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Original Research Article

Staging of Plasma Cell Myeloma and its Correlation with Clinico Pathological Profile in a Tertiary Hospital (JNIMS)- A 3 Year Study

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Abstract

Background: Plasma cell myeloma (PCM) is a neoplastic proliferation of plasma cells, confined in bone marrow usually associated with an M protein in serum and/or urine and evidence of organ damage related to the disease. Various staging systems and risk stratification are being proposed to prognosticate the cases.

Aims and objectives: To categorize the newly diagnosed or treatment naïve PCM cases attending JNIMS into stages and to correlate the different stages with the clinicopathological features.

Method: This is a retrospective cross-sectional study. All the information were obtained from bone marrow registers maintained in the Pathology Department and Hematology unit, Medicine Department, JNIMS Imphal. Newly diagnosed and untreated patients of PCM coming to JNIMS over a period of 3 years from July 2018 to July 2021 were included.

Results: 20 PCM patients were included in the study. Majority of the cases were in the age group of 5^{th} to 6^{th} decades (range: 38 to 79 years) and a mean age of 58 years. 9(47%) patients were male, and 11(53%) patients were female with male-to-female ratio of 1:1.2. 11(55%) were presented with backache and other bone pains, 8(40%) had generalized weakness and easy fatigability,1(5%) had symptoms of spinal cord compression. 8 patients (40%) were in stage I,10 patients (50%) were in stage II and 2 patients (10%) were in stage III. Stage I patients had equal proportion of IgA and IgG PCM. Regarding distribution of light chain restriction 3(37.5%) cases had kappa and 5(62.5%) had lambda light chain restriction. Stage II patients had predominantly IgG PCM (60%) and lambda light chain restriction. One case of plasma cell

leukemia presenting in stage III with intermediate risk molecular profile (t 4;14) was also included. All the different stages had significantly variable beta-2 microglobulin level.

Conclusion: We concluded that though most patients were in 6th decade, however we got significant involvement in young age group. Bone pain mostly low backache was the most common presenting symptom along with weakness and fatigue. The majority of the patient had IgG PCM. As staging of the disease has prognostic implication, this finding needs to be explored further.

Keywords: Plasma cell myeloma, M band, IgG PCM, IgD PCM, IgM PCM, IgA PCM, IgE PCM, light chain restriction.

Introduction

Plasma cell myeloma (PCM) is a neoplastic proliferation of plasma cells mainly confine to bone marrow usually associated with an M protein in serum and/or urine and evidence of organ damage related to the disease[1]. PCM accounts for 10% of all haematological malignancies and 1% of all neoplastic disorders with average age of presentation in the 6th and 7th decade of life.

Exact incidence in India is not clear, but data from 6 population based cancer registries shows 0.3 to 1.9 per 1,00,000 men and 0.4 to 1.3 per 1,00,000 women, with highest incidence in Delhi[2]. The diagnostic criteria for plasma cell disorders had been set by international myeloma working group,2009. The details are given in table 1

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Table. 1: Diagnostic criteria of plasma cell disorders by international myeloma working group (IMGW)

	MGUS	SMOULDERING MYELOMA	SYMPTOMATIC
Proportion of plasma cell in bone marrow	<10%	≥10%	≥10%
M protein in serum	<30g/L	≥30g/L	Detectable in serum and/or urine
End organ damage (CRAB)	No	No	Present

There are different types of PCM based on monoclonal immunoglobulin produced by the malignant plasma cells such as IgG, IgD, IgM, IgA, IgE, light chain PCM types. About 3% cases may present without a detectable M protein, these are categorized as nonsecretory type.

Various risk stratification has been proposed based on the molecular finding[3]. International Staging System (ISS) for plasma cell myeloma have laid down certain criteria for staging. The details of the staging system are given in table 3.

