A Case Series of Monoclonal Immunoglobulin-Depositing Proliferative Glomerulonephritis

Abstract

Proliferative glomerulonephritis with monoclonal immunoglobulin deposition disease (PGNMIDD) is a rare entity. We evaluated the clinicopathological features of PGNMIDD and the effectiveness of different treatment regimens in 13 cases diagnosed using kidney biopsy. Most had chronic kidney disease followed by acute nephritic syndrome, rapidly progressive glomerulonephritis, and nephrotic syndrome. Membranoproliferative glomerulonephritis was the most common pattern of renal injury. Three patients had abnormal bone marrow studies. Different treatment regimens were deployed; >60% had partial remission at the end of six months and 30.7% progressed to end stage renal disease.

Keywords: *Bortezomib, Cyclophosphamide, Renal replacement therapy, Steroids*

Introduction

Monoclonal gammopathy of renal significance (MGRS) is a group of hematological disorders linked to kidney diseases.[1] A rare form of this is called Proliferative glomerulonephritis with monoclonal immunoglobulin G deposition disease (PGNMIDD). A subset of PGNMIDD cases may be associated with underlying hematological neoplasms or viral infections.[2,3] Here, we present one of the largest series of PGNMIDD concerning its clinical characteristics, treatment modality, and outcomes from India.

Case Series

A total of 13 cases of renal biopsy–proven PGNMIDD were studied. Diagnosis was based on (1) Light microscopy of renal biopsy: presence of proliferative/membranoproliferative glomerulonephritis and presence of membranous glomerulonephritis. (2) Immunofluorescence: positivity for immunoglobulin class and presence of a single light chain isotype. (3) Absence of clinical/laboratory evidence of cryoglobulinemia. Definitions: (a) Acute nephritic syndrome – presence of hypertension, micro/macroscopic hematuria, edema, renal dysfunction, and proteinuria >500 mg/day. (b) Nephrotic syndrome – presence of proteinuria >3.5 gm/day with hypoalbuminemia, edema, and hypercholesterolemia. (c) Chronic kidney disease – documented raised serum creatinine >1.5 mg/dl of >3 months duration which was collected from the patients when they first attended our hospital. (d) RPGN– rapidly declining GFR of more than 50% for less than 3 months (the serial GFR was obtained by the documented serum creatinine values from elsewhere which were collected from the patients when they first attended our hospital). (e) Complete remission was defined as 24-hour urine protein <500 mg/day with serum creatinine <1.3 mg/dl. (f) Partial emission was defined as 50% reduction in serum creatinine and 50% reduction in proteinuria from baseline. Clinical characteristics, treatment regimens, and outcomes are shown in Table 1. Of the 13 cases, 10 (76.9%) were males. Low C3 was seen in three (23%) cases. Antinuclear Antibody (ANA) and Antinuclear Cytoplasmic Antibody (ANCA) profiles were negative in all. Only one patient had an M spike in Serum Protein Electrophoresis (SPEP), whereas serum and urine immunofixation was normal in all the cases. Serum-free light chain assay reports were available for three cases (case nos. 7, 9, 12); in cases 9 and 12 both individual chains (kappa and lambda) were elevated up to 10 times the upper limit of normal but the ratio was within normal limits, whereas in case no. 7 it was within normal limits. Bone marrow studies were done in three cases. Complete skeletal survey was done in all cases and none had lytic lesions. Beta 2 microglobulin was done in three patients and were elevated. FISH (Fluorescence in situ hybridization) was done in two patients and both were negative. Among the 13 cases, 10 received oral prednisolone (1 mg/kg prednisolone tapered to 10 mg/day at 6 months). Three of them received dexamethasone+bortezomib+cyclophosphamide [(I.V. cyclophosphamide 0.5 gm/m^2 on day 1, dexamethasone 40 mg orally on days 1–4, 9–12, 17–20, and injection bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11). Each cycle comprised 28 days. This regimen was administered for four cycles]. Immunosuppressive medications were stopped for patients who were hemodialysis dependent at the end of 6 months. Patients who showed complete or partial response at 6 months continued with steroids at the lowest effective dose, 10 mg/7.5 mg/day. At the end of 6 months, one patient (7.7%) had complete remission, eight (61.5%) had partial remission, and four (30.7%) were on maintenance hemodialysis. The follow-up was for 6 months and none of the patients had plasma cell disorder.

Discussion

In our study, most cases were males which is similar to the findings of other studies done by Gumber *et al.*[4] and Nasr *et al*.[5] PGNMIDD can be seen at any age, but most of our patients were in the fourth decade. Nephrotic syndrome was seen in 7% of our study subjects whereas it was seen in one-half of the patients with PGNMIDD elsewhere. Hematuria (microscopic/macroscopic) was found in 53% of our patients whereas it can be found in as much as 80%

