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STUDY OF IMMUNOHISTOCHEMICAL PROFILE OF NODAL NON-HODGKIN LYMPHOMA IN A TERTIARY CARE CENTRE

Pathology

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ABSTRACT

BACKGROUND: According to World Health Organization (WHO) lymphomas are classified into Hodgkin's lymphoma and Non-Hodgkin lymphoma. Non-Hodgkin lymphoma is further subclassified based on the stage of maturation and cell of origin.

MATERIALS AND METHODS: The immunohistochemical profile of nodal Non-Hodgkin lymphoma (NHL), using CD3, CD5 (T cell lineage), CD19, CD20 (B cell lineage) CD10, CD23, CD30, CD43, CD79a, Bcl2, Bcl6, ALK, EMA and Cyclin D1 was done to categorize and validate nodal NHL.

RESULTS: Morphological diagnosis on haematoxylin and eosin staining of 41 cases of nodal NHL, 31 were diffuse type, five small lymphocytic lymphomas and five follicular lymphomas. After IHC, 30 cases were DLBCL, four follicular lymphomas, three small lymphocytic lymphomas, three mantle cell lymphomas and one peripheral T cell lymphoma not otherwise specified.

CONCLUSION: Lymphomas can be diagnosed on morphology, and with the application of monoclonal antibodies and identification of immunophenotypic profile, enhances the diagnostic accuracy and reproducibility.

KEYWORDS

Non-Hodgkin lymphoma, DLBCL, Mantle cell lymphoma, Follicular lymphoma.

INTRODUCTION

According to World Health Organization (WHO) lymphomas are classified into Hodgkin's lymphoma (HL) and Non-Hodgkin lymphoma (NHL). Non-Hodgkin lymphoma is further subclassified based on the stage of maturation (immature& mature) and cell of origin (B cell, T cell, or Natural Killer cell (NK) cell).[1] NHL is more common in men compared to women and constitutes 5.1% of all cancer cases and 2.7% of all cancer deaths.[2] In India every year 23,718 new cases were reported.[3] NHL is more common in developed countries with highest incidence rates reported in North America, Australia and North, Western, and Southern Europe as compared with developing countries.[4] Highest incidence rate is seen in people aged between 65-74 years and highest mortality rate between 75-84 years aged people.[5]

Exact aetiology of NHL is not known. The risk factors are severe immunodeficiency, infections such as Human Immunodeficiency Virus (HIV), Epstein Barr Virus, Hepatitis C Virus, Human T-cell Leukaemia Virus (HTLV), Helicobacter pylori and exposure to chemicals.[6]

Morphologic diagnosis takes into account the anatomic architectural alterations in the lymphoid compartment i.e. B-cell follicle (follicle centre, mantle or marginal zone) or T-cell regions (interfollicular or sinus areas).[1] If there is presence of abnormal population (polymorphic or monomorphic), the determination of pattern (diffuse or nodular), cell size (small, intermediate, large) and nuclear characteristics (round, irregular, cleaved with condensed or dispersed or blastic chromatin and the character of the nucleoli) are made.[1] Immunohistochemistry (IHC) with various antibodies identifies the specific lineage and developmental stage of lymphoma.

The present study examined the immunohistochemical profile of nodal Non-Hodgkin lymphoma(NHL) and to categorize and validate nodal NHL as per the WHO classification using CD3, CD5 (for T cell lineage), CD19, CD20 (for B cell lineage) CD10, CD23, CD30, CD43, CD79a, Bcl2, Bcl6, ALK, EMA and Cyclin D1.

Materials and Methods

This prospective study on lymph node biopsies was carried out in the Department of Pathology, SVIMS, Tirupati over a period of one year and six months from February 2017 to August 2018. The study was conducted after obtaining Institutional ethics committee approval. All lymph node biopsies sent in 10% buffered formalin were included in the study. The biopsies were processed, embedded, cut into 4 µ thick sections, which were stained with haematoxylin and eosin (H&E)[7], mounted and histopathologically reported.

