CLINICAL PROFILE OF MULTIPLE MYELOMA IN A TERTIARY CARE CENTER FROM NORTH EAST INDIA

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ABSTRACT

Multiple Myeloma is a neoplastic disease of the plasma cells characterized by clonal proliferation of terminally differentiated B lymphoid cells, which accumulate in bone marrow and produce a monoclonal protein (Immunoglobulin), usually IgG or IgA, often referred to as M or myeloma protein.

AIMS AND OBJECTIVES

Our study aims to describe the common clinical and laboratory features, stages and outcome of patients with Multiple Myeloma coming to a Tertiary Care Center in North East India.

MATERIALS AND METHODS

Newly diagnosed and previously diagnosed untreated patients of MM coming to Assam Medical College over a period of one year from June 2013 to May 2014 were randomly included in this prospective observational study. Diagnosis was confirmed by the 2009 updated criteria of International Myeloma Working Group and clinical features, laboratory findings and outcome were studied.

RESULTS AND OBSERVATIONS

44 Multiple myeloma mostly from 5th and 6th decade with the age varying from 38 to 82 and a mean age of 57.7 years (SD 10.29); 27 (61%) patients were male and 17 (39%) were females with a male-to-female ratio of 1.6:1; 38 (86%) presented with backache and other bone pains, 35 (80%) had generalized weakness and easy fatigability, 13 (30%) had symptoms of spinal cord compression, 14 (32%) had fever. On examination 37 (84%) had pallor, 34 (77%) had bony tenderness, 14 (32%) had paraplegia; 40 (91%) cases revealed positive M Band by serum protein electrophoresis. In rest of the 4 cases, band was determined by immunofixation method. Urinary Bence-Jones protein was estimated in 28 out of 44 patients and of them 4 (14%) were positive; 40 (91%) had radiologically detectable abnormalities; 35 (80%) had lytic lesions, 17 (39%) had pathological fractures, 21 (48%) had generalized osteoporosis and only 4 (9%) had normal skeletal survey. Out of 35 cases of lytic lesions, most frequent area was spine in 25 (71%); 7 (16%) cases were found to be in stage I, 20 (45%) were found to be in stage II and 17 (39%) were in stage III.

CONCLUSION

We conclude that though most patients were in sixth decade, but we got significant involvement in younger age group. Bone pain, mostly low backache was the most common presenting symptom along with fatigue and weakness. Majority of patients were in higher stages (ISS II, III) at the time of diagnosis and severe anaemia, lytic lesions, pathological fractures and renal insufficiency were most observations in these patients in higher stages.

KEYWORDS

Multiple Myeloma, Haematological Malignancies, M Band, Myeloma Protein, Urinary Bence-Jones Protein.

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INTRODUCTION

Multiple Myeloma has most likely been present for thousands of years, but first well-documented case was a patient, Sarah Newbury, described by Samuel Solly in 1844.¹ This 39-year-old woman developed fatigue and bone pain from multiple fractures. The best known case of MM was that of Thomas Alexander McBean, "a highly respectable tradesman," 45 years of age. He developed fatigue and had noted that his "body linen was stiffened by his urine."

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For two years before his death on January 1, 1846, he complained of severe recurrent bone pains on multiple occasions.²

Multiple Myeloma is a neoplastic disease of the plasma cells characterized by clonal proliferation of terminally differentiated B lymphoid cells, which accumulate in bone marrow and produce a monoclonal protein (Immunoglobulin), usually IgG or IgA, often referred to as M or myeloma protein. Multiple Myeloma comprises 10% of all haematological malignancies and 1% of all neoplastic disorders with usual age of presentation in 6th and 7th decade of life. Exact incidence in India is not known, but data from 6 population based cancer registries (Covering <0.3%) shows 0.3 to 1.9 per 1,00,000 men and 0.4 to 1.3 per 1,00,000 women, highest in Delhi.³

AIMS AND OBJECTIVES

In India clinical study of Multiple myeloma is very much limited, especially in North East India.

