Original article:

An analysis of clinical profile and laboratory parameters in multiple myeloma

[1]Aadarsh Sharma, [2]Dr.Swaroop N Shashidhar, [3]Karuna Rameshkumar, [4]L.N Samaga, ,

[5] Kishan Prasad HL, [6]Jayaprakash Shetty K

Post Graduate and Tutor[1], Assistant Professor[2]

[1] - Department of Pathology, KSHEMA,Mangalore,Karnataka, India

[2] - Department of Pathology, Karuna Medical College, Vilayodi, Chittur, Kerala, India

Corresponding author: Dr. Swaroop N Shashidhar

ABSTRACT

Background: Bone marrow (BM) examination continues to be the gold standard in establishing the diagnosis of multiple myeloma (MM). Along with clinical, radiological and laboratory parameters, the histological criteria for grading and staging will help in determining the prognosis as well assist to determine the therapeutic strategies.

Objectives: To evaluate and correlate the clinical and radiological findings with laboratory parameters in the diagnosis and staging of multiple myeloma in the southern part of the state of Karnataka.

Materials and methods: The study was both retrospective and prospective study from January 2013 to June 2015. The clinical and radiological findings, laboratory parameters and BM examination were analyzed and correlated.

Results: 50 patients were included in the study. The most common morphologic type of MM was mature myeloma followed by plasmablastic type accounting 50% and 34% each. Amongst the various prognostic variables, haemoglobin value and the presence of bone lesions in single or multiple sites were found to be statistically significant

Conclusions: The patients with plasmacytic morphology have a better prognosis compared to those with plasmablastic subtype. Application of the revised International myeloma working group (IMWG) where one myeloma defining event (MDE) is adequate for the diagnosis even without the organ damage was comparable to Durie and Solomon diagnostic criteria in inclusion of the patients for the study. The Durie and Salmon criteria and staging still holds good in setups with limited resources for further management of myeloma patients.

Key words: Bone marrow; Multiple myeloma, morphology

INTRODUCTION

Multiple myeloma (MM) is a haematological malignancy characterized by neoplastic proliferation of monoclonal plasma cells and expansion of the malignant plasma cells throughout the bone marrow (BM) leading to cytopenias, bone resorption and production of monoclonal immunoglobulins known as Mcomponent or paraproteins. It accounts for 1% of all malignancies and about 10% of hematological malignancies .Although the M-component can also be found in benign or pre malignant conditions (e.g. Monoclonal gammopathy of undetermined significance, MGUS) its presence usually indicates a malignant condition such as MM[1]. The typical findings are destruction of bone (causing pain in bone mostly due to pathological fracture), hypercalcaemia, paraprotein in urine and/or blood, immunodeficiency, anaemia, bone marrow failure and renal failure. A combination of radiological, laboratory and pathological findings provides the

diagnosis of MM. Diagnosis of MM according to Durie and Salmon has major and minor criteria[2].

The major criteria include:

- Marrow plasmocytosis (≥30%)
- Plasmacytoma on Biopsy
- M-component serum : IgG>3.5 g/dl,IgA>2g/dl

The minor criteria comprise of:

- Marrow plasmacytosis (10-30%)
- M-Component –present but less than above
- Lytic bone lesions
- Reduced normal immunoglobulin (<50% normal)

  -IgG<600mg/dl, IgA<100mg/dl, IgM<50 mg/dl.

The diagnosis can be made with presence of one major and one minor criterion or the presence of three minor criteria, having the first two criteria is mandatory.

The proposed Durie and Salmon clinical staging system of 1977 has been replaced by The International Staging System (ISS) but Durie and Salmon diagnostic criteria and staging is still being used in many centres. Many advances like MRI, immunophenotyping, FISH and markers like beta-2 microglobulin and serum IL-6 level estimation has come to the picture in determining the prognosis[3].

