (37.5)	0.928
Bone marrow examination (n, %) [†]			
Plasma cells, % [Median (range)]	2.5 (0–6)	0 (0–14)	0.330
Plasma cells > 10%	0	1 (14.3)	0.335
Immunohistochemistry [†]			
No restriction	6 (100)	6 (100)	
Kappa restriction	0	0	
Lambda restriction	0	0	
Baseline histopathological parameters (N = 16)			
Light microscopy (N = 16)			
Number of glomeruli	13.6 ± 4.9	15.1 ± 7.6	0.652
Globally sclerosed glomeruli [median (IQR)]	10 (6.7–33.3)	26.7 (15.1–31.9)	0.366
Glomerular lesions (n, %)			
Light microscopy patterns			<0.001
Membranoproliferative pattern	7 (100)	0	
Mesangial proliferation	0	5 (55.6)	
Diffuse endocapillary proliferation	0	2 (22.2)	
Focal endocapillary proliferation	0	2 (22.2)	
Crescents	2 (28.6)	2 (22.2)	0.772
Tuft necrosis	1 (14.3)	0	0.438
Glomerular neutrophil infiltration	4 (57.1)	2 (22.2)	0.302
Tubular lesions (n, %)			
Acute tubular injury	2 (28.6)	3 (33.3)	0.838
Interstitial (n, %)			
Interstitial inflammation (focal, diffuse) (n, %)	7, 0 (100, 0)	6, 2 (66.7, 22.2)	0.475
IFTA moderate-severe (n, %)	6 (85.7)	8 (88.9)	0.849
Vascular lesions (n, %)			
Arterio(lar)sclerosis	7 (100)	7 (77.8)	0.475
Immunofluorescence staining (N = 16)			
Heavy chain (n, %)			0.657
IgG	6 (85.7)	7 (77.8)	
IgM	1 (14.3)	1 (11.1)	
IgA	0	1 (11.1)	
Light chain restriction (n, %)			0.949
Kappa	4 (57.1)	5 (55.6)	
Lambda	3 (42.9)	4 (44.4)	
Site of immunofluorescence staining			0.315
Glomerular capillary wall	3 (42.9)	4 (44.4)	
Mesangium	2 (28.6)	0	
Glomerular capillary wall + mesangium	2 (28.6)	5 (55.6)	

(Continued)

Table 4: Continued

Parameter	MPGN pattern (N = 7)	Other LM patterns (N = 9)	p value
Electron microscopy (N = 16)			
Site of deposits (n, %)			
Mesangial deposits	5 (71.4)	5 (55.6)	0.633
Subendothelial deposits	7 (100)	6 (66.7)	0.213
Subepithelial deposits	1 (14.3)	3 (33.3)	0.585
Foot process effacement (focal, diffuse) (n, %)	1, 6 (14.3, 85.7)	3, 4 (33.3, 44.4)	0.202
Treatment characteristics (N = 16)			
Renin-angiotensin system inhibitors (n, %)	1 (14.3)	3 (33.3)	0.585
Type of therapy (n, %)			0.915
Conservative therapy	1 (14.3)	2 (22.2)	
Immunosuppression	5 (71.4)	6 (66.7)	
Plasma cell targeted chemotherapy	1 (14.3)	1 (11.1)	
Outcome at last follow-up (N = 13)			
>3 months of follow-up (n, %)	6 (85.7)	7 (77.8)	0.127
Duration of follow-up, months [median (range)]	25 (3-35)	4 (3-27)	
Renal outcomes (n, %)			0.003
Complete remission	1 (16.7)	1 (14.3)	
Partial remission	5 (83.3)	0	
Persistent renal dysfunction	0	1 (14.3)	
Kidney failure	0	5 (71.4)	
Other outcomes (n, %)			
Infections	2 (33.3)	1 (14.3)	0.333
Death	0	1 (16.7)	0.296

BP: Blood pressure, CKD-EPI: Chronic kidney disease-Epidemiology collaboration, eGFR: Estimated glomerular filtration rate, FLC: Free light chain, IFTA: Interstitial fibrosis and tubular atrophy, IQR: Inter-quartile range, LM: Light microscopy, MPGN: Membranoproliferative glomerulonephritis, PGNMID: Proliferative glomerulonephritis with monoclonal immunoglobulin deposits. †Evaluable patients (N) for hypercalcemia = 13, serum immunofixation electrophoresis = 12, serum free light chain assay = 13, bone marrow examination = 13, bone marrow immunohistochemistry = 12, N= total number, n=pathology present.