A total of 185 lymph node biopsies were received out of which 144 were excluded from the study (39-reactive lymphadenitis, 29-granulomatous lymphadenitis, 4 - kikuchii lymphadenitis, 1-sarcoidosis, 15-Hodgkin lymphoma, 56 -metastatic). The remaining 41 cases were reported as NHL and were subjected to immunohistochemical staining with CD19, CD20, CD3, CD5, CD10, CD23, CD30, CD43, CD79a, Bcl2, Bcl6, ALK, EMA and Cyclin D1. The sections were deparaffinized in xylene and passed through absolute alcohol.

Antigen retrieval in citrate buffer (pH9 Lab vision cat# AP9003) was used after the sections were treated in a microwave at 8 W for 5-6 minutes, then at 3 W for 10 minutes, and the sections were left to cool for 20 minutes. Peroxidase and protein blockades were done and the sections were later incubated overnight with the primary antibodies at room temperature using pre-diluted monoclonal antibodies, CD3(PP160/Rabbit), CD5(RBT-CD5/Rabbit), CD19(EP169/Rabbit), CD20 9PM080/Mouse), CD10(56C6/Mouse), CD23(AR460-R/Rabbit), CD30(PM081/Mouse), CD43(PM154/Mouse), CD79a(JCB117/Mouse), Bcl2(PR004/Rabbit), Bcl6(RBT-bcl6/Rabbit), ALK(PM158/Mouse), EMA(E29/Mouse) and Cyclin-D1(AR447-10R/Rabbit), followed by rinsing in PBS (phosphate buffered saline, PH 7.6). This was followed by incubation with the secondary biotin conjugated antibody for one hour and finally incubation with peroxidase conjugated streptavidin for another hour. Diaminobenzidine tetrachloride (DAB) was added and kept for 25 minutes and then counter stained in Haematoxylin, followed by dehydration, clearing and mounting. Positive control sections were prepared from reactive node for CD3, CD5, CD19, CD20, CD10, CD23, CD43, CD79a, Bcl2 and Bcl6, Normal small intestine cells for ALK, Salivary gland for EMA and Endocervix for Cyclin-D1. Negative controls were done by excluding primary antibody and its replacement with PBS. Presence of immunoreactivity in >10% of

lesional cells was taken as positive and absence was taken as negative.

Statistical Analysis:
Data entered in Microsoft Excel 2010. Continuous variables are summarized as mean ± standard deviation, median (range) as appropriate. Categorical variables are presented as percentages. The frequency distribution of different morphological sub-types including immunohistochemical markers in each subtype of Nodal NHL as per the WHO Classification is presented as percentages.

Results

The subjects were aged between 36 years to 83 years. The youngest was 36year old male and the eldest was 83year old female. Majority of the patients were in 6th decade (13 cases, 31.7%) followed by 5th (10 cases, 24.3%), 8th (9 cases, 21.9%), 7th (5 cases,12.19%) and 4th, 9th (2 cases each, 4.87%) decades respectively. The male: female ratio is 1.7:1. The mean age being 59.5 years.

In diffuse large B cell lymphoma (DLBCL) (30cases) the male: female ratio is 2.75:1, most common in 6th decade. In follicular lymphoma (4 cases) the male: female ratio is 1:3 and is common in the 5th decade. In small lymphocytic lymphoma (SLL/CLL) (3 cases) the male: female ratio is 2:1 and is common in the 5th decade, mantle cell lymphoma(3cases) the male: female ratio is 1:2 and seen in the 5th, 6th & 7th decades respectively. Peripheral T cell Lymphoma not otherwise specified (PTCL, NOS) (1case) seen in 67year old female. Anatomical distribution wise, the nodes affected were cervical nodes (25 cases,61%) followed by inguinal nodes (7 cases,17%), supraclavicular (3 cases, 7.4%), axillary (3 cases, 7.4%) and retroperitoneal, mesenteric, intra-parotid (1 case each, 2.4%). Out of 41 cases of Nodal NHL initial morphological diagnosis on H&E, 31 cases were reported as NHL diffuse type, 5 small lymphocytic lymphomas and 5 follicular lymphomas. After IHC 30 cases (73.17%) were reported as DLBCL, 4 cases (9.75%) as follicular lymphomas, 3 cases (7.31%) as small lymphocytic lymphomas, 3 cases (7.31%) as mantle cell lymphomas and 1 case (2.43%) as peripheral T cell lymphoma not otherwise specified. One case initially diagnosed as follicular lymphoma on H&E after IHC turned out to be mantle cell lymphoma.

