Multiple Myeloma-Clinicopathological Features and Risk Stratification

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ABSTRACT

Objective: To evaluate the clinic pathological features and to risk stratify patients of multiple myeloma in our population

Study Design: Cross sectional study.

Place and Duration of Study: Department of Hematology, Armed Forces Institute of Pathology (AFIP) Rawalpindi Pakistan, from Jan to Jun 2019.

Methodology: Patients that were newly diagnosed multiple myeloma on the basis of International Myeloma Working Group (IMWG) 2014 criteria were included in the study. Blood counts, peripheral film examination, bone marrow aspirate and trephine were examined. Biochemical profile, serum protein electrophoresis and skeletal survey was assessed.

Results: A total of 65 newly diagnosed Multiple Myeloma patients were included. Of these, 43 (66.2%) were males and 22 (33.8%) females. Mean age of the patients was 58.5 years with a range of 36-76 years. The most common presenting symptom was bone pain in 33 (50.8%) patients, followed by backache in 32 (49.2%) patients. Mean percentage of plasma cell on bone marrow examination was 40.89% ± 23.2. On risk stratification based on International staging system, 20 (30.7%) patients were in stage I, 19 (29.1%) patients were on stage II while 26 (40.2%) patients were in stage III.

Conclusion: Bone pain and backache along with anemia were found the predominant complaints of patients presenting with multiple myeloma in our setup with male predominance. Risk stratification of multiple myeloma according to ISS revealed that stage III was the most predominant in our population.

Keywords: Anemia, Bone pain, Multiple myeloma, International myeloma working group, International staging system.

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INTRODUCTION

Multiple myeloma is a cancer of plasma cells resulting in its uncontrolled cellular proliferation leading to secretion of various monoclonal immunoglobulin which can be detected in the serum or urine. Osteolytic lesions, anemia, hypercalcemia and renal impairment are among the common manifestation of this disease, leading to end stage organ damage.[1]

Multiple myeloma is the second most common hematological malignancy after non Hodgkin lymphoma. Approximately 1.8% of all newly diagnosed malignancies and 10% over all cancers include multiple myeloma.[2] Global survey conducted in 2015 revealed that 488,000 individuals were affected with Multiple myeloma and it resulted in mortality in 101,000 patients.[3] Very few tertiary care centers in Pakistan have conducted studies on its clinical features, diagnosis and management.

Multiple Risk factors have been proposed in the etiology of multiple myeloma which include exposure to radiations, chemicals such as asbestos, benzene, carbon mono oxide, pesticides etc.[4] Translocation at chromosome 14 between immunoglobulin heavy chain gene (locus q32) and an oncogene (often 11q13, 4p16.3, 6p21, 16q23 and 20q11) is frequently observed in patients with multiple myeloma.[5]

Presence of anemia in a patient without any explainable cause, renal dysfunction, raised Erythrocyte sedimentation rate, elevated beta 2 microglobulin levels and increased immunoglobulin levels may warrant further investigations for MM.[6] Diagnostic procedure for MM starts with serum or urine Protein electrophoresis along with histopathological examination of bone marrow.[2] Skeletal survey which includes X-rays of the skull, axial skeleton, and proximal long bones, bone scan, CT scan and MRI is also done in order to evaluate osteolytic bone lesions.[7]

Due to multiple organ involvement there exists great heterogeneity in the clinical features of MM which is the major cause of potential delay in diagnosis and proper treatment planning. Thus, risk stratification and identification of clinical features associated with this disease are of paramount importance in timely prediction of disease and its prognosis. Most of the available data on MM is from the western countries. So we undertook this study in our setup on

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symptomology in our patient and determine the ISS scoring of our population so that patients can be diagnosed early and properly counselled about the prognosis of disease and urgency of treatment.

