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Original Research Article

A Clinicopathologic Study of Bone Marrow involvement in Hodgkin Disease

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Abstract

Introduction: Bone marrow involvement is not very common in Hodgkin Lymphoma (HL) and when present has an implication on the treatment strategies and prognosis of the patient. This study evaluates the various bone marrow changes seen in Hodgkins Lymphoma.

Methods: This is a one year retrospective study carried out in the cilinical laboratory of Kasturba Hospital, Manipal, India. All the patients diagnosed as HL on lymph node biopsy in whom bone marrow aspirate and biopsy were done were included in the study.

Results: A total of 24 patients of HL were included in the study. Bone marrow infiltration was seen in only 2 patients (8.3%). 4 cases (16.6%) showed Hodgkin associated changes in the bone marrow whereas remaining 18 patients (75%) did not show any changes in the bone marrow. The cases with infiltration showed presence of mononuclear variant of Reed Sternberg cells with increased eosinophils and lymphocytes. Hodgkin associated changes included increased eosinophils, monocytes and histiocytes, dyspoeticmegakaryocytes, presence of atypical lymphocytes and increased activated histiocytes but absence of RS cells or its variants. 18 patients received the ABVD chemotherapy regimen whereas 6 patients did not receive treatment in our hospital. Out of the 18 patients only one patient relapsed in one year follow up.

Conclusion: The incidenceof BMI is rare in HL as compared to Non Hodgkin lymphoma. The BMI can be in the form of frank infiltration or non infiltrative Hodgkin associated changes. The relationship between Hodgkin associated changesand prognosis of the disease is not yet clearly understood. However bone marrow examination is a must in all cases of HL to aid in appropriate staging and to decide on treatment modifications required.

Keywords: Hodgkin lymphoma; Bone marrow; Reed Sternberg cell; Histiocytes.

Keymessage: Bone marrow involvement in Lymphomas has an important impact on the course of the disease but in Hodgkin Lymphoma though BMI is not very common but the bone marrow can show other associated changes which can impose a difficulty in diagnosis so this study particularly emphasises on the careful evaluation of bone marrow in HL to avoid misdiagnosis.

Introduction

Hodgkin lymphoma (HL) is a malignant neoplasm of the lymphoid tissue found in the lymph nodes, spleen, liver, bone marrow, and other sites. Bone marrow involvement (BMI) at the time of diagnosis is rare, usually focal, and associated with extensive disease, systemic symptoms, and unfavourable

prognosis. The incidence of BMI in HL varies between 4% to 14 % in the series reported during the past 20 years.[1] The demonstration of BMI is important in staging of the disease which has an implication on the treatment strategies and prognostic classification of the disease.Bone marrow biopsy (BMB) from the iliac crest is the gold standard method for diagnosing BMI in lymphomas.[2] Definitive histopathologic criteria have been established for BMI in HL and are strictly followed.[3] In addition to the established criteria, a variety of non infiltrative changes have also been reported in the bone marrow of patients with HL.[4]

Aims and Objectives

To study the incidence of bone marrow involvement in Hodgkin disease and to analyse the implication of Hodgkin associated changes seen in bone marrow in HL.

Materials and Methods

This is a one year retrospective study carried out in the clinical laboratory of Kasturba Hospital, Manipal, India. All the patients diagnosed as HL on lymph node biopsy in whom bone marrow aspirate and biopsy were done were included in the study. The data collected included age, gender, clinical presentation, basic blood counts, lymph node histopathology and bone marrow findings. The clinical data was retrieved from the medical records. Anemia was defined as Hb value <12 g/dL, leukopenia and thrombocytopenia were defined when TLC and PLT were <4.00 × 10^3/μL and <150 × 10^3/μL, respectively. Bone marrow aspiration and trephine biopsy was performed from posterior iliac crest, under local anaesthesia with minimal discomfort. The bone marrow aspirate slides stained with Leishman stain and the BMB slides stained with Haematoxylin and Eosin were retrieved and analysed for the various morphological changes.

Results

In the one year study period, a total of 24 patients of HL were were diagnosed in our lab. There were 17 males and 7 females with a male to female ratio of 2.4:1. The age ranged from 5 years to 73 years with a mean of 37.4 years.

