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ORIGINAL RESEARCH

Immunohistochemical Evaluation of Lymphoid Neoplasms

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Abstract

Background: Cancer is one of the leading causes of death worldwide and accounted for 7.6 million deaths (13% of all deaths) in 2008 according to the World Health Organization. The age-world-standardized incidence rate (per 100000) for non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) are 6.7 and 2 respectively. Non-Hodgkin's lymphoma (NHL) is a common hematological malignancy. The age-adjusted incidence rates for NHL in men and women in India are 2.9/100,000 and 1.5/100,000, respectively as per epidemiological data. IHC staining is essential for the diagnosis of various lymphomas. It is crucial that we select appropriate markers according to the histopatholgy results and clinical situation of the patient, and accurately interpret the IHC results for an optimal lymphoma diagnosis.

Aims and objectives: This study was conducted to evaluate Immunohistochemical pattern of Lymphoid neoplasms.

Material and methods: The present prospective study was conducted for three years. A total number of 83 biopsies which were diagnosed as lymphoma on histopathology slides were subjected to an IHC panel based upon morphology. We used IHC panel of LCA, CD3, CD20, Ki67 followed by CD5, CD10, CD15, CD30, CD23, BCL2, BCL6, MUM1, ALK, CyclinD1. The association of lymphoid neoplasm with different IHC markers was studied.

Result: Non-Hodgkin's lymphoma was the most common type of lymphoma seen (79 cases, 95.2%).Hodgkin's lymphoma was whereas seen only in four cases (4.8%).Diffuse Large B-Cell lymphoma (DLBCL) was the most common type of lymphoma encountered in the current study (40 cases, 48.2%). Most of the other types of lymphoma were less than 10% of the cases. Of the DLBCL cases, majority of the cases were of ABC types (32 cases out of 40, 80%), while majority of Hodgkin's Lymphoma cases were of Mixed Cellularity type (2 cases, 50%).

Conclusion: Immunohistochemistry although indispensable in the diagnosis and classification of hematopoietic and lymphoid neoplasms, has to be used cautiously with knowledge of the antibodies used. No antigen is totally lineage specific hence, immunostaining must be performed in the context of a panel.

Keywords: Lymphoma, Immunohistochemistry, Hodgkin, Non-Hogdkin, B-cell, T-cell.

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Introduction

Lymphomas are classified into two major categories, Hodgkin Lymphoma (HL) and Non-Hodgkin Lymphoma (NHL). HL has five subtypes: nodular lymphocyte predominant (NLPHL), nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte rich (LRHL) and lymphocyte depleted (LDHL). Non-Hodgkin lymphomas are: B-cell and T-cell types, which are sub-classified into different subtypes using immunohistochemistry, according to WHO classification.[1]

According to global cancer facts and figures, the estimated age-standardized incidence and mortality rates (per 100,000), 2008, for NHL was 10.3 and 3.6 respectively for developed countries and 4.2 and 3 for developing countries. The estimated age-standardized incidence and mortality rates (per 100,000) for HLwere 2.2 and 0.4 in developed countries and, 0.9 and 0.6 in developing countries.[2] NHLis the seventh leading cause of cancer death in the United States and represents 3.3% of all cancer deaths.[2] The age-adjusted incidence rates for NHL in men and women in India are 2.9/100,000 and 1.5/100,000, respectively. Within India, the incidence is several-fold higher in urban cancer registries compared to rural areas; the incidence being higher in metropolitan cities and Indian immigrants suggesting that urban lifestyles and economic progress may increase the cancer incidence.

NHL incidence rate is highest in people aged 65 - 74 years and mortality rate is highest in people aged 75 - 84 years. Incidence rate for NHL has been rising on average 0.5% each year spanning over the last 10 years.[3] Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma and accounts for 30% to 40% of new diagnoses.[3,4] The International Prognostic Index (IPI) has been the primary clinical tool used to predict outcome for patients with aggressive NHL.[5]

Aim

This study was conducted to evaluate Immunohistochemical pattern of Lymphoid neoplasms.

Material and Method

A Three year prospective study was conducted at the Department of Pathology of IMS & SUM Hospital.

