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An Approach to Nodal T- and NK-Cell Lymphomas—A Systemic Review

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Abstract

T-cell lymphomas are rare neoplasms that have complex pathology. The multiparameter approach has been recommended by World Health Organization (WHO) for the classification of T-cell lymphomas taking into account morphology, immunophenotype, genetics, and clinical features. This also includes division established on the possible cell-of-origin (COO) from T regulatory or T-follicular helper (TFH) cells. The recent WHO-HAEM5 has classified entities as precursor T-lymphoblastic neoplasms, mature T-cell neoplasms, Epstein-Barr virus (EBV)-related T- and NK/T-cell lymphomas, and tumor-like lesions with T-cells predominance. Distinct entities have been recognized within the anaplastic large cell lymphoma (ALCL) family founded on the status of anaplastic lymphoma kinase (ALK) gene rearrangement: ALK-positive and molecularly heterogeneous ALK-negative. The family of lymphomas arising from TFH cells consists of three distinct nodal TFH cell lymphoma entities: angioimmunoblastic-type, follicular-type, and not otherwise specified. These three entities show significant clinical and immunophenotypic overlap. The cases that do not qualify for ALCL or nodal TFH cell lymphomas are labelled as peripheral T-cell lymphomas-not otherwise specified after ruling out nodal EBV-positive T- and NK- cell lymphoma. The new category termed tumor-like lesions with T cell predominance has a high chance to be misdiagnosed as lymphoma. This category includes entities such as Kikuchi-Fujimoto disease, indolent T-lymphoblastic proliferation, and autoimmune lymphoproliferative syndrome. For pathologists, diagnosing nodal T-cell lymphomas may be thought-provoking due to their broad histopathologic spectrum that mimics reactive as well as other neoplastic processes. This review provides a comprehensive diagnostic criterion of the most commonly encountered nodal T-cell and NK cell lymphomas in day-to-day training and an algorithmic approach.

Keywords

- pathology
- T-cell lymphoma
- NK cell lymphomas
- T-follicular helper cells
- WHO-HAEM5

Introduction

The nodal T-cell lymphoma classification is difficult because of its rarity and broad spectrum of pathological aspects. T-cells are derived from their precursors in the bone marrow and attain maturation in the thymus.[1] The thymocytes mature in the medulla and acquire either surface CD4 or CD8. These mature thymocytes migrate to peripheral lymph nodes and extranodal regions (spleen, gastrointestinal tract, skin, etc.) and participate in adaptive and innate immune responses. Most nodal and extranodal T-cell lymphomas are derived from T cells of the adaptive and innate immune systems, respectively.[2] Mature T-cell lymphomas, both nodal

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Table 1 The classification of commonly encountered nodal T- and NK-cell lymphomas based on WHO-HAEM5[3]

A) Mature T-cell lymphomas
a) Anaplastic large cell lymphoma (ALCL):
• Anaplastic lymphoma kinase (ALK)-positive ALCL
• ALK-negative ALCL
• Breast implant-associated ALCL
b) Nodal T-follicular helper (TFH) cell lymphoma:
• Nodal TFH cell lymphoma, angioimmunoblastic type
• Nodal TFH cell lymphoma, follicular type
• Nodal TFH cell lymphoma, not otherwise specified (NOS)
c) Peripheral T-cell lymphