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Clinicopathological Features of Bone Marrow Infiltration in Hodgkin Lymphoma. Should Bone Marrow Staging Be Done Only in High Risk Patients?

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ABSTRACT

Objective: The frequency of bone marrow infiltration by Hodgkin lymphoma is low and varies from 3 to 18%. Hence there exists a dilemma whether bone marrow staging should be done only in the high risk cases. This study aims to study the clinicopathological features and the histomorphology of bone marrow infiltration by Hodgkin Lymphoma.

Material and Method: Bone marrow aspirates and biopsies from cases of Hodgkin lymphoma diagnosed between 2007 and 2015 were studied. Immunohistochemistry with CD15 and CD30 were done in necessary cases. Bone marrow infiltration was correlated with various clinicopathological parameters.

Results: Ten of the 81 cases (12.3%) studied showed infiltration by Hodgkin lymphoma in the bone marrow biopsy sections. All the aspirates were negative. Bone marrow in the involved cases showed Reed-Sternberg cells and/or mononuclear Hodgkin cells positive for CD30 in a polymorphous inflammatory background. Cases of lymphocyte depleted subtype (66%) and those with leucopenia/ thrombocytopenia (100%) were frequently associated with bone marrow infiltration. B-symptoms, anemia and mixed cellularity were the other risk factors. However none of these risk factors were noted in two out of the ten cases with bone marrow infiltration.

Conclusion: As the role of bone marrow aspirate is minimal in the staging of Hodgkin lymphoma, bone marrow biopsy should be the method of choice. Immunohistochemistry helps in the doubtful cases. Bone marrow involvement was frequent but not confined to the high risk groups. Our findings suggest that bone marrow staging should not be restricted to the high risk cases alone.

Key Words: Hodgkin lymphoma, Tumor staging, Bone marrow biopsy

INTRODUCTION

Bone marrow (BM) studies are done in Hodgkin lymphoma (HL) as a part of the staging work-up since BM involvement indicates Stage IV disease (1-3). Studies have shown that the frequency of BM involvement in HL is low and varies from 4 to 18% (4-7). Hence some authors have suggested that BM studies can be done in selected high risk cases alone (5,8,9). However, a controversy exists as few other authors suggest that BM should be done in all the adult cases (1,10). This study was done to detect the frequency and morphology of BM involvement in HL, to study the association of BM involvement with various clinical and hematological parameters and to find whether BM involvement is restricted to certain high risk groups alone.

MATERIALS and METHODS

Cases of HL diagnosed from 2007 to 2015 in which BM aspiration and BM biopsy studies were done were included in our study. The study was conducted in accordance with the ethical guidelines stated in the Declaration of Helsinki. Informed consent was obtained from all patients. Clinical and peripheral blood features were obtained from case sheets and hospital records. Patients less than 13 years of age were considered as pediatric patients and patients greater than or equal to 13 years of age were considered as adults. Clinical staging was done based on Cotswold modification of Ann-Arbor staging as recommended by World Health Organization (WHO) after a complete clinical and radiological examination (2).

BM aspiration smears (stained with Leishman and May-Grunwald Giemsa stains) and BM biopsy sections (stained with Haematoxylin and eosin) were examined in all these cases. When histopathological features were suspicious of BM involvement, immunohistochemistry was done with CD 15 and CD 30 (DAKO) to confirm BM involvement. Since HL had already been diagnosed in the lymph nodes of these patients by histopathological and immunohistochemical

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examination, presence of mononuclear Hodgkin cells or classic Reed-Sternberg (RS) cells positive for CD30 in an appropriate inflammatory background was considered confirmatory of BM infiltration by HL. This is also in accordance with the WHO 2008 criteria (2).

RESULTS

We included a total of 81 cases of HL having both BM aspirates and biopsies in our study. Fifteen (18.5%) patients belonged to the pediatric age group and 66 (81.5%) patients were adults. Sixty (74.1%) patients were male and 21(25.9%) were female. Among the histological subtypes, 54 cases were of the nodular sclerosis subtype, 20 were mixed cellularity HL, four were lymphocyte rich HL and three were lymphocyte depleted HL.

Ten of the 81 cases (12.3%) of HL showed infiltration by HL in the trephine biopsy sections. However, none of these cases showed features of infiltration in BM aspirate smears.

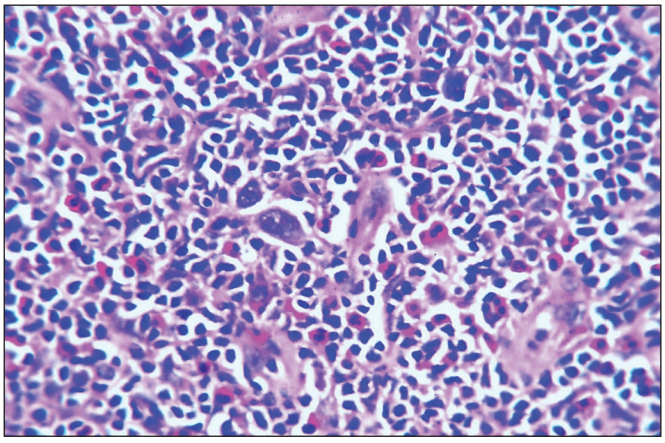

Figure 1: Few Reed-Sternberg and Hodgkin cells amidst the characteristic polymorphous inflammatory background (H&E; x200).

