Original Article

Bone marrow involvement in Hodgkin's lymphoma: Data from a cancer hospital

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ABSTRACT

Objective: Bone marrow examination is essential for staging Hodgkin's Lymphoma (HL) at the time of diagnosis to determine the correct treatment and prognosis of the disease. The aim of this study was to analyze clinical presentation, hematological profile, biochemical profile, radiological presentation and patterns of bone marrow involvement in patients with Hodgkins lymphoma retrospectively. **Materials and Methods:** Bone marrow procedures were done in 49 cases of Hodgkins lymphoma a part of staging procedure. **Results:** 9 patients showed involvement of bone marrow by Hodgkins lymphoma. Clinically, 1 patient was staged as stage II (CSII), 2 patients as stage III (CSIII) and the remaining 6 as stage IV (CSIV) on the basis of extra nodal evidence of disease in liver, bone, lung or pleura on PET scan. The pattern of bone marrow infiltration was diffuse in 3 patients and focal in 6 patients. Length of the biopsy varied from 0.5 cm to 3.0 cm. **Conclusion:** BME should not be performed in all patients diagnosed with HL as a routine staging procedure. In an already known CS IA, IIA the incidence is very low and in CSIV it provides no additional therapeutic or prognostic information. However, patients with stage IIB, IIIB, IIIA and with any of the following: leucopenia, elevated LDH or ALP levels, splenomegaly should undergo biopsy of adequate length as additional prognostic information may be obtained. If it is suspicious of involvement, serial sections and contralateral biopsies should be examined so that even a single atypical cell or focus is not missed.

Key words: Bone marrow biopsy, bone marrow involvement, Hodgkin's lymphoma

INTRODUCTION

Hodgkin's lymphoma (HL) is staged at the time of diagnosis to determine the correct treatment and prognosis of the disease. A detailed clinical history, physical examination, hematological, biochemical, radiological investigations and bone marrow examination (BME) are performed as a part of routine staging procedure. Bone marrow involvement (BMI) in HL represents stage IV disease. In adult population, the incidence is estimated between 2% and 32%, with an average of 10%. The incidence of BMI in patients staged as clinical stage (CS) IA or IIA has been shown to be <1% in most series.[1]

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The aim of this study was to analyze clinical, hematological, and biochemical findings predictive of BMI, necessity of performing a bone marrow, patterns of infiltration in bone marrow, and importance of serial sectioning and contralateral biopsies in rendering definite diagnosis.

MATERIALS AND METHODS

A total of 1023 bone marrow aspirations and biopsies were performed during a period of 1 year (i.e., September 1, 2013, to August 31, 2014), out of which 49 patients were diagnosed with HL as a part of staging procedure. The clinical details, hematological, biochemical, and radiological findings of all patients were noted retrospectively which included age, sex, presence of "B" symptoms, hemoglobin (Hb), total leukocyte count (TLC), platelet count, lactic acid dehydrogenase (LDH) levels, alkaline phosphatase (ALP) levels, positron emission

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tomography (PET) scan, spleen status, and CS. Anemia was defined as Hb value <13 g/dL in males and <12 g/dL in females. Leukopenia and thrombocytopenia were defined when TLC and PLT were <4.00 × 10^3/μL and <150 × 10^3/μL, respectively. Bone marrow aspirates (BMAs) and trephine biopsies were obtained from posterior-superior iliac spine using Jamshidi needle. BMA smears were stained with Giemsa stain. Bone marrow biopsies were decalcified and then stained with hematoxylin and eosin. The aspirates and biopsies were examined by hematopathologists to study the cellularity, megakaryocytes, pattern and arrangement of tumor cells, and fibrosis. Reticulin stain was done in all positive cases. Immunohistochemistry was done in four cases.

