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Original Article

Pathology Section

Spectrum of Renal Histopathological Changes in Multiple Myeloma

THUNDI PARAMBIL RAGHAVAN NISHA[1], CHETTITHODI SIVASANKARAN BINDU[2], BHASKARAN K SINDHU[3]

ABSTRACT

Introduction: Renal involvement is very common in myeloma. The evaluation of renal status plays an important role in diagnosis and prognosis of patients with myeloma. The kidney biopsy will show various patterns of injury and the chronicity of the disease which help in planning the treatment options. Myeloma comprises a significant number of malignancies but no data regarding renal biopsy changes in myeloma is available from North Kerala, India.

Aim: To describe the various morphological patterns of renal involvement in all myeloma patients who required a renal biopsy for evaluation of renal dysfunction.

Materials and Methods: It was a retrospective, descriptive study conducted at Government Medical College, Kozhikode, India, a tertiary care centre from January 2016 to December 2019. A total of 63 patients of myeloma who underwent a renal biopsy for evaluation of renal dysfunction as the initial presentation or immediately after diagnosis were included in this study. Serum electrophoresis, skeletal survey, complete blood counts, bone marrow study and biochemical evaluation for serum creatinine, total protein, albumin globulin ratio were done in all patients. Data was analysed using standard analytical techniques with Statistical Package for the Social Sciences (SPSS) version 16.0 for windows.

Results: A total of 63 patients presented with renal dysfunction as initial symptom underwent renal biopsy. Most common age group of the study population was between 50-70 years. In 47 (74.6%) patients the renal dysfunction was the initial presenting symptom of myeloma. The presenting features were acute renal failure, nephrotic syndrome and acute nephritis. The renal biopsy findings included myeloma cast nephropathy, amyloidosis, proliferative glomerulonephritis and tubulointerstitial nephritis with cast nephropathy being most common pattern. Acute renal failure was more common in cast nephropathy while amyloidosis presented with nephrotic syndrome. The serum creatinine and calcium levels, plasma cell counts and degree of anaemia had a correlation with histological pattern of injury.

Conclusion: Acute kidney injury due to myeloma cast nephropathy is a medical emergency and prompt therapy with measures to reduce light chain load along with correction of dehydration can reduce renal damage and increase the patient survival. Many newly described entities like fibrillary and immunotactoid nephropathy can occur in myeloma and these can be identified only by electron microscopic evaluation of kidney tissue. They have important prognostic impact and significance when renal transplants are planned for. So, renal biopsy supported by newer methods like immunohistochemistry and electron microscopy is a must to keep pace with newer advances in myeloma treatment like autologous stem cell transplantation.

Keywords: Clinical profile, Haematological, Renal biopsy

INTRODUCTION

Renal dysfunction is one of the most important causes for mortality and morbidity in myeloma patients. Frequently, it is the presenting complaint or it may develop during the course of disease. The immunoglobulins and light chains produced by the neoplastic clone of plasma cells are excreted through the kidney which makes them vulnerable to damage. Renal involvement may take various forms as cast nephropathy, amyloidosis or renal tubular defects, each of which has distinct therapeutic and prognostic effects. The extent of renal damage is also an important prognostic factor in myeloma. Therefore, even though haematology, serology, radiology and bone marrow studies are needed for confirmation of myeloma, a renal biopsy is a must in the management of myeloma patients who present with renal dysfunction. It is required for evaluation of the extent of renal damage and for categorising the type of kidney involvement which aids in further treatment decisions and prognostication of the disease. Even though, myeloma comprises about 2% of malignancies in Kerala, India, no data regarding renal biopsy findings in myeloma are available from Kerala [1].

Hence, the present study was conducted with an aim to describe the various histopathological patterns of involvement of kidney in all patients with myeloma who presented with renal dysfunction and required a renal biopsy. A correlation of biopsy findings with clinical and haematological parameters was also made.

MATERIALS AND METHODS

This was a retrospective, descriptive study conducted at Government Medical College, Kozhikode, India, a tertiary care centre, retrospectively from 1st January 2016 to 31st December 2019. Data was collected in March 2020 and ethical approval was obtained from the Institutional Ethics Committee (IRC2017/Protocol 142). A total 451 cases of myeloma were diagnosed by examination of bone marrow in the institutional lab during this period. Myeloma diagnosis was made based on the 2016 updated International Myeloma Working Group criteria [2].