Our study aims to describe the common clinical and laboratory features, stages and outcome of patients with Multiple Myeloma coming to a tertiary care center in North East India.

MATERIALS AND METHODS

Newly diagnosed and previously diagnosed untreated patients of MM coming to Assam Medical College over a period of one year from June 2013 to May 2014 were randomly included in this prospective observational study. Diagnosis was confirmed by the 2009 updated criteria of International Myeloma Working Group.⁴ (Table No. 1). Patients with monoclonal gammopathy of undetermined significance, other coexisting malignancy, non-secretory myeloma, solitary plasmacytoma of bone and previously diagnosed case of MM under treatment were excluded from the study. Informed consent and ethical clearance were taken. Patients were evaluated on the basis of proper history, clinical examination and laboratory and imaging investigations. Evidence of end organ damage was assessed by the ROTI criteria.⁵ Staging of the cases was done on the basis of International Staging System (ISS).

Diagnostic criteria for Symptomatic Multiple Myeloma by International Multiple Myeloma Working Group 2003, Updated in 2009		
1	Monoclonal protein present in serum and/or urine	
2	Clonal bone marrow plasma cell or plasmacytoma	
3	Related organ or tissue impairment (ROTI)	
	C	Hypercalcaemia (Corrected calcium >2.75 mmol/L)
	R	Renal insufficiency attributable to myeloma
	A	Anaemia (Haemoglobin <10 g/dL)
	B	Bone lesions (Lytic lesions or osteoporosis with compression fractures)

Table 1: Diagnostic Criteria for Symptomatic Multiple Myeloma

All the data was entered into Microsoft Excel 2010 spreadsheet and analysed by GraphPad Prism Version 6.05 software. Various data were correlated with ISS stage using the contingency coefficient analysis (Cross tabs procedure). The significance of study parameters between the three ISS stage was assessed using Freeman-Halton extension of Fisher's exact test. Significance was assessed at 5% level of significance (p <0.05).

RESULTS AND OBSERVATIONS

44 MM cases were included in the study with 5 patients from 31 to 40 years, 7 from 41 to 50 years, 16 from 51 to 60 years, 14 from 61 to 70 years and 2 cases above 71 years. The age varied from 38 to 82 with a mean age of 57.7 years (SD 10.29). 27 (61%) patients were male and 17 (39%) were females with a male-to-female ratio of 1.6:1 (Table No. 2).

Parameters	Patients (n = 44)	Percentage
Age Wise Distribution		
31-40 years	5	11.4%
41-50 years	7	15.9%
51-60 years	16	36.4%
61-70 years	14	31.8%
>70 years	2	4.5%
Sex		
Male	27	61%
Female	17	39%

Table 2: Demographic Profile of Our Patients

38 (86%) patients presented with backache and other bone pains which was the most common symptom; 35 (80%) patients had generalized weakness and easy fatigability, 13 (30%) had symptoms of spinal cord compression, 14 (32%) had fever, 10 (23%) had cough, 4 (9%) had burning micturition and urgency, 8 (18%) had bleeding manifestation, 16 (36%) had constipation, 12 (27%) had polydipsia, 6 (14%) had nausea and vomiting, 3 had somnolence and 2 patients had confusion (Table No. 3).

Parameters	Patients (n = 44)	Percentage
Symptoms		
Backache and other bone pains	38	86%
Generalized weakness	35	80%
Symptoms of spinal cord compression	13	30%
Fever	14	32%
Cough	10	23%
Burning micturition and urgency	4	9%
bleeding manifestation	8	18%
Constipation	16	36%
Polydipsia	12	27%
Nausea and vomiting	6	14%
Somnolence	3	6.8%
Confusion	2	4.5%
Signs		
Pallor	37	84%
Bony tenderness	34	77%
Paraplegia	14	32%
Oedema	6	14%
Splenomegaly	2	4.5%
Hepatomegaly	1	2.3%
Laboratory results		
Positive M Band by serum protein electrophoresis	40	91%
Urinary Bence-Jones protein	4 (28 tested)	14%
Skeletal involvement		
Radiologically detectable abnormalities	40	91%
Lytic lesions	35	80%
Spine	25	71%
Lumbosacral spine	24	69%
Thoracic spine	12	34%
Skull	23	66%
Ribs	15	43%
Long bones in and	12	34%
Pelvis in	8	23%
Clavicle in	4	11%
Scapula	3	8.5%
Pathological fractures	17	39%
Vertebra	14	87%
Ribs	7	44%
Long bones (Femur)	2	12.5%
Generalized osteoporosis	21	48%
Normal skeletal survey	4	9%