The individual IHC marker positivity among DLBCL (30cases) is given in Table-1. Among the 30 cases all were positive for CD19, CD20 and Bcl2, 22 cases were positive for CD43, 12 cases were positive for CD10& CD23, 8 cases were positive for Bcl6 and 6 cases were positive for CD30 & EMA. None of DLBCL cases were positive for CD3, CD5, ALK &Cyclin-D1.

Among the 4 cases reported (Table-1) as follicular lymphomas all were positive for CD19, CD20, CD79a, CD10, Bcl2 and negative for CD30, CD23, CD43, CD3, CD5, Bcl6, ALK, EMA & Cyclin D1.

Among the 3 cases reported (Table-1) as SLL all were positive for CD19, CD20, CD23, CD79a & Bcl2 .CD5 was positive in 1 case only and the rest of the makers were negative.

Out of the 3 cases of mantle cell lymphoma reported (Table-1) CD19, CD20, CD79a, Bcl2, Cyclin D1were positive in all the cases. CD5 & CD43 were positive in 2 cases and CD10 and Bcl6 were positive in one case. CD5 was negative in one case and the rest of the markers were negative.

Single case of peripheral T cell lymphoma not otherwise specified reported (Table-1) was positive for CD3, CD5, CD43 & Bcl2 only and negative for the rest of the markers.

Table-1: Percentage of positivity of the immunohistochemical markers in different subtypes of lymphoma.

IHC marker	DLBCL (n=30)	Follicular lymphoma (n=4)	CLL/SLL (n=3)	Mantle cell lymphoma (n=3)	PTCL, NOS (n=1)
CD3	0(0%)	0(0%)	0(0%)	0(0%)	1(100%)
CD5	0(0%)	0(0%)	1(33%)	2(66%)	1(100%)
CD19	30(100%)	4(100%)	3(100%)	3(100%)	0(0%)
CD20	30(100%)	4(100%)	3(100%)	3(100%)	0(0%)
CD10	12(40%)	4(100%)	0(0%)	1(33%)	0(0%)
CD23	12(40%)	0(0%)	3(100%)	1(33%)	0(0%)
CD30	6(20%)	0(0%)	0(0%)	0(0%)	0(0%)
Cd43	22(73%)	0(0%)	0(0%)	2(66%)	1(100%)
CD79a	29(96%)	4(100%)	3(100%)	3(100%)	0(0%)
Bcl2	30(100%)	4(100%)	3(100%)	3(100%)	1(100%)
Bcl6	8(26%)	0(0%)	0(0%)	1(33%)	0(0%)
ALK	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
EMA	6(20%)	0(0%)	0(0%)	0(0%)	0(0%)
CyclinD1	0(0%)	0(0%)	0(0%)	3(100%)	0(0%)

DISCUSSION

NHL occurs most frequently in adults and is more common in older adults than younger adults, hence age presents to be strong risk factor for this disease. In the present study age of the patients ranged from 36 to 83 years. Majority of the patients were between 51 to 60 years. The mean age of occurrence in the present study was 59.5yrs, which is slightly higher compared to Devi AA et al[8](54yrs), Shahid et al[9](50yrs) and Sadia sultan et al[10](48.5yrs) studies. Study done in Darjeeling, India the mean age was 39.9yrs.[11] Studies in western and Asian countries revealed mean age between 50-60yrs. [12,13] Male to female ratio being 1.7:1 which is nearly comparable with study done by Sharma M etal[14](1.6:1), slightly lower compared to shahid et al[9](2:1), Sadia sultan et al[10](3:1) and slightly higher than Devi AA et al[8](1.2:1) and North American and European studies (1.2:1& 1.1:1) respectively.[12]

