Challenges Encountered and Pattern-Based Analysis of Bone Marrow Biopsy in Lymphomas: An Institutional Experience

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Abstract

Objective The evaluation of bone marrow (BM) status is an integral part of the initial workup of patients diagnosed with lymphoma as it plays an important role in staging and predicting prognosis in these patients. This article determines the incidence and pattern of BM involvement in lymphoma cases and distinguishes benign from malignant lymphoid aggregates in BM biopsies.

Materials and Methods The study group included 121 cases of Hodgkin and non-Hodgkin lymphomas for which BM biopsies were performed, fixed in acetic acid-zinc formalin solution, decalcified using 10% formic acid, and subjected to hematoxylin and eosin and immunohistochemistry.

Results The overall incidence of BM biopsy involvement in our study was 31.4% (37/118), including 34.7% (35/101) in cases of B cell lymphomas, 25% (2/8) in cases of T cell lymphomas, and no involvement in Hodgkin lymphoma. The predominant histological pattern of BM involvement was diffused (14/37; 37.8%), followed by interstitial (10/37; 27.1%). Five cases revealed benign nonparatrabecular lymphoid aggregates which could be confused with lymphomatous involvement, especially in low grade lymphomas.

Conclusion A careful examination of the BM biopsies along with clinical history, peripheral blood examination, flow cytometry, and immunohistochemistry will help in arriving at the correct diagnosis.

Keywords
- marrow
- lymphomas
- Hodgkin lymphoma
- non-Hodgkin lymphoma

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Introduction

The evaluation of bone marrow (BM) status is integral in the initial workup of patients diagnosed with lymphoma as it is the most common site of extranodal involvement[1] in lymphoid malignancies and plays an important role in staging and predicting prognosis in patients with lymphomas. The frequency of BM involvement varies according to the lymphoma subtype. Compared with aggressive lymphomas, relatively high frequencies have been reported in indolent lymphomas, such as mantle cell lymphoma (MCL), follicular lymphoma (FL), and marginal zone lymphoma (MZL).[2] Frequency of marrow involvement is even less in Hodgkin lymphoma (HL) ranging between 2 and 32% with an average of around 10%.[3] Also, BM can be the initial site of detection of lymphoma in patients with unexplained symptoms or cytopenias.[2] Another important consideration is the presence of benign lymphoid aggregates which is relatively uncommon in BM biopsy (BMB) specimens, but when present, their distinction from non-Hodgkin lymphoma (NHL), particularly B cell lymphomas (BCLs), can represent a diagnostic challenge. Therefore, a complete evaluation of BM should be undertaken in all lymphoma patients including complete blood counts, peripheral smears, BM aspiration, BMB, immunohistochemistry (IHC), and flow cytometry.

The aim of this study was to determine the incidence and pattern of BM involvement in lymphoma cases in our institution and to distinguish benign from malignant lymphoid aggregates in BMBs.

Materials and Methods

This is a retrospective study and included 121 cases of NHL and HL received in the Department of Pathology, Homi Bhabha Cancer Hospital and Research Centre, Punjab, India, from January 2015 to December 2019. All the treatment-naive cases of lymphoma for which BM was performed were included despite the primary site being nodal or extranodal while the cases of plasma cell neoplasms were excluded from the study. The BMB was done using a Jamshidi needle from the posterior superior iliac spine and fixed in acid-zinc formalin solution. Decalcification was done using 10% formic acid for 4 to 6 hours. Serial sections of 3 to 4 µm thickness were cut and stained by hematoxylin and eosin. The pertinent patient details regarding age, clinical details, diagnosis, blood counts, peripheral blood smears, and BM aspirate smears were also studied.

Sections were studied for cellularity, normal hematological elements, presence of infiltration, and the extent, histologic pattern, and morphology of infiltration. The morphology and

Table 1 Incidence of BMA and BMB involvement in various histologic subtypes of non-Hodgkin and Hodgkin lymphoma according to the WHO classification

Types of cases	No. of cases	BMB involved	BMB not involved	Inadequate	Percentage of cases with BMB involved (%)	Percentage of cases with BMA involved (%)
DLBCL	57	7	49 (3 benign)	1	12.5	3.5
SLL/CLL	15	13	1 (1 benign)	1	92.8	92.8
Follicular Lymphoma	11	4	7 (1 benign)	–	36.4	27.3
Mantle cell lymphoma	8	6	2	–	75	62.5
Marginal zone lymphoma	3	2	1	–	66.7	33.3
Plasmablastic lymphoma	2	0	2	–	0	0
Primary mediastinal B cell lymphoma	1	0	0	1	–	–
Lymphoplasmacytic lymphoma	1	1	0	–	100	100
T lymphoblastic lymphoma	2	0	2	–	0	0
Anaplastic large cell lymphoma	3	1	2	–	33.3	0
Peripheral T cell lymphoma	3	1	2	–	33.3	0
Unclassified between DLBCL and HL	1	0	1	–	0	0
Unclassified between DLBCL and Burkitt's lymphoma	1	0	1	–	0	0
Hodgkin lymphoma	9	0	9	–	0	0
B cell NHL	4	2	2	–	50.0	50.0
Total	121	37	81	3	31.4	22.9

