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Original Research Article

Clinicopathological Study of Multiple Myeloma in a Tertiary Care Hospital of North-East India

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Abstract:

Introduction: Multiple myeloma is a plasma cell malignancy. The present study aims to investigate the spectrum of clinical, haematological and biochemical features and histopathological findings of bone marrow (BM) biopsy in patients with multiple myeloma attending a tertiary care hospital of North-east India.

Methods: The present hospital based cross-sectional study was carried out in the Department of Pathology, Gauhati Medical College and Hospital, Guwahati (GMCH)along with Department of Clinical Haematology, GMCH during July 2019 to June 2020 including 34 newly diagnosed multiple myeloma patients. Complete clinical examination along with bone marrow aspiration and bone marrow biopsy samples were collected and reviewed. The diagnosis was established according to International Myeloma Working Group (IMWG) 2014 criteria. The study approval was obtained from the Institutional ethics committee of GMCH, Guwahati. Data analysis was done using SPSS v21.

Results: Multiple myeloma is more frequent among patients in sixth decade (35.3%) and male gender (58.8%). Low backache and bone pain was the most common presenting symptom (67.6%). Heamoglobin level, erythrocyte sedimentation rate (ESR) and Beta-2 microglobulin levels differed significantly between genders (p-value<0.05). Monoclonal protein (M-protein) was detected 33 (97%) patients. In comparison to the BM aspirate, the mean plasma cell percentage on the BM biopsy (65.4%) was greater. In addition, substantially more instances had > 50% plasma cells on the BM biopsy than the BM aspiration (p-value 0.05).

Conclusion: Multiple myeloma is more common among adult and male patients. Clinical manifestations are not necessarily gender free. Discrepancies exist between bone marrow biopsy and bone marrow aspiration.

Keywords: Beta-2 microglobulin, bone marrow biopsy, bone marrow aspiration Hypercalcemia.

Introduction

Multiple myeloma is a hematologic malignancy defined by the development of aberrant clonal plasma cells in the bone marrow and is characterized by an anomalous rise in monoclonal immunoglobulins [1,2]. The excessive creation of these plasma cells, if left unchecked, can eventually result in end-organ damage [2]. It is potentially uncontrollable and can cause severe bone lesions, kidney damage, anemia, and hypercalcemia [1].

Multiple myeloma is the second most common hematological malignancies accounting almost 10-15% of all malignant disorders [3]. Myeloma incidence is lower in India (1.0/ 100,000) than in the Western countries (4.1/100,000), however it is rapidly increasing in major Indian cities [4]. Significant variations in incidence of multiple myeloma were documented with regard to age, sex and geographic regions. Multiple myeloma etiology in diverse racial groups is characterized by variances in hereditary vulnerability and the variety of molecular changes [5].

The diagnostic procedure of multiple myeloma includes differential complete blood count (CBC), beta-2 microglobulin testing, immunoglobulin investigations, skeletal examination, and bone marrow biopsy. Serum protein electrophoresis, which is commonly used to detect M-protien spike, is the standard diagnostic test for multiple myeloma. However, lack of monoclonal gammopathy on protein electrophoresis or normal immunofixation does not necessarily indicate absence of multiple myeloma [6]. Various patterns of plasma cell infiltrate can be found histologically in bone marrow biopsies. Plasma cells can vary from mostly mature to immature or plasmablastic forms in aspirate smear morphology [7].

Complex associations exist between plasma cells, the antibodies they produce, the surrounding bone and bone marrow environment, and other organs. Although there is no cure for multiple myeloma, there are plenty of effective treatments that can extend and enhance the quality of life for those who have the condition. Induction therapy is the cornerstone of myeloma treatment, which is thereafter consolidated with autologous stem cell transplantation. However, in developing countries with limited resources like India, treatment affordability is a major constraint.

The present study aims to investigate the spectrum of clinical, haematological and biochemical features along with histopathological findings of bone marrow biopsy in patients with multiple myeloma attending a tertiary care hospital of North-east India.