In our study the median age was 57 years. In West the median age of disease onset was 65 years with around 60.8% of patients being diagnosed above 60 years.[15]

In our study in DLBCL majority of cases were in 51 to 60 years age group and male: female ratio was 2.75:1 which is nearly comparable with study done by Mustaq et al.[16] Unlike our study Zubairet al[17] found majority of cases in 31to 40 years age group and male: female ratio 1.7:1. In follicular lymphoma majority of cases were in 41 to 50 years which is similar to studies done by Zubair et al[17] and Mustaq et al[16]. The male: female ratio is 1:3 where as in above studies there was slight male predominance. In CLL/SLL majority of cases were in 41 to 50 years age group with a male: female of 2:1 , studies done by Zubair et al[17] and Mustaq et al[16] reported higher age group but with a male: female ratio of 1:1. In mantle cell lymphoma majority of cases were in 47-71 age group which is nearly comparable with studies done by Zubair et al[17] and Mustaq et al[16] with a male: female ratio of 1:2 .Studies done by Zubair et al[17] and Mustaq et al[16] showed slight male predominance. In PTCL, NOS only one case was reported, a female in the 61-70 years age group. Studies done by Zubair et al[17] and Mustaq et al[16] revealed majority cases in 46-60 years age group. The only PTCL,NOS case was a female, whereas studies done by Zubair et al[17] and Mustaq et al[16] showed male predominance.

In our study the most common group of lymph nodes involved were the cervical lymph nodes (25 cases, 60.9%), followed by inguinal (7cases, 17%) supraclavicular, axillary (each 3 cases,7.3%), then retroperitoneal, mesenteric and intra-parotid (each 1 case, 2.4%). Similar to our study Devi AA et al[8] and Laurent etal[18] reported that cervical lymph nodes were most commonly involved, followed by inguinal lymph nodes, axillary, supraclavicular and intra-parotid lymph nodes.

In our study the most common subtype was DLBCL (30 cases, 73.17%)(Fig 1:A), followed by follicular lymphoma (5 cases, 12.19%)(Fig 4:A), small lymphocytic lymphoma (3 cases, 7.31%)(FIG-6:A), mantle cell lymphoma (2 cases, 4.87%)(Fig 8:A) and T cell lymphoma, NOS (1 case, 2.43%)(Fig10:A). Naresh et al[19] also reported DLBCL (34%) as the most common subtype, followed by follicular lymphoma (12.6%), small lymphocytic lymphoma (5.7%), mantle cell lymphoma (3.4%) and T cell lymphoma, NOS (2.9%).

In our study 20% of DLBCL cases apart from expression of B cell markers (Fig1:B,C,D,E,H,I,J) showed expression of CD30(Fig 2:F) and EMA(Fig 3:K) and they were ALK negative. These immunophenotypic features were reported in Anaplastic variant of DLBCL. Similar findings were reported by Haralambiva et al[24,20]. Noorduyn et al[25,21] reported that there is no difference in clinical course between anaplastic and non-anaplastic morphology of large B cell lymphoma. In contrast Tilly et al[26,22] reported anaplastic B cell lymphoma which showed better survival than non-anaplastic B cell lymphoma.

DLBCL

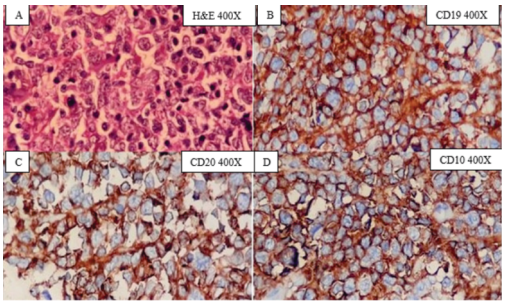


Figure-1. A. Photomicrograph showing large to medium sized lymphoid cells arranged diffusely (H&E 400x).
B. Photomicrograph showing CD19 diffuse moderate membranous positivity in lesional cells(400x).
C. Photomicrograph showing CD20 diffuse moderate membranous positivity in lesional cells (400x).
D. Photomicrograph showing CD10 patchy moderate membranous positivity in lesional cells(400x).