The most common group of lymph nodes involved were cervical LN followed by abdominal LN. The common abdominal LN involved were periportal, peripancreatic and para aortic LNs. Pelvic LN was involved only in 1 patient (Table 1).

Table 1: Shows the different group of lymph nodes involved.

Lymph nodes (LN)	No of Patients	%
Cervical LN	16	66
Supraclavicular LN	2	8.3
Axillary LN	5	20.8
Abdominal LN	8	33.3
Mediastinal LN	5	20.8
Pelvic LN	1	4.2

Majority of cases were Mixed cellularity type (17 cases) followed by 6 cases of Nodular Scerosis type and 1 case of Lymphocyte rich. There were no cases of lymphocyte depleted HL (Table 2).

Table 2: Shows the classification of the HL in our patients.

Type of HL	No of Patients	%
Mixed cellularity type	17	70.8
Nodular Sclerosis	6	25
Lymphocyte rich	1	4.2

The mean haemoglobin (Hb) level was 10.3 gm/dL, mean total WBC count was 10.37 X 10^3/μL, and the mean platelet count was 278.2 X 10^3/μL. Only 2 patients presented with severe anemia with Hb level of < 7 gm/dL. Three patients had mild thrombocytopenia but nobody had platelet count below 1 lakh.4 out of 24 patients showed leucocytosis with WBC count ranging between 12.5–33.9 X 10^3/μL. Only one patient showed eosinophilia with 12% eosinophils.

Bone marrow infiltration was seen in only 2 patients (8.3%), 4 cases (16.6%) showed Hodgkin associated changes in the bone marrow whereas remaining 18 patients (75%) did not show any changes in the bone marrow. The cases with infiltration showed presence of mononuclear variant of Reed Sternberg (RS) cells with increased eosinophils, histiocyte and fibrosis. One of the patient also showed associated bone marrow infarct. The Reed Sternberg cells were confirmed with immunohistochemical staining with CD30 and CD15. Table 3 summarises the details of the 2 patients with BMI.

Table 3: Shows the details of the 2 patients with BMI in HL.

Sr. No.	Age/Sex	Hb (gm/dL)	Total WBC Count (103/μL)	Platelet Count (103/μL)	LN involved	Type of HL
1	23/M	5.4	3.7	171	Cervical	Mixed cellularity
2	63/M	8.6	5.5	250	Cervical, Mediastinal and abdominal	Mixed cellularity

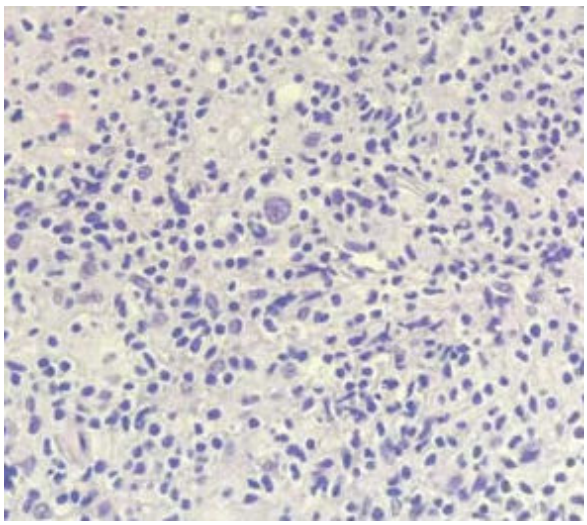

Fig. 1: BMB showing diffuse infiltration of atypical lymphocytes,histiocytes with occasional mononuclear variant of RS cell (Leishman stain 100X).

