Clinicopathological Spectrum of Multiple Myeloma: Experience of an Institute in Eastern India

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Abstract

Introduction: Multiple myeloma (MM) is a neoplastic plasma cell disorder characterized by clonal proliferation of malignant plasma cells in the bone marrow. Incidence of MM is increasing rapidly in Asian countries. In a developing country like India diagnosis, risk stratification and access to novel treatment is still a major hurdle Objective: To study the clinico-pathological features of newly diagnosed multiple myeloma patients. Methods: This was a cross sectional hospital based retrospective study conducted in a hospital in eastern India. During the four years of study, 74 cases of multiple myeloma were diagnosed on the basis of International Myeloma Working Group: Criteria for the classification of multiple myeloma and related disorders. The clinical and laboratory characteristics of newly diagnosed patients were studied. Results: Out of the 74 patients, 69% were men and 31% were women. Median age at diagnosis was 55 years (range: 32-81 years). The commonest symptoms observed were fatigue and bone pain. Anemia was present initially in 81% of patients, hypercalcemia in 31.4%, and a serum creatinine level of 2 mg/dL or more in 24.6% patients. The most common monoclonal gammopathy was IgG kappa (44%). Diffuse pattern of bone marrow infiltration, the most common pattern observed in 59% patients. Conclusion: MM patients had male preponderance. Median age of patients was lower compared to western countries with higher percentage of patients with age less than 40 years. Quality of life in MM patients can be improved significantly if there is access to early diagnosis, risk stratification and novel treatment.

Keywords: Neoplasm; Multiple Myeloma; Bone Marrow

Introduction

Plasma cell neoplasms (PCN) encompass a group of disorders characterized by clonal proliferation of plasma cells in the bone marrow [1]. The spectrum of PCN encompasses a continuum of disease states, each exhibiting distinct clinical, pathological and molecular features. At one end of the spectrum is asymptomatic precursor condition monoclonal gammopathy of undetermined significance (MGUS) and other end is multiple myeloma (MM) with features of end organ damage. Smouldering multiple myeloma (SMM) represents an intermediate stage between MGUS and symptomatic MM. Other entities in this spectrum include plasmacytoma, plasma cell leukemia and monoclonal immune deposition diseases [2]. Diagnosis of multiple myeloma requires more than 10% of clonal bone marrow plasma cells or biopsy proven plasmacytoma and ≥1 of the following myeloma defining events. 1) End organ damage (CRAB- hypercalcemia, renal

failure, anemia and lytic bone lesions) attributable to plasma cell disorder. 2) Clonal bone marrow plasma cell percentage ≥60% 3) an involved-to-involved serum free light chain (SFLC) ratio ≥100. 4) >1 focal lesion on magnetic resonance imaging (MRI) [3]. The International staging system (ISS) of multiple myeloma provides strong survival estimate, which is based on pretreatment levels of serum β2microglobulin and serum albumin [4].

In year 2020, MM was the third most common hematological malignancy worldwide after Non-Hodgkin lymphoma and leukemia and contributed about 14% of all cases [5]. In 2020, the age standardized incidence of multiple myeloma was 1.78 (95% UI 1•69–1•87) per 100 000 people globally and mortality was 1•14 (95% UI 1•07–1•21) per 100 000 people globally [6]. In India, Age standardised rates (ASRs) of multiple myeloma was 0.7/100 000. According to National Cancer Registry Programme (NCRP) 2020, heterogeneity in Age standardised rates (ASRs) of multiple myeloma was observed between urban and rural areas of India. ASR of multiple myeloma in rural areas was 0.2 per 100 000 people, while in large cities it was 1.8 per 100 000 people [7].

Treatment strategies for multiple myeloma have evolved significantly in recent years. Induction chemotherapy consists of bortezomib, lenalidomide, dexamethasone (VRd) followed by autologous stem cell transplantation (ASCT) which remains a standard treatment option for eligible patients [8]. There are very few studies related to multiple myeloma from eastern India. This study thus aims to evaluate the clinico-pathological spectrum of multiple myeloma in an institute in eastern India.

