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Clinico-pathological profile of multiple myeloma in a tertiary care centre in North West Rajasthan

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Abstract

Introduction: Multiple myeloma is a malignant neoplasm of plasma cells that accumulate in bone marrow which leads to bone destruction and marrow failure. The main aim of this study was to evaluate clinical features, bone marrow findings and biochemical parameters in multiple myeloma.

Method: This was a prospective as well as retrospective study conducted in Sardar Patel Medical College and PBM Hospital, Bikaner. A total of 95 patients were included who were evaluated using clinical history and relevant laboratory investigations including bone marrow.

Result: The highest peak i.e. 34 patients (35.78%) were aged between 61 and 70 years with male to female ratio 1.71:1. Bone pain was presenting complaint in 73 patients (76.85%). Multiple osteolytic lesions were found in 68 (71.57%) patients. Anaemia, raised ESR, hypaercalcemia and elevated serum creatinine were recorded in 97.9%, 96.85%, 48.4%, 71.57% respectively. 45.26% patients were in ISS stage III. 43.16% patients had 20-50% plasma cells in bone marrow aspiration and diffuse pattern of infiltration was seen in 49.02% patients in bone marrow biopsy. In 55.8% cases monoclonal gammopathy was of IgG kappa type.

Conclusion: Majority of patients were of age group 51 years to 70 years with male predominance. Most common presenting feature was bone pain. Most common findings were anemia Hb < 10 mg/dl (81%), elevated ESR, elevated serum creatinine >2 mg/dl, low albumin level 3.5 g/dl. The most common monoclonal gammopathy was of IgGkappa type and bone marrow plasma cells between 20%-50% in majority of patients.

Keywords: multiple myeloma, clinical features, bone marrow

Introduction

MM comprises about 1% of malignant tumors, 10-15% of hematopoietic neoplasms,causes 20% of deaths from hematological malignancies and it is second most

common hematological malignancy after Non-Hodgkin lymphoma.[1] The mean age of affected individuals is 62 years for men (75% older than 70 years) and 61 years for women (79% older than 70 years)[2]. Myeloma is most commonly evolve from a monoclonal gammopathy of undetermined clinical significance (usually known as MGUS) that progresses to smoldering myeloma and, finally, to symptomatic myeloma.[3]

MM is slightly more common in males than in females with a male to female ratio of 1.4:1. Approximately 90% of multiple myeloma cases occur over age of 50 years and median age at diagnosis of about 70 years. It is a rare in patients younger than 40 years of age and seen in less than 2% of cases. The major features of multiple myeloma result from the abnormal accumulation of neoplastic plasma cells in the bone marrow from which normal bone marrow function is disrupted, reflected by anemia or low white cell count or low platelet count, destruction of bone surrounding the bone marrow cavity and monoclonal protein released by neoplastic cells in blood and/or urine. Normal immune function is reduced.[3,4]

Bone pain is presenting clinical feature in 80% cases. Seventy five percent cases present with punched out lytic lesions, osteoporosis or fractures on radiography. Vertebral collapse may lead to nerve root compression. 18-30% cases present with hypercalcaemia as a result of bone destruction.[5]

Diagnosis of Multiple myeloma is made by combination of pathological, radiological and clinical features.

Diagnostic criteria

Revised International Myeloma Working Group Criteria for Diagnosis of multiple myeloma (2014)[6]

Both criteria must be met:

1. Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma
2. Any one or more of the following myeloma defining events:

CRAB: 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)

*R*enal insufficiency: creatinine clearance <40 mL/min or serum creatinine >177 μmol/L (>2 mg/dL)

*A*nemia: hemoglobin value of >2 g/dL below the lower limit of normal, or a hemoglobin value <10g/dL

*B*one lesions: one or more osteolytic lesions on skeletal radiography, computed tomography, or positron emission tomography

Other myeloma defining event (new 2014):

Clonal bone marrow plasma cell percentage ≥60%

Involved: uninvolved serum free light chain (FLC) ratio ≥100 (involved FLC level must be ≥100 mg/L)

>1 focal lesions on magnetic resonance imaging studies (at least 5 mm in size)

The dysfunctional plasma cells secrete one of five major classes of immunoglobulins (IgG, IgA, IgM, IgD and IgE) or in some cases produce only light chain of immunoglobulins. Sometimes cells do not secrete any paraproteins, known as non–secretory type myeloma. The most common type of monoclonal antibody is IgG and the least common is IgE.[7]

Aims and objectives

1. To study the age and gender occurrence of Multiple Myeloma
2. To study bone marrow aspiration and bone marrow trephine biopsy in Multiple Myeloma.

