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Case Series

Unusual lymphomas: Unusual sites

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ABSTRACT

Lymphomas, both Hodgkin's and Non-Hodgkin's, are malignant neoplasms of lymphocytes which usually involve lymph nodes, bone marrow, and extranodal sites. With the advent of adjuvant chemotherapy, lymphomas (most subtypes) have now shifted from the category of fatal hematological neoplasms to the category of treatable hematological neoplasms. Many lymphomas, however, still need to be treated aggressively and promptly making the diagnosis quintessential. However, diagnosis is very challenging in cases presenting at unusual sites with unusual morphologies. Biopsy and immunohistochemistry remain the initial most investigative modalities to document the diagnosis; thus, the histopathologist needs to be alert of the "not-so-common" lymphomas. We discuss here four cases that have posed great challenge in diagnosis and included in this case series. However, recent World Health Organization classification recognizes the significance of genetic and molecular data in the evaluation of a lymphoid neoplasm. Where in, it ascertains a neoplasm into a category, family/class, entity/type, and subtype. This has been formulated in such a manner that it is possible in settings globally; however, consideration is given to the fact that these resources are not universally available.

Keywords: Diffuse large B-cell lymphoma, Follicular dendritic sarcoma, Follicular lymphoma, Gray zone lymphoma, Reed–Sternberg cell

INTRODUCTION

Lymphomas, both Hodgkin's and Non-Hodgkins, are malignant neoplasms of lymphocytes that usually involve lymph nodes, bone marrow, and extranodal sites.[1] Non-Hodgkin's lymphoma (NHL) is the most common hematological malignancy worldwide, and it refers to a group of heterogeneous B-cell and T-cell proliferation and natural killer (NK) cells.[2]

Among these, follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL) are more common NHLs in the Western population, whereas diffuse large B-cell lymphoma (DLBCL) is rapidly emerging as the most prevalent NHL in India.[3] Outside the lineage specific lymphomas, gray zone lymphomas (GZLs) were first introduced in World Health Organization (WHO) classification as a distinct entity in 2008.[4] The term GZLs are defined as lymphomas sharing features both that of classical Hodgkin's lymphoma (CHL) and DLBCL. Despite advances in immunophenotyping, molecular diagnostics, and a precise morphological based discrimination, the diagnosis of GZL still remains complex.[5] Initially, they were thought to arise primarily from mediastinum, but now further analyses indicate both mediastinal and systemic presentations. Regardless of the presentation of the patient, the GZLs have comparatively inferior survival rates to that of CHL or DLBCL.[5]

Many lymphomas, however, still need to be treated aggressively and promptly, making the diagnosis quintessential.[6] It is pertinent to note that the diagnostic algorithms are smoother

in the case of nodal lymphomas and is challenging in cases presenting at unusual sites with unusual morphologies.[7] Biopsy and immunohistochemistry remain the initial investigative modalities used to document the diagnosis.[7] Thus, the histopathologist must be alert to the "not-so-common" lymphomas.[8] In this article, we have tried to highlight and discuss some crucial categories of challenging lymphomas, wherein strictly guided by the "blue book," we have arrived at a diagnosis; all these patients have responded to treatment.[9]

CASE SERIES

Case 1

The first case was a 14-year-old male who underwent cervical lymph node dissection as a part of a diagnostic workup for generalized lymphadenopathy, fever, night sweats and malaise. The lymphadenopathy was present since 2 months and was unrelenting to therapy. What initially began as discrete nodes matted themselves into a large diffuse mass. On work up, computed tomography revealed that he had a mediastinal mass. However, due to ease of accessibility, he underwent a cervical nodal biopsy. The predominant morphological features were that of Hodgkin's lymphoma. Focally, however, these cells were seen in a sheet-like arrangement. With immunohistochemistry, these cells were strongly positive for leukocyte common antigen (LCA), Cluster of differentiation (CD20), and CD30, along with a weak expression for Paired box 5 (PAX5). There were CD3 positive T cells rosetting around these large mononuclear Reed–Sternberg cells [Figure 1a-f]. A final diagnosis of B-cell lymphoma (BCL), unclassifiable with features intermediate between DLBCL and CHL, was rendered. This case was diagnosed neither as a Classical Hodgkin's with CD20 positivity nor as a DLBCL with CD30 positivity in view of a strong reactivity for both these markers.

Case 2

A 35-year-old male underwent axillary lymph node excision. On histology, there was diffuse effacement of architecture with prominence of small lymphoid cells in a vague nodular pattern. Interspersed among these cells were larger binucleate and multilobate cells reminiscent of popcorn-like cells of Hodgkin's lymphoma (HL). These cells had small basophilic nucleoli and were intermixed with mature lymphocytes and plasma cells. On immunohistochemistry (IHC), the large cells were positive for LCA, CD20, BCL6, and PAX5. epithelial membrane antigen (EMA) positivity was noted. They were negative for epstein barr virus receptor (EBVR), CD15, and CD30. Further, an additional panel of IHC was performed using CD3, BCL2, and CD68. The tumor cells were positive for both BCL2 and CD68, and CD3 was positive in the lymphocytes surrounding the multilobate cells [Figure 2a-f]. Based on morphology and IHC, a diagnosis of nodular lymphocyte predominant HL (NLPHL) and T-cell/histiocyte-rich BCL was rendered.

