

Distribution of serum creatinine, calcium and protein levels in multiple myeloma patients - a hospital based study at Gauhati Medical College and Hospital, Guwahati, Assam

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Abstract

Introduction: Multiple Myeloma (MM) is a clonal plasma cell neoplasm characterized by the proliferation of plasma cells, monoclonal protein, Osteolytic bone lesions, renal disease and immunodeficiency. It accounts for 15% of lymphohematopoietic cancers (LHC) and 2% of all cancers in the US. **Objectives:** To see distribution of serum creatinine, calcium and protein level among MM cases. **Methods:** A hospital based cross-sectional descriptive study was conducted in the OPD of the clinical Haematology Department of Gauhati Medical College & Hospital, Guwahati, Assam during November, 2010 to October, 2013 with a study population of 100 in number of newly diagnosed MM cases. **Results:** Serum creatinine - 54 (54%) patients had < 1.2 mg/dl, 26 (26%) patients had 1.3-1.9 mg/dl and 20 (20%) patients had > 2 gm/dl. Serum calcium - > 11 mg/dl in 36 (36%); < 8 mg/dl in (8%); 8-11 mg/dl in 56 (56%) patients. Serum total protein - higher level in 52 (52%) patients. Serum albumin - < 3.5 gm/dl in 26 (26%) patients, > 3.5 gm/dl in 4 (4%) patients, Normal value in 70 (70%) patients. Serum globulin - < 3.5 gm/dl in 28 (28%) patients, > 3.5 gm/dl in 72 (72%) patients. **Conclusion:** The most frequently detected SC was < 1.2 mg/dl (84% patients), serum calcium 8-11 mg/dl (56% patients); serum total protein, albumin and globulin level were > 6.3-8.2 gm/dl (52%), > 3-5 gm/dl (70%) and > 3.5 gm/dl (72% patients) respectively.

Key words: Myeloma, Patients, Serum Albumin, Serum calcium.

Introduction

Multiple Myeloma (MM) is a clonal plasma cell malignancy characterized by the proliferation of neoplastic plasma cells [1]. MM is the most important class which is included under plasma cell dyscrasias. More importantly, delineation of the mechanisms mediating plasma cell proliferation, survival and migration in the bone marrow microenvironment may enhance the understanding of pathogenesis, and a better understanding of the molecular pathogenesis is fundamental for developing more effective prognostic, therapeutic and preventive approaches. Various studies show different observations in connection to distribution of serum creatinine, serum calcium and serum proteins

in MM patients. But to our knowledge, such studies in the North – Eastern part of India has not been carried on.

Materials and Methods

Research type- Hospital based cross-sectional descriptive study.

Study setting- OPD of the Clinical Haematology Department of Gauhati Medical College & Hospital, Guwahati, Assam.

Study period- November, 2010 to October, 2013.

Study population- the study population comprise of 100 numbers of newly diagnosed cases of MM

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attending the OPD of the Clinical Haematology Department of Gauhati Medical College & Hospital, Guwahati, Assam during the period of November, 2010 to October, 2013. Before undergoing the study clearance from institutional ethical committee was obtained. Analysis of data was done in the year 2014-15.

The sample- One hundred number of cases.

Selection of cases- Initially patients were selected purely on clinical ground and then negative cases were excluded after diagnosis based on International Myeloma Working Group (IMWG) criteria for diagnosis of monoclonal gammopathy.

Inclusion criteria- newly diagnosed cases of multiple myeloma of all age group from.

Exclusion criteria- (1) Old diagnosed cases of multiple myeloma that are under treatment. (2) Monoclonal gammopathy of undetermined significance

(MGUS) (3) Asymptomatic (smouldering) multiple myeloma.

Protocol- The proforma was prepared based on universal standard protocols for evaluation of MM which contains separate history, examination and investigation parts. The International Myeloma Working Group.(IMWK) criteria for classification of monoclonal gammopathies, MM and related disorders were used for diagnosis of the disease. During the study period Immunofixation electrophoresis test (for serum/urine) was not available in the institute. So this test was not included into the study. Then staging was made according to International Staging System (ISS). All the patient's history, clinical examination, investigation findings, and diagnosis data were recorded in a pre-designed and pre-tested proforma.

