Original Article

Multiple Facets of Multiple Myeloma in Kidney Biopsy: A Multicenter Retrospective Study

Abstract

Introduction: Multiple myeloma is a type of plasma cell dyscrasia, which causes clonal proliferation of plasma cells and deposition in various organ systems. At presentation, 50% of patients with multiple myeloma have kidney dysfunction, which is considered a poor prognostic indicator. Data on the histopathological manifestations of multiple myeloma are sparse. **Objective:** To look at the kidney histopathological lesions in patients with the clinical diagnosis of multiple myeloma. **Materials and Methods:** A retrospective analysis of all kidney biopsies in patients with the clinical diagnosis of multiple myeloma was performed from June 1, 2020 to May 30, 2022, from three tertiary care nephrology referral centers. **Results:** A total of 61 patients with multiple myeloma and biopsy-proven kidney involvement were included in the study. The mean age at presentation was 55.39 ± 11.91 years, with male predominance (male to female ratio -1.6:1). The most common lesion on kidney biopsy was myeloma cast nephropathy (72.1%), followed by light chain deposition disease (21.3%) and AL amyloidosis (18%). About 26% of patients had dual lesions on kidney biopsy, 3% had three types of lesions on kidney biopsy In 48% of patients, the diagnosis of multiple myeloma was made only after the kidney biopsy. **Conclusion:** Patients with multiple myeloma and kidney involvement should be biopsied as the type of histopathological lesion influences the treatment options and prognosis.

Keywords: *Kidney biopsy, kidney dysfunction, multiple myeloma*

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Introduction

In 1848, Dr. Bence Jones observed a "new substance" in the urine of a patient with "mollities ossium."[1] This was later termed as the Bence Jones protein, and an association of this new substance with plasma cell proliferation was established. The earliest disease state described with plasma cell proliferation is multiple myeloma (MM), which is defined as a clonal proliferation of plasma cells that produce monoclonal proteins that, in turn, cause organ damage. Fifty percent of patients with MM have kidney involvement at the time of presentation. The involvement of the kidney is associated with a poor prognosis and an increased mortality risk.[2]

The most common kidney lesions in MM are myeloma cast nephropathy (MCN), monoclonal immunoglobulin deposition disease (MIDD), and AL amyloidosis.[3] An autopsy study showed acute tubular necrosis in 34% of biopsies.[4] There are very few studies on kidney involvement in multiple myeloma, all of them include fewer than 50 patients[5-7], with the exception of two studies. Montseny *et al*.[8] showed that MCN was the commonest (41%) histopathologocal lesion followed by AL amyloidosis (30%) and MIDD (19%). Another study from the Mayo Clinic[3] also showed that MCN was the most common histopathological lesion (33%) followed by MIDD (22%), and AL amyloidosis (21%). In the past decade, we have witnessed an increase in the understanding of kidney lesions in MM, with the identification of newer lesions such as C3 glomerulopathy[9]. We report the histopathological lesions in patients with clinical diagnosis of MM.

Materials and Methods

A retrospective, multicenter study was conducted at three tertiary care referral centers in India: the Institute of Nephro Urology, Bengaluru; Nizam's Institute of Medical Sciences, Hyderabad; and Yashoda Hospitals, Secunderabad. Kidney biopsies conducted at these three centers from June 1, 2020 to May 30, 2022 were reviewed.

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Inclusion criteria: Biopsies with a clinical diagnosis of MM, made before or shortly after the kidney biopsy were included in the study. MM was defined as clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma and any one of the following myeloma-defining events[10,11]: serum calcium >11 mg/dl; serum creatinine >2 mg/; hemoglobin <10 g/dl; osteolytic lesions on skeletal survey radiography, computed tomography [CT, or positron emission tomography [PET-CT; serum-free light chain ratio >100, or more than one focal lesion on magnetic resonance imaging [MRI.