Case 3

A 22-year-old female underwent large bowel (ascending colon) resection due to subacute intestinal obstruction. Grossly, a tumor was seen centered in the submucosa, invading all the layers of the intestine with normal mucosal layer. The individual tumor cells were pleomorphic, often spindle-shaped, with irregular nuclear membrane and scant eosinophilic cytoplasm. The overlying mucosa was unremarkable. Based on morphology and initial IHC panel of Pan cytokeratin (CK), LCA, Synaptophysin, Chromogranin, EMA, and Vimentin yielded positivity for LCA, and a diagnosis of lymphoma was considered. A secondary panel of IHC including CD3, CD19, CD20, CD10, multiple myeloma oncogene-1 (MUM1), BCL2, BCL6, CD5, CD23, CD117, and CD138 was performed, of which the tumor cells showed uniform strong positivity for BCL2 and CD23 with a Kiel-67 (Ki67) index of 40% [Figure 3a-h]. Based on morphology and IHC, the possibility of follicular dendritic cell sarcoma was considered. This was an isolated lesion, and no associated nodal or extranodal disease was diagnosed.

Case 4

A 62-year-old female presented with a nasal cavity mass. On histopathology, fragments of soft tissue were seen infiltrated by the tumor cells in sheets. The tumor cells were small, with a hyperchromatic nucleus and scant cytoplasm. Extensive necrosis and karyorrhexis were noted throughout the tumor. A morphological diagnosis of nasopharyngeal carcinoma was made. The initial panel for IHC based on site and morphology was performed for LCA, CK, Vimentin, and Ki-67, revealing LCA positivity in large cells with a Ki67 index of more than 70%. Pan CK and Vimentin were negative. A secondary panel was done, including CD19, CD20, CD3, and CD5, all of which were negative [Figure 4a-h]. Based on morphology and IHC, a diagnosis of high-grade undifferentiated lymphoma was made. Tissue was too scant for any other IHC.

DISCUSSION

Lymphomas are broadly divided into two categories HL and NHL. HL is again further categorized into CHL and NLPHL. CHL is further subdivided into four subgroups: Nodular sclerosis HL, lymphocyte-rich HL, mixed cellularity HL, and lymphocyte depleted HL. With modern treatment protocols, the Hodgkin's subtypes have lost most of their prognostic relevance.[9] However, the WHO in its latest classification

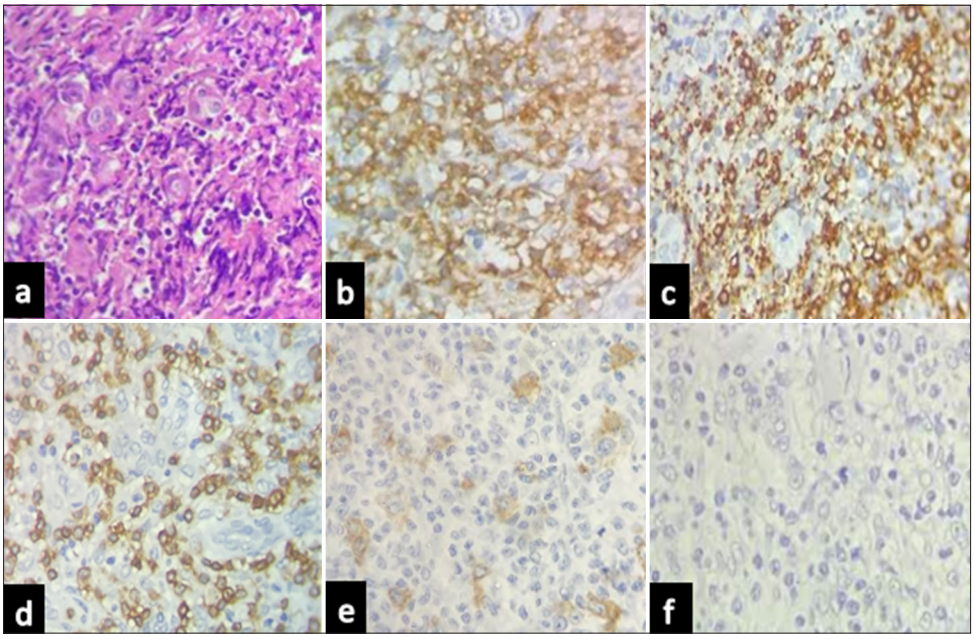

Figure 1: Histology and IHC of B-cell lymphoma unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Classical Hodgkin's Lymphoma. (a) Hematoxylin and eosin stained sections show diffuse effacement of architecture with prominence of Reed-Sternberg cells (10×). (b) Immunohistochemical stain for LCA is positive (10×). (c)Immunohistochemical stain for CD20 was positive (10×). (d) Immunohistochemical stain for CD3 was positive in surrounding T cells (10×). (e) Immunohistochemical stain for CD30 is positive (10×). (f) Immunohistochemical stain for PAX5 shows dim expression (10×). CD: Cluster of differentiation, LCA: Leucocyte common antigen, PAX 5: Paired box 5.