DLBCL

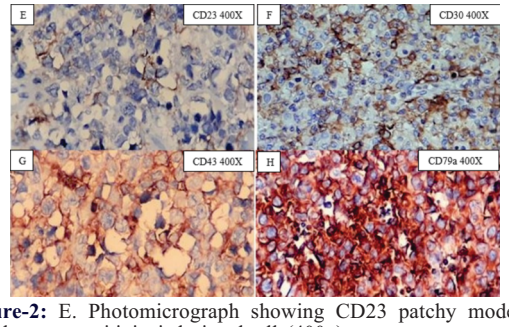


Figure-2: E. Photomicrograph showing CD23 patchy moderate membranous positivity in lesional cells(400x).
F. Photomicrograph showing CD30 diffuse moderate membranous & cytoplasmic positivity in lesional cells(400x).
G. Photomicrograph showing CD43 patchy moderate membranous positivity in lesional cells(400x).
H. Photomicrograph showing CD79a diffuse moderate membranous positivity in lesional cells(400x).

DLBCL

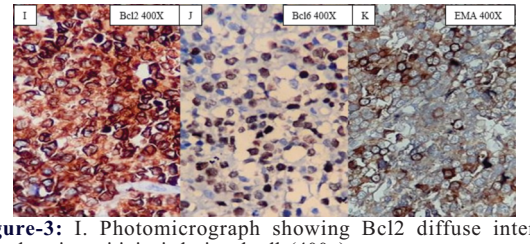


Figure-3: I. Photomicrograph showing Bcl2 diffuse intense cytoplasmic positivity in lesional cells(400x).
J. Photomicrograph showing Bcl6 moderate nuclear positivity in occasional lesional cells(400x).
K. Photomicrograph showing EMA diffuse moderate membrane and cytoplasmic positivity in lesional cells(400x).

In our study all 4 cases (9.25%) of follicular lymphoma showed 100% expression of CD19, CD20, CD10(Fig 4:B,C,D) CD79a and Bcl2(Fig 5:E,F) and none for Bcl6. Studies conducted by Nurija Bilalovic etal showed that Bcl6 negative cases were found to be associated with a poor overall survival[23].

Follicular lymphoma

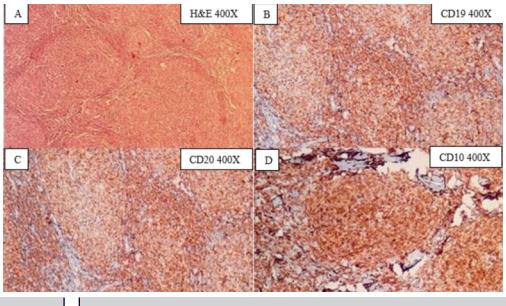


Figure-4: A. Photomicrograph showing effacement of lymphnodal architecture by neoplastic follicles (H&E 200x).
B. Photomicrograph showing CD19 diffuse moderate membranous positivity in lesional cells(200x).
C. Photomicrograph showing CD20 moderate membranous positivity in germinal centre cells(200x).
D. Photomicrograph showing CD10 moderate membranous positivity in germinal centre cells(200x).

Follicular lymphoma

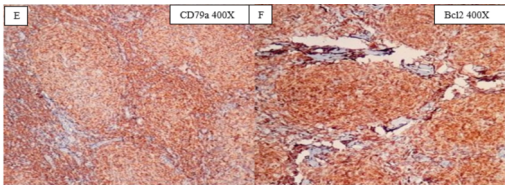


Figure-5: E. Photomicrograph showing CD79a moderate cytoplasmic positivity in germinal centre cells(200x).
F. Photomicrograph showing Bcl2 moderate cytoplasmic positivity in germinal centre cells(200x).