Inclusion criteria: Cases with clonal marrow plasmacytosis confirmed by M band in serum or urine and an adequate renal biopsy done cases were included in the study.

Exclusion criteria: All patients in which monoclonality of plasma cell population was not confirmed or had an inadequate renal biopsy sample were excluded from the study.

A clonal marrow plasmacytosis was confirmed based on the presence of monoclonal immunoglobulins in serum or urine along with any two of the following features as anaemia, lytic bone lesions, renal dysfunction or hypercalcaemia to diagnose myeloma. A total of 63 patients of myeloma who underwent a renal biopsy for evaluation of renal dysfunction as the initial presentation or immediately after diagnosis were included in the present study. Serum electrophoresis, skeletal survey Complete Blood Counts (CBC), bone marrow study

and biochemical evaluation for serum creatinine, total protein, albumin globulin ratio were done in all patients. Serum free light chain assay or Immunohistochemistry (IHC) for Kappa, Lambda was done in a few cases.

STATISTICAL ANALYSIS

Statistical analysis of data was done by entering data in the spread sheets of Microsoft excel. The variables were analysed using standard analytical techniques with SPSS software version 16.0 for windows. The quantitative variables were expressed as mean and qualitative variables were expressed as percentages. The association between variables was analysed using Chi-square test. The p-value was calculated and values <0.05 were taken as statistically significant. The correlation was done using Pearson's Chi-square test and r-value of ±1 was noted.

RESULTS

Of the 451 patients diagnosed with myeloma during the study period, 63 (14%) developed evidence of renal dysfunction requiring a renal biopsy. The most common age group involved was between 50-70 years, only 8 (12.7%) patients were below 50 years and majority were males (60%). In 47 (74.6%) patients, the initial presentation was a symptom related to renal dysfunction and in the rest it was related to bone or marrow involvement like bone pains, lytic lesions and anaemia. The most common clinical symptoms identified were features of acute kidney injury like oliguria, low back ache and oedema, fever and tiredness. The distribution of presenting complaints is shown in [Table/Fig-1].

Presenting complaint	n (%)
Acute kidney injury	14 (22.2)
Low backache	13 (20.6)
Pallor	3 (4.8)
Fatigue	5 (8.0)
Oedema	13 (20.6)
Loss of appetite	7 (11.1)
Arthralgia	1 (1.6)
Fever	3 (4.8)
Infection	4 (6.3)
Total	63 (100)

[Table/Fig-1]: Distribution of presenting complaints in the study population expressed as both numbers and percentages.

Acute renal failure was the most common clinical presentation of renal involvement followed by nephrotic syndrome, sub nephrotic proteinuria, rapidly progressive renal failure and chronic kidney injury. A precipitating event for renal dysfunction was identified in 36 (57.1%) patients, the most common being drugs like Non Steroidal Anti-inflammatory Drugs (NSAIDs) and indigenous medications (89%) followed by infections. A 15 patients had associated diabetes and four had underlying hypertension.

Anaemia which was defined as haemoglobin below 10 mg/dL, which was seen in 40/57 (70.1%) of cases, 9/57 (15.7%) had severe anaemia with haemoglobin below 5 gm/dL and 8/57 (14.03%) had normal values with haemoglobin above 10 gm/dL [Table/Fig-2]. The Erythrocyte Sedimentation Ratio (ESR) values were available only in 44 patients of which elevated ESR was seen in 98% of the cases. Plasma cells in marrow were increased in 55 (87.3%) patients and were more than 50% in approximately 32% with one having a plasmablastic morphology. Serum creatinine levels of more than 1.4 mg/dL were seen in 92% of patients and of this, it was more than 5 mg in 38% of patients. Serum calcium was available in 36 patients only and in this hypercalcaemia was seen only in 36%. Urine free light chains were increased in 61% and the serum electrophoresis revealed M band in 69% of the cases. Skeletal survey showed lytic lesion in 40% cases which involved commonly a single bone or rarely multiple sites. Ultrasound abdomen was done in 28 cases, of which nine showed enlargement of the kidneys.

