Prognostication of Histomorphological Characteristics in Multiple Myeloma

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Abstract

Objective: To study the utility of Bartl's histological grade and staging in the prognostication of multiple myeloma.

Methods: It was both a retrospective and prospective study done using all the cases of multiple myeloma from January 2001 to December 2002 with 2 years follow up. These cases were studied with special reference to Plasma cell morphology, biopsy growth pattern and tumor burden. In addition the effects of chemotherapy on post therapy marrow were also studied.

Results: During this period we studied 40 cases, of which 34 cases were Marschalko type, 6 cases Plasmablastic. The volume of infiltration, 29 cases showed > 50% of volume of infiltration, 3 cases showed 20-50% of volume of infiltration and 8 cases showed <20% of volume of infiltration. In the Pattern of involvement, Interstitial+Nodular type of involvement was commonly noted in 18 cases, interstitial type was seen in 15 cases and diffuse type was observed in 7 cases.

Conclusion: Bone marrow aspiration along with trephine biopsy is essential for the diagnosis and management of multiple myeloma.

Keywords: Multiple myeloma; Bartl's histological grading and staging

Introduction

Multiple myeloma (Naeim and Schiller, 1998) is the most frequent lymphoid disorder of bone marrow composed of mature and immature plasma cells. The clinical manifestations of this disorder result from the proliferation and accumulation of these cells, the effect of marrow replacement by them and pathologic manifestations are due to the over production of certain proteins and constituent polypeptide chains (M-component). Histological variables have been correlated with the clinical features to determine factors of value in predicting prognosis. Multiple myeloma (Bartl et al., 1987) has been classified into six histological types (1) Marschalko type (2) Small cell type (3) Cleaved type (4) Polymorphous type (5) Asynchronous type & (6) Blastic type. These six types were subsequently combined into 3 prognostic grades-Low, intermediate and high grades. The quantity of plasma cell burden in the biopsy has proved to be a useful criterion for histological staging of Multiple myeloma, supplementing any clinical staging system. Both these parameters Grade and Stage provide information required for decisions on treatment modalities, while the effects of therapy can be monitored by sequential biopsies. As our institution is a large referral centre with many patients of multiple myeloma being referred, we decided to study the utility of Bartl's histological grade and stage in the prognostication of multiple myeloma.

Aims and objectives

- **1.** To study all the cases of multiple myeloma from January 2001 to December-2002 cases with minimum of 2 years of follow up.
- **2.** To review the trephine sections using the Bartl's histological grading and staging system
- **3.** To study the prognostic importance of growth pattern and tumor cell burden in bone marrow biopsies
- **4.** To study the effects of chemotherapy on diagnosed cases by monitoring sequential biopsies.

Materials and Methods

Prior Institutional approval was taken for the study and It was decided to do a retrospective study using all cases of multiple myeloma diagnosed from January 2001 to December 2002, allowing minimum of 2 years follow up. The emphasis would be on giving histological grading and staging.

Inclusion criteria

- 1. All cases diagnosed as multiple myeloma using Salmon and Durie criteria.
- 2. All cases in which adequate and well processed trephine biopsy was available.
- 3. Cases with at least one year of follow up.

Exclusion criteria

1. Cases that are not fulfilling the criteria 2. Inadequate biopsy.

The diagnosis of multiple myeloma was based on Salmon and Durie criteria (Terpos and Rahemtullah, 2005; Foerster and Paraskevas, 1999). After explaining the procedure to the patient and to the attendant, informed consent was taken. Bone marrow aspirate and biopsies were obtained from the site of procedure; anterior or posterior iliac crest after giving local anaesthesia with 4% xylocaine. Peripheral smears and imprints were made; these were stained by,

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Leishman's stain. Biopsies were kept in B5 fixative solution, After 2 hrs; they were transferred into formalin solution, kept for overnight fixation. Next day morning they were transferred into EDTA- 9.5% HNO3 mixture for decalcification and then neutralization was done with glacial acetic acid. Then the biopsies were taken for routine tissue processing and sections were cut and H&E, and Reticulin stain done on biopsies.

Clinical details/ biochemical parameters/ imageology: At the time of bone marrow procedure the clinical details were obtained from the Patient. The hematologic, biochemical parameters were noted. The follow up details were obtained from the files of medical oncology department. For some patients who had stopped attending Out Patient Department messages were exchanged with the patient's attenders to enquire about the patient's condition.

Study of peripheral smear: Smears were taken at the time of biopsy, and were stained with leishman stain and studied the red cell morphology, and leucocyte count and platelets. Peripheral smear was also examined for rouleaux formation.