Type of light chain restriction on immunofluorescence

Patients with kappa light chain restriction (kappa-PGNMID) were younger (36.4 ± 13.3 vs. 48.4 ± 11.2 years, p = 0.077) with a male preponderance (M:F ratio 2:1 vs. 0.4:1, p = 0.315) [Supplemental Table 2]. Baseline proteinuria, eGFR, and serum complement levels were comparable between patients with kappa and lambda light chain restriction (lambda-PGNMID). Twenty-nine and fifty percent of kappa-PGNMID patients had a circulating monoclonal kappa light chain detected by serum IFE and FLC assay, respectively. Whereas none of the lambda-PGNMID patients had circulating monoclonal lambda light chain. One of these seven patients with lambda restriction had a circulating kappa monoclonal light chain. Subepithelial granular electron-dense deposits were more commonly seen in kappa-PGNMID (4/9, 44.4% vs. 0/7, p = 0.088). However, renal outcomes did not differ between the two groups (kidney failure: kappa-PGNMID 3/8, 37.5% vs. lambda-PGNMID 2/5, 40%, p = 0.862).

Discussion

PGNMID is a rare entity classified under the umbrella of monoclonal gammopathy of renal significance (MGRS) (biopsy incidence of 0.1%). To our knowledge, this is the largest case series of PGNMID from Indian subcontinent. The mean age of our cohort was much lower than previous studies³⁻¹³ with an equal incidence in males and females [Supplemental Table 2]. This is in contrast to the study by Nasr *et al.* who first described this entity primarily in elderly white female population.⁴ We observed that kappa-PGNMID patients were younger with a male preponderance. In a series of 17 cases of “light chain only” variant PGNMID described by Nasr *et al.*, majority (71%) had kappa restricted deposits. The median age at presentation however was 62 (range, 44–84) years, with majority (76%) being males.¹³

The most common presentation was nephritic-nephrotic syndrome (69%). The median eGFR at presentation was 36 (IQR, 24–75) mL/min/1.73 m², which was comparable to

previous studies.^{3,4} We observed that patients with MPGN patterns and those with detectable circulating MIg had more proteinuria at presentation. None of our patients had extra-renal involvement as reported in previous studies.⁶

A circulating MIg by IFE was detected in only 25% cases, which was similar to previous studies (20–37%) [Supplemental Table 2].^{4,8} An abnormal serum kappa: lambda FLC ratio was observed in 38% of our cases. None of the seven lambda-PGNMID patients had circulating monoclonal lambda light chain, whereas, half of the kappa-PGNMID patients had detectable circulating monoclonal kappa light chain. This may be explained by the low rate of monoclonal protein production in PGNMID which may be below the diagnostic threshold of currently available tools.⁶ PGNMID patients who undergo kidney transplantation experience high rates of early recurrence after renal transplantation with almost half of the patients losing their graft over a median period of three years.^{9–11} And again only 20% of these patients with recurrent PGNMID have a detectable circulating MIg (10). The other possible hypothesis is a “glomerular sieving phenomenon” due to the ability of IgG3 (the predominant heavy chain in PGNMID) to bind to negatively charged glomerular basement membrane and self-aggregate leading to high intraglomerular concentration.^{7,12} This explains why patients with “light chain only” variant of PGNMID have higher rates of detectable serum paraprotein (73% by serum electrophoresis and 83% by serum FLC assays).¹³

Only 8% (1/13) of our patients had bone marrow plasmacytosis >10% as reported in previous studies (0–17%).³ Patients with circulating MIg had a higher median percentage of plasma cells on bone marrow biopsy. None of our patients showed monoclonal restriction of marrow plasma cells by IHC. In contrast, half of the patients of “light chain only” variant of PGNMID had bone marrow plasmacytosis >10% with monoclonal light chain restriction.¹³ Bhutani *et al.* detected a nephropathic clone in 25% of PGNMID patients by bone marrow flow cytometry and in 11% by peripheral blood flow cytometry. The nephropathic clones detected were plasma cell (60%), B cell (30%), and lymphoplasmacytic cell (10%).³ In a study by Gumber *et al.*, a nephropathic clone was detected in 32% of patients by bone marrow flow cytometry. The detected clones were plasma cell (50%), B cell (33%), and lymphoplasmacytic cell (17%).⁸

MPGN was the most common light microscopy pattern seen in our study, similar to previous studies [Supplemental Table 2].^{4,8} Nasr *et al.* classified PGNMID into four stages based on the timing of kidney biopsy from the onset of disease. Stage 1 is a latent phase associated with monoclonal deposits in kidney with no mesangial proliferation and is clinically silent. Stage 2 is characterized by mesangial proliferation and mild proteinuria. Stages 3

and 4 PGNMID patients have endocapillary proliferative and membranoproliferative glomerulonephritis, respectively.⁹ None of our patients had membranous nephropathy, which is a rare pattern of PGNMID.^{14,15} In a series of 26 patients with allograft PGNMID, MPGN pattern was one of the predictors of allograft loss.¹⁰ We observed that patients with MPGN pattern had better renal outcomes despite higher degree of proteinuria at presentation.