Methods

The present hospital based cross-sectional study was carried out in the Department of Pathology, Gauhati Medical College and Hospital, Guwahati (GMCH)along with Department of Clinical Haematology, GMCH. The study included 34 newly diagnosed multiple myeloma cases of all age group, who were diagnosed in the department of Clinical Haematology and had undergone examination of bone marrow aspiration and bone marrow biopsy specimens in the department of Pathology, GMCH. The study approval was obtained from the Institutional ethics committee of GMCH.

The diagnosis was established according to International Myeloma Working Group (IMWG) 2014 criteria (8) The duration of the study was 1 year from July 2019 to June 2020. All cases of multiple myeloma newly diagnosed in the Department of Clinical Haematology; GMCH, Guwahati were included. Patients who were on therapy were excluded from the study. Complete clinical examination was done for each case and in-depth elicitations of the patient's history were obtained. The bone marrow aspiration and bone marrow biopsy samples were collected from the study group and respective smears were prepared. All the smears and sections were being reviewed for morphological details.

Peripheral blood smear preparation and staining was done using Bain's methods (9). RBCs were evaluated to see the variations in size, shape, hemoglobin distribution, the presence of cellular inclusions and rouleaux formation. Bone marrow aspiration was done from posterior superior iliac spine using Salah bone marrow aspiration needle. Smears were stained with May-Grunewald-Giemsa.

Bone marrow biopsy was done using Jamshidi-Swaim needle, taking all the aseptic precaution measures. Biopsy samples were collected from the iliac crest, fixed and decalcified and routinely processed for paraffin embedding. Staining was done by haematoxylin and eosin. The biopsy sections were studied in detail for haematopoiesis, percentage of PC infiltration, and histologic pattern of infiltration

All the data were recorded in a structured proforma. Data analysis was done using SPSS v.21. Chi-square test was used to test association between categorical variables. Difference in mean of continuous variables was assessed using t-test. A p-value below 0.05 was considered significant.

Results: A total of 34 newly diagnosed multiple myeloma cases were included in the study. The age of the patients ranged from 35 to 80 years with a mean age of presentation of 57.5±10.7 years. Sixth decade was found to be the most common age group (35.3%). Slight male (58.8%) preponderance was observed among the cases with male to female ratio 1.4:1 (Table 1)

Table 1: Age distribution of patients

Age	Male (%)	Female (%)	Total
Up to 40 years	1 (2.9%)	1 (2.9%)	2 (5.9%)
41-50 years	7 (20.6%)	3 (8.8%)	10 (29.4%)
51-60 years	4 (11.8%)	8 (23.5%)	12 (35.3%)
61-70 years	5 (14.7%)	1 (2.9%)	6 (17.6%)
> 70 Years	3 (8.8%)	1 (2.9%)	4 (11.8%)

Low backache and bone pain was the most common presenting symptom (67.6%) followed by generalized weakness (44.1%). Only 1 patient showed neurological manifestations (**Fig 1**).

