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Original Research Article

A Study on Clinico-pathological assessment of lymphomas Based on latest WHO classification of lymphoid neoplasms

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Abstract:

Introduction: Lymphomas are heterogeneous group of malignancies prevalent in developed countries. They arise from clonal proliferation of B cell, T cell and Natural Killer (NK cell) subtypes of lymphoid population at different stages of maturation. Lymphomas are broadly classified into non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) by WHO.

Materials and Methods: Overall cases of lymphomas were retrospectively assessed over a period of two years and categorised according to latest WHO classification of lymphoid neoplasms based on historical morphology and immunohistochemistry (IHC) results. Clinical and radiological data were correlated with pathological findings.

Results: Total 43 proven cases of lymphomas were recorded in the present study, out of which 33 cases (77%) were reported as Non-Hodgkin's lymphoma and 10 cases (23%) we are reported as Hodgkin's Lymphoma. Among Non-Hodgkin's lymphoma, DLBCL was found to be most common subtype accounting for 42% followed by follicular lymphoma (12%), Marginal zone lymphoma including MALT lymphoma (9%), T cell lymphoma (7%), mantle cell lymphoma (5%) and Small lymphocytic lymphoma accounting for 2%. Among Hodgkin's lymphoma, mixed cellularity was the most common subtype accounting for 14% followed by lymphocyte rich type (7%) and 2% of nodular sclerosis variant were reported.

Conclusion: Incidence of NHL is higher compared to HL. Follicular lymphomas are lower compared to western studies with DLBCL being the most common subtype of NHL. Mixed cellularity is the most common subtype of HL unlike enodularsclerosis subtype in Western world. Keywords: Tertiary care hospital, Lymphomas, World Health Organisation (WHO), Immunohistochemistry (IHC), Non-Hodgkin Lymphoma (NHL), Hodgkin Lymphoma (HL).

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Introduction

Lymphoma comprises of heterogeneous malignancies that arise from the clonal proliferation of lymphoid cells [2]. It represents approximately 5% of malignancies with overall survival rate of 72% [1]. It can affect both young and older adults. Medianage of lymphoma diagnosis is 63years [4]. Various etiological agents which predispose to lymphoma include environment, infectious agents, and genetic factors. The common symptoms of this disease are persistent fevers, drenching night sweats, unintentional weight loss, and generalised or localised swelling of the lymph nodes.

According to World Health Organisation (WHO), lymphomas are broadly classified in to Hodgkin lymphoma (HL) which accounts for 10% of lymphomas and Non- Hodgkin lymphoma (NHL) accounts for 90%. HL is further classified into classical and non-classical types and NHL into B-cell, T- cell and natural killer (NK) cell types13.

Lymphoma are commonly diagnosed by fine-needle aspiration, core biopsy, incision/wedge biopsy, and excision biopsy. Excision biopsy is considered the "gold standard" as it allows for the assessment of whole lymph node architecture [14]. Biomarkers that can be assessed by immunohistochemistry are extremely helpful for distinguishing between two entities that share morphological and histopathological features, and they can be applied simply as a part of routine clinical practice [7]. After confirming the diagnosis of lymphoma by tissue biopsy, further evaluation involves the determination of tissue where disease activity is the greatest. PET/CT scans by measuring uptake of radiolabelled fluorodeoxyglucose (FDG) are used to

measure the biological activity of lymphoma. [5,6] Clinical staging for both HL and NHL is performed by using Ann Arbor (AA) staging system, before the initiation of therapy for lymphoma.

Aims & Objectives: Very few studies have been conducted on lymphomas from India, hence present study aims at analysing the frequency of various lymphomas at a tertiary care hospital in India. To correlate clinical and radiological data with pathological features according to latest WHO classification of lymphoid neoplasms. Integrated approach including diagnosis, baseline staging, treatment, and monitoring is required in adequate management of lymphomas.

Materials & Methods

All cases diagnosed as lymphomas by histopathology examination were included in the study. Clinical data was collected from patients' case records, and all peripheral blood, bone marrow smears, and histopathology slides were reviewed. Radiology data, including CT/PET-CT scan uptake, were recorded. Treatment regimens and follow-up details were obtained from Medical Oncology records. Peripheral blood and bone marrow aspirate were stained with Giemsa and Oil Red-O stain. Histological sections were stained using Hematoxylin–Eosin stain. Immunohistochemical studies were performed on formalin fixed, paraffin embedded tissue sections of trephine biopsy, lymph node biopsy or extra nodal biopsy specimens. Based on histology features combined with IHC findings lymphomas were classified according to latest WHO classification.