METHODOLOGY

This cross sectional study was conducted on newly diagnosed patients of multiple myeloma at the department of Hematology/Molecular Pathology from Janu to June 2019, Armed Forces Institute of Pathology, Rawalpindi. AFIP is a tertiary care referral Centre receiving patients from different parts of the country.A sample size of 28 was calculated using WHO sample size calculator, with prevalence of 1.8% and confidence level of 95%, however 65 patients were included in our study. Sampling criteria was Non probability consecutive sampling technique. Patients who were newly diagnosed with multiple myeloma according to the criteria mentioned by international myeloma working group IMWG in 2014,[8] of either gender irrespective of age were inducted into the study. Patients with monoclonal gammopathy of undetermined significance (based on Bone marrow biopsy <10% plasma cells), plasma cell leukemia, smoldering myeloma/relapsed myeloma and hematological malignancies and other bleeding disorders were excluded from the study.

After taking permission from the ethical committee review board(Ref No. FC-HEM 117-34/ READ-IRB/400 Dated 07 Aug 2018), written informed consent was taken from the patients. Patient age, gender, presence or absence of fatigue and findings of skeletal survey including osteolytic lesions, bone pain and backache were endorsed in the proforma. 3-4 ml of blood was taken into EDTA tube and plain tube containing clot activator via venipuncture. Hb, MCV, Platelet count, ANC and WBC count was analysed using automated analyzer SYSMEX-XE5000. ESR levels was measured by automated analyser VACUETTE SRS 20/II. Chemistry screening including serum calcium, albumin and creatinine levels was done by automated analyzer ADVIA 1800. β2microglobulin levels were analysed using SPAPLUS. Bone marrow plasma cell percentage was evaluated by examining bone marrow aspirate and trephine biopsy.

Patients were stratified according to the scoring systempublished in 2005 by the International Myeloma working groupknown as International Staging System ISS.[9]

Stage-1: β2microglobulin (β2M) <3.5 mg/L albumin ≥ 3.5 g/dl.

Stage-2: β2microglobulin<3.5 mg/L and albumin <3.5 g/dl.

OR

β2microglobulin levels between 3.5–5.5 mg/L regardless of the levels of serum albumin.

Stage-3: β2microglobulin ≥ 5.5 mg/L.

Data was analyzed using SPSS version 25.0. Mean and SD was calculated for numerical variables. Percentage and frequency was calculated for categorical variables. Chi-square test was used for evaluation of association of various stages of disease with age and gender. *p*-value ≤0.05 was considered to be significant.

RESULTS

Out of total 65 patients, 33 (66.2%) were male and 22 (33.8%) were female with a mean age of 58.56 ± 11.91 years. Minimum age at diagnosis was 36 years and maximum was 76 years.

The most common presenting symptom (Figure-1) was bone pain in 33 (50.8%) patients, followed by back ache 32 (49.2%). Fatigue and osteolytic bone lesions were present in 22 (33.8%) and 21 (32.3%) cases respectively. Hypercalcemia was present in 16 (24.6%) cases.

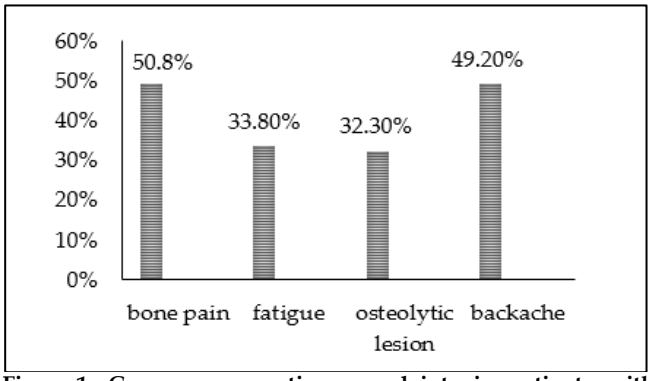

Figure-1: Common presenting complaints in patients with multiple myeloma.