Material and Methods

This was a cross sectional hospital based retrospective study after obtaining approval from the Institutional Research Committee. During 4-year period of study from June 2018-June 2022, we identified 74 cases of multiple myeloma. The diagnosis of MM was based on the International Myeloma Working Group criteria for the classification of monoclonal gammopathies, multiple myeloma, and related disorders [3].

Medical record of all the patients who were diagnosed as MM was reviewed. Patient characteristics and clinical history including age, sex, presenting symptoms, skeletal survey were recorded. Laboratory parameters including complete blood cell count, serum calcium, serum creatinine, serum protein electrophoresis, immunofixation assay, serum albumin, serum β2 microglobulin, bone marrow study results were obtained.

Data Analysis

For the statistical analysis, the statistical software SPSS version 22.0 for Windows (SPSS Inc., Chicago, IL, USA) was used.

Results

Out of 74 patients, 51 (69%) were men and 23 (31%) were women. The man to female ratio was 2.2:1. The age of the patient ranged from 32 to 81 years with a median age of 55 years. Sixth decade was the most common age group in our study and only 7 (9.4%) patients were younger than 40 years (Table 1).

Age	Men	Women	
<40	6	1	6:01
41-50	13	4	13:04
51-60	17	7	17:08
61-70	12	8	3:02
71-80	3	2	3:02
81-90	0	1	0:01
	51	23	2.2:1
Median Age: 55 years			
Range: 32-81 years			

Table 1: Demographic data of patients with Multiple myeloma (n=74).

Clinical Features

The most common clinical presentations were fatigue 60 (81%) and bone pain 48 (65%).

Laboratory Parameters

	No. of Patient	Results		Distribution	No.	Percentage
		Median	**Range**			
Hemoglobin (Gm/Dl)	74	7.9	3.4-14.1	≤8	39	52.7
				8.1-10.0	21	28.3
				10.1-12	9	12.1
				>12	5	6.7
Creatinine (Mg/Dl)	61	1.2	0.43-10.05	<1.3	33	54.1
				1.3-1.9	13	21.3
				≥2	15	24.6
Calcium (Mg/Dl)	54	9.83	6.9-17.4	<8.5	8	14.8
				8.5-10.9	29	53.8
				≥11	17	31.4
ß2 Microglobulin(MG/L)	18	3344	2.48-14400	<3.5	2	
				3.5-5.5	2	
				>5.5	14	

Table 2: Laboratory test results in patients with Multiple myeloma.

