

Incidence and Prognostic Implication of Bone Marrow Involvement in Hodgkin's Lymphoma

Rimpi Bansal^{1*}, Puneet Kaur¹, Jatin Sarin², Anureet Kaur¹, Akshita Sarin³

¹Department of Pathology, Gian Sagar Medical College And Hospital, Punjab, India

²CCDC, Chandigarh, India

³Government Medical College and hospital, Chandigarh India

ABSTRACT

Introduction: Conducting Bone marrow examination in a Hodgkin's Lymphoma (HL) patient at the time of diagnosis is done routinely to determine the stage of the disease. The aim of this study was to analyze the incidence and prognosis of bone marrow involvement in patients with Hodgkin's lymphoma, retrospectively.

Materials and Patients: Ten patients of Hodgkin's lymphoma were incorporated in the current study. Bone marrow aspiration and biopsy was done in all ten cases as part of staging procedure.

Results: Three patients showed involvement of bone marrow by Hodgkin's lymphoma and both the patients had clinically poor outcome.

Discussion and Conclusion: Bone marrow examination is important in stage II and III of Hodgkin's lymphoma because positive result will upstage the disease. Also, bone marrow involvement indicates an aggressive disease and poor prognosis for the patient.

Keywords: Hodgkin's Lymphoma, RS cells, Bone Marrow biopsy

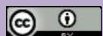
Introduction

Bone marrow aspiration and biopsy is done in patients of Hodgkin's Lymphoma (HL) as part of staging procedure. The incidence of involvement of marrow varies according to the subtype of disease; mixed cellularity being the predominant subtype. The incidence also varies with the stage of the disease (1,2). Clinically, marrow involvement in most instances resulted from widely disseminated disease, is associated with B symptoms, bulky disease, involvement of lymph nodes both above and below the diaphragm and is usually uncommon with a large mediastinal mass. We present a short series of ten cases of Hodgkin's lymphoma and incidence of bone marrow involvement in them. We have also revisited the bone marrow and biopsy findings in cases of suspected involvement.

Material and Methods

The study was carried out in a small oncology centre in North India. We retrieved all the cases diagnosed with

Hodgkin's lymphoma between June 2015 and June 2016. In all total number of patients who visited during this period were 673. Ten patients were diagnosed with Hodgkin's lymphoma. After the primary diagnosis was made on lymph node biopsy examination, bone marrow aspiration as well as biopsy was done in all the patients. During follow up it was done only if the patient had abnormal hemogram, complaints of bony pain or if radiological investigation revealed any abnormality, for instance, increased FDG uptake in PET scan, bony lesion on CT scan etc. Bone marrow aspiration smears were air dried and stained with Leishman Stain. Biopsy was initially quick fixed, decalcified using diluted HNO₃, processed in fully automatic Leica- tissue processor. Thin sections were cut on Leica rotatory microtome, and stained with Hand E staining technique. Immunohistochemistry (IHC) was done in cases where involvement was suspected on aspiration smears and tissue sections. DAKO antibodies for CD15, CD30 and LCA were used for IHC. All the patients were followed up for three years. The results were compiled and interpreted.



Results

Out of a total of 10 cases of Hodgkin's lymphoma, three cases showed involvement of bone marrow by the disease. Age of these patients were 32 years (patient-3 and 8) and 25

bone marrow sections (Figure-4), (Table -1). Figure 1 and Figure 2 show total leukocyte count and platelet distribution in all patients included in the study. We confirmed our bone biopsy findings by IHC using LCA, CD 20, CD15, CD 30 and PAX 5. Additionally, OCT 2, BOB 1 and MUM1 can be

Table 1: Age and sex wise distribution of all cases in the study. Bone marrow aspiration was positive in one of the cases

S. No	Age	Sex	Hodgkin's Lymphoma subtype	Bone marrow aspiration	BM biopsy	Three-year follow-up
1	12	M	Mixed Cellularity	Negative	Negative	Remission
2	17	M	Mixed Cellularity	Negative	Negative	Remission
3	18	F	Mixed Cellularity	Negative	Positive	Relapse
4	23	M	Nodular Sclerosis	Negative	Negative	Remission
5	23	M	Mixed Cellularity	Negative	Negative	Remission
6	25	M	Mixed Cellularity	Negative	Negative	Remission
7	26	M	Mixed Cellularity	Positive	Positive	Relapse
8	32	F	Mixed Cellularity	Negative	Positive	Remission
9	37	M	Mixed Cellularity	Negative	Negative	Remission
10	61	M	Lymphocyte Depleted	Negative	Negative	Remission

years (Patient-7). Patient 3, came with chief complaints of fever and night sweats. He had mediastinal mass and intraabdominal lymphadenopathy. Patient 7 and 8, came with history of fever, night sweats and enlarged nodes in cervical region. Histopathological diagnosis of all was HL – mixed cellularity type.