Study of bone marrow aspirate/imprint: Smears were stained with routine Leiashman stains and studied. In the Bone marrow first cellularity was assessed then percentage of plasma cells was calculated by counting 100 cells along with other hemopoietic precursors. The morphological classification was made using Bartl's (Bartl et al., 1987) morphological variants of plasma cells. It was done by counting 500 Plasma cells, the morphological categorization was done by Plasma cell variety which accounts more than 50%.Imprints were studied in the same manner in cases of dry aspirate.

Study of bone marrow biopsy: Biopsy sections were studied for adequacy of biopsy, cellularity, distribution of hemopoietic precursors, Plasma cells and fat spaces. Reticulin stain was used for grading marrow fibrosis. Volume of infiltration of plasma cells, i.e the amount of tumor burden and various pattern of involvement of plasma cells in the biopsy like interstitial, nodular, diffuse etc were studied.

Results

A total of 40 cases which had clinical, imageological, biochemical investigations for multiple myeloma were analyzed during the study period. All the 40 cases had bone marrow aspiration and biopsies. 4 cases of tissue plasmacytomas and 1 case of amyloid kidney were included in the study. There were 28 males and 12 females accounting for 70% and 30% respectively with a male: female ratio of 2.35:1. The median age at diagnosis was 55.

The most common clinical presentations were symptoms of anemia, bony pain and low back ache.

Peripheral smear study

The most common abnormality seen was moderate to severe anemia with raised ESR. Majority of the cases has showed rouleaux formation. 50% of the cases showed mild shift to left in their differential count.

Radiological study

21 cases showed lytic lesions and 10 cases had shown fractures. Ribs being the common site for lytic lesions followed by skull. In fractures the vertebrae's, were common site for fractures followed by ribs.

Biochemical parameters

Elevated Calcium levels were noted in 14 cases. We had Serum Protein Electrophoresis reports available in 26 cases with 19 cases showing M – peak in gamma region. Bence Jones Proteinuria was found positive in 4 cases with κ light chains and λ light chains in two cases each. Elevated serum creatinine levels were noted in 14 cases.

Bone marrow evaluation: Both bone marrow aspiration and biopsy was done in all 40 cases.

Bone marrow aspirate: Dry aspirate was noted in 11 cases. Increased cellularity was found in 17 cases. After a count of 500 plasma cells it was found that 34 cases had Marshalko type and 6 cases had Blastic type morphology. The percentage of plasma cells ranged from 8% to 92%, with a median of 60%. Other hemopoietic precursors like Erythroid and myeloid precursors were reduced in 24 cases.

Trephine biopsy: Trephine biopsy was done in all 40 cases. It showed normal cellularity in 26 cases, increased cellularity in 9 cases and varying cellularity in 3 cases. The volume of plasma cell infiltration in marrow i.e the amount of tumor burden was more than 50% in 29 cases and 20-50% in 3 cases and 08 cases showed less than 20%. Interstitial and nodular type of marrow involvement was the most common type pattern seen in 18 cases and interstitial pattern as seen in 15 cases , 7 cases showed diffuse type of marrow involvement. Reticulin fibrosis was seen 10 cases and Collagen fibrosis was seen in 2 cases.



Figure 1:



Figure 2:



Discussion

All the 40 cases were diagnosed based on Salmon and Durie Criteria into Multiple myeloma (Terpos and Rahemtullah, 2005; Foerster and Paraskevas, 1999). There is slight male predominance with M:F ratio of 2.35:1. In our study the median age of presentation was 55 years, which is similar to that reported by Advani et al. (1978); Venugopal



Figure 4:

et al. (1989). This suggests that Indian Patients present earlier than that reported in literature. The common clinical presentations were symptoms of anemia, bone pain and low back ache. In peripheral smear findings (Figure1) majority are of Normocytic normochromic anemia, red cells show rouleaux formation, WBC showed neutophilic leucocytosis with mild shift to left. ESR was elevated with a median value of 96mm/hr. Regarding Serum Protein Electrophoresis reports of 26 patients only available due to financial constraints of the patients. Out of 26 cases 19 patients showed M- spike in γ globulin region.