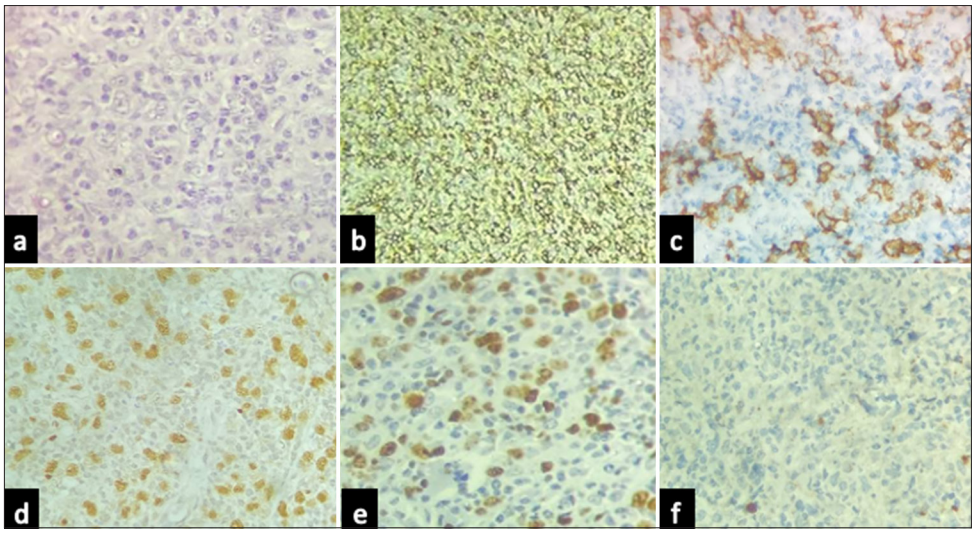

Figure 2: Histology and IHC of NLPHL and T-cell/histiocyte-rich B-cell lymphoma. (a) Hematoxylin and eosin stained sections show diffuse effacement of architecture with prominence of small lymphoid cells in a vague nodular pattern. Interspersed among these cells were large binucleate and multilobate cells (10×). (b) Immunohistochemical stain for LCA is positive (4×). (c-e) Immunohistochemical stains for CD20 (10×), PAX5 (10×) and BCL2 (10×) were positive. (f) Immunohistochemical stain for CD30 was negative (10×). CD: Cluster of differentiation, LCA: Leukocyte common antigen, PAX 5: Paired box 5, BCL2: B-cell leukemia/lymphoma 2 protein.

