ORIGINAL RESEARCH PAPER
Volume - 9 | Issue - 7 | July - 2020 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

IMMUNOHISTOCHEMICAL PROFILE OF PATIENTS WITH NON-HODGKIN'S LYMPHOMA AT A TERTIARY CARE CENTER

Pathology

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ABSTRACT

Introduction- Non-Hodgkin's Lymphoma is a common hematological malignancy. According to Globocan 2018, it is the 11th most common malignancy occurring in India accounting for 2.6% of new cancer cases and 3.2% of all cancer deaths. Therefore, it is important to have an insight into the pathology of each subtype of NHL to have optimum management and improved treatment outcome.

Subjects And Method- A retrospective study of 200 cases diagnosed as NHL on biopsy and confirmed on IHC, in the time period of January 2018 to June 2018 was carried out at the department of Oncopathology at a tertiary care center.

Results-Out of 200 cases, 131 (65.5%) were males and 69 (34.5%) were females. B-cell lymphomas (89.5%) outnumbered the cases of T-cell lymphoma (10.5%). DLBCL (40.5%) was the most common B-cell lymphoma, whereas T-lymphoblastic lymphoma was the leading T-cell lymphoma. The distribution according to the primary site of presentation was nodal NHL- 110 cases (55%) and extra-nodal NHL- 90 cases (45%). Among the nodal NHLs, the most common lymph node site involved was cervical (29%) and among extra-nodal, it was head and neck (14%).

Conclusion- It is important to study the clinicopathological and immunohistochemical profile of different lymphomas to give optimum treatment and correctly prognosticate each case.

KEYWORDS

B-cell lymphoma; Immunohistochemistry; Non-hodgkin's Lymphoma; T-cell Lymphoma

INTRODUCTION

Non-Hodgkin's lymphoma (NHL) is a heterogeneous group of malignancies of the lymphoid tissue. Each entity is distinct and shows varying patterns of behavior, etiology, morphology, and response to treatment. This is not a single cancer but a group of cancers each with different geographical distribution, development, age profile, and prognosis. [1]

Non-Hodgkin's Lymphoma is a common hematological malignancy. It is more common in developed countries such as North America, New Zealand, Australia and parts of Europe. Whereas, a lower incidence is seen in South-Central and Eastern Asia, along with the Caribbean. [1]

According to Globocon 2018, it is the 11th most common malignancy occurring in India accounting for 2.6% of new cancer cases and 3.2% of all cancer deaths. [2] Within India, the incidence is several-folds higher in urban cancer registries compared to rural areas; the incidence being higher in metropolitan cities and suggesting that urban lifestyles and economic progress may increase the cancer incidence. [3]

Compared to developed nations, the key differences in the presentation in India include median age of 54 years (almost a decade less), higher male to female ratio, a higher proportion of patients with B-symptoms (40–60 vs. 20–30%), poor Eastern Cooperative Oncology Group (ECOG) performance status (≥2) at diagnosis (50 vs. 20–30%), higher frequency of diffuse large B-cell lymphomas (60–70 vs. <40%), lower frequency of follicular NHL (<20 vs. 30–40%) and T-cell type in 10–20 vs. <10%. [3] This could be attributed to the poor infrastructure, delays in diagnosis, and treatment along with inappropriate or suboptimal therapy for the patient. [3]

The WHO classification classifies NHL's as far as possible according to their normal counterparts in B or T lymphocyte lineage. This classification was updated recently in 2016. The main aim of the revised update was to include new clinical information to refine diagnostic criteria for previously described lymphoma, change nomenclature to convey better clinical information and to introduce newly recognized disease entities. [4] The list of genetic aberrations seen in NHLs that are used either in the diagnosis or prognosis of the disease is continuously on the rise.