Results

In the present study 43 cases of biopsy proven lymphomas were included. Male patients accounted for 25 cases (58%) and 18 cases were female patients (42%), with Male to female ratio of (1.4:1) Mean age of study group was 52 years with age range between 20-85 years. Lymphnodes were commonly involved in 36 cases (84%) with cervical lymphnode being the most common site of involvement. Extra-nodalsites were involved in 7 cases (16%). Among extra-nodal lymphomas gastrointestinal lymphomas were more common, accounting for 2 cases followed by Thymic lymphoma, nasopharyngeal lymphoma, skin lymphoma, renal lymphoma and sternal mass lymphoma accounting for one case each were noted in the present study. (Table 1)

Table 1: Distribution of lymphoma based on site of involvement

Site of Lymphoma	Number of cases (%)
Cervical lymphnode	27(63%)
Axillary lymphnode	4(9%)
Inguinal lymphnode	3(7%)
Para-aortic lymphnode	1(2%)
Mesentric lymphnode	1(2%)
Gastrointestinal system	2(5%)
Thymus	1(2%)
Nasopharynx	1(2%)
Skin	1(2%)
Renal	1(2%)
Suprasternal mass	1(2%)
Total	43(100%)

Panel of IHC markers were applied in all the 43 cases, to categorise the types and sub-types of lymphoma. Positive and negative staining IHC markers with proliferation IHC markers are applied in all the cases. Results of IHC staining with lymphoma type has been tabulated in (Table 2 & Table 3). Radiology data were collected in all the cases; hepato-splenomegaly was found.

Table 2: IHC results in Non-Hodgkin's Lymphoma

CD 10	CD 20	PAX5	BCL2	BCL6	MUM1	MYC	CD 30	CD3	CD5	TdT	Cyclin D1	ALK	Mib1/ Ki67(%)	Lymphoma Type
+	+	+	+	+	-	+	+	-	-	-	-	-	85	**DLBCL**
-	+	+	+	-	+	-	-	-	-	-	-	-	50-60	**DLBCL**
+	+	-	+	+	-	+	-	-	-	-	-	-	80	**DLBCL**
-	+	+	-	-	+	-	+	-	-	-	-	-	70-80	**DLBCL**
-	+	+	-	-	+	-	-	-	-	-	-	-	25-30	**DLBCL**
+	+	+	+	-	-	-	-	-	-	-	-	-	70	**DLBCL**
+	+	-	-	+	-	+	-	-	-	-	-	-	40-50	**DLBCL**
+	+	+	+	-	-	-	-	-	-	-	-	-	30	**DLBCL**
+	+	-	+	-	-	-	-	-	-	-	-	-	30	**DLBCL**
+	+	-	+	+	-	+	-	-	-	-	-	-	70-80	**DLBCL**
+	+	+	-	-	-	-	-	-	-	-	-	-	40-50	**DLBCL**
+	+	+	-	+	-	-	-	-	-	-	-	-	50	**DLBCL**
+	+	-	+	-	-	-	-	-	-	-	-	-	40	**DLBCL**
+	+	-	+	-	+	-	+	-	-	-	-	-	80-90	**DLBCL**
-	+	-	+	+	+	+	+	-	-	-	-	-	80-90	**DLBCL**
+	+	-	+	-	+	+	+	-	-	-	-	-	80-90	**DLBCL**
+	+	-	+	-	-	+	-	-	-	-	-	-	90	**DLBCL**
+	+	-	-	-	+	+	-	-	-	-	-	-	80	**DLBCL**
+	+	-	+	+	-	-	-	-	-	-	-	-	15-20	**FL**
+	+	-	+	-	-	-	-	-	-	-	-	-	20	**FL**
+	+	-	+	+	-	-	-	-	-	-	-	-	30-40	**FL**
+	+	-	-	+	-	-	-	-	-	-	-	-	20-30	**FL**
+	+	-	-	-	-	-	-	-	-	-	-	-	10	**FL**
-	+	-	+	-	-	-	-	-	-	-	-	-	30	**MZL**
-	+	-	+	-	-	-	-	-	+	-	-	-	25-30	**MZL**
-	+	-	-	-	+	-	-	-	-	-	-	-	20-25	**MZL**
-	+	+	+	-	-	-	-	-	-	-	-	-	60	**MZL**
-	-	-	-	-	-	-	+	+	+	-	-	-	70	**TCL**
-	-	-	-	-	-	-	-	+	+	-	-	-	60	**TCL**
+	-	-	-	+	-	-	-	+	+	-	-	-	70	**TCL**
-	+	-	-	-	+	-	-	-	-	-	+	-	80-90	**MCL**
-	+	-	-	-	-	-	-	-	-	-	+	-	90	**MCL**
-	+	-	+	-	-	-	-	-	+	-	-	-	20-30	**SLL**