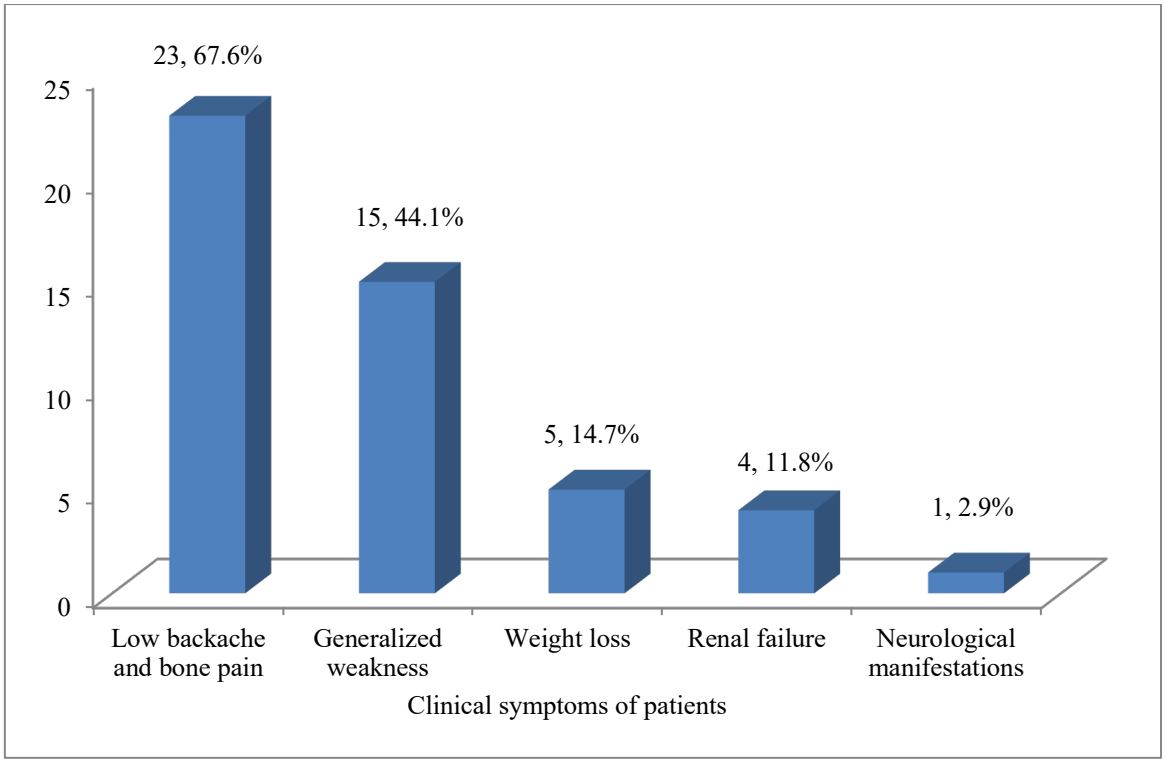

Figure 1: Clinical symptoms of patients

Hemoglobin values ranged from 3.4g/dL to 14g/dL with a mean of 8.4g/dL. Significant difference was observed in mean hemoglobin level between genders (p-value<0.05). ESR of the patients ranged between 4mm after end of first hour (AEFH) to 180mm/AEFH with a mean of 68.41mm/AEFH. The mean ESR level was significantly higher among males (p-value<0.05). The mean Beta-2 microglobulin level was considerably higher in females (p-value<0.05). Serum calcium ranged from 8mg/dL to 14.5mg/dL with a mean of 10.56mg/dL (**Table 2**).

Table 2: Hematological and biochemical profile of patients

Haematological and biochemical parameters	N	Mean±SD			p-value for t test
		Overall	Male	Female	
Haemoglobin (g/dL)	34	8.42±3.06	9.42±2.89	7.00±2.82	0.02
Platelet (x10^3/µL)	34	114.06±35.44	109.50±34.05	120.57±37.63	0.39
ESR (mm/AEFH)	34	68.41±44.86	83.70±45.68	46.57±34.42	0.01
Beta-2 microglobulin	34	4.12±1.08	3.82±1.17	4.55±0.80	0.036
Calcium	34	10.56±1.14	10.65±1.39	10.43±0.64	0.55
Creatinine	34	2.57±3.86	2.83±4.18	2.19±3.46	0.63

As seen from **Table 3**, Hemoglobin level was <10g/dL in 19 (55.9%) patients and 32.3% cases presented with severe anemia. Female patients were significantly more anemic than males (p-value<0.05). In the peripheral blood smear, rouleaux formation was observed in 18 (52.94%) patients while plasma cells were found in 1 (2.94%) case. Thrombocytopenia (Platelet count <100 x10^3/µL) was present in 9 (26.47%) cases. An ESR of more than 100 mm after 1 hour was seen in 7 (20.58%) cases. Highly significant difference was observed in ESR values between males and females (p-value<0.01). Serum β_2-microglobulin (S.β_2M) level raised (>3.5mg/L) in 73.52%. Renal failure (i.e. S. creatinine >2mg/dL) was seen in 6 (17.6%) patients.

