Bone Marrow and Peripheral Blood Evaluation in Non-Hodgkin Lymphoma – A Cross Sectional Study of 78 Cases in a Tertiary Care Centre in Kerala

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ABSTRACT

BACKGROUND

In the evaluation of patients with non-Hodgkin lymphoma (NHL), determination of bone marrow involvement is an integral part of staging work up. Peripheral blood counts and examination of blood smears are also done in patients with lymphoma as part of pre-treatment investigations.

METHODS

A cross sectional study of 78 patients with a prior histopathological diagnosis of NHL was conducted. Peripheral blood counts were performed on an automated haematology analyser to look for various cytopenias. Peripheral blood smears and bone marrow aspirate (BMA) / imprint smears were examined in detail for atypical lymphoid cells. Bone marrow trephine biopsies of these patients were studied to assess the NHL involvement and the various patterns of involvement. Adjuvant immunohistochemistry (IHC) was performed in bone marrow biopsies with scant cellularity or crush artefact to discern the marrow involvement.

RESULTS

Bone marrow trephine biopsy showed involvement by lymphoma in 65.4 % cases. The incidence of involvement was higher in B-cell lymphomas, especially in low grade types. The predominant pattern of involvement was interstitial pattern (41.2 %). Discordant histology between bone marrow and the primary anatomic site was found in 7.8 % of the cases, which was seen more in diffuse large B-cell lymphomas. Majority of the patients with bone marrow infiltration by NHL had anaemia (84.3 %). Bicytopenia and pancytopenia were also observed. On peripheral blood smear examination atypical lymphoid cells were present in 23 % cases.

CONCLUSIONS

Bone marrow examination is an important aspect in the diagnosis of NHL, because of its both prognostic and therapeutic implications. Hence, the presence of atypical lymphoid cells and other changes in the peripheral blood should be detected in these patients.

KEYWORDS

Non-Hodgkin Lymphoma, Bone Marrow Biopsy, Bone Marrow Aspirate / Imprint, Peripheral Blood Smear, Atypical Lymphoid Cells

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BACKGROUND

Non-Hodgkin lymphomas (NHL) are malignant neoplasms arising as monoclonal disorders from lymphoid cells at different stages of differentiation, forming a heterogeneous group of neoplasms each with distinct clinical, morphological, immunophenotypic, genetic features and different response to therapy. The incidence rates of NHL have been rising in India like in other parts of the world.[1,2,3] Part of the increase has been attributed to recent diagnostic improvements as well as AIDS-related neoplasms following the human immunodeficiency virus (HIV) epidemic.[4,5] Non-Hodgkin lymphomas have the propensity to infiltrate extra lymphatic tissues, especially bone marrow as part of their natural history. The most common site of extranodal involvement in lymphoid malignancies is bone marrow and the frequency of bone marrow involvement varies depending on the lymphoma type.[6] Compared to aggressive lymphoma, indolent lymphomas have got relatively high frequencies of bone marrow involvement.[6,7] As the bone marrow involvement in lymphoma is definite evidence of disseminated disease, assessment of bone marrow status in patients with lymphoma provides important information for decisions regarding treatment.[8]

Currently, non-invasive clinical staging by computed tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography (PET) scan cannot fully assess bone marrow involvement, which is possible only by pathological staging (aspiration and trephine biopsy). Determining bone marrow status is important for the prognosis of patients, which is best assigned using the international prognostic index (IPI). IPI consists of five clinical risk factors: Age ≥ 60 years, serum lactate dehydrogenase levels elevated, performance status ≥ 2 eastern co-operative oncology group (ECOG), Ann Arbor stage III or IV and > 1 site of extranodal involvement. Of these, bone marrow statuses can influence both stage and extranodal involvement.[9]

Non-Hodgkin lymphomas are characterized by frequent abnormalities in the peripheral blood counts, commonly involving various types of cytopenias and leucoerythroblastic blood picture. In patients with bone marrow infiltration, the peripheral blood manifestations are more frequent and more severe. Occasionally, atypical lymphoid cells (lymphoma cells) spill over in the peripheral blood and can be recognized in the peripheral blood smear on careful inspection. It is probable that the presence of atypical lymphoid cells in the peripheral blood would be more in patients presenting late and with bone marrow infiltration.