However, quantifying the volume of plasma cell infiltration and assessing the degree of plasma cell dysplasia in the bone marrow aspirate and trephine biopsy is still remains the gold standard[4].MM is not uncommon in India with reported incidence of ranges from 0.5 to 1.2 per 100,000[5].The availability of investigations like β2microglobulin levels, Interleukin-6, labelling index, MRI etc is restricted to very few centres in India.

OBJECTIVE

The objective of the current study is to correlate the clinical presentation and laboratory parameters in patients diagnosed with multiple myeloma and apply the international multiple myeloma working group criteria in diagnostic and prognostic evaluation in comparison with Durie and Salmon criteria.

MATERIALS AND METHODS

Study period:

Retrospective period was from 1/1/2013 to 31/08/2014

Prospectively the period was from 1/9/2014 to 31/06/2016

SOURCE AND METHODS

For retrospective study, the case records and the laboratory parameters of the patients who were diagnosed as multiple myeloma were obtained from the medical records department and the slides from the archives of the department.

For the prospective study, the clinical and the laboratory parameters of the patients presenting to the OPD who were confirmed with diagnosis of myeloma after the clinical diagnosis were included.

The bone marrow aspirate smears were reviewed and the diagnosis was confirmed. Whenever biopsy slides were available, the findings were correlated with the aspirate findings. Follow up was done for both the groups.

SAMPLE SIZE AND SELECTION

50 (Fifty) including both retrospective and prospective cases.

a. INCLUSION CRITERIA

- Clinical history
- Bone marrow aspiration and biopsy

b. EXCLUSION CRITERIA

- The patients' profile not fitting with diagnostic criteria in spite of clinical history.

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- Patients suspicious of MGUS

CLINICAL PROFILE

The patients' presenting complaints were noted. Whenever there was a suspicion of pathological fractures, imaging studies were done to confirm the diagnosis.

LABORATORY PARAMETERS

Hematology - Hemogram, Erythrocyte Sedimentation Rate (ESR), Peripheral smear, Bone marrow aspiration, Trephine Biopsy

Biochemistry - Blood Urea, Serum Creatinine, Serum calcium, Electrophoresis for abnormal Serum protein, Urine Bence Jones Proteins, Serum Albumin

TECHNIQUES

1. Leishman Stain for peripheral smear and bone marrow aspiration smears.

2. Hematoxylin and Eosin stain for bone marrow biopsy sections.

DATA MANAGEMENT AND STATISTICAL ANALYSIS

1. Descriptive statistics for demographic data.

2. SPSS 21 was used for analysis of results of clinical profile and laboratory parameters.

RESULTS AND ANALYSIS

A total of 50 patients were confirmed with the diagnosis of MM in this study.

Clinical presentation

1. Age

The age of presentation ranged from 41 to 80years with an average age of 62 years. The highest peak i.e. 9 patients (18%) were aged between 71 and 80 years and 16 patients(32%) were in the second highest peak between 61 and 70 years. 19 patients (38%) were found in the age between 51 and 60 years. The rest 6 patients were in the age between 41 and 50 years (12%).

2. Gender

The male to female ratio was 1.95:1, with a male predominance by nearly two folds. 33 patients were males (66%) and 17 (34%) were females.

3. Presenting complaints

Lower backache was the most common, 22 (44%) patients followed by generalized weakness 15 (30%) patients. 2 (4%) patients had fracture of humerus and 1 (2%) patient presented with femoral fracture. There were associated complaints like cough, urinary tract infection and fever.

4. Radiological findings

Out of 50 patients, radiological data were available in 47 patients. The skeletal lesions were present in these patients in the form of osteoporosis, osteolytic lesions and fractures; either in single or in combinations. Osteolytic lesions at various sites were found to be the commonest radiological findings which were seen in 45 (97.8%) patients. 27(57.4%) had radiological evidence of fractures at various sites. In 17(37%) patients, radiological evidences of only osteoporosis were observed.

Laboratory parameters

1. Hemoglobin: Hemoglobin values ranged from 3.9g% to 14.40g% with a mean of 9.11g%. Hemoglobin was > 7 g % in 10 (20%) patients.