Table 2: showing the diagnostic criteria for plasma cell myeloma adopted by IMGW

Both criteria must be met: 1.Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma 2.Any one or more of the following myeloma-defining events: (a) Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically: ***Hypercalcemia***: serum calcium.1mg per dL(0.25mmol per L) higher than the upper limit of normal or> 11mg /dL (>2.75mmol per L) ***Renal insufficiency***: creatinine clearance <40ml per minute per 1.73m^2(0.67ml per second per m^2) or serum creatinine >2mg per dl ***Anemia***: hemoglobin >2g per dl (20 g per L) below the lower limit of normal, or a hemoglobin value <10g per dl (100g per L) ***Bone lesions***: one or more osteolytic lesions on skeletal radiography, CT, or positron emission tomography/CT (b) Clonal bone marrow plasma cell ≥60% (c) Involved: uninvolved serum free light chain ratio≥100 (involved free light chain level must be ≥100mg per L) (d) More than one focal lesion on MRI studies (≥5mm size)

Table 3: International staging System (ISS) for plasma cell myeloma

Stage	Criteria	Median survival(months)
I	Serum beta-2 microglobulin <3.5g/dl Serum albumin≥ 3.5g/dl	62
II	Not stage I or III	44
III	Serum beta-2microglobulin≥5.5mg/L	29
There are two categories for stage II: (1) Serum beta-2 microglobulin <3.5mg/L but serum albumin <3.5g/dL (2) Serum beta-microglobulin of 3.5 to <5.5mg/L, irrespective of the serum albumin level		

Aims and objectives

The aim was to categorize the newly diagnosed or treatment naïve PCM cases attending JNIMS into stages and to correlate the different stages with the clinicopathological features.

Material and Methods

This is a retrospective cross-sectional study done at JNIMS hospital. Newly diagnosed and untreated patients of plasma cell myeloma coming to JNIMS over a period of 3 years from July 2018 to July 2021 were included in this study. Diagnosis was confirmed by the 2009 updated criteria of International Myeloma Working Group (Table no.3). Patients with MGUS, other co-existing malignancy, smouldering plasma cell neoplasm, solitary plasmacytoma of bone were excluded from the study. Informed consent and ethical clearance were taken. Cases were evaluated based on the history, clinical examination findings and laboratory and imaging investigations reports available in the

respective Department. In certain cases, the archived bone marrow aspirate smears and biopsy sections were reviewed. Staging of the cases was done on the basis of International Staging System (ISS). All the data was entered into Microsoft Excel 2010 spreadsheet and transferred into SPSS-22 version. Cleaning all the data then we analysed by using descriptive statistic like frequency, mean, SD etc. were applied. Analytical statistic like chi-square and F-Test was applied. If the p –value is <0.05, we take as statistically significant.

Characteristic of the study population

20 cases of plasma cell myeloma mostly from 5th and 6th decades with the age varying from 38 to 79 and a mean age of 58 years; 9(47%) patients were male, and 11(53%) patients were female with male-to-female ratio of 1:1.2(fig.1). 11(55%) presented with backache and other bone pains,8(40%) had generalized weakness and easy fatigability,1(5%) had symptoms of spinal cord compression. Majority of the patients (50%) presented in stage II.40% of the cases were in stage I, only 10% in stage III.