Objectives

1. To evaluate the histological patterns of bone marrow involvement in different types of Non-Hodgkin lymphomas.
2. To evaluate the changes in peripheral blood counts including various types of cytopenias and presence of atypical lymphoid cells in different types of NHL.

METHODS

A hospital based cross sectional study was done in the Department of Pathology, Government Medical College, Thrissur, Kerala from November 2017 to August 2019. A total of 78 patients with a prior histopathological diagnosis of NHL, belonging to all age groups and both sexes were included. Peripheral blood counts were performed on an automated haematology analyser. Peripheral blood smears were stained using the Leishman stain and a 100 - cell differential leucocyte count was performed. The percentage and morphology of atypical lymphoid cells were noted. Bone marrow aspirate / imprint smears were stained using the Wright stain and a 500-cell differential leucocyte count were performed.

Marrow lymphocytosis was detected by examination of the marrow smear and defined as the presence of more than 20 % lymphocytes. Bone marrow trephine biopsies were fixed in Bouin's fluid, decalcified using 4 % nitric acid. 4 micron-thick sections were stained with haematoxylin and eosin. Presence of NHL infiltrates and pattern of involvement was assessed.

Statistical Analysis

Data thus obtained was entered in Microsoft Office Excel sheet. This was then analysed using statistical package for social sciences (SPSS) software.

RESULTS

The 78 cases of NHL studied comprised of 46 male and 32 female patients and the age of patients ranged from 16 to 83 years. There were 70 (89.7 %) cases of B-cell lineage and 8 cases of T-cell lineage. The overall incidence of marrow involvement by NHL was 65.4 % (51 / 78). Of the B-cell lymphomas, 66 % cases (46 / 70) and 63 % cases (5 / 8) was of the T-cell lymphomas showed bone marrow involvement. Among the B-cell lymphomas, marrow involvement was found to be more in follicular lymphoma (FL) (92 %) compared to that by diffuse large B-cell lymphoma (51 %).

NHL Type	Frequency	BM Involved	Atypical Lymphoid Cells in Peripheral Blood
B cell NHL	70	46	20
FL	12	11	6
DLBCL	37	19	7
SLL	3	3	2
MCL	2	2	2
LBL	1	1	0
Others	15	10	3
T cell NHL	8	5	3
PTCL	6	4	2
MF	1	0	0
AITL	1	1	1

Table 1. NHL Cases with Bone Marrow Infiltration and Atypical Lymphoid Cells in Peripheral Smear

The predominant histological pattern of involvement by Non-Hodgkin lymphoma was interstitial (41.2 %), followed by mixed (39.2 %), diffuse (13.7 %) and paratrabecular pattern (3.9 %). Of the mixed pattern, 11 of the 20 cases

had predominantly interstitial and paratrabecular involvement and comprised mainly of follicular lymphoma (five cases) and mantle cell lymphoma (two cases). Follicular lymphoma showed a predilection for paratrabecular area, with most of the cases showing mixed pattern with paratrabecular and interstitial pattern (5 / 10) and only paratrabecular pattern in two cases.

Paratrabecular pattern was also seen in two cases of mantle cell lymphoma and a single case of diffuse large B cell lymphoma. Diffuse and interstitial patterns were observed in T-cell neoplasms. Discordant histology between bone marrow and the primary anatomic site was also found in 4 cases of diffuse large B-cell lymphoma. All the involved marrows were normocellular to hypercellular.

The normal hematopoietic elements were markedly decreased in cases with diffuse involvement. An increase in reticulin was seen in cases with bone marrow infiltration. Immunohistochemistry was done for B and T cells antigens to demonstrate the bone marrow involvement in cases with minimal involvement and also to distinguish from reactive lymphoid aggregates.