All patients with a clinical diagnosis of MM and kidney dysfunction were biopsied. Indications for kidney biopsy were classified as syndromes: (1) acute kidney injury (AKI); (2) chronic kidney disease (CKD); (3) nephrotic syndrome (NS); and (4) rapidly progressive renal failure (RPRF). Demographic and clinical parameters of the patients were recorded.

Kidney biopsy samples were processed for light microscopy and immunofluorescence. Light microscopy specimens were stained using hematoxylin and eosin, periodic acid–Schiff (PAS), Masson's trichrome, and Jones' methenamine silver. Polyclonal antibodies to IgG, IgM, IgA, C3, C1q, kappa, and lambda were stained for immunofluorescence.

Statistical methods

Descriptive and inferential statistical analyses were carried out. Results on continuous measurements are presented as mean ± SD (min.–max.), and results on categorical measurements are presented as number and percentages (%). Significance was assessed at a 5% level of significance. Student's *t* test (two-tailed, independent) was used to find the significance of study parameters on a continuous scale between two groups (intergroup analysis) on metric parameters. Levene's test was performed to assess the homogeneity of variance. Chi-squared or Fisher's exact test was used to find the significance of study parameters on a categorical scale between two or more groups in the non-parametric setting for qualitative data analysis. Fisher's exact test is used when cell samples are very small.[12,13] The IBM SPSS Statistics version 22.0 and R environment version 3.2.2 were used for the analysis of data. Microsoft Word and Excel were used to generate graphs, tables, etc.

Results

A total of 4263 kidney biopsy samples were reviewed, including 92 with a clinical diagnosis of MM. 31 samples did not have complete data; hence, 61 kidney biopsy samples were included in the study. The incidence of multiple myeloma–related kidney injury was 1.4%.

Population in the fifth and sixth decade of life were most commonly affected [Table 1], majority were males (62.3%). Hypertension was seen in 50.8% of patients, and diabetes mellitus in 14.8%. 70.5% of patients had a single lesion on kidney biopsy, 26.2% had dual lesions, and 3.3% had three lesions. The majority presented with AKI, followed by NS [Table 2]. A majority had proteinuria of >1 gm/24 hours (83.6%); two-thirds had a serum creatinine level >4 mg/dl. 93.4% had anemia and 26.2% had hypercalcemia at presentation. About one-third required kidney replacement therapy at presentation. Involvement of the heart was seen in 9.8% at presentation, and 4.9% had an infection at presentation. Among the histopathological lesions, the most common was MCN, followed by MIDD (light chain deposition disease [21.3%] and light and heavy chain deposition disease [3.3%],

Table 1: Comparison of clinical/biochemical assessment in relation to kidney replacement therapy of patients studied

Variables	Requirement of kidney replacement therapy		Total	*P*
	No	Yes		
Age in years	53.89±13.33	57.87±8.84	55.39±11.92	0.209
24-hour urine protein (grams)	3.58±2.27	3.88±3.46	3.7±2.76	0.687
Serum creatinine at presentation (mg/dl)	4.11±3.03	10.18±3.37	6.4±4.32	<0.001**
B urea (mg/dl)	89.39±57.82	158±60.49	115.26±67.28	<0.001**
Hemoglobin (gm%)	8.32±1.85	7.44±1.56	7.99±1.79	0.060+
Calcium (mg/dl)	9.29±1.31	9.62±3	9.41±2.1	0.553
Phosphorous (mg/dl)	4.74±1.43	6.01±1.36	5.22±1.52	<0.001**
Uric acid (mg/dl)	8.5±3	10.97±6.58	9.43±4.78	0.049*
Alkaline phosphates (U/L)	179.84±152.45	113.43±81.93	154.8±133.59	0.059+
Albumin (gm/L)	2.71±0.78	3.36±0.74	2.96±0.82	0.002**
Globulins (gm/L)	6.78±1.94	6.01±2.1	6.49±2.02	0.154
Cholesterol (mg/dl)	178.89±96.51	145.78±55.31	166.41±84.42	0.139
Triglycerides (mg/dl)	189.5±79.12	209.61±112.29	197.08±92.63	0.416
Right kidney size (cm)	10.33±1.05	10.09±1.03	10.24±1.04	0.379
Left kidney size (cm)	10.45±1.01	10.15±0.84	10.34±0.95	0.232