Abbreviations: BMA, bone marrow aspirate; BMB, bone marrow biopsy; DLBCL, diffuse large B cell lymphoma; SLL/CLL, small cell lymphoma/chronic lymphocytic leukemia; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; WHO, World Health Organization.

histological pattern of infiltration was categorized as diffuse, interstitial, focal nonparatrabecular (FNPT), paratrabecular (PT), and mixed patterns. Diffuse pattern was defined when there was extensive replacement of the marrow elements, both hematopoietic tissue and fat, so that the marrow architecture was effaced; interstitial pattern, when individual neoplastic cells were interspersed between hematopoietic cells and fat; focal, where nodular aggregates were seen separated by normal hematopoietic marrow; and PT, when lymphoma aggregates were seen immediately adjacent to bony trabeculae. IHC was applied for confirmation.

Results

The 121 cases comprised of 77 males and 44 females, male: female ratio being 1.9:1. The age varied from 14 to 89 years. There were 112 cases of NHL including 104 cases of BCLs and 8 cases of T cell lymphomas (TCLs) and 9 cases of HL. Three cases were excluded because the BMB was inadequate including one case of diffuse large BCL (DLBCL), one case of small cell lymphoma/chronic lymphocytic leukemia (SLL/CLL), and one case of primary mediastinal BCL. The cases were classified according to the World Health Organization classification except for four cases of B cell NHL. The BMB was involved in 31.4% (37/118) of the cases with BCL accounting for 34.7% (35/101) and TCL accounting for 25% (2/8) of the cases. No involvement was seen in the cases of HL (►**Table 1**).

The predominant histological pattern of BM involvement was diffuse (14/37; 37.8%), followed by interstitial (10/37; 27.1%), mixed (6/37; 16.2%), PT (4/37; 10.8%), and FNPT (3/37; 8.1%). The diffuse pattern was most commonly seen in cases of SLL/CLL (7). The second common pattern was interstitial seen in four cases of SLL/CLL and two cases of MZL. PT pattern was seen in only one case of FL while seen in two cases of MCL and one case of DLBCL. BM was involved in only two cases of TCL, one anaplastic large cell lymphoma (ALCL) and one peripheral TCL (PTCL) with the patterns of involvement being diffuse and interstitial, respectively (►**Table 2**). The cell morphology at the primary site and BMB was similar in all the cases, no discrepancy was observed in any of the cases. Five of the cases revealed presence of small, ill-defined non-PT aggregates in the biopsies which turned out to be benign lymphoid aggregates on further evaluation and IHC (►**Table 3**).

Table 2 Distribution of different patterns of involvement in various histologic subtypes of non-Hodgkin and Hodgkin lymphoma

Types of cases	No. of cases	BMB involved	Diffuse	Interstitial	Focal (nonparatrabecular)	Paratrabecular	Mixed
DLBCL	57	7	2	1	1	1	2
SLL/CLL	15	13	7	4	–	–	2
Follicular lymphoma	11	4	–	1	1	1	1
Mantle cell lymphoma	8	6	1	1	1	2	1
Marginal zone lymphoma	3	2	–	2	–	–	–
Plasmablastic lymphoma	2	0	–	–	–	–	–
Primary mediastinal B cell lymphoma	1	0	–	–	–	–	–
Lymphoplasmacytic lymphoma	1	1	1				
T lymphoblastic lymphoma	2	0	–	–	–	–	–
Anaplastic large cell	3	1	1	–	–	–	–
Peripheral T cell lymphoma	3	1	–	1	–	–	–
Unclassified between DLBCL and HL	1	0	–	–	–	–	–
Unclassified between DLBCL and Burkitt's lymphoma	1	0	–	–	–	–	–
Hodgkin lymphoma	9	0	–	–	–	–	–
B cell NHL	4	2	2	–	–	–	–
Total	121	37	14	10	3	4	6

Abbreviations: BMB, bone marrow biopsy; DLBCL, diffuse large B cell lymphoma; SLL/CLL, small cell lymphoma/chronic lymphocytic leukemia; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma.

Table 3 List of antibodies used in the current study

Serial no.	Antibody	Source
1	CD20	Dako
2	CD3	Dako
3	CD10	Biocare
5	CD23	Dako
6	CD5	Dako
7	Bcl2	Dako
8	Bcl6	Cell Marque

Discussion

Lymphomas are the most common hematological malignancies, accounting for 5% of all cancers in both genders. Incidence of HL is approximately 2.8 new cases per 100,000 people per year; overall incidence of NHL is approximately 19.7 new cases per 100,000 people per year.[4] BMBs are commonly performed for the staging or initial diagnosis of malignant lymphoma and the frequency of BM involvement in staging marrows for lymphoma are quite variable in literature.[5] Whereas immunophenotyping and molecular genetic studies are useful in some cases, morphology is still considered the gold standard for evaluation of marrow involvement by NHL.[6]

NHL includes a variety of lymphomas ranging from BCL to TCL. The incidence of B cell NHL involving BM varies by the subtype. In general, indolent small cell B-NHL involves BM much more frequently than aggressive B-NHL. SLL involves BM in more than 80% of cases[7,8] and FL involves BM in approximately 40 to 70% of cases.[9,10] Splenic MZL (SMZL) almost always involves BM.[9,10] In contrast, aggressive lymphomas such as T cell/histiocyte-rich large BCL involves marrow in 15 to 60% of cases,[11] whereas DLBCL involves marrow in only 10 to 30% of cases.[12,13] BMB specimens are also crucial for staging and establishing the pattern and extent of BM infiltration by lymphoma.