RESULTS

Of the total 49 patients in the study, 35 patients were in the age range of 14–60 years and 14 patients belonged to the pediatric age group (<14 years). Thirty-seven patients were male and 12 patients were female. Bone marrow procedure was performed in all the patients. Nine patients were found to have bone marrow infiltration by HL, remaining forty patients showed no evidence of bone marrow infiltration. Table 1 summarizes the clinical, hematological, biochemical, and radiological findings in the nine patients' positive for bone marrow infiltration by HL. B symptoms and splenomegaly were found in 8 out of 9 patients (88.8%). LDH levels were elevated in all nine patients. ALP levels were elevated in 7 out of 9 patients (77.7%). Anemia, leukopenia, and thrombocytopenia were found in 6 (66.6%), 3 (33.3%), and 1 (11.1%) patient, respectively. B symptoms included the presence of fever, weight loss, and night sweats, of which fever was the most common complaint. It was found that the presence of B symptoms (P = 0.017, <0.1), elevated LDH levels (P = 0.0001, <0.01), elevated ALP levels (P = 0.021, <0.1), leukopenia (P = 0.0023, <0.01),

Table 1: Clinical, hematological, biochemical, radiological findings and staging in patients with marrow involvement by Hodgkin's lymphoma

Serial number	Age/sex	B symptoms	Hb (g/dl)	TLC (10^3/cu mm)	PC (lakhs/cu mm)	LDH (u/dl)	ALP (u/dl)	PET scan findings	CS before marrow	Stage after marrow
1	8/female	Fever, weight loss	6.8	12.33	1.46	552	211	Cervical Axillary Abdominal nodes Spleen$^+$ B/L pleura ?marrow$^+$	IVB	IVB
2	12/male	Fever	8.4	1.82	2.71	589	1890	Neck and abdominal nodes Spleen, liver, marrow$^+$	IVB	IVB
3	15/male	Fever Weight loss	8.5	2.44	71	819	245	Neck and abdominal nodes Spleen, liver, marrow$^+$	IVB	IVB
4	42/male	Fever	11.1	5.79	1.35	507	77	B/L neck Nodes Spleen$^+$	IIB	IVB
5	24/male	Fever	9.9	17.02	3.99	864	165	Neck and abdominal nodes Focal uptake in 6th rib and pleura	IVB	IVB
6	21/male	Absent	11.6	5.42	2.23	702	158	Neck and abdominal nodes Spleen$^+$ Marrow$^+$	IIIA	IVA
7	40/male	Fever Weight loss	12.2	15.34	2.38	482	134	Neck and abdominal nodes Spleen$^+$ Liver$^+$?Marrow	IVB	IVB
8	7/male	Fever, night sweats	10.5	9.46	1.77	554	304	Neck and abdominal nodes Liver$^+$ Lung$^+$	IVB	IVB
9	30/male	Fever	8.3	27.05	4.92	600	114	Neck and abdominal nodes Spleen$^+$?Marrow	IIIB	IVB

Hb: Hemoglobin, TLC: Total leukocyte count, PC: Platelet count, LDH: Lactic acid dehydrogenase, ALP: Alkaline phosphatase, PET: Positron emission tomography, CS: Clinical stage, B/L: Bilateral

and spleen involvement ($P < 0.0001$) were significantly associated with BMI. However, age, sex, anemia ($P = 0.117$), and thrombocytopenia ($P = 0.44$) did not have any significant association with BMI by HL. Clinically, one patient was staged as stage II (CS II), two patients as stage III (CS III), and the remaining six as stage IV (CS IV) on the basis of extranodal evidence of disease in liver, bone, lung, or pleura on PET scan.

BME includes both aspirate and trephine biopsy. In all the nine patients, BMA provided no evidence of infiltration and was either normal cellular or diluted with blood. Bone marrow biopsy (BMB) on the other hand was found to be highly sensitive. The pattern of infiltration was diffuse in three patients and focal in six patients. The length of the biopsy varied from 0.5 cm to 3.0 cm. Table 2 summarizes the aspirate and biopsy findings in the nine patients showing BMI.