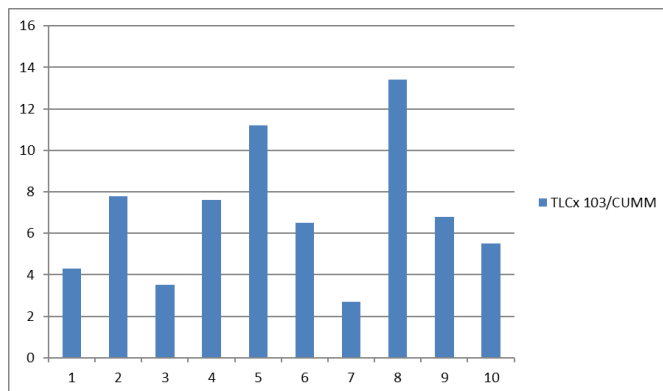


Figure 1 TLC distribution in all patients included in the study. Two patients with BM involvement show neutropenia.

Patient-3 and 8 presented with stage –IV disease on PET scan. Patient-7 was stage- II-B clinically but due to bone marrow involvement was upstaged to IV-B. He had mild thrombocytopenia. All three patients showed presence of large, multinucleated, RS like cells on bone marrow aspiration (Figure -3) and diffuse pattern of involvement in

used. On follow up, all the cases with bone marrow involvement showed either progression during treatment or early relapse and patients died during the follow up period whereas rest of the patients are currently in remission.

Discussion

The incidence of bone marrow involvement in Hodgkin's lymphoma varies widely in adults; different studies found incidence from as low as 2% to about 32% of all cases (1). This is still higher in children. Higher preponderance of marrow involvement is seen in lymphocyte depleted HL subtype followed by mixed cellularity and nodular sclerosis (1,2,3). Muncher R reported an incidence of 49% involvement in mixed cellularity HL.4 All three patients in current series were mixed cellularity type. A thorough analysis of peripheral blood film (PBF) is often indicative (3) as our patients had leukopenia and one of the patients had thrombocytopenia. Diagnosing bone marrow involvement in Hodgkin's lymphoma requires diligent search for the RS cells in smears. BM aspirates are found to be positive only in 10% of cases in which the BMB (bone marrow biopsy) is infiltrated by HL. This infers that for

definitive diagnosis of bone marrow involvement in a case Hodgkin's disease, bone biopsy is mandatory. (4,5) Aspirates show presence of RS cells in cases where the involvement is diffuse. Presence of fibrosis, necrosis or atypical histiocytes, eosinophilia, lymphocytosis calls for search of RS cells in aspiration smear.

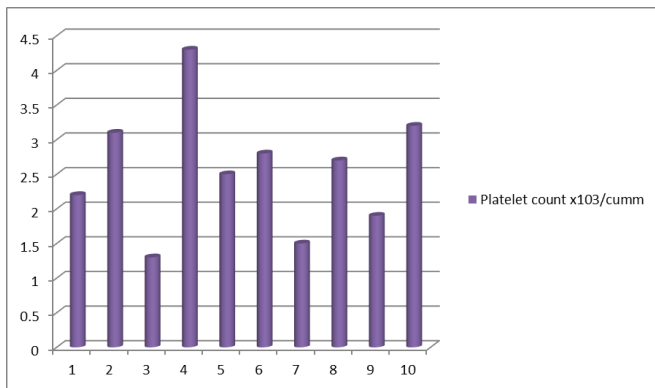


Figure 2 Platelet count in patients in the study.