S. No.	Haemoglobin values	Frequency (n)	Frequency (%)
1	Normal/mild anaemia (above 10 gm/dL)	8	14.03%
2	Moderate anaemia (5-10 gm/dL)	40	70.1%
3	Severe anaemia (<5 gm/dL)	9	15.7%
4	Values not available	6	

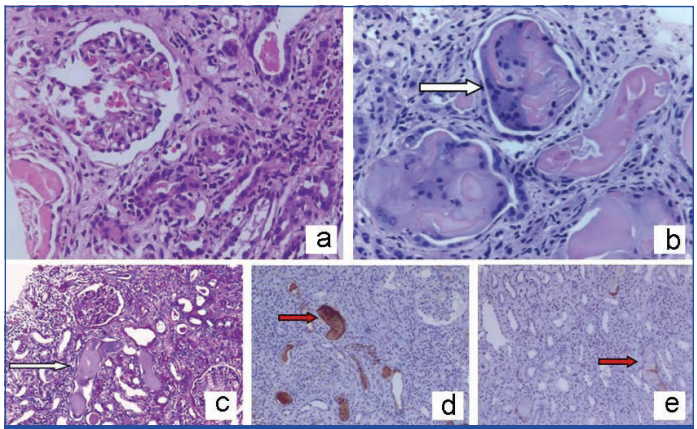
[Table/Fig-2]: Data regarding occurrence of anaemia in the study population.

Renal histology revealed a spectrum of abnormalities affecting the glomerular, tubular, interstitial or vascular components. The spectrum of patterns revealed in renal biopsy is given in [Table/Fig-3].

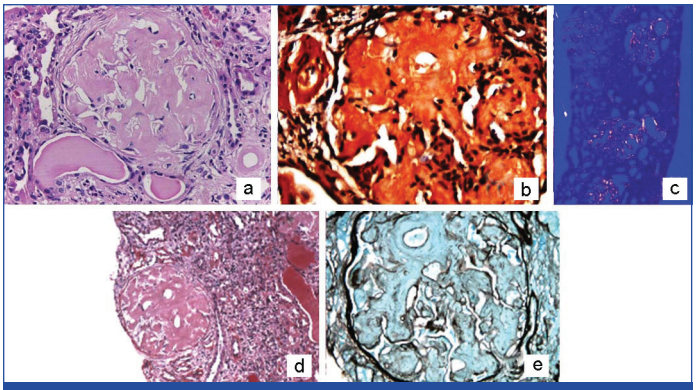
Renal histology	Frequency	Percent (%)
Cast nephropathy	36	57.1
Amyloidosis	13	20.6
Tubulointerstitial nephritis	11	17.5
Membranoproliferative glomerulonephritis	2	3.2
Light chain deposition disease	1	1.6
Total	63	100

[Table/Fig-3]: Patterns of renal histomorphology in the study subjects.

Myeloma cast nephropathy was the most common histological pattern of injury. This was characterised by intratubular fractured casts with giant cell reaction as displayed in [Table/Fig-4]. The renal tubules usually showed pale eosinophilic casts on Periodic Acid-Schiff (PAS) stained sections with fracture planes and mononuclear or a giant cell reaction; in comparison to the usual hyaline casts which were brightly PAS positive and lacked the cellular reaction. In 41 patients typical myeloma casts were identified and 26 (41.2%) had multiple fractured casts. In amyloidosis, the glomerular mesangium was expanded with pale eosinophilic acellular material which was congophilic in Congo red stain and negative by Jones methenamine silver staining. The amyloid deposits were also seen in the interstitium and around vessels. In two of the cases, amyloid deposits were seen in bone marrow and in one the liver also showed a perisinusoidal distribution of the same [Table/Fig-5]. One patient showed nodular eosinophilic glomerular deposits which were negative for Congo red stain and positive for PAS stain. This showed Lambda restriction on IHC confirming a light chain deposition disease. Two cases showed a membranoproliferative pattern on renal biopsy. An electron microscopical examination could not be done in them. Tubulointerstitial nephritis with plasma cell infiltrates and eosinophils were seen in 11 patients. A 20 patients underwent immunofixation or immune histochemistry and of this 14 had lambda restriction and the rest had Kappa.



