ORIGINAL ARTICLE

# Clinicopathologic Spectrum of Newly Diagnosed Multiple Myeloma Presenting with Severe Renal Impairment Requiring Dialysis : A Tertiary Care Center Experience from North India

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**ABSTRACT :**

**Background :** Renal involvement may be the first manifestation of multiple myeloma (MM). Impaired kidney function occurs in up to 50% patients of MM and 1-5% may require renal replacement therapy. We describe the clinicopathological spectrum of MM patients presenting as acute kidney injury (AKI) requiring dialysis.

**Methods :** This prospective observational study included all patients of MM presenting with AKI requiring dialysis between July 2016 and June 2017. Diagnosis of MM was made according to the International myeloma working group guidelines 2014. Demographic, clinical and laboratory data of the patients were recorded in a standard proforma

**Results :** Out of 531 patients admitted with AKI, 32 (6.0%) had AKI due to MM. Mean age of study population was 55.5±12.1 years and 66% were males. Most common symptoms were anorexia (57%), 81% had severe anemia (Hb<8gm/dl), 72 % had albumin globulin ratio reversal (<1). Hypercalcemia (S. $Ca^{2}$+ >11mg/dl) was present in 25% of patients while 41% had hypocalcemia (S.$Ca^{2}$+<8.2mg/dl). Osteolytic lesions were detected in 8 (25%) patients. Mean plasma cells percentage in bone marrow biopsy was 22.25 (±11.9). Most common lesion on renal biopsy was myeloma cast nephropathy (MCN) (81%), followed by light chain deposition disease (LCDD) (19%).

Serum calcium (9.3±2.2 vs. 7.5±0.37, p=0.01), serum creatinine (12.27±4.8 vs.5.0±0.75, p=0.02), and ratio of involved and uninvolved light chain (373.0 IQR: 155.7-959.90 vs. 55.0, IQR: 23.24-55.00, p=0.04) were significantly higher in MCN patients as compared to LCDD patients while 24 hrs urinary protein (0.9±0.57 vs. 2.8±0.9, p= 0.007) was lower in MCN patients.

**Conclusion :** MM is a common cause of AKI especially in older age. MCN is the most common cause of severe renal failure followed by LCDD. MCN patients have higher serum creatinine , higher calcium level, higher ratio of involved and uninvolved light chain and lower urinary protein excretion at presentation compared to LCDD patients.

**Keywords :** Multiple myeloma, Cast Nephropathy, Light Chain deposition disease, Acute kidney injury, Dialysis

## INTRODUCTION :

Multiple myeloma (MM) is a hematologic malignancy, characterized by the neoplastic proliferation of plasma cells producing a monoclonal immunoglobulin. Most patients with MM present with signs or symptoms related to the infiltration of plasma cells into the bone or other organs or to kidney damage from excess light chains. Renal involvement

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a common feature of MM and may be the first manifestation of the disease.

Impaired kidney function in MM, occurs in up to 50% of patients and is an independent factor for poor prognosis[1,2]. Acute kidney injury (AKI) requiring dialysis generally occurs in 1 to 3 percent of patients with MM but in some studies it has been reported in up to 12 percent[3]. Majority of renal complications are because of deposition of monoclonal immunoglobulins (paraproteins) or free light chains in the glomeruli or tubules. Pathological spectrum of renal disease due to paraprotein deposition includes myeloma cast nephropathy (MCN), amyloid light chain (AL) amyloidosis, monoclonal immunoglobulin deposition disease (MIDD), membranoproliferative glomerulonephritis (MPGN), and light chain proximal tubulopathy[4-7]. There may be many other causes of renal impairment like acute tubular necrosis due to hypocalcaemia, nonsteroidal anti-inflammatory drugs, dehydration and nephrocalcinosis (in the setting of tumor lysis syndrome or hypercalcemia) and acute interstitial nephritis. There is a strong correlation between the presence and severity of renal function impairment and patient survival. Survival is particularly poor among dialysis-dependent patients with MM[3-8].

There is paucity of clinicopathological studies of MM presenting as AKI requiring dialysis. In this study we describe the clinicopathological spectrum of MM patients presenting as AKI requiring dialysis.