Selection of Cases

- In this study, all lymph node biopsies, received with features suspicious of lymphoma clinically and cytologically were evaluated.
- The H&E stained slides of all the cases were reviewed by experienced pathologists with an aim to apply proper IHC panel to reach to a final diagnosis.
- A total number of 200 biopsies were evaluated and 83 cases were diagnosed as lymphoma based on anatomical architectural alteration and a IHC panel of LCA, CD3, CD20, CD5, CD10, CD15, CD30, CD23, PAX5, BCL2, BCL6, cyclinD1, MUM1, Tdt, ALK, Ki67. Rest 117 cases were considered as control group of our study.

Exclusion Criteria

- Paraffin embedded tissue blocks with sections from the non-representative areas and sections with quantitatively inadequate material were not included in the study.
- Cases having infective and metastatic lesions were excluded.
- H & E stained sections showing extensive histomorphological artifacts such as cautery/crush artifacts were also excluded from the study.

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Clinical Data

The relevant clinical data with respect to all the cases for the study was acquired from the requisition forms sent with the specimen ,the data register in the medical-oncology and surgical-oncology OPD and from the ward.

Procedure

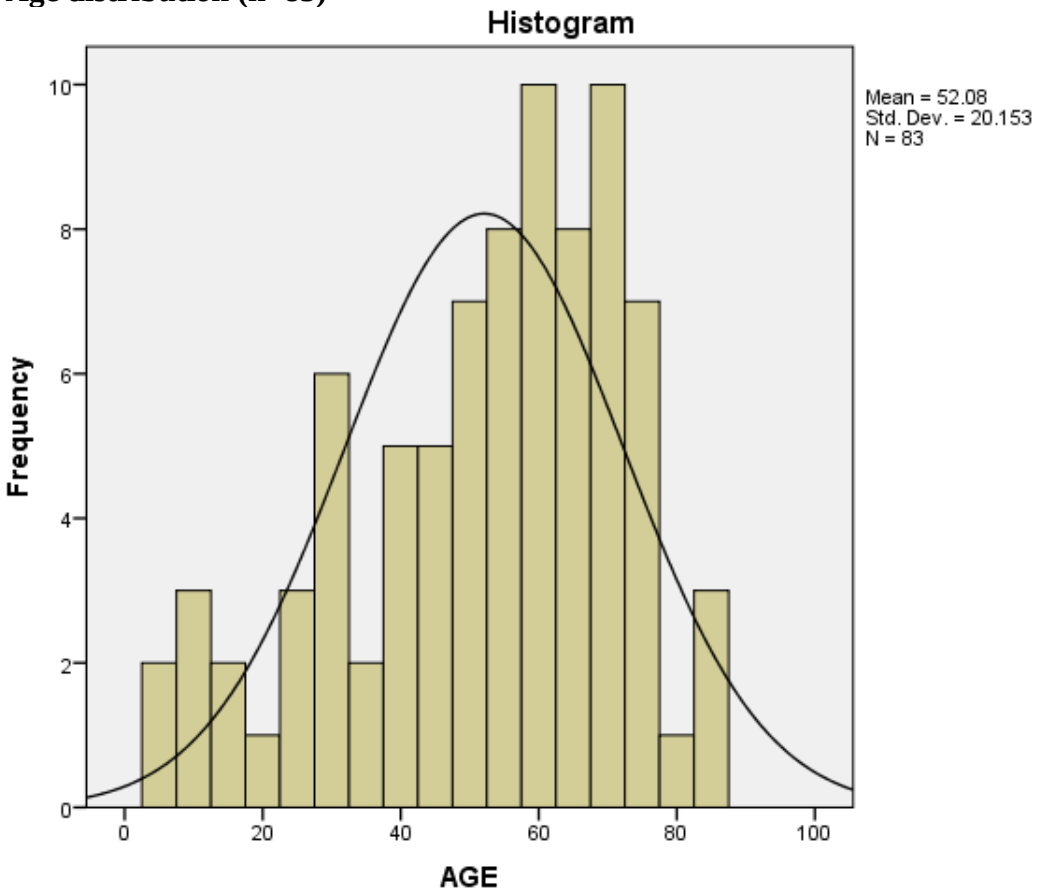
Tissue received in the histology section were fixed in 10% formalin and processed in automatic tissue processor. From all the paraffin embedded tissue blocks, sections of 3 to 4 micron thickness were made on separate glass slides. The slides to be used for Hematoxylin and Eosin stain were coated with egg albumin and those to be subjected for Immunohistochemistry were coated with poly-L-lysine. All the sections stained by H & E and IHC methods were reviewed.