DISCUSSION

The incidence of BMI on diagnosis has been reported with a variable range in the literature (2–32%).[2] The incidence in our study is 18.3% (9/49). The range varies in the developing and developed nations and also depends on the patient selection (adult/pediatric). In accordance to other studies, we found that B symptoms,[1-5] leukopenia,[2,3,5] high-LDH levels,[4,5] high ALP levels,[2] and splenomegaly[5] significantly correlate with BMI, whereas anemia,[1,3,5,6] thrombocytopenia,[1,6] and age[1,7,8] did not have any significant association with BMI. The current children oncology group protocols[9,10] stratify patients with HL into three groups of disease based on stage: early (stages IA, IIA), intermediate (stages IB, IIB, IIIA, and IVA), and advanced (stages IIIB, IVB). In accordance with these definitions, in our study, seven patients belonged to

Table 2: Bone marrow aspirate and biopsy findings in the cases with involved marrow

Serial number	BMA findings	BMB length (cm)	BMB findings	Diagnosis	Deeper section or contralateral BMB findings
1	Diluted marrow	0.5	Small focus of epithelioid cell granuloma	Suspicious of BMI by HL	Contralateral biopsy revealed diffuse infiltration by histiocytes, granulomas and mononuclear RS cells with fibrosis
2	Cellular reactive marrow	1.5	Focal BMI showing epithelioid histiocytes and classical RS cells	Definite for BMI by HL	Not needed
3	Diluted marrow	3	Diffuse infiltration by epithelioid cell granulomas, mononuclear and classical RS cells in a background of lymphocytes and fibrosis	Definite for BMI by HL	Not needed
4	Cellular reactive marrow	1.0	Mainly trilineage hematopoiesis with a single lymphoid nodule at one end and scattered atypical histiocytes in a fibrotic background	Suspicious of BMI by HL	Serial sections revealed mononuclear RS cells along with histiocytes making BMI by HL certain
5	Diluted marrow	0.7	Diffuse infiltration by histiocytes, lymphocytes, and eosinophils	Suspicious of BMI by HL	Serial sections revealed mononuclear RS cells along with histiocytes making BMI by HL certain
6	Cellular reactive marrow	1.2	Mainly trilineage hematopoiesis with a very small focus of atypical histiocytes	Suspicious of BMI by HL	Serial sections provided no additional information. Contralateral biopsy showed mononuclear RS cells in a polymorphous background and fibrosis
7	Cellular reactive marrow	1.3	Focal infiltration by epithelioid cells in a background of fibrosis	Suspicious of BMI by HL	Serial sections revealed mononuclear and classical RS cells along with histiocytes making BMI by HL certain
8	Cellular reactive marrow	1.0	Focal infiltration by epithelioid cell granulomas and mononuclear RS cells in a background of fibrosis	Definite for BMI by HL	Not needed
9	Diluted marrow	3.0	Diffuse infiltration by histiocytes, epithelioid cell granulomas, mononuclear and classical RS cells with fibrosis and areas of necrosis	Definite for BMI by HL	Not needed

BMA: Bone marrow aspirate, BMB: Bone marrow biopdsy, HL: Hodgkin's lymphoma, BMI: Body mass index, RS: Reed-Sternberg cell

advanced stage and two patients belonged to intermediate stage. Thus, the identification of BMI altered the treatment recommendation in only two patients, which is a small fraction. Munker *et al*. and Hines-Thomas *et al*.[11,12] found no change in the 5-year relapse-free survival of patients with stage IV disease who did and did not have BMI. Specht and Nissen[13] have reported BMI to be an independent risk factor in stage IV disease. Furthermore, neither the site of extranodal disease nor their number significantly affects the overall survival of patients with stage IV HL.[12] Hasenclever and Diehl[4] found only a small difference in the freedom of progression of disease according to the site of infiltration. With increasing sensitivity of imaging modalities such as fludeoxyglucose-PET, more extranodal sites of disease are being detected and are being widely used to stage patients with lymphomas, thereby decreasing the need of performing BME.[1,6,12] PET scan is also able to detect focal or multifocal BMI, with a sensitivity of 76% and specificity of 92%.[14]

A definite diagnosis of BMI was rendered in only four patients. The remaining five patients were either suspicious or suggestive of BMI. The diagnosis in these patients was limited by the absence of classical/mononuclear Reed-Sternberg (RS) cells or granulomas and a smaller size of biopsy. The only evidence was the presence of atypical histiocytes and fibrosis. However, deeper/serial sectioning revealed the presence of classical/mononuclear RS cells in three patients. In the remaining two patients, a contralateral biopsy of an adequate length was obtained revealing RS cells in a cellular background making the diagnosis certain.