Hematological Factors

Hematological factors- At presentation anemia (hemoglobin levels <10 gm/dl) was present in 60 (81%) patients. Severe anemia (hemoglobin < 8 gm/dl) was present in 39 (52.7%) patients and only 5 (6.7%) patients had hemoglobin >12 gm/dl. The anemia was predominately normocytic normochromic. Microcytic hypochromic anemia was observed in 17 (23%) patients and macrocytic anemia in 5 (6.7%) patients. Rouleaux formation Figure 2A on peripheral blood smear was observed in 35 (47.3%) patients. The total leukocyte counts less than 4 x 109/L was observed in 11 (14.8%) patients and leucocytosis was noted in 13 (17.5%) patients. Thromobocytopenia (platelet counts less than 100 x 109/L) was present in 7 (9.4%) patients. Circulating plasma cells were observed in 6 (8%) patients and 2 patients were diagnosed as Plasma cell leukemia (plasma cells>20% of total leukocyte count). Erythrocyte sedimentation rate (ESR) were available in 37 cases, out of which 35 patients had ESR more than 20mm/hr and more than 100mm/hr in 9 patients. Serum creatinine more than 2 mg/dl was present in 15 (24.6%) patients and hypercalcemia was observed in 17 (31.4%) of patients. Serum lactate dehydrogenase level was performed in 27 patients, 22 (81.4%) of which showed levels more than 260 U/L
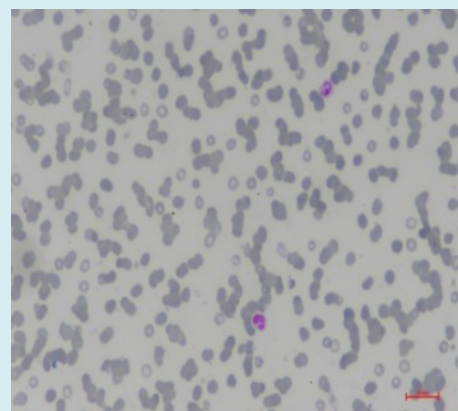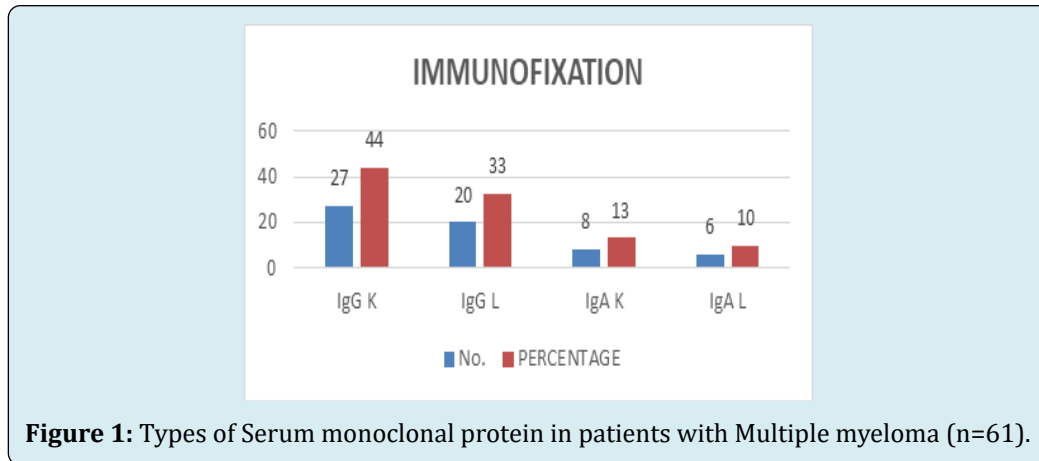

Figure 2A: Peripheral Blood Film Smear Showing Rouleaux Formation (Leishman Stain, 400x).

Serum Protein Electrophoresis

Serum protein electrophoresis showed an M-protein in all the 74 patients. Serum Immunofixation was performed in 61 patients. The most common monoclonal gammopathy was IgG kappa in 27 (44%) patients followed by IgG lambda in 20 (33%) patients. IgA kappa was noted in 8 (13%) and IgA lambda in 6 (10%) patients (Figure 1).

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Figure 1: Types of Serum monoclonal protein in patients with Multiple myeloma (n=61).

Bone Marrow Examination

The bone marrow plasma cell count was estimated on aspiration smears by differential count of 1000 nucleated cells. All the patients had more than 10% of plasma cells and median value of plasma cells was 52%. More than 60% plasma cells were observed in 31 (42%) patients. Bone marrow biopsy was adequate for evaluation in 59 patients. Most common pattern was diffuse infiltration, observed in 35 (59%) patients followed by interstitial pattern in 16 (27%) patients and nodular pattern in 8 (14%) patients (Table 3), (Figures 2B-D).

Plasma Cells	No. of Patients	Percentage
<10	0	0
20-Oct	10	13.5
21-30	11	14.8
31-40	9	12.1
41-50	6	8.1
51-60	7	9.4
61-70	13	28.9
71-80	4	5.4
>80	14	18.9

Table 3: Bone Marrow Plasma Cells in Patients with Multiple myeloma (n=74).
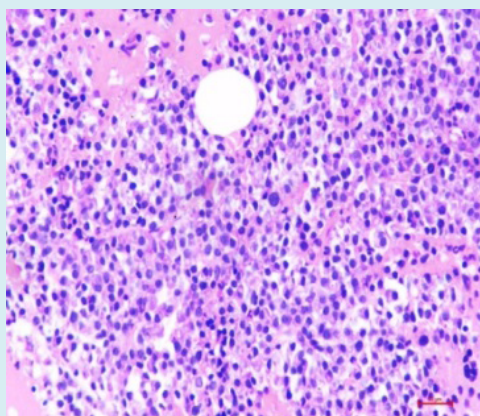