Table 3: Clinical Presentation

On examination 37 (84%) patients had pallor and 34 (77%) patients had bony tenderness; 14 (32%) patients presented with paraplegia; 6 (14%) patients had oedema.

Splenomegaly and hepatomegaly were seen in 2 and 1 patient respectively; 40 (91%) cases revealed positive M Band by serum protein electrophoresis. In rest of the 4 cases, band was determined by immunofixation method. Urinary Bence-Jones protein was estimated in 28 out of 44 patients and of them 4 (14%) were positive. Immunofixation electrophoresis (IFE) was done on 8 patients of whom 6 had IgG, 1 had IgA and 1 had light chain myeloma.

40 (91%) had radiologically detectable abnormalities; 35 (80%) had lytic lesions, 17 (39%) had pathological fractures, 21 (48%) had generalized osteoporosis and only 4 (9%) had normal skeletal survey. Out of 35 cases of lytic lesions, most frequent area was spine in 25 (71%) followed by skull in 23 (66%), ribs in 15 (43%), long bones in 12 (34%), pelvis in 8 (23%), clavicle in 4 (11%) and scapula in 3 (8.5%) cases. In 24 (69%) cases, lytic lesion were seen in lumbosacral spine and in 12 (34%) they were seen in thoracic spine. Femur was the most common long bone to be involved with 8 (23%) followed by humerus in 3 (8%) and radius in 1 (3%). Out of 17 cases of pathological fractures 14 (87%) were in the vertebra, 7 (44%) were in ribs and 2 (12.5%) were in long bones (Femur).

The mean Hg was 7.12 gm/dL; 18 (41%) has severe anaemia with Hg <7 gm/dL, 23 (52%) had moderate anaemia with Hg between 7 to 10 gm/dL and 3 had mild anaemia with Hg between 10 to 12 gm/dL; 4 cases had leucopenia with total count <4000/cumm and 5 had leucocytosis with total count >12,000/cumm (Mean total count was 8002). The mean platelet count was 1.6 lack and mean ESR 124.8 mm AEFH. Mean serum creatinine was 1.66 mg/dL with 9 (20%) cases having serum creatinine >2 mg/dL. Mean corrected serum calcium was 10.37 mg/dL with 10 (23%) cases having raised serum calcium >11 mg/dL; 29 (66%) had hypoalbuminemia; 26 (59%) had serum globulin >3.5 to 5.5 and 17 (39%) had >5.5 gm/dL; 11 (25%) had serum beta-2 microglobulin level <3.5 mg/L, 16 (36%) from 3.6 to 5.5 mg/L and 17 (39%) had >5.5 mg/L.

Bone marrow study showed that out of 44 cases, 6 (14%) cases had bone marrow plasma cell concentration between <20%, 8 (18%) cases between 20 to <30%, 11 (25%) cases between 30 to <40%, 10 (22%) cases between 40 to <50% and 9 (20%) cases above 50%. The mean bone marrow plasma cell concentration was 37%.