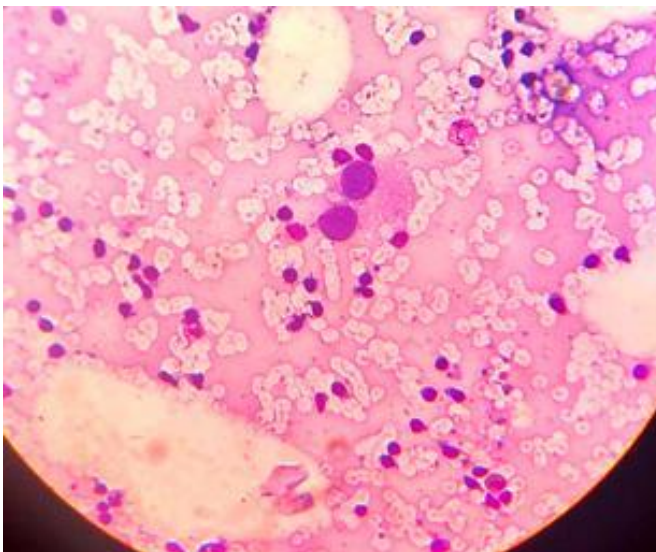


Figure 3 Bone marrow aspirate smear showing typical RS cell surrounded by small lymphocytes (400X, Leishman stain).

Immunohistochemistry is helpful in the cases which are suspicious for bone marrow involvement. Presence of increased number of CD34, CD 20, CD 15/30 and PAX5 positive cells is confirmatory of bone marrow involvement in a case of HL. In corollary, the aspirates are never positive with a negative BMB. (6) IHC should be used as

ancillary technique for confirmation. (4,6)

In many patients, particularly lymphocyte depletion type, bone marrow biopsy may be the first diagnostic specimen (7,8). Such patient usually presents with one or more cytopenia's. However, the histopathological classification of Hodgkin's lymphoma should not be based on bone marrow examination alone because of different manifestation of the disease in bone marrow and lymph node (9,10).

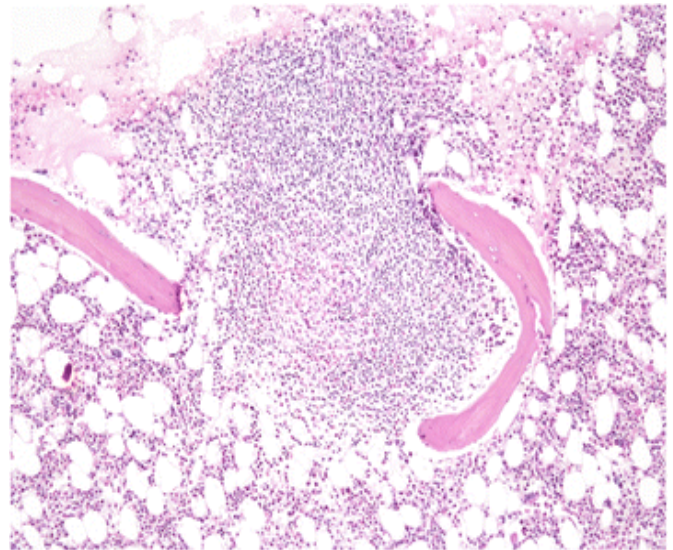


Figure 4 Bone biopsy section shows nodular deposit composed of large cells surrounded by motley bunch of reactive cells. Large cells on IHC showed positive staining with CD 30 and negative staining with CD45.

The definitive diagnosis of marrow involvement should be made if typical RS cells or mononuclear RS variant (if the typical RS cells are seen in lymph node biopsy) are seen in cellular background of HL. The presence of large atypical cells in typical HL should be reported as highly suspicious for involvement. Also, presence of foci of fibrosis should be viewed as suspicious. Areas of necrosis may be present in post therapy cases. The extent of marrow involvement in HL ranges from diffuse to focal; from single small focus to complete replacement of multiple biopsy specimen (13,14). The degree of involvement does not have any effect on prognosis. Uninvolved areas of marrow in specimens with infiltration may be hypercellular, normocellular or hypocellular. Nonspecific changes in marrow due to Hodgkin's lymphoma include stromal damage, inflammatory cell infiltration or disturbed hematopoiesis (6, 11, 12).

Some authors have suggested certain criteria, presence of which would be an indication of bone marrow biopsy in patients of HL. These are age >40 yr., ESR >50 mm/h, fibrinogen >5 g/L, alkaline phosphatase >130 U, LDH >400, Leukocytosis >10 000, Anemia Hb < 10 g/L, Leukopenia, thrombocytopenia, B-symptoms, chest and abdominal lymphadenopathy (3,4,5).