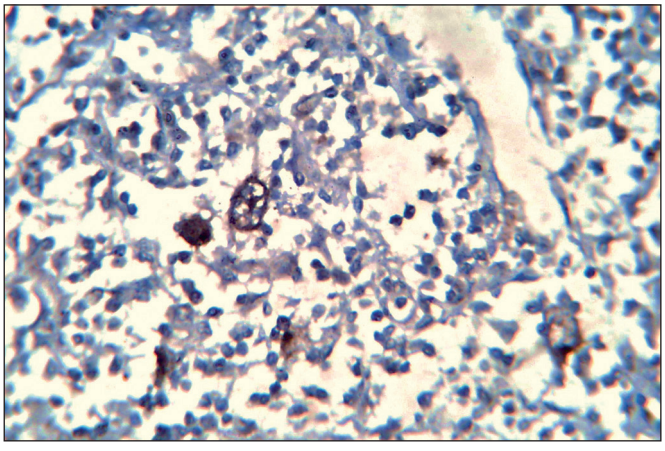

Figure 2: CD30 positivity in Reed-Sternberg and Hodgkin cells (CD30; x200).

Seven of the ten cases with BM infiltration showed diffuse involvement and the other three showed focal involvement. One case showed focal BM necrosis while another case showed marrow fibrosis along with tumor cells. Classical or multinucleated Reed-Sternberg and mononuclear Hodgkin cells amidst were seen in a polymorphous inflammatory background of eosinophils, lymphocytes, plasma cells and neutrophils (Figure 1) in eight cases (80%) while mononuclear Hodgkin cells alone were recognized in two cases (20%). CD30 was positive in all the cases (Figure 2), but CD15 positivity was seen in eight cases (80%).

The clinicopathological features in these ten cases are presented in Table I. All ten cases with BM infiltration were adults. Thus none of the pediatric HL cases showed BM infiltration. Three of the 21 female patients (14.3%) and seven of the 60 male cases (11.7%) showed BM infiltration. B symptoms (fever, night sweats, weight loss) were noted in 32 patients. Out of these 32 patients, 8 patients had BM infiltration (25%). In the B symptoms negative group, only two out of the 49 patients had BM infiltration (4.1%).

Four out of the 54 cases with nodular sclerosis subtype (7.4%), four out of the 20 cases with mixed cellularity HL (20%) and two out of the three lymphocyte depleted type HL cases (66.7%) showed BM infiltration. None of the four cases of lymphocyte rich HL showed BM involvement.

Table I: Correlation of clinicopathological features with bone marrow involvement in Hodgkin lymphoma

Parameter	Total number of cases	Number of cases with bone marrow involvement (%)
Age group		
Pediatric (<13 yrs)	15	None
Adults	66	10 (15.2%)
Gender		
Male	60	7 (11.7%)
Female	21	3 (14.3%)
B symptoms		
Present	32	8 (25%)
Absent	49	2 (4.1%)
Histological subtype		
Nodular sclerosis	54	4 (7.4%)
Mixed cellularity	20	4 (20%)
Lymphocyte rich	4	None
Lymphocyte depleted	3	2 (66.7%)
Cytopenia		
Present	25	8 (32%)
Absent	56	2 (3.6%)

Peripheral blood cytopenia was noted in 25 of the total 81 patients. Eight out of the 25 cases with cytopenia had BM involvement (32%). Among these eight cases, peripheral blood showed anaemia alone in 4 cases, anaemia with thrombocytopenia in three cases and leucopenia with thrombocytopenia in one case. All the 17 cases of cytopenia in which BM was not involved had only anemia. Leucopenia and thrombocytopenia were not seen in these cases. Among the 56 patients without cytopenia, only two had BM involvement (3.6%).

Out of the 10 cases with BM involvement, 8 cases were thought to be of a lower clinical stage before BM examination was done (Stage IA-1 case, Stage IB-2 cases, Stage IIA-1 case, Stage IIB-2 cases and Stage IIIB-2 cases). Because of BM involvement, these patients were upgraded to Stage IV.

DISCUSSION

BM studies are a part of the staging workup for HL as BM involvement is considered Stage IV disease (1,2). In spite of the advances like positron emission tomography, BM biopsy is still essential to confirm BM involvement in HL (11). Although BM involvement has been reported to be less common in HL when compared to Non-Hodgkin lymphomas (4), it is still essential to do BM staging in HL as it has prognostic significance (5). The incidence of BM involvement in HL in our study is consistent with the literature, which indicates a range between 3-18 % in many studies (4-8).

