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CLINICOPATHOLOGICAL PROFILE OF PATIENTS WITH MULTIPLE MYELOMA IN A TERTIARY CARE CENTRE IN NORTH EAST INDIA

Pathology

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ABSTRACT

Introduction: Multiple myeloma(MM) is a neoplastic disorder characterized by clonal proliferation of plasma cells with production of immunoglobulins. **Aim:** To study the spectrum of clinical, hematological and biochemical findings in patients of MM. **Materials and Methods:** The present study was a cross sectional hospital based retrospective study.During our study period from January 2023 to March 2024, we identified 28 cases of multiple myeloma diagnosed in the Department of Pathology, Assam Medical College on the basis of International Myeloma Working Group criteria.Medical record of all the patients who were diagnosed as MM was reviewed. **Result:** Out of 28 patients, 57% were men and 43% were women. The mean age was found to be 53.5 years and 3.5% patients were younger than 40 years.The major presenting complaint was bone pain in 85.7% of patients. Anemia was observed in 75% of the patients, renal insufficiency in 53.5% patients, and hypercalcemia in 14.3% patients. The commonest radiological findings were osteolytic lesions present in 22 (78.5%) patients. Serum protein electrophoresis showed an M-spike in 92.8% patients and the most common monoclonal gammopathy was IgG kappa (50%).1 case presented with biclonal M spike. 17.8% of the patients had more than 60% plasma cells on bone marrow aspirate.The most common pattern of infiltration on biopsy was diffuse pattern.(60.7%). **Conclusions:** Our study highlights younger age of involvement contrast to western countries. Majority of our patients had anemia and skeletal involvement. Biclonal gammopathy is very rare accounting for 1% of myeloma cases. Diffuse pattern of infiltration was most commonly observed on bone marrow biopsy.

KEYWORDS

Multiple Myeloma, Bone Marrow, Plasma Cells

INTRODUCTION

Plasma cell neoplasms are a group of hematological malignancies characterized by clonal proliferation of plasma cells with production of monoclonal immunoglobulins. At one end of the spectrum, lies Monoclonal Gammopathy of Undetermined Significance (MGUS) which is a silent disorder, while at the other end lies multiple myeloma(MM), the more aggressive entity with features of end organ damage.[1]

MM accounts for 1% of all neoplastic disorders, 10-15% of hematological malignancies. It is seen in all races with a higher incidence in African Americans in comparison to Asians. In India, Age standardised rates(ASRs) of multiple myeloma in 2020 was 0.7/100000.[2]

International Myeloma Working Group (IMWG)[3] has laid down the diagnostic criteria of MM which includes- Clonal bone marrow plasma cells more than 10% or biopsy proven plasmacytoma and ≥1 of the following myeloma defining events. 1) End organ damage CRAB-hypercalcemia (serum calcium>11mg/dl), renal insufficiency (serum creatinine >2mg/dl), anemia (hemoglobin level <10g/dl) and lytic bone lesions attributable to plasma cell disorder. 2) Clonal bone marrow plasma cells ≥60%. 3) an involved-to-uninvolved serum free light chain (SFLC) ratio ≥100. 4) >1 focal lesion on MRI studies.

Owing to the paucity of data in the medical literature on MM from North East India, the present study was undertaken in the Department of Pathology, Assam Medical College and Hospital, Dibrugarh. The aim was to study the spectrum of clinical, hematological and biochemical findings in patients of MM.

MATERIALS AND METHODS

This was a cross sectional hospital based retrospective study. During our study period from January 2023 to March 2024, we identified 28 cases of multiple myeloma diagnosed in the Department of Pathology, Assam Medical College on the basis of International Myeloma Working Group criteria.

Medical record of all the patients who were diagnosed as MM was reviewed. Demographic profile and clinical history of the patients 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: The data was gathered using a structured proforma. Data was entered in a Microsoft Excel spreadsheet. Qualitative data was presented as frequency (percentage) and quantitative data as mean ±SD / Median (IQR) based on the normality of the data.