[Table/Fig-4]: Myeloma cast nephropathy; a) Normal glomeruli and tubules with fractured casts (H&E, 200X); b) Tubules showing fractured casts with giant cell reaction, arrow pointing to giant cell reaction (H&E, 400X); c) Fractured casts are pale pink (PAS stain 200X); d) IHC for light chain restriction- Kappa showing intense positivity (D) and Lambda negativity (E) in the casts of the same patient.



[Table/Fig-5]: Amyloidosis Kidney; a) Glomeruli showing pale acellular eosinophilic material in the mesangial region in H&E stain which is; b) Positive for Congo red, c) Birefringence in polarised light, d) Pale in PAS; and e) Negative for silver, JMS in (a-e-400X).

DISCUSSION

Involvement of the kidney in myeloma cases occurs in 15-20% of patients [3-5]. In this study, 14% of the patients had evidence of renal dysfunction at the initial diagnosis, requiring a renal biopsy. In 47 (74.6%) of the patients, the initial presentation was a symptom related to renal dysfunction and in the rest, it was related to bone or marrow involvement like bone pains, lytic lesions and anaemia. The most common clinical symptoms identified were body ache, joint pain, oliguria, oedema and tiredness.

A wide spectrum of histological lesions were seen in the kidney, predominant being cast nephropathy (57%), glomerular deposition diseases like amyloidosis (21%), light chain deposition disease (1.6%), membranoproliferative glomerulonephritis (3%) and tubulointerstitial nephritis (17.5%). These findings are similar to the studies by Sakhuja V et al., Montseny JJ et al., and Nasr SH et al., [3,6,7]. As per Nasr SH et al., 75% of renal dysfunction in myeloma occur due to monoclonal immune deposits and the rest are caused by other associated renal diseases like acute tubular necrosis, diabetic nephropathy, drug toxicity, etc., which have to be treated differently. The differentiation of these possibilities can only be made by a renal biopsy. In cast nephropathy, the renal tubules showed pale eosinophilic casts on PAS stained sections with fracture planes and mononuclear or a giant cell reaction; in comparison to usual hyaline casts which were PAS positive and lacked the cellular reaction. In cases of amyloidosis, the glomerular mesangium was expanded with pale eosinophilic acellular material which was congophilic in Congo red stain and negative in Jones methenamine silver staining [Table/Fig-5]. The amyloid deposits were also seen in the interstitium and around vessels. In two of the cases, amyloid deposits were seen in marrow and in one the liver also showed a perisinusoidal distribution of the same. One patient showed nodular eosinophilic glomerular deposits which was negative for Congo red and positive for PAS stain but showed Lambda restriction on IHC confirming a light chain deposition disease. Proliferative glomerulonephritis with a predominantly membranoproliferative pattern can also be produced by monoclonal deposits as in two of the present cases. These may be due to newly described entities like C3 glomerulonephritis, fibrillary and immunotactoid glomerulonephritis or cryoglobulinaemia [8,9]. Electron microscopy is a must to differentiate them since prognosis of fibrillary glomerulonephritis is poor and in addition they may show an increased tendency to recur after renal transplant. Immunohistochemistry with DNAJ B9 can identify fibrillary GN in cases where electron microscopy is not available. But both could not be done in the present study patients.

The crux of all the pathology in plasma cell dyscrasias is increase in quantity of light chains, whole immunoglobulins and rarely heavy chains in the blood followed by its deposition in various tissues. Though, every immunoglobulin molecule is produced by two light and heavy chains; in the body the production of light chains is 40% more than heavy chains [9]. These free light chains in plasma are filtered through the slit diaphragm and reach the proximal tubules, were they are endocytosed by the megalin cubilin complex of the tubular epithelial cells and get metabolised within them. During this process, they are not deposited in the kidney and so do not produce any renal damage.