Most patients affected by NHLs present with generalized lymphadenopathy. Few patients may have an extranodal disease and show involvement commonly of the gastrointestinal tract, head and neck, or skin. The most well-established risk factor of NHL is immunosuppression. Others include primary disorders of immune dysfunction, organ-transplant recipients, HIV/AIDS, infectious agent (Epstein–Barr virus, human T-cell leukemia virus type1, human herpesvirus 8, Helicobacter pylori), and autoimmune and other chronic inflammatory disorder [5]

The unique feature of lymphoma is that it represents a clonal proliferation of lymphocytes arrested in different stages of development. Hence, immunohistochemistry (IHC) can be used to identify the cells by recapitulating stages of normal lymphocyte differentiation. A panel of markers designed based on morphological diagnosis includes- leukocyte common antigen (LCA), B-cell markers (CD20, CD79a), T cell markers (CD3, CD5) and other markers like CD23, BCL2, cyclin D1, CD10, CD15, CD30, CD138 and so on based on the cytoarchitectural pattern. Immunohistochemistry in cases of NHL plays an important role in subtyping of the lymphoma, its prognostication, and targeted therapy potential. [6]

The aims of this study are-

1. Compare the results such as age, sex, site of malignancy with similar studies in different geographical regions.
2. Evaluate the role of IHC in NHL
3. Subtyping cases of NHL according to the WHO classification

MATERIALS AND METHODS -

A retrospective study of 200 cases diagnosed as NHL on biopsy and confirmed on IHC, in the time period of January 2018 to June 2018 was carried out at the Department of Oncopathology at a tertiary care center.

Relevant clinical data such as age, sex, site of the biopsy was obtained from the request forms and clinical files. The histopathological and IHC findings were obtained from the laboratory data. Imaging reports such as chest X-rays, abdominal and pelvic ultrasounds, Computed Tomography scans of brain, head and neck, thorax and abdomen, and magnetic resonance imaging scans were also reviewed.

The study excluded the cases which had insufficient biopsy material, inconclusive IHC, improper history, cases on which IHC was not given, cases with only slide submission without a block for review, cases with crushing on which immunohistochemistry was not possible. All the biopsies were fixed in 10% neutral buffered formalin and processed for paraffin embedding, sectioning, and staining with

Hematoxylin and Eosin (H&E). Immunohistochemistry was done on a 3 µm thick section of representative tumor areas.

Procedure for H&E staining-
1. De-paraffinization (removal of paraffin wax with xylene)
2. Hydration using graded alcohols to water
3. Nuclear staining using hematoxylin
4. Differentiation using acid alcohol
5. Bluing agent- ammonia water
6. Counterstaining using eosin
7. Dehydration- application of graded alcohol to 100% alcohol
8. Clearing agent- Xylene (transition from alcohol to non-aqueous state)

IHC Panel employed in the Study

The panel for antibodies used for immunohistochemistry included-
B-cell markers-
CD10 (RTU, Ventana), CD15 (1:50, Carb3, Dako), CD19 (1:100, MRQ36, CellMarque), CD20 (1:100, L26, CellMarque), CD79a (1:50, CB117, CellMarque), CD23 (1:50, DAK-CD23, Dako), CD30 (1:30, Ber-H2, CellMarque), CD38 (1:50, MI15, Dako), CD138 (1:75, MI15, Dako), BCL-2 (1:100, 124, CellMarque), BCL-6 (1:100, G1191E/A8, CellMarque), Cyclin D1 (1:30, EP12, Biogenex), PAX5(1:50, 24, CellMarque)

T and NK cell Markers:

CD2 (1:50, MRQ11, CellMarque), CD3 (1:50, F22.38, Dako), CD5 (1:50, 4C7, Dako), CD1a (1:30, O10, Biogenex), CD43 (1:30, DF-11, Dako), CD56 (1:100, 56CO4, Thermo), CD68 (1:100, Kp-1, CellMarque)