3. To study the common modes of clinical presentation of Multiple Myeloma.

Material and method

This study was conducted for a period of 4 years both prospectively and retrospectively in the Department of Pathology, Sardar Patel Medical College and PBM Hospital, Bikaner. All cases diagnosed with Multiple Myeloma during the study period were analyzed in regard to clinical features, laboratory parameters, biochemical profile, bone marrow morphology. A total of 95 patients were included in the present study.The parameters evaluated in all subjects were: Hemoglobin estimation, total leucocyte count and platelet count, ESR, Total proteins, Albumin and Globulin, Serum calcium, Serum creatinine, Serum protein electrophoresis, β2 microglobulin, Radiological assessment for bony abnormalities , Bone marrow aspiration, Bone marrow trephine biopsy. Serum protein electrophoresis, Immunofixation electrophoresis, Free light chain assays were sent to outsource laboratories

Results

The presenting age of the patients ranged from 39 to 78 years. Out of the 95 patients, the highest peak i.e. 34 patients (35.78%) were aged between 61 and 70 years and the second highest peak was between 51 and 60 years involving 33 patients (34.73%). Only 2 patients (2.1%) were less than 40 years of age. The male : female ratio was 1.71:1. 60 patients were males (63.16%) and 35 (36.84%) were females.

Distribution of clinical features

Clinical features	**No. of patients**	**Percentage (%)**
Low backache and bone pain	73	76.85
Generalized weakness	42	44.21
Neurological manifestations	27	28.43
Breathlessness	18	18.95
Fever	15	15.80
Fracture	6	6.31
Soft tissue mass	5	5.26
Epistaxis	1	1.05

The skeletal lesions were present in as osteoporosis, osteolysis and fractures; either singly or in combinations. The commonest radiological findings were multiple osteolytic lesions found in 68 (71.57%) patients. Hb values ranged from 3.8 to 12.4 g/dl with a mean value of 8.03±1.8 g/dl. Majority of patients had anaemia (97.9%). Hb value <10g/dl was seen in 77 (81%) cases. Majority of patients had normocytic normochromic anaemia (84.2%). On peripheral smear examination rouleaux formation is seen in 76 (80%) patients. ESR ranged from 15 mm in 1st hour to 160 mm in 1st hour. It was raised in 92(96.85%). It was more than 100 mm in 1st hour in 22 patients. Serum creatinine levels ranged from 0.5 to 7.2 mg/dl with a mean of 2.44±1.45 mg/dl. Raised levels (>1.4 mg/dl) were seen in 68 (71.57%) cases. Serum creatinine >2mg/dl was seen in 52 (54.74%) cases. Serum calcium levels ranged from 6.7 to 15.6 mg/dl with a mean of 10.1±2 mg/dl. Hypercalcemia (serum calcium >10.2 mg/dl) was seen in 46 (48.4%) cases. Thirty-four (35.78%) patients presented with Serum Calcium >11 mg/dl. Serum albumin value ranged from 1.24 g/dl to 5.88 g/dl with a mean of 3.27±0.95 g/dl. Fifty-six (58.95%) patients presented with serum albumin levels

lower than 3.5 g/dL. Of the 95 patients, values in 30 (31.57%) patients were <3500ng/ml with levels exceeding 5500ng/ml in 43 (45.27%). These patients with serum beta 2 microglobulin values were staged as stage I, II and III according to international staging system for plasma cell myeloma

Table 1: Distribution of cases on the basis of International Staging System (ISS)

ISS Staging	No. of patients	Percentage (%)
STAGE I ($S. \beta_2$ M<3500ng/ml and S. albumin≥3.5g/dl)	11	11.58
STAGE II Nor stage I or III	41	43.16
STAGE III ($S. \beta_2$ M ≥5500ng/ml)	43	45.26

Bone marrow aspiration

Table 2: Percentage of plasma cells in bone marrow aspiration

Percentage of pcs in aspirate	no. of patients	Percentage (%)
<20%	30	31.57
20%-50%	41	43.16
>50%	24	25.27
Total	95	100

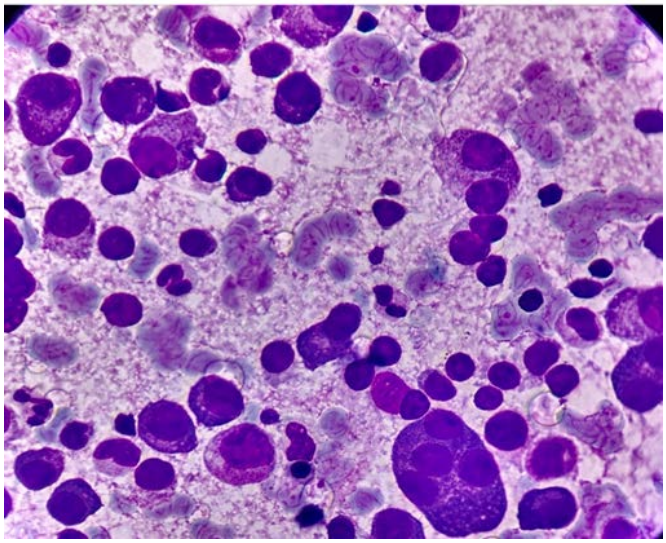

Figure 1: Multinucleated Plasma Cell In Bone Marrow Aspiration (100x)