2. Peripheral Blood picture: 70% (35) of patients had NCNC anemia. 8 (16%) patients had dimorphic anemia. MCHC anemia was seen in 2(4%) patients. Pancytopenia was observed in one patient.In42 patients, rouleaux formation was observed in the peripheral smear.

3. Serum Calcium: 12 patients had normal calcium levels. 21 (42%) patients had hypercalcemia.

4. Serum Creatinine: In 14 patients, the creatinine level was more than 2mg/dL indicating the impaired renal function.

5. Serum Albumin: 88% had hypoalbunemia and normal range was observed only in 6 patients.

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6. Serum electrophoresis: Data was available for 43 patients. 38 (97.4%) cases had the M band in the gamma (γ) region and 1 case (2.5%) had it in the beta (β) globin region. There was no M band in the α region.

Urinary Bence Jones protein was not observed.

Bone marrow aspiration and biopsy

Bone marrow aspiration data was available for 44 patients. The percentage of plasma cells ranged from 10% to 85% with a mean of 45.50%. Majority of the patient i.e. 22(50%) were of mature myeloma type followed by plasmablastic type in 15 (34%) patients. 6(14%) patients were of immature type. Only 1(2%) patient featured in the category of intermediate myeloma.

Bone marrow biopsies were reviewed and the following parameters were assessed: cellularity, plasma cell morphology and their infiltration pattern. Well differentiated histological type of myeloma was the predominant type in this study with 17 (39.5%) followed by the rest of the histological type i.e. intermediate differentiated and poorly differentiated histological type of 13 (30.2%) each.

Normoblastic type of maturation was observed. When the hematopoiesis was correlated with morphology of plasma cells, it was observed that in mature plasmacytic type, the hematopoiesis was within normal range in 14(63%) patients.

Table 1: Relation between hematopoiesis and percentage of plasma cell in BMA

Parameters	**Nature of bone marrow in BMBs**	**MORPHOLOGICAL TYPE**				**P value**
		PLASMACYTIC		PLASMABLASTIC		
		Count	%	Count	%	
Hematopoiesis	NORMAL	14	63.60%	0	0.00%	**<0.001**
	SUPPRESSED	8	36.40%	15	100.00%	

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As elaborated in the table no.1, the relation between hematopoiesis in the BMB and the plasma cell infiltration BMA was found significant.

The correlation between the percentage of plasma cells in bone marrow biopsy and the morphology type of myeloma in BMA was found to be significant with p value less than 0.001 as shown in the Table 2.

Table 2: Percentage of PC infiltrate in Bone Marrow Biopsy

Parameter	**PC% in bone marrow biopsy**	**MORPHOLOGICAL TYPE**				**P value**
		PLASMACYTIC		PLASMABLASTIC		
		Count	%	Count	%	
BMB%PCs	<=20%	0	0.00%%	2	13.30%	**<0.001**
	20-50%	4	18.20%	11	73.30%	
	>50%	18	81.80	2	13.30%	

The most common pattern observed was interstitial pattern in 20(46%) patients followed by the diffused pattern which was observed in 17(40%) patients. 4(10%) patients and 2(4%) patients had mixed and nodular pattern of infiltration respectively.

Comparison of diagnostic criteria

As per the Durie and Salmon diagnostic criteria, the 50 patients who were included in the study had one major (Marrow Plasmocytosis (≥30%) in aspiration or Plasmacytoma on Biopsy) and one minor criteria(Presence of M-Component /Lytic bone lesions). As per IMWG criteria only 38 patients fulfilled all three criteria (Monoclonal plasma cells in marrow ≥10%, monoclonal protein in serum or urine, evidence of myeloma related organ or tissue impairment) For 12 patients, only 2 parameters were available. Thus DS criteria helped to include more patients.

STAGING

DURIE SALMON STAGING- Majority of the patients were found to be in Stage III, having 25 (57%). 12 (27%) patients were in Stage I. The number patients present in Stage II were 7(16%).