Mean percentage of plasma cell on bone marrow examination was 40.89 ± 23.2. The mean β2 microglobulin level was 5.65 ± 3.21 gm/dl and the mean serum albumin level was 37.7± 6.28 gm/dl. Mean ESR levels were calculated to be 83.09 ± 45.07 mm/ hour with a range of 21-187. Anemia was present in 55 patients with a minimum value of 5.40 g/dl and a maximum value of 12.70 g/dl and a mean of 8.89 g/dl SD 1.89. Mean MCV of 86.30 ± 6.9fL was observed.[4] Patients showed a TLC of 12.3 ± 2.3 x10^3 /µL. Mean WBC count was 5.81 ± 4.3 x10^3 /µL. Mean platelet count of 208 × 10^9/L SD $10^{3.5}$ Mean absolute neutrophil count of 2.86

x10^9 /L with a range of 0.59-10.57 (87%) patients showed raised serum creatinine levels which shows renal impairment. Minimum levels observed were 0.9 mg/dl and maximum were 9.40 mg/dl with a mean of 3.46 ± 2.8 mg/dl (Table-I).

Table-I: Chemical and haematological parameters in multiple myeloma.

	Minimum	Maximum	Mean ± SD
Bone Marrow Plasma Cell %	0.00	95.00	40.89 ± 23.24
Hb (g/dl)	5.40	12.70	8.83 ± 1.89
MCV (fl/ red cell)	76.00	102.00	86.31 ± 6.19
WBC (x10^3 /µL)	1.90	12.40	5.82 ± 2.46
ANC (x10^9/L)	0.59	10.00	2.86 ± 1.70
Platelet (x10^9/L)	16.00	378.00	208.23 ± 103.53
ß2 Microglobulin (mg/L)	1.80	15.10	5.66 ± 3.21
Serum Albumin (g/dl)	23.00	49.00	37.71 ± 6.28
Creatinine	0.90	9.40	3.46 ± 2.85

On risk stratification based on International staging system, 20 (30.7%) patients were in stage I, 19 (29.1%) patients were on stage II while 26 (40.2%) patients were in stage III Table-II, (Figure-2).

Table-II: Stage of disease according to age.

Age	Stage of Disease			*p*-value
	I	II	III	
30-40 years	2 (3%)	3 (4.6%)	3 (4.6%)	0.300
40-60 years	6 (9.2%)	10 (15.3%)	7 (10.8%)	
60-80 years	12 (18.5%)	6 (9.2%)	16 (25%)	

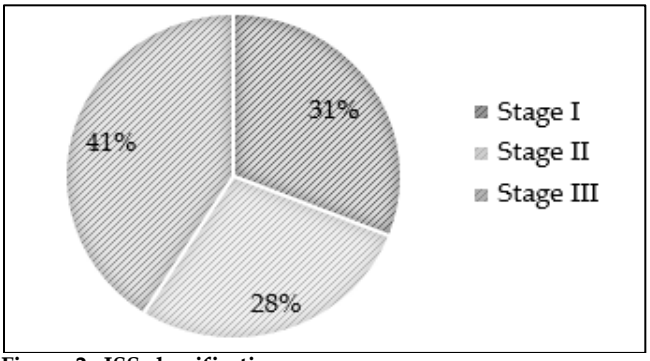

Figure-2: ISS classification.

Stage I and III were common in males whereas, females were predominantly having stage II multiple myeloma (*p*=0.02). Stage I and III comprised largely of patients in 60-80 years age group however, stage II had patients of 40-60 years age Table-III.

Table-III: Stage of disease according to gender.