BM infiltration by HL more often showed a diffuse pattern in our study. However, focal infiltration was noted in three cases. This indicates the importance of adequate sampling while doing a BM staging in cases of HL. Cases with focal involvement can be missed unless an adequate length of BM is sampled (1). BM necrosis and fibrosis were seen in one case each. BM necrosis and fibrosis are findings often associated with BM infiltration of HL and, when present, should raise the suspicion of BM involvement in a given case (1,7,12).

BM in eight of the ten cases infiltrated by HL showed classical RS cells and mononuclear Hodgkin cells in an inflammatory background composed of variable number of eosinophils, plasma cells, lymphocytes and neutrophils. In the remaining two cases, only mononuclear Hodgkin cells were seen (without classical RS cells) in a similar inflammatory background. Mononuclear Hodgkin cells in these two cases were positive for CD 30 as well as CD15. Since according to the WHO 2008 criteria, mononuclear Hodgkin cells positive for CD30 in an appropriate inflammatory background is sufficient for the diagnosis of BM infiltration in a known case of HL, a diagnosis of BM infiltration by HL was made in these two cases (2,13). The immunophenotype of the tumor cells was CD30+ / CD15+ in eight cases and CD30+/ CD15- in two cases. This is understandable as CD15 expression in HL differs between studies (14,15). Since CD15 positivity is not essential for the diagnosis of BM infiltration, a diagnosis of BM infiltration by HL was made in the two CD30+ CD15- cases (2). Detailed knowledge of the histomorphological features of BM infiltration by HL is essential, because in some cases HL may be primary diagnosed in a BM biopsy done for other purposes (16-18).

Although BM biopsy showed infiltration by HL in ten cases, BM aspirates did not reveal BM involvement in any of these cases. Studies have shown that BM involvement by HL usually cannot be detected in a BM aspirate (5,19,20). Thus BM aspirate has limited value in the BM staging of HL and BM biopsy should be the method of choice.

When analyzing the clinical and hematological features associated with BM infiltration, we noted that none of the pediatric patients of HL showed BM involvement in our study whereas 15.2% of the adults showed BM involvement. Mahoney et al. reported in their study that the frequency of BM involvement was very low (1.8%) in pediatric HL (21). Hence Franco et al. suggested that BM studies can be avoided in stage I to IIIA cases of pediatric HL (1). Our results add strength to his proposal.

BM involvement was more common in the lymphocyte depleted (66.7%) and mixed cellularity (20%) subtypes of HL when compared to the nodular sclerosis (7.4%) and lymphocyte rich (none) subtypes in our study. Vassilakopoulos et al. had also observed that BM involvement is more common in the lymphocyte depleted and mixed cellularity subtypes of HL (9). Thus these two subtypes are the high risk subtypes for BM involvement in HL.

BM involvement was more common in patients with B symptoms and cytopenia when compared to patients without these findings. In our study, among cytopenias, thrombocytopenia and leucopenia were seen in HL patients only when there was BM involvement. B symptoms and cytopenia were frequently associated with BM involvement in other studies as well (9,10,22).

B symptoms, cytopenias, lymphocyte depleted and mixed cellularity subtypes are therefore risk factors for developing BM involvement in HL. In particular, leucopenia and thrombocytopenia indicate a high degree of risk. When

multiple risk factors are coexistent in a particular patient, the likelihood of having BM involvement is increased. BM studies must be performed in these patients, even bilaterally as it yields better results (23).

In our study, eight patients were upgraded to stage IV because of BM involvement, which explains the importance of doing a BM examination in patients with HL. Although some authors recommend that BM staging in HL may be restricted to certain high risk groups alone (5,8), Vassilakopoulos et al. noted in their study that upstaging of HL based on BM studies had prognostic and therapeutic significance at least in certain subgroups of patients (9). This supports the findings of our study, in which six cases with clinical stage I and II (including a stage IA case with anemia and a stage IIA case without any cytopenia) were upgraded to stage IV because of BM involvement. BM infiltration in patients with otherwise early stage disease has been reported by Kini et al. as well (10). All these data suggest that doing BM staging only in high risk patients might not be sufficient.

Considering that HL is a unique neoplasm that exhibits geographical variations in its histological subtypes, Epstein-Barr virus association and immunophenotype, it may be assumed that BM infiltration in HL also differs between populations (2,14,15). Hence large scale studies on individual populations is necessary before deciding whether BM staging procedures in HL can be restricted in that population to only certain high risk patients. Until then, it is advisable to perform BM staging in all patients with HL, at least in adults.

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CONFLICTS of INTEREST

The authors declare no conflict of interest.

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