It has also been documented that BMAs provide no additional information to that provided by a trephine biopsy (BMB) [1] and that biopsy is superior to BMA,[15,16] which was also observed in our study. Hence, BMA should be abandoned for staging because focal or patchy patterns of infiltration can be only picked up in a biopsy.[17] Bartl *et al*.[2] and Vassilakopoulous *et al*.[3] have stressed upon the adequacy of BMB to evaluate infiltration. Single large biopsies exhibit the highest incidence similar to bilateral smaller biopsies.[2] We found that focal patterns of infiltration could be picked up only if the biopsy was large enough (at least 2 cm). A contralateral biopsy was needed if the initial biopsy was inadequate and the risk factors predictive of BMI were present. We also found that deeper or serial sections also helped in picking up small foci of infiltration. The patterns of infiltration can be diffuse or focal. Diffuse pattern is more common. Focal type is found in a minority of patients and can show small patchy or nodular lesions surrounded by normal marrow.[18] The diagnosis of BMI requires identification of RS cells with granulomas or atypical mononuclear cells in a suitable background in an already documented case of HL [Figure 1a and b].[2,7,19] In the present study, it was seen

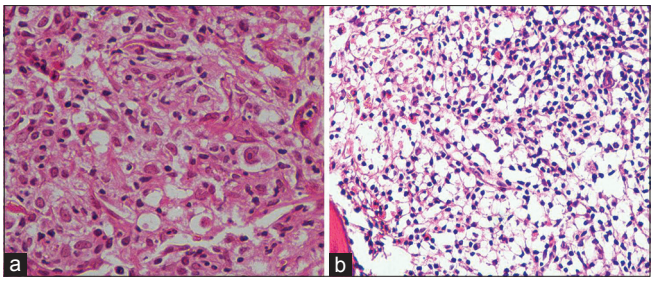

Figure 1: (a) Atypical mononuclear Reed-Sternberg cells in a background of histiocytes and fibroblastic reaction (×100). (b) Mononuclear Reed-Sternberg cell in a polymorphous background of lymphocytes and eosinophils (×40)

that even a single focus of epithelioid cells, granulomas, fibrosis, or necrosis on deeper sections or contralateral biopsies revealed diagnostic mononuclear cells in a cellular background. Hence, a detailed evaluation of the biopsy is needed. No abnormal cell or focus should be missed.

Hence, BME proved to be valuable in three patients only in whom BMI upstaged them to stage IV. In CS IV patients, BME does not offer any additional benefit. No patient having BMI with HL was CS I. Therefore, BME should no longer be performed as a routine staging procedure in all patients with HL since it is an invasive and painful procedure, causes discomfort to the patient, and carries its own risk. A complete workup including presence of B symptoms, elevated LDH and ALP levels, leukopenia, and splenomegaly in patients with CS II, III should be done before a BME as they are the predictive risk factors. In CS IV patients and CS I patients, BME can be avoided as it provides no additional information in the former and is very rare to be positive in the later.

CONCLUSION

On the basis of the findings and the data presented, it can be concluded that:

1. BME should not be performed in all patients diagnosed with HL as a routine staging procedure
2. BMB should not be performed in already known CS IV, IA, IIA patients as it provides no additional therapeutic or prognostic information in the former and because of very low incidence in the later
3. Patients with stage IIB, IIIB, IIIA and with any of the following: leukopenia, elevated LDH or ALP levels; splenomegaly should undergo BMB as additional prognostic information may be obtained
4. BMB should have an adequate length (at least 2 cm)
5. If BMB is suspicious of involvement, serial sections and contralateral biopsies should be examined before giving a negative diagnosis so that even a single atypical cell or focus is not missed.

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Conflicts of interest
There are no conflicts of interest.

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