Table 1: Clinical characteristics, treatment regimen, and outcomes of our cases

Case	Age (years)	Sex	Clinical syndrome	24-hour urine protein (gm)	Hematu-ria	Serum creatinine (mg/dl)	Light microscopy	IF	IFTA	Bone marrow	Treatment regimen	Outcome at the end of 6 months
1	34	M	Nephritic syndrome	5.5	Yes	2.5	MPGN	IgG 3+ C3 3+ K 3+	Nil	Not available	Oral prednisolone	CR
2	60	M	Nephritic syndrome	3.2	Yes	3.2	MPGN	IgG 3+ C3 3+ K 3+ C1q 2+	Moderate	Not available	Oral prednisolone	MHD
3	65	M	CKD	0.15	No	4.8	Endocapillary proliferation+ crescents	IgG 3+, C3 3+, C1q 2+ K 3+	Severe	Not available	Oral prednisolone	MHD
4	33	M	Nephrotic syndrome	9.2	No	1.6	Membranous form	IgG 3+, C3 3+, L 3+	Mild	Not available	Oral prednisolone	PR
5	33	F	RPGN	3.7	Yes	6.9	Endocapillary proliferation+ crescents	IgG 3+, C3 2+, K 2+	Moderate	Not available	Oral prednisolone	PR
6	75	M	CKD	0.4	No	1.8	MPGN	IgM 3+ L 3+	Nil	Not available	Dexamethasone+ bortezomib+ cyclophosphamide	PR
7	45	M	CKD	6.8	Yes	6.6	Mesangial + endocapillary proliferation	IgG 3+ C3 1+ C1q 1+ K 3+	Moderate	Hypercellular normoblast	Oral prednisolone	MHD
8	49	F	CKD	7.4	Yes	4	MPGN	IgG 3+ C3 2+ C1q 1+ K 3+	Nil	Not available	Dexamethasone+ bortezomib+ cyclophosphamide	PR
9	38	F	CKD	6.6	No	1.5	MPGN	G3+ C33+ L3+	Nil	Not available	Oral prednisolone	PR
10	74	M	RPGN	0.5	Yes	19.2	Mesangial+ endocapillary proliferation	IgG 3+ IgA 2+ IgM 2+ C3 3+ C1q 1+ K 3+	Mild	Normoblast with 3% plasma cell	Dexamethasone+ bortezomib+ cyclophosphamide	PR
11	45	M	CKD	0.5	No	3.2	MPGN	IgG3+ C3 2+ C1q 2+ L3+	Mild	Not available	Oral prednisolone	PR
12	65	F	CKD	2	Yes	7	Mesangial+ endocapillary proliferation	Ig G3+ IgM 2+ C32+ C1q 1+ K 3+	Moderate	Normoblast with 5% plasma cell	Oral prednisolone	MHD
13	40	M	CKD	0.8	No	2	MPGN	IgG 3+ IgM 2+ C3 2+ C1q 1+ K 3+	Mild	Not available	Oral prednisolone	PR

CKD-Chronic kidney disease, MPGN- Membranoproliferative glomerulonephritis, MHD-Maintenance hemodialysis, CR- Complete remission, PR- Partial remission, IF- immunofluorescence, IFTA- Interstitial fibrosis and tubular atrophy, K-Kappa Light chain restriction, L- Lambda Light chain, restriction RPGN - rapidly declining GFR

of patients.[6] Two-thirds of the patients may have azotemia, and less than 10% required dialysis at the time of diagnosis. Hypertension is a common finding in PGNMIDD, seen in 84% of our subjects. Hypocomplementemia is uncommon with low C3 and/or low C4 levels seen in 20% of patients;[6] 23% of our study subjects had low C3 and all had normal C4. Bone marrow studies are essential in PGNMIDD to detect the clone. Three (23%) patients had abnormal marrow, whereas it was 32% in the study done by Gumber *et al*.[4] In this study, MPGN was seen in 53.8% of the cases, similar to the findings of other studies. The unique renal histology findings noted here were combined mesangial and endocapillary proliferation in 23% and in membranous form in 7.6% of our patients, respectively. C1q deposition is seen in 60% of our patients. Specific treatment for PGNMIDD remains uncertain. In resource-constrained settings, cost of chemotherapeutics hinders treatment modalities. Various treatment regimens were deployed in this study with varying outcomes. More than 60% of our patients had partial remission at the end of 6 months, whereas in the study done by Gumber *et al.*[4] 13 of 17 (76%) treated patients had a response to their initial therapy, 6 (35%) of whom experienced a complete response; however, the treatment regimens employed were different from our study. There is sparse information in literature to compare the renal remission rates with other studies. A major challenge in PGNMIDD is clonal detection. Of the three patients who received combination therapy, one was a post-transplant female with recurrence of PGNMIDD, followed up for the next 4 years. She received a total of 64 doses of bortezomib to keep the disease in remission and another patient underwent autologous stem cell transplantation in view persistent proteinuria and worsening renal functions. Following stem cell transplantation she lost to our follow up.

The main limitations of this study where its retrospective nature and the lack of bone marrow studies, serum-free light chain assays, beta 2 microglobulin, and FISH were not done in some cases.

Conclusion

PGNMIDD is a heterogeneous disorder with the absence of any detectable clonal proliferation, thus making its management challenging. This study helps us to know the varied renal presentations, histological features, and treatment responses to various regimens in the Indian population.

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To our patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Conflicts of interest

There are no conflicts of interest.

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