Why some patients with myeloma develop cast nephropathy and some others develop glomerular amyloid or light chain deposits have been pondered for long. This may be due to the alteration in the quantity or quality of the monoclonal deposits. In 80% myeloma patients, there is increase in serum immunoglobulins and 95% of them also show a concomitant increase in free monoclonal light chains [10]. The increased quantity of free light chains produced gets filtered into proximal convoluted tubules. When the ability of tubular epithelial threshold of uptake of free light chains is crossed, they spill over to the distal convoluted tubules. The Tamm-Horsfall proteins normally produced in the distal convoluted tubules have a very high affinity for the light chains and thereby create an optimal environment for formation of intratubular casts. These casts may cause obstruction and sometimes rupture of the distal tubules leading to tubulointerstitial nephritis with inflammatory reaction to the casts. Free light chains get easily filtered through urine and sulphosalicylic acid tests will be positive. But the urine dipstick test will be negative as this will not be associated with albuminuria.

In contrast to myeloma cast nephropathy which is caused by increase in quantity of the monoclonal light chains; the glomerular deposits like amyloid and light chain deposition results from alteration in the quality of secreted globulins. Kappa light chains are more common in myeloma cast nephropathy and light chain deposition disease, while lambda chains are more amyloidogenic.

The glomerular deposits occur due to trapping of the whole immunoglobulin secretions by the glomerular mesangial cells. They are larger than free light chains and so are less easily filtered by the glomerulus. These deposits lead to alteration in the mesangial matrix and rarely mesangial cell proliferation [11-13]. When the monoclonal proteins interact with serum amyloid P and get organised in a beta pleated configuration it produces amyloidosis whereas if they are deposited without any definite structure, they form light chain deposition disease. In both of these the glomerular filtration barrier is affected and so the patients present with albuminuria and nephrotic syndrome in contrast to myeloma cast nephropathy.

Acute renal failure was the most common clinical presentation of renal involvement followed by nephrotic syndrome, sub nephrotic proteinuria, rapidly progressive renal failure and chronic kidney injury which was in accordance with most previous studies [7,14]. Acute kidney injury was the most common presentation in myeloma cast nephropathy and tubulointerstitial nephritis, but nephrotic proteinuria was also present in four of these cases. Incidence of nephrotic syndrome in myeloma as per previous studies is 15-25% of the total cases and in the present study was 21%. The renal histology in 62% of patients with nephrotic syndrome showed amyloidosis and the rest had light chain deposition or a normal glomerular histology on light microscopy.

The precipitating factors for renal damage could be identified in 57% of cases, incidence of which is similar to previous studies but the commonest triggering factor identified in the present series were drugs similar to the series by Balwani MR et al., [15]. In most of the other series it had been hypercalcaemia and infections [3,16]. The most common drugs identified were NSAID and indigenous medications. The incidence of hypercalcaemia was 36% which is similar to that reported by Prakash J et al., [16]. Hypercalcaemia and NSAID causes vasoconstriction leading to reduced Glomerular Filtration Rate (GFR) and oliguria due to which precipitation of light chains within tubules occur and predisposes to cast nephropathy. Dehydration leads to reduced plasma volume in turn a reduced urine output which also causes precipitation of myeloma casts [16,17].

The serum creatinine levels at diagnosis are found to be an important prognostic factor in myeloma [16,17]. A serum creatinine levels of more than 1.4 mg/dL were seen in 92% of patients and of this, it was more than 5 mg in 38% of patients. This is similar to the previous studies. Though, the association of creatinine levels and histological diagnosis was not found to be significant, majority of patients with cast nephropathy had markedly elevated creatinine values while in amyloidosis it was either normal or less than 5 mg/dL.

The plasma cell numbers were also seen to be increased in cast nephropathy compared to those with the glomerular deposition diseases. Only 2% of the patients with cast nephropathy had plasma cell numbers less than 10%. This indicates increased tumor burden in cast nephropathy and thereby an increased quantity of light chain production leading to acute severe renal injury. Anaemia which was defined as haemoglobin below 10 mg/dL was seen in 80% of cases, of which 21% had severe anaemia with haemoglobin below 5 gm/dL. The incidence of anaemia, lytic bone lesions and hypercalcaemia were also more common in cast nephropathy. Hypercalcaemia was seen only in 13 (36%) cases of the present study, of which 11 (85%) had a myeloma cast nephropathy. Hypercalcaemia in myeloma occurs due to dysregulated bone turnover, leading to secretion of osteoclast activating and osteoblast inhibiting factors. Lytic lesions were seen in 21 cases of which 16 had myeloma cast nephropathy on renal biopsy. A 94% of cast nephropathy patients had anaemia while only 30% with amyloidosis had a low haemoglobin. This has been described in previous studies [17]. Urine free light chains were increased in 61% and the serum electrophoresis revealed a M band in 69% of the cases. A 20 patients underwent immunofixation or immune histochemistry and of this 14 had lambda restriction and the rest had kappa.

