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Prognostic Significance of Hematological and Biochemical Parameters in Multiple Myeloma

Authors
Deepthi Raj M.L[1], Roshny Jacob*[2], Rema Priyadarsini[3]
[1,2]Assistant Professor, Dept of Pathology, Govt. Medical College, Trivandrum, Kerala
[3]Additional Professor, Dept of Pathology, T .D Medical College, Alappuzha, Kerala
* Corresponding Author
Dr Roshny Jacob
Email: *roshnijacob@yahoo.com*

Abstract
Background: *Multiple myeloma accounts for 1% of all types of malignancies and about 10 % of hematologic malignancies. Several clinical and laboratory variables help us to determine the prognosis of the disease. The present study is aimed at analyzing the various clinical presentations and studying hematological and biochemical parameters in determining prognosis in Myeloma.*
Materials and Methods: *100 patients diagnosed as Multiple Myeloma who registered at hematology laboratory in a tertiary health care centre over a span of 3 years were studied. Clinical & radiological findings were recorded. Hematological & biochemical parameters were analyzed and compared between alive and expired patients. Based on the International Staging System (ISS) for multiple myeloma patients were staged as I, II & III and assessed correlation with prognosis. Statistical analysis was done by Student T test & ANOVA test.*
Results: *Most common clinical presentation was bone pain. Among the variables considered, serum creatinine and serum Beta 2 microglobulin showed statistically significant correlation with prognosis. The mean value of Serum creatinine and serum beta 2 microglobulin were 3.03 mg/dl and 5.8 mg/L respectively in expired patients. Staging by International Staging System was found to have good correlation with prognosis.*
Conclusion: *Serum beta 2 microglobulin and serum creatinine were found to be statistically significant and reliable prognostic indicators. Staging by International Staging System with prognostic correlation was also achieved by the present study.*
Keywords: *Multiple myeloma, serum Beta 2 microglobulin, prognosis.*

Introduction

Multiple myeloma (Plasma cell myeloma) is a neoplastic disorder characterized by proliferation of a single clone of plasma cells in the bone marrow and the production of large amounts of a monoclonal immunoglobulin or paraprotein [(1)]. It accounts for about 1 % of all types of malignancies and slightly more than 10 % of hematologic malignancies[(2)]. The incidence has increased in recent years with a tendency for younger age at diagnosis. The reported incidence in India varies from 0.3-1.9/100,000 for males and o.4-1.3/100,000 for females[(3)]. The median age for myeloma in India is 55 years and the male to female ratio is 1.4 to 1 [(4)].

The exact etiology of multiple myeloma is still unknown. But the research suggests possible associations with a decline in the immune system, certain occupations, exposure to radiation and exposure to some chemicals. Cytokines play an important role in myeloma cell proliferation especially IL-6 [5]. A genetic abnormality such as c-myc oncogenes and others have also been associated. The tumor, its product and the host response to it result in a number of organ dysfunctions and symptoms of bone pain, fracture, anemia, hypercalcemia, clotting abnormalities, susceptibility to infection, neurologic symptoms and manifestations of hyperviscosity.

Various blood, urine, bone marrow and imaging studies are required for the diagnosis, staging and monitoring of the disease and to determine prognosis. For final confirmation, demonstration of malignant plasma cells on histological examination of bone marrow or a soft tissue plasmacytoma, with clonality usually established by IHC or flow cytometry for light chain restriction is required [6,7]. In 40-73 % patients a hemoglobin concentration of less than 12g/dl occurs at presentation which contributes to weakness and fatigue in as much as 82% patients. Approximately 25% of myeloma patients show a serum creatinine level of >2 mg/dl at diagnosis and about 50% become uremic during the course of the disease. Hypercalcemia occurs in 18-30 % of patients. Since C – Reactive protein level correlate with IL-6 levels, it may be offered as a surrogate marker for IL-6. High Serum lactate dehydrogenase identifies patients with poor outcome. Higher levels of Beta 2 microglobulin is also associated with adverse prognosis.

The Durie and Salmon clinical staging system proposed in 1975, is still being used today, though it has been replaced by the ISS staging at many places. This system divides myeloma into 3 stages based only on the serum beta 2 microglobulin and serum albumin levels[8]. A revised International Staging System(R-ISS) has been developed that incorporates the original staging system with chromosomal abnormalities and serum lactate dehydrogenase.

The purpose of this study was to analyze the clinical features of Myeloma and to determine the prognostic significance of hematological and biochemical parameters.