Myeloid markers-

CD117 (1:100, YR145, CellMarque), MPO (1:100, Ab1, Thermoscientific), Other antibodies also included were – TdT (1:30, EP266, Biogenex), MUM1 (1:100, MRQ43, CellMarque), MIB1 (1:50, MIB1, Dako), ALK-1 (1:75 ALK1, Dako), CD45 (1:50, Ab2, Thermo) , EMA (1:100, E29, CellMarque), TTF1 (1:100, 6G7G3/1, CellMarque), AE1 (1:100, AE1&3, CellMarque), CK5/6 (1:100, D5&16B4, CellMarque), CK7 (1:50, OV-TL12/30, Dako), desmin (1:30, D33, Biogenex), vimentin (1:200, V9, Biogenex), S-100 (1:100, 4[4.9], Thermoscientific), FLT1 (1:50, MRQ1, CellMarque) and CEA (1:50, 11-7, Dako).

The panel of antibodies used in a given case was dependent on the morphological evaluation.

Immunohistochemistry was performed on the paraffin tissue section by Ventana Benchmark XT (fully automated slide staining system) and Autostainer using DAB detection kits.

Procedure for IHC -

The tumor tissue blocks were obtained from the archives of the Pathology Department of the Institute. 3µm thin sections were cut on a microtome (Leica, Germany) and taken on 3-Aminopropyl triethoxysilane (APES) coated slides. Immunohistochemical localization of markers was performed on formalin-fixed paraffin-embedded (FFPE) tissue blocks containing primary tumor by staining on Ventana Benchmark XT autoimmunostainer using Ventana reagents (Ventana, USA).

The protocol includes the following steps-
1. deparaffinization using EZ solution
2. antigen retrieval for 60 minutes using retrieval solution Cell conditioning1 (Cc1), and incubation with Ultra View DAB inhibitor for 4 minutes
3. 100µl of respective primary antibodies were added for a specified amount of time for each antibody.
4. This was followed by Ultra View HRP Multimer for 8 minutes, Ultra View DAB Detection kit for 8 minutes, counterstaining with hematoxylin for 8 minutes, bluing reagent for 4 minutes.
5. Finally, the slide was mounted with DPX.

RESULTS

A total of 200 cases were collected, of which 65.5% cases were males and 34.5% cases were female. The majority of the cases in both sexes (23%) were seen in the age group of 61-70 years of age as shown in Table I.

The distribution according to the primary site of presentation was nodal NHL 110 cases (55%) and extra-nodal NHL 90 cases (45%). Amongst the nodal NHLs, the most common lymph node sites involved were cervical (29%), followed by axillary (8.5%), inguinal (6.5%), Waldeyer's ring (1.5%), and abdominal group of nodes (1.5%). (Table II)

Organ involvement in extra-nodal cases of NHL showed head and neck as the most common site of presentation accounting for 14% of cases in which the central nervous system (CNS) constituted 5.5% cases. This was followed by the gastrointestinal tract (GIT) making up 10.5% cases, bone (4.0%), mediastinal mass (3%), skin (2.5%), and others. (Table III)

Based on the immunophenotype, B-cell lymphomas outnumbered the cases of T-cell lymphoma. B-cell lymphoma formed 85.5% of cases, whereas T-cell lymphoma accounted for 14.5% of cases. As shown in Table IV, among the B-cell lymphoma cases diffuse large B-cell lymphoma (DLBCL) seen in 40.5% constituted majority of the cases, followed by B-cell NHL (NOS) making up for 10%, follicular lymphoma (6.5%), Burkitt's lymphoma (6.5%), chronic lymphocytic lymphoma / small lymphocytic lymphoma (CLL/SLL) (5.5%) and others.

The majority of the T-cell lymphomas were T-lymphoblastic lymphoma (5%), Pre-T cell lymphoblastic lymphoma/leukemia (3%), anaplastic large cell lymphoma (2%), peripheral T-cell lymphoma (1%) and mycosis fungoides (1%) as depicted in Table V.