In previous studies, there was increased significant association of renal failure with male gender. Hence, Bence Jones protein excretion, anaemia, thrombocytopaenia, hypercalcaemia, elevated serum Lactate Dehydrogenase (LDH), low albumin, high serum b2 micro globulin, higher International Staging System (ISS) stage, light chain only myeloma and IgD myeloma [17,18]. In present series too, a raised creatinine, hypercalcaemia and anaemia were more in myeloma cast nephropathy. Also, there was no significant difference in interstitial or tubular changes between cast nephropathy and glomerular deposition disease.

The most common age group involved was between 50-70 years and majority was males (60%). The male preponderance and the median age of involvement were in accordance with previous studies by Sakhuja V et al., and Prakash J et al., [3,16]. Patients belonging to less than 50 years were only 13%. Similar to the earlier studies the most common clinical presentation was acute kidney injury, oedema and body ache [19]. Elevated ESR is a common feature of plasma cell dycrasias due to the hyperglobulinaemia causing an increase in rouleaux formation. Elevated ESR was seen in 94% which is in accordance with an earlier studies by Hussain S et al., and Alexandrakis MG et al., [20,21].

The severity of kidney injury is always related to the quantity of free light chains in myeloma and renal function can be preserved by reducing the free light chain load in the kidney. Various methods have been tried like plasmapheresis and high cut-off dialysis for the same. Another fact that was identified by Paul and Sanders in 1990 was that the affinity of free light chains for Tamm-Horsfall proteins depend on not only the type of light chains; but also the difference in Complement Determining Region 3 (CDR3) of the light chains [22]. So, studies are being done to identify the use of a competitive inhibitor peptide to CDR3 which can depress the binding of free light chains with Tamm-Horsfall protein and thereby decreasing its intratubular precipitation and cast formation [23].

Limitation(s)

An electron microscopical examination of renal tissue is essential to assess even small amounts and the nature of monoclonal deposits in glomerular mesangium. This could not be done and is a limitation of this study.

CONCLUSION(S)

Incidence of renal dysfunction at initial diagnosis is 14% in myeloma. The renal pattern of injury is varied the main being cast nephropathy and amyloidosis. Acute kidney injury, a high marrow plasma cell count, lytic lesions of bone and anaemia are more common in myeloma cast nephropathy while a nephrotic presentation with low marrow plasma cell burden favour amyloidosis. Involvement of heart should be ruled out in cases of amyloidosis as it affects the patient survival. Acute kidney injury due to myeloma cast nephropathy is a medical emergency and prompt therapy with measures to reduce light chain load like plasmapheresis and early chemotherapy assisted by correction of dehydration and hypercalcaemia can reduce renal damage and increase the patient survival. Many newly described entities like fibrillary and immunotactoid nephropathy can occur in myeloma and these can be identified only by electron microscopy. They have important prognostic impact and significance when planning for renal transplant. So, a renal biopsy supported by newer methods like immunohistochemistry and electron microscopy is a must to keep pace with newer advances in myeloma treatment like autologous stem cell transplantation.

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PARTICULARS OF CONTRIBUTORS:
1. Associate Professor, Department of Pathology, Government Medical College, Kozhikode, Kerala, India.
2. Assistant Professor, Department of Pathology, Government Medical College, Kozhikode, Kerala, India.
3. Professor, Department of Pathology, Government Medical College, Kozhikode, Kerala, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Chettithodi Sivasankaran Bindu,
Assistant Professor, Department of Pathology, Government Medical College, Kozhikode, Kerala, India.
E-mail: binducs12@gmail.com

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