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Epidemiology and Spectrum of Lymphoma in a Single Tertiary Care Hospital of North India

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ABSTRACT

Background: Non-Hodgkin's Lymphoma is a common hematological malignancy. Its incidence and distribution in India are slightly different from developed nations. The study was initiated to obtain the epidemiological, clinical and histopathological spectrum of lymphoma in a single tertiary care hospital of North India.

Methods: 104 eligible consecutive cases of lymphoma were retrospectively analyzed from January 2016 to March 2020. Morphology and immunohistochemistry were performed and clinical details were captured from hospital information system. Cases were reclassified according to WHO classification of Tumors of Hematopoietic and Lymphoid Tissue 2017 and also clinically as nodal and extra nodal lymphomas and analyzed.

Results: Among the included patients 14.4% patients are diagnosed as Hodgkin's lymphoma (HL) while 85.5% belonged to non-Hodgkin's lymphoma (NHL). Median age for NHL is 52.5 years. Male outnumbered females in both NHL and HL with ratio of 1.87 and 1.5. Majority of NHL are mature B-cell neoplasm (83.1%), while mature T-cell and NK cell neoplasm are less (14.6%). Most common subtype found is Diffuse large B-cell lymphoma (52.8%) followed by Primary diffuse large B cell lymphoma of CNS (15.7%). Primarily nodal Vs extranodal involvement is seen in 51.9% and 48% of cases. Most common extranodal site is CNS followed by GIT and spine.

Conclusion: In the present study DLBL is the most common subtype seen in 52.8% of cases in concordance with other studies but the sticking difference here is low incidence of follicular lymphoma and CLL/SLL and a much higher incidence of Primary DLBCL of CNS. There is an Inherited selection bias because the cases are collected from single institution; however, causes and reasons should be more extensively investigated.

Key-words: Lymphoma, Hodgkin's, Non-Hodgkin's, Nodal, Extranodal

INTRODUCTION

Lymphoma is a malignant lymphoproliferative disorder of immune system arising predominantly in the lymph nodes with variable clinical, histological and immunohistochemical presentations. They are histologically categorized into Hodgkin's and non-Hodgkin's type (NHL) and clinically as nodal and extranodal lymphomas. [1]

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NHL is the most common hematopoietic neoplasm, comprising approximately 4.3% of all cancers and ranking seventh in frequency among all cancers [2], while Hodgkin lymphoma also known as Hodgkin disease (HD) is rare. On an average NHL is more than 5 times as common as HD. [2] NHL can be divided into two groups, indolent and aggressive group but for better understanding of the disease among oncologists, clinicians and pathologists World Health Organization developed a new classification of lymphoma in 2001 based on the principles in part on the earlier REAL classification (Revised European American classification of Lymphoid Neoplasm). Latest update of which was made and published by the International Agency for Research on

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Cancer (IARC) in 2017.[3] This classification includes all available morphology, immunophenotyping, genetic and clinical features to define a disease. There is no single gold standard by which this disease can be defined. In India immunphenotyping is being routinely used while genetic testing is only reserved for lymphoid neoplasm where specific genetic abnormality is the key defining criterion.

Majority of NHL, approximately 80-85% are the clonal proliferation of immature or mature B-cells, however the behavior and response to treatment is different among them. [4] They are driven by abnormal genetic alterations, aberrant pathway activation, disordered epigenetic regulation and complex tumor microenvironment interaction to make diagnosis and classification difficult. [5]

A lot of research work and epidemiological studies are carried out on lymphoma worldwide but spectrum of lymphoma, epidemiology, classification, nodal verses extranodal involvement was rarely reported from the north eastern region of the India which comprises a huge population of 231 million.

Thus, the present study was carried out with the aim to know the epidemiological distribution among the various subtypes of lymphoma according to the WHO classification of Tumors of Hematopoietic and Lymphoid Tissue 2017 and also to know the distribution according to the site involved in a single tertiary care hospital over the period of January 2016 to March 2020.

MATERIALS AND METHODS

Study Design: Retrospective cross-sectional study

Study Population- The clinical, histological and immunohistochemical data of patients diagnosed as lymphoma from January 2016 to March 2020 in a tertiary care hospital at Lucknow, Uttar Pradesh

Exclusion Criteria- Cases excluded from the study are given below:

1. Plasmacytoma and Multiple Myeloma, Hairy cell leukemia, Hairy cell leukemia variant, Prolymphocytic leukemia.
2. Disagreement between the provisional light microscopic diagnosis and final diagnosis after immunohistochemistry.
3. Cases with limited biopsy specimen, insufficient material, poor fixation and staining pattern.
4. Cases where no paraffin blocks were available for further study.

