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DIAGNOSTIC EVALUATION OF MULTIPLE MYELOMA BY CLINOPATHOLOGICAL AND BIOCHEMICAL ASSESSMENT- AN INSTITUTIONAL STUDY OF 50 CASES

Oncopathology

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ABSTRACT

Multiple Myeloma (MM) (Synonym-Plasma cell myeloma) is the second most common hematological malignancy. Aim of the present study is to know statistical significance among various biochemical parameters, staging of patients and morphological features of plasma cell myeloma with outcome of patients. Total 50 cases were retrieved during a period of July 2011 to November 2012 at Gujarat cancer and Research Institute. Follow-up of patients was done till October 2013. Patients with bone marrow showing plasma cells with immature and plasmablastic morphology and diffuse pattern of infiltration had significantly poor outcome of the patients. Patients with high beta2 microglobulin level, high serum creatinine level and patients in Durie & Salmon stage IIIB show poor outcome. Serum protein electrophoresis is a useful investigation in multiple myeloma works up.

KEYWORDS

Multiple Myeloma, Durie & Salmon staging, beta2 microglobulin level, Bone marrow aspiration and biopsy

INTRODUCTION

Multiple Myeloma (MM) (Plasma cell myeloma- PCM) the second most common hematological malignancy is a severely debilitating and fatal clonal proliferative disorder of terminally differentiated immunoglobulin secreting B-cells. The diagnosis depends on identification of clonal plasma cells in the bone marrow/plasmacytoma, Monoclonal (M)-protein in the serum/urine and end organ damage. The clinical signs and symptoms of MM result from: Predominant distribution of tumor cells within the bone marrow leading to anemia, leucopenia and thrombocytopenia. Secretion of M-protein causing hyperviscosity syndrome and amyloidosis. Renal failure is thought to be due to excretion of monoclonal light chains along with hypercalcemia and amyloidosis.Clinically patients usually present with acute lower back pain or bone pain. Symptomatic MM is defined by presence of end-organ damage (CRAB: hypercalcemia, renal insufficiency, anaemia, bone lesions) in a patient with an M component and clonal BM plasma cells.

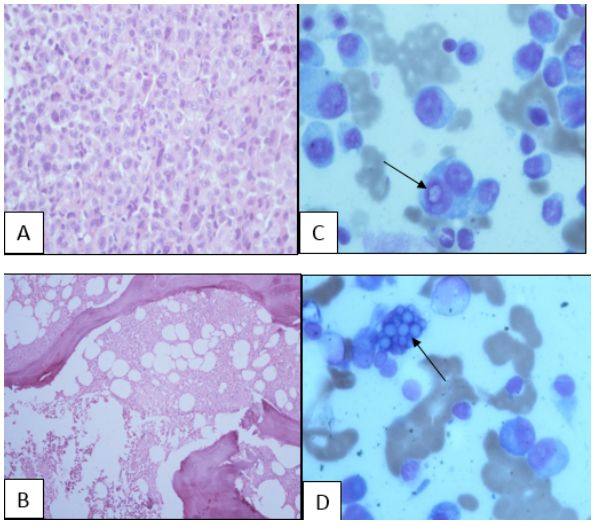
AIMS AND OBJECTIVES

To study the morphological features and percentage of plasma cells in bone-marrow aspirates of subjects with multiple myeloma.To study the pattern of involvement in bone-marrow biopsy . To study age occurrence, gender occurrence ,the Durie and Salmon staging and International Staging System for multiple myeloma..To study is there any statistical significance between various biochemical parameter and outcome of the patient.

METHODOLOGY

Patients diagnosed at Gujarat Cancer And Research Institute (GCRI), Ahmedabad as having Multiple myeloma according to WHO[1] criteria were selected. Cases diagnosed or treated outside were excluded from study. Only those cases of MM received with representative bone marrow biopsies with adequate tumor tissue and had all other biochemical parameter included in our study including serum electrophoresis finding were included in study. Those bone marrow biopsies showing poor or fragmented yield and extensive crushing artifact were excluded from the study. Total 50 cases which were fulfilling inclusion & exclusion criteria were retrieved from the case files of the patients during a period of July 2011 to November 2012.Laboratory parameters such as haemoglobin, β2-microglobulin, serum protein electrophoresis finding including serum total protein level, serum albumin, serum calcium, serum creatinine were obtained from medical records. Clinical stage was obtained according to durie and salmon.[2]and international staging systems.[4] Radiological findings were recorded.

