RETROSPECTIVE ANALYSIS OF MULTIPLE MYELOMA PATIENTS IN A TERTIARY CARE CENTRE OF UTTARAKHAND

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Abstract

Introduction: Multiple myeloma (MM) is a hemato-lymphoid malignancy of B-cell type. It occurs due to the accumulation of malignant monoclonal plasma cells. The exact incidence of MM in India is not well-known. The current study presented the clinical characteristics, radiological findings and laboratory findings of MM patients who were initially treated at the tertiary care centre, Dehradun, Uttarakhand (India).

Material and methods: Retrospective analysis of the medical records of 123 consecutive patients with MM who were initially presented to Hemato-Oncology department during the period from January 2014 to December 2018. Peripheral blood finding, bone marrow diagnosis, flow-cytometry analysis, serum protein and immunofixation electrophoresis finding, biochemical parameter, histo-pathological and cytological diagnosis, if any, urine examination finding and radiological examination of cases shall be compiled and tabulated. Diagnosis of symptomatic multiple myeloma was done based on The International Myeloma Working Group criteria for the diagnosis of MM.

Result: The study included 123 cases of multiple myeloma with male: female ratio of 2:1, mean age of 59.88 ±11.08 years and range of 32-87 years. The back pain (n=106, 86.2%) was the common presenting complaint followed by inability to walk (n=90, 73.2%). CT scan and/or MRI scan finding of MM patients, the lytic lesion was found in 107 patients (87%) and was found significant with its correlation with ISS/DS plus staging system (pvalue 0.013). The most location was dorso-lumbar spine (n=72, 67.28%) followed by skull (n=37, 34.58%) and ribs (n=19, 17.75%). Hemoglobin (Hb) analysis showed 92.7 % (n=114) cases were anemic with mostly had normocytic (n=95, 77.2%). 62.6% (n=77) of cases showed rouleaux formation while 23.57% (n=29) cases were circulating plasmacytoid lymphocytes or plasma cells. The raised ESR values was found in 89.33% (n=67) of cases. Diagnosis of cases shows 99.2% (n=122) of cases diagnosed as secretory MM while 1 (0.8%) case diagnosed as non-secretory MM.

Conclusion: MM is a disease with a inconsistent clinical presentation with multiple system involvement. Younger age of disease onset is some noteworthy features of myeloma in Uttarakhand state of India. Bony pain associated with generalized weakness is the commonest presentation, normocytic normochromic anemia with rouleaux formation, raised ESR, raised total protein with hypoalbuminemia, hypercalcemia, presence of M band and presence of >10% plasma cell in bone marrow is clue to diagnosis in MM cases.

Keywords: Multiple Myeloma, Uttarakhand, Hemato-lymphoid malignancy

INTRODUCTION

Multiple myeloma (MM) is a hemato-lymphoid malignancy of B-cell type. It occurs due to the accumulation of malignant monoclonal plasma cells. It is associated with presence of large quantities of

abnormal immunoglobulin proteins secreted by malignant monoclonal plasma cells called monoclonal (M) protein alongwith bone destruction in the form of lytic lesions, anemia, increase serum calcium levels and renal dysfunction (1). It has a median overall

survival of 2 – 4 years (2). The 10% of all hematolymphoid malignancies and 1 % of all neoplastic disorders comprises MM. Its incidence in North America is 4.8 per 100000 for men and 3.3 per 100000 for women (3). The exact incidence of MM in India is not well-known. Based on data available from literature of 6 population based cancer registry, its incidence varies from 0.3 to 1.9 per 100000 for men and 0.4 to 1.3 per 100000 for women (4). In India, median age of MM patients is 55 years which is 10 years less than that west population affecting from MM (5, 6). The American Cancer Society had estimated that 24,050 new cases of MM were about to be diagnosed in 2014 and about 11,090 deaths were expected to occur (7). For the diagnosis of MM, all the three criterias must be met, which are presence of monoclonal bone marrow plasma cells which are >10% or biopsy proven plasmacytoma, presence of serum and/or urinary M protein (except in patients with true non-secretory MM) and confirmation of end organ damage that can be recognized as the underlying plasma-cell proliferative disorder, specifically increased serum calcium level (>11.5 mg/dL), renal insufficiency in the form of increased serum creatinine (> 1.73 mmol/L or >2 mg/dL) or estimated creatinine clearance less than 40 mL/min, normochromic normocytic anemia with Hb value <10 g/dL, bony lesions in the form of lytic lesions, severe osteopenia, or presence of pathologic fractures (8,9).