BM involvement with HL represents stage IV according to the Ann Arbor staging classification, that is, disseminated involvement of an extranodal organ which might lead to modification of treatment. However, the incidence of BM involvement in these patients varies between 4 and 14% in various series reported during the past 20 years.[14]

Lymphoid aggregates being an uncommon and confusing finding in biopsy specimens require diligent distinction from lymphoma involvement to avoid overstaging of the disease. It has been reported that benign lymphoid aggregates tend to

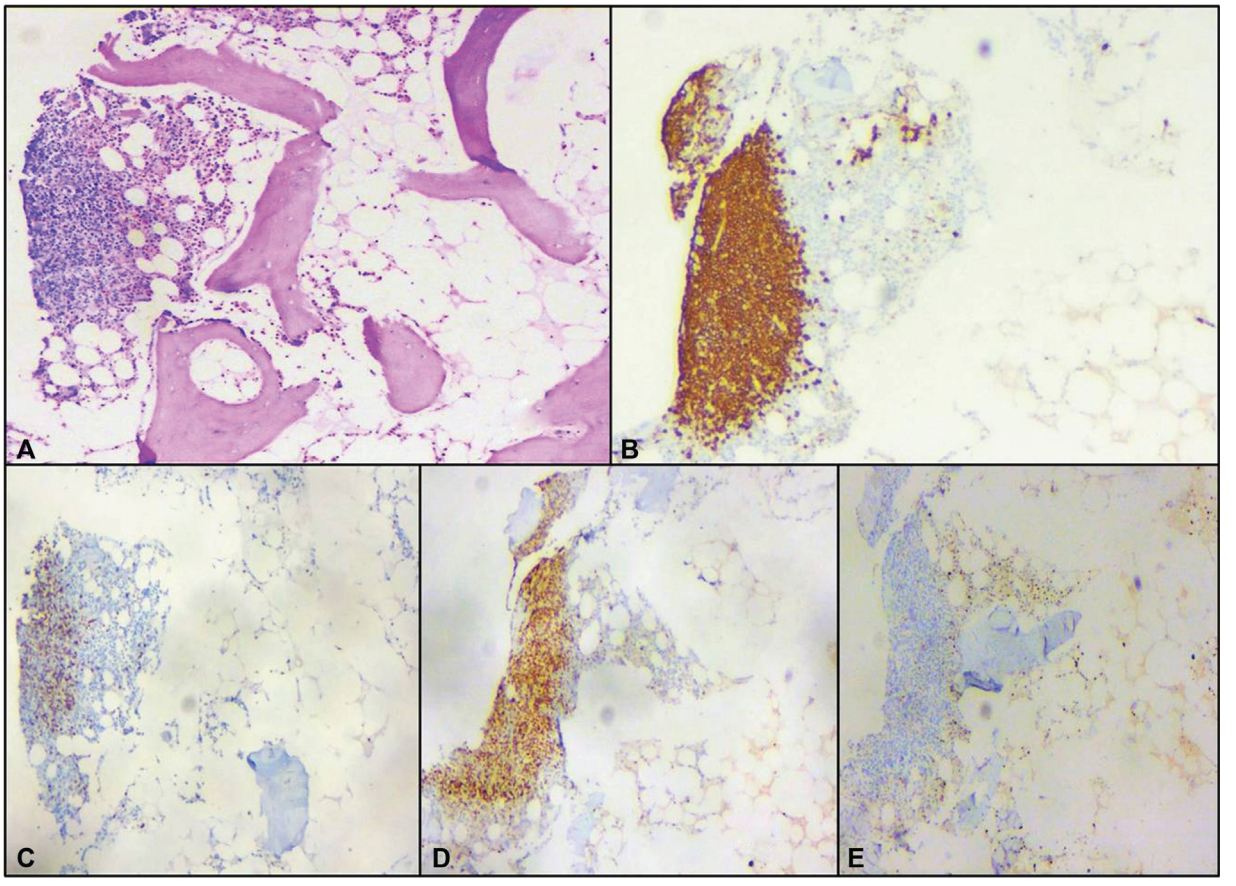

Fig. 1 Benign lymphoid aggregates showing mixed population of B and T cells. (**A**) Hematoxylin and eosin (H&E), 100× magnification; (**B**) CD20 positivity in B cells, 100× magnification; (**C**) CD3 positivity in T cells, 100× magnification; (**D**) Bcl2 positivity in B and T cells, 100× magnification; (**E**) low Mib-1 labeling index, 100× magnification.

have a non-PT location, distinct borders without interstitial spillage of lymphoid cells, and are typically small (< 600 µm).[15,16] Moreover, the loss of benign aggregates in deeper sections is considered a prominent indicator of a benign process.[17] Also, an increased incidence of benign lymphoid aggregates in patients with lymphoma who have been treated with rituximab has been reported. These aggregates are often found in postchemotherapy BM specimens and can mimic residual lymphoma[18] (►**Figs. 1** and **2**).