FOLLOW UP - The follow up period ranged from 6 months to three years. Among the 50 patients 33 (66%) patients had follow-up details while 17 patients were lost to follow up. 32(64%) patients are being followed up in the oncology department. 1 patient had expired.

DISCUSSION

In many developing countries including India continue to follow the Durie Salmon Staging (DSS) system as well as the diagnostic criteria laid by Durie and Salmon. Serum β2 microglobulin level

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used for staging is done only in a few centres. The serum free light chains analysis is also not done in many centres

The current study followed the criteria laid by Durie and Salmon and its system to stage the patients is based on serum calcium, serum creatinine, serum electrophoresis and skeletal survey by plain radiography. Computed tomography (CT) and magnetic resonance imaging (MRI) were considered wherever available. When IWMG criteria were applied, where all three criteria were mandatory including end organ damage, only 38 patients could be included. By applying revised IMWG criteria where one of the myeloma defining events is adequate to diagnose multiple myeloma, all 50 patients diagnosed by DS (WHO) can be included in the study. By applying bone marrow aspiration and imaging studies which are the common diagnostic techniques, used in the evaluation of myeloma, revised IMWG diagnostic criteria can be used. This will also help in early diagnosis in the patient.

Table 3: Comparison of distribution of M component with other studies

Study	**No of cases with M band**	**M band in Gamma Region**	**M band in Beta region**	**M band in Alpha region**	**BICLO-NAL**
Tripathy S 2012[5]	16	14 (87.5%)	2(12.5%)	NIL	NIL
Col.G S Chopra et al[6]	94	84(89%)	7(8%)	NIL	2(2%)
Present Study	39	38 (97.4%)	1(2.5%)	NIL	NIL

Renal impairment is a known complication of multiple myeloma. In the present study,36 patients had serum creatinine levels less than 2mg/dl. 14 patients had the creatinine value of more than 2mg/dl. The findings are comparable to other studies as given below.

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Table 4: Comparison of serum creatinine with other studies

Study	No. of cases	S. Creatinine<2 mg/dl(%)	S. Creatinine>2 mg/dl(%)
Blade et al[7]	423	77.7	22.2
Almueilo S H[8]	64	73.4	26.6
Present Study	50	72	28

Comparison of plasma cells in BMA and bone marrow BMB

The correlation between variables in BMAs and BMBs was significant in the present study. It was observed that as the plasma cells in the aspiration increased, in bone marrow biopsy decreased haematopoiesis and diffuse pattern of infiltration were seen. The following table summarises the correlation between aspirate and biopsy. (Table-5)

Table 5: Correlation between the BMA and BMB findings

Parameters	**Nature of bone marrow**	**MORPHOLOGICAL TYPE**				**P value**
		PLASMACYTIC		PLASMABLASTIC		
		Count	Column N %	Count	Column N %	
Hematopoiesis	NORMAL	14	63.60%	0	0.00%	**<0.001**
	SUPPRESSED	8	36.40%	15	100.00%	
	<=20%	0	00.00%	2	13.30%	**<0.001**

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	20-50%	4	18.20%	11	73.30%	
BMB%PCs	>50%	18	81.80%	2	13.30%	
	Diffuse	2	9.10%	12	80.00%	**<0.001**
Pattern	Interstitial	17	77.30%	1	6.70%	
	Mix	3	13.60%	1	6.70%	
	Nod	0	0.00%	1	6.70%	

Morphological Variants of Myeloma

Mature myeloma was the most common variant in the present study and the least common variant was the intermediate variant of myeloma. The results was in contrast with the studies done in Ludhiana by Kuriakose et al[9] where the most common variant was immature myeloma and no cases presenting as intermediate myeloma. The study done by Griepp et al at the Mayo clinic has found the intermediate myeloma as the most common variant followed by mature myeloma and plasmablastic myeloma to be the least common variant[10]. With reference to morphological features on BM aspiration and biopsy, Bartl et al. had first published the histological classification and staging criteria. Plasma cells were classified into 2 categories: plasmacytic – with predominantly non nucleolated PCs and plasmablastic – with predominantly nucleolated PCs[11].In the present study, plasmacytic morphology accounted 52% and plasmablastic morphology was of the rest 48%.