## MATERIAL AND METHODS :

**Study design :** Prospective observational study

**Study Period :** July 2016 to June 2017.

**Study centre :** Nephrology department of Sawai Man Singh Medical College and hospital, Jaipur, India

**Inclusion criteria :** All patients of MM admitted in our department with severe renal failure requiring dialysis.

**Exclusion criteria:**

1. Those patients, whose renal function recovered with conservative management like adequate hydration, treating infections and stopping nephrotoxic drugs were not included in the study.
2. Those patients who had history of renal dysfunction for more than three months or having contracted kidneys (< 8.5 cm in length) were excluded from study.

**Method :** Clinical data, including demographic information and laboratory findings on presentation were obtained by reviewing medical records and interviewing the patients. For the diagnosis of MM, other than routine investigations, bone marrow biopsy, Serum protein electrophoresis and immune electrophoresis, serum free light assay with kappa lambda ratio and skeletal X-rays were done.

Diagnosis of MM was made according to the International myeloma working group guidelines 2014. Renal biopsy was done as a part of standard clinical practice to find out the cause of acute renal injury, if there was no contraindication for renal biopsy. Standard processing of kidney biopsy specimens included light microscopy, immun of luorescence, and electron microscopy.

**Statistical analysis :** Continuous variables are presented as mean ± standard deviation or median and inter quartile range (IQR) and compared using Student t test or Mann-Whitney U test, where appropriate. Categorical variables are presented as proportions and compared using Pearson's chi- square test. A p-value <0.05 was considered significant. The statistical analysis was performed using the SPSS software (version 20).

**Ethical approval :** Approved by Institute's ethics committee.

## RESULTS :

Out of 531 patients admitted with AKI requiring dialysis during the study period, 32 (6.0%) had AKI

due to MM. Twenty one (65%) were males. Mean age of study population was 55.5±12.1 years.

Most common symptoms were anorexia (57%) followed by edema (41%), nausea or vomiting (39%), weakness (29%), decreased urine output (24%), breathlessness (20%). Bone pain was present in 17% of patients while fever at presentation was found in only 11% of patients.

Anemia (Hb<10gm/dl) was present in all patients while 81% patients were found to have severe anemia (Hb<8gm/dl).Hypertension (BP>140/90 mm Hg) at presentation was detected in 21(66%) patients. Hepatomegaly was found in 15% and splenomegaly in 6% of patients.

Albumin globulin (A:G) ratio was reversed in 23 (72%) patients. Hypercalcemia (S. Ca2+ >11mg/dl) was present in 25% of patients while 41% of patients were having hypocalcemia (S. Ca2+<8.2mg/dl). Hyperuricemia was found in 68% of patients. Osteolytic lesions were detected in 8 (25%) patients. All patients were found to have monoclonal light chain in serum with abnormal kappa lambda ratio (<0.26 or >3.1).Serum protein electrophoresis revealed monoclonal band in all patients. Mean serum M band was 4 . 12 ± 1 . 96 gm. S. immune electrophoresis revealed that 15 (47%) patients were having IgG while only light chain was found in 13 (41 %) patients. Remaining 4(12%) patients were having IgA as monoclonal immunoglobulin. In bone marrow biopsy mean plasma cells percentage was 22.25 (±11.9).

Most common lesion on renal biopsy was MCN in 26(81%) patients followed by light chain deposition disease (LCDD) in 6(19%). One patient with MCN also had tubular LCDD while another patient with MCN had glomerular amyloid deposition. Five patients (83%) of LCDD were having nodular glomerulosclerosis. 24 hrs Urine protein in LCDD group (2.8±0.9gms) was significantly higher compare to MCN group ( 0.9±0.57gms) (P=0.007).Two patients in LCDD group (33.3%) had nephrotic range proteinuria.

Serum calcium (9.3±2.2 vs. 7.5±0.37, p=0.01) and serum creatinine (12.27±4.8 vs.5.0±0.75, p=0.02), were significantly higher in MCN patients as compared to LCDD patients (Table 2). Kappa was the predominant light chain in LCDD patients (kappa/lambda-2:1) while MCN patients have kappa, lambda involvement in almost equal frequency (6:7). S. M band level was significantly higher in MCN patients compared LCDD patients (4.6±2.0 vs 2.4±0.99 gm, p=0.03). Similarly, ratio of involved and uninvolved light chain (373.0 IQR: 155.7-959.90 vs. 55.0, IQR: 23.24-55.00, p=0.04) was significantly higher in MCN patients as compared to LCDD patients.