On IHC, benign aggregates often consist predominantly of normal-appearing T cells, contain a central core of T cells surrounded by B cells, or have a mixed haphazard distribution of B and T cells. The predominance of B cells within the aggregates, the presence of a core of B cells surrounded by T cells (except in germinal center formation), cytologic atypia, PT location, infiltrative edges, and large lymphoid aggregates that increase in size in deeper sections are all features that should raise suspicion of BM involvement by a lymphoproliferative disease[19] (►**Figs. 1** and **2**).

In addition, many problems arise during evaluation of lymphomatous involvement of the BM as the cytological features and IHC findings are difficult to interpret on decalcified biopsy sections. Thus, selection of a proper decalcification agent is of prime importance along with the standardization of staining procedure.

In our study, the involvement of BM in cases of NHL was 31.4% (37/118) while the nine cases of HL in our study did not show BM involvement. Other studies have described a considerable variation in the BM involvement in lymphoproliferative disorders, ranging between 27.6 and 53%.[8,20–23] The variation in the studies may be due to unequal proportion of various lymphomas included and also the unequal percentages of early and advanced cases.

The maximum BM involvement was seen in lymphoplasmacytic lymphoma (LPL; 100%), followed by SLL/CLL (92.8%), MCL (75%), and MZL (66.7%). This is in accordance with the fact that low grade indolent lymphomas have a predilection for marrow involvement. The lowest incidence of marrow involvement was seen in DLBCL (12.5%) which was also the case with that of Arber and George[8] and Kumar et al.[24]

The predominant pattern of involvement in our study was diffuse followed by interstitial which might be due to the greater number of SLL/CLL cases in which the marrow was involved. This was different from that of Arber and George for whom the predominant pattern was mixed,[8] and also that of Foucar et al[21] who found the marrow involvement to be predominantly focal.

SLL/CLL had the highest incidence of marrow involvement (13/14; 92.8%). The incidence of BM involvement in SLL/CLL varies from 30 to 90% in the reported series.[25] The predominant histological pattern was diffuse (7) followed by interstitial (4) and mixed pattern (2). The mixed pattern consisted of one case with nodular and interstitial pattern and the other with nodular and PT pattern. Some workers have found the diffuse pattern to have a worse prognosis than the nondiffuse pattern (interstitial and nodular).[26] On IHC, the lymphoid cells were positive for CD20, CD5, and CD23 while they were negative for cyclin D1.[2] The incidence of aspirate involvement was similar to that of biopsy, being 92.8% (13/14) (►**Fig. 3A–C**).

MCL revealed BM involvement in six out of eight cases (75%; 6/8) out of which one case was high grade and the other