Results

Age distribution

The study participants were having a mean age of 52 years with a standard deviation of 20.15 years. (Mode 60 years).

Fig 1: Age distribution (n=83)



Gender distribution

A total of 65 cases were male (78%), and the rest were female (18 cases, 22%).

Clinical features

Nodal involvement was seen in majority of the patients (50 cases, 60%). Cervical lymphadenopathy was the most common presentation and was present in 34 cases (40.96% of

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all cases). This was followed by axillary nodes and inguinal nodes (7 each, 8.43%) Multiple sites were also involved in few cases as can be seen from table 1.

Site of lymphadenopathy among the cases (n=83)

	N	%
Nodal	**50**	**100%**
AXILLARY	5	10.00%
AXILLARY,INGUINAL	1	2.00%
AXILLARY,SUPRACALAVICULAR	1	2.00%
CERVICAL	32	64.00%
CERVICAL,INGUINAL	2	4.00%
ILIAC	1	2.00%
INGUINAL	4	8.00%
SUBMANDIBULAR	2	4.00%
SUPRACLAVICULAR	2	4.00%
Extranodal	**33**	**100%**
ANTRUM	1	3.03%
CAECUM	2	6.06%
CNS	4	12.12%
COLORECTAL	1	3.03%
DUODENUM	2	6.06%
FLOOR OF MOUTH	1	3.03%
ILEOCECAL	1	3.03%
MEDIASTINAL MASS	1	3.03%
NASOPHARYNX	2	6.06%
PARANASAL MASS	1	3.03%
SKIN BX	2	6.06%
SPLEEN	5	15.15%
STOMACH	4	12.12%
TESTIS	2	6.06%
THYROID	1	3.03%
TONSIL	3	9.09%

Table 1: Lymph node involvement in lymphoma cases (n=83)

Types of lymphoma

Non-Hodgkin's lymphoma was the most common type of lymphoma seen (79 cases, 95.2%). Hodgkin's lymphoma was whereas seen only in four cases (4.8%). Diffuse Large B-Cell Lymphoma (DLBCL) was the most common type of lymphoma encountered in the current study (40 cases, 48.2%) (Fig2). Most of the other types of lymphoma were less than 10% of the cases. Of the DLBCL cases, majority of the cases were of ABC types (32 cases out of 40, 80%), while majority of Hodgkin's Lymphoma cases were of Mixed Cellularity type (2 cases, 50%).