Statistical analysis - data were analysed using statistical package and results and observations were presented in tabular form. Statistical tests were applied wherever required.

Results

Table-1: Distribution of serum creatinine level of the patients (N=100)

Distribution of serumcreatinine(mg/dl)	Males		Females		Total	
	No	%	No	%	No	%
<1.2	36	53.73	18	54.55	54	54
1.3 – 1.9	18	26.87	8	24.24	26	26
>2	13	19.40	7	21.21	20	20
Total	67	100	33	100	100	100

The table-1 shows that 54 (54%) patients had serum creatinine (SC) less than 1.2 mg/dl, 26 (26%) patients had 1.3-1.9 mg/dl and 20 (20%) patients had > 2 gm/dl, maximum level 13.8 mg/dl, minimum levels 0.8 mg/dl ; median value 1.80 gm/dl; mean 1.96 with a S.E of 0.36 and S.D of 3.601. The statistical analysis from the table-1 suggest that significant ($p=0.000051$) in number of patients falls within a reference range of serum creatinine level as highly significant number of patients have creatinine <1.2 mg percent. (Test statistics: 'X²' test for independences of attributes, calculated value of 'X²' =19.762)

Table-2: Distribution of serum calcium level of the patients(N=100)

Distribution of serum calcium (mg %)	Males		Females		Total	
	No	%	No	%	No	%
< 8	5	7.46	3	9.09	8	8
8 – 11	38	56.72	18	54.55	56	56
>11	24	35.82	12	36.36	36	36
Total	67	100	33	100	100	100

The table-2 shows that hypercalcaemia (serum calcium > 11 mg/dl) was noted in 36 (36%) patients < 8 mg/dl in (8%) patients, 8 -11 mg/dl in 56 (56%) patients; range 7.2-13.8 mg/dl., mean 10.39 mg/dl with SE of 0.16 and SD of 1.69, median value 8.56 mg/dl. Thus hypercalcaemia was a common finding in our study, even though majority had calcium within normal range. The statistical analysis from the table-2 suggest that there exists significant difference ($p<0.00001$) in

number of patients with reference to serum calcium and a highly significant number of patients have creatinine 8-11mg/dl.(Test statistics: 'X²' test for independences of attributes, calculated value of 'X²' =34.883)

Table -3: Distribution of serum total protein level of the patients (N=100)

Distribution of serum total protein (gm %)	Males		Females		Total	
	No	%	No	%	No	%
<5.5	00	00	00	00	00	00
5.6-8	32	47.76	16	48.48	48	48
8.1-10	33	49.25	17	51.51	50	50
>10.1	2	2.99	00	00	2	2
Total	67	100	33	100	100	100

The above table-3 shows that 52 (52%) patients had higher level of total proteins. The rest had within range. None had hypoproteinemia. The median value was 8.13 gm/dl. mean 8.01 gm/dl with a SE of 0.205 and SD of 2.05; minimum protein 6.2 gm/dl and maximum was 15.2 gm/dl. The statistical analysis from in the table-3 suggest there exists significant difference (p=0.045) in number of patients with reference to levels of serum total protein. A highly significant number of patients had protein level greater than 8 gm percent. (Test statistics: 'Z' test for differences of two proportions, calculated value of 'Z' =2)

Table-4: Distribution of serum albumin level of the patients

Distribution of serum albumin (gm %)	Males		Females		Total	
	No	%	No	%	No	%
<1.5	2	2.98	1	3.03	3	3
1.6-3.5	15	22.39	8	24.24	23	23
3.6-5.5	47	70.15	23	69.70	70	70
>5.6	3	4.48	1	3.03	4	4
Total	67	100	33	100	100	100

In our laboratory, the normal value of albumin is 3-5 gm/dl (N=100). The above table-4 shows that hypoalbuminemia (< 3.5 gm/dl) was found in 26 (26%) patients whereas only 4 (4%) patients had higher values. Normal range 70 (70%) patients; median value 4.12 gm/dl.; mean 3.995 with a SE of 0.505 and SD of 3.05; minimum value 1.3; maximum value 5.8 gm/dl. The statistical analysis from the table-4 suggest that there exists significant difference (p<0.00001) in the number of patients with reference to serum albumin levels and it is found that a highly significant number of patients had serum albumin in the range 3.6-5.5 gm/dl. (Test statistics: 'X²' test for independences of attributes, calculated value of 'X²' =43.39)