**DISCUSSION :**

MM is one of a common cause of AKI requiring dialysis in our center. It is a disease of older age. However the mean age of presentation in our subject was 55.5 years, lower than that reported in literature (66 years)[1].

Most common symptoms of MM patients are weakness and easy fatigue due to rapidly developing severe anemia followed by bone pain because of bone invasion and pathological fractures[1] . Renal impairment is common in MM patients. About 20-50% patient may have renal involvement at presentation and thus many patients may present first time with symptoms related to renal impairment[1,3,7]. Decreased urine output and symptoms related to volume overload were found in about quarter of patients and were more common in patients of LCDD which may be because of glomerular pathology in LCDD. Many patients of MCN were dry and dehydrated at presentation and urine output recovered in most of them with adequate hydration. In an Indian study, non-steroidal anti-inflammatory drugs were the most common precipitating factor for AKI in multiple myeloma[9]. Bone pain was present in 17% of patients at presentation while fever was found in 11% of patients. Kyle et al found bone pain at presentation in 58% of patients while fever was found in less than

1% of cases[1]. Hypercalcemia was present in 25% of patients. Kyle et al. found hypercalcemia in 28% cases of MM and in 13% cases of MM with renal failure[1]. Osteolytic lesions were detected in only quarter of our patients by conventional radiography which was significantly different from other studies[1,6,10] in which lytic lesions were reported in up to 60% of cases. Sakhuja et al found that hypercalcemia and skeletal abnormalities were more frequent in those with renal involvement while in our study hypocalcemia (41%) was more common which might be because of severe renal failure[6,7]. Sakhuja et al found light chain myeloma in 68% of those with renal involvement[7]. In our study too, only light chains were detected in 41% cases which was higher than that reported in literature and indicates that light chain myeloma patients have high risk of renal injury. Mean plasma cell in bone marrow was 22.25% which was lower in comparison to other studies[1,6-7] while serum M band was found to be high (4.12 gms) in comparison to others[1,6]. It indicates that severity of renal involvement is not related to high tumour burden but was related to high level of monoclonal immunoglobulin.

In renal biopsy only 2 types of lesions were found, first and most common lesion was MCN (81%) followed by LCDD (19%) while in other studies various type of lesions have been described which may or may not be related to monoclonal immunoglobulins[4-7]. Reason behind this may be that we have included only those patients who were having severe renal failure requiring renal replacement therapy and these two lesions are known to cause severe renal injury. Nasr et al also found MCN as most common lesion (33%) followed by MIDD (22%)[6]. Two patients of MCN were having interstitial infiltration by plasma cells but none of the patient was having isolated interstitial nephritis as a cause of renal failure which is contrary to previous literature in which tubulointerstitial nephritis has been described as an important cause of renal failure in MM patients[6,7]. Mean interstitial fibrosis and tubular atrophy (IFTA) was found to be high in MCN group (26.5%) in comparison to LCDD group (15.0%) but it was not statistically significant. S. Creatinine was significantly high in MCN group in comparison to LCDD group which signify that patients of MCN have severe renal failure and it was observed that patient having very high S.Creatinine at presentation, were having cast nephropathy. 24 hours urinary protein was significantly high in LCDD group in comparison to MCN group which is explainable because LCDD patients were having glomerular pathology. Hematuria and proteinuria are the known features of LCDD

LCDD patients have predominantly κ light chain involvement while MCN patients have both κ and λ light chain involvement in almost equal frequency which was similar to previous literature[11]. Mean serum M band level was significantly high in MCN patients which indicates that cast nephropathy is associated with high concentration of free light chains in serum. Nasr et al. found that mean bone marrow plasma cell percentage was significantly high in MCN group in comparison to LCDD group[6], no such difference found in our study.

Our study included MM patients with severe AKI requiring dialysis, a scenario commonly seen in tertiary care nephrology centers. Our study is limited by small sample size. Further our study intended to describe the clinic-pathological spectrum of these patients. We did not follow treatment and outcomes of these patients. Larger prospective studies will be needed to better define clinic-pathological spectrum and outcome of these patients.

## CONCLUSION :

MM is a common cause of AKI especially in older age. MCN is the most common cause of severe renal failure followed by LCDD. MCN patients have higher serum creatinine, calcium level and lower urinary protein excretion and lower ratio of involved and uninvolved light chain at presentation compared to LCDD.

**Conflict of interest :** None

**Acknowledgement :** None

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