In our study, IgG was the predominant monoclonal immunoglobulin detected in kidney, as reported in previous studies.^{3,4} There was almost an equal distribution of kappa and lambda PGNMID cases in our series unlike kappa predisposition seen in adults^{3–7,16} and lambda predisposition seen in pediatric series.^{17,18} Biconality (mismatch in monoclonal light chain detected in circulation and kidney biopsy) was seen in 8% of patients, similar to previous studies (7–14%).^{3,8,13} Subepithelial granular electron-dense deposits were more commonly seen in kappa-PGNMID patients.

One-third of patients in our cohort progressed to kidney failure (18–67% in previous studies) despite majority (81%) receiving some form of immunosuppression.^{3,8,13,16} Clone-directed therapy in PGNMID is gaining a lot of interest in recent years.^{8,19–21} In a case series of the eight ‘light chain only’ variant PGNMID cases treated with plasma cell targeted chemotherapy, six attained complete hematological and renal remission, one attained partial hematological remission with worsening kidney function and one had neither hematological nor renal remission.¹³ In a cohort of 64 PGNMID patients from China, Zhou *et al.* reported CR rates of 23%, 53%, and 50% with steroid, immunomodulatory drugs (thalidomide or lenalidomide) along with dexamethasone, and bortezomib-based plasma cell chemotherapy, respectively.²² Complete or partial renal remission was attained in 73%, 54%, and 29% of PGNMID patients (65 patients from 3 case series) treated with clone-directed, immunosuppressive, and conservative therapy, respectively.²³ In a series of 10 PGNMID patients treated with daratumumab (monoclonal anti-CD38 antibody), four attained CR, and remaining six attained PR. There was a significant decline in proteinuria from 4.3 g/day at baseline to 1.2 g/day at the end of 12 months.²⁴ In a series of five cases of bortezomib-resistant PGNMID treated with daratumumab for a median duration of 11.2 (range 5–19.1) months, one attained complete renal and hematological remission, two attained PR and two had no remission (of which one patient had histological improvement of immune deposits).²⁵ The other major cohorts are compared with this study in Supplementary Table 3. The major limitations of clone-directed therapy are low detection rate of nephropathic clones (25–32%), therapy-related toxicity, and absence of detectable clone to assess response to therapy.^{6,24–27} Supplemental Table 4 summarizes the recommended workup in PGNMID and the currently available treatment options.

Supplementary Figure 2 summarizes the current treatment recommendations of PGNMID.

Our study is not without limitations. The small size of our cohort and short duration of follow-up is a major limitation of our study. IgG subtyping is not routinely done at our center due to resource limitations. All our patients showed a clear light chain restriction by IF microscopy and each antibody testing was repeated at least twice by different technicians and interpreted by two renal pathologists to confirm concordance in reporting. All patients had typical granular electron-dense deposits without substructure in mesangial, subendothelial, and/or subepithelial locations on EM. Almost 70% of our patients received immunosuppression tailored to regimens used in glomerulonephritis (27–81% in previously reported cohorts). This depicts the real-world scenario wherein nephrologists and hematologists shy away from using toxic chemotherapeutic regimens in absence of detectable clones. Zhou *et al.* reported lower rates of M protein detection in PGNMID patients treated with steroid (3%) as compared to those treated with bortezomib-based plasma cell chemotherapy (40%).²² Bone marrow flow cytometry was not done in any of our patients, which could have increased the likelihood of detecting small pathogenic clones.

PGNMID is a rare renal disease with a biopsy incidence of 0.1% in our registry data spanning over 8 years. Only a quarter of patients with PGNMID had circulating MIg. The presence of circulating MIg, type of monoclonal light chain restriction in kidney biopsy, and type of therapy did not predict renal outcomes. Patients with MPGN pattern had favorable renal outcomes despite a higher degree of proteinuria at presentation. One-third of patients progressed to kidney failure despite immunosuppressive therapy necessitating the need for aggressive clone-directed chemotherapy. The future directions would be to develop sophisticated diagnostic techniques sensitive to pick up small nephropathic clones, unravel the pathomechanisms of renal injury, and need for a combined hemato-renal clinic for early diagnosis and initiation of clone-directed chemotherapy.

Conflicts of interest: There are no conflicts of interest.

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