Table -5: Distribution of serum globulin level of the patients (N=100)

Distribution of serum globulin (gm %)	Males		Females		Total	
	No	%	No	%	No	%
<3.5	19	28.36	9	27.27	28	28
3.6-6	28	41.79	14	42.42	42	42
6.1-9	12	17.91	6	18.18	18	18
>9	8	11.94	4	12.12	12	12
Total	67	100	33	100	100	100

In our laboratory, the normal value of globulin is 2.8-3.2 gm/dl. The table-5 shows that 28 (28%) patients had a globulin levels less than 3.5 gm/dl.; hyperglobulinemia 72 (72%) patients; maximum level 13.2 gm/dl; minimum 2.6; median value of 4.59 gm/dl.; mean 3.816 with a SE of 0.302 and SD of 3.02. The 28 (28%) patients had hypoproteinemia at diagnosis, which was mainly due to increase in the globulin fractions. The statistical analysis from the table-5 suggest there exists significant difference (p=0.000011) in the number of patients with reference to serum globulin levels and it is found that a highly significant number of patients have serum globulin in the range of more than 3.2 gm/dl. (Test statistics: 'Z' test for differences of two proportions, calculated value of 'Z' =4.4)

Discussion

Pathophysiology of Multiple Myeloma

(A) Increased osteoclastic activity- Cytokines such as IL-6, macrophage colony-stimulating factor (M-CSF), IL-1 β , TNFs, and IL-11 are shown to have osteoclast activating function (OAF). Furthermore, molecules such as the receptor activator of nuclear factor-kappa B (RANK-KB), its ligand (RANKL), osteoprotegerin (OPG) and macrophage inflammatory protein-1 alpha (MIP-1 α) have also been implicated in osteoclast activation and osteoblast inhibition. Studies have shown that myeloma cells adhere to BMSCs through binding of VLA-4 present on the surface of MM cells to VCAM-1, which is expressed on stromal cells. Moreover, this binding of myeloma cells to BMSCs/osteoblasts increases the production of RANKL, M-CSF, and other cytokines with OAF activity (IL-6, IL-11, IL-1 β , TNFs, bFGF), while it suppresses the production of OPG (the decoy receptor of RANKL). These cytokines are also involved in modifying the bone marrow microenvironment by up-regulating RANKL expression and secretion by dint of both BMSCs and osteoblasts. Besides this, MIP-1, HGF and VEGF produced by myeloma cells also contribute to proliferation and differentiation of osteoclast precursors [2].

(B) Suppression of osteoblast function- The transcription factor Runx2/Cbfa1 has shown to play an important role in the formation and differentiation of osteoblasts from mesenchymal stem cells. Co-culture of myeloma cells with osteoprogenitor cells has been shown to inhibit osteoblast differentiation in long-term bone marrow cultures, reduce the number of early osteoblast precursors, fibroblast colony-forming units (CFU-Fs), and the more differentiated osteoblast precursor, the osteoblast colony-forming units (CFU-OBs), and decrease the expression of osteoblast differentiation markers, alkaline phosphatase, osteocalcin, and collagen I. This effect was demonstrated to be mediated by blocking Runx2/Cbfa1 activity in human osteoprogenitor cells [3].

Aetiology of Multiple Myeloma

(A) Radiation exposures (ionizing radiation)- Shimizu Y et al. described that among the atomic bomb survivors in Hiroshima and Nagasaki, it was estimated that there was a 3.3 fold increase in mortality of MM (RR= 3.3) per Gray (Gy) of radiation delivered to the bone marrow {(95% (CI), 1.7-6.3) (1 Gy=100 rad)}. It also reported that myeloma occurs after a long latent

period (approximately 20 years), in atomic bomb survivors exposed to high doses of radiation[4].

Hayakawa N et al. reported that individuals who entered the bombed areas in the city of Hiroshima within 3 days after the blast, nearly 60 percent greater risk of myeloma mortality than those not exposed[5].

