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Clinicopathological profile of multiple myeloma at a tertiary care hospital in a resource-poor setting: A retrospective study

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ABSTRACT

Objectives: The objective of this study was to study the clinicopathological profile of multiple myeloma (MM) presenting to Jawaharlal Nehru Hospital and Research Center (JLNH&RC) Bhilai and document the disease in central India.

Material and Methods: This was a retrospective observational study using patient data from January 2013 to December 2019. The clinical and radiological findings, laboratory parameters, and bone marrow examination were analyzed.

Results: About 35.38% of patients presented in the 6th decade of life with a male-to-female ratio of 1.3:1. About 91.93% of patients had low backache and bone pain, and 96.92% of patients had Anemia. About 63.01% of patients had serum creatinine >2 mg/dL, and 92.30% of patients had A/G ratio reversal. About 64.70% of patients had serum beta-2 microglobulin (≥3.5 μg/mL). About 80.7% had osteolytic lesions, predominantly in the skull and pelvis. About 46.15% of patients had >50% plasma cells on bone marrow aspirate. About 85.71% exhibited hypercellularity, and 8.92% of patients had grade 2 marrow fibrosis. About 76.92% of patients presented with Durie Salmon stage III disease, and 58.82% presented with international staging system (ISS) stage II disease.

Conclusion: MM has an inconsistent clinical presentation with multiple system involvement. It should be considered as a differential in patients above 50 years of age presenting with normocytic normochromic Anemia and bony pain. Bone marrow study is important in resource-poor settings where specialized laboratory testing is limited. The Durie and Salmon staging and the ISS can be used for the prognosis with equal efficacy.

Keywords: Multiple myeloma, Clinical profile, Beta-2 microglobulin, Osteolytic lesions, Central India

INTRODUCTION

Multiple myeloma (MM) is the second most common hematologic malignancy and is associated with significant morbidity due to its potential for end-organ destruction.[1] Timely diagnosis of myeloma remains challenging due to non-specific symptomatology, consequently requiring a high index of suspicion.

In a suspect, blood and urine tests for antibodies and protein detection act as screening tools, followed by an examination of bone marrow, biochemical tests, and radiological parameters to assess for end-organ damage and classify, stage, and prognosticate the disease.[2,3]

We present the clinical manifestations of myeloma and its correlation with hematologic and laboratory profiles to help document the disease in this part of the country.

MATERIAL AND METHODS

Records of MM patients who presented to the Jawaharlal Nehru Hospital and Research Center, Bhilai, C.G, over seven years (January 2013–December 2019) were reviewed after the Ethical Committee approval (AIIMSRPR/IEC/JLNH-5/2019/382). Demographic, clinical, laboratory, radiographic, treatment, and follow-up data were collected. Bone marrow aspirate smears, and biopsy slides were reviewed to study the histomorphological characteristics.

The following laboratory parameters were evaluated in all the patients: complete blood count with an erythrocyte sedimentation rate (ESR), renal and liver function tests, urinary Bence-Jones proteins, serum protein electrophoresis (SPEP) with immunofixation, a skeletal survey by X-ray, bone marrow aspiration and biopsy, immunohistochemistry with CD 138, anti-k, and anti-l light chains.

Patients were administered the VRD regimen (Bortezomib 1.3 mg/m^2 s.c, Lenalidomide 10 mg oral, Dexamethasone 40 mg i.v) with injection Zoledronic Acid (4 mg i.v once every four weeks), tablet Acyclovir 400 mg BD, tablet Trimethoprim 160 mg + tablet Sulfamethoxazole 800 mg, as induction and tablet Lenalidomide 10 mg as maintenance monotherapy. Treatment response was assessed with clinical profile, SPEP, and immunofixation.

The data were analyzed using mean, median, and percentage with MS Excel.

RESULTS

Seventy-two patients of plasma cell neoplasm were registered, of which 65 (*n*) were diagnosed as MM and seven as other plasma cell neoplasms. Clinical and laboratory workup was recorded for the 65 patients. Response to treatment and outcomes were recorded for 36 of 65 patients, as 29 were excluded (1 death before initiating therapy, two deaths during ongoing therapy, four discontinued therapy <1 month, five after > one month, and 17 lost to follow-up).