Legend: +Suggestive significance (*P*: 0.05<*P*<0.10), * Moderately significant (*P*: 0.01<*P*≤0.05), ** Strongly significant (*P*: *P*≤0.01)

AL amyloidosis, C3 glomerulonephritis, proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID), nodular sclerosis, plasma cell infiltration, and interstitial nephritis. [Figure 1, Tables 3 and 4].

Among patients with low C3 (36.1%), the majority had light chain cast nephropathy (72.72%) followed by light chain deposition disease (31.8%), AL amyloidosis (13.63%), C3 glomerulopathy (9.09%), light and heavy chain deposition disease (9.09%), and light chain proximal tubulopathy (9.09%). Dual lesions were significantly associated with low C3.

In this series, the primary diagnosis of MM was made on kidney biopsy in 47.54% of patients. These patients were biopsied for their renal indications, and the diagnosis of MM was not clinically considered before the biopsy.

Among the biochemical parameters, high serum creatinine, uremia, phosphorous, hyperuricemia, anemia, hypoalbuminemia; AKI and RPRF; presence of MCN and higher levels of involved free light chains were significantly associated with the requirement of kidney replacement therapy (KRT).

Table 2: Nephrological syndrome-frequency distribution in relation to kidney replacement therapy of patients studied

Nephrological syndrome	Requirement of kidney replacement therapy		Total
	No	Yes	
Acute kidney injury	16 (42.1%)	19 (82.6%)	35 (57.4%)
Nephrotic syndrome	12 (31.6%)	0 (0%)	12 (19.7%)
Rapidly progressive renal failure	5 (13.2%)	3 (13%)	8 (13.1%)
Chronic kidney disease	5 (13.2%)	1 (4.3%)	6 (9.8%)
Total	38 (100%)	23 (100%)	61 (100%)

P=0.002**, significant, Fisher's exact test. Legend: +Suggestive significance (*P*: 0.05<*P*<0.10, * Moderately significant (*P*: 0.01<*P*≤0.05), ** Strongly significant (*P*: *P*≤0.01)

Discussion

About half of all patients with multiple myeloma present with kidney dysfunction[14], in concordance with this study. Also, the incidence of myeloma-related pathology among all the kidney biopsies performed was found to be 1.4%. Most patients were males in their sixth and seventh decades of life. This is consistent with previous studies.[15–18] Hypertension is seen in patients with kidney involvement, especially in MCN and light chain deposition disease (LCDD).[19] The presence of anemia, hypercalcemia, and hyperuricemia, was consistent with a study by Sakhuja *et al.*[16] However, there was no association between creatinine levels and histopathological severity of the disease. Higher creatinine levels presented as AKI and RPRF, and patients with AL amyloidosis presented with NS and normal creatinine levels. This study had a majority of samples with trace and/or 1+ proteinuria on dipstick (60.7%), and the mean 24-hour proteinuria was 3.7 ± 2.76 g, while Nasr *et al*.[3] reported mean proteinuria of 2.5 g.As India is a developing country, patient's presentation to a tertiary care center is delayed due to lack of awareness and poor socioeconomic status.

The most common indication for kidney biopsy was non-recovering AKI which was similar to previous studies.[3,18,19,20]

Among patients with low C3, majority had MCN followed byLCDD, AL amyloidosis, and C3 glomerulopathy. Dual lesions were significantly associated with low C3. Zand *et al.*[21] proposed the hypothesis that abnormal monoclonal immunoglobulins dysregulated the complement system leading to low C3 levels[22].