(B) Diagnostic radiation- In 2011, Cogliano VJ et al. (which was reviewed in 2014) depicted that X- radiation and gamma radiation are classified by International Agency for Research on Cancer(IARC) as probable causes of myeloma, based on limited evidence[6]. Boice JD et al. showed association between diagnostic radiation and MM[7] van Kaick G et al. showed that exposure to thorium dioxide (an X-ray contrast medium) used between 1930 and 1950, had been reported to increase risk of Plasmacytoma more than 4-fold among patients examined with cerebral angiography or arteriography of the limbs [8].

(C) Radiation related industry: Positive association of MM has been demonstrated following exposure to radiation of different workplace like nuclear facilitates radium dial painting industry. However, some studies opine that in most instances, chronic exposure at the workplace for 10-15 years is necessary for the development of MM [9].

(D) Familial multiple myeloma- The overall risk of MM in first degree relatives of persons with multiple myeloma is reported to be increased by a factor of two to four [10].

Treatment Protocol of Multiple Myeloma

Primary Therapy (Transplant Candidates)

Bortezomib/Cyclophosphamide/Dexamethasone-

This combination may be used in any of the following regimens: Bortezomib 1.3 mg/m² IVP on days 1, 4, 8, and 11 + cyclophosphamide 300 mg/m²/day PO on days 1, 8, 15, and 22 + dexamethasone 40 mg PO daily on days 1-4, 9-12, and 17-20; 28-d cycle for three or four cycles. [11]

Bortezomib/Doxorubicin/Dexamethasone-

Either of the following two regimens may be used: Bortezomib 1.3 mg/m² IVP on days 1, 4, 8, and 11 + doxorubicin 9 mg/m² IVP on days 1-4 + dexamethasone 40 mg PO daily on days 1-4, 8-11, and 15-18 (cycle 1), then days 1-4 (cycles two-four); 21-d cycle for three or four cycles. [12].

Bortezomib/Lenalidomide/Dexamethasone-

Bortezomib 1.3 mg/m² IVP on days 1, 4, 8, and 11 + Lenalidomide 25 mg PO daily on days 1-14 +dexamethasone 20 mg PO daily on days 1, 2, 4, 5, 8, 9, 11, and 12 or 40 mg PO daily on days 1, 8, and 15; 21d cycle for three or four cycles. [13]

Bortezomib/Thalidomide/Dexamethasone-

Bortezomib 1-1.3 mg/m² IVP on days 1, 4, 8, and 11 +Thalidomide 50-200 mg (titrate to tolerance) PO daily at bedtime on days 1-21 +Dexamethasone 40 mg PO daily on days 1, 2, 4, 5, 8, 9, 11, and 12 or40 mg on days 1-4 and 9-12 or 40 mg on days 1-4 and 8-11; 21d cycle for three or four cycles [14].

Lenalidomide/dexamethasone- Either of the following two regimens may be used:Lenalidomide 25 mg PO daily on days 1-21 +dexamethasone 40 mg PO daily on days 1, 8, 15, and 22 or 40 mg PO daily on days 1-4, 9-12, and 17-20; 28-d cycle for three or four cycles[15].

Primary treatment (non-transplant candidates)- One of the following six regimens may be used:Bortezomib 1-1.3 mg/m² on days 1, 4, 8, 11, 22, 25, 29, and 32, followed by a 10-d rest period + Melphalan 9 mg/m² PO +Prednisone 60 mg/m² PO, both on days 1-4; every 6 weeks for four cycles then a maintenance phase consisting of Bortezomib 1-1.3 mg/m² on days 1, 8, 22, and 29, followed by a 13-d rest period +Melphalan 9 mg/m² PO + Prednisone PO 60 mg/m²; every 5 wk for five cycles

Serum Creatinine- Gupta P et al described creatinine more than 2mg/dl in 37 percent of the MM patients[16]. In 2003, Kyle RA et al in his study of 1027 myeloma patients, observed serum creatinine level of 2 mg/dl or more in 19 percent of the patients with median value of 1.2 mg/dl[17]. Riccardi A et al observed renal failure (serum creatinine >1.2 mg/dl) in 33 percent of the MM patients[18]. Kyle RA.(1975) in his study which was carried out between 1950-1971 observed serum creatinine of more than 1.2 mg/dl in 56 percent of the patients of MM at presentation. The study again found a similar result in his 2003 study where still the median was more than 1.2 mg/dl in 48 percent patients. There, only 0.7 percent patients had a creatinine of more than 8 mg/dl at presentation [19]. Renal insufficiency (serum creatinine of >1.3 mg/dl) is found at presentation in almost 50% of patients with myeloma (27,28-31), and severe renal insufficiency (serum creatinine >2.0 to 2.5 mg/dl) is seen in >15 to 20% of cases [20]. Thus in our study results of serum creatinine levels are to some

amount lower than the above studies. It may be due to early detection of MM before renal involvement.