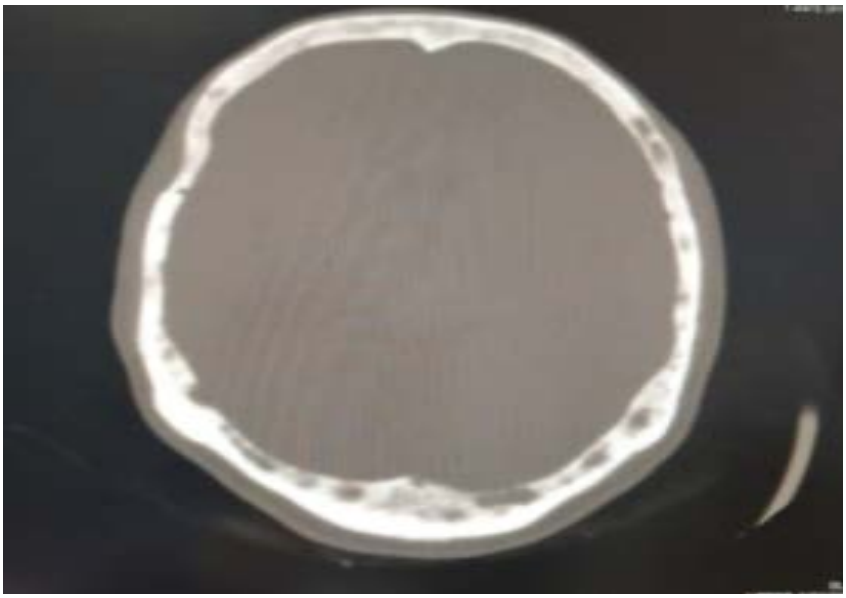

Figure1: Lytic lesion of skull in plasma cell myeloma patient.

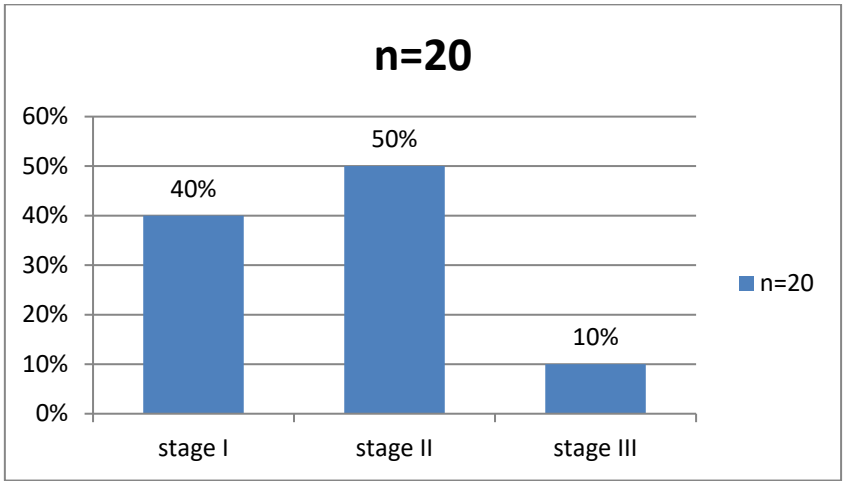

Figure 2: Bar chart showing stage wise distribution of the cases

Clinicopathological findings of stage I PCM

Among the 20 cases, 8 patients (40%) were in the stage I. Male female ratio was 1:1.6. The average age of presentation was 58 years. Stage I patients had a mean bone marrow plasma cell of 36.3±19.3%. The mean beta-2 microglobulin was 0.66±0.62. Among these patients, one had only 6% plasma cell in the bone marrow aspirate however there was diffuse sheets of plasma cell in the bone marrow biopsy. Bone marrow aspirate show 6 hypercellular,1 normocellular and 1aparticulate marrow. Bone marrow trephine biopsy was done in 7 cases. All biopsies show interstitial excess of plasma cell and in addition, one case showed sheets of plasma cell completely replacing the normal haematopoietic elements in some of the intertrabecular spaces. In another case, a few paratrabecular aggregates were noted. M band was detected in all the 8 cases with 3 cases show kappa light chain. These cases showed IgA band on IFE. The remaining 5 cases show lambda light chain with IgG M band on IFE (table 4).

Clinicopathological findings of stage II PCM

Among the 20 cases, 10 cases (50%) were in the stage II with equal proportion of males and females. The average age of presentation was 59.3 and mean plasma cell of 43.8±15.40% in the bone marrow. The mean beta-2 microglobulin was0.85±0.53. Bone marrow aspirate smear showed hypercellular marrow in 5, pauciparticulate in 1 and aparticulate in 4 cases. Bone marrow trephine biopsy was done in 9 cases. All the 9 biopsies showed interstitial excess of plasma cell. In addition, 5 cases show sheets of plasma cell in the marrow space and in 2 cases intertrabecullar space was completely replaced by plasma cell nodules .M band was detected in all cases.4 cases show kappa light chain, and 6 cases show lambda light chain. Among the kappa chain, two had IgG band and 2 had IgA. Among the lambda chain, 4 had IgG band and 2 had IgA (table 4).