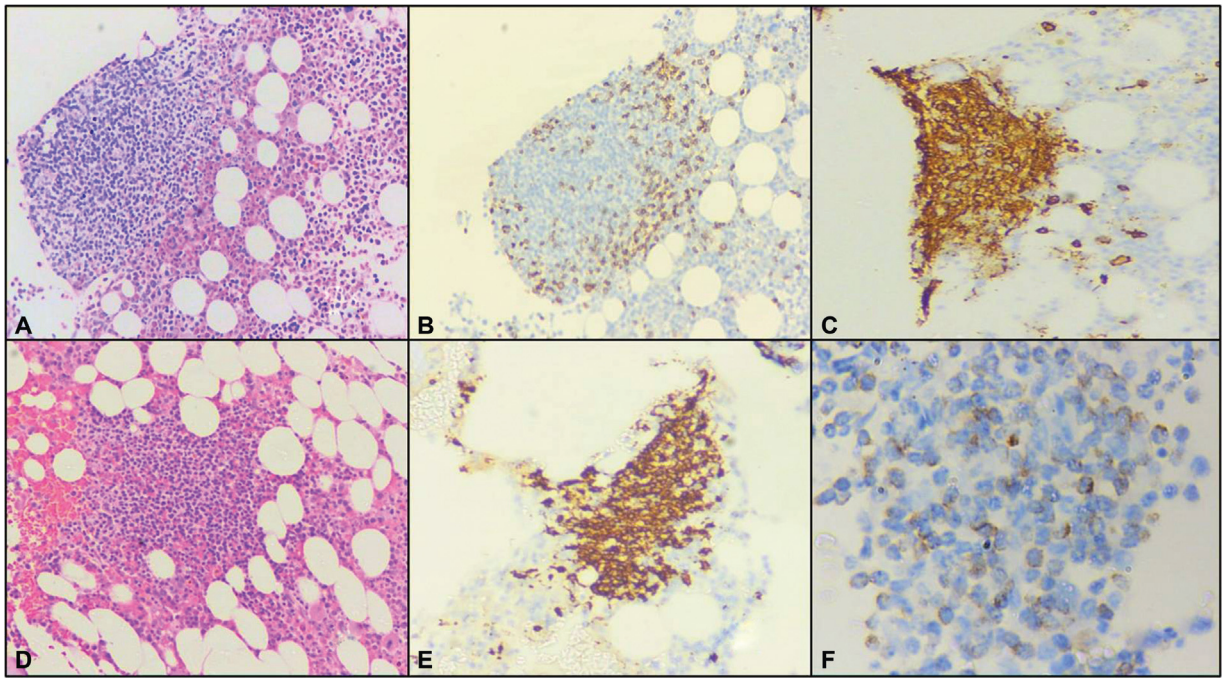

Fig. 2 Benign lymphoid aggregates showing mixed population of B and T cells: (**A**) Hematoxylin and eosin (H&E), 100× magnification; (**B**) CD20 positivity in B cells, 100× magnification; (**C**) CD3 positivity in T cells, 100× magnification; Benign lymphoid aggregates showing predominantly B cells: (**D**) H&E, 100× magnification; (**E**) CD20 positivity in B cells, 100× magnification; (**F**) Bcl-2 highlighting scattered cells, 400× magnification.

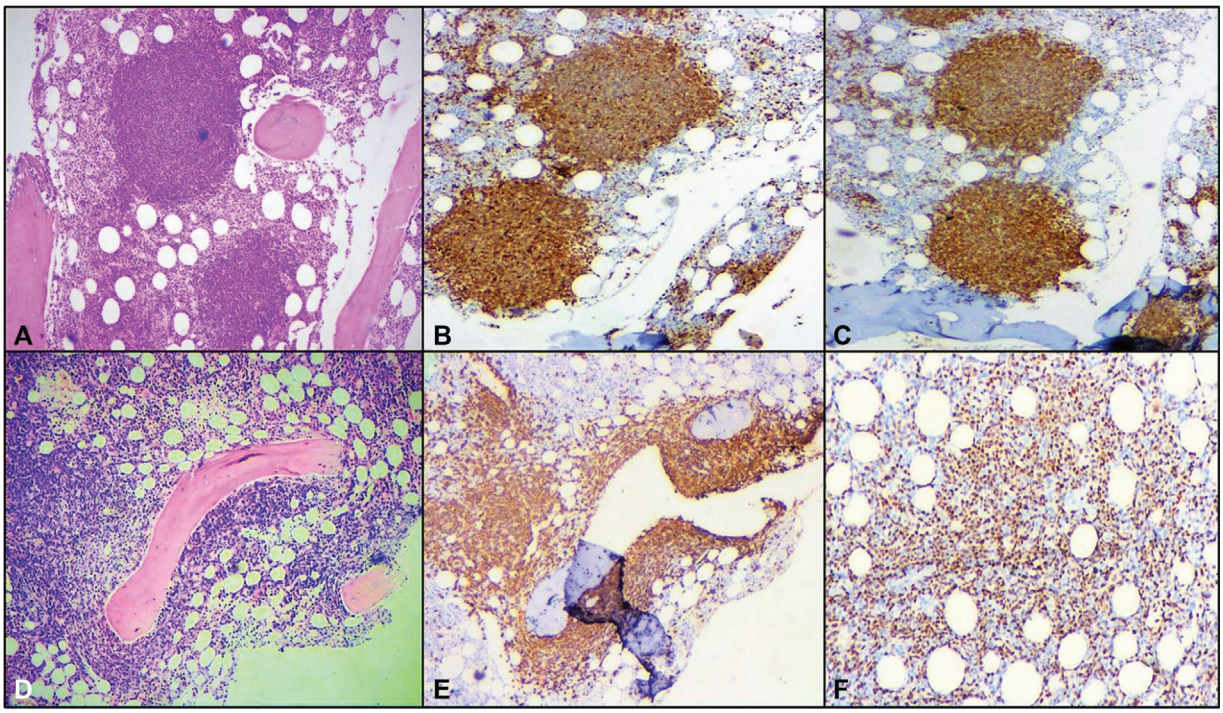

Fig. 3 (**A**) Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) nodular pattern, hematoxylin and eosin (H&E), 40× magnification; (**B**) CLL/SLL, CD5 positivity, 40× magnification; (**C**) CLL/SLL, CD23 positivity, 40× magnification. (**D**) Mantle cell lymphoma (MCL), paratrabecular pattern, H&E, 400× magnification; (**E**) MCL, CD20 positivity, 40× magnification; (**F**) MCL, cyclin-D1 positivity, 100× magnification.