Table 3: IHC results in Hodgkin's Lymphoma

CD15	CD30	PAX5	CD45	CD20	EBV	CD3	Ki67	Hodgkin Lymphomasub-type
+	+	Weak+	-	-	-	-	30%	**Mixedcellularity**
+	+	Weak+	-	-	+	-	40%	**Mixedcellularity**
+	+	Weak+	-	-	-	-	40%	**Mixedcellularity**
+	+	+	-	-	-	-	30-40%	**Mixedcellularity**
+	+	Weak+	-	-	-	-	50-60%	**Mixedcellularity**
+	+	Weak+	-	-	-	-	50%	**Mixedcellularity**
+	+	+	-	-	+	-	20%	**Lymphocyte rich**
+	+	+	-	+	-	-	40%	**Lymphocyte rich**
+	+	Weak+	-	-	-	-	30%	**Lymphocyte rich**
+	+	+	-	-	-	-	40%	**Nodular sclerosis**

In majority of the cases of lymphoma 32 cases (74%). CT findings showed a diagnosis of lymphoma in 15 cases (35%).

Based on histopathology data combined with IHC markers, lymphoma typing and subtype has been made according to latest WHO classification of lymphoid neoplasms in the present study. Among 43 cases of biopsy-proven lymphomas, 33 cases (77%) were reported as Non-Hodgkin's lymphoma and 10 cases (23%) were reported as Hodgkin's lymphoma. Among Non-Hodgkin's lymphoma, DLBCL was found to be most common subtype accounting for 18 cases (42%) followed by follicular lymphoma, Marginal zone lymphoma including MALT lymphoma, T cell lymphoma, mantle cell lymphoma

and Small lymphocytic lymphoma accounting for 5 cases (12%), 4 cases (9%), 3 cases (7%), 2 cases (5%) and 1 case (2%) respectively. Among Hodgkin's lymphoma, classical Hodgkin lymphoma was found to be most common type with majority of them being mixed cellularity subtype accounting for 6 cases (14%) followed by 3 cases (7%) lymphocyte rich type and 1 case (2%) of Nodular sclerosis variant (Table 4)

Table 4: Lymphoma type based on WHO classification of lymphoid neoplasm

CD15	CD30	PAX5	CD45	CD20	EBV	CD3	Ki67	Hodgkin Lymphomasub-type
+	+	Weak+	-	-	-	-	30%	**Mixed cellularity**
+	+	Weak+	-	-	+	-	40%	**Mixed cellularity**
+	+	Weak+	-	-	-	-	40%	**Mixed cellularity**
+	+	+	-	-	-	-	30-40%	**Mixed cellularity**
+	+	Weak+	-	-	-	-	50-60%	**Mixed cellularity**
+	+	Weak+	-	-	-	-	50%	**Mixed cellularity**
+	+	+	-	-	+	-	20%	**Lymphocyte rich**
+	+	+	-	+	-	-	40%	**Lymphocyte rich**
+	+	Weak+	-	-	-	-	30%	**Lymphocyte rich**
+	+	+	-	-	-	-	40%	**Nodular sclerosis**

Discussion

In the present study, lymphomas were more commonly diagnosed in male patients, with a male-to-female ratio of 1.4:1. Similarly, studies done by Yako RT et al. [8] and Mondal SK et al. [9] showed male-to-female ratios of 2:1 and 3:1, respectively. The mean age of patients diagnosed with lymphoma was found to be 52 years in the present study; however, patients in a younger age group were diagnosed with lymphoma among the Western population in studies done by Armitage JO et al. [10], Morrison VA et al. [11], and Yako RT et al. [8] (Table 5).