Prognosis in MM depends on various patient related factors (age, performance status, and associated comorbidities), stage of the disease, disease aggressiveness, and response to chemotherapy (10). A risk stratification model, that based on a number of independent molecular cytogenetic markers to evaluate the aggressive nature of disease, is useful for both counseling of the patients and therapeutic choice for the treatment (11). The low risk patients have hyperdiploidy, t (11;14), t (6;14). Intermediate risk patients have t (4;14), deletion 13 or hypodiploidy by conventional karyotyping. Higher risk patients have 17p deletion, t (14;16), t (14;20) or high-risk gene expression profiling signature (12). The current study presented the clinical characteristics, radiological findings and laboratory findings of MM patients who were initially treated at the tertiary care centre, Dehradun, Uttarakhand (India).

Aims and objective:

To study and compare various clinical manifestations, imaging information and laboratory finding (biochemical findings, peripheral blood smear examination findings, urine examination, plasma cell morphology in bone marrow, flow cytometry, serum protein and immunofixation electrophoresis, and cytopathological or histo-pathological findings) of multiple myeloma patients in Uttarakhand region.

Material and methods:

After approval of the local ethical committee, there is no need for informed consent from the patients as the study has no risk to any of the study subjects. Retrospective analysis of the medical records of 123 consecutive patients with MM who were initially presented to Hemato-Oncology department during the period from January 2014 to December 2018. Inclusion Criteria of cases include all newly diagnosed patients of multiple myeloma in a tertiary care centre and being reported in Department of Pathology during the study duration will be included while exclusion criterias are patients who have received any form of treatment or follow up cases of MM. The clinical features and occupational details shall be compiled. Peripheral blood finding, bone marrow diagnosis, flow-cytometry analysis, serum protein and immunofixation electrophoresis finding, biochemical parameter, histo-pathological and cytological diagnosis, if any, urine examination finding and radiological examination of cases shall be compiled and tabulated. The association of these parameters will be studied. Cytogenetic analysis was not performed in our institution. Diagnosis of symptomatic multiple myeloma was done based on The International Myeloma Working Group criteria for the diagnosis of MM(13). Patients were staged according to international staging system (ISS)/ Durie-Salmon (DS) plus staging system(14). Statistical analysis was carried out using SPSS version 20. Qualitative data were presented in terms of frequencies and percentages. Mean and median shall be used as the measure of central tendency and standard deviation shall be used as the measure of dispersion for descriptive statistics. Chi-square test will be applied as the test for significance.

Result:

The study included 123 cases of multiple myeloma with male:female ratio of 2:1, mean age of 59.88 ±11.08 years and range of 32-87 years. Most common age of presentation was 61-70 years with commonest ISS/DS plus staging system was 2. The age wise

association with ISS/ DS plus staging system was found significant ($p < 0.05$). The most common occupation of male cases were retired from job ($n=33, 26.8\%$) followed by government job ($n=23, 17.1\%$) and in female cases were mostly housewife ($n=41, 33.33\%$). The back pain ($n=106, 86.2\%$) was the common presenting complaint followed by inability to walk ($n=90, 73.2\%$) and generalized weakness ($n=87, 70.7\%$). Other complaint were fever ($n=29, 23.6\%$), neck /shoulder/limb pain ($n=25, 20.3\%$), weight loss ($n=18, 14.6\%$), constipation ($n=12, 9.8\%$), frequent infection ($n=11, 8.9\%$), neuropathy ($n=16, 13\%$), coagulopathy ($n=21, 17.1\%$), nausea and vomiting ($n=19, 15.4\%$), loss of appetite ($n=26, 21.1\%$), renal insufficiency ($n=42, 34.1\%$), history of repeated blood transfusion ($n=17, 13.8\%$), addiction history to smoking and tobacco chewing ($n=75, 60.97\%$), and risk of exposure to petrochemical products or pesticides or insecticides ($n=7, 5.7\%$).

On radiological investigation including x-ray, CT scan and/or MRI scan finding of MM patients, the lytic lesion was found in 107 patients (87%) and was found significant with its correlation with ISS/DS plus staging system (p value 0.013). The most location was dorso-lumbar spine ($n=72, 67.28\%$) followed by skull ($n=37, 34.58\%$) and ribs ($n=19, 17.75\%$). Other sites were clavicle, sacro-iliac joint, iliac, mandibular, femur, humerus, and pelvis. The multiple lytic lesion was found in 6 cases (5.6%).