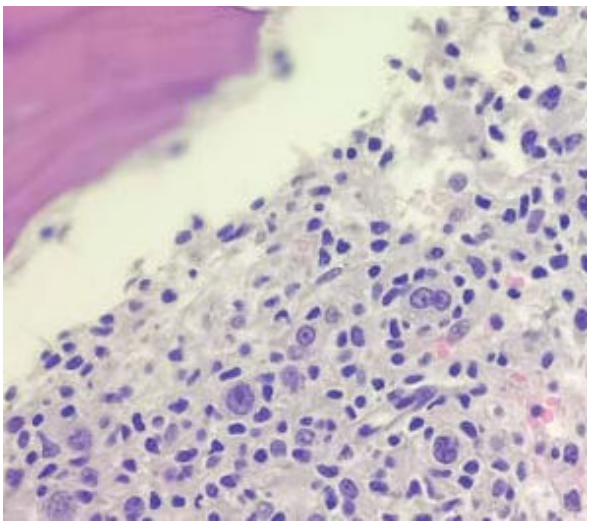

Fig. 2: BMB showing classical and mononuclear variants of RS cells (Leishman stain 400X).

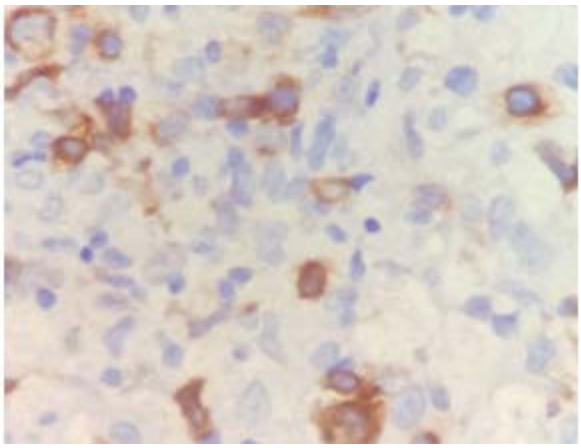

Fig. 3: BMB showing CD30 positivity in the mononuclear variant of RS cells (Leishman stain 400X).

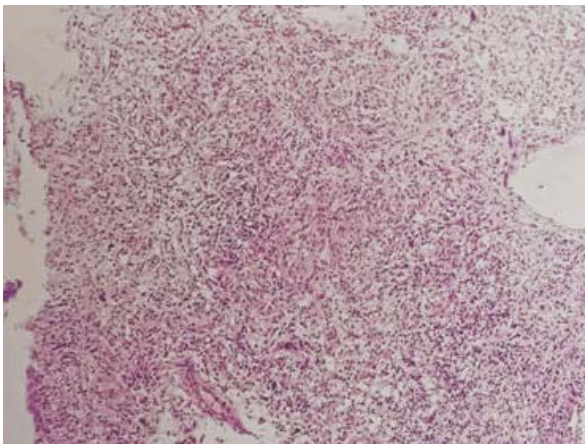

Fig. 4: BMB showing diffuse fibrosis with histiocytic proliferation and dyspoetic megakaryocytes in Hodgkin associated disease without presence of RS cells (Leishman stain 100X).

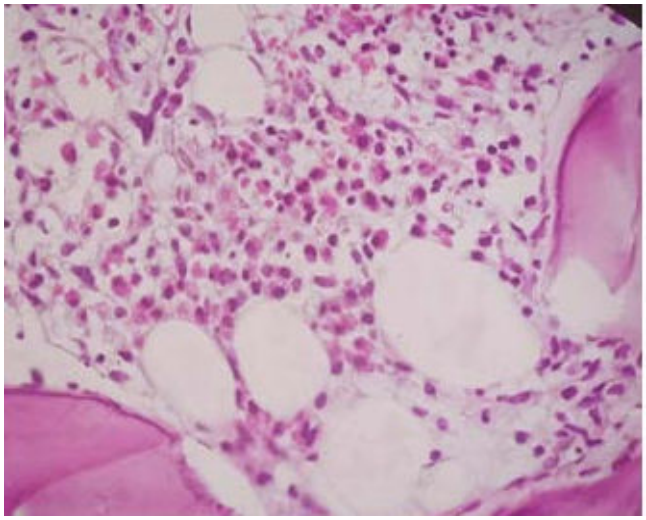

Fig. 5: BMB showing diffuse infiltration of eosinophils with dyspoetic megakaryocytes in Hodgkin associated disease (Leishman stain 400X).

Hodgkin associated changes included increased eosinophils, monocytes, dyspoetic megakaryocytes, presence of atypical lymphocytes and increased activated histiocytesbut absence of RS cells or its variants.