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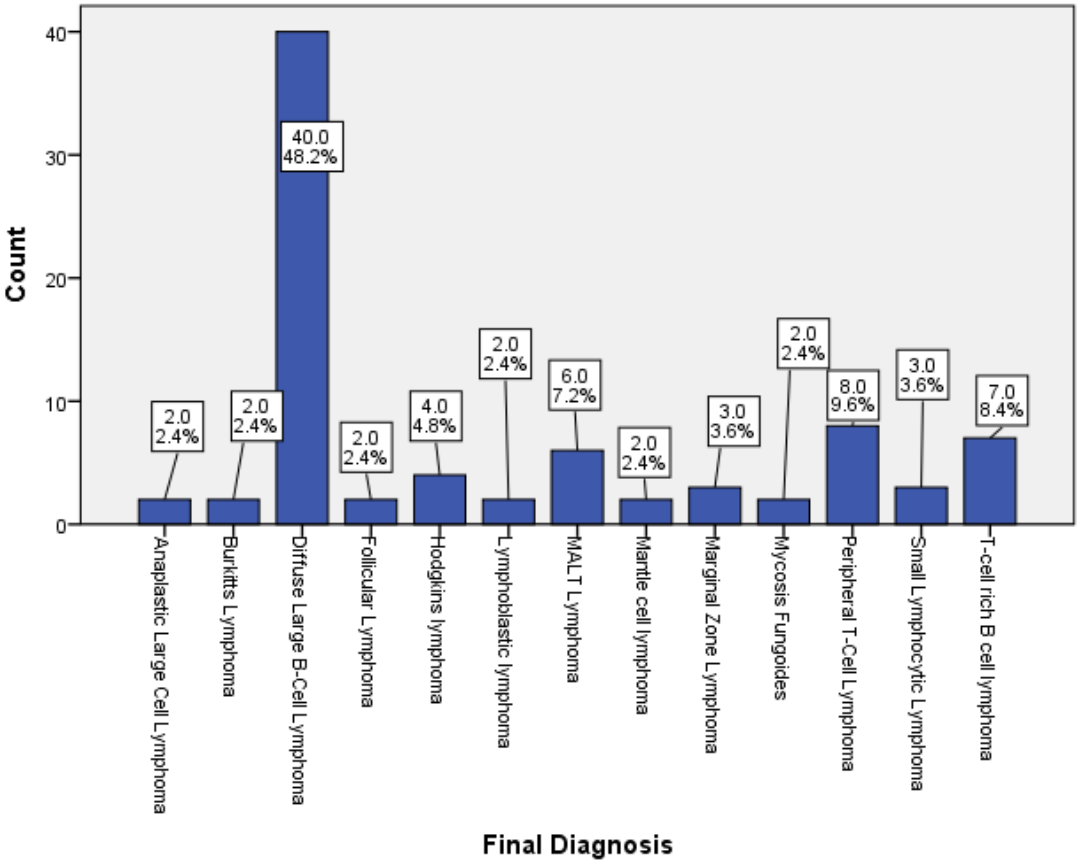
Fig 2: Final diagnosis of the lymphoma cases (n=83)



B-symptoms

B symptoms were present in 63 cases (76%), and absent in the remaining. Distribution of B-symptoms was seen in similar proportion among Hodgkin's and non-Hodgkin's lymphoma and this was not statistically significant ($p>0.05$). It was seen that B-symptoms had a significant association ($p=0.007$, Chi-square test) with the type of lymphoma diagnosed, with B-symptoms being present most commonly with DLBCL type of lymphoma.

Markers

Distribution of the markers among Hodgkin's and non-Hodgkin's lymphoma was analysed. It was seen that LCA and CD15 markers were found in different proportions among both the groups (LCA positive more in non-Hodgkin's and CD15 more in Hodgkin's lymphoma), and this was statistically significant at $p=0.05$ levels.

		Type of lymphoma			
		Hodgkin's lymphoma		Non Hodgkin's Lymphoma	
		Count	Column N %	Count	Column N %
LCA#	Positive	1	50.0%	51	100.0%
	Negative	1	50.0%	0	0.0%
CD3	Positive	1	25.0%	30	38.5%
	Negative	3	75.0%	48	61.5%
CD20	Positive	2	50.0%	66	83.5%
	Negative	2	50.0%	13	16.5%
CD5	Positive	0	0.0%	24	32.0%
	Negative	3	100.0%	51	68.0%

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CD10	Positive	0	0.0%	19	25.0%
	Negative	3	100.0%	57	75.0%
CD15[#]	Positive	3	75.0%	2	8.3%
	Negative	1	25.0%	22	91.7%
CD30	Positive	4	100.0%	15	55.6%
	Negative	0	0.0%	12	44.4%
CD23	Positive	0	0.0%	3	16.7%
	Negative	3	100.0%	15	83.3%
PAX5	Positive	3	100.0%	42	79.2%
	Negative	0	0.0%	11	20.8%
BCL2	Positive	1	33.3%	46	69.7%
	Negative	2	66.7%	20	30.3%
BCL-6	Positive	0	0.0%	29	45.3%
	Negative	3	100.0%	35	54.7%
Cyclin-D1[$]	Positive	0	0.0%	2	22.2%
	Negative	0	0.0%	7	77.8%
MUM-1	Positive	1	100.0%	25	67.6%
	Negative	0	0.0%	12	32.4%
Tdt[$]	Positive	0	0.0%	1	10.0%
	Negative	0	0.0%	9	90.0%
ALK[$]	Positive	0	0.0%	2	66.7%
	Negative	0	0.0%	1	33.3%

Table 2: Markers detected among the lymphoma cases type wise (n=83)

[#]*Significant at p=0.05 using Chi-square test*

[$]*Chi-square could not be computed as one or more cell values is zero*

It was seen that LCA was seen most commonly with DLBCL type of lymphoma (28, 52.8%), significant association (p=0.004 using Chi-square test) could not be ascertained due to low cell values. Marginal Zone lymphoma, Peripheral T cell lymphoma and T-cell rich B cell lymphoma were also found to be positive for LCA (5 cases each, 9.4%).There is a significant association of CD3 with the type of Lymphoma diagnosed (p=0.000), with the marker being always positive in all cases of PTCL and TRBCL. This marker was negative mostly when it was a case of DLBCL.