A wide range of markers were used in the IHC panel for the sub-classification of NHLs. Markers specific for B-cell NHL, T-cell NHL, myeloid lineage, and others to rule out epithelial malignancies were employed. The markers ranged from 5-13/case. On an average, 9-13 markers were required per case in B-cell NHLs whereas, T cell lymphoma required 5-8 markers/case.

Table I- Incidence of B-cell and T-cell Lymphoma according to age and sex

Age	B-cell Lymphoma		T-cell Lymphoma		
	Male	Female	Male	Female	Total (%)
0-10	5	2	2	2	11 (5.5%)
11-20	9	2	3	-	14 (7%)
21-30	11	2	2	-	15 (7.5)
31-40	16	5	2	1	24 (12%)
41-50	21	12	-	2	35 (17.5)
51-60	21	14	4	-	39 (19.5)
61-70	25	18	2	1	46 (23%)
71-80	5	7	-	-	12 (6%)
>80	3	1	-	-	4 (2%)
Total	116	63	15	6	200 (100%)

Table II- Nodal sites on initial presentation

Nodal sites on presentation (n=110)	
Nodal sites	Number (%)
Abdominal nodes	5 (2.5%)
Axillary nodes	17 (8.5%)
Cervical Nodes	58 (29%)
Inguinal nodes	13 (6.5%)
Mediastinal nodes	3 (1.5)
Mesenteric nodes	2 (1%)
Para-aortic nodes	3 (1.5%)
Retroperitoneal nodes	1 (0.5%)
Supraclavicular nodes	3 (1.5%)
Waldeyers ring	5 (2.5%)

Table III- Extra-nodal sites on initial presentation

Extranodal sites on presentation (n=90)	
Extranodal sites	Number (%)
Abdominal mass	3 (1.5%)
Breast	3 (1.5%)
Bone	8 (4%)
Gastrointestinal tract (GIT)- Large bowel Small intestine Stomach	21 (10.5%) 3 (1.5%) 5 (2.5%) 13 (6.5%)

Head and Neck –	28 (14%)
Alveolus/Hard palate	2 (1%)
CNS	11 (5.5%)
Oral cavity/Oropharynx	3 (1.5%)
Orbit	3 (1.5%)
Nasopharynx/Nasal cavity	7 (3.5%)
Thyroid	2 (1%)
Liver	4 (2%)
Mediastinal mass	6 (3%)
Pelvic mass	4 (2%)
Pleural Fluid	2 (1%)
Retroperitoneal mass	2 (1%)
Skin	5 (2.5%)
Soft tissue	4 (2%)

Table IV- Distribution of B-cell lymphoma subtypes

S No.	Lymphoma Subtype	Number (n=171)		Total (%)
		Nodal site (96)	Extranodal site (75)	
A	Precursor B-cell neoplasm			
	B-Lymphoblastic Lymphoma	2	4	6 (3%)
B	Mature B-cell Neoplasms			
	B-cell chronic lymphocytic Lymphoma/small lymphocytic lymphoma	11	-	11(5.5%)
	B-cell Non-Hodgkins lymphoma (NOS)	10	10	20 (10%)
	Burkitt's lymphoma	6	7	13(6.5%)
	Diffuse large B-cell lymphoma	40	41	81(40.5%)
	Follicular lymphoma	12	1	13(6.5%)
	Lymphoplasmacytic Lymphoma	-	1	1 (0.5%)
	Mantle cell lymphoma	6	1	7 (4%)
	Marginal zone lymphoma of mucosa associated lymphoid tissue	-	3	3 (1.5%)
	Nodal marginal zone lymphoma	1	-	1 (0.5%)
	Non- Hodgkin's lymphoma large cell type	4	3	7 (3.5%)
	Plasmablastic lymphoma	2	3	5 (2.5%)
	Splenic marginal zone lymphoma	-	1	1 (0.5%)
	T-cell and histiocytic rich B-cell lymphoma	2	-	2 (1%)