Demographics

Patient ages ranged from 24 years to 85 years, with an average of 61 years.

The 6th decade was the most prevalent, with 35.38% (*n* = 23) patients, followed by the 5th decade with 24.61% cases. Only 3.07% (*n* = 2) of patients were aged <40 years. A male-to-female ratio of 1.3:1 was recorded with 56.92% (*n* = 37) males and 43.07% (*n* = 28) females.

Clinical features

Low backache and bone pain were the most common presenting symptoms in 91.935% (*n* = 57) patients, followed by generalized weakness in 85.48% and pallor in 61.53% (*n* = 40) [Table 1].

Table 1: Clinical features.

Clinical features of patients (*n*=65)	*n* (%)
Backache and bone pain	57 (91.93)
Generalized weakness	53 (85.48)
Pallor	40 (61.53)
Abdominal pain	10 (15.3)
Fever	8 (12.3)
Weight loss	5 (7.69)
Breathlessness	4 (6.1)

Investigations

Screening tests

- Hemoglobin values ranged from 3.5 g% to 13.5 g%, with 96.92% of patients having Anemia.
- ESR ranged from 1 mm to 175 mm/1st h with a mean of 104.1 mm/1st h. An ESR of >100 mm/1st h was noted in 58.46% of patients.
- Serum creatinine ranged from 0.6 mg/dL to 10.8 mg/dL, with a mean of 2.80 mg/dL. Levels >2 mg/dL were recorded in 63.01% of patients.
- Mean serum calcium was 11.47 mg/dL, 36.92% had hypercalcemia, and 63.07% had normal levels.
- Mean serum albumin of 2.81 g/dL was observed, and 78.46% had hypoalbuminemia (serum albumin <3.5 g/dL).
- It increased serum globulin with consequent albumin: globulin Albumin: Globulin (A: G) reversal was seen in 92.30% (*n* = 60) patients.
- Urine Bence-Jones protein was positive in 14% (*n* = 7).

Radiological investigations

Radiological findings were available for 57 patients.

Osteolytic lesions were noted in 80.7% of patients, the majority in the axial skeleton (60.86%, *n* = 28), followed by appendicular skeleton (39.14%) and skull involvement in 45.65% of patients.

Three flat bones, namely, the ribs, scapula, and mandible, were involved.

Osteoporosis was noted in 31 patients.

Pathological fractures were recorded in 16 cases, 87.5% involving the axial skeleton and 12.5% involving the appendicular skeleton.

Specific diagnostic tests

Confirmatory diagnosis of MM was made using the criteria laid down by the World Health Organization (2016), adapted from the international myeloma working group updated criteria.

Active MM was diagnosed in patients with >10% clonal myeloma cells along with one or more of the "CRAB" features (Hypercalcemia, renal insufficiency, Anemia, and bone lesions) or "MDE" (Myeloma defining events).

Bone marrow aspiration

The percentage of plasma cells ranged from 15% to 95%, with a mean of 48.56% among 65 patients.

Bone marrow biopsy

A total of 56 available specimens were reviewed, and 85.71% (n = 48) exhibited hypercellularity, with 60.71% (n = 34) having plasma concentration >50%. About 48.21% of patients (n = 27) had suppressed hematopoiesis. Grade 2 bone marrow fibrosis was seen in 8.92% (n = 5) patients [Table 2].

Markers of end-organ damage

Among the CRAB features, Anemia was the most common sign in 90.76% (n = 59) cases, followed by bone lesions in 80.7%, renal impairment in 63.07%, and hypercalcemia in 38.46% of patients.

Serum monoclonal proteins

Among 34 cases, immunoglobulin G (IgG) Kappa was the most common monoclonal subtype in 55.88% of cases (n = 19), followed by IgG Lambda in 32.35%.

Table 2: Bone marrow biopsy findings.