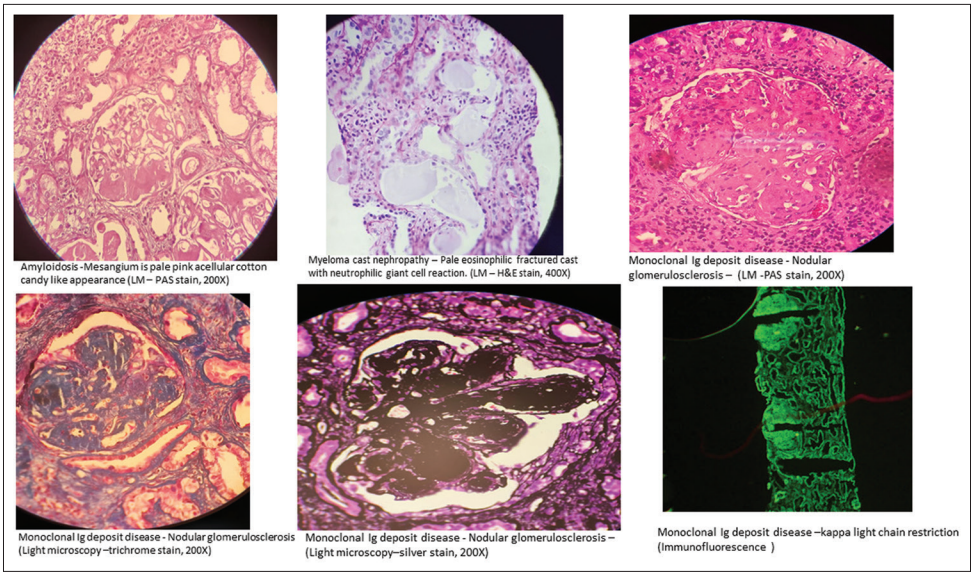

Figure 1: Spectrum of histopathology lesions in multiple myeloma. Image credit: Dr. Vinay. K. S.

Table 3: Spectrum of histopathological lesions in multiple myeloma

Variables	Requirement of kidney replacement therapy		Total	*P*
	No	Yes		
Light chain proximal tubulopathy				
No	35 (92.1%)	20 (87%)	55 (90.2%)	0.663
Yes	3 (7.9%)	3 (13%)	6 (9.8%)	
Light chain cast nephropathy				
No	17 (44.7%)	0 (0%)	17 (27.9%)	<0.001**
Yes	21 (55.3%)	23 (100%)	44 (72.1%)	
AL amyloidosis				
No	27 (71.1%)	23 (100%)	50 (82%)	0.004**
Yes	11 (28.9%)	0 (0%)	11 (18%)	
Light chain deposit disease				
No	31 (81.6%)	17 (73.9%)	48 (78.7%)	0.529
Yes	7 (18.4%)	6 (26.1%)	13 (21.3%)	
Light and heavy chain deposit disease				
No	36 (94.7%)	23 (100%)	59 (96.7%)	0.522
Yes	2 (5.3%)	0 (0%)	2 (3.3%)	
C3Glomerulonephritis				
No	37 (97.4%)	22 (95.7%)	59 (96.7%)	1.000
Yes	1 (2.6%)	1 (4.3%)	2 (3.3%)	
Proliferative glomerulonephritis with monoclonal immunoglobulin deposits	1 (2.6%)	1 (4.3%)	2 (3.3%)	
Nodular sclerosis	1 (2.6%)	1 (4.3%)	2 (3.3%)	
Plasma cell infiltration				
No	37 (97.4%)	23 (100%)	60 (98.4%)	1.000
Yes	1 (2.6%)	0 (0%)	1 (1.6%)	
Interstitial nephritis				
No	37 (97.4%)	23 (100%)	60 (98.4%)	1.000
Yes	1 (2.6%)	0 (0%)	1 (1.6%)	
Total	38 (100%)	23 (100%)	61 (100%)	

