RESEARCH ARTICLE

Bone marrow infiltration by Non-Hodgkin lymphoma: An experience in a tertiary care centre

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Abstract

Objective: To determine the frequency and patterns of bone marrow infiltration in non-Hodgkin lymphoma patients.

Method: The cross-sectional study was conducted at the Armed Forces Institute of Pathology, Rawalpindi, Pakistan, from April to October 2021, and comprised patients of either gender aged 20-80 years who had been diagnosed with non-Hodgkin lymphoma. Following assessment and as per standard protocol, bone marrow aspirate and trephine biopsy were done on all patients from the posterior superior iliac spine, and slides were prepared and assessed. Data was analysed using SPSS 25.

Results: Of the 100 patients, 67(67%) were males and 33(33%) were females. The overall mean age was 54.99±12 years, and mean duration of symptoms was 11.7±1.5 months. Diffuse large B-cell lymphoma was the commonest type 43(43%). Infiltration of marrow occurred in 38(38%) patients, with 12(12%) of them being cases of mantle cell lymphoma. The commonest infiltration pattern was diffuse in 17(17%) cases, followed by focal/nodular in 10(10%).

Conclusion: Diffuse large B-cell lymphoma was found to be the commonest type of non-Hodgkin lymphoma, and marrow infiltration occurred most frequently in cases of mantle cell lymphoma.

Key Words: Bone marrow, Infiltration, Non-Hodgkin lymphoma.

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Introduction

Non-Hodgkin lymphoma (NHL) is a diverse category of lymphoma which consists of different tumours that exhibit variable behaviour clinically[1]. It tends to be an old-age disease in Europe and North America1. It has been estimated to account for 4% of all cancers worldwide[2]. It is featured by neoplastic transformation of the lineage of lymphoid tissue and has a greater propensity for spreading to different tissues all over in the body, particularly to bone marrow, liver and spleen[3].

An important component while staging NHL is bone marrow biopsy [4]. Patients who present with bone marrow infiltration with or without the involvement of other tissues are in stage IV of the disease and have a poor prognostic outcome and poor response to treatment[5]. It has been consistently reported that in the developing countries, patients present often at an advanced stage compared to the individuals in the Western countries[6]. Bone marrow infiltration occurs in 50-80% and 25-40% of low- versus high-grade NHL, respectively[7].

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The trephine biopsy of bone allows an evaluation of bone marrow infiltration along with tumour, and assesses the pattern as well as the extent to which infiltration has occurred, which plays an important role in terms of diagnosis and prognosis[8]. Some studies have shown that trephine biopsy may reveal lymphoma even when on peripheral as well as bone marrow smear, there are no abnormal cells detected[9]. The infiltration of marrow by lymphoid tissue occurs in different patterns that are distinct from each other[10].

There is paucity of local data regarding the rate of bone marrow infiltration in NHL patients. The current study was planned to fill the gap by determining the frequency of bone marrow infiltration in NHL patients.

Patients and Methods

The cross-sectional study was conducted at the Armed Forces Institute of Pathology (AFIP), Rawalpindi, Pakistan, from April 15 to October 14, 2021. After approval from the institutional ethics review committee, the sample size was estimated using the World Health Organisation (WHO) calculator while keeping the expected NHL incidence to be 4%[2] and at 95% confidence interval (CI) and 4% margin of error. The sample was raised using non-probability consecutive sampling technique. Those included were patients of either gender aged 20-80 years who were histologically proven NHL on tissues other than bone

marrow. Patients who had chronic lymphocytic leukaemia, hairy cell leukaemia, Hodgkin lymphoma, involvement of bone marrow due to some other primary tumour or were on systemic therapy were excluded.

Data was collected after taking written informed consent from all the patients. Demographic detail, clinical history and details of physical examination carried out by the researchers themselves were noted using a predesigned proforma. Blood samples were taken from all the patients for baseline laboratory investigations. Bone marrow aspirate and trephine biopsy were carried out from posterior superior iliac crest as per the standard protocol. The biopsy specimen was then assessed independently for bone marrow involvement. The findings of bone marrow infiltration on biopsy were considered positive if on histopathological examination of Haematoxylin and Eosin (H&E) slides of biopsy specimen obtained from bone marrow, there was presence of increased lymphoid cells resulting in the effacement of architecture. Immunohistochemistry (IHC) was applied to rule out reactive lymphocytosis. IHC panel included monoclonal antibodies for cluster of differentiation (CD)-3, CD-20, CD-5, CD-23, CD-10, B-cell lymphoma 2 (BCL-2), BCL-6, nuclear protein Ki67, cyclin D1 protien and multiple myeloma 1 (MUM1).