Table 3: Association of haematological and biochemical parameters with gender

Variables	Categories	Total	Sex		P-value for chi-square
			M	F	
Heamoglobin	<10 g/dl	19 (55.9)	8 (23.5)	11 (32.4)	0.038
	Hb>=10g/dl	15 (44.1)	12 (35.3)	3 (8.8)	
Rouleaux formation	Absent	16 (47.1)	11 (32.4)	5 (14.7)	0.31
	Present	18 (52.9)	9 (26.5)	9 (26.5)	
Thrombocytopenia	No	25 (73.5)	13 (38.2)	12 (35.3)	0.25

	Yes	9 (26.5)	7 (20.6)	2 (5.9)	
ESR (mm/hour)	<20	5 (14.7)	0 (0.0)	5 (14.7)	<0.01
	20-100	22 (64.7)	14 (41.2)	8 (23.5)	
	>100	7 (20.6)	6 (17.6)	1 (2.9)	
S.β2 microglobulin	Not raised (<3.5)	9 (26.5)	8 (23.5)	1 (2.9)	0.033
	Raised (≥3.5)	25 (73.5)	12 (35.3)	13 (38.2)	
Hypercalcaemia	No (Ca≤10.4)	16 (47.1)	8 (23.5)	8 (23.5)	0.32
	Yes (Ca>10.4)	18 (52.9)	12 (35.3)	6 (17.6)	
S.creatinine	Upto 1.5	19 (55.9)	11 (32.4)	8 (23.5)	0.90
	1.6-2	9 (26.5)	5 (14.7)	4 (11.8)	
	>2	6 (17.6)	4 (11.8)	2 (5.9)	

Serum protein electrophoresis was done in all patients out of whom monoclonal protein (M-protein) was detected 33 (97%) patients. Radiologic investigations showed skeletal lesions in 26 (76.5%) cases among which lytic lesions (67.6%) were mostly observed. (Fig: 2.1 and 2.2).

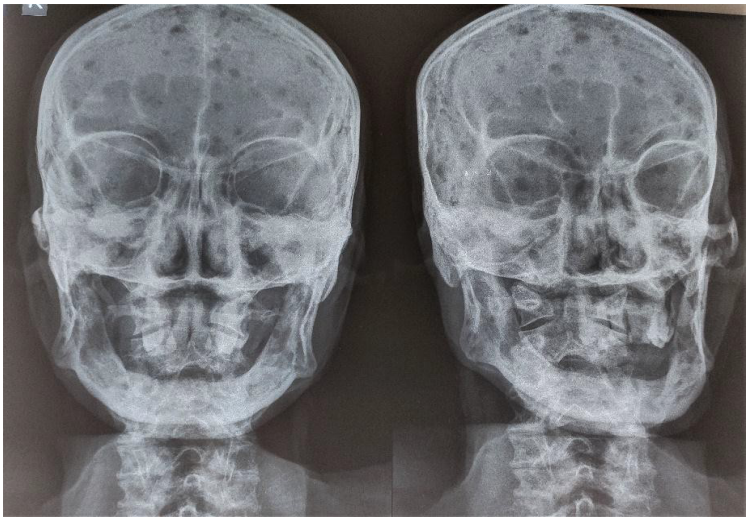

Figure 2.1: Radiograph of the skull showing multiple lytic lesions

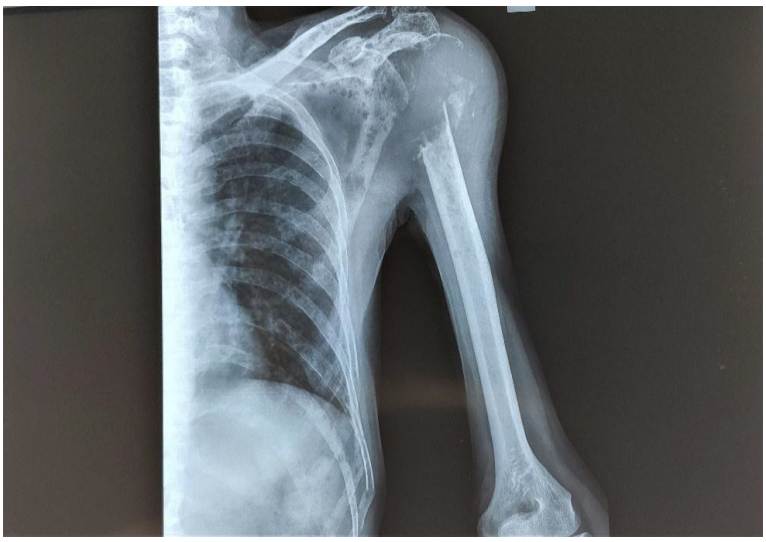

Figure 2.2: Radiograph of the proximal humerus showing lytic lesions

Bone marrow aspiration (BMA) was performed in all the 34 patients of whom 31 cases had adequate bone marrow aspirate smears. The percentage of plasma cells ranged from 12% to 92% with a mean of 48%. Majority of the cases (61.3%) had plasmacytic morphology with non-nucleolated plasma cells.

Total 31 bone marrow biopsy (BMB) specimens

were reviewed for assessment of cellularity, percentage of plasma cells and their infiltration pattern. The marrow was hypercellular in 80.6% cases. Hematopoiesis is suppressed in 48.4% cases. The percentage of plasma cell in BMBs ranged from 38% to 90% with a mean of 65.4%. The pattern of infiltration was mostly interstitial (48.4%) and diffused (35.5). The plasma cell burden in biopsy with volume of infiltration >50% was observed in 21(67.7%) cases (**Table 4**).

Table 4: Bone marrow biopsy findings

Parameter		No of cases(n=31)	Percentage
Cellularity	Hyper cellular	25	80.6
	Normal	6	19.4
Hematopoiesis	Normal	16	51.6
	Suppressed	15	48.4
Percentage of plasma cells	<20%	0	0
	20-50%	10	32.3
	>50%	21	67.7
Pattern of infiltration	Nodular	2	6.4
	Interstitial	15	48.4
	Mixed	3	9.7
	Diffuse	11	35.5

Significant number of patients with plasmablastic cell type had a diffuse pattern of infiltration, whereas majority of the plasmacytic cell type had an interstitial pattern (**Table 5**).

Table 5: Pattern of infiltration and plasma cell morphology

Pattern of infiltration	Plasmacytic(n=19)	Plasmablstic (n=12)	p-value for chi-square
Nodular	1 (5.3)	1 (8.3)	0.02
Interstitial	13 (68.4)	2 (16.7)	
Mixed	2 (10.5)	1 (8.3)	
Diffuse	3 (15.8)	8 (66.7)	

Out of 31 cases 4 cases had less than 20% plasma cells in the bone marrow aspirate. The difference between the plasma cell count in the bone marrow aspirate and biopsy was statistically significant (Table 6).

Table 6: Percentage of PC infiltrate in Bone Marrow Aspirate and Biopsy

Percentage of PC BMA	Percentage of PC in BMB		p-value for chi-square test
	≤50%	>50%	
≤50%	9	10	0.02
>50%	1	11	

Discussion

The age of the patients ranged from 35 to 80 years with a mean age of presentation of 57.5±10.7 years which is consistent with other studies (10,11). The male to female ratio in the current study was 1.4:1 Male preponderance in multiple myeloma was also documented previously (10,12,13).