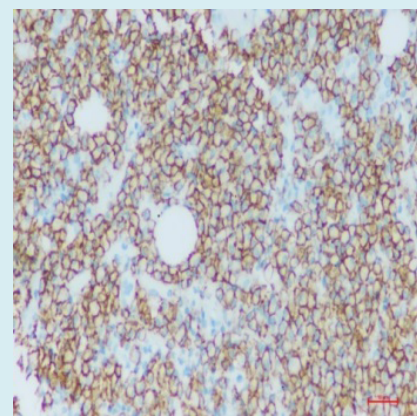**Figure 2B:** Bone marrow aspirate, smear showing many plasma cells (MGG stain, 400x).

Figure 2C: Bone marrow trephine biopsy section, showing diffuse infiltration by plasma cells (H&E, 400x).
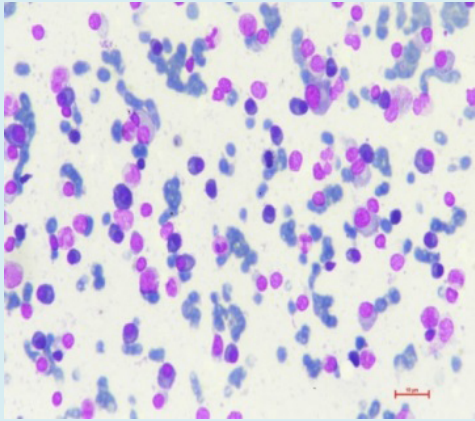
Figure 2D: Bone marrow trephine biopsy section, CD138 immunohistochemistry highlighting plasma cells (400x).

Bony Lesions

Different modalities including conventional X-ray radiography, low dose computed tomography (CT) and magnetic resonance imaging (MRI) are available for detecting osseous lesions in MM. Imaging findings were available in 62 out of 74 patients. Lytic lesions were found in 39 (63%) patients and 13 (21%) patients showed punched out lesions. Compression fracture of spine was observed in 3 patients. No radiographic abnormalities were observed in 7 (11%) patients at the time of diagnosis (Table 4).

Prognosis and Predictive Factors

Findings	Number	Percentage
Lytic Lesions	39	63
Punch Out Lesions	13	21
Compression	3	5
Negative	7	11
Total	62	

Table 4: Radiographic findings in patients with Multiple myeloma (n=62)**.**

International staging system (ISS) that predicts the patient survival includes combination of serum albumin and β2 microglobulin [4]. Serum albumin was less than 3.5 gm/dl in 42 (56.7%) patients. Values of β2 microglobulin were available in 18 patients only, out of which 14 had value more than 5.5 mg/L. These 14 patients were classified under stage III of ISS. Value of β2 microglobulin was <3.5 mg/L in 2 patients and were classified in stage I and between 3.5 mg/L to 5.5 mg/L in 2 patients and were classified under stage II of ISS. Table 5 ISS staging of 56 patients were not feasible due to unavailability of β2 microglobulin levels.

Stage I	Stage II	Stage III
2	2	14

Table 5: International Staging System (N=18).

Discussion

MM is considered as a disease of the old with median age of 60-70 years in western countries [9]. The median age of patients in our study was 55 years which was lower compared to western countries. Sixth decade was the most common age group at presentation in other Indian studies by Jacob et al and Kaur, et al. [10,11] Our study showed higher percentage of patients (9.4%) with age less than 40 years compared to 2% and 2.2% in study by Kyle, et al. [9] and Blade, et al. [12] Indian study by Yanamandra, et al. [13] reported higher incidence (9.6%) of MM in the patients less than 40 years of age similar to our result. A high male: female ratio observed in our study was similar to the study by Asian myeloma network and other India studies [10-14]. Fatigue and bone pain was the most common clinical presentation similar to other study [9].