Bone marrow examination	Frequency	Percentage
ASPIRATE		
% of plasma cells		
>50%	3	46.15
20–50%	32	49.23
<20%	30	4.61
BIOPSY		
Cellularity		
Hypercellular	48	85.71
Normal	8	14.28
Hematopoiesis		
Markedly suppressed	9	16.07
Suppressed	27	48.21
Normal	20	35.71
Percentage of plasma cells		
>50%	34	60.71
20–50%	22	39.28
<20%	00	0
Marrow fibrosis		
Grade 2	5	8.92
Grade 1	25	44.64
Grade 0	26	46.42

Biclonal and IgM Kappa monoclonal proteins were detected in one patient each, and two patients showed only free Lambda monoclonal protein.

Serum beta-2 microglobulin

Among 34 cases, 64.7% (n = 22) had levels >3.5 μg/mL, and 35.29% (n = 12) had levels <3.5 μg/mL.

Clinical staging

Durie salmon staging (DSS)

The DSS (hemoglobin, serum calcium, the extent of bone lesions, level of serum, and urine M-component, along with serum creatinine for sub-categorization into A and B) was used to classify the patients.

About 76.92% of the patients were classified as class III, 18.75% were classified as class II, and only 4.61% as class I.

International staging system (ISS)

The ISS utilizes only two parameters: serum beta-2 microglobulin levels and serum albumin levels.

A total of 34 patients were assessed using the ISS, of which the majority (58.82%) were classified as stage II. About 26.74% were assigned to stage III and 17.64% to stage I.

Treatment outcomes

Twenty-one of the 36 patients (58.82%) demonstrated complete response to therapy (i.e., negative immunofixation on the serum and urine and disappearance of any soft-tissue plasmacytomas and <5% plasma cells in bone marrow). In contrast, 9 (25%) showed very good partial response (serum and urine M-protein detectable by immunofixation but not on electrophoresis or > 90% reduction in serum M-protein plus urine M-protein level <100 mg/24 h), 4 (11.11%) showed partial response (>50% reduction of serum M-protein and reduction in 24 h urinary M-protein by >90% or to <200 mg/24 h), and 2 (5.55%) were non-responders (not meeting any of the above criteria) [Figure 1].

A total of 13 of 36 patients (36.11%) patients relapsed in the course of the study, one during therapy, one within six months of completing therapy, and 11 patients after six months of therapy completion.

Significant adverse events noted in those who completed therapy were as follows: neuropathy in 9 (25%), anemias in 4 (4.23%), diarrhea in 1 (2.77%), and cytopenia in 1 (2.77%) patients [Figure 2].

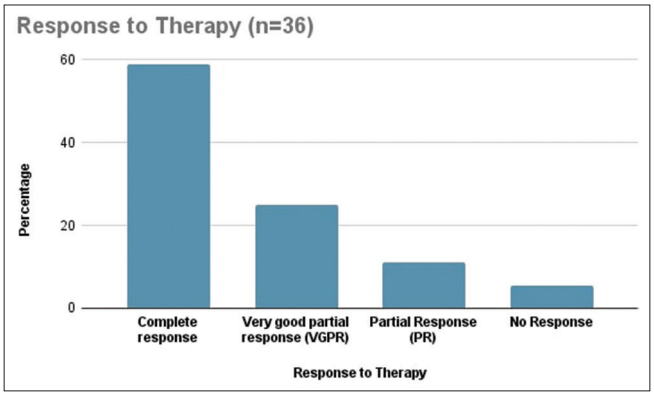

Figure 1: Response to therapy.

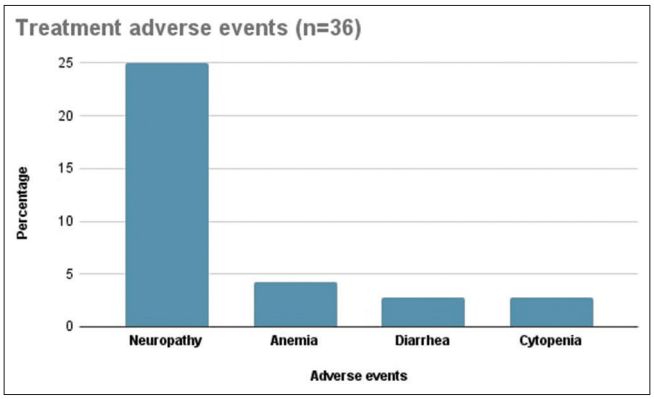

Figure 2: Treatment adverse effects.