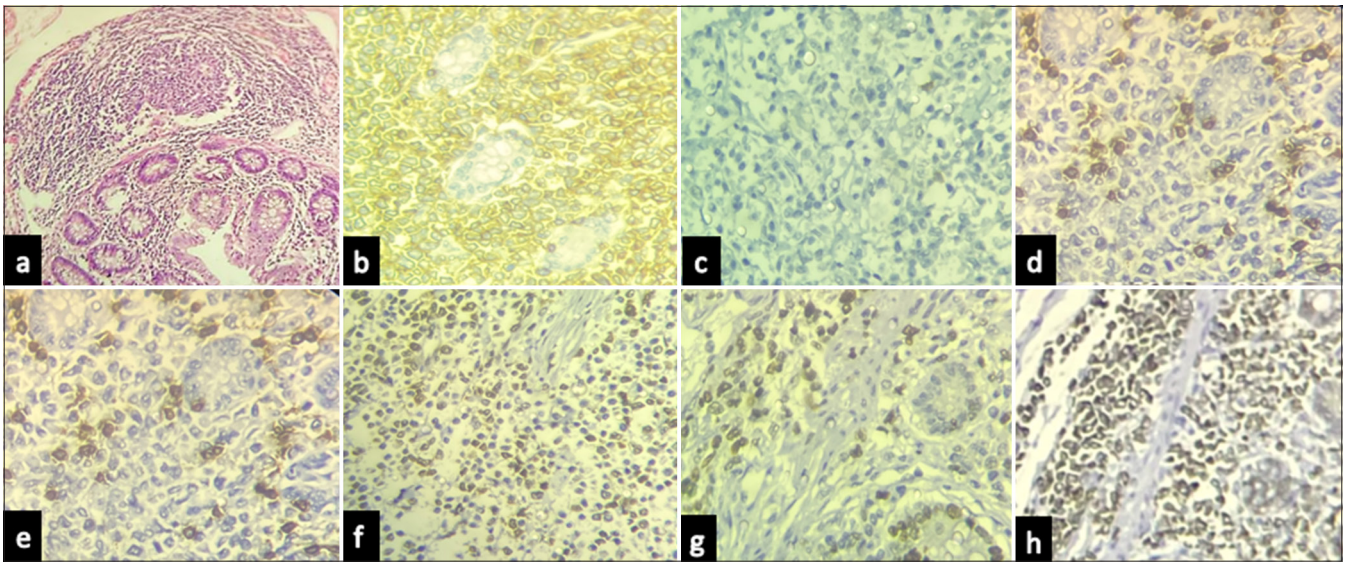

Figure 3: Histology and IHC of follicular dendritic cell sarcoma (a) hematoxylin and eosin section shows tumor cells which appear pleomorphic, often spindle shaped with irregular nuclear membrane and scant eosinophilic cytoplasm. The overlying mucosa was unremarkable (4×). (b) Immunohistochemical stain for LCA is positive (10×). (c) Immunohistochemical stain for EMA is negative (20×). (d and e) Immunohistochemical stain for CD20 (20×) and CD3 (20×) were both positive. (h) Ki67 labelling index was 40% (10×) Pan CK, Vimentin, CD117, and synaptophysin were all negative-not shown in the figure. CD: Cluster of differentiation, LCA: Leukocyte common antigen, Ki 67: Kiel-67, BCL2: B-cell leukemia/lymphoma 2 protein.

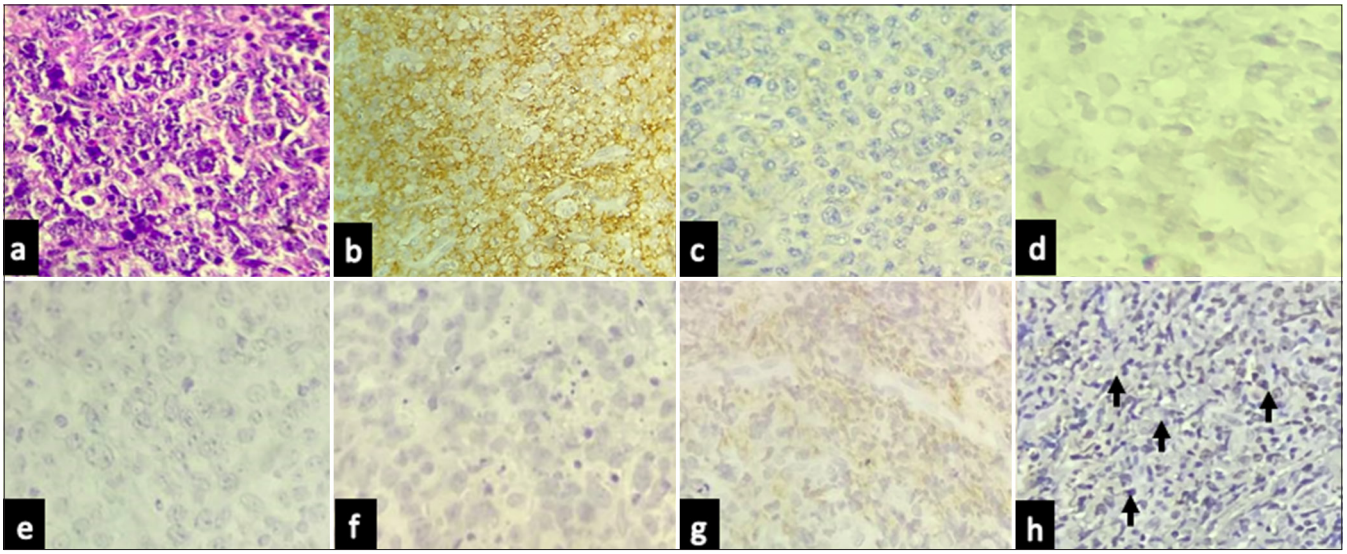

Figure 4: Histology and IHC of high-grade undifferentiated lymphoma. (a) hematoxylin and eosin stained section shows tumor cells with high degree of pleomorphism with prominent nucleoli (10×). (b) IHC for LCA is positive (10×). IHC for CD19 (10×), CD3 (40×), CD5 (40×), CD138 (40×) and CD30 all were negative (c-g from left to right). Ki 67 labelling index is > 70% (10×) (black arrows). CD: Cluster of differentiation, LCA: Leukocyte common antigen, Ki 67: Kiel-67.