There is a significant association of CD20 with the type of Lymphoma diagnosed (p=0.000), with the marker being positive in 37 (54%) of the cases in DLBCL.CD5 was found to be positive in cases of DLBCL (15 cases, 62.5%) followed by 3 cases each of SLL and TCRBCL (12.5%) out of all 24 cases found positive. There was a statistically significant association observed between CD5 and lymphoma, with DLBCL cases showing positivity more than expected (p= 0.007). CD15was seen to be positive in Hodgkin's lymphoma and PTCL. This was however not found to be statistically significant (p=0.069).CD30 marker was found to be positive in cases of PTCL (36.8%) followed by Hodgkin's lymphoma cases. This was found to be statistically significant (p=0.001). However, the association had poor interpretation due to low cell values.CD23 marker was found to be positive only in cases of SLL (3 cases, 100%) and this was found to have significant association (p=0.007).PAX5 was found to be positive in 34 cases of DLBCL (75.6%), and this was found to be statistically significant (p=0.000).BCL2was found to be positive mostly in cases of DLBCL (31 cases, 66%), and this was found to have statistically significant association (p=0.006).BCL6 positivity was seen mostly in cases of DLBCL (17 cases, 58.6%) followed by TCRBCL (6 cases, 20.7%). The test of association was seen to be significant with TCRBCL being mostly association with BCL6, with cases occurring more than expected in this group

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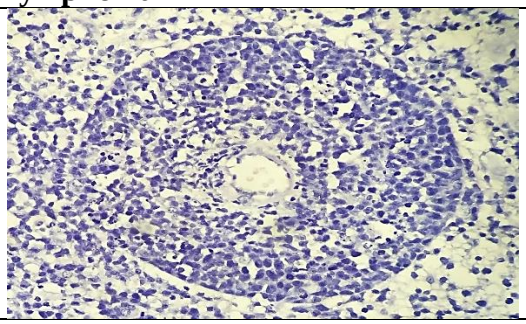
(p=0.007).Cyclin D1 was found to be positive only in cases of Mantle cell lymphoma cases (2 cases, 100%), but this association was not statistically significant (p=0.174). There was no statistically significant association of MUM1 with any type of lymphoma. It was seen most commonly in DLBCL type (24 cases, 92.3%). Tdt was positive in only one case of Lymphoblastic lymphoma (100%), but this was not found have statistically significant association with the type of lymphoma (p=0.349) . ALKwas found to be positive in Anaplastic Large B Cell Lymphoma, but there was no significant association at p value of 0.05. KI67 values were found to be very high for Burkitts lymphoma followed by Lymphoblastic lymphoma as can be seen from the table. One-way ANOVA showed a significant difference between the mean values of KI67 among all the groups (p=0.000).

CNS lymphoma



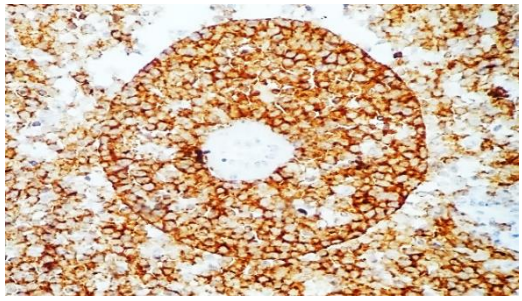
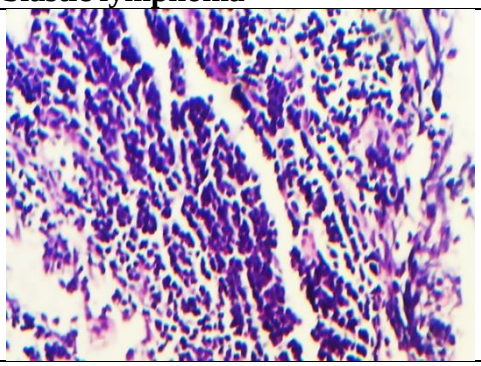