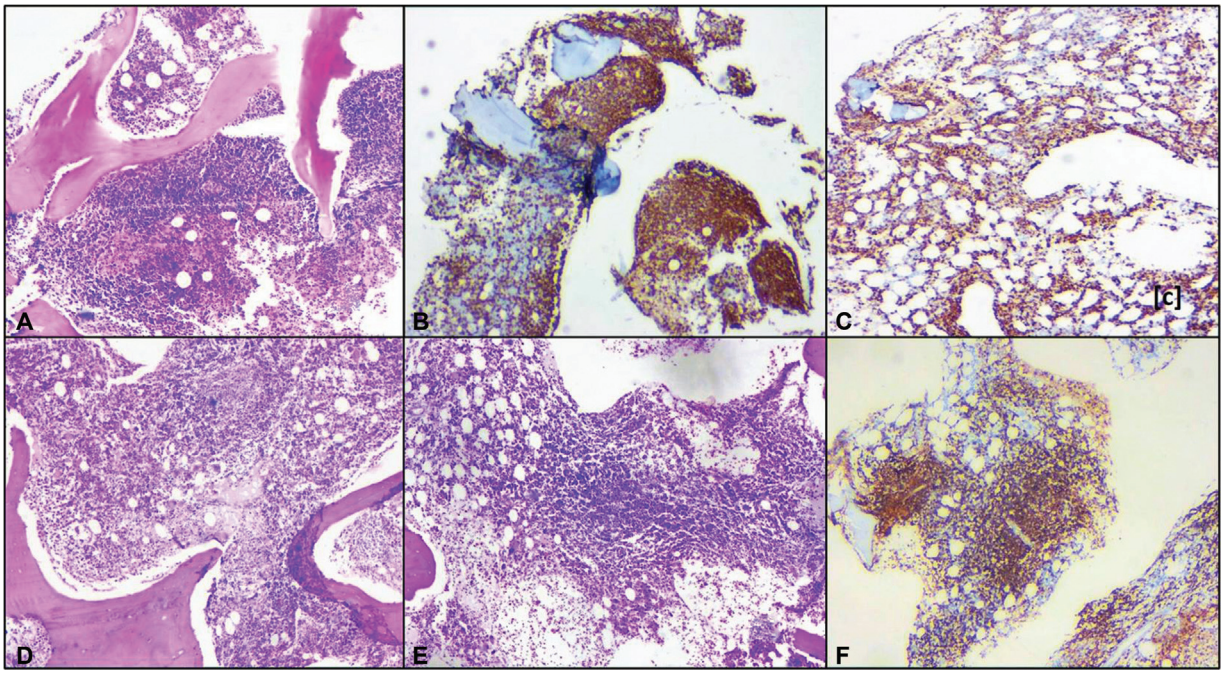

Fig. 4 (**A**) Follicular lymphoma (FL), interstitial pattern, hematoxylin and eosin (H&E), 40× magnification; (**B**) FL, CD20 positivity, 40× magnification; (**C**) FL, CD10 positivity, 100× magnification; (**D** and **E**) Marginal zone lymphoma (MZL), interstitial pattern, H&E, 400× magnification; (**F**) MZL, CD20 positivity, 40× magnification.

was blastoid variant. The predominant pattern of involvement was PT (2) followed by diffuse (1), interstitial (1), focal (1), and mixed pattern (1) consisting of interstitial and PT patterns. The lymphoid cells were highlighted by IHC for CD20, CD5, and cyclin D1 while they were negative for CD23 and CD10.[2] The incidence of aspirate involvement was 62.5% (⅝) (►**Fig. 3D, E**).

FL revealed biopsy involvement in 4 out of 11 cases (36.4%; 4/11) while the aspirate was involved in 3 cases (27.3%; 3/11). The patterns of involvement were PT,

interstitial, FNPT, and mixed. The classic PT pattern[2,8] was seen in only one case in our study. The biopsy involvement in our case was comparable with that of Arber and George.[8] The involvement was confirmed by positivity for CD20, CD10, and bcl-2 and negativity for CD5, CD23, cyclin D1, and bcl-6[2] (►**Fig. 4A–C**).

MZL including SMZL revealed involvement in biopsy in two out of three cases (2/3; 66.7%) and 33.3% (1/3) in aspirates with the histomorphological pattern of involvement being interstitial. A predilection for sinusoidal infiltration is highly characteristic of SMZL in BM[2] which was not observed in our case. The aggregates were positive for CD20 and bcl2, while being negative for CD10, CD5, CD23, and cyclin D1[2] (►**Fig. 4D, E**).

LPL is an indolent B cell lymphoproliferative disorder with variable plasmacytoid differentiation. In blood and BM, a spectrum of small lymphocytes, plasmacytoid lymphocytes, and plasma cells is typical.[2] We only had a single case of LPL which revealed BM involvement (100%; 1/1). BM aspiration also revealed lymphocytosis and these cells were positive for CD20 and weakly positive for bcl2 with IHC.

Out of the seven cases of DLBCL showing biopsy involvement (12.5%; 7/56), two cases revealed diffuse pattern, two cases mixed pattern, and one case each of FNPT, interstitial, and PT pattern. The mixed pattern included FNPT and PT pattern in one case and diffuse, interstitial, and PT pattern in the other case. The involved areas were highlighted by diffuse positivity for CD20.[2] Marrow infiltration portends a poor prognosis, especially the diffuse pattern that was seen in two of the cases.[2] The aspirate revealed involvement of 5.5% (3/55) in DLBCL cases (►**Fig. 5A–D**).