Table V- Distribution of T-cell lymphoma sub-types

S No.	Lymphoma sub type	Number (n=29)		Total
		Nodal site (14)	Extra-nodal site (15)	
A	Precursor T-cell neoplasms			
	Pre-T cell lymphoblastic lymphoma/leukemia	2	4	6 (3%)
	T-lymphoblastic Lymphoma	5	5	10 (5%)
B	Mature T and NK-cell neoplasms			
	Anaplastic large cell lymphoma	4	-	4 (2%)
	Extra nodal T/NK cell lymphoma- nasal	-	1	1 (0.5%)
	Mycosis fungoides	-	2	2 (1%)
	Peripheral T-cell lymphoma	2	-	2 (1%)
	Primary cutaneous T-cell lymphoma	-	1	1 (0.5%)
	T-cell lymphoproliferative disorder	-	2	2 (1%)
	T-cell prolymphocytic lymphoma	1	-	1 (0.5%)

DISCUSSION-

Non-Hodgkin's lymphoma is a common hematological malignancy occurring in India. However, the age-standardized incidence rates in India for NHL are (0.8-5.1 for males) and (0.6 to 3 for females) which is much lower than that seen in the USA (16.1 males and 10.8 females). [9] India reports about one-fourth of the incidence rates reported in Western Europe and North America. [3]

Based on the sex, the incidence of NHL was seen in greater numbers in men than women. The male to female ratio in Asia is 1.6 compared to 1.2 and 1.1 in North America and Western Europe, respectively. [1] Our study had a male: female ratio of 1.8:1. This was comparable to another study conducted by Hamid KH which had a male: female ratio of 1.6:1. [10] Other studies showed male predominance as well with ratios ranging from 1.2: to 1.5:1. [1,5,8]

Non-Hodgkin's lymphoma is a malignancy known to be occurring more commonly in adults. The mean age of occurrence of NHL in most western and Asian countries is between 50-60 years of age. [5] The median age in our study was 51 years. A similar study conducted by Vallabhajosyula et al. reported the median age of their study as 55.5 years. [11]

Many studies showed bimodal occurrence of NHL, peaking in ages 31-40 followed by 61-70. [1,8] However, our study showed a gradual increase in the incidence of cases from the age of 30 to 70. The majority of the cases were seen in the age group of 61-70 (46%). It is believed that the incidence of NHL in India occurs almost a decade before the West. This may be explained by the fact that increased frequency of infectious diseases and chronic antigenic stimulation may be responsible. Since this tends to occur in India at an earlier age, it is proposed to be the reason. [9]

The most frequent site of initial presentation of disease in our study was cervical swelling. The cervical group of lymph nodes was seen involved first in 29% of all cases followed by axillary lymph node (8.5%) and inguinal lymph node (6.5%). Another study conducted by Chakrabarti et al. showed similar results in which the cervical group was involved in 78% cases followed by axillary (55.3%).[12] A study conducted in Pakistan however, showed para-aortic nodes to be most commonly involved followed by cervical and axillary. [13]

In our study, hepatomegaly was seen in 25% cases and splenomegaly in 18.5% cases. Other studies documented slightly varying results. Devi et al. reported hepatomegaly and splenomegaly in 44% and 30% cases respectively. [5]

Forty-five percent of our cases showed an extranodal presentation of NHL. This was consistent with other studies conducted in the North-eastern part of India (43%), South India (42.6%), and North India (44.2%). [5,7,14] The nodal: extranodal ratio in our study for B-cell and T-cell lymphomas was 1.2:1 and 0.8:1 respectively. T-cell lymphomas showed preponderance to extra-nodal sites.