Bone marrow evaluation

Singhal et al. (2004) presented an approach to grading and staging of multiple myeloma on the basis of histomorphology of bone marrow biopsies which is based upon 1.Grading of myeloma cells, 2.The mass of neoplastic tissue within marrow and 3.The growth pattern of infiltrate. These histological criteria for Grading and staging have an impact on survival time of the patient. So, the Bone marrow biopsy is an essential investigative procedure in diagnosis of myeloma and may provide better choice in comparision to bone marrow aspirate as it provides histologic parameters of prognostic significance. Pich et al. (1997) found that mean percentage of plasma cell infiltration was higher in biopsies (50.3%) than aspirates (32.89%). The extent of marrow invasion by plasma cells can be exactly estimated on biopsy specimens only. The presence of Fibrosis has been associated with poor survival. The extent of fibrosis can only be assessed exactly by using biopsy in patients with multiple myeloma. The normal hematopoietic reserve can be studied on bone marrow biopsy, which is particularly important for monitoring therapy. During treatment, trephine biopsy may also detect 1.Relapse 2. Transformation to less favorable histological type 3. May document a stable phase in which further treatment may be withheld and 4.Regeneration of previously suppressed hematopoiesis. In our study the commonest morphological type is Marschalko variant (Figure 2) 34/40 cases as seen in Bartls classification of myeloma (363/674, 59%). And the next one is Plasmablastic type (Figure 3) 6/40 cases. Under Pattern of involvement in Bartls series the main growth pattern seen was Interstitial pattern only (Figure 4) but we have noticed the combination of Interstitial + Nodular pattern in 18/34 cases. Under the Volume of infiltration out of 40 cases 29 cases showed >50% of tumor burden, 3 showed 20-50% and 8 cases showed <20% when compared to Bartls series majority 216 showed <20% of infiltration,

Criteria	Sailer et al	A.Pich et al	Bartl et al	Niti Singhal et al	ourstudy
(no.of cases)	(153)	(150)	(674)	(11)	(16)
Grading					
WD	54	64	51	58	26
ID	42	21	23	56	0
PD	13	9	9	11	3
Volume of infiltration					
<20%	72	60	53	66	22
20-50%	62	21	25	52	22
>50%	44	9	15	1	27
Pattern of neoplastic cells					
Interstitial	65	57	46	61	22
Nodular	40	27	20	45	33
Diffuse	25	12	16	11	26
Fibrosis					
Absent	45	31	52	63	23
Moderate	25		23	31	37
Marked	22		13	10	
Hemopoiesis					
Normal	65			64	21
Poducod	55			12	26.5

WD-well differentiated ID-intermediatedifferentiation PD-Poorly differentiation

Table 1: We compared the median survival (in months) of histological parameters of bone marrow biopsies of myeloma patients in our study with other studies.

next 210 cases showed 20-50% of infiltration and 93 cases showed >50%. these variations are due to less number of cases we studied. Under fibrosis out of 40 cases, 10 cases showed reticulin fibrosis, accounting to 25% which is higher than the usually reported 10% fibrosis in myeloma again this may be due to less number of cases. Hemopoiesis was reduced in 33 cases.

Follow-up of patients

We had followed up with Patients in 20 cases that had completed their 6 cycles of chemotherapy. We observed the following post treatment changes in 11 cases. The changes included were as follows 1.Reduction in volume of infiltration, 2.Variable cellularity, 3.Stromal edema and 4.One patient developed AML-M2 20 months after diagnosis and treatment of myeloma. Acute myeloid Leukemia (AML) following treatment has been reported by Kyle etal. (1975), Pandita et al. (1987), Skinnider and Ghadially (1975). A case of Pure red cell aplasia was also noted on follow-up which was also reported earlier by Orchard et al. (1997).

Statistical significance

we tried to establish statistical significance with survival period in relation with other histological and clinical parameters. There was no correlation but we obtained significance with frequency test using Chi-square test. The test revealed significance for plasma cell morphology (p=0.012), Volume of infiltration of plasma cells (p=0.010), fibrosis (p=.022) and hemopoiesis (p=.046) for the 16 cases. The reasons for not getting any statistical correlation may be due to 1.Less number of samples, 2.Incomplete follow-up data. We compared the median survival (in months) of histological parameters of bone marrow biopsies of myeloma patients in our study with other studies (Table 1).

Conclusion

Bone marrow aspiration along with the trephine biopsy is essential for the diagnosis, prognosis and management of multiple myeloma. Using Bartl's histological grading and staging, the Marschalko type of plasma cells (85%) was most commonly observed followed by Plasmablastic (15%). The study of growth pattern, volume of infiltration (tumor burden), fibrosis, hemopoiesis is important. The P-value was significant in regards to plasma cell morphology, volume of infiltration, hemopoiesis and fibrosis. In Post treatment biopsies the common changes observed include reduction in cellularity, volume of infiltration and stromal edema. The changes like AML, Pure red cell aplasia was also noted as a part of Post treatment change which have been frequently reported .

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