As a group, mature T cell and natural killer cell lymphomas account for only 7% of all NHLs with a broad range in the incidence of BM involvement.[7,8] The immature T cell neoplasms consisted of T lymphoblastic lymphomas which did not show marrow involvement in our study. Also probably, a lower number of TCLs in our study led to an overall lower incidence of marrow involvement in these cases (25%; 2/8) which was comparable with that of Arber and George.[8] The presence of a mixture of atypical cells with histiocytes, small vessels, plasma cells, and eosinophils are helpful clues to BM involvement by TCL.[8]

In our study, marrow involvement was seen in one case of ALCL (33.3%; 1/3) with a diffuse pattern of involvement which was supplemented with diffuse membranous positivity for CD30 (►**Fig. 6A, B**). One out of three cases (33.3%; 1/3) of PTCL revealed marrow involvement with an interstitial histomorphological pattern (►**Fig. 6C, D**). However, no pattern is characteristic of lymphoma involvement in TCLs.[2] In

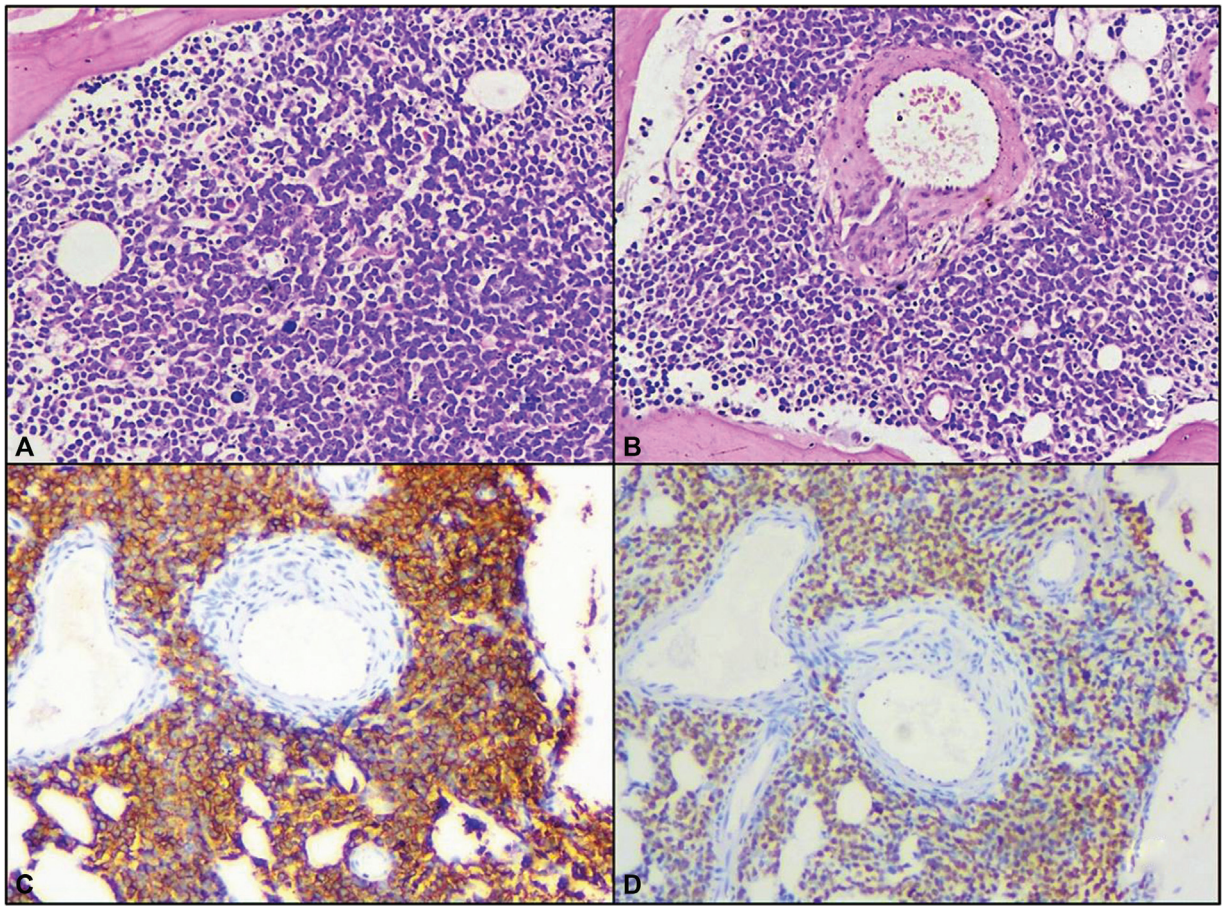

Fig. 5 (**A**) Diffuse large B cell lymphoma (DLBCL), diffuse pattern, hematoxylin and eosin (H&E), 100× magnification; (**B**) DLBCL, diffuse pattern, H&E, 100× magnification; (**C**) DLBCL, CD20 positivity, 100× magnification; (**D**) DLBCL, high Mib-1 labeling index, 100× magnification.