On hematological investigation of cases, hemoglobin (Hb) analysis showed 92.7% ($n=114$) of cases were anemic in which 27.6% ($n=34$) showed severe anemia, 47.2% ($n=58$) showed moderate anemia, 17.9% ($n=22$) showed mild anemia. RBC parameters of MM cases shows most of cases were low RBC count ($n=102, 86.2\%$), mostly belongs to moderate anemia with most of cases had normal MCH, MCV, MCHC ($n=95, 77.2\%$) and raised RDW values. Nucleated RBCs were present in 19.5% of cases with presence of rouleaux formation in 62.6% ($n=77$) cases with mostly normal reticulocyte count and mostly had mild poikilocytosis with normocytic normochromic RBC morphology. There is significant association was found between Hb and rouleaux formation with ISS/DS plus staging system. Most of the cases had normal TLC with mostly had normal peripheral polymorph, lymphocytes, monocytes, eosinophils, and basophil count. Additional finding of WBC on peripheral blood smear shows 13.83% ($n=17$) cases had hyersegmented neutrophils, 23.57% ($n=29$)

of cases had plasmacytoid lymphocytes, 12.19% of cases had circulating plasma cells and 2.43% of cases showing presence of reactive lymphocytes. All the cases showed normal platelet morphology with most of cases were normal counts and few cases ($n=6, 4.9\%$) were showing platelet clumps. Leucoerythroblastic picture was noted in 4.1% ($n=5$) cases and most of cases 89.33% ($n=67$) have raised ESR. There is significant association was found between platelet count with ISS/DS plus staging system. Urine examination showed 81.30% of cases had presence of urinary albumin and 17.07% of cases were showing increased WBC count.

Serum electrophoresis showed most of the cases were showing presence of M band ($n=83, 80.58\%$) which mostly lie in gamma region ($n=72, 58.80\%$). Immunofixation studies showed most of the cases were showing presence of M spike in gamma region with presence of IgG and lambda. There is significant association was found between presence of M band in different region in serum electrophoresis and immunofixation analysis with ISS/DS plus staging system.

Total 22 cases of FNAC or biopsy of lesions of MM cases showed 81.81% ($n=18$) of cases shows plasmacytoma while 0.8% ($n=1$) of each shows adeno-carcinoma, amyloidosis, small cell carcinoma and squamous cell carcinoma. Diagnosis of cases shows 99.2% ($n=122$) of cases diagnosed as secretory MM while 1 (0.8%) case diagnosed as non-secretory MM.

Bone marrow finding in MM cases showed that most of cases ($n=121, 98.8\%$) were showing particulate hypercellular smears with normoblastic erythroid maturation ($n=98, 79.7\%$), normal myeloid maturation ($n=96, 78\%$) and adequate functional megakaryocytes ($n=93, 75.6\%$). Most of the cases had suppressed M:E ratio ($n=65, 52.8\%$) and increased number of plasma cells. There is significant association was found between increased number of metamyelocytes and increased plasma cells number in bone marrow with ISS/DS plus staging system. Other finding showed that presence of hemophagocytic syndrome ($n=6, 4.9\%$), lymphoglandular bodies ($n=3, 2.4\%$), positive congo red staining ($n=1, 0.8\%$) and all cases were showing biopsy proven infiltration by plasma cells. Flowcytometry investigation of 14 cases on peripheral blood showed that plasma cell dyscrasia in 0.8% ($n=1$) and presence of circulating plasma cells in 10.57% ($n=13$) of cases.

Table 1:

Biochemical Parameters	Below Normal Range n (%)	Normal Range n (%)	Above Normal Range n (%)	Total n	ISS / DS plus Staging System p value
Albumin	90(90)	10(10)	0(0)	100	0.002
Globulin	03 (3)	20(20.2)	76 (76.8)	99	0.131
A:G	93(91.2)	09(8.8)	0(0)	102	0.468
Total Protein	0(0)	46(41.8)	64(58.2)	110	0.093
Creatinine	0(0)	43(35.8)	77(64.2)	120	0.006
Calcium	0(0)	72(63.2)	42(36.8)	114	0.017
LDH	0(0)	39(83)	08(17)	47	0.789
Uric Acid	0(0)	19(21.8)	68(78.2)	87	0.376
Alkaline Phosphatase	0(0)	60(63.8)	34(36.2)	94	0.608
BUN	0(0)	14(28)	36(72)	50	0.565
Beta 2 microglobulin	0(0)	0(0)	40(100)	40	0.042
Serum IgG	4(14.28)	8(28.57)	16(57.14)	28	0.034
Serum IgA	14(51.85)	6(22.22)	7(25.92)	27	0.039
Serum IgM	16(59.25)	11(40.74)	0(0)	27	0.010

Table 1 shows variation in values of various biochemical parameters in MM cases and its correlation with ISS/ DS plus staging system in MM cases. Most of the cases showed hypoalbuminemia, hyperglobulinemia, decreased A:G ratio, increased total protein, high creatinine value, normal range of calcium, LDH, alkaline phosphatase, hyperuricemia, increased levels of BUN, increased values of beta2 microglobulin, serum IgG levels with decreased serum IgA, and serum IgM values. There is significant association was found between serum albumin, calcium, creatinine, beta2 microglobulin, serum IgG, IgA and IgM values with ISS/DS plus staging system.