Bone marrow biopsy findings

Table 3: Distribution of cases on the basis of patterns of infiltration on Bone Marrow Biopsy

BMB	No. of patients	Percentage (%)
Diffuse	25	49.02
Interstitial	23	45.10
Focal/Nodular	2	3.92
Mixed	1	1.96

Serum Protein Electrophoresis and Immunofixation

Monoclonal gammopathy as M band was detectable in all (n =95) cases.

Table 4 : Paraprotein fraction frequency

Paraprotein fraction	No. of patients	Percentage (%)
IgG kappa	53	55.8
IgG lambda	24	25.3
IgA lambda	12	12.6
IgA kappa	6	6.3

Discussion

Table 5: Comparison of age and sex distribution

Authors	Mean age (years)	M: F ratio
Cavo et al (1989)[8]	60.3	1.2:1
Kyle et al (2003)[5]	66	1.4:1
Choudhury S et al (2012)[9]	63.25	2.5:1
P. Kaur et al (2014)[10]	58.8	1.5:1
Diwan et al (2014)[11]	62	1:1
Kalita et al (2016)[12]	56	2:1
Kaushik et al (2017)[13]	58	2.8:1
Fousad C et al (2018)[14]	64	1.3:1
Present study	59	1.71:1

Table 6: Comparison of clinical features

Study	Bone pain	Generalized weakness
Blade et al (1996)[15]	66	26
Kyle et al (2003)[5]	58	32
Subrammanian et al (2009)[16]	82	73
Kalita et al (2012)[12]	44	41
P. Kaur et al (2014)[10]	50	46.4
Diwan et al (2014)[11]	85	55
Present study	76.85	44.21

Severe anemia was seen in 53.7% of our patients which is in accordance with Kaushik et al[13] (45%) but much higher compared to Kyle et al[5] (7%). However the anemia was normocytic normochromic in majority of our patients as reported in literature. (Kyle et al,[5] P. Kaur et al[10]).

In our study ESR was raised in 96.85 % cases. However, very high ESR (>100 mm in 1st hour) was observed in 23.15% patients. These observations were close to the studies of P. Kaur et al[10] and Kaushik et al[13] who observed a raised ESR in all of their cases(100%). M band was detectable in all patients (100%) on serum protein electrophoresis. In various studies by Advani et al,[17] Kyle et al,[5] P. Kaur et al,[10] Kaushik et al[13] and Diwan et al[11] M band was observed in 74% 75.4%, 82%, 92.8%, 94% and 100% patients respectively. Hypercalcaemia (serum calcium>10.2 mg/dl) was seen in 46 (48.4%) patients in the present study. However, hypercalcaemia in studies conducted by P. Kaur et al[10] was seen in 42.8% patients . Raised creatinine levels (serum creatinine >1.4mg/l) were seen in 71.57% cases. Study by P. Kaur et al[10] revealed raised levels in 86.4% cases. In present study serum β_2 M levels were raised in 68.43% patients. Similar findings were seen in studies conducted by Kyle et al[5] and P. Kaur et al[10] raised values were observed in 75% and 71.4% cases respectively.

24 patients (25.3%) had >50% plasma cells in bone marrow aspirate at the time of presentation as was also found in studies by Kalita et al[12] (26%). Diffuse (Sheeting) pattern of bone marrow infiltration which indicates poor prognosis was seen as predominant pattern of marrow involvement in the present study in 49.02% cases and is concordant to observations by Kaushik et al (54%),[13] P. Kaur et al (71.4%),[10] Subramanian et al (64%)[16] .

The most common immunoglobulin type (heavy chain) of myeloma seen in the study population was IgG in 77 (81.1%), followed by elevated IgA in 18 (18.9%)

patients. In a study by kihyunkim et al[18] 55.2% patients had IgG myeloma and 22% had IgA myeloma, 17.9% also showed light chain myeloma which was not ssen in present study population.

Conclusion

In conclusion multiple myeloma is a disease with a wide variety of clinical presentations and multiple system involvement. In our study mostly patients were elderly and middle aged. Majority of patients presented with complaints of bone pain and generalized body weakness. Mostly patients had normocytic normochromic anaemia with normal leucocyte and platelet count. Mostly patients had raised ESR. Majority of patients were in ISS stage III followed by stage II. Majority of patients had 20-50% plasma cells in bone marrow and in serum immunofixation, IgG kappa was most common type of monoclonal gammopathy.

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