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Original Article

Clinical Pattern of Multiple Myeloma in Low Socioeconomic Group Patients of South India

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Abstract

Background: Multiple myeloma (MM) forms~10% of hematological malignancies. Our aim and objective were to find the clinical profile, and presenting feature of MM in patients presented in a government hospital that treats below poverty line group of patients.

Materials and Methods: Medical records of all patients diagnosed with plasma cell neoplasm between December 2014 and December 2019 were taken from data registry and analyzed.

Results: One hundred and forty-two patients fit into MM diagnosis. Eighty-three were male (58.5%) and 59 were female (41.5%) with male to female ratio of 1.4. The median age of the study patients was 59 years (range 33–82 years). About 3.5% (5) patients were <40 years of age. One hundred and five patients (73.9%) had bone pathology, including lytic lesions and osteopenia with lumbar vertebra being the most common site, followed by thoracic vertebra and pelvis. The neurological compromise was present in 32 patients (22.5%). One hundred and twelve patients (78.8%) had Grade 1 or 2 anemia. Seventy-eight patients (54.9%) had creatinine >2 mg/dl with 25 of them had acute kidney injury. Twenty-seven patients (19%) had hypercalcemia. Twenty-three patients (16.2%) had infection during presentation with most common focus as lungs. Serum protein electrophoresis showed M band in 85.2% of patients and urine Bence Jones protein was positive in 61.3% of patients. Serum lactate dehydrogenase was elevated in 41.5% of patients and beta-2 microglobulin was elevated in 72% of patients.

Conclusions: MM patients presented at an early age, with an advanced stage and more end-organ damage that requires much attention.

Key words: Clinical pattern, Low socio-economic group, Multiple myeloma

INTRODUCTION

Plasma cell dyscrasias include various disorders that result from monoclonal proliferation of plasma cells. The clinical behavior of each disorder varies from benign to malignant. The common among them, known as monoclonal gammopathy of undetermined significance (MGUS) is asymptomatic and can be diagnosed in the general population. Other related disorders include smoldering multiple myeloma (SMM), MM, and Waldenstrom macroglobulinemia. MM is a malignant proliferation of terminally differentiated plasma cells. Dr. Henry Bence Jones first described clinical features of myeloma in a patient in 1850, and the term MM was later coined by Rustizky in 1873. It forms around 17% of all hematological malignancies and around 1.8% of all malignancies.[1] It is a disease of the elderly with a median age of presentation being 69 years[2] and median age of death being 74 years. In India, it is noted that the median age of presentation is 60–69 years, which is earlier than that of west.[3] Only 5% of the patients are below 40 years of age. MM is almost always preceded by MGUS[4] which is asymptomatic and can be diagnosed incidentally in the general population. The spectrum of disease starts from MGUS to SMM and then to MM.[5] The rate of progression from MGUS to SMM is 0.5% to 1% per year, while it is around 10% per year for SMM to MM.[6] The exact etiology for MGUS or MM is unknown. Some of the risk factors identified are older age, male sex, and African American and African compared to Americans

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Mexican Americans and also Europeans.[7] The reason may be due to the genetic susceptibility and molecular biology involving the pathogenesis of MM. Some familial cause for MM is also reported, but the exact extent is unknown. First degree relatives have a 3.7-fold increased risk than that of the general population.[8] Some of the presenting features of MM in the descending order of frequency are anemia, bone pain, elevated creatinine, fatigue, hypercalcemia, and weight loss.[9] Patients from India present in an advanced stage compared to the western population.[10-13] The analysis of the descriptive nature of plasma cell dyscrasias in India is important as there is variation between the patient characteristics and disease presentation between the western population and Indian population. This study will help us in understanding the lack of knowledge among our population and possibly improve early diagnosis and treatment.