DISCUSSION

In our study, patient ages ranged from 24 to 85 years with a mean age of 61 years, with maximum patients belonging to the 6th decade and late 5th decade, similar to data by Kaur *et al.*, Kyle *et al.*, Kaushik *et al.*, and Marla.[4-7] A high male-to-female ratio of 1.3:1 is similar to Indian studies by Fousad *et al.*, Kaushik *et al.*, and Stifter *et al.*[6,8,9]

Bone pain and backache are the most common presenting symptoms in the Indian subcontinent, as corroborated by our study (91.93%, 57 of 65 patients) and reported by Fousad *et al.* (96.9%) and Subramanian *et al.*[8,10]

Fifty patients (73.84%) had Anemia, in agreement with Subramanian *et al.* (71%) and Kaur *et al.* (75%) but considerably lower than those reported by Chowdhury.[4,10,11] Anemia was mostly normochromic and normocytic. The probable causes could be renal impairment, bone marrow infiltration by plasma cells, or coexisting iron deficiency.

The mean ESR of 100.4 mm/1st h reported in 58.46% of our patients is comparable to Kaushik *et al.* (51%) but considerably lower than Kaur *et al.* (85.7%) and Chowdhury (100%).[4,6,11]

Prominent Rouleaux formation was seen in 66.1% of patients, as compared to 82.1% by Kaur *et al.* and 91% by Subramanian *et al.*[4,10]

Hypercalcemia was recorded in only 36.92% (24) patients, although 70.76% (46) patients had evidence of osteolytic lesions. Comparable data were seen in studies by Sharma *et al.* (42%) and Kaur *et al.* (42.8%).[4,12]

Renal failure (S. creatinine > two g/dL) was seen in 63.07% of patients (41), which was considerably higher than values reported by Jacob *et al.* (27%) and Sharma *et al.* (28%).[12,13]

The high proportion of patients with renal failure can explain Anemia in a large number of our patients.

Osteolytic lesions were the most common skeletal manifestation (80.7%, 46 of the 57 patients) presenting either in isolation or with osteoporosis and pathologic fractures, comparable to Pegu *et al.* 80%) and Diwan *et al.* (85%).[14,15] Most of the lesions were concentrated in the axial skeleton (60.87%), with the skull being the most common site (45.65%). Of the 39.13% appendicular skeletal involvement, the pelvis was the most common bone involved (21.73%).

Even though vertebral involvement was only 10.86%, vertebral fractures accounted for 87.5% (n = 14) of the total pathologic fractures noted (n = 16); thoracolumbar vertebrae fractures were the most common, in 62.5%. This discrepancy between the low incidence of vertebral osteolytic lesions and the high vertebral fracture rate could be explained due to the presence of osteoporosis in 51.38% of the study population.

Low serum albumin concentrations (<3 g/dL) were seen in 67.69% (n = 44) patients, similar to the studies by Pegu *et al.* (66%) and Hussain *et al.* (55%).[15,16]

A: G ratio reversal appeared to be the most sensitive laboratory indicator of MM, seen in 92.30% of patients, and similar percentages have been recorded by Shukla *et al.* (91.2%) and Ramani *et al.* (80%).[17,18]

Among the serum monoclonal proteins, IgG Kappa was the most common subtype in 55.88% of patients, similar to the study by Mohammed *et al.* (53.3%).[19] Serum beta-2 microglobulin (which reflects tumor load and is the most important prognostic marker) was positive (>3.5 μg/mL) in 70.58% of patients. It should be noted that beta-2 microglobulin is a cause of renal dysfunction and serum levels of it are raised. High serum beta-2 levels were also seen in the studies by Pegu *et al.* (75%), Chowdhury (84.37%), Kaur *et al.* (71.4%), and Kyle *et al.* (75%).[4,5,11,15]

In our study, bone marrow aspiration demonstrated >50% plasma cells in 49.23% of patients, while 60.71% of patients were detected on bone marrow biopsy. Aspiration may tend to underestimate the plasma cell burden because it is subject to various preanalytical variables (poorly representative bone marrow aspirate due to technical faults such as blood dilution

Table 3: Comparison of response to therapy.