RESULTS

Out of 28 patients,16 (57%) were men and 12(43%) were women. The male to female ratio was 1.3:1. The ages of the patients included in the study ranged from 38 years to 86 years, with the mean age being 53.5 years. 3.5% patients were younger than 40 years and 25% were 70 years and older. (Table-1)

Table-1: Demographic Data Of Patients With MM

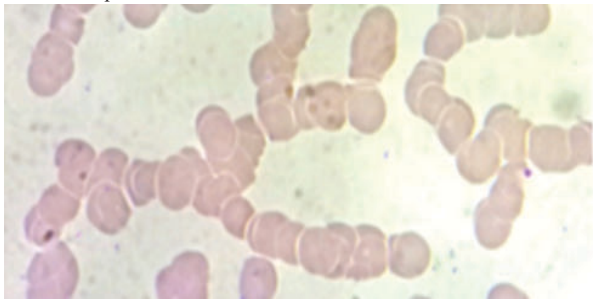
Age (years)	No of participants	Male	Female
31-40	01	01	00
41-50	03	02	01
51-60	10	05	05
61-70	07	04	03
71-80	05	04	01
81-90	02	00	02

The most frequent initial symptom observed in 85% of patients was bone pain, followed by generalised weakness and fatigability in 53% of cases.

Hematological Findings

21(75%) patients had anaemia (Hb <10g/dl) at the time of presentation. 14(50%) cases had severe anemia (Hb < 8g/dl) and only 03(10.7%) patients had hemoglobin > 12g/dl(Table-2). The anemia was predominantly normocytic normochromic. Prominent rouleaux formation was observed on the peripheral smear of 16(57.14%) patients(Fig-1).Total leucocyte count was less than 4000/cu mm in 5(17.8%) patients and leucocytosis was observed in 7(25%) patients. Circulating plasma cells were observed in 3 (10.7%) patients.(Fig-2)

Erythrocyte sedimentation rate (ESR) were available in 19 cases, out of which 16 patients had ESR more than 20mm/hr.



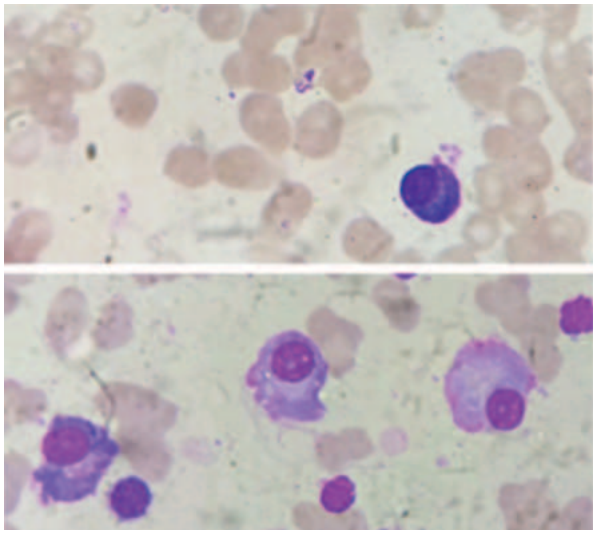


Fig-1: Peripheral Smear Showing Rouleaux Formation (1000x,leishman Stain)
Fig-2: Peripheral Smear Showing A Plasma Cell (1000x,leishman Stain)
Fig-3: Bone Marrow Aspirate Showing Flame Cells (leishman Stain,1000x)

Biochemical Findings
Renal insufficiency (Serum creatinine >2mg/dl) was seen in 15 (53.5%) patients whereas hypercalcemia (Serum Calcium ≥ 11mg/dl) was present in 04(14.3%) patients. Serum beta-2 microglobulin levels were available in 18 cases ,out of which 11 cases showed values more than 3 µg/ml.Serum albumin levels were available in 25 patients and hypoalbuminemia (serum albumin <3 g/dl) was present in 13 patients(Table-2)

