

ORIGINAL ARTICLE

FREQUENCY AND PATTERN OF BONE MARROW INVOLVEMENT
AMONG PATIENTS WITH NON HODGKIN LYMPHOMA

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Background: Non-Hodgkin lymphoma (NHLs) are a heterogeneous group of lymphoid neoplasms, characterized by an irregular pattern of spread and may present with extranodal involvement. This study was conducted to determine the frequency and pattern of Bone marrow involvement on trephine biopsy in cases of Non-Hodgkin lymphoma (NHL). **Methods:** This cross sectional study was conducted in Pathology department of Fauji Foundation Hospital (FFH)/Foundation University medical college (FUMC) Rawalpindi, from 14th December 2010 to 14th December 2011. One hundred and six patients with histopathologically confirmed Non-Hodgkin lymphoma on lymph node (LN) biopsy, who had not received any chemotherapy were selected and Bone Marrow (BM) trephine biopsies for staging were performed on them. **Results:** Out of one hundred and six patients, forty five (42.5%) were diagnosed to have Bone Marrow involvement on staging. The most common pattern was diffuse, i.e., 44.44%, followed by the interstitial infiltrate in 28.89%, focal and mixed constituted 11.11% each, and paratrabeular pattern was found in 4.44%. **Conclusion:** This study highlights the high incidence of involvement and diffuse pattern in the Bone marrow biopsies of newly diagnosed Non-Hodgkin lymphoma, both of which indicate poor prognosis.

Keywords: Non-Hodgkin lymphoma; bone marrow; prognosis; staging.

J Ayub Med Coll Abbottabad 2016;28(3):497-500

INTRODUCTION

Lymphomas represent malignant disorders of cells of lymphoid tissues and are classified into two main types; Hodgkin lymphoma (HL) and Non-Hodgkin lymphoma (NHL).¹ NHLs are a heterogeneous group of lymphoid neoplasms, characterized by an irregular pattern of spread and may present with extranodal involvement.² The disease accounts for about 3.4% of all cancer deaths, which makes it the sixth most common cause of death among cancer patients.^{3,4} The diagnosis of NHL depends upon histopathological findings on Lymph node (LN) biopsy whereas other invasive and non-invasive procedures are employed to evaluate the extent of the disease, also termed as staging.¹ The Ann Arbor staging system reveals the anatomic stage of NHL by number of tumour sites (nodal and extranodal), their location and presence or absence of systemic symptoms.¹ Bone marrow (BM) involvement by NHL indicates stage IV disease and is associated with poor prognosis.⁵ Bone marrow trephine biopsy is one of the most important procedures for the staging of NHL at the time of initial diagnosis to assess prognosis of the patient and also after the treatment to evaluate response to treatment.⁶ Both Bone marrow aspirate and trephine biopsies are performed but trephine biopsy is a preferred procedure and thus mandatory for detection of marrow involvement in NHL.⁷

The histopathological pattern of BM infiltration which is observed on trephine biopsy comprises of diffuse, interstitial, focal, paratrabeular or mixed patterns. These patterns have a prognostic significance with diffuse pattern having worst, whereas

nodular having best prognosis and the mixed pattern lies in between.⁶

Non-Hodgkin lymphoma is one of the common malignancies in Pakistan.⁸ According to annual cancer registry report-2008 published by Shaikat Khanum Memorial Cancer Hospital and Research Center (SKMCH & RC), 4.40% cases of NHL have been reported.⁹ Data from one of Asian country shows that BM involvement by NHL is 55.1%.⁶ The frequency and Bone marrow involvement of various subtypes of NHL varies worldwide.¹⁰ According to published data, the frequency of Bone marrow involvement in various subtypes of NHL is also variable, i.e., SLL (75%), Lymphoblastic lymphoma (56.3%), Lymphoplasmacytic lymphoma (50%), MCL (45.5%), BL (33.3%), FL (30%), DLBCL (4.6%).¹¹ Another study shows that predominant histological pattern of Bone marrow involvement was mixed (51.85%), followed by focal (22.22%), paratrabeular (11.11%), diffuse and interstitial (7.4% each).⁶

As few local studies are available, so the present study was done to observe the incidence of Bone marrow involvement and histopathological patterns of involvement in NHL at initial presentation and also its comparison with international data as it varies worldwide.