The most common presenting symptom was low backache and bone pain (67.6%) followed by generalized weakness (44.1%). Bone pain is the most prevalent presenting symptom of multiple myeloma accounting more than half to two thirds of patients present with it upon diagnosis. It typically manifests as a persistent ache in the back and ribcage or as an ethereal, migrating discomfort in the back or pelvis. A quick attack of severe pain may indicate a pathological fracture (14).

Hypoferremia and decreased iron availability for the developing erythrocyte cause anemia in myeloma patients (15). In the current study, significant difference was observed in mean hemoglobin level between genders (p-value<0.05) and 32.3% cases presented with severe anemia. Female patients were found to be more anemic (p-value<0.05). Earlier studies also recognized female gender as a risk factor of anemia in multiple myeloma (16). Anaemia has a detrimental effect on patients' quality of life and is a potential indicator of a poor chance of survival (17).

An ESR of more than 100 mm after 1 hour was seen in 7 (20.58%) cases. Highly significant difference was observed in ESR values between males and females (p-value<0.01). Typically, the ESR is higher in females than in males, and it rises progressively with age (18). However, among multiple myeloma patients the mean ESR level was observed to be significantly higher among male patients (p-value<0.05). Thrombocytopenia was present in 9 (26.47%) cases. It is a significant dose-limiting hematologic hazard of anti-myeloma therapy (19). Serum beta-2-microglobulin is an independent predictor of prognostication of both symptomatic and asymptomatic multiple myeloma (20). The mean beta-2-microglobulin level was considerably higher in females (p-value<0.05) in

the present study indicating a rapid progression of the disease among females. Earlier studies demonstrated that serum beta 2 microglobulin levels are not always independent of sex, race, and ethnicity (21,22). Almost 53% cases had serum calcium level above 10.4 mg/dL suggesting mild to moderate hypercalcemia. Hypercalcemia in myeloma patients is mostly brought on by severe tumor-induced bone loss. As myeloma patients frequently have irreversible renal function impairment and increased renal tubular calcium reabsorption, the kidneys are overburdened to eliminate the excessive amount of calcium load from the blood resulting in high serum calcium levels (23).

In the present study M-protein was detected in 97% cases which is comparable to other similar studies (10,24). Skeletal lesions (76.5%), mostly lytic lesions (67.6%), were observed in the present study is in agreement to previous findings (10,24,25). The diagnosis of multiple myeloma and other plasma cell dyscrasias, as well as the management of therapy, depend heavily on microscopic analysis of the bone marrow. For diagnosis and prognosis, it is essential to quantify plasma cells. In the present study, the plasma cell burden in bone marrow biopsy with volume of infiltration >50% was observed in 67.7% cases which is concordant to other similar studies (10,12). Bone marrow parameters like the pattern of infiltration of the plasma cells correlate well with the plasma cell morphology.

The mean plasma cell percentage on the BM biopsy (65.4%) was higher than that on BM aspirate (47.5%). Also, the number of cases with > 50% plasma cells on the BM biopsy were significantly higher than the BM aspiration (p-value<0.05). The findings suggest that BM biopsy plasma cell percentage is a better indicator of tumour load than BM aspirate. Discrepancies in BM aspirate and BM biopsy findings are previously documented (26,27). Plasma cell counts on BM aspirate or BM biopsy alone run the risk of underrepresenting the genuine plasma cell burden. For the prediction of prognosis in multiple myeloma, combined examination of the bone marrow aspirate and biopsy is advocated (28,29).

Limitation

The present study is a time bound hospital-based study including patients from only one tertiary care hospital comprising small sample size. Multi-centric study with larger sample size may provide a better overview of the findings.

Conclusion

Multiple myeloma is more prevalent among adults and males. It has a wide variety of clinical presentation and multisystem involvement. The clinical manifestations of the disease are not always gender free. Lytic lesions are mostly observed in radiologic investigations. Bone marrow examination continues to be the gold standard in establishing a diagnosis. A bone marrow analysis is crucial, particularly in a country like India where the majority of centers lack access to many of the biochemical criteria for determining treatment response.

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