Clinicopathological findings of stage III PCM

Among the 20 cases, 2 cases (10%) were in stage III. Average age of presentation was 58 years and average plasma cells was 35.5±13.4% in the marrow. The mean beta-2 microglobulin was 5.65±0.21. One had plasma cell leukemia with 32% circulating plasma cells. On fluorescence in situ analysis (FISH), t(4;14) was detected. On flowcytometric immunophenotyping analysis, the plasma cells expressed CD45(dim), CD38 (bright), CD56, CD117 and CD 138 (bright) and negative for CD19 and CD10. There was no rouleaux formation. On serum electrophoresis a small M spike was noted, and IgG band was detected on IFE. Kappa light chain restriction was detected. She did not respond to treatment and succumbed after 3 months of diagnosis. The other patient had normal karyotype with diffuse sheets of plasma cell in the bone marrow biopsy. Kappa light chain restriction was detected (table 4).

Table 4: showing the clinicopathological findings in different stages of the disease.

Parameter		Stage 1 8(%)	Stage 2 10 (%)	Stage 3 2 (%)	Total	P-value
Sex	Male n(%)	3 (37.5)	5 (50.0)	1(50.0)	9	0.859
	Female n(%)	5(62.5)	5(50.0)	1(50.0)	11	
Average plasma cell in marrow n(Mean±Sd)		36.3 ± 19.3	43.8 ± 15.40	35.5 ± 13.4	20	0.615

Type of PCM	IgG n(%)	4(50.0)	6(60.0)	1(50.0)	11	0.904
	IgA n(%)	4(50.0)	4(40.0)	1(50.0)	9	
Light chain restriction	kappa	3(37.5)	4(40.0)	2(100)	9	0.256
	lambda	5(62.5)	6(60.0)	0(0.0)	11	
Beta-2 microglobulin (Mean±Sd))		0.66 ± 0.62	0.85 ± 0.53	5.65 ± 0.21	20	0.000* <0.05

Discussion

Diwan AG et al.[4] reported that sixth decade is the common age group with a mean of 62 years. However, in our study we found majority of cases in7th decade with a mean 0f 71 years. Similarly in the series of Kyle RA et al.[5], reported a higher mean age of 66 years with 2% younger than 40 and 38% older than 70 years. In contrast, Kumar L et al.[6], reported that in India the median age is 55 years;2 decades earlier than that in USA. Madu AJ et al.[7] (2014) found male: female ratio 1.2:1 and Kumar L et al found 1.5:1.However in our study, we found a male:female ratio of 1:1.2.This may reflex difference in sample size and geographical variation.

In the series of Diwan AG et al.[4], bone pain was the commonest symptom (85%).Similar finding were reported by Madhu AJ et al.[6],(78.1%) and Rahman AAU et al.[8],(78%) .However in our study 55% patient complaint of bone pain. A similar finding was reported by Durie BGM et al.[9], (58%). In our study symptoms of spinal cord compression was seen in 5%. In contrast, Riccardi A et al.[10] reported symptoms of spinal cord compression in 34%, Dancaster CP et al.[11] in 15%, Madu AJ et al.[6] in 13.8% and Diwan AG et al.[4] in 10%. Kyle RA et al.[5], Diwan AG et al.[4] and Madu AJ et al.[7] found positive M band in 82%,100% and 90.5% respectively. Similarly, we found M band in 100%. Kumar L et al.[6] found 6.4%,12% and 81.7% in stage I,II and III, whereas Li SD et al.[12] found it to be 17.2%, 47.5% and 35.5%. Dimopoulos MA et al.[13] found 29%,38% and 33% in stage I,II and III and we found the same in 40%, 50% and 10% respectively.

Conclusion

We concluded that though most patients were in 6th decade, but we got significant involvement in young age group. Bone pain mostly low back ache was the most common presenting symptom along with weakness and fatigue. In the evaluation of a suspected case of PCM, bone marrow trephine biopsy is strongly suggested as the criterion of >10% plasma cells may be missed on bone marrow aspirate smears. Though the majority of the patient had IgG PCM but stage I disease had equal distribution of IgA and IgG type. As staging of the disease has prognostic implication, this finding needs to be explored further.

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