Association of pattern of infiltration and stage of disease

In the present study, bone marrow biopsies of 43 cases were studied for pattern of plasma cell infiltration. Most common pattern was interstitial, followed by diffuse, mixed and nodular pattern. The association of pattern of infiltration with the Durie and Salmon staging at the time of diagnosis has been suggested. Subramanian et al. has reported 64% of cases with Stage III disease had diffuse pattern of infiltration[12].In the present study, all the cases with nodular and diffuse pattern of infiltration had stage III disease. In addition, 12 (28%) cases with plasmablastic morphology had diffuse pattern of infiltration.

Staging

The current study followed the DSS system and staged patients based on hemoglobin, serum calcium, serum creatinine, serum electrophoresis and skeletal survey by plain radiography. Computed tomography (CT) and magnetic

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resonance imaging (MRI) were considered wherever available.

The maximum number of patients was seen in the third stage similar to the study by Subramanium et al. This probably suggests the common pattern observed in Indian patients when they present late to the hospital. This associated with poor compliance to treatment may result in poor outcome.

Table 6: Comparison of staging with other studies

Study	No. of Cases	Stage I (%)	Stage II (%)	Stage III (%)
Griepp et al,[10] 1985	100	7	70	23
Stiffer S et al,[13] 2008	59	13.6	39	37.4
Subramanium et al,[12] 2009	55	7.3	16.4	76.4
Present Study,	50	27.3	15.9	56.8

CONCLUSION

The present study highlights the correlation between clinical presentation, radiological findings and laboratory parameters in establishing the diagnosis of multiple myeloma. Throughout the evolution of diagnostic criteria of multiple myeloma from Durie and Salmon's time through WHO and now revised IMWG, the bone marrow aspirate study has remained one of the important criteria, though the percentage of plasma cells have varied.

The present study has shown the application of revised Durie and Salmon criteria and its system of staging in the limited resource setting for diagnosis. Bone marrow study is of importance especially in India because assessment for response to treatment with the necessary biochemical parameters is not available in most centres.

The other findings which include correlation of presence of anemia, levels of serum creatinine with the percentage of plasma cells and morphology and the number of patients presenting in different stages are comparable to other studies in literature.

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Figure 1: BMA smear showing sheets of immature, atypical plasma cells, and plasmablasts (Leishman stain;40x)

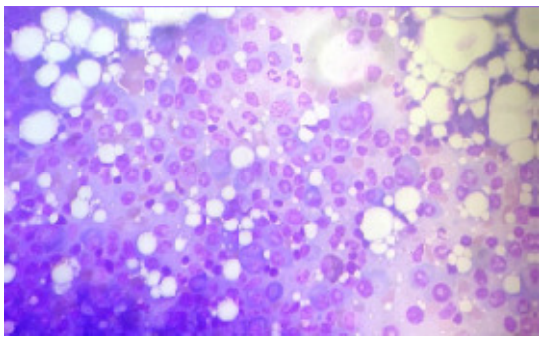
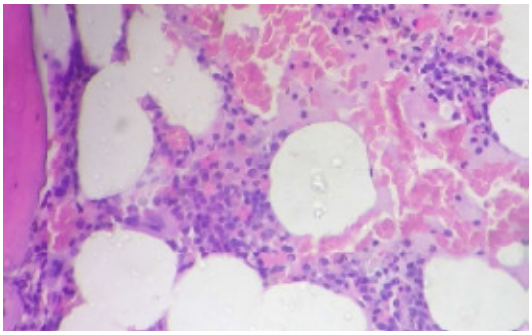


Figure 2: Bone marrow biopsy showing interstitial patterns of plasma cell infiltration, H and E(40x)



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