Data Collection- Age, sex, site of biopsy, clinical information, all investigative parameter results were captured through Hospital Information System (HIS).

Of the total 115 cases which were provisionally diagnosed as various subtypes of lymphoma on light microscopy with hematoxylin and eosin staining supported by PAS (Periodic shiff's staining) and Reticulin staining are retrospectively analyzed by two independent pathologists. All the cases were subjected to immunohistochemical staining and analyzed. Long battery of markers are used according to the primary morphology which includes CD45, CD20, CD3, C5, CD10, CD30, CD7, CD23, CD43, CD15, CD30, CD56, CD4, CD8, CD7, Bcl2, Bcl6, Cyclin D1, Tdt, EMA, CD99, CD117, PAX 5, Alk 1. Non lymphoid markers were also used in differentiation with other round cell tumors like AE1/AE3, CK7, CK20, TTF, Synaptophysin, HMB-45, Calcitonin, Thyroglobulin, Vimentin etc.

Statistical Analysis- The continuous data were summarized in Mean, median and range whereas discrete (categorical) in number (n) and percentage (%). Data was tabulated and compared and Pie chart was made.

Ethical Approval- This diagnostic study was approved by Institutional review board. The committee waived the informed consent to the participants in view of retrospective nature of study with review of records only.

RESULTS

A total number of 115 consecutive cases from January 2016 to March 2020 were reviewed in the study. All the cases are independently reviewed by two pathologists. Disagreement between the provisional light microscopic diagnosis and final diagnosis after immunohistochemistry was seen in two cases only. In one case testicular biopsy showing high grade NHL on light microscopy turned out to be leukemic infiltration of AML M2 (Acute myeloid leukemia M2). Another case which was diagnosed as gastric MALT lymphoma on morphology later on turn to be malignant GIST (Gastrointestinal smooth muscle tumor). Both cases were excluded from the study.

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Four cases were not further followed up due to insufficient material, poor staining and fixation and five cases could only be diagnosed as non-Hodgkin's lymphoma as the paraffin blocks were already being issued to the patients thus were excluded from the study. Thus total 104 cases were finally selected. Distribution of lymphoid neoplasm, patient demography, age range, median age, male to female ratio, nodal and extra nodal site distribution is shows in Table 1.

Table 1: Epidemiological and Histological distribution of cases

	Lymphoma Subtypes	No	Age (yrs)		Sex			Site		%
			Range	Median	Male	Female	M:F	Nodal(%)	Extra nodal	
	Non-Hodgkin lymphoma	89	77 (8-85)	52.5	58	31	1.87:1	43(48.3%)	47 (52.8%)	85.5
A	Precursor lymphoid neoplasm T cell lymphoblastic lymphoma	2	8 (4-12)	10	0	2	-	1 (50%)	1 (50%)	2.24
B	Mature B-cell neoplasm									
1	Chronic lymphocytic leukaemia/small lymphocytic lymphoma	1	58	-	1	-	-	1	-	1.12 (NHL)
2	Splenic Marginal Zone Lymphoma	2	4 (65-69)	67	0	2	-	-	2	2.24 (NHL)
3	Extranodal marginal zone lymphoma of mucosa associated lymphoid tissue (MALT Lymphoma)	4	28 (43-71)	61	2	2	1:1	-	4	4.49 (NHL)
4	Follicular lymphoma	3	20 (50-70)	57	3	-		3	-	3.37 (NHL)
5	Mantle cell lymphoma	1	79		1			1	-	1.12 (NHL)
6	Diffuse large B-cell lymphoma (DLBCL), NOS	47	59 (26-85)	55	35	12	2.9:1	29 (61.7%)	18 (38.3%)	52.8 (NHL)
7	Primary	14	49	53	8	6	1.3:1	-	14	15.7