Bone marrow aspirate showed lymphocytosis in 45 / 78 (57.7 %) cases. Bone marrow aspirate was negative in 11.7 % (6 / 51) cases showing positive bone marrow biopsy. This was especially seen in cases of diffuse large B-cell lymphoma (DLBCL). Peripheral blood counts showed various cytopenias, of which anaemia was the commonest one (84.3 %), followed by thrombocytopenia (25.5 %) and leucopenia (13.7 %) respectively.

Among those patients who presented with leucocytosis (15.6 %; 8 / 51), 7.8 % (4 / 51) had significant lymphoma cell spill over in the peripheral blood and of the rest, three cases had leukoerythroblastic blood picture. Atypical lymphoid cells were identified in the peripheral blood. Smears of 45.1 % of cases. In three cases, atypical cells were > 40 %. Morphology of atypical lymphoid cells depends on the histological type of NHL.

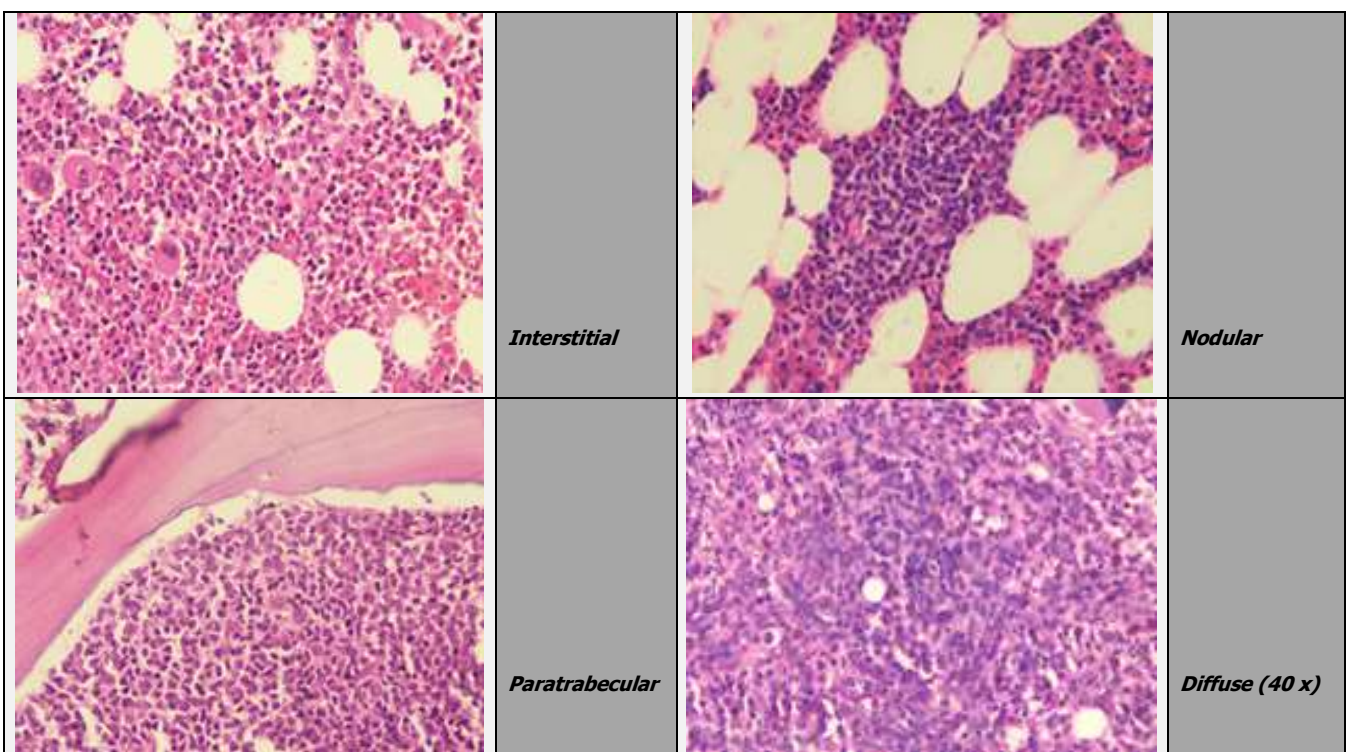


Figure 1. Patterns of Bone Marrow Involvement in Trephine Biopsy

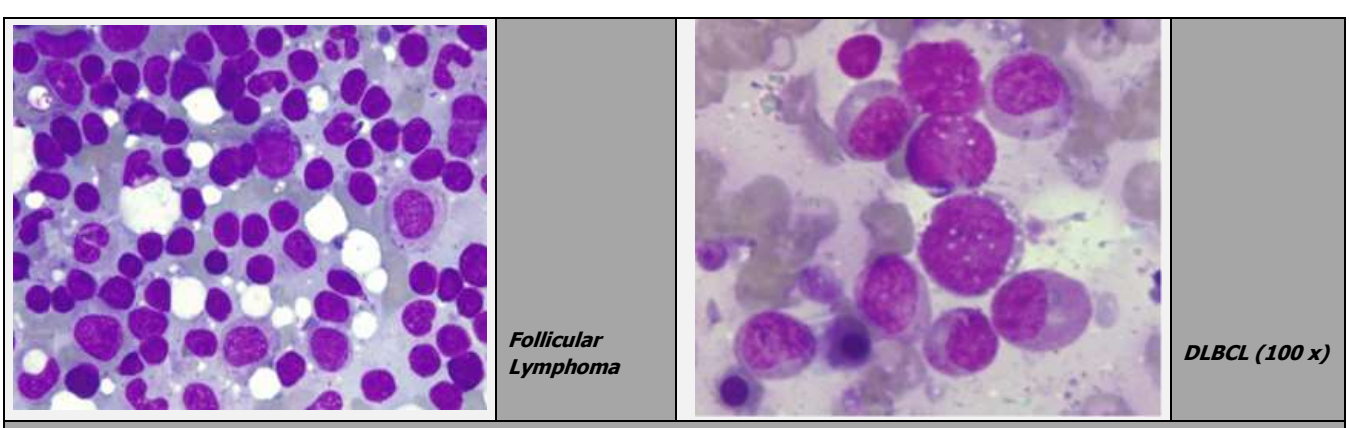
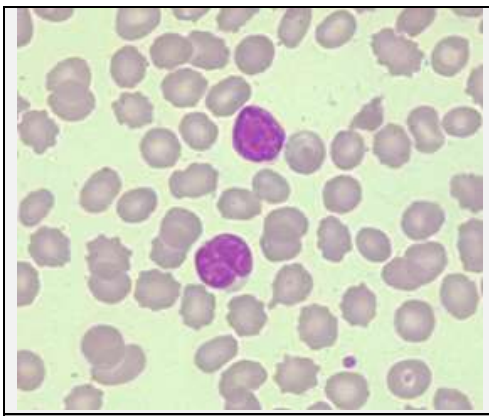
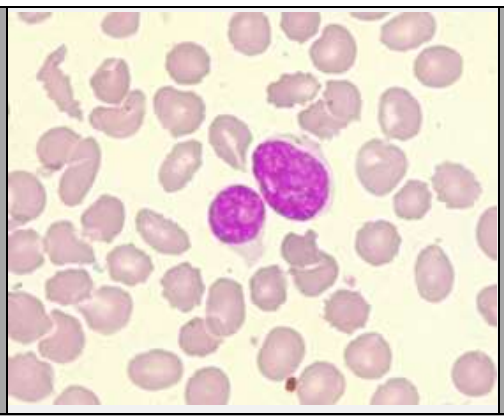


Figure 2. Bone Marrow Lymphocytosis in Bone Marrow Aspirate / Imprint



Follicular Lymphoma



DLBCL (100 x)