Materials and Methods

The study was conducted in a tertiary health care centre over a span of 3 years. 100 patients diagnosed as Multiple Myeloma were studied. Clinical history and radiological findings were recorded. Results of biochemical investigations like serum creatinine, serum calcium, serum albumin, serum globulin and serum beta 2 microglobulin were collected from case sheet. Hematological tests were done including peripheral smear examination. Bone marrow study was performed in all cases. Patients were followed up for a minimum period of 6 months from the time of diagnosis. Hematological & biochemical parameters of those expired and those alive were compared. Based on the International Staging System (ISS) for multiple myeloma, patients were staged as I (Serum beta-2 microglobulin < 3.5 mg/L and serum albumin ≥ 3.5 g/dL) , II (Neither stage I nor stage III ie,beta 2 microglobulin level is between 3.5 and 5.5 with any albumin level or Albumin is <3.5 while beta 2 microglobulin is <3.5) & III (Serum beta-2 microglobulin ≥ 5.5 mg/L) and the prognosis assessed.

Statistical analysis: Student T test was used to compare the hematological & biochemical parameters between alive and expired patients and statistical significance assumed to be present if p value is <0.05. For the comparison of the 3 stages based on International Staging System, the ANOVA test was used.

Results

A total of 100 cases of Multiple myeloma were studied which included 58 males and 42 females. Maximum cases were noted in the age group between 50-59. Median age was 58 years. Youngest patient in the present study was a 26

year old male and the oldest an 82 year old male. 58 % of the patients were males. Bone pain was the most common clinical presentation. One case presented with multiple skin lesions, macroglossia and alopecia. Skin biopsy revealed deposits of amyloid in dermis. Other less common presentations were fever, dyspnoea, dysphagia, oedema, chest pain, abdominal pain, bone swelling, bleeding and incidentally detected increased ESR. Radiological findings were noted in 93% of patients. The most commonly occurring abnormality was lytic lesion (63% of patients) . Other abnormalities noted were pathological fracture, osteoporosis and compression fracture.

Peripheral smear examination showed increased rouleaux formation in all cases. A normocytic normochromic anemia was observed in 87% of cases while the rest showed hypochromia. A case of primary plasma cell leukemia was also diagnosed which showed more than 20% plasma cells in the peripheral smear. Bone marrow aspiration was done in all the cases. Bone marrow plasma cell percentage was 43.41 and 43.74 in alive and expired patients respectively. A plasma cell percentage of more than 50 was noted in 29 % of cases.

86% of patients had a hemoglobin value of <10 gm/dl. Erythrocyte sedimentation rate was > 20mm/hr in 95% of patients, more than 100mm/hr in 53% and a markedly elevated value above 150mm/hr was noted in 15%. Thrombocytopenia was noted in 7% of cases and thrombocytosis in 2%.

Serum electrophoresis revealed a localized M band in 93 cases. The pattern was normal in 4 cases. Results were inconclusive in remaining cases. Immunofixation electrophoresis of serum and urine was done in 2 patients which revealed a λ monoclonal light chain. (Figure 1)

Biochemical parameters estimated were serum calcium, serum albumin, serum globulin, serum creatinine and serum β-2 microglobulin. Serum creatinine value of > 1.3 mg/dl was noted in 50% of patients and more than 2 mg/dl in 24%. Hypercalcemia (>11 mg/dl) was noted in 18% of cases. Serum Beta 2 microglobulin was available only in 55 patients.

Serum creatinine and serum Beta 2 microglobulin showed statistical significance and can be considered as reliable prognostic indicators. (Table 1)

Prognosis based on ISS staging

Based on the S. Beta 2 microglobulin and S. Albumin values, patients were staged as I, II and III according to the new International Staging System for multiple myeloma. Maximum number of cases were in Stage II (40%). Stage III patients showed the highest mean value for serum beta 2 microglobulin and the lowest mean value of albumin. Table 2 shows the outcome of patients.

A high value for serum beta 2 microglobulin and low value for serum albumin were found to have significant correlation with survival.