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Shukla *et al.*, 2022
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	diffuse large B cell lymphoma of CNS		(26-75)							NHL)
8	Extranodal marginal zone lymphoma of mucosa associated lymphoid tissue of the dura	1	45	-	-	1	-	-	1	1.12 (NHL)
9	T cell/ histiocytic – rich B cell lymphoma	1	50	-	-	1	-	1	-	1.12 (NHL)
C	Mature T- and NK-cell neoplasms									
1	Extranodal NK/T- cell lymphoma, nasal type	2	15 (15-30)	22.5	-	2	-	-	2	2.24 (NHL)
2	Intestinal T-cell lymphoma (monomorphic epitheliotropic intestinal T cell lymphoma)	1	30	-	-	1	-	-	1	1.12 (NHL)
3	Hepatosplenic T- cell lymphoma	1	42	-	1	-	-	-	1	1.12 (NHL)
4	Peripheral T-cell lymphoma, NOS	6	39 (33-72)	55.5	5	1	5:1	5	2	6.74 (NHL)
5	Angioimmuno blastic T-cell lymphoma	2	4 (42-46)	44	1	1	1:1	2	-	2.24 (NHL)
6	Anaplastic large cell lymphoma, ALK Negative 1	1	45	-	1	-	-	-	1	1.12 (NHL)
	Hodgkin lymphoma	15	60 (7-67)	20	9	6	1.5:1	12	3	14.4 (Total)

%= Percentage

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Among the included patients, 15 (14.4%) patients were diagnosed as Hodgkin's lymphoma while 89(85.5%) were belong to Non-Hodgkin lymphoma group. As the focus of the study was non-Hodgkin's lymphoma, further Hodgkin's lymphoma categorization was not evaluated. Majority of NHL were mature B-cell neoplasm (n=74, 83.1% of NHL), while mature T-cell and NK cell neoplasm were less (n=13, 14.6% of NHL). Precursor lymphoid neoplasm were rarely found in only two cases (n=2, 2.24%). On further categorization of NHL, most common subtype found was Diffuse large B-cell lymphoma (DLBCL, n=47, 52.8%) followed by Primary diffuse large B cell lymphoma of CNS (CNS DLBCL, n=14, 15.7%). Peripheral T-cell lymphoma, NOS (PTCL, NOS, n=6, 6.74%), extranodal marginal zone lymphoma of mucosa associated lymphoid tissue (MALT lymphoma, n=4, 4.49%), Follicular lymphoma (FL, n=3, 3.37%), Splenic marginal zone lymphoma (SMZL, n=2, 2.24%), Angioimmunoblastic T-cell lymphoma (AITL, n=2, 2.2-24%) were in decreasing order of frequency. Anaplastic large cell lymphoma (ALCL), Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), Mantle cell lymphoma (MCL), T cell/Histiocytic-rich B cell lymphoma (THRLBCL), Intestinal T cell lymphoma (MEITL), Hepatosplenic T-cell Lymphoma (HSTL) each seen in one patient only (n=1, 1.12%).

Male outnumbered females in both non-Hodgkin and Hodgkin lymphoma. In non-Hodgkin male to female (M/F) ratio was1.87 while in Hodgkin lymphoma it was 1.5. Median diagnosis age for NHL is 52.5(8-85) years while for HL it is 20 (7-67) years. Commonest subtype DLBCL, NOS showing median age 55 (26-85) years and male to female ratio 2.9: 1, while CNS DLBCL revealed median age 53 years (26-75) and male to female ratio 1.3:1. Among the most common T- cell lymphoma, PTCL, NOS median age was 55.5 years and male to female ratio 5:1.

In this study 54 cases were showing primarily lymph node involvement (51.9%) while 50 cases showed extranodal involvement (48%). Nodal involvement is common in Hodgkin's lymphoma (80%), while in non-Hodgkin's lymphoma it was seen in 60.6 % cases only. Distribution in term of nodal and extranodal site is show in Table 2 and Fig. 1.

Table 2: Distribution of cases nodal vs extranodal

	Lymphoma site	No	Percentage(%)	Age (Yrs)		Sex		
				Range	Median	Male	Female	M:F
A.	Nodal	54	51.9					
B	Extra nodal	50	48.0					
1	Central nerous system Brain- 14 Frontal- 4 Parietal-3 Temporal- 2 Corpus callopsum-2 Third ventricular, thalamic, Posterior fossa- one each Meninges-1	15	30 extranodal, 14.4 total	49(26-75)	53	8	6	1.3:1
2	Gastrointestinal tract Stomach 9 Small intestine 1 Large intestine 1	11	22 extranodal, 10.5 total	41(30-71)	45	8	3	2.7:1
3	Testis	5	10 extranodal, 4.8 total	20(57-77)	70	5	-	-

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4	Spine	7	14 extranodal, 6.7 total	20 (50-70)	39	4	3	1.3:1
5	Breast	2	4 extranodal, 1.9 total	1(44-45)	44.5	-	2	-
6	Thyroid	1	2 extranodal, 0.9 total	60			1	
7	Urinary bladder	1	2 extranodal, 0.9 total	26		1		
7	Orbit	1	2 extranodal, 0.9 total	69			1	
8	Mediastinum	4	8 extranodal, 3.8 total	37(8-45)	22.5	1	3	1:3