18 patients received the Adriomycin, Bleomycin, Vinblastin and Dacarbazine (ABVD) chemotherapy regimen whereas 6 patients did not receive treatment in our hospital. Out of the 18 patients only one patient relapsed in one year follow up and this patient had stage IV disease.

Discussion

Bone marrow evaluation is a must in lymphomas for staging of the disease and evaluating the further prognosis of the patient. Non Hodgkin lymphoma (NHL) is more commonly associated with bone marrow infiltration as compared to HL.TheIncidence of bone marrow infiltration in NHL varies from 15% to 75% whereas in HL varies from 2 to 38%. The wide variation in the range is due to heterogeneous inclusion criteria used by different studies 5.

In our study we included 24 cases of HL diagnosed over a period on one year and evaluated the bone marrow changes and correlated with the clinical presentation, basic lab parameters and prognosis of the patient.

The age group of our patients ranged from 5 years to 73 years with a mean of 37.4 years. There were only 2 patients in the paediatric age group, Krithi et al in their study of 49 patients of HL have reported 35 adults in the age group of 14–60 years and 14 patients in the paediatric age group who were less than 14 years.[6] Ankith Mangla et al in their study have reported a median age of 34 years with 25.5% patients being older than 45 years.[7] Ayaz Lone et al in their study of 50 cases of HL had patients from 7 to 80 years with a mean of 28.1 years and they had 10 (20%) patients in the paediatric age group.[8]

The male to female ratio in our study was 2.4:1 whereas Fransesco Guadeo et al have reported a ratio of 1.56:1 in their study of 384 cases of HL.[9] Ayaz et al have reported a much higher M:F ratio of 3.5:1. All studies show a higher incidence of HL in males but the gender has not found to be associated with any clinical outcome in HL.

The most common group of lymph nodes involved in our study were the cervical group of lymph nodes (66%) followed by the abdominal lymph nodes(33.3%). Majority of cases in the study done by Ayaz Lone et al presented with cervical lymphadenopathy (42%) followd by generalised lymphadenopathy (12%).[8] Eleven (45.8%) of our patients showed generalised lymphadenopathy.

The predominate type of HL seen in our study was Mixed cellularity type followed by Nodular sclerosis which correlates with the study done by Ayaz et al. But the study done by Muthu et al showed a higher incidence of Nodular sclerosis (66.6%) but most of the studies in literature mention BMI to be most commonly associated with mixed cellularity type of HL. Table 4 shows the different types of HL in various studies.

In our study bone marrow involvement was seen in only 2 patients giving an incidence of 8.3%. Literature gives a highly variable range of BMI in HL which varies from 2 to 30% with an average incidence of 10%.[11] Kirthi et al have reported an incidence of 18.4%, Muthu et al 12.3% whereas Ayaz et al have reported an incidence as high as 38% and R Munker[12] et al have reported as low as 4.3%. The wide variation in the incidence could be because of the variable number of patients involved in the study and also because of the variation in the age groups included in the study .

Both the patients in our study showing BMI were classified as Mixed cellularity type of HL.Muthu et al in their study have reported 20% of their cases with Mixed cellularity HL to have BMI whereas only 7.4 % cases of Nodular sclerosis HL showed BMI. But the predominate type associated with BMI in their study was the lymphocyte depleted type (66.7%) but our study did not have any case of lymphocyte depleted HL. Ayaz et al also have reported a higher incidence of BMI in Mixed cellularity type of HL. 89.5% of their cases with BMI were Mixed cellularity HL whereas 10.5% cases were Nodular sclerosis type.

Bone marrow biopsy is found to be a more reliable tool for demonstrating BMI in HL as RS cells can be often missed on aspirate and aspirates can often yield dry tap in HL owing to fibrosis. Hence bone marrow aspirates have limited value in staging of HL.[13] Both our patients were diagnosed

Table 4: Shows the incidence of different types of HL in various studies.