Figure 3. Peripheral Smear Showing Atypical Lymphoid Cells

DISCUSSION

The patients diagnosed with NHL of any histological type are subjected to bone marrow examination, to evaluate for stage IV disease. This is required to determine prognosis of the patient, selection of appropriate therapeutic protocols and response to therapy.[8,10] Also, peripheral blood counts including careful examination of the blood smears are an important part of pre-treatment laboratory protocol.[11]

In the present study, 78 cases of biopsy-proven cases of Non-Hodgkin lymphoma were studied. Overall incidence of marrow involvement by NHL was 65.4 % (51 / 78). This is similar to the incidence in the study conducted by Bartl et al.[12] in a larger series of 3229 patients with lymphoproliferative disorders, which showed bone marrow involvement in 64 % of NHLs. Other studies have shown a much variation in the frequency of marrow disease.[13,14] These variations can be due to the inclusion of unequal proportions of patients with early and advanced disease. Also, as the incidence of bone marrow involvement varies greatly according to the histological sub-type, inclusion of different proportions of various histological subtypes of Non-Hodgkin lymphomas in the different studies may account for this variation.[15]

The relative frequency of bone marrow involvement showed a great variability with the different histopathological subtypes of the NHL. In the present study, the incidence of the bone marrow involvement by B-cell lymphomas (65.7 %) was greater than that of T-cell lymphomas 62.5 %. This was similar to other studies.[6,7]

Among all the B-cell lymphomas, marrow involvement was found to be more in low-grade lymphomas like follicular lymphoma (92 %) compared to that by diffuse large B-cell lymphoma (51 %). The predominance of myelo-involvement in the indolent group of Non-Hodgkin lymphomas is in agreement with other authors.[16] DLBCL had a relatively lower frequency of marrow involvement in other studies also.[17,18]

Various patterns of bone marrow involvement were encountered in the bone marrow biopsies of different lymphomas.[19] The predominant histological pattern of involvement by Non-Hodgkin lymphoma was interstitial (41.2 %), followed by mixed (39.2 %), diffuse (13.7 %) and paratrabecular pattern (3.9 %). The study conducted by Lee et al.[18] also reported the predominance of the interstitial patterns (56 %). But this is different from other studies like that conducted by Arber et al.[17] which showed a much lower incidence of the interstitial pattern. This could be best explained by the differences in the histopathological sub-types included in the study. Of the mixed pattern, 11 of the 20 cases had predominantly interstitial and paratrabecular involvement and comprised mainly of follicular lymphoma (five cases) and mantle cell lymphoma (two cases).

Follicular lymphoma showed a predilection for paratrabecular area, with most of the cases showing mixed pattern with paratrabecular and interstitial pattern (5 / 10) and only paratrabecular pattern in two cases. Paratrabecular pattern was also seen in two cases of mantle cell lymphoma and a single case of diffuse large B cell lymphoma. Higher incidence of paratrabecular pattern in follicular lymphoma was also seen in the study conducted by Arber et al.[17] In none of the cases of Peripheral T cell lymphoma, unspecified, mixed patterns were observed. Diffuse and interstitial patterns were observed in T-cell neoplasms. The focal nodular pattern was found as part of a mixed pattern only.

The histopathological quantitation of tumour cell burden in bone marrow biopsies with lymphoma is clinically more beneficial because of the prognostic significance. Accordingly, diffuse involvement of marrow indicates high-risk patients, having an advanced disease as well as an unfavourable histology and a worse prognosis. Lymphoma patients with focal paratrabecular bone marrow involvement only, have a more favourable prognosis and correlate with a low or intermediate grades lymphomas of favourable histology.[20] Bone marrow aspiration may have a contribution in this context as the degree of involvement is quantitated by the percent of lymphoid element infiltration to the total marrow cellularity.[21] But the distortion of normal bone marrow architecture, differences in procedure performed and possible dilution of bone marrow by blood during suction may render this accuracy questionable. Discordant histology between bone marrow and the primary anatomic site was also found in 7.8 % (4 / 51) of the cases. "Discordance" refers to those lymphoma cases where two distinct histologic sub-types coexist in at least two separate anatomic sites. Histologic discordance is most commonly observed between the bone marrow and lymph nodes. Often an aggressive lymphoma is typically found in the lymph node and an