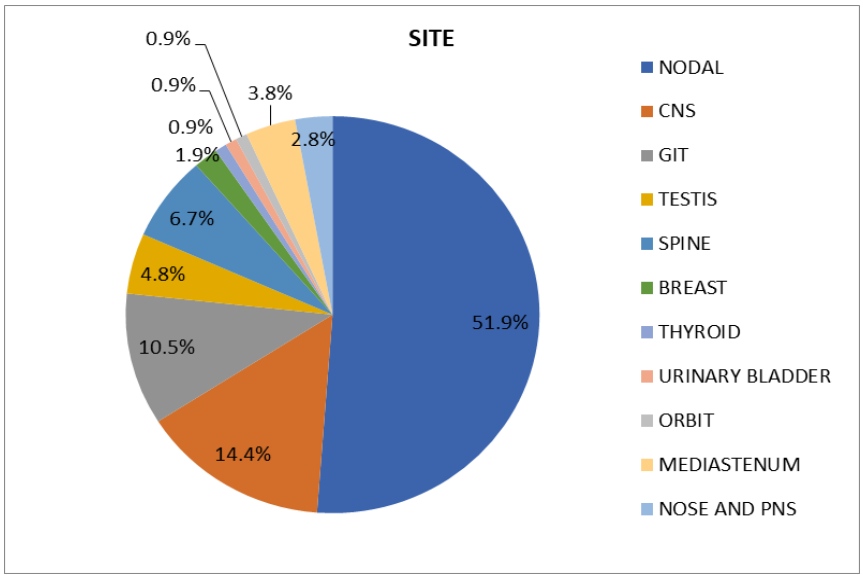

Fig. 1: Pie chart showing lymphoma cases according to site of involvement

Most common extranodal site was CNS seen in 15 cases (n=15/50, 30%) followed by GIT (n=11/50, 22%). Involvement of spine was third most common (n=7/50, 14%). Among the primary CNS lymphoma, Frontal region was the most common site (4/15,26.6%) followed by Parietal region (3/15, 20%) temporal region (2/15, 13.3%) and corpus callosum (2/15, 13.3%). Third ventricular, thalamic, posterior fossa involvement were seen in one case each (n=1, 6.6%). Median age was 53 years with age ranged from 26 to 75. Maximum (8 cases) seen in fifth decade of life.

Primary lymphoma of dura mater was seen in one case, which was mimicking meningioma clinically and radiologically; later on, proved to be MALT lymphoma on histology and immunohistochemistry.

Among the primary GIT, Gastric lymphoma is seen in 9 cases, out of which DLBL seen in 5 cases, MALT lymphoma in 3 cases while one case of 45 yrs male with histomorphological features of high-grade lymphoma labeled as Anaplastic large cell lymphoma- ALK negative.

Primary testicular lymphoma was seen in 4.8% of all NHL and 10.0% of extranodal lymphoma with mean age of 67.8 years and age range from 57-77 years. Four cases were of unilateral involvement while one patient with B/L involvement left > right with paratesticular, soft tissue and spermatic cord and inguinal lymph node metastasis.

Primary B cell NHL involving thyroid, urinary bladder, orbit, breast are found while nose and paranasal sinuses were primarily involved by T- Cell NHL. Out of three cases of primary mediastinal involvement two were diagnosed as T-cell Acute lymphoblastic lymphoma, while one is primary mediastinal B-Cell NHL.

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Table 3: Distribution of Non-Hodgkin's lymphoma in various studies from India, China and US

Histological Type	Arora *et al.* [5] (n=4026%)	Mondal *et al.* [6] (n=455%)	Gogia *et al.* [7] (n=390%)	Meng *et al.* [8] (n=2027%)	Al-Hamadani *et al.* [9] (n=596476%)	Present study (n=89%)
DLBCL	46.9	35.2	68.5	41.3	32.5	52.8
EN/NK T CL	0.9	-	1.3	13.4	-	2.24
MALT	2.4	2.0	2.3	8.0	8.3	4.49
FL	10.5	19.3	9.0	6.6	17.1	3.37
MCL	1.6	2.6	5.0	4.0	4.1	1.12
AITL	1.4	1.4	0.75	3.6	-	2.24
CLL/SLL	4.1	5.5	1.3	3.5	18.6	1.12
PTCL, NOS	5.9	1.7	3.85	2.9	1.7	6.74
ALCL	5.1	12.1	1.8	2.2	1.0	1.12

DLBCL: Diffuse large B-cell lymphoma, EN/NK T CL: Extranodal NK/T cell lymphoma, MALT:Extranodal marginal zone lymphoma of mucosa associated lymphoid tissue, FL: Follicular lymphoma, MCL: Mantle cell lymphoma, AITL: Angioimmunoblastic T- cell lymphoma, CLL/SLL: Small lymphocytic lymphoma, PTCL, NOS: Peripheral T-cell lymphoma, not otherwise specified, ALCL:Anaplastic large cell lymphoma.