Discussion:

MM is a very diverse disease with a unusual manifestation, course of disease, and response to treatment. The biology of malignant cell as well as the microenvironment of the bone marrow account for such heterogeneity, offering novel targets for therapeutic approach (15). The diagnosis of MM depends on identifying monoclonal plasma cells in the bone marrow, identifying monoclonal protein (M-protein) in the serum or urine, evidence of end-organ damage, and a clinical picture consistent with MM. However, the early clinical manifestations of MM are complex and atypical, and they often lead to misdiagnosis (16). We have observed that there is a high risk of MM in rural areas, and also the risk of MM showed higher tendencies towards lower profession patients such as farmers who had somehow exposure of insecticides and/or pesticides .

One of the reasons for this can be of the total population of Uttarakhand state, around 69.77 percent live in the villages of rural areas and 30.23% people live in urban regions (Census 2011). So our most of the patients are from rural area and hence rural patients predominate.

The another question, which we have addressed in this study is to monitor and compare hematological and biochemical parameters of the patients. For this, we have measured various factors into considerations such as ESR, creatinine, BUN, uric acid, calcium, alkaline phosphatase, total protein, TLC, albumin, kappa/lambda and beta 2 microglobulin.

Kumar et al. (5) did a retrospective study of 534 patients of MM over 10 years (1988–97) in India and compared it with the literature of West. He found that in Indian patients, MM occurred at a younger age with a median age of 55 years, as compared to the west where median age was 66 years and male to female ratio was 2.2:1 (5). The present study was conducted on 123 newly diagnosed cases of MM . Median age of presentation was 59.88 years which was similar to the west (5) and a comparable range reported in a retrospective study done by Mattar et al. (17) with mean age of 58.5 years (range, 27–80 years). In Saudi Arabian and Moroccan studies, the median ages were 56 years, 59 years, respectively (17). There was male preponderance with a male to female ratio 2:1, which was almost similar as compared to the study of Kumar et al where male to female ratio was 2.2:1 (5). In the present study we

found that most of the patients retired from job but connected to rural areas and most common presenting symptoms were back pain, inability to walk and generalized weakness. In another study by Subramanian et al. found that bony pains and easy fatigability were the most common symptoms in MM patients(18). Renal impairment was found in 34.1% of MM cases and renal failure is a common presenting feature and presents as one of the major complications of the disease. Renal impairment is observed in about 50% of the patients during the course of their disease (6). The risk of pesticides or insecticides exposure was found in 5.7%. MM patients often develop bone disease that results in severe bone pain, osteolytic lesions, and pathologic fractures. We observed that 87% of MM patients had osteolytic lesions at presentation. These bony complications have not only a depressing impact on quality of life but also effect the overall survival. In MM, osteolytic bone lesions arise from the altered bone remodeling due to both increased osteoclast activation and decreased osteoblast differentiation(19). Approximately 75% of MM patients had reported bone lesions included punched-out lytic lesions, osteoporosis or pathological fractures on radiographic investigation (20).

Complete hemogram showed that 92.7% cases are anemic in which 47.2% cases had moderate anemia and 74% of cases were showing normocytic normochromic RBC morphology (p value <0.05). Rouleaux formation was noted in 62.6% of cases (p value <0.05) and circulating plasmacytoid lymphocytes or plasma cells were found in 23.57%. The raised ESR values was found in 89.33% (n=67) of cases (p value <0.05). NICE guidelines currently recommend the use of ESR when myeloma is suspected (21). Results from the current study strongly support the recommendation of NICE guidelines. ESR has been reported as a good prognostic marker for MM with higher values of ESR associated with a more advanced stage of disease (22).

Biochemical parameters in our study showed hypoalbuminemia(90.0%)(p value <0.05), raised total protein(58.2%), raised creatinine (64.2%)(p value <0.05), raised uric acid(78.2%), raised BUN(72.0%), and beta2 microglobulin (100%)(p value <0.05). Almost 36.8% of the patients from our study were reported with hypercalcaemia(p value <0.05), which is comparatively less then the reports in literature (5).