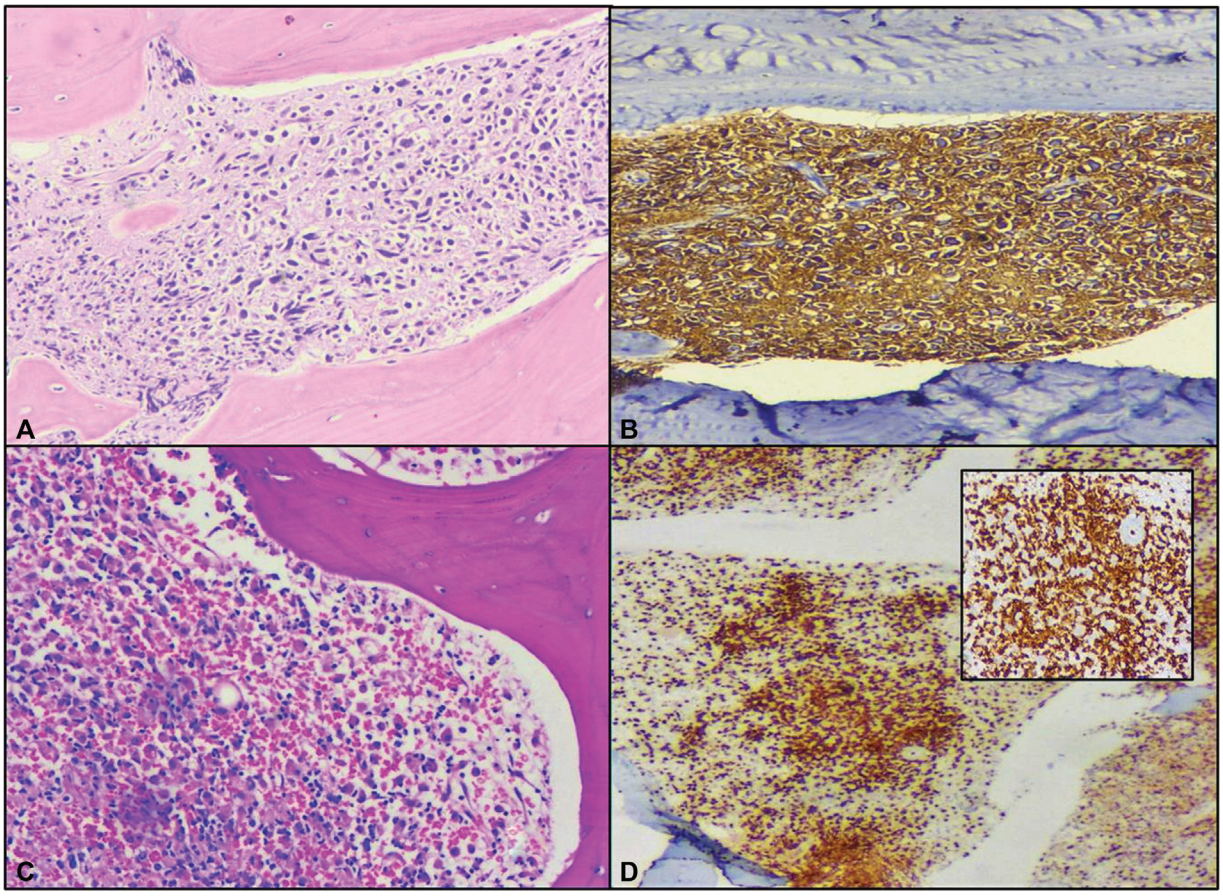

Fig. 6 (**A**) Anaplastic large cell lymphoma (ALCL), diffuse pattern, hematoxylin and eosin (H&E), 100× magnification; (**B**) ALCL, CD30 positivity, 100× magnification. (**C**) Peripheral T cell lymphoma (PTCL), interstitial pattern, H&E, 100× magnification; (**D**) PTCL, CD3 positivity, 40× magnification; inset shows CD3 positivity at 100× magnification.

the BM aspirate, no involvement was seen in ALCL while 33.3% (1/3) involvement was seen in PTCL cases.

Conclusion

BMB is an important investigation for staging and evaluation of lymphomas and is performed even when the likelihood of involvement is low, as it may portend an inferior clinical outcome and impact therapy selection. The BMB was involved in 31.4% (37/118) of the cases, which might be due to the higher number of DLBCL cases in our institute astounding the fact that high grade lymphomas tend to involve the marrow in lesser number of cases. The most common pattern of involvement was diffuse (37.8%; 14/37) followed by interstitial (27.1%; 10/37). An important finding to be kept in mind is the presence of benign lymphoid aggregates in BMBs which may lead to overstaging in lymphoma patients. A good knowledge of morphology and IHC along with the clinical details and peripheral blood picture helps in guiding the pathologist toward the correct diagnosis.

Conflict of Interest
None declared.

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