Figure 1: Immunofixation electrophoresis showing M band as lambda light chain

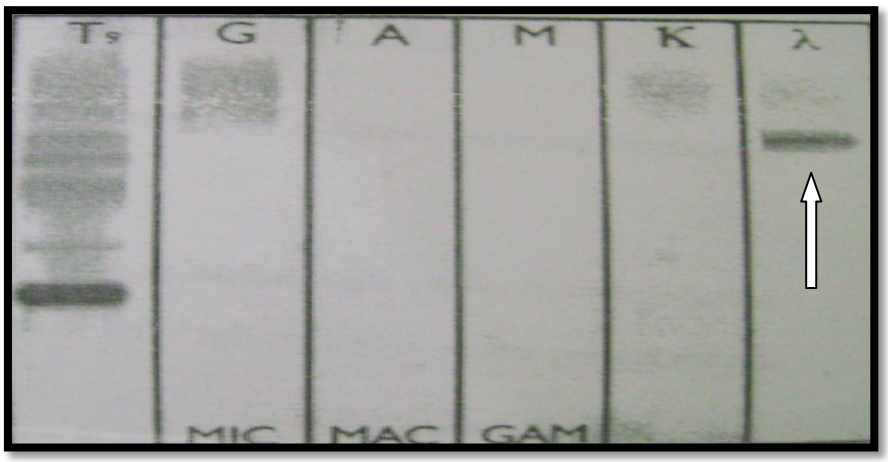

Table 1: Comparison of hematological and biochemical parameters in alive and expired cases

Test	Alive		Expired		T Value	P value
	Mean	S.D	Mean	S.D		
S.Creatinine(mg/dL)	1.86	1.58	3.03	2.37	2.33	0.024*
S Calcium(mg/dL)	10.22	1.11	10.67	1.22	1.59	0.118
S Albumin (g/dL)	3.64	0.72	3.32	0.67	1.79	0.078
S Globulin (g/dL	4.05	1.26	4.2	1.55	0.41	0.118
Beta2 microglobulin (mg/L)	3.84	2.13	5.8	1.82	3.17	0.003*
Hemoglobin(g/dl)	8.53	2.01	8.03	1.83	1.12	0.268
ESR(mm/hr)	97.75	46.47	99.06	47.21	0.12	0.905
B.M Plasma cell %	43.41	21.12	43.74	21.72	0.07	0.949

*statistically significant

Table 2 : Prognosis based on ISS staging

Stage	Number	Percentage	Outcome					
			Alive		Expired		Lost to follow up	
			No	%	No	%	No	%
1	13	23.6	13	100	0	0	0	0
11	22	40	10	46	7	32	5	22
III	20	36.4	2	10	16	80	2	10

Table 3 : Comparison of the laboratory findings with the study by Kyle R.A. et al.

	Hb (g/dl) (Median & Range)	Creatinine (Mg/dl) (Median& Range)	Calcium (Mg/dl) (Median& Range)	Beta2micro globulin(mg/l) (Median& Range)
Present study	8.35 (3.6-13.3)	1.5 (0.6-8.6)	10.2 (9-13)	3.92 (1.1-8.84)
Study by Kyle R.A. et al	10.9 (2.7-17.2)	1.2 (0.5-18.2)	9.6 (7-17.2)	3.9 (0.8-8.2)

Discussion

Multiple myeloma is a hematological malignancy characterized by clonal proliferation of immunoglobulin secreting plasma cells in the bone marrow.

100 patients of multiple myeloma were studied over a span of 3 years. Multiple myeloma accounted for 15% of all hematological malignancies. Reports indicate that multiple myeloma has increased in incidence during the past few decades.

Incidence of multiple myeloma increases with age. In most Western series, the median age of patients with multiple myeloma is around 66 years. However in the present study the median age was only 58 years, which was comparable to a study by Kaur et al in which the median age was 57.5 years [(3)]. Youngest patient in this study was a 26 year old male who presented with bone pain and fatigue and was diagnosed as a case of plasma cell leukemia. In multiple myeloma males are usually affected more than females. This was confirmed in the present study in which 58% of

patients were males and 42% females. A comparative study was made by Kyle R.A et al which showed a male preponderance (59% males) [2]

The most common clinical presentation in the current study was bone pain (65%). Generalised weakness and malaise was noted in 43 patients which was related to anemia. Interestingly weight loss which is not a common feature of myeloma was reported by 23% of patients which is comparable to a study by Kyle R.A. et al. They reported 24% of patients with weight loss, no specific cause being postulated [2].

One case presented with multiple skin lesions, alopecia and macroglossia and was diagnosed as amyloidosis by skin biopsy. The reported incidence of amyloidosis associated with multiple myeloma is 10-15%. Becker et al reported a case of light chain multiple myeloma with cutaneous AL amyloidosis which presented with painful sclerotic skin lesions and macroglossia [9].

Roentgenography has immense diagnostic value in myeloma, but MRI shown to be superior to both CT and skeletal surveys. Conventional radiographs showed abnormalities consisting of punched out lytic lesions, osteoporosis or fracture in 93% of our patients, most common abnormality being the lytic lesion (63%). This is comparable to a study of 268 patients by Mai Yu Jie et al, in which lytic lesions were found in 63.7% of patients and 22.7% had pathologic or compression fractures [10].