Legend: + Suggestive significance (*P*: 0.05<*P*<0.10, * Moderately significant (*P*: 0.01<*P*≤0.05), ** Strongly significant (*P*: *P*≤0.01)

Table 4: Light chain/heavy chain restriction in immunofluorescence

Light chain/heavy chain restriction	No. of patients	%
Kappa chain	32	52.45
Lambda chain	29	45.54
IgG and K	5	8.1
IgG and L	1	1.6
IgA and K	1	1.6
Kappa only	26	42.62
Lambda only	27	44.26
Total	61	100.0

Patients who presented with renal symptoms prior to the diagnosis of MM had significantly more anemia and hypercalcemia than those already diagnosed with MM who presented with predominantly bony pain and fracture. However, there was no significant difference in the type of histopathological lesion between the two groups. This was in accordance with previous studies.[16,17,23]

The kidney injury pattern depends on the immunoglobulin's physicochemical properties and host factors.[24] Similar to previous studies,[3,16–18,25] MCN was also the most common lesion in this study and was characterized by fractured casts in the tubules along with giant cell reaction. Sanders *et al.*[26] studied 36 patients across the spectrum of paraproteinemia and found AL amyloidosis as the most common lesion. In contrast, this study showed that MIDD was slightly more common than AL amyloidosis, similar to the study by Nasr *et al*.[3] This study included established cases of MM leading to selection bias, as bone marrow plasma cells <10% were not included. There is also a possibility that the diagnosis of AL amyloidosis might have already been established by fat pad biopsy or tongue biopsy, and hence, kidney biopsy might have been deferred. Proliferative glomerulonephritis was seen in four patients. Two of these had dominant C3 deposits on immunofluorescence and were thus diagnosed as C3 glomerulonephritis; the remaining two cases had lambda light chain restriction, thereby confirming PGNMID.[27]

Not all kidney biopsy lesions of MIDD, AL amyloidosis, and C3 glomerulopathy are mutually exclusive; about 30% had more than one lesion. Similar to previous studies,[3,28] proximal light chain tubulopathy was uncommon. This

might not be completely represented because we included patients who had been diagnosed with MM. Proximal light chain tubulopathy precedes the development of MM by months and years and might have been missed.

The pathological lesions demonstrated from this study were diverse and heterogeneous.[3,26,16,17] This could be due to the small number of cases studied previously and newer lesions such as C3 glomerulopathy being identified only during the last decade. Published studies are more than a decade old. Additionally, the studies from the Indian population are more than two decades old.[16,17]

Among the biochemical parameters, high serum creatinine, uremia, phosphorous, hyperuricemia, anemia, and hypoalbuminemia were significantly associated with the requirement for KRT. This is indicative of a hypercatabolic state. This was consistent with a study by Knudsen *et al.*[29] This study showed that high levels of free light chain were associated with increased kidney dysfunction, similar to results of Yadav *et al.*,[30] irrespective of the involved paraprotein. The secreted free light chains are very high in quantity and nephrotoxic. The proximal tubular cells are unable to reabsorb the excess amount of filtered free light chains, thereby leading to kidney injury.[31] Serum protein electrophoresis (SPEP) was positive for M spike in 86.9% of patients. There was no association found between SPEP positivity and kidney histology.

Among the histological lesions, the presence of MCN was significantly associated with the requirement of KRT. In contrast to this, patients with AL amyloidosis did not require KRT. These findings were similar to *previous studies.*[32,33]

EM is essential to identify the deposits of paraprotein, but it was not done due to financial constraints. As the patients were referred to the department of medical oncology for further management there was lack of data on treatment modalities and outcome.

Conclusion

This multicentric study shows a diverse and heterogenous spectrum of kidney lesions in MM. Kidney biopsy is essential to identify kidney lesions with important prognostic and therapeutic implications.

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Conflicts of interest

There are no conflicts of interest.

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