The most common extra-nodal site involved in our study was head and neck (14%) followed by GIT (10.5%) and bone (4%). In the head and neck, the most common site of involvement was CNS and in the GIT it was the stomach. The study conducted by Mishra et al. showed identical results with head and neck being the most common site lead by CNS involvement followed by GIT in which stomach was the most common site. [15] Our results also matched with studies conducted in China and Japan showing head and neck to the most common site for extranodal NHL. [16] However, in the western countries, GIT is the most common site of extranodal disease. [9]

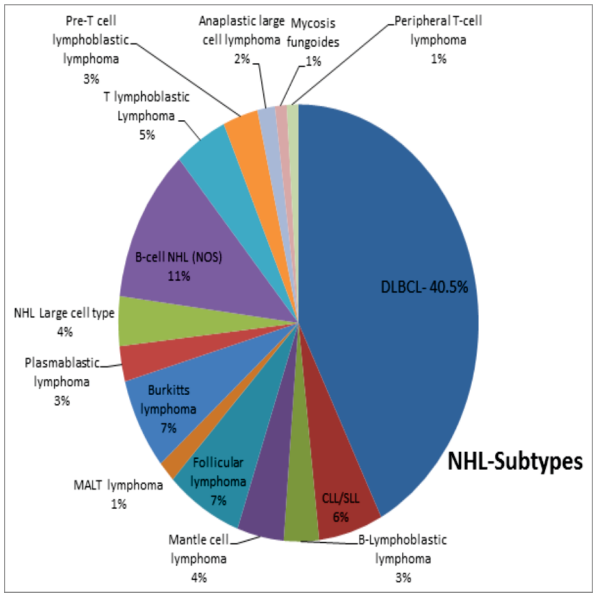
In our study, the B-cell lymphomas constituted 85.5% cases and the T-cell lymphomas made up 14.5% of cases. Our data was comparable with other authors such as Sharma et al. and Mansoor et al. who showed corresponding results of 89.3/10.7 and 87.5/7.5 for B-cell/T-cell lymphomas respectively. [1,8] (Table VI)

Table VI- Incidence of B-cell and T-cell Lymphoma in various studies

Author's Name (year)	Total number of cases	B-cell lymphoma	T-cell lymphoma	NOS
Padhi S et al., (2012) [7]	68	96%	4%	-
Rao A et al., (2013) [6]	324	56%	38%	-
Manisha Sharma et al., (2014)[1]	77	89.3%	10.7%	-
Mansoor et al., (2017) [8]	40	87.5%	7.5%	5%
Devi et al., (2018) [5]	100	66%	23%	11%
Current study	200	85.5%	14.5%	

In B-cell lymphomas, the majority of cases were of DLBCL (40.5%) followed by B-cell NHL (NOS) making up for 10%, follicular lymphoma (6.5%), Burkitt's lymphoma (6.5%) and chronic lymphocytic lymphoma / small lymphocytic lymphoma (CLL/SLL) (5.5%). A study conducted by Devi et al. showed DLBCL (45%) to be the most common B-cell lymphoma followed by Burkitt's lymphoma (6%) and follicular lymphoma (5%). [5] (Illustration 1)

Illustration 1- NHL subtypes



Diffuse large B-cell lymphoma constituted in different countries, Iran 37.8%, Korea 43.2%, Taiwan 47.2% / 39%, China 35.1%, Thailand 50.5%, Japan 33%, Asia 41.2%, UK 41.3% and USA 20%. [8] Our results were similar to those of Asia and UK.

Peripheral T-cell lymphoma not otherwise specified, lymphoblastic lymphoma and anaplastic large-cell lymphoma are the three common subtypes of T-cell NHL seen in the Indian subcontinent. [3] However, in our study T-lymphoblastic lymphoma was the most predominant type constituting 5% of all cases. This was followed by Pre-T cell lymphoma (3%) and anaplastic large cell lymphoma (2%). Other studies have reported anaplastic large cell lymphoma in greater numbers, ranging from 2.5-6%. [5,8] We had fewer cases in our study.

CONCLUSION

The incidence of Non-Hodgkin's lymphoma is on the rise in India as well as the rest of the world. The wide spectrums of lymphomas that come under this category have different clinical presentations, pathological profile, prognosis, and IHC marker expression. It is hence important to have a thorough insight into the pathology of each subtype of NHL to have optimum management and improved treatment outcomes.

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