merits the continuity of describing these subtypes to supports the ongoing clinical trials and specific subtypes are associated with different clinical features and different biological pathways.[9] Whereas CHL is characterized by the presence of large mononuclear, Hodgkin cell and multi-nucleated macronucleolar Reed–Sternberg cell which are usually surrounded by non-neoplastic T-cells in a background of inflammatory cells, the NLPHL lacks typical R-S cells. The reed sternberg (RS) cells show positive immunoexpression for CD30, CD15, and PAX-5 (attenuated) and are specifically LCA negative. On the other hand, positive IHC expression of LCA and CD20 is seen in neoplastic NLPHL cells. While NLPHL lacks the typical RS cells, it is characterized by a nodular or nodular and diffuse proliferation of small

lymphocytes with singly scattered large neoplastic cells known as lymphocyte predominant (LP) or "Popcorn cells." The LP cells or "Popcorn cells" are seen scattered singly amidst a nodular or diffuse proliferation of small lymphocytes in NLPHL. NLPHL has varied presentation occurring in cervical, axillary, or inguinal lymph nodes but can rarely arise in mesenteric lymph nodes unlike CHL which occurs more commonly in cervical lymph nodes. An important issue arises in NLPHL, in recognizing the different growth patterns [Table 1] overlapping with T-cell histiocyte rich large BCL (THRLBCL). These patterns occur across all age groups and patterns-C, D, and E have been associated with more aggressive behavior in clinical trials.[10]

The morphology of NHLs is highly variable, and distinction into a specific lymphoma is based on the demonstration of IHC. The IHC panel used could be highly variable and might require the application of a gene profile whenever necessary.[9]

The IHC panel discussion here is based on the categorization of NHLs into DLBCL and its variants: mature B-cell neoplasms other than DLBCL, T/NK cell neoplasms, and precursor lymphomas. Conventional IHC is used for DLBCL, and its variants include CD3, CD20, Ki-67, CD10, BCL-6, MUM-1, BCL-2, cellular MYC protooncogene, and Epstein Barr virus In-situ hybridisation (EBV ISH). The typical DLBCL-NOS is usually CD3 negative and CD20 positive, with a Ki67 index of more than 80%. The further categorization for the cell of origin is based on CD10, BCL6, and MUM-1. In the latest WHO classification, the names of some entities have been modified for reasons of consistency, from DLBCL to "large B-cell lymphoma," acknowledging the fact that a diffuse growth pattern is either not apparent/present or cannot be assessed in some entities (e.g., fibrin-associated large BCL or fluid-overload associated large BCL). Furthermore, it is recommended to continue the categorization of the cell of origin into germinal center and non-germinal center (activated B-cell) types, even though the distinction between these is of little merit outside the clinical trials.[11]

Among mature B-cell neoplasms outside DLBCL and its variants, here we discuss FL, CLL/small lymphocytic leukemia, marginal zone lymphoma (MZL), and Mantle cell lymphoma (MCL) [Table 2]. All these lymphomas express B-cell markers, namely, CD19, CD20, and CD79a. In the latest WHO classification, FL classification has undergone a revision from grading to grouping and is now grouped into Classical FL. FL with uncommon features due to the lack of consensus regarding the morphological spectrum of centroblasts and using conventional methods for counting has negatively impacted reproducibility.[12-14] According to the latest WHO classification, MCL has been further categorized

Table 1: Features of CHL and NLPHL.

Features	CHL	NLPHL
Positive immune markers	CD15, CD30, PAX5	CD20, CD45, BCL6
Negative immune markers	CD20, CD45, BCL6	CD15, CD30
Patterns of growth	NSHL, MCHL, LRHL, LDHL.	Classic B cell nodular (A), Serpiginous or Interconnected (B), Prominent extranodular LP cells (C), T-cell rich nodular (D), Diffuse THRLBCL/DLBCL like (E), Diffuse moth eaten, B-cell rich (F).
Gray zone	B cell lymphoma unclassifiable with features in between CHL and DLBCL.	Diffuse NLPHL versus T-cell histiocyte rich large B-cell lymphoma

NSHL: Nodular sclerosis Hodgkins lymphoma, MCHL: Mixed cellularity Hodgkins lymphoma, LRHL: Lymphocyte rich Hodgkins lymphoma, LDHL: Lymphocyte depleted Hodgkins lymphoma, CD: Cluster of differentiation, LP: Lymphocyte predominant, THRLBCL: T cell/histiocyte rich large B-cell lymphoma, NLPHL: Nodular lymphocyte-predominant Hodgkin lymphoma, CHL: Classic Hodgkins lymphoma, BCL-6: B-cell lymphoma-6 Alaggio *et al*., PAX5: Paired box 5

Table 2: IHC expression in mature B-cell lymphomas outside DLBCL and its variants.