	Mixed Cellularity	Nodular Sclerosis	Lymphocyte Rich	Lymphocyte Depleted
Present study	17 (70.8%)	6 (25%)	1(4.2%)	NIL
Ayaz Lone[8]	39 (78%)	7 (14%)	3 (6%)	1 (2%)
MuthuSudalaimuthu et al[10]	20 (24.7%)	54 (66.6%)	4 (5%)	3 (3.7%)

to have BMI on bone marrow biopsy. Some studies recommend bilateral trephine biopsy as the probability of detecting BMI in HL increases by 16 to 33% by taking bilateral bone marrow biopsy.[14]

The pattern of infiltration in HL is usually diffuse and shows a dense stromal reaction in the form of fibrosis, necrosis and granuloma formation. The confirmation of BMI requires demonstration of classical RS cells or mononuclear variant of RS cells in the typical background as mentioned earlier in an already documented case of HL.[15] Our both patients with BMI showed mononuclear variant of RS cells in polymorphous background of eosinophils, histiocytic and fibroblastic proliferation.The RS cells were confirmed by using immunohistochemical markers such as CD30 and CD15. CD30 was positive in both the patients. One of the patient also showed associated bone marrow necrosis. Rakhee Khar et al 16 have also described necrosis in 5 out of 6 cases of HL with BMI in their case series of HL.

There were 4 patients in which there were no classical or mononuclear variants of RS cells but the bone marrow showed stromal Hodgkin associated changes like increased eosinophils, histiocytic proliferation, fibrosis and dyspoetic megakaryocytes. Deeper sections of the trephine biopsy as well as immunohistochemistry failed to demonstrate RS cell variants in these cases. Hence they were reported as Hodgkin associated changes without RS cells. Franco V et al[17] in their study have described three different diagnostic categories for HL with BMI as certain, suggestive and suspicious diagnosis.They have mentioned that presence of atypical histiocytes, fibrosis and necrosis should be considered as highly suspicious of HL infiltration. They have also described various nonspecific changes in non involved marrows of HL such as myeloid hyperplasia, megakaryocytic hyperplasia, plasmacytosis, histiocytic proliferation, fibrosis, necrosis and lymphoid nodules. Some studies have mentioned that these non infiltrative changes may be associated with poor prognosis.[18] But in our study 3 out of the 4 patients with Hodgkin associated changes received treatment in our hospital and all 3 showed good response to treatment and were in remission during the one year follow up period.

Vassilakopoulos et al.[19] have published a clinical prediction rule for predicting BMI in HL where they used six simple clinical features of HL: B symptoms-X1, stage III/ IV prior to BMB-X2, anemia-X3, leukocytes fewer than 6 x 109/L-X4, age ≥35 years-X5 and iliac/inguinal involvement-X6. Each factor was graded as 1 point if present or 0 if absent. A simplified score Zs= 8X1+6X2+5X3+ 5X4+3X5+3X6–8 was assigned for each patient.The aforementioned group determined the three risk groups of patients: 0.44% of patients had a low risk for BMI – 0.3%, Zs<0, standard risk was found in 37% of patients, with Zs 0–9 and their risk for BMI was 4.2%, and finally a high risk group including 20% of all patients, with Zs≥10 had 25.5% risk for BMI. But this scoring system could not be applied in our study due to the less number of subjects.B symptoms, cytopenias, lymphocyte depleted and mixed cellularity subtypes are considered as reliable risk factors for developing BM involvement in HL,in particular, leucopenia and thrombocytopenia indicate a high degree of risk.[10]

18 patients in our study received the regular ABVD regimen of chemotherapy whereas 6 patients were referred to other hospital or were lost for follow up. Among the 18 patients who were treated in our hospital only one patient relapsed in a one year follow up period and he was a stage IV disease with BMI thus showing that BMI is an important prognostic factor in HL. Studies have mentioned that BMI alone does not define a special high-risk group in HL in which a different treatment approach is indicated.[12] Prognosis of the patients with BMI is not worse than the prognosis of other advanced-stage HL patients.

Conclusion

Bone marrow trephine biopsy is a must in all cases of lymphomas for staging purpose.Though BMI is not very common in HL but when present implies stage IV disease and a poor prognostic indicator. Various non specific changes can be seen in the bone marrow of HL, hence a thorough search for RS cells should be done with adequate sampling of the tissue and immnuhistochemistry should be done wherever indicated.

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