Age	Stage of Disease			*p*-value
	I	II	III	
Male	14 (21.5 %)	8 (12.3 %)	21 (32.3 %)	0.02
Female	6 (9.2 %)	11 (17 %)	5 (7.7 %)	

DISCUSSION

Multiple myeloma is a disease with diverse clinicopathologic features. Median age of patients presenting with this ailment in our study was 58.5 years. Similarly, Kyle *et al,* in 2003 suggested that the median age of patients at diagnosis was approximately 66-70 years with 37% of patients being younger than 65 years of age.[10] Very few patients were diagnosed before 30 years of age and accounts for only 0.02-0.3% as reported by Jurczyszyn *et al*.[11] Ghazala *et al,* in 2005 reported a case of MM in a 25 year old patient.[12]

A gender predilection towards males was observed in our study with a male to female ratio of 1.5:1. This was in accordance with the findings reported by Sadia *et al*,[13] This may be attributed to an early and larger exposure to chemicals and agricultural pesticides. Raziq *et al,* in his study revealed a male to female ratio of 2.5:1, which also supported the findings of our study.[14]

According to the IMWG criteria evidence of end organ damage can be seen in the form of hypercalcemia, renal insufficiency, anemia and evidence of bone lesions.[15] It remains a diagnostic challenge for the clinician to analyse the prevalence of symptoms over time in MM. Two main etiological reasons can be identified which include disease-related or treatment-related factors. Bone pain (50.8%), back ache (49.2%) and fatigue (33.8%) were among the most commonly presenting complaints of the patient reporting to our tertiary care hospital. Similar findings were reported by Ramsenthaler *et al,* in a systematic review categorizing fatigue (98.8%) and pain (73%) as the most prevailing symptoms in MM patients.[16] Bone pain and osteolytic lesions were present in 77% cases as depicted in a study conducted by Sagale *et al* in 2017.[17]

Bone pain and Hypercalcemia in multiple myeloma is attributed to the osteolytic bone lesions which are identified as a part of skeletal survey and screening procedure. Hypercalcemia as present in 24% of our cases. This was much lower as compared to 51.2% patients with hypercalcemia as depicted by Mansoor *et al*.[18] Osteolytic bone lesions occur due to increased activity of osteoclast and suppression of osteoblastic activity leading to impaired remodelling.[19] Nearly 90% of the patients develop some kind of bony lesions during the course of disease which may end up in pathological fractures.[20] Anemia was present in 84.6% patients which is the most common cause of fatigue. Sagale *et al,* showed similar findings with anemia in 85% of the cases.[17] Bone marrow infiltration by plasma

cells, decrease in erythropoietin levels due to renal insufficiency have been attributed as major causes of anaemia in MM.

Renal dysfunctionwas depicted by raised serum creatinine levels was present in 87% of the patients in our study. Incidence of renal impairment at presentation was much higher in our study as compared to Yadav *et al,* who reported that 55% patients at the time of presentation have renal impairment.[21] This is attributed to monoclonal immunoglobulin secretion which leads to tubular nephropathy.

As far as staging was concerned 20 (30.7%) patients were in stage I, 19 (29.1%) patients were on stage II while 26 (40.2%) patients were in stage III. However, Saira *et al,* in her study depicted that 27 patients (33.75%) had stage-I disease, 28.75% (n=23) were stage-II and stage-III was present in 30 patients (37.5%).[22] Survival rate according to WHO is 62 months, 44 months and 29 months for stage I, II and III respectively.[23] ISS system was used as an isolated predictor for MM in past but cytogenetic abnormalities were over looked in this classification which lead to the development of various new prognostic factors such as fluorescent in situ hybridization FISH, serum free light chain evaluation and karyotyping. In our study male predominance was seen in stage I and III only however Shaikh *et al,* showed contradicting results showing male predominance in all the three stages.[22]

CONCLUSION

Patients with Multiple myeloma usually presented at an older age group with predominance in male gender, with bone pain, back ache, fatigue and osteolytic lesions the most commonly presenting complaint. Hematologically patients present with anemia and on chemical screening hypercalcemia and raised serum creatinine levels are observed. Multiple myeloma should be included in the workup of male patients havinganemiaof unknown cause after 50 years age.

Conflict of Interest: None.

Authors' Contribution

MH: Direct contribution, conception, design, analysis, interpretation, AM: Data analysis, RM:, NK: Intellectual contribution, analysis, data interpretation, HI: Manuscript preparation, AK: Data collection.

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