Conclusion

In conclusion, bone marrow biopsy evaluation is mandatory in cases of Hodgkin's Lymphoma, stage 2 or more. Bone marrow aspiration is usually indicative of disease infiltration and steers a pathologist to search diligently for RS cells in bone biopsy specimen.

Reference

1. Subramanian R, Basu D, Badhe B, Dutta TK. Role of Bone marrow trephine biopsy in the diagnosis of marrow involvement in Hodgkin's disease. *Indian J Pathol Microbiol* 2007;50:640-3.
2. Cavalieri E, Anselmo AP, Gianfelici V, Frattarelli N, Pescarmona E, Foa R, et al. Is bone marrow trephine biopsy always mandatory in Hodgkin's disease? *Haematologica* 2005;90:134-6.
3. Munker R, Hasenclever D, Brosteanu O, Hiller E, Diehl V. bone marrow involvement in Hodgkin's disease: an analysis of 135 consecutive cases. *J Clin Oncol* 1995, 13:403-409
4. Franco V, Tripodo C, Rizzo A, Stella M, Florena AM. Bone marrow biopsy in Hodgkin's lymphoma. *Eur J Haematol* 2004;73:149-155.
5. Kini JR, Suresh PK, Sinha R, Sahu KK, Kumar S, Prasad K. Value of bone marrow examination in Hodgkin lymphoma: Report of three cases with review of literature. *J Can Res Ther.* 2012;8:457-459
6. Barbara J. Bain, David M. Clark, Bridget S. Lymphoproliferative Disorders. In *Bone Marrow Pathology* 4th edition. London: Willy-Blackwell. 2011; 300-420
7. Howell SJ, Grey M, Chang J, Morgenstern GR, Cowan RA, Deakin DP, Radford JA. The value of bone marrow examination in the staging of Hodgkin's lymphoma: a review of 955 cases seen in a regional cancer centre. *Br J Haematol.* 2002;119(2):408-411.
8. Kar R, Dutta S, Tyagi S. Clinically unsuspected Hodgkin's lymphoma diagnosed primarily from bone marrow trephine biopsy: Report of six cases. *Indian J Pathol Microbiol.* 2008;5:186-189.
9. Park Y, Park BB, Jeong JY, et al. Assessment of bone marrow involvement in patients with lymphoma: report on a consensus meeting of the Korean Society of Hematology Lymphoma Working Party. *Korean J Intern Med.* 2016;31(6):1030-1041. doi:10.3904/kjim.2015.006
10. Agbay RLMC, Loghavi S, Zuo Z, Fayad L, Dabaja B, Medeiros LJ, Houry JD. Bone Marrow Involvement in Patients with Nodular Lymphocyte Predominant Hodgkin Lymphoma. *Am J Surg Pathol.* 2018 ;42(4):492-499.
11. Chauhan K, Jain M, Shukla P, Grover RK. Bone marrow involvement in Hodgkin's lymphoma: Data from a cancer hospital. *Clin Cancer Investig J* 2016;5:516-20
12. Moid F, DePalma L. Comparison of relative value of bone marrow aspirates and bone marrow trephine biopsies in the diagnosis of solid tumor metastasis and Hodgkin lymphoma. *Arch Pathol Lab Med* 2005;129:497-501.
13. Howard MR, Taylor PRA, Lucraft HH, Taylor MJ, Proctor SJ. Bone marrow examination in newly diagnosed Hodgkin's disease: Current practice in the United Kingdom. *Br J Cancer* 1995;71:210-212.
14. Wang J, Weiss LM, Chang KL, et al. Diagnostic utility of bilateral bone marrow examination: significance of morphological and ancillary technique study in malignancy. *Cancer* 2002; 94: 1522-1531.

Corresponding Author:

Dr. Rimpi Bansal

Professor, Department of Pathology, Gian Sagar Medical College And Hospital, Punjab, India, Postal address- house no.-320, Sector-32-A Chandigarh-160030.

Date of Submission	24 December 2020
Date of Final Revision	11 August 2021
Date of Acceptance	26 October 2021
Date of Publication	30 November 2021