MATERIAL AND METHODS

A total of one hundred and six patients with histopathologically confirmed Non-Hodgkin lymphoma on lymph node (LN) biopsy and who had not received any chemotherapy were included in the study.

Data was collected from the patients who presented in the outpatient department and wards of Fauji Foundation Hospital/Foundation University medical college (FUMC), Rawalpindi from 14th December 2010 to 14th December 2011.

Patient's detail including age, gender, history, physical examination and diagnosis of NHL with its subtype were recorded. Bone marrow aspirate and trephine biopsies were performed from posterior superior iliac spine (PSIS) with disposable trephine biopsy needle (a modified type of Jamshidi needle made by TSK). The trephine biopsies of more than 1.5cm length were considered and sent for processing to Histopathology laboratory of FUMC.¹²

The specimen was placed immediately in 10% formal saline for 24 hrs. After fixation, the specimen was decalcified in 4% sulphuric acid for 4–6 hrs. It was processed in automatic tissue processor (SAKURA TISSUE TEST TEK@ TEC 5 MODEL 220-240). After paraffin embedding, 2–4 µm thick sections were cut by rotatory microtome (SAKURA ACCU-CUT MODEL SRM 200CW) and were mounted on glass slides. These slides were stained with hematoxylin and eosin (H&E) and examined for BM involvement by using 4x, 10x, 20x and 40x power fields by hematologist and histopathologist.

Data was analyzed by using the SPSS version 17. Mean and standard deviation were calculated for the quantitative variable, i.e., age. Frequency and percentage were presented for qualitative variables, i.e., gender, BM involvement, types of NHL, histopathological pattern of NHL in BM biopsy. Results were presented in the form of tables and graphs.

RESULTS

In the present study, 106 diagnosed cases of NHL were considered out of which 60 (56.6%) were males whereas 46 (43.4%) were females. Age of the patients studied, ranged between 15–78 years and mean age was 50 years.

Out of total, 45 (42.5%) were found to have BM involvement. Gender wise 26 patients were males, whereas 19 were females. Patients older than 45 years showed higher incidence of BM involvement (64.15%) as compared to younger age group which ranged between 15–45 years (35.85%).

Among all subtypes of NHL, the commonest was DLBCL (64.2%), out of which 33.8% of cases showed BM involvement at initial diagnosis.

In patients with BM involvement, the histopathological pattern varied with the various subtypes of NHL. The most common pattern was diffuse, i.e., 20/45 (44.44%), followed by the 13/45 (28.89%) cases of interstitial infiltrate, focal and mixed constituted 5/45 (11.11%) cases each of subtype. Paratrabeular pattern was found in 2/45 (4.44%) cases.

The diffuse, interstitial and focal patterns of BM involvement were predominantly present in DLBCL, whereas mixed pattern seen mainly in FL (2/5). One case of DLBCL and one of FL showed paratrabeular pattern.

Table I shows frequency of different patterns among various histological subtypes of NHL.

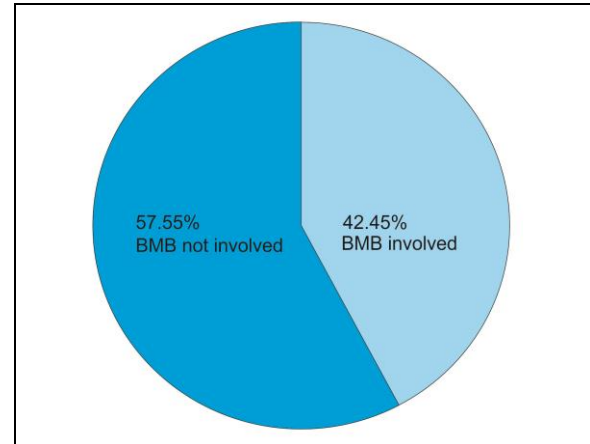


Figure-1: Frequency of bone marrow involvement in NHL patients.