Fig. 1: Stages of Presentation

7 (16%) cases were found to be in stage I, 20 (45%) were found to be in stage II and 17 (39%) were in stage III. One (1) out of 7 (14.29%) in stage I, 6 out of 20 (30%) in stage II and 11 out of 17 (64.7%) in stage III were having haemoglobin <7 gm/dL. There was a trend towards higher percentage of cases having CRP >6 mg/L with higher ISS stage, but this correlation was statistically insignificant ($p=0.42$). A statistically significant ($p=0.02$) correlation of serum LDH with stage of the disease was found showing serum LDH (>285 IU/L) in 0%,

40%, 58.8% of patients with ISS-I, II and III respectively. Serum creatinine ≥ 2 mg/dL was observed in 0%, 10% and 41.2% of cases of ISS-I, II and III respectively ($p=0.029$). Higher percentage of cases with high ISS stage had serum calcium >11 mg/dL, but it was found to be statistically insignificant ($p=0.186$). Similar results were found with serum uric acid ($p=1$).

Five (5) (71.43%) cases of stage I, 18 (90%) cases of stage II and 17 (100%) cases of stage III had skeletal lesions, which was statistically significant ($p=0.07$); 3 (42.86%) of stage I, 16 (80%) of stage II and 16 (94.12%) cases of stage III had lytic lesion which was also statistically significant ($p=0.024$). Statistically significant correlation also exists between pathological fracture and the ISS stage of disease ($p=0.004$) as none, 6 (30%) and 11 (64.7%) of stage I, II and III respectively had pathological fractures. Association of generalized osteoporosis with the ISS stage was not statistically significant ($p=0.922$). There exists significant correlation between the ISS stage and serum beta 2 microglobulin ≥ 3.5 ($p<0.001$).

None, 16 (80%) and 17 (100%) cases of stage I, II and III respectively had serum beta 2 microglobulin ≥ 3.5 . Similarly, there exists significant correlation between stages and serum albumin <3.5 ($p=0.002$) as 1 (14.29%) case of stage I, 13 (65%) cases of stage II and 15 (88.24%) cases of stage III had serum albumin <3.5. A statistically significant correlation also exists between bone marrow plasma cell (BMPC) $\geq 33\%$ and the ISS stage of the disease ($p=0.002$). In this study 14.29%, 55% and 88.24% cases in stage I, II and III respectively had BMPC $\geq 33\%$.

DISCUSSION

Diwan AG et al (2014).⁶ reported that sixth decade is the common age group with a mean of 62 years. Kyle RA et al (2003).⁵ reported that the mean age was 66 years with 2% younger than 40 and 38% older than 70 years. Kumar L et al (2006).⁷ reported that in India the median age is 55 years; 2 decades earlier than that in USA we found 5 (11.4%) patients from 31 to 40 years and a mean age of 57.7 years. Madu AJ et al (2014).⁸ found male:female ratio 1.2:1 and Kumar L et al⁵ found 1.5:1. We also found a male:female ratio of 1.5:1.

Bone pain was reported by Diwan AG et al⁶ in 85%, Madhu AJ et al⁸ in 78.1%, Rahman AAU et al⁹ in 78% and Durie BGM et al¹⁰ in 58%. We found them in 86.3%. Riccardi A et al¹¹ reported symptoms of spinal cord compression in 34%, Lancaster CP et al¹² in 15%, Madu AJ et al⁸ in 13.8% and Diwan AG et al⁶ in 10%. In our study, symptoms of spinal cord compression was seen in 29.55%.

Diwan AG et al⁶ found anaemia in 100% and Rahman AAU et al⁹ found mean haemoglobin of 7.56. We found 93% anaemia and mean haemoglobin of 7.12 gm/dL. However, Grepp PR et al¹³, Blade J et al¹⁴ and Durie BGM et al¹⁰ showed mean haemoglobin level >8.5 gm/dL.

Madu AJ et al⁸, Diwan AG et al⁶, Kumar L et al⁷ and Bade J et al¹⁴ showed serum creatinine level >2 mg/dL in 13.8%, 30%; 31.3% and 22.3% respectively, which was 20.45% in our study. Dimopoulos MA et al¹⁵, Li SD et al¹⁶, Kyle RA et al⁵ and Lancaster CP et al¹² reported hypercalcaemia in 16%, 19.5%, 13% and 22% respectively, whereas we found it in 22.73%. Grepp PR et al¹³ and Madu AJ et al⁸ found mean serum beta 2 microglobulin of 3.8 and 4 mg/L, whereas we found it to be 4.92 mg/L.