DISCUSSION

The incidence of lymphoma increasing steadily over the last two decades. According to International agency for Research on Cancer; Globocan Non-Hodgkin's lymphoma (NHL) affecting 2.8% of all new cases of cancer worldwide with mortality of 2.6% of all cancer death while Hodgkin lymphoma (HL) is affecting 0.44% of new cancer cases with death percentage of 0.27% globally. Incidence in India is almost similar to world figure. Here NHL comprises of 2.7% of all new cancer cases with mortality in 2.4% of all cancer deaths annually while HL seen in 0.59% of new cancer cases with mortality in 0.41% of cases of cancer death.[6]

Numerous studies worldwide showed a higher median age for Non-Hodgkin lymphoma in western population in comparison with Asian figures. In India the median age for NHL is only almost a decade less than western figures. In our study the median age of NHL is 52.5 years similar to other studies from India. [1,7,8] However the males outnumbered the female in both western and Indian figures.

Distribution and comparison from various types of Non-Hodgkin lymphoma on histology from various studies from India, China and US. [9-13]

In the present study DLBL is the most common subtype seen in 52.8% of cases in concordance with other studies but the sticking difference here is low incidence of follicular lymphoma and a much higher incidence of Primary DLBCL of CNS. Low rate of FL in this study and also in the developing countries might be due to late detection of cases and DLBCL might progressed from previously undiagnosed FL.[14] Higher incidence of Primary DLBCL of CNS should be more widely searched and studied in comparison with overall neurosurgery patients and surgically resected neurosurgical specimens.

Lymphoma are also being classified clinically as nodal or extranodal type. Extranodal lymphoma, by definition, involves sites other than lymph nodes, spleen, thymus and the pharyngeal lymphatic ring. Involvement of the spleen in HL is considered as nodal disease but in the case of non-Hodgkin lymphoma (NHL) the spleen is regarded as an extranodal site.[15] Extranodal involvement is more common in NHL than HL.

In the present study Primary extranodal lymphoma was seen in 48% of cases. The key defining criteria used here as when the extranodal site is the only site of disease or the bulk of disease is confined to extranodal sites. There is a changing trend of extranodal lymphoma now a days

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due to increasing usage of immunosuppressive therapy, indolent viral infection and HIV.[13] Most common extranodal site involvement was seen as head and neck region or GIT in previous studies. [17,18]

In the present study Central nervous system (CNS) is the most frequent site for extranodal lymphoma, seen in 30% of all cases of extranodal lymphoma. This is in contrast to the previous literature where it has been described as only 4-6% of all extranodal lymphoma.[18] The median patient age and localization is in concondrance with previous studies. [19] All of the cases belong to diffuse large B-cell lymphoma of the CNS and confined to brain except for one case which was arising from dura.

Second common extranodal site in our study is GIT, seen in 20% of cases of extranodal lymphoma. This incidence is almost similar to the previous studies. DLBCL was the most common histologic type in GIT comparable to observations made by studies from India and other parts of the world. [20,21] The second common histologic type found was ENMZL/MALT lymphoma.

CONCLUSIONS

Lymphoma at a glance in a single tertiary care hospital revealed higher incidence of NHL over HL. Median age of NHL is almost a decade less than western figures and male outnumbered female. DLBCL is the most common subtype, however incidence of FL and CLL/SLL are less. Primary extranodal lymphoma belongs to 48% of cases and CNS being the most common extranodal site followed by GIT. Causes for this must be meticulously searched. The major limitation of the present study was inherited selection bias because the cases collected from single institution where major bulk of cases belonging to neurosurgery, gastroenterology and nephrology. Pediatric population catered by the hospital is less, and the patient's population is also from surrounding states.

This is just an attempt to overview the lymphoma in the population of this region, which was getting unnoticed since inception.

CONTRIBUTION OF AUTHORS

Research concept- Anju Shukla
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