Morphological assessment of plasma cells was carried out and cells were categorized according to greipp[3] plasma cell grading system into four types mature, intermediate, immature and plasmablastic. Bone marrow (bm) aspiration smears were stained with wright stain and percentage of plasma cells were calculated counting 500 nucleated cells. Pattern of bm infiltration was studied on bm trephine biopsies fixed in formaliln, decalcified in 5% nitric acid, embedded in paraffin wax and stained with haematoxylin and eosin (H & E). Growth pattern were categorized into 3 types, interstitial, nodular and diffuse. When cytoplasm of plasma cell contain multiple immunoglobulin inclusion, such studded plasma cell is called mott cell. Such intranuclear inclusion is known as Dutcher bodies



A- Bone biopsy showing diffuse involvement by plasmablast(40 X view)
B- Bone biopsy showing interstitial involvement by plasma cells(10 X view)
C- Bone marrow aspiration showing dutcher body in binucleated plasma cells and plasmablast (100 X view) (arrow mark)
D- Bone marrow aspiration showing mott cell (100 X view) (arrow mark)

All patients received the treatment according to standard protocol for MM (chemotherapy or bone marrow transplantation). Only single case underwent auto bone marrow transplantation, rest of the cases received chemotherapy and palliative radiotherapy for pain relief. Symptomatic treatment and specific intervention therapy like hemodialysis for renal failure was also given if necessary. Out of 50 patients, 32 patients died. Follow-up of patients was done till October 2013.

Statistical Analysis

All statistically analysis was done with Epi Info-7 software. Chi square test was applied. Test was considered significant when P value was <0.05, considered just significant when P value was 0.05 and considered non-significant when P value was >0.05.[5]Following parameter were correlated with outcome of the patient: Age, Sex, Morphology of plasma cells in BMA, Pattern of the involvement in bone biopsy, Durie & Salmon stage, International Staging System, S. Creatinine & Serum beta2 microglobulin.

RESULTS

The age of patients ranged from 30 to 80 years. Maximum cases were noted in the age group between 51 to 60 years with mean age of 55.64 years.Out of 50 cases 27(54%) were males and 23(46%) were females. M:F ratio was 1.17:1.The commonest presenting feature were bone pain- back pain and generalized weakness, fatigue, 26% cases had hypercalcemia. All the cases were presented with anemia, high Erythrocyte Sedimentation Rate (ESR). Multiple lytic lesions were seen in skeletal survey in all patients.According to Greipp system, 6(12%) cases were of mature myeloma, 16 (32%) cases were of intermediate myeloma, 18(36%) cases were of immature myeloma and 10 (20%) cases were of plasmablastic myeloma.10(20%)cases showed interstitial pattern of infiltration, 7(14%) cases showed nodular pattern and 33(66%) cases showed diffuse pattern of infiltration.All the 50 patients presented in Durie & Salmon stage III. Out of which 32(64%) cases presented in stage IIIA & 18(36%) cases presented in stage IIIB.32(64%) cases presented in ISS stage III, 16(32%) cases presented in ISS stage II & 2(4%) cases presented in ISS stage I.

Statistical results are as follow

1.Correlation between pattern of involvement on BM biopsy and outcome of the patients:

BM biopsy-Pattern of involvement	Outcome of Patient		Total
	Alive	Death	
Diffuse	8	25	33
Interstitial+nodular	10	7	17
TOTAL	18	32	50

Test	Chi-Square	P. Value
Chi-square	5.82	0.01

Result- Statistically significant

2.Correlation between morphology of plasma cells and outcome of the patients:

BMA-Morphology of plasma cells	Outcome of Patient		Total
	Alive	Death	
Mature+Intermediate	14	8	22
Immature+Plasmablast	4	24	28
TOTAL	18	32	50

Statistical Test	Chi-Square	P. Value
Chi-square	13.02	0.0003

Result- Statistically significant.

3.Correlation between Durie & Salmon Staging and outcome of the patient:

Durie & Salmon Staging	Outcome of Patient		Total
	Alive	Death	
IIIA	15	17	32
IIIB	3	15	18
TOTAL	18	32	50

Statistical Test	Chi-Square	P. Value
Chi-square	4.56	0.03

Result: Statistically significant.