MATERIALS AND METHODS

Patients registered between December 1, 2014, and December 31, 2019 (5 years) were searched from the database and analyzed. This is a retrospective study where all details were taken from the patient's master case sheets from the Department of Medical Oncology, Madras Medical College, Chennai. The diagnosis of MM, SMM, MGUS, solitary plasmacytoma, and plasma cell leukemia was searched and analyzed. The updated International Myeloma Working Group (IMWG) criteria are used for the diagnosis of MM [Table 1]. Conditions where reactive plasma cells are seen such as metastasis, long-standing infections, connective tissue diseases, and liver disease were removed. Laboratory results were checked whether it is done within 1 month of diagnosis of plasma cell disorder to avoid error. All myeloma work-up was checked whether it is done in same institution laboratory to avoid any interlaboratory errors. If any extra information was needed apart from those available in master case sheets of individual patients, the patients or their attenders were communicated through telephone or letter and requested to provide the missing details. Data including name, age, sex, address, and contact details of patients were tabled in the master sheet. All statistical analysis was made with the help of IBM SPSS statistical software version 23. Percentage, ratio, mean, median, mode, and range were calculated. Microsoft office version 2016 was used for tables and appropriate charts wherever required.

RESULTS

One hundred and sixty-eight patients were registered as plasma cell neoplasm in the 5-year period. Among 168 patients, three had solitary plasmacytoma involving mandible, clavicle, and lung, respectively, four patients had SMM, and six patients had MGUS. Data could not be analyzed for 13 patients due to various reasons, and hence they were excluded [Table 2]. There were 142 patients who met the revised IMWG[14] criteria, as shown in Table 1. There were 83 (58.5%) male patients and 59 (41.5%) female patients with a M:F ratio of 1.4. The majority of the patients were in their sixth decade with a median age of 59 years (range 35–84 years) at the time of presentation. Five (3.5%) patients were below 40 years of and the majority were between 50 and 60 years of age (41.5%), age-wise distribution is listed in Table 3. Fifteen patients (10.6%) were smokers and 28 patients (19.7%) were alcoholic.

Clinical Profile

The neurological compromise was present in 32 patients (22.5%). They had the various extents of paraparesis, paraplegia, quadriplegia, and uncontrolled bladder function depending on the site of cord compression with the majority of patients presenting as quadriplegia (22 patients). About 66.1% of patients (n = 94) had fatigue, which is defined in NCCN guidelines as cancer or its treatment-related distressing, persisting feeling of tiredness which is not proportional to the activity done and interferes with our daily living. Back pain was seen in 45.1% of patients with most of them having low backache and spine tenderness was present in 40.1% of patients. Significant weight loss with ≥10% of their body weight was present in 38.2% of patients. Bony pain in any part of the body, including back pain, was present in 64.1% of patients. Pallor was present in 62.7% of patients, and 23 patients (16.2%) had an infection during the presentation with the most common site as lung. Fever was present in 19 patients, and 42 patients had pedal edema [Table 4].

Lab and Radiological Profile

One hundred and five patients (73.9%) had bone pathology, including lytic lesions and osteopenia, with lumbar vertebra being the most common site, followed by thoracic vertebra and pelvis. The percentage of involvement in each bone site is mentioned in Table 5. The most common method used to diagnose bone involvement was skeletal radiography (54%), followed by computed tomography (CT) scan (40%) and remaining cases were by positron emission tomography CT and magnetic resonance imaging scan. One hundred and twelve patients (78.8%) had anemia of all grade, with 47.8% (68 patients) had Hb <10 g/dl as per IMWG end-organ damage definition. Seventy-eight patients (54.9%) had creatinine >2 mg/dl, with 25 of them having acute kidney injury (AKI), and 50.7% of patients had uremia. The median creatinine clearance among patients with kidney involvement was 35 ml/min. Twenty-seven patients (19%) had hypercalcemia which is defined in IMWG as >11 mg/dl and 13 among them had symptoms related to hypercalcemia, while

Table 1: IMWG revised diagnostic criteria

Revised International Myeloma Working Group diagnostic criteria for multiple myeloma and smoldering multiple myeloma

Definition of multiple myeloma
Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma-defining events:

• Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
  • Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
  • Renal insufficiency: creatinine clearance <40 mL per min¶ or serum creatinine >177 µmol/L (>2 mg/dL)
  • Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L
  • Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CTΔ

• Any one or more of the following biomarkers of malignancy:
  • Clonal bone marrow plasma cell percentage* ≥60%
  • Involved:uninvolved serum free light chain ratio◇ ≥100
  • >1 focal lesions on MRI studies§

Definition of smoldering multiple myeloma
Both criteria must be met:
• Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 hours and/or clonal bone marrow plasma cells 10 to 60% • Absence of myeloma defining events or amyloidosis
Definition of monoclonal gammopathy of undetermined significance
All three criteria must be met:
• Serum monoclonal protein <30 g/L • Bone marrow plasma cells <10% • Absence of myeloma defining events or amyloidosis (or Waldenström macroglobulinemia in the case of IgM MGUS)

PET-CT: ^{18}F-fluorodeoxyglucose positron emission tomography with computed tomography.
* Clonality should be established by showing kappa/lambda-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.
¶ Measured or estimated by validated equations.
Δ If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.
◇ These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L.
§ Each focal lesion must be 5 mm or more in size.

Table 2: Distribution of plasma cell disorders

Diagnosis	Number (%) *n*=168	Male	Female
Solitary plasmacytoma	3 (1.8)	2	1
SMM	4 (2.4)	4	0
MGUS	6 (3.5)	4	2
MM	142 (84.5)	83	59
Missing data	13 (7.7)	7	6

SMM: Smoldering multiple myeloma, MM: Multiple myeloma, MGUS: Monoclonal gammopathy of undetermined significance

others were asymptomatic. Serum protein electrophoresis showed M band in 85% of patients and urine Bence Jones protein (BJP) was positive in 61% of patients. Serum lactate dehydrogenase (LDH) was elevated in 42% of patients, and beta-2 microglobulin was elevated in 72% of patients. Platelets less than a lakh were present in 15 patients (10.5%), and erythrocyte sedimentation rate was high in 36.6% of patients as per the lab cutoff for males and females. M band is identified in 121 patients (85.2%) with serum protein electrophoresis and seven patients (4.9%) were picked up by immunofixation electrophoresis in serum or urine. Urine BJP was identified in 87 patients (61.3%), and elevated LDH was present in 59 patients (41.5%). Serum hypoalbuminemia (albumin <3.5 g/dl) was present in 41 patients (28.9%).

Patients were classified as per the International Staging System for myeloma, as shown in Table 6. Stage 3 was the most common presentation, and 88 patients (61.9%) presented in that stage, while 32 patients (22.6%) and 22 patients (15.5%) presented in stage 2 and stage 1, respectively.

Table 3: Age-wise distribution of MM

Age group	Number (%) n=142	Male (%) n=83	Female (%) n=59
Below 40	5 (3.5)	4	1
40–50	52 (36.6)	27	25
50–60	59 (41.5)	35	24
60–70	19 (13.4)	12	7
70–80	6 (4.2)	4	2
Above 80	1 (0.7)	0	1

Table 4: Clinical and Lab profile of MM

Symptom/sign	Number (%) total *n*=142	Lab profile	Number (%) total *n*=142
Fatigue	94 (66.1)	Lytic bone lesion	105 (73.9)
Neurological deficit	32 (22.5)	Creatinine >2 mg/dl	78 (54.9)
Back pain	64 (45.1)	Acute kidney injury	25 (17.6)
Spine tenderness	57 (40.1)	Uremia	72 (50.7)
Recent weight loss	54 (38.2)	Hypercalcemia	27 (19)
Bone pain	91 (64.1)	Anemia all grades	112 (78.8)
Pallor	89 (62.7)	Thrombocytopenia	15 (10.5)
Infection	23 (16.2)	Erythrocyte sedimentation rate elevation	52 (36.6)
Fever	19 (13.4)	M band in SPE	121 (85.2)
Edema	42(29.5)	Urine BJP	87 (61.3)
		Elevated LDH	59 (41.5)
		Hypoalbuminemia	41 (28.9)
		β2M >3.5 mg/L	102 (71.8)