Figure 3: Perivascular arrangement of neoplastic cells Figure 4: Neoplastic cells showing membranous staining for CD20

Lymphoblastic lymphoma



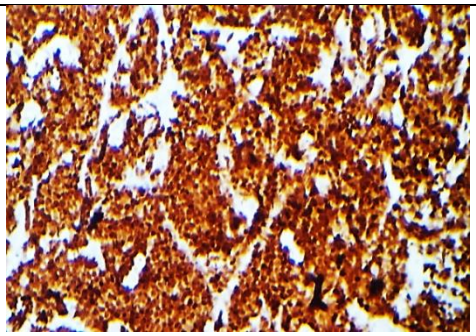
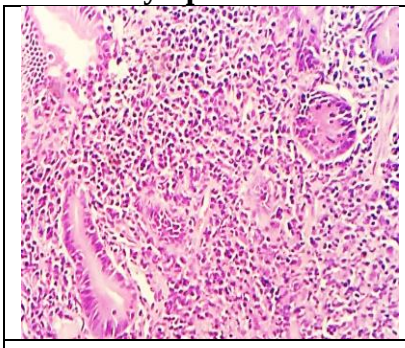
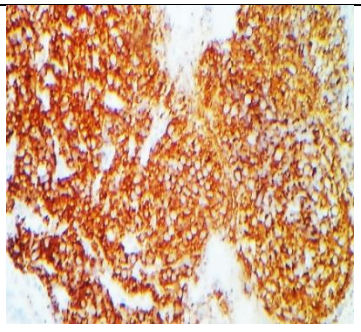


Figure 5:Indian file pattern Figure 6:Neoplastic cells showing nuclear staining for Tdt

MALT Lymphoma





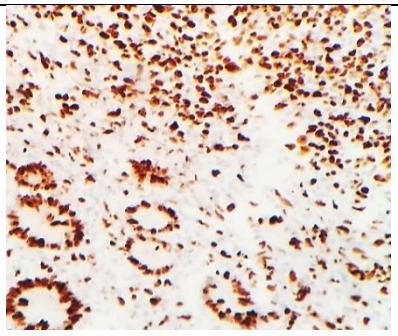


Figure 7: Lymphoepithelial lesion Figure 8:Membranous staining for CD20 Figure 9: Ki67>30%

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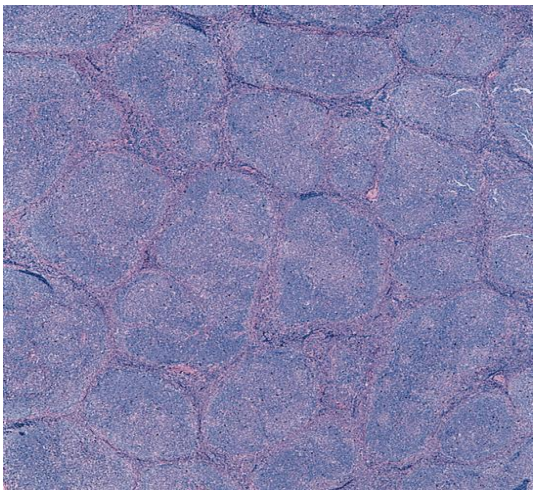
Follicular Lymphoma



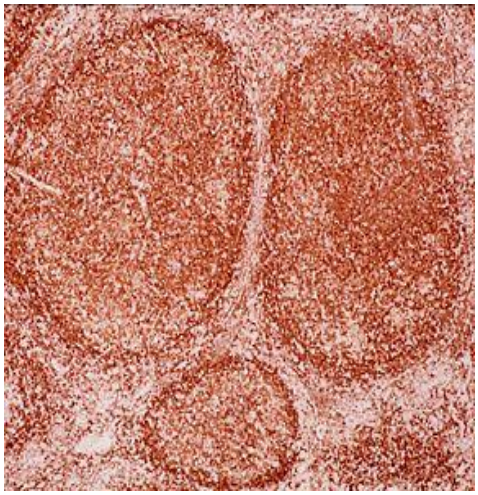


Figure 10: Closely packed neoplastic follicles without discernible germinal center
Figure 11: BCL2 strongly positive in the center of neoplastic follicles