4.Correlation of ISS & Outcome of patient:

International Staging System	Outcome of Patient		Total
	Alive	Death	
I+II	7	11	18
III	11	21	32
TOTAL	18	32	50

Statistical Test	Chi-Square	P. Value
Chi-square	0.1	0.74

Result: Statistically Not Significant

5. Correlation between beta2 microglobulin level and outcome of patient

Beta 2 microglobulin level(mg/L)	Outcome of Patient		Total
	Alive	Death	
>6	5	24	29
≤6	13	8	21
TOTAL	18	32	50

Statistical Test	Chi-Square	P. Value
Chi-square	10.54	0.001

Result: Statistically significant.

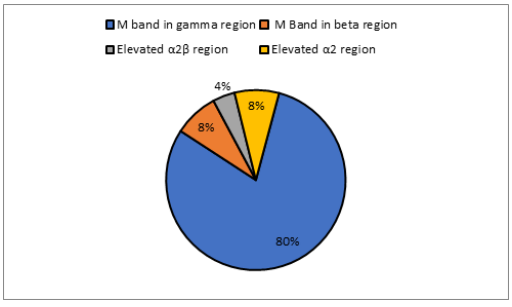
6. Correlation between S. Creatinine level and outcome of patient:

S.Creatinine(mg/dl)	Outcome of Patient		Total
	Alive	Death	
>1.2	7	22	29
≤1.2	11	10	21
TOTAL	18	32	50

Statistical Test	Chi-Square	P. Value
Chi-square	4.21	0.04

Result: Statistically Significant.

7. Electrophoresis Findings:



DISCUSSION AND CONCLUSION

Multiple myeloma is a disease resulting from the proliferation in the bone marrow of neoplastic B cells that are closely related, both morphologically and functionally to plasma cells. It constitutes 1% of all malignancies, but is the second most common haematological malignancy after lymphoma. Clinicopathological studies have been done in the past to explore the prognostic strength and significance of various criteria used in the diagnosis of multiple myeloma.

Comparison of incidence of morphological variants of myeloma

Study	NO. of Case (n)	Mature Myeloma (%)	Intermediate myeloma (%)	Immature Myeloma (%)	Plasmablastic myeloma (%)
Griepp et al,1985	100	28.0	38.0	19.0	15.0
Carter et al,1987	139	21.6	-	54.7	23.7
Kuriakose et al, 1995	89	13.5	-	59.6	26.9
Present study, 2014	50	12	32	36	20

In the present study, immature myeloma was most common variant while mature myeloma was least common variant. This was comparable with studies done at Ludhiana by Kuriakose et al and at Israel by Carter et al have shown immature myeloma to be the most common variant and mature myeloma to be the least common variant.[6,7] However, the Mayo clinic study by Griepp et al had seen intermediate myeloma followed by mature myeloma to be the most common variants and plasmablastic myeloma to be the least common variant.[3]

Age & Sex of the patients did not show any statistically significant with outcome of the patients. Most of the patients presented very late in the disease and this could be the cause for all the 100% cases of our patients belonged to Durie & Salmon stage III, patients with stage IIIB showed poor outcome than stage IIIA. ISS did

not show any statistically significant with outcome of the patients.We found correlation between degree of nuclear immaturity and overall survival. The neoplastic pcs often show a variable degree of immaturity or atypia. Asynchronous maturation of the nucleus and cytoplasm, dispersed chromatin, a high nuclear/cytoplasmic ratio, and prominent nucleoli are features of immaturity. Plasmablastic morphology has been shown to associated with poor prognosis.[8,9]Cases were categorized based on degree of nuclear immaturity into two groups: mature and intermediate versus immature and plasmablastic. Patients with marrow showing immature and plasmablastic morphology had significantly lower survival compared to patients having mature and intermediate cell morphology.Majority cases of Durie & Salmon stage IIIB had Immature + plasmablastic morphology and diffuse pattern of involvement and these factors were associated with poor outcome of the patients.

Beta2 microglobulin level show tumor load and considered an important prognostic parameter,[10,11,12,13] It showed statistically high significance with outcome of patient. Serum creatinine level is important for subclassification of Durie & Salmon stage III into IIIA & IIIB and higher level show poor outcome of the patients. Hypercalcemia seen in many cases, but it not showed any statistically significance with outcome of the patient.

Serum protein electrophoresis is a use-full investigation in multiple myeloma works up. It shows a dense, well localized band in gamma region. Identification of monoclonal protein is made by immunoelectrophoresis or immunofixation using monoclonal antisera.

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