In our study anemia (Hemoglobin levels <10 gm/dl) and severe anemia (Hemoglobin < 8 gm/dl) at presentation was observed in 81% and 52.7% of the patients respectively. Although in majority of the patients, anemia was normocytic normochromic, 23% patients had microcytic anemia. Compared to study by Kyle, et al. [9] incidence of severe anemia and microcytic anemia is higher in our studies. In a developing country like ours, anemia could be multifactorial in origin. Other etiologies including iron deficiency needs to be evaluated at presentation before attributing it solely to MM. Thrombocytopenia was present in 9.4% of the patients, which was similar to Kyle, et al. [9].

In patients with MM, circulating plasma cells of >5% is associated with poor prognosis [15]. In our study only 6(8%) patients had circulating plasma cells, out of which 5 had >5% circulating plasma cells. Two patients had more than 20% plasma cells and these cases were labelled as plasma cell leukemia. Patient having >5% circulating plasma cells had higher proportion of bone marrow plasma cells (median 86% vs. 52%) and this correlation was statistically significant (p value <0.05) and these findings were similar to study by Granell, et al. [15].

Hypercalcemia and renal dysfunction are two important diagnostic criteria of MM. The primary cause of hypercalcemia in MM is tumor induced increased osteoclastic bone resorption [16]. In our study, hypercalcemia was observed in 31.4% of the patients, 53.8% of the patients diagnosed as MM had normal calcium levels. All the patients with

hypercalcemia had anemia and 8 (47%) of them had severe anemia. Six out of 17 (35%) patients with hypercalcemia had renal dysfunction. Study by Bao, et al. [17] showed that in a newly diagnosed case of MM, hypercalcemia was associated with high levels of serum creatinine, low hemoglobin level and poor outcome.

Toxic effect of monoclonal light chain is the major reason of development of renal dysfunction in MM [18]. Incidence of renal dysfunction is reported in 15% to 40% of the patients with MM and up to 10% of them require dialysis [19]. In our study, renal dysfunction was reported in 15% of the patients.

Serum immunofixation revealed IgG M protein in 77% of the patients followed by IgA in 23% and IgG kappa being the most common type. In the study by Kyle, et al. [9] IgG M protein was observed in 52% of the patients. No case of light chain myeloma was observed in our study. The median value of plasma cells in the bone marrow was 52%, which was similar to study by Kyle, et al. [9] in a newly diagnosed case of MM, more than 60% plasma cells is one of the myeloma defining lesion and associated with poor outcome. Study by Al saleh, et al. [20] showed that 39% of the patient had more than 60% plasma cells which is comparable to what we observed (42%) in our study. Our study showed diffuse pattern as the most common pattern (59%) of infiltration by plasma cells similar to Subramanian, et al. [21].

Medical imaging is crucial for the diagnosis of MM. Increased osteoclastic activity and reduced osteoblastic functions are main pathogenic mechanism of bone lesions in MM [22]. Kyle, et al. [9] reported lytic lesions in 66% patients similar to our study.

At the time of initial presentation, serum albumin and β2 microglobulin levels are two important parameters to predict the patient outcome [4]. In our study 56.7% patients had Serum albumin <3.5 gm/dl which is an indicator of poor outcome. Study by Asian myeloma network, which included 3405 patients from various Asian countries reported serum albumin <3.5 gm/dl in 52% of the patients, which was quite similar to our findings [14]. Due to financial constraints of our study group, β2 microglobulin levels were available in only 18 cases and hence ISS staging was not feasible in all the cases. This is one of the important limitations of our study. Other limitations of our study are unavailability of cytogenetics, treatment and survival outcome data.

Key Message

Multiple myeloma is a disease with multi system involvement. Our study from eastern India reiterates that Indian population has onset of MM at younger age. At presentation our study group had higher proportion of anemia and advance disease.

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