Table 5: Comparison of Male : Female ratio and mean age of study population with other studies

Study done by	Male: Female ratio	Mean age in years
Yako RT et al	2:1	-
Mondal SK et al	3:1	-
Armitage JO et al	-	40
Morrison VA et al	-	38
Present study	1.4:1	52

Most common site of lymphoma was found to be cervical lymph node in the present study, which was in correlation with studies conducted by Ramani A et al. [12], Chakrabarti S et al. [15], and Mondal SK et al. [9]. In a rare case, Chen WL et al. [16] reported extra-nodal lymphomas to be more common than nodal lymphomas. Among extra-nodal sites of lymphoma, Mondal SK et al. [9] reported intestinal lymphomas as the most frequent site in 24%, Narang V et al. [17] reported small intestinal lymphomas to be the frequent extra-nodal site in 17.8% cases, and Raginelli A et al. [18] reported GI lymphomas as the most frequent extra-nodal sites in 43% cases (Tables 6 & 7).

Table 6: Comparison of common site of lymphoma involvement with other studies

Study done by	Most comm on site of lymphoma
Ramani A et al	Nodal lymphoma
Chakrabarti S et al	Nodal lymphoma
Mondal SK et al	Nodal lymphoma
Chen WL et al	Extra-nodal lymphoma
Present study	Nodal lymphoma

Table 7: Comparison of extra-nodal site of lymphoma involvement with other studies

Study done by	Extra-nodal site of lymphoma (%of cases)
Mondal SK et al	Intestinal lymphoma(24%)
Narang V et al	Small Intestinal Lymphoma (17.8%)
Raginelli A	Gastrointestinal Lymphoma (43%)
Present study	Gastrointestinal Lymphoma(16%)

In the present study Non-Hodgkin lymphoma was reported to be most common type of WHO lymphoma, similar to study done by Mondal S K et al[9], Jaffe ES et al20, Nimmagadda et al[21], Naresh et al [22] and Mukherjee M et al [23]. However few studies done by Chakrabarti S et al [15]and Haddadin WJ et al[19]reported Hodgkin lymphoma to be common than compared with non-Hodgkin lymphoma. Among Non-Hodgkin lymphomas present study shows DLBCL as most common sub- type followed by follicular lymphoma. Mantle cell lymphoma and small lymphocytic lymphoma were least common subtype of Non-Hodgkin lymphoma in the present study. Similar results were reported in studies conducted by Jaffe ES et al [20], Nimmagaddaet al [21], Naresh et al [22] and Mukherjee M et al [23]Among Hodgkin lymphomas, in the present study mixed cellularity was found to be the most common subtype. Similar results were found in study done by Mondal SK et al [9]. However Shanbag S et al [24]and Kaseb H25reported nodular sclerosis variant to be most common subtype of classical Hodgkin lymphoma (Table 8 & 9).

Table 8: Comparison of distribution of lymphoma type with other studies

Study done by	Most common type of lymphoma
Mondal SK et al	Non-Hodgkin lymphoma
Jaffe ES et al	Non-Hodgkin lymphoma
Nimmagadda et al	Non-Hodgkin lymphoma
Nareshetal	Non-Hodgkin lymphoma
Mukherjee M et al	Non-Hodgkin lymphoma
Chakrabarti S et al	Hodgkin lymphoma
Haddadin WJ et al	Hodgkin lymphoma
Present study	Non-Hodgkin lymphoma

Table 9: Comparison of distribution of subtype of lymphoma with other studies

Study done by	Most common type of Non Hodgkin lymphoma	Most common type of Hodgkin lymphoma
Jaffe ES et al	Diffuse Large B Cell Lymphoma	Nodular Sclerosis
Nimmagadda et al	Diffuse Large B Cell Lymphoma	-
Naresh M et al	Diffuse Large B Cell Lymphoma	-
Mukherjee M et al	Diffuse Large B Cell Lymphoma	Nodular Sclerosis
Mondal SK et al	Follicular lymphoma	Mixed Cellularity
Shanbag S et al	Follicular Lymphoma	Nodular Sclerosis
Kaseb H et al	Follicular lymphoma	Nodular Sclerosis
Present study	Diffuse Large B Cell Lymphoma	Mixed Cellularity

Conclusion

The present study from tertiary care centre in Indian shows higher number of NHL cases (77%) then HL cases (23%) and male–female ratio is 1.4:1. DLBCL was found to be most common subtype of NHL (55%), a lower percentage of follicular lymphoma is seen in present study compared to western population. Among the extranodal NHL, thymus is most frequently involved site in our study. Classical Hodgkin lymphoma was the common type of HL with mixed cellularity being the most common subtype like in other Asian, and Indian studies; however, unlike western studies where nodular sclerosis is the commonest type.

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