Feature	Present study (*n*=65)	ICMR data[23]	Jacob *et al*.[13] (*n*=389)	Diwan *et al*.[14] (*n*=20)	Fousad *et al*.[8] (*n*=32)	Kaur *et al*.[4] (*n*=28)
Median age (years)	61	52–61	54	62	64	58
M: F	1.3:1	1.3:1	2.1:1	1.3:1	1.2:1	1.5:1
Mean Hb	8.7 g/dL			9.3 g/dL		
Anemia	92%	70%	72%	100%	50%	92.8%
Creatinine >1.9 mg/dL	11.7%	20%	27%	30%	21%	86.4%
Skeletal involvement	47%	60–90%	71%	85%		80%
Complete response (or) VGPR	82.5%	70%	80%			

VGPR: Very good partial response, ICMR: Indian Council of Medical Research

and sample clotting, among others). Therefore, a biopsy should always be performed, preferably simultaneously with aspiration, to prevent diagnostic delay and patient inconvenience. Bone marrow aspiration studies demonstrated hypercellular marrow in 85.71% of patients and reduced hematopoiesis in 64.28%, in agreement with Subramanian *et al*. (93%) and Marla (67%).[7,10] The biopsies also showed >50% plasma cells in 60.71% of patients, consistent with other studies, and 8.92% had high-grade bone marrow fibrosis.

ISS staging is the standard of practice in developed countries, while developing nations follow the DSS. The ISS staging is simpler, requiring only blood samples and consequently a faster turnaround time. Various international comparison studies have demonstrated equivalent outcomes and prognostication between both systems.

In our study, all the patients were classified under the DSS. About 76.92% of patients were classified as DSS stage III, similar to Subramanian *et al*. (76%) and Griepp *et al*. (66%).[10,20] Only 34 out of the 65 participants were classified under the ISS system, with 58.82% designated as stage II, similar to the studies by Pegu *et al*. (45%) and Dimopoulous *et al*. (38%).[15,21]

In our study, 83.82% of patients demonstrated satisfactory response to therapy (either complete response or VGPR) as compared to 70% by the ICMR consensus document 2017 and 80% by Jacob *et al*.[13,22] [Table 3].

Peripheral neuropathy (tingling and numbness of the extremities) was the predominant adverse effect seen in 25% of patients. Supplementing methylcobalamin, folate and the addition of gabapentinoids helped increase therapy compliance by reducing peripheral neuropathy symptoms.

CONCLUSION

The present study concludes that MM is a disease of the middle-aged and elderly with male preponderance. A differential of myeloma should be borne in mind for such an age group, presenting with diffuse bone pain and normochromic normocytic Anemia. Monitoring for gamma gap and A: G reversal can hasten diagnosis as these are the most sensitive markers of the disease.

Bone marrow aspiration should always be coupled with biopsy, helping prevent false negatives, reduce diagnostic delay, and prevent patient discomfort if a biopsy is planned separately. Bone marrow examination continues to be the gold standard for diagnosis and is advantageous in resource-poor countries like India, where laboratory tests are not available uniformly. ISS staging should preferably be used for its simplicity and faster turnaround.

The Velcade (Bortezomib) - Revlimid (Lenalidomide) - d (Dexamethasone) regimen leads to disease remission in a substantial proportion of patients. This should encourage clinicians to keep a low threshold for diagnosis of myeloma, as treatment can significantly alter morbidity and increase survival.

Ethical approval

The research/study is approved by the Institutional Ethics Committee at AIIMS, Raipur, Number AIIMSRPR/IEC/JLNH-5/2019/382, dated 19 November 2019.

Declaration of patient consent

Patient's consent is not required as the patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript, and no images were manipulated using AI.

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