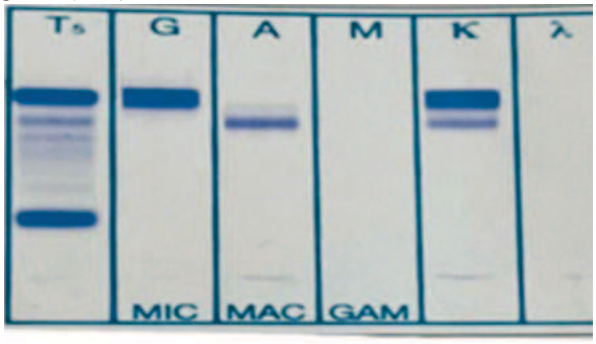
Table-2: Laboratory Parameters

Parameter	Level	No. of patients	Percentage(%)
Hemoglobin (g/dl)	≤8.0	14	50.0
	8.1-10.0	07	25.0
	10.1-12.0	04	14.3
	>12.0	03	10.7
Serum creatinine(mg/dl)	<1.3	07	25.0
	1.3-1.9	04	14.2
	≥2	15	53.5
	NA	02	7.14
Serum calcium(mg/dl)	<10.2	11	39.2
	10.3-10.9	10	35.7
	≥11	04	14.3
	NA	03	10.7
2 microglobulin (µg/ml)	<3	07	25.0
	≥3	11	39.2
	NA	10	35.7
Serum albumin (g/dl)	<3	13	46.4
	>3	12	42.8
	NA	03	10.7

Radiological Findings
The skeletal lesions were present in 24(85.7%) patients as osteolytic, osteoporosis and fractures; either singly or in various combinations. The commonest radiological findings were osteolytic lesions present in 22 (78.5%) patients. Fractures were found in 8(28.5%) patients. No radiographic abnormalities were observed in 4(14.2%) patients at the time of diagnosis.

Serum Protein Electrophoresis
Serum protein electrophoresis showed M-spike in 26(92.8%) patients. Serum Immunofixation was performed in 22 patients. The most common monoclonal gammopathy was IgG kappa in 11 (50%) patients followed by IgG lambda in 07(31.8%) patients. 1 case exhibited biclonal nature of M spike with both IgG kappa and IgA kappa.(Fig-4)

Bone Marrow Aspiration and Biopsy
The bone marrow plasma cell count was estimated on aspiration smears by differential count of 500 nucleated cells. 04 (14.2%) patients had plasma cells percentage <20% while 05(17.8%) patients had > 60% plasma cells in bone marrow aspirate. The most common pattern of infiltration on biopsy was diffuse pattern, (60.7%)(Fig-6) followed by mixed pattern(17.8%), while the least common was nodular pattern.(7.2%).



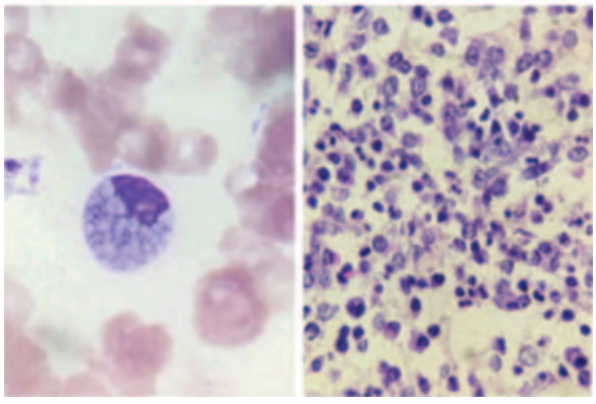


Fig-4: Immunofixation electrophoresis(IFE) showing biclonal nature of M spike to be IgG kappa and IgA kappa.
Fig-5: Mott cell with rounded intracytoplasmic inclusions-Russel bodies (Leishman stain,1000x)
Fig-6: BM biopsy showing diffuse infiltration by sheets of plasmablasts with central nuclei, open nuclear chromatin, prominent nucleoli and few plasma cells with eccentric nuclei and abundant cytoplasm (H&E,1000x)

DISCUSSION
The present study comprised of 28 cases of MM, diagnosed on the basis of International Myeloma Working Group criteria.

MM is considered as a disease of the old with median age of 60-70 years in western countries.[4] The median age of patients in our study was 53.5 years which was lower compared to western countries. This is in concordance with Indian studies conducted by Kaur et al[5] and Advani et al[6] which reported mean ages of 58.8 and 51 years respectively.

In our study, 3.5 % of patients were younger than 40 years and 25% were 70 years and older. This is comparable with the observations of Kyle et al[4], in whose study 2% patients were younger than 40 years and 38% patients were 70 years and older. However, Parwaiz A,et al.[7] and Yanamandra et al.[8] showed higher percentage of patients with age less than 40 years.