Peripheral smear examination showed increased rouleax formation in all the cases. Hypochromia was evident in 13 cases, all the rest showed a normocytic normochromic anemia. Platelet count was normal in majority of cases. One case of plasma cell leukemia was noted which presented with bone pain and fatigue and on examination the patient had hepatosplenomegaly and lymphadenopathy. The bone marrow aspirate showed 32% of plasma cells. This is in accordance with the various reports of authors on leukemic mylomatosis who have observed that plasma cell leukemia resemble an acute leukemia, with high incidence of hepatosplenomegaly and less bone involvement. In a study of 7 cases of plasma cell leukemia by Mital Chokshi et al, anemia, bone pain, splenomegaly or hepatomegaly thrombocytopenia and plasmacytosis in peripheral blood were the most striking findings [11].

Bone marrow aspiration revealed a plasmacytosis ranging from 12%-90%. In 29% of cases plasma cell percentage was more than 50. Subramanian et al observed that more than 50% plasma cells in the marrow smears indicate a bad prognosis [12].

In the present study anemia (Hb<10g/dl) was noted in 86% of patients and the median hemoglobin value was 8.35 g/dl. A hemoglobin level of <8/dl was detected in 38% of patients. The mechanism of anemia in most patients is inadequate production of red blood cells due to either erythropoietin deficiency or pronounced marrow replacement by myeloma cells or from accompanying renal failure. In some patients anemia is disproportionate to renal failure or marrow involvement and is thought to be due to cytokine mediated marrow suppression [2,13].

Thrombocytopenia is seen in advanced cases of multiple myeloma. In this study 7% of patients had a platelet count of <1.5 lakhs/mm^3 which included the case of Plasma cell leukemia.

Serum electrophoresis showed a localized M Band in 93% of cases. The pattern appeared normal in 4 cases out of which 2 cases on immunofixation showed monoclonal lambda light chain. Thus immunofixation is more sensitive in identifying small amounts of M protein. According to the literature 1-2% of all myeloma can be Non secretory and in such cases immunofluorescence or immunohistochemical staining are reported to be valuable. It is suggested that electrophoresis becomes positive in myeloma when atleast 20gms of tumour is present. In a study of 1027 patients by Kyle R.A. et al a localized M band was identified in 82% of patients. The remaining patients had hypogammaglobulinemia or a normal appearing pattern [2].

Biochemical data helps to assess tumor mass and renal involvement. In this study the serum

creatinine level was increased in 50% of the patients and 24% of patients had values >2mg/dl. Serum creatinine value showed a significant statistical correlation with survival in the current study. The major cause of renal failure are myeloma nephropathy, and hypercalcemia. Other causes include dehydration, hyperuricemia and amyloidoisis.[2]Hypercalcemia was noted in 18% of patients. Increased osteoclastic activity with inhibited osteoblastic activity results in hyperclacemia [(2)].

Serum Albumin has also been identified as a reliable prognostic factor in various studies. In the present study the mean serum albumin level obtained was 3.48g/dl. A correlation with prognosis could not be obtained for serum albumin in our study. Serum Beta 2 microglobulin was assessed in 55 patients. Mean value obtained was 4.82mg/l. Elevated beta 2 microglobulin level have been repeatedly shown to have independent prognostic value in myeloma. In this present study also this showed significant correlation with survival. When combined with serum B2 Microglobulin, serum albumin was known to add significantly to prognostication. A study by Bettini R, et al found that the serum level of β_2M was inversely correlated with the survival while a direct correlation was found between the serum albumin and the survival [(14)].

On comparing our data with the study by Kyle R.A. et al, we found that the laboratory findings of the myeloma patients in our centre had some differences; more severity of anemia and renal insufficiency as evidenced by increased creatinine value.(Table 3). This may be due to the advanced stage of presentation in our cases.

Patients were staged according to the International Staging System for myeloma as stage I, II, III. According to Griepp et al, the median survival for each stage were as follows: Stage I- 62 months stage II-45 months and stage III- 29 months (15). This is comparable to the present study since of the patients in which follow up was obtained, 80% of patients in stage III and 32% of patients in stage II expired. Stage I patients showed a 100% survival rate. (Table 2)

Conclusion

Our data suggests that the level of Serum beta 2 microglobulin and serum creatinine may be used as reliable prognostic indicators for Multiple Myeloma .The recently developed International Staging system for Myeloma will be useful in identifying various risk groups and will have better prognostic and therapeutic value.

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