Discussion

In the study by Kate R Shankland et al.[6] Hodgkin's lymphoma constituted for about 10% of all lymphomas, and the remaining 90% being non-Hodgkin lymphoma. In present study Non-Hodgkin's lymphoma was the most common type of lymphoma seen (79 cases, 95.2%).Hodgkin's lymphoma was seen only in four cases (4.8%). Sudipta Chakrabarti et al.[7] in a study showed a lower median age of onset (28.1 versus 39.9 years) and and higher male to female ratio (3.8:1 versus 3.2:1) were noted for HL compared to NHL. In present study participants were having a mean age of 52 years with a standard deviation of 20.15 years. A total of 65 cases were male (78%), and the rest were female (18 cases, 22%).

Gary M. Reynolds et al.[8] showed various phenotypic features are helpful predictors of unfavourable outcome. These include the presence of systemic B symptoms, such as fever, night sweats, and pruritis, which are thought to be due, at least in part, to altered cytokine levels.In present study B symptoms were present in 63 cases (76%), and absent in the remaining. Distribution of B-symptoms was seen in similar proportion among Hodgkin's and non-Hodgkin's lymphoma and this was not statistically significant ($p>0.05$). It was seen that B-symptoms had a significant association ($p<0.05$, Chi-square test) with the type of lymphoma diagnosed, with B-symptoms being present most commonly with DLBCL type of lymphoma.In a study by Geissinger et al.[9] 61% of peripheral T-cell lymphomas, not otherwise specified, they detected a highly disturbed expression of the T-cell receptor/CD3 complex and in most of the systemic anaplastic large cell lymphomas. In present study there is a significant association of CD3 with the type of Lymphoma diagnosed ($p=0.000$), with the marker being always positive in all cases of PTCL and TRBCL.Chu PG et al.[10] in their study showed positivity of CD20 in 90% of B cell lymphomas, although B cell lymphomas are CD20 negative after rituximab, and other B cell markers should be used. In our study there is a significant association of CD20 with DLBCL, the marker being positive in 37 (54%) of the cases in DLBCL. Canioni et al.[11] found CD20 positivity in 80% of nodular lymphocyte predominant Hodgkin lymphoma, 20% of classic Hodgkin lymphoma and may prove to be an adverse prognostic factor. In present study CD20 was positive in 50% of cases of CHL. Mohrmann RL et al.[12] and Sun T et al.[13] showed rare cases of PTCL being positive for CD20 i.e. 1% of cases in their study. In present study only 14% of cases PTCL showed CD20 positivity. Nikhil Sangle et al.[14] in their study showed 100% of cases of Burkitts lymphoma to be positive for CD10. In the present study also 100% Burkitts lymphoma are positive for

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CD10. Dogan et al.[15] in their study showed 39% of DLBCL and 78% of follicular lymphoma showed positivity for CD10. In present study 44% of cases of DLBCL and 100% of cases of follicular lymphoma were positive for CD10.Von Wasielewski R et al.[16] showed 83% of the cases showing a classical immunophenotype (CD15+, CD30+, CD20-), twelve percent lacked CD15 positivity (CD15-, CD30+, CD20-), and five percent showed other combinations.In present study expression of CD15 , CD30, CD20 was seen in 75% of Hodgkins lymphoma rest being other combinations. Barry et al.[17] reported reported 11(9%) cases of PTCL coexpressed CD30 and CD15.In present study only 29% of PTCL showed concurrent expression of CD15 and CD 30. Whereas individually CD30 marker was found to be positive in cases of PTCL (36.8%) followed by Hodgkin's lymphoma cases. This was found to be statistically significant (p=0.001). However, the association had poor interpretation due to low cell values.