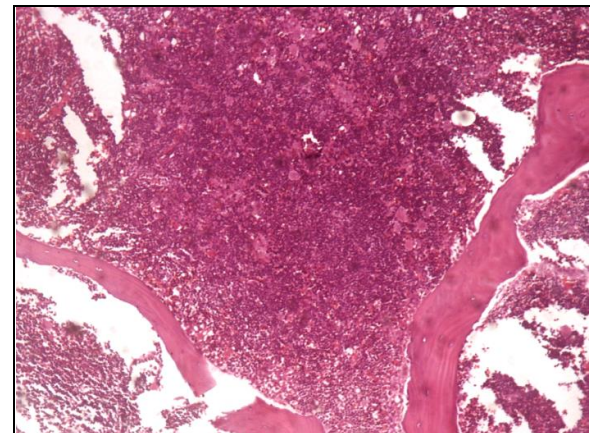


Figure-2: SLL with diffuse Bone marrow infiltrate (H & E X 10).

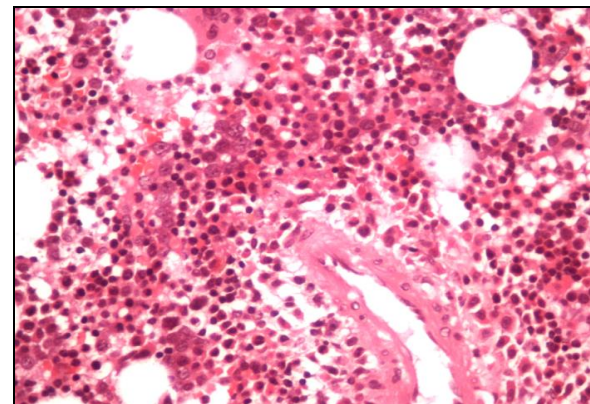


Figure-3: DLBCL with interstitial pattern of Bone Marrow infiltrate (H & E x 40)

Table-1: Frequency of different patterns among various histological subtypes of NHL

Type	Pattern				
	Diffuse	Interstitial	Paratrabeular	Focal	Mixed
DLBCL	11	7	1	3	1
Follicular lymphoma	0	2	1	0	2
Small lymphocytic lymphoma	3	1	0	1	1
Lymphoblastic lymphoma	2	0	0	1	0
Anaplastic large cell lymphoma	1	1	0	0	0
Mantle cell lymphoma	0	0	0	0	1
Marginal zone lymphoma	1	1	0	0	0
Burkitt lymphoma	1	0	0	0	0
Lymphoplasmacytic lymphoma	1	1	0	0	0
Total	20	13	2	5	5

DISCUSSION

This study was conducted to find out the frequency and pattern of BM involvement among several subtypes of NHL in our local setup as data regarding this is scanty. The pattern of BM involvement is also important to find out as it bears prognostic significance. BM involvement by NHL indicates stage IV disease and trephine biopsy is still considered gold standard for detecting BM infiltration.¹³ Among various histologic sub-types, the incidence and clinical importance of marrow involvement varies.⁶

In our study, 42.5% of NHL patients had BM involvement at initial diagnosis, which is almost in agreement with Arber and George who conducted their study on a large series of 450 patients and detected a 44% BM involvement at initial diagnosis. Similarly, in another study conducted by Tarek M.N. el Bolkainy et al in Egypt found 44.8% of BM involvement.^{5,10}