IHC Expression	Follicular lymphoma	CLL/SLL	MCL	MZL
Positive	BCL6, , and rarely IRF4/MUM1[#]	CD5, CD43, CD23, and CD200	BCL2, CD5, CD43, Cyclin D1, and SOX11	CD43, Kappa, and lambda[&]
Negative	CD5 and CD43	FMC7[^] and SOX11	CD10 and BCL6	CD10, CD5, CD23, cyclin D-1, and SOX11
Variable expression	BCL2*	MUM1	FMC7 and CD23	

*BCL2 expression is decreased in higher grades of FL and in cases with mutation in the BCL2 epitopes. [#]In these cases, expression of CD10 is negative. [^]CLL/SLL with atypical phenotype is CD5- and CD23- but FMC7+. [&]MZL is post-germinal in origin and demonstrates variable degree of plasma cell differentiation. BCL-6: B-cell lymphoma 6, BCL-2: B-cell leukemia/lymphoma 2 protein, CD: Cluster of differentiation, IRF4/MUM1: Interferon regulatory factor 4/multiple myeloma oncogene-1, SOX11: SRY-box transcription factor 11, CLL/SLL: Chronic lymphocytic leukemia/small lymphocytic leukemia

based on risk stratification into *in situ* mantle cell neoplasm, MCL, and non-nodal MCL.[9] In the latest WHO classification, extranodal MZL (EMZL) and nodal MZL (NMZL) have been retained along with a separate entity designated as per cutaneous MZL (PCMZL).[9] EMZL, NMZL, and PCMZL have overlapping histologic and immunophenotypic features: the neoplastic cells are mature small B cells typically negative for CD5 and CD10. Plasmocytic differentiation is common, and associated reactive lymphoid follicles are often present.

However, despite some shared features, they differ in etiopathogenesis, with further differences among EMZLs arising in different anatomic sites.[15]

The T/NK cell neoplasms although are of many types; here, we discuss peripheral T-cell lymphoma, not otherwise specified (NOS), angioimmunoblastic T-cell lymphoma, anaplastic large cell lymphoma (ALCL), and extranodal NK/T-cell lymphoma (ENKTL) [Table 3]. These tumors are positive for pan T-cell markers except for ALCL which may demonstrate CD3 negativity, although ALCL demonstrates CD4 positivity as they are follicular T-cell lymphomas. A common family terminology of nodal T-follicular helper cell lymphomas (NTFHLs) is introduced in WHO-HAEM5, with previously recognized diseases now regarded as entities within this family. Accordingly, diseases previously referred to as "angioimmunoblastic T-cell lymphoma," "follicular T-cell lymphoma," and "peripheral T-cell lymphoma with TFH phenotype" are renamed NTFHL angioimmunoblastic-type, NTFHL follicular-type, and NTFHL-NOS, respectively.[9] This is due to recognition of their significant clinical and immunophenotype overlapping as well as similar *T follicular helper cell (TFH)* gene expression signature and mutation profiles.[16,17] ENKTL nasal-type has been renamed to ENKTL and the suffix "nasal type" has been dropped in WHO-HAEM5 as there is recognized presentation of this disease at various extranodal sites.[9] Recently, a treatment against CD30 has been introduced and is often performed on various T-cell lymphomas.[18]

T-lymphoblastic lymphoma/leukemia (T-LBL) and B-lymphoblastic lymphoma/leukemia (B-LBL) are morphologically indistinct on routine histology. In such cases, a terminal deoxynucleotidyl transferase and CD99 establish a precursor lesion and further differentiation into T- and B-cell can be established by CD3 and CD20. T-LBL expresses CD3 positivity while B-LBL is CD3 and CD20 negative. Possibility of a B-cell lineage can be demonstrated further by CD79a, PAX, or CD19. In the latest WHO classification, T-LBL and B-LBL have been renamed as T-LBL NOS and B-LBL not further classified (Whenever, genetic testing is not used to classify it otherwise).[9] Outside the specific lineage lymphomas, tumors with expression of features of both CHL and DLBCL were termed as GZLs. Although the disease when first described was thought to be primarily mediastinal in presentation, now it is clear that it can be both mediastinal and disseminated presentation with or without mediastinal involvement. While the former is termed Mediastinal GZLs, characterized by younger age, early stage, the presence of a bulky tumor, and the latter termed as non-mediastinal GZLs tends to appear at an older age with bone marrow, and extranodal organ involvement.[19] Recent literature reports suggest that the non-mediastinal B-cell lymphomas are more common than the mediastinal lymphomas.[20] However, in the recent WHO classification, GZLs outside mediastinum are thought to have different genetic alterations and they are to be considered as DLBCL NOS.[9]

Case 1

B-cell lymphoma unclassifiable (BCLU) – This case was difficult to diagnose. It had features intermediate between DLBCL and CHL. They are more common in the mediastinal region but do occur in peripheral lymph nodes. Mediastinal cases are referred to as mediastinal GZLs and in peripheral lymph nodes as non-mediastinal GZLs. In these cases, there is discordance between cytomorphology and IHC. As in our case, the morphology was that of CHL, but on IHC, the tumor cells were positive for LCA, CD20, and CD 30 and showed weak expression of PAX5; CD3 was positive in the surrounding T cells and negative for CD 15. The results

Table 3: IHC expression in various T/NK cell lymphomas.