Kyle RA et al⁵, Diwan AG et al⁶ and Madu AJ et al⁸ found positive M band in 82%, 100% and 90.5% respectively and we

found in 90.91%. Urine for Bence Jones was found by Dancaaster CP et al¹², Kyle RA et al⁵ and Madu AJ et al⁸ in 38%, 16% and 48%, but we found in only 14.3%.

Kumar L et al⁷ found 6.4%, 12% and 81.7% patients in stage I, II and III, whereas Li SD et al¹⁶ found it to be 17.2%, 47.5% and 35.5%. Dimopoulos MA et al¹⁵ found 29%, 38% and 33% in stage I, II and III and we found the same in 15.9%, 45.45% and 38.64% respectively.

Despite the limitation of the study as regards the relatively small sample size and short duration of study, the results obtained in the study were a good indicator in respect to the clinical findings and laboratory profile of multiple myeloma.

CONCLUSION

We conclude that though most patients were in sixth decade, but we got significant involvement in younger age group. Bone pain, mostly low backache was the most common presenting symptom along with fatigue and weakness. Majority of patients were in higher stages (ISS II, III) at the time of diagnosis and severe anaemia, lytic lesions, pathological fractures and renal insufficiency were most observations in these patients in higher stages.

REFERENCES

1. Solly S. Remarks on the pathology of mollities ossium with cases. *Med Chir Trans* 1844;27:435-98.
2. Kyle RA. Multiple myeloma: an odyssey of discovery. *Br J Haematol* 2000;111(4):1035-44.
3. National cancer registry program: two year report of the population based cancer registries 1999-2000. New Delhi: ICMR 2005.
4. Palumbo A, Anderson K. Multiple myeloma. *N Engl J Med* 2011;364:1046-60.
5. Kyle RA, Morie GA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clinic Proc* 2003;78(1):21-33.
6. Diwan AG, Gandhi SA, Krishna K, et al. Clinical profile of the spectrum of multiple myeloma in a teaching hospital. *Med J DY Patil Univ* 2014;7(2):185-8.
7. Kumar L, Vikram P, Kochupillai V, et al. Recent advances in the management of multiple myeloma. *National Medical journal of India* 2006;19(2).
8. Madu AJ, Ocheni S, Nwagha TA, et al. Multiple myeloma in Nigeria: an insight to the clinical, laboratory features and outcomes. *Niger J Clin Pract* 2014;17(2):212-7.
9. Rahaman AAU, Shah SZA, Devrajani BR, et al. International staging system: a tool to predict survival in patients with multiple myeloma. *World Appl Sci J* 2012;16(7):1004-8.
10. Durie BMG, Salmon SE. A clinical staging system for multiple myeloma, Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. *Cancer* 1975;36(3):842-54.
11. Riccardi A, Gobbi PG, Ucci G, et al. Changing clinical presentation of multiple myeloma. *EUR J Cancer* 1991;27(11):1401-5.
12. Dancaaster CP, Hussain OAN, Jackson WPU. Clinical features of multiple myeloma: a review of clinical manifestations and laboratory investigations in 40 cases. *Postgrad Med J* 1959;35(410):662-70.
13. Greipp P, Miguel SJ, Durie BG, et al. High serum levels of lactic dehydrogenase identify a high-grade lymphoma like myeloma. *Ann Intern Med* 1989;110(7):521-5.
14. Blade J, Rozman C, Cervantes F, et al. A new prognostic system for multiple myeloma based on easily available parameters. *Br J Haematol* 1989;72(4):507-11.
15. Dimopoulos MA, Kastritis E, et al. The International Scoring System (ISS) for multiple myeloma remains a robust prognostic tool independently of patients' renal function. *Annals of Oncology* 2012;23:722-9.
16. Li SD, Wang YF, Qi JY, et al. *Indian J Haematol Blood Transfus*. Springer 2010;26(3):83-8.