In contrast, other studies have described a considerable variation in the BM involvement in NHL. In a study conducted over a period of five years, by the Pathology department of Allama Iqbal Medical College Lahore, BM infiltration was noted in 134 (54.7%) out of 245 patients with NHL.¹⁴ Moreover, in a larger series of 3229 patients with NHL, the incidence of marrow disease was higher than that of the present study showing involvement in 64% of patients.⁵ In an Indian study carried out by Kumar S, Rau AR et al the overall incidence of marrow involvement by NHL was 55.1%.⁶

The variation in results of previous and this study can be due to inclusion of uneven distribution of patients with early and advanced disease. In addition, the inclusion of different proportions of various histological sub-types of NHL in the different studies may be the reason for this variation, as the incidence of BM involvement varies significantly according to the histological sub-types.⁶

In our study, DLBCL was found to be the commonest subtype of NHL (64.2%) reported with a BM involvement in 33.8% of cases. This is consistent with other studies, one of which was conducted on 59

DLBCL cases, out of which 20 (33.9%) showed evidence of BM involvement and another reported a figure of 30%.¹⁰

Out of eight cases of lymphoblastic lymphoma, diffuse involvement was seen in two and focal in one case. SLL had a high incidence of marrow involvement (6/8), having three diffuse, and one interstitial, focal nodular and mixed pattern each but no paratrabeular involvement in any, almost similar to what was observed by Foucar *et al.*¹⁵

The predominant histopathological pattern of involvement encountered in the BM biopsies of different subtypes of NHL was diffuse (44.44%), followed by interstitial infiltrate (28.89%), focal and mixed constituted (11.11%) each, and paratrabeular pattern was found in (4.44%) cases. This differs from the findings of Foucar et al. and Arber and George,⁶ who found the marrow involvement to be predominantly focal and mixed respectively. On the other hand, an Asian series described mainly an interstitial and diffuse patterns (56% and 31%, respectively).¹⁶ This discrepancy could be best explained by the fact that they studied a large number of cases and also due to the difference in the frequencies of various histopathological subtypes in different parts of the world.⁶

The histopathological pattern of involvement in BM biopsies of patients with NHL is important due to the fact that it carries a prognostic significance. Diffuse marrow infiltration indicates an advanced disease and puts patient in high risk group. This, along with unfavorable histology carries a worse prognosis. However, NHL patients with an interstitial, focal or paratrabeular patterns of BM show a much more favorable prognosis. They are associated with low or intermediate grade lymphomas.⁶

Bone marrow biopsy has a high diagnostic value and is a procedure of choice for BM Involvement based on both architectural and morphologic changes.⁷ BM involvement indicates stage IV disease with subsequent bearing on risk assessment and management plan.¹⁷ Evidence of both burden and marrow disease pattern has a prognostic

relevance. Moreover, imprint preparation obtained from fresh BM biopsy supports its diagnostic validity and helps in making a preliminary report if BM is involved or not, on the basis of which treatment could be started.¹⁸ Bilateral BM trephine biopsy is recommended because it increases the rate of detecting marrow involvement in NHL, as observed by Jung *et al.*⁴ In our study, bilateral trephine biopsies could not be performed due to inconvenience to the patient, otherwise BM involvement rate could have been higher than detected.

We observed in this study that the rate of BM involvement were comparable to many previous studies,^{5,11} Most of the patients presented with BM involvement on staging and many of them showed diffuse pattern, which is the sign of poor prognosis. This might be due to the fact that many of the patient present late in our setup.

In view of this study, it is recommended that all the diagnosed patients of NHL should be staged as soon as possible along with other required investigations before making a proper management plan. Other investigations for diagnosis and staging like immunohistochemistry, MRI, CT and PET scan may not be available in all centers.¹⁹ Therefore, morphology on tissue biopsy for proper diagnosis and BM biopsy for staging is still of great importance and helps in proper diagnosis and management plan of the patient.

CONCLUSION

This study highlights the high incidence of involvement in the BM biopsies of newly diagnosed NHL, which indicates a poor prognosis.

AUTHORS' CONTRIBUTION

All the authors contributed equally.

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