Data was analysed using SPSS 25. Quantitative variables were presented as mean and standard deviation, and qualitative variables as frequencies and percentages. Chi square test was used to see any significant associations. $P<0.05$ was considered statistically significant.

Results

Of the 100 patients, 67(67%) were males and 33(33%) were females. The overall mean age was 54.99+12 years, and mean duration of symptoms was 11.7±1.5 months. Diffuse large B-cell lymphoma (DLBCL) was the commonest type 43(43%), followed by mantle cell lymphoma (MCL) 23(23%), follicular lymphoma (FL) 16(16) %, high-grade B cell lymphoma (HGBCL) 4(4%), splenic marginal zone lymphoma (SMZL) 4(4%), peripheral T-cell lymphoma (PTCL) 4(4%), T-cell lymphoblastic leukaemia/lymphoma (T-LBL) 4(4%) and Burkitt lymphoma (BL) 2(2%).

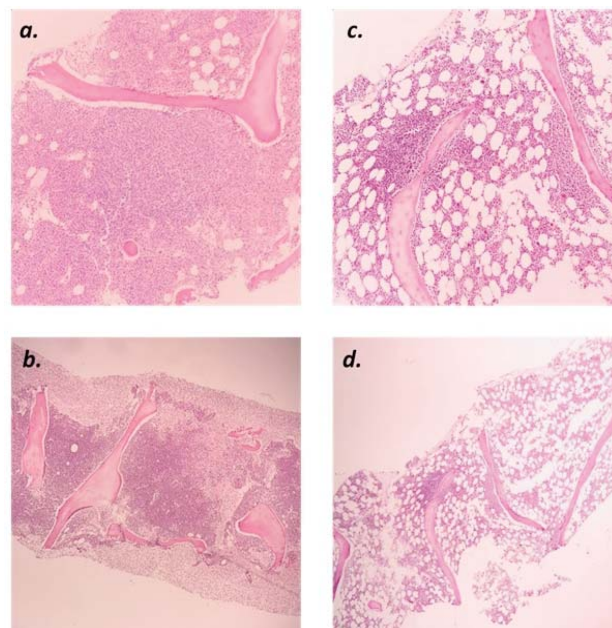

Figure: Haematoxylin and Eosin (H&E) slides showing infiltration patterns – a (10x) and b (4x) show nodular infiltration, while paratrabecular infiltration is seen in c (10x) and d (4x).

Infiltration of marrow occurred in 38(38%) patients, with most of them 12(12%) being MCL cases of mantle cell lymphoma. However, within each type, 9(56.25%) of the FL case had bone marrow infiltration (Table 1).

Hepatosplenomegaly was positive in 22(22%) cases and

Table-1: Marrow infiltration and type of infiltration in different types of non-Hodgkin lymphoma (NHL)

Type of Non-Hodgkin Lymphoma	Bone Marrow Infiltration		n=100 Type of Infiltration				
	Yes (n)	No (n)	None (n)	Diffuse (n)	Nodular (n)	Interstitial (n)	Paratrabecular (n)
Diffuse large B cell lymphoma	10%	33%	33%	9%	0%	1%	0%
Mantle cell lymphoma	12%	11%	11%	2%	7%	1%	2%
Follicular lymphoma	9%	7%	7%	1%	3%	0%	5%
Burkitt lymphoma	2%	0%	0%	2%	0%	0%	0%
High grade B cell lymphoma	1%	3%	3%	1%	0%	0%	0%
Splenic Marginal Zone Lymphoma	2%	2%	2%	1%	0%	1%	0%
T-cell lymphoblastic leukaemia/lymphoma	1%	3%	3%	1%	0%	0%	0%
Peripheral T-cell lymphoma	1%	3%	3%	0%	0%	1%	0%

Table-2: Hepatosplenomegaly, lymphadenopathy and reticulin in different types of non-Hodgkin lymphoma (NHL)..

n=100 (percentage)