Gong JZ et al.[18] emphasize that, MCL can be differentiated reliably from CLL/SLL using CD23. In present study CD23 marker was found to be positive only in cases of SLL (3 cases, 100%) and this was found to have significant association (p=0.013).Tiacci E et al.[19] showed blasts from 150B-cell ALLs showed strong PAX5 nuclear expression, paralleling that of CD79a in the cytoplasm. Conversely, PAX5 was not detected in 50 T-cell ALLs, including 20 cases aberrantly coexpressing CD79a. In present study PAX5 was found to be positive in 62% of B-cell lymphomas and 100% of cases of Hodgkins lymphoma. PAX5 marker was found to be positive in 34 cases of DLBCL (75.6%), and this was found to be statistically significant (p=0.000).Kramer MH et al.[20] studied 156 patients with de novo DLBCL for rearrangements of the BCL2, BCL6, and MYC oncogenes by Southern blot analysis . Structural alterations of BCL2, BCL6, and MYC were detected in 25 of 156, 36 of 116, and 10 of 151 patients, respectively. Three cases showed a combination of BCL2 and BCL6 rearrangements. In present study 43% of DLBCL showed dual positivity for BCL2 and BCL6, incidence being higher than the study mentioned. BCL6 positivity was seen mostly in cases of DLBCL (17 cases, 58.6%) followed by TCRBCL (6 cases, 20.7%). The test of association was seen to be significant with TCRBCL being mostly association with BCL6.

In a study by Christine P. Hans et al.[21] of the 152 cases, 64 (42%) were considered GCB and 88 (58%) were considered non-GCB. Of the, 34% expressed bcl-6 alone, and 57% expressed both CD10 and bcl-6 . MUM1 expression was seen in 17% of the GCB cases. Of the non-GCB cases, 36% expressed MUM1 alone, 31% expressed both MUM1 and bcl-6, and 33% were negative for all of these markers.Expression of bcl-6 or CD10 was associated with better overall survival, whereas expression of MUM1 or cyclin D1 was associated with worse outcome. In present study the incidence of ABC was found to be more than GCB being 82.5% for ABC and 17.5% for GCB. It was seen that CD10, BLC2 and BCL6 were the markers that were found significantly different between ABC and GCB types of lymphoma. BCL2 was mostly associated with ABC type while BCL6 with GCB type. CD10 marker was more associated with GCB type. KI67 was found to be more in cases of ABC compared to GCB. In GCB group CD10 positivity was seen in 75% of cases and BCL6 positivity in 87.5% of cases. Whereas in ABC group CD10 positivity was seen in 19.4% of cases and BCL6 in 32.3% of cases. MUM1 expression was seen in 77.4% cases of ABC type.BCL2 positivity was mostly associated with ABC group being 90.6%.

Orazi A et al.[22] showed neoplastic cells from 33 of the 35 (94%) patients with lymphoblastic lymphoma were TdT positive. In present study Tdt marker was positive in only one case of Lymphoblastic lymphoma, but this was not found to have statistically significant association with the type of lymphoma. Gascoyne RD et al.[23] in his report describes the clinical and laboratory findings in 70 adults with systemic ALCL who were treated with curative intent. The expression of ALK protein was found in 51% of the cases. However, ALK protein expression is an independent predictor of survival and serves as a useful biologic marker of a

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specific disease entity within the spectrum of ALCL. In present study ALK marker was found to be associated with Anaplastic Large B Cell Lymphoma, but there was no significant association at p value of 0.05. Higgins R.A. et al.[24] showed Burkitt lymphoma typically has a high proliferation rate (approaching 100%) as detected by immunostaining for MIB-1 (Ki-67). In present study Ki67 values were found to be very high for Burkitts lymphoma(Mean-0.98)(SD-0.04) followed by Lymphobalstic lymphoma(Mean-1.85).

Conclusion

Immunophenotyping, although indispensable in the diagnosis and classification of hematopoietic and lymphoid neoplasms, has to be used cautiously with knowledge of the antibodies used. No antigen is totally lineage or lymphoma specific, and for this reason, immunostaining must be performed in the context of a panel. Each lymphoid neoplasm has a characteristic immunophenotype, but a potential pitfall is the small number of otherwise typical cases that can express phenotypic markers of other neoplasms or lack their characteristic markers. In addition, familiarity with the diagnostic criteria and differential diagnosis of each lymphoid tumor and ultimately correlation with clinical history, morphology, ancillary molecular genetic and cytogenetic/FISH studies are essential to confirm the diagnostic impression.

Conflict of interest

None

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