IHC expression	PTCL NOS	AITL	ALCL	ENKTL
Positive	CD3 and CD4	CD3, CD8, CD10*, BCL6, CXCL3*, and PD1	CD30, CD25, ALK$, and CD4	EBV ISH^
Negative	CD8, CD30, and CD10		CD3-#, BCL2, and CD8	
Variable expression	CD4 and CD8		CD45 and CD45RO	CD3& and CD56&

*CXCL3 and CD10 are the most specific. #Pan T-cell markers are negative in case of null phenotype, and T-cell markers such as CD2, CD4, and CD5 can be used. $Further ALCL is differentiated into ALK+and ALK- ALCL. ^Epstein Barr virus *in situ* hybridization. &Tumors that express CD3- and CD56- with EBV positivity are classified as EKNTL. On the other hand, tumors that are CD3+and CD56- but negative for EBV should be diagnosed as PTCL NOS Alaggio *et al*. CD: Cluster of differentiation, BCL-6: B-cell lymphoma 6, CXCL3: C-X-C motif chemokine ligand 3, PD-1: Programmed cell death 1, ALK: Anaplastic lymphoma kinase, PTCL NOS: Peripheral T-cell lymphoma, not otherwise specified, AITL: Angioimmunoblastic T-cell lymphoma, ALCL: Anaplastic large cell lymphoma

were not concordant with the morphological diagnosis, and a further IHC panel was conducted for BCL6 and Anaplastic lymphoma kinase (ALK). The tumor cells showed variable positivity for BCL6 and negative for ALK, shifting the diagnosis toward DLBCL. Therefore, a diagnosis of BCLU was made based on histomorphology and IHC.

Case 2

In this case, possibilities were given for that NLPHL and THRLBCL. The morphological features were that of NLPHL, but on IHC, the tumor cells were positive only for CD 20 and negative for CD15, CD30, and PAX5, not confining to the morphological diagnosis. Further, an additional panel was run for BCL2, CD3, and CD68, of which the tumor cells were positive for CD68, BCL2, and CD3 which were positive in the lymphocytes surrounding the tumor cells. This rendered the shift of diagnosis toward THRLBCL, but going against the diagnosis was CD3 lymphocyte positivity surrounding the tumor cells, which was conflicting. CD3 rosettes surrounding large tumor cells is rather a feature of NLPHL than, *de novo*, THRLBCL. However, EBV ISH was not performed due to unavailability to determine whether the tumor was *de novo* THRLBCL or NLPHL progressing toward diffuse THRLBCL.

Case 3

In this case of follicular dendritic cell sarcoma, morphologically extensive pleomorphism with spindle-shaped and ovoid cells was seen with cellular atypia, and differentiation was not possible. For further differentiation, IHC was employed for CK, LCA, Synaptophysin, Chromogranin, EMA, and Vimentin, which was performed. Of these, only LCA was positive, and categorization into lymphomas was made. Further, IHC panel of CD3, CD19, CD20, CD10, MUM1, BCL2, BCL6, CD5, CD23, CD117, and CD138 was employed of them that only BCL2 and CD23 were positive. Based on IHC, a diagnosis of follicular dendritic cell sarcoma was made. However, further testing with CD21, a more specific marker for follicular dendritic cells, was not employed.

Case 4

High-grade undifferentiated lymphoma, morphologically tumor cells were small with a hyperchromatic nucleus and scant cytoplasm. Extensive necrosis and karyorrhexis were noted throughout the tumor. To categorize, IHC was performed for CK, LCA, and Vimentin, of which the tumor cells were positive for LCA with a Ki-67 index >70%. A further panel for categorization using CD19, CD20, CD3, and CD5 was employed, and all of these were negative. In addition, immaturity markers such as terminal deoxynucleotidyl transferase and CD99 were not employed as the lineage-specific markers were negative, and a diagnosis of high-grade undifferentiated lymphoma was made.

Limitations

Our study is a descriptive study with a small sample size. Likewise, there was a limitation in application of IHC due to limited resource constraints and no further molecular studies were performed for any of these cases.

CONCLUSION

Immunohistochemistry serves a major role in the diagnosis of lymphoma, especially in identifying the following characteristics: Cell lineage, maturation phase, cell proliferation, specific genetic alterations, and various therapeutic targets. However, recent WHO classification recognizes the significance of genetic and molecular data in the evaluation of a lymphoid neoplasm. Where it ascertains a neoplasm into a category, family/class, entity/type, and subtype, this has been formulated in such a manner that it is possible in settings globally; however, consideration is given to the fact that these resources are not universally available. In resource limited settings, a strict morphological and IHC-based categorization helps in reaching at an appropriate diagnosis.