indolent lymphoma in the bone marrow biopsy.[22,23] In the present study, discordance was seen in diffuse large B-cell lymphomas. This is similar to other studies also.[24,25] All the involved marrows were normocellular to hypercellular. The normal hematopoietic elements were markedly decreased in cases with diffuse involvement. Another feature seen in association with bone marrow infiltration is fibrosis, which can be used as a parameter to look for atypical lymphoid cell infiltration.[21,26] Some of the bone marrow biopsies free of lymphoma in the present study had a reactive benign lymphocytosis. In histological sections, both the pattern of infiltration and cytological characteristics should be taken into consideration. Interstitial and nodular infiltration can occur both in neoplastic and reactive conditions. Paratrabecular pattern and a 'packed marrow' (diffuse infiltration) almost always indicate neoplasia.[27] Nodular infiltrates should be distinguished from reactive nodular hyperplasia. Benign lymphoid nodules were mostly encountered in indolent small cell lymphomas of elderly patients. This is in agreement with Arber et al.[17] who described benign follicular structures in of a series of follicular lymphoma.

Reactive lymphoid nodules are usually small with well-defined margins and have heterogeneous and free of atypia.[28] Neoplastic nodular lymphoid infiltrates are usually larger with less well-defined margins, often extending outwards around fat cells, and have a relatively homogeneous cellular composition.[27] In a few cases where morphological distinction were difficult, IHC was done for B and T cells antigens to demonstrate the heterogeneous (mostly T-cell populated) nature of reactive lymphoid aggregates versus the neoplastic nodules. This has been recommended in several studies.[29] Bone marrow biopsies having a minimal involvement with a concealed interstitial pattern distribution were difficult to diagnose.[29,30] IHC was done in these cases to demonstrate the spare neoplastic population.[31,32] Bone marrow aspirate showed lymphocytosis in 45 / 78 (57.7 %) cases. The reliability of bone marrow biopsy was much higher than that of bone marrow aspirate in the diagnosis of the disease. This is in accordance with many different studies.[18,30] Bone marrow aspirate was negative in 11.7 % (6 / 51) cases showing positive bone marrow biopsy. This was especially seen in cases of DLBCL. Bone marrow biopsy was necessary for a conclusive diagnosis.[33] False-negative results or deferred inconclusive diagnosis in bone marrow aspirate were best explained by inadequacy or dry tap of packed marrow or in cases with myelofibrosis, non-representative sample of a focal disease (i.e. an early concealed paratrabecular infiltration) or bland tumour cell cytomorphology, mostly in the indolent small cell NHLs.[34,35] The rate of false results of smears can be reduced by the use of ancillary studies of cytochemistry and flow cytometry for confirmation of clonality and phenotype.[10] In the case of dry tap or inconclusive diagnosis, a combination approach of an additional bilateral bone marrow biopsy (BMB) with fresh tissue cytology imprint preparation obtained from the can be used biopsy.[36,37]

Peripheral blood counts are essential for the pre-treatment workup in cases of non-Hodgkin lymphoma and they also have prognostic implications, especially if there is deviation from normalcy (3). Although, Bhatia et al.[19] have observed that haemogram of patients of NHLs does not have a dependable predictive value for bone marrow infiltration, other workers have noted a low frequency of bone marrow infiltration in patients presenting with Hb level > 11.5 g/dl and platelet count > 10 x 10^9/l.5 l