LDH: Lactate dehydrogenase, BJP: Bence Jones protein, SPE: Serum protein electrophoresis

Table 5: Individual bone involvement in MM

Site of bone lesion	Number (%) total *n*=105
Lumbar	77 (73.3)
Thoracic	43 (40.9)
Pelvis	39 (37.4)
Cervical vertebra	9 (8.5)
Femur	28 (26.6)
Tibia	14 (13.3)
Humerus	19 (18.1)
Small bones	5 (4.7)

Table 6: International Staging System of MM

ISS stage (old)	Definition	Number (%) total *n*=142
1	β2M <3.5 mg/L; ALB ≥3.5 g/dL	88 (61.9%)
2	β2M <3.5 mg/L; ALB ≥3.5 g/dL; or β2M 3.5–5.5 mg/L	32 (22.6%)
3	β2M >5.5 mg/L	22 (15.5%)

ALB: Albumin

Treatment

Most of the patients (67%) received cyclophosphamide, vincristine, and prednisolone (CVP) regimen, which includes CVP once in 3 weeks. About 28% of patients received CVP along with thalidomide while remaining patients received bortezomib based regimen. When patients received thalidomide, they were put on antiplatelet therapy to prevent thromboembolic events. Patients also received bone modifying agents along with chemotherapy such as zoledronic acid or ibandronate if the creatinine clearance is very low.

DISCUSSION

This study included a good number of patients over a period of 5 years and analyzed their clinical and laboratory profile. Fousad *et al.*[15] in their prospective study which is from South India showed a slight male predominance with a M:F ratio of 1.3 and our study also showed a ratio of 1.4. The median age in our study was 59 years while it is a bit late in western study which reports as seventh decade[16,17] and a little higher percent of patients younger than 40 years of age (3.5%) compared to 2%[17] as described in western literature. Neurological involvement and spinal compression are rare in western population but it is very high in Indian scenario and especially in low socioeconomic group (22.5% in this analysis) where there is very late presentation with frank paraplegia and many patients with paraplegia do not recover with spinal decompression surgery or radiotherapy to the involved compression site. Although fatigue is less reported in large studies, our study found 66.1% of patients had fatigue probably due to late and advanced stage of presentation in our population. Most of the back pain and bone pain in any site is being managed symptomatically without working up for the cause in initial treatment centers. Renal involvement was more in our study group (54.9%) with higher percentage of AKI (17.6%), where it was the presenting feature as mentioned by Dr. Winearls in his study.[18] Kidney involvement was due to either light chain nephropathy of hypercalcemia, with many of them not requiring biopsy since the light chain was elevated in many patients. There was around 9% lesser incidence of hypercalcemia (19%) compared to that reported by Kyle *et al.*[16] and the reason is unknown, which may need a prospective study. Many patients with anemia (72%) had increased number of plasma cell percentage with a mean of 29% ± 8.7%, which could explain the cause of anemia in the majority of patients. The most common type of anemia was normocytic and normochromic. Weight loss was more by 10% compared to that reported by Kyle *et al.*[16] MM patients are prone to many infections because of the impaired functioning of immunoglobulin and plasma cells. In our study, 16.2% of patients had an infection during the

initial workup among which pneumonia was found in many. Hypoalbuminemia was present in 28.9%, and increased beta-2 microglobulin was found in 71.8% of patients, both of which determine the stage of the disease in the International Staging System, and hence more patients had stage 3 at the time of presentation which leads to poor overall survival.

CONCLUSION

MM patients present in an advanced disease condition compared to the West. Increased awareness is needed for this increasing hematological malignancy among the general public and also to primary physicians so that early treatment can prolong the progression-free survival and probably the overall survival.

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ETHICAL APPROVAL

Obtained as per the institution protocol.

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