Type of Non-Hodgkin Lymphoma	Hepatosplenomegaly		Lymphadenopathy		Reticulin (P=0.262)			
	Yes (P=0.194)	No	Yes (p=0.001) *	No	MF 0	MF I	MF II	MF III
DLBCL	7%	37%	39%	4%	15%	20%	6%	2%
MCL	6%	16%	23%	0%	9%	9%	4%	1%
FL	4%	12%	16%	0%	2%	8%	5%	1%
BL	0%	2%	2%	0%	0%	1%	1%	0%
HGBCL	1%	3%	3%	1%	1%	1%	1%	1%
SMZL	4%	0%	0%	4%	2%	0%	1%	1%
T-LBL	0%	4%	1%	3%	4%	0%	0%	0%
PTCL	0%	4%	1%	3%	4%	0%	0%	0%
TOTAL	22%	78%	85%	15%	37%	39%	18%	06%

DLBCL: Diffuse large B-cell lymphoma, MCL: Mantle cell lymphoma, FL: Follicular lymphoma, BL: Burkitt lymphoma, HGBCL: High-grade B cell lymphoma, SMZL: Splenic marginal zone lymphoma, T-LBL: T-cell lymphoblastic leukaemia/lymphoma, PTCL: Peripheral T-cell lymphoma, MF: Marrow fibrosis..

lymphadenopathy in 85(85%) (Table 2).

On IHC, infiltration of DLBCL was positive for CD-20, BCL-6, MUM1 and had high Ki67 index. MCL was positive for CD-20, CD-5 and cyclin D1, while FL showed positivity for CD-10 and BCL-2.

The commonest infiltration pattern was diffuse in 17(17%) cases, followed by focal/nodular in 10(10%) (Figure).

Discussion

In NHL patients, the commonest type was DLBCL, followed by MCL and FL in the current study. Nodular and paratrabecular patterns were only found in MCL and FL patients, but nodular was seen predominantly in MCL, and paratrabecular in FL, respectively.

Studies have determined the frequency as well as the patterns of involvement of bone marrow in individuals with NHL[11], and have show variability from as low as 27%[12] in Australia to as high as 61.4% in Israel[13]. A study in the United States reported the involvement of bone marrow in 32% NHL patients,[14] while in Croatia it was seen in 33.8%[15] patients. In a study conducted in Rawalpindi, the rate of infiltration of bone marrow was 51.4%[16], and in another study, conducted in Jamshoro, the rate was 31.5%[1]. The current study found the rate to be 38%. The higher rates reported in previous studies were mainly because the majority of the participants had advanced stage lymphoma.

Local studies revealed that the infiltration pattern of lymphoma predominantly was diffuse in 46.3% patients[1] and 66% patients[17], followed by nodular infiltration and paratrabecular infiltration. The current study had similar findings. Studies conducted in the Western countries revealed that infiltration was mainly of nodular type, followed by paratrabecular or interstitial, and intermittently there was diffuse pattern[18]. These findings are not supported by the current findings. The reason for this difference may be the different stages at which the patients presented.

There is limited data regarding lymphomas regionally and therefore an insight is required for the identification of the spectrum of disease and the burden that it creates in the local setting[18]. The risk of NHL increases with age[19]. Majority of the patients are diagnosed when they are in the 6th or 7th decade of life[19]. In European countries, it is an old-age disease[19]. However, in the current study the mean age of NHL patients was 54.9 years. Studies conducted in southern Punjab and India reported mean age 40-45 years, in the late middle age, which correlates well with the current findings[1]. The discord between the findings of Western countries in terms of age may be explained by life expectancy rates that are relatively longer and there is a more older population in Western nations[19].

NHL staging is critical in making clinical decisions regarding the therapeutic management of such patients[20]. An infiltration that is lymphomatous in nature indicates that a lymphoma is at the advanced stage 420. Such infiltrations are marked by distinct patterns, such as an interstitial pattern, in which loosely dispersed lymphoid cells can be seen in between the haematopoietic tissue; a diffuse pattern, where densely packed lymphoid cells are present within the spaces of bone marrow; a lymphoid nodular pattern, in which numerous nodules aggregate that are partly confluent; and a paratrabecular pattern, in which the lymphoid infiltrate lies adjacent to the bony trabeculae[20].

The current study had certain limitations. Firstly, it was carried out at a single centre and the sample size was small, which means the results cannot be generalised. Secondly, the outcome of treatment in relation to bone marrow infiltration was not assessed.

Conclusion

DLBCL was found to be the commonest type of NHL, and bone marrow infiltration occurred most frequently in FL and MCL cases. A high suspicion of bone marrow infiltration should be kept in mind when evaluating NHL subtypes

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