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REFERENCES

1. Mugnaini EN, Ghosh N. Lymphoma. Prim Care 2016;43: 661-75.
2. Thandra KC, Barsouk A, Saginala K, Padala SA, Barsouk A, Rawla P. Epidemiology of non-hodgkin's lymphoma. Med Sci (Basel) 2021;9:5.
3. Sandhu DS, Sharma A, Kumar L. Non-Hodgkin's lymphoma in northern India: An analysis of clinical features of 241 cases. Indian J Med Paediatr Oncol 2018;39:42-5.
4. Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: Evolving concepts and practical applications. Blood 2011;117:5019-32.
5. Evens AM, Kanakry JA, Sehn LH, Kritharis A, Feldman T, Kroll A, *et al*. Gray zone lymphoma with features intermediate between classical Hodgkin lymphoma and diffuse large B-cell

lymphoma: Characteristics, outcomes, and prognostication among a large multicenter cohort. Am J Hematol 2015;90:778-83.
6. Smith S. Transformed lymphoma: What should I do now? Hematology Am Soc Hematol Educ Program 2020;2020:306-11.
7. Falini B, Martino G, Lazzi S. A comparison of the international consensus and 5th World health organization classifications of mature B-cell lymphomas. Leukemia 2023;37:18-34.
8. Dotlic S, Ponzoni M, King RL, Oschlies I, Ferry J, Calaminici M, *et al.* The broad and challenging landscape of extranodal lymphoproliferations. Virchows Arch 2020;476:633-46.
9. Alaggio R, Amador C, Anagnostopoulos I. The of the world health organization classification of haematolymphoid tumours: Lymphoid neoplasms. Leukemia 2022;36:1720-48.
10. Hartmann S, Eichenauer DA, Plütschow A, Mottok A, Bob R, Koch K, *et al.* The prognostic impact of variant histology in nodular lymphocyte-predominant Hodgkin lymphoma: A report from the German Hodgkin study group (GHSG). Blood 2013;122:4246-52; quiz 4292.
11. Cucco F, Barrans S, Sha C, Clipson A, Crouch S, Dobson R, *et al.* Distinct genetic changes reveal evolutionary history and heterogeneous molecular grade of DLBCL with MYC/BCL2 double-hit. Leukemia 2020;34:1329-41.
12. Cree IA, Tan PH, Travis WD, Wesseling P, Yagi Y, White VA, *et al.* Counting mitoses: SI(ze) matters! Mod Pathol 2021;34:1651-7.
13. Laurent C, Adélaïde J, Guille A, Tesson B, Gat E, Evrard S, *et al.* High-grade follicular lymphomas exhibit clinicopathologic, cytogenetic, and molecular diversity extending beyond grades 3A and 3B. Am J Surg Pathol 2021;45:1324-36.
14. Brunner P, Rufle A, Dirnhofer S, Lohri A, Willi N, Cathomas G, *et al.* Follicular lymphoma transformation into histiocytic sarcoma: Indications for a common neoplastic progenitor. Leukemia 2014;28:1937-40.
15. Olszewski AJ, Kurt H, Evens AM. Defining and treating high-grade B-cell lymphoma, NOS. Blood 2022;140:943-54.
16. Dobay MP, Lemonnier F, Missiaglia E, Bastard C, Vallois D, Jais JP, *et al.* Integrative clinicopathological and molecular analyses of angioimmunoblastic T-cell lymphoma and other nodal lymphomas of follicular helper T-cell origin. Haematologica 2017;102:e148-51.
17. Ye Y, Ding N, Mi L, Shi Y, Liu W, Song Y, *et al.* Correlation of mutational landscape and survival outcome of peripheral T-cell lymphomas. Exp Hematol Oncol 2021;10:9.
18. Kim SJ, Yoon DH, Kim JS, Kang HJ, Lee HW, Eom HS, *et al.* Efficacy of brentuximab vedotin in relapsed or refractory high-CD30-expressing non-hodgkin lymphomas: Results of a multicenter, open-labeled phase II trial. Cancer Res Treat 2020;52:374-87.
19. Simon Z, Virga B, Pinczés L, Méhes G, Miltényi Z, Barna S, *et al.* Transition between diffuse large B-cell lymphoma and classical Hodgkin lymphoma- our histopathological and clinical experience with patients with intermediate lymphoma. Pathol Oncol Res 2021;27:625529.
20. Mallipudi RM, Alquran L, Shenoy VA, Leslie LA, Conti JA. A rare case of grey zone lymphoma successfully treated with brentuximab vedotin and R-CHP chemotherapy. Case Rep Oncol Med 2019;2019:4121234.

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