This could be due to different environmental factors, or may also due to varying food habits. Inter-gender comparisons for the hypercalcaemia, revealed that most of the females with MM have tendency to have hypercalcaemic conditions as well. This suggests that hypercalcaemia is not always a part of MM and hence a high index of suspicion is necessary to diagnose MM. A comparable study by Shin et al. found that 29% of patients had anemia, 23%, had hypercalcaemia (above 10 mg/dL) and 28% had hypoalbuminemia (less than 3.5 g/dL), 13% had renal impairment, 48% had elevated beta2-microglobulin and 65% had biopsy-proven plasmacytoma (23).

In Terebello et al. (24), they found that studied patients had hypercalcaemia (14.7%), low serum albumin levels (65.2%), and elevated beta2-microglobulin concentrations (66.7%). Another similar study by Kyle RA et al(6) showed anemia (73%), bone pain(58%), elevated creatinine (48%) fatigue or generalized weakness (32%), and hypercalcaemia (28%) which was almost similar to our study. In a study by Rossi D et al. suggested that the levels of beta 2 microglobulin are extremely consistent with survival prediction at the time of diagnosis, remission, and early relapse of MM, with higher beta 2 microglobulin levels in each occurrence favors the poorer prognosis. Finally, they concluded that beta 2 microglobulin levels is an extremely useful marker in initial stratification and follow-up of patients with MM(25).

Raised serum IgG levels, decreased serum IgA and IgM levels and immunofixation analysis was found significant with increasing ISS staging (p value <0.05) in our study. Serum protein electrophoresis in our study showed presence of M band in 80.58% (p value <0.05) of cases with most common location is in gamma region (58.80%) (p value <0.05) similar to previous studies(26,27). The biclonal gammopathy was found in 6% of cases. Retrospective studies showed that the incidence of biclonal gammopathies represents 2–6% of all monoclonal gammopathies. Riddell et al. (28) reported a double monoclonal gammopathy in 2.5% of their 1135 studied patients with monoclonal gammopathies while Kyle et al.(6) detected double monoclonal gammopathy in 6% of the 1383 patients studied with monoclonal gammopathies. Recently, in a Spanish study, 2.6% serum double monoclonal gammopathy were reported(29). Lolin et al.(30) found an incidence of 11.5% in the south-east of Asia. Alno- Bouvet et al.(31) identified biclonality, based exclusively on the

presence of 2 tight bands by serum protein electrophoresis on cellulose acetate, in 92 cases (13.5%), but many patients lacked immunoelectrophoresis or immunofixation confirmation. FNAC or Histopathological examination of associated lesion showed 18 cases were showing plasmacytoma (p value <0.05).

Bone marrow examination showed that marrow was packed with plasma cells in 8.9% of cases with >10% of plasma cells infiltration in 71.5% of cases. There was significant association was found between increase plasma cells in bone marrow with increasing ISS/DS plus staging system of the cases. In our study almost all cases shows increased plasma cell infiltration in bone marrow biopsy. Flowcytometry evaluation showed that 10.57% of cases were showing plasma cell leukemia with immunoprofile of CD20(-), CD19(-), CD22(-), variable positivity of CD138,CD38, with variable immunoprofile of CD56, CD117, skappa, slambda, ckappa, clambda. Out of total 123 cases, only 76 cases were treated in our hospital. Most of cases were received chemotherapy in form Bortezomib and/or Cyclophosphamide with Zolidronic acid/ Thalidomide/ Lenolidamide/ Pomalidomide/ Melphalan in combination or alone Bortezomib or Cyclophosphamide with dexamethasone(n=72,94.73%). EBRT alone or in combination with chemotherapeutic drugs was also given in 19.73% of the cases(n=15). Bone marrow transplant was done in 9 cases as part of treatment (11.84%).

Conclusion:

MM is a disease with a inconsistent clinical presentation with multiple system involvement. Younger age of disease commencement is some noteworthy features of MM in Uttarakhand state of India. Clinical, hematological and biochemical features are appearing similar to published data. Bony pain associated with generalized weakness is the commonest presentation, normocytic normochromic anemia with rouleaux formation, raised ESR, raised total protein with hypoalbuminemia, hypercalcemia, presence of M band and presence of >10% plasma cell in bone marrow is clue to diagnosis in MM cases . Furthermore, MM should be considered as a differential diagnosis in the workup of normocytic normochromic anemia in patients above 60 years ago with initial presentation of bony pain.

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