Various cytopenias are frequently observed in all types of non-Hodgkin lymphomas.[38] These are more frequent and may be severe in patients who present with bone marrow infiltration by the disease. The presence of at least one abnormal parameter in the complete blood counts is observed in 57 – 85 % of NHL patients in different studies.[39,40]

In the present study among the various cytopenia observed, anaemia was the commonest one (84.3 %), followed by thrombocytopenia (25.5 %) and leucopenia (13.7 %) respectively. Bicytopenia was observed in 15.6 % and pancytopenia in 9 % of patients. These cytopenias are caused by the cytokines released by the malignant clones of cells and also due to bone marrow replacement by lymphoma cells at a later stage.[41] Those patients who presented with leucocytosis (15.6 %; 8 / 51), 7.8 % (4 / 51) had significant lymphoma cell spill over in the peripheral blood and of the rest, three cases had leukoerythroblastic blood picture.

Also, a careful examination of the peripheral blood smears was done for the atypical lymphoid cells. In the study, atypical lymphoid cells were identified in 45.1 % of cases. In three cases, atypical cells were > 40 %. In previous studies, some workers have observed the relatively low frequency of atypical cells in the peripheral blood, and others have shown a higher tendency towards such a phenomenon.[39] Arber et al.[17] observed peripheral blood involvement in 29 % of their 197 cases of various types of NHL. Jeong et al.[15] observed peripheral blood involvement by lymphoma in 35.6 % of their cases. There is a greater tendency of the appearance of lymphoma cells in the peripheral blood in follicular lymphomas and mantle cell lymphoma.[42] Morphology of atypical cells in the peripheral blood usually depends on the histological type of NHL.[41] In small cell lymphoma, these cells are essentially normal-looking mature lymphocytes with coarse chromatin pattern, no nucleolus and a round nucleus, with no evidence of nuclear cleavage. The cells in follicular lymphoma are typically small-sized, with scant cytoplasm and cleaved nucleus with an irregular nuclear outline. In mantle cell lymphoma, the cells are smaller than the blast cells and larger than mature lymphocytes, have a scanty-moderate amount of cytoplasm and round or irregular-outlined nuclei with distinct nucleoli.[43] In diffuse large B cell lymphomas, these cells are large-sized, having relatively loose chromatin patterns and distinct nucleoli.[44]

It is important to detect the presence of these atypical lymphoid cells, as further bone marrow evaluation can be performed in such patients. Thus, can come to an earliest diagnosis in such patients.

CONCLUSIONS

This study highlights the incidence and different patterns of involvement in the bone marrow by NHL. Bone marrow trephine biopsy showed involvement by lymphoma in 65.4 % cases. The incidence of involvement was higher in B-cell lymphomas when compared with T-cell lymphomas, especially in low grade in B-cell lymphomas. The predominant pattern of involvement was interstitial. Diffuse large B-cell lymphomas had the lowest incidence in all the B-cell lymphomas. Discordant histology between bone marrow and the primary anatomic site was found in 7.8 % of the cases, which was seen more in DLBCL. Adjuvant immunohistochemistry, when performed in bone marrows with scant cellularity or crush artefact, helped to increase the diagnostic accuracy by unmasking obscured patterns and morphology.

The bone marrow biopsy had a higher diagnostic validity compared to bone marrow aspirate. However, BMA served as a good positive screening test in lymphomas for marrow disease. However, a negative BMA does not exclude involvement, hence taken as a complementary procedure rather than a substitute for bone marrow biopsy.

In patients of NHL showing bone marrow infiltration, cytopenias are a common feature. Anaemia was the commonest haematological manifestation (84.3 %). Bicytopenia and pancytopenia were also observed. Careful and detailed scanning of stained blood smear detected atypical lymphoid cells in the peripheral blood of 45.1 % patients.

Peripheral blood parameters, as well as the thorough examination of the smear hence, are important for early diagnosis. As the anatomical staging is an important aspect of NHL because of its both prognostic and therapeutic implications, accurate determination of bone marrow infiltration is important for the lymphoproliferative disorders.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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