A high male to female ratio observed in our study was similar to the study by Asian myeloma network and other Indian studies conducted by Kaur et al.[5] and Advani et al.[6]

Clinical history was taken in all our patients and the major presenting complaint was bone pain in 85.7% of our patients. Approximately one third to two third of patients with MM are known to present with this symptom because of vertebral collapse, osteopenia or fractures. In studies by Gupta et al[9] and Kyle et al [4], 79% and 58% patients respectively had bone pains at diagnosis. Generalized weakness and fatigability were present in 53.5% of our patients which is in concordance with the findings of Kyle et al.[4] and is attributable to anemia.

In our study anemia (hemoglobin <10 gm/dl) was observed in 75% of the patients. This finding was in concordance with the findings of Sultan S et al., (63.9%)[10] and Aditi Gupta et al.(64.29%).[11] Severe anemia was present in 50% of our patients while Gupta et al reported a 40% incidence of severe anemia in their subset of patients.[9] In a developing nation such as ours, the cause of anaemia may be complex. Additional causes such as iron deficiency must be assessed at presentation before attributing it only to MM.

Rouleaux formation was seen in 16 (57.14%) patients. This finding was consistent with the study of Vahini G et al., (50%)[12] while Subramanian R et al.[13] and Kaur P et al.[5] have reported rouleaux formation on peripheral smear in 91% and 82% cases respectively.

3(10.7%) patients were found to have circulating plasma cells in peripheral smear, out of which two patients had more than 5% plasma cells and was labelled as plasma cell leukemia. These findings were similar to study by Parwaiz A,et al.[7]

Hypercalcaemia is one of the most important diagnostic criteria of CRAB symptoms. However, it was seen only in 04 (14.3%) patients. These findings were in concordance with the studies of Kaushik R et al.[14] and Chowdhury MRK et al.[15], where hypercalcaemia was reported in 11.76% and 9.38% patients respectively. This suggests that hypercalcaemia is not always a part of MM. Renal failure in myeloma patients and Vitamin D deficiency could be factors contributing to hypocalcaemia in such patients.

Renal dysfunction in MM is mostly caused by the toxic effects of monoclonal light chain.[16] In our study, raised serum creatinine i.e., ≥2 mg/dL was found in 15(53.5%) patients, which is similar to the findings of Kaur P et al.,(77.3%)[5]

In our study, serum electrophoresis revealed an M band in 26(92.8 %) patients while it showed a normal study in two of our patients. Both of them had normal serum protein levels. The M band is detectable in 97% of myeloma patients. They may have either intact Ig or fragment or a free light chain on serum/urine protein electrophoresis, whereas cases with non detectable monoclonal proteins are referred to as non secretors (1-3%).[17] Serum immunofixation revealed M protein of IgG type in 77% of the patients followed by IgA in 23% . IgG kappa was the most common type. 1 case exhibited biclonal nature of M spike with both IgG kappa and IgA kappa.Such pattern is very rare if we consider the various immunofixation patterns observed in different gammopathies.

The median plasma cell percentage in bone marrow was 49%, which was similar to study by Kyle, et al.[4] 17.8% of the patients had more than 60% plasma cells. Our study showed diffuse pattern as the most common pattern (60.7%) of infiltration by plasma cells similar to Subramanian, et al.[13]

Radiological findings were available in all patients in whom osteolytic lesion was the most common skeletal lesion (78.5%) followed by osteoporosis, which was seen in 64.29% cases. In our study, osteoporosis was reported in a higher percentage of patients (64.29%) compared to Diwan AG et al.(40%)[18].

Hypoalbuminemia (serum albumin <3 g/dL) was seen in 13(46.4%) patients. However in studies conducted by Chowdhury MRK et al., and Kyle RA et al., hypoalbuminemia was reported in 15% and 43.75% patients, respectively. A higher percentage of cases with hypoalbuminemia in our study might be because of late stage of presentation and enrolment of a limited number of patients. Owing to financial constraints in our setup, β2 microglobulin levels were obtained in only 18 cases.

Limitations

Unavailability of beta-2 microglobulin levels was a major limitation in our study due to resource constraint set up. The lack of data on treatment, survival outcomes, and cytogenetics are other drawbacks of our study.

CONCLUSION

Our study highlights younger age of involvement compared to western countries. Majority of our patients had anemia and skeletal involvement. Biclonal gammopathy is very rare accounting for 1% of all myeloma cases. Diffuse pattern of infiltration was most commonly observed on bone marrow biopsy. By striving for a deeper understanding of the clinicopathological landscape of multiple myeloma, we can advance towards more effective interventions and better quality of life for affected individuals.

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