Serum Calcium- Greer JP, Rodgers GM et al reported hypercalcaemia in 18 to 30 percent of the MM patients [21]. Kyle RA. et al. (2003) in their study of 1027 myeloma patients, observed hypocalcaemia (> 11 mg/dl) in 13 percent of the MM patients with a median value of 9.6 gm/dl [17]. Blade J. and Kyle R.A. (1995) Observed hypercalcaemia (serum calcium > 120 mg/L) in 30 percent cases of multiple myeloma [22]. In India, Gupta P et al. (1995) described calcium more than 12mg/dl in 11 percent of MM patients[16]. Riccardi A et al. (1991) demonstrated hypercalcaemia in 18 percent of the MM patients[18]. It has been seen that 34 percent of patients are asymptomatic at presentation with incidental abnormalities on total protein, creatinine, calcium, or haemoglobin laboratory panels[23]. Thus the present study was also having near similar observation with the studies of Greer JP, Rodgers GM et al., Blade J. and Kyle R.A. and Ong F et al.

Total Serum Protein- Riccardi et al. (1991), found that the total protein was more than 8 gm/dl in 65 percent of the myeloma patients [18]. Thus, the present study was also having near similar observation with the study of Riccardi et al.

Serum Albumin- Kyle RA et al. (2003) in their study observed low level of albumin in 15 percent of the myeloma patients [17]. Riccardi et al. found hypoalbuminemia in 7 percent of the MM patients[18]. Gupta P et al. (1995) observed less than 3 gm/dl albumin in 24 percent of the myeloma patients [16]. Thus, our study results are almost similar to the observations made by Gupta P et al. and so can be comparable with the study of Gupta P et al.

Conclusion

Most frequently detected serum creatinine and serum calcium were less than 1.2 mg/ dl (observed in 84% patients) and 8-11 mg/dl (observed in 56% patients) respectively.

Most frequently detected serum total protein, albumin and globulin level were more than 6.3-8.2gm/dl (detected in 52% patients), more than 3-5 gm/dl (detected in 70% patients) and more than 3.5 gm/dl (detected in 72 % patients) respectively.

Recommendations

Original Research Article

1. The common nonspecific symptoms of MM like fatigue, bone pain, easy bruising and bleeding and recurrent infections are similar to symptoms of some common diseases. So it becomes necessary for physicians to keep a high level of suspicion for the possibility of these being for MM and thorough evaluation to be undertaken to detect all MM cases.

2. Moreover, some screening tests like detection of serum creatinine, calcium and protein should be held periodically by the health agencies to detect the disease early specially in elderly people who are at risk of having environmental, occupational and life style factors for development of MM. For this, hospital should be well equipped with uninterrupted supply of materials necessary for early detection of multiple myeloma. Health agencies should be encouraged to organize periodic camps for screening of the disease.

3. Environmental, occupational and life style factors which are risk for development of multiple myeloma should be included into the health education programmes so that the disease can be prevented. Information, Education and Communication (IEC) activities should be strengthened to disseminate these information to the people. Moreover, periodical orientation course to medical and paramedical staff should be undertaken.

4. The study was a descriptive study which was conducted with limited number of patients. So it needs community based study with a large number of populations. So any conclusions drawn will have to be guarded and will have to confirm with further trials in India.

Authors contribution

- Dr. Lohit Kumar Kalita conceived and planned the study, took the lead in writing the manuscript.
- Dr. Mansi Mondol contributed in sample preparation, manuscript preparation and interpretation of the results.
- Dr. Pabitra Kamar Gogoi and Dr. Umesh Ch. Sarma provided critical feedback and helped shape the research, analysis and manuscript.

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