In our study all the 3 cases of small lymphocytic lymphoma showed 100% expression of CD19, CD20(Fig 6:C, D), CD79a, Bcl2 and CD23(Fig 7: F, G&E) and only one case showed CD5 Positivity (FIG 6:B) and rest of the 2 cases were negative. Usually CD5 negative cases are associated with atypical immunophenotypes[26,27]. All the 3 cases of SLL are negative for CD10 marker similar to the other studies [26,27].

Small lymphocytic lymphoma

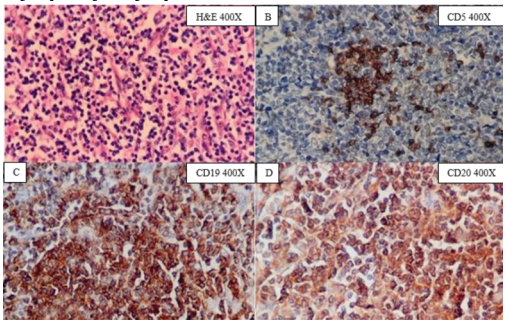
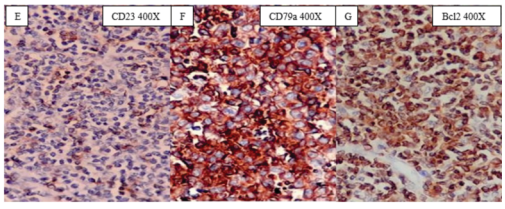


Figure-6: A. Photomicrograph showing small sized lymphoid cells arranged diffusely (H&E400x).
B. Photomicrograph showing CD5 moderate membranous positivity in occasional lesional cells(400x).
C. Photomicrograph showing CD19 diffuse moderate membranous positivity in lesional cells(400x).
D. Photomicrograph showing CD20 diffuse moderate membranous positivity in lesional cells(400x).

Small lymphocytic lymphoma



FigureE- 7: E. Photomicrograph showing CD23 moderate membranous positivity in scattered cells(400x).
F. Photomicrograph showing CD79a diffuse cytoplasmic & membranous positivity in lesional cells(400x).
G. Photomicrograph showing Bcl2 diffuse moderate cytoplasmic positivity in lesional cells(400x).

In our study one case (33%) of mantle cell lymphoma apart from CD19, CD20(Fig 8:B,C), CD79a, Bcl2(Fig 9:H,F) and Cyclin-D1(Fig 9:I) showed expression of CD10(Fig 8:D), CD23(Fig 9:E) and Bcl6(Fig 9:G) which is not a usual immunophenotype seen in mantle cell lymphoma.

CD10 expression in mantle cell lymphoma has been associated with blastoid morphology. Zanetto et al[24] revealed five cases showed

expression of CD10 and all these five cases showed blastoid morphology. Morice et al[25] reported a mantle cell lymphoma case with both classical and blastoid components. The classic component showed typical immunophenotype of MCL, whereas blastoid component had CD5-/CD10+. Gao etal[28,] reported 4 cases with CD10 expression showed classical morphology of MCL. In our study one case showed CD10+/CD5- with classic morphology. MCL with CD5-/CD10+ immunophenotype cause diagnostic difficulty which leads to misdiagnosis of classical MCL as follicular lymphoma because of the nodular arrangement of the lymphoid cells. CyclinD1 played an important role in this scenario for correct diagnosis.

CD23 expression was seen in 33% of cases in our study. Evens et al[29] revealed CD23 expression in 26% of cases. CD23+ cases are associated with more indolent course and improved outcome compared with classic CD23 negative mantle cell lymphoma.

Bcl6 expression was seen in 33% of cases in our study. Zanetto et al[24] reported among 13 cases of CD10 positive mantle cell lymphoma, 5 cases showed Bcl6 expression. Some of the cases showed Bcl6 translocations, amplifications including IGVH mutations.

Mantle cell lymphoma

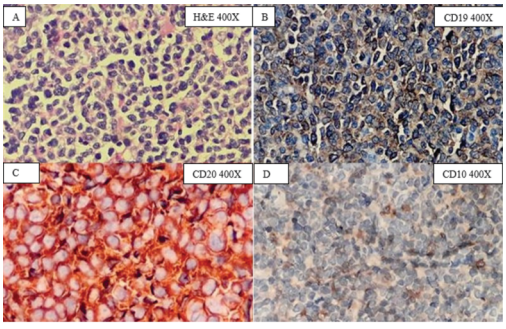


Figure-8: A. Photomicrograph showing monomorphous small to medium sized lymphoid cells arranged diffusely(H&E400x).
B. Photomicrograph showing CD19 diffuse moderate membranous positivity in lesional cells(400x).
C. Photomicrograph showing CD20 diffuse moderate membranous positivity in lesional cells(400x).
D. Photomicrograph showing CD10 patchy moderate membranous positivity in lesional cells(400x**).**

Mantle cell lymphoma

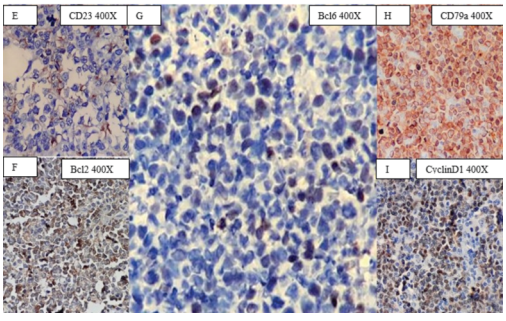


Figure-9: E. Photomicrograph showing CD23 patchy mild membranous positivity in lesional cells(400x).
F. Photomicrograph showing Bcl2 diffuse moderate membranous positivity in lesional cells(400x).
G. Photomicrograph showing Bcl6 moderate nuclear positivity in occasional lesional cells(400x).
H. Photomicrograph showing CD79a diffuse moderate membranous positivity in lesional cells(400x).
I. Photomicrograph showing Cyclin D1 patchy moderate nuclear positivity in lesional cells(400x).

In our study only case of PTCL, NOS which showed positivity for CD43, CD3, CD5 and Bcl2(Fig 10:B,C,D&E). Bcl2 expression in one study showed 40%-60% positivity of cases[30]. Peripheral T-cell lymphoma case did not show positivity to CD20 and CD79a as seen in cases with aberrant expression.
The limitations in our study are small sample size and a short duration.

Peripheral T cell lymphoma, NOS

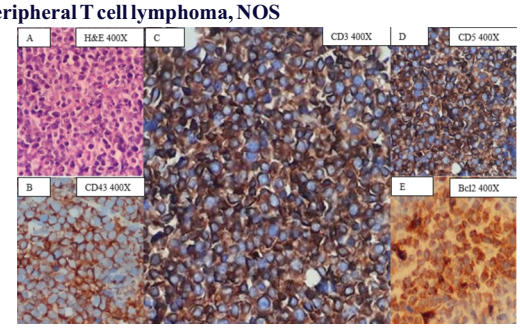


Figure-10: A. Photomicrograph showing monomorphic medium to large sized lymphoid cells arranged diffusely(H&E400x).
B. Photomicrograph showing CD43 diffuse membranous positivity in lesional cells(400x).
C. Photomicrograph showing CD3 diffuse moderate membranous positivity in lesional cells(400x).
D. Photomicrograph showing CD5 diffuse moderate membranous positivity in lesional cells(400x).
E. Photomicrograph showing Bcl2 diffuse cytoplasmic positivity in lesional cells(400x).

CONCLUSION

Lymphomas can be diagnosed on morphology, application of monoclonal antibodies and identification of immunophenotypic profile will enhance the diagnostic accuracy and reproducibility. Immunophenotyping is vital for better management, prognosis and for pathological evaluation of lymphomas. From our study we suggest application of preliminary panel of CD3, CD5, CD19 and CD20 to broadly classify NHL into B and T cell type. Further IHC markers like Bcl2, Bcl6, CD10, CD23, CD43, CD30, ALK, EMA, CyclinD1 will help in sub classifying lymphomas according to WHO classification. Our study demonstrated variations in immunophenotype are quite frequent in mantle cell lymphoma. Some of the variant immunophenotypes could lead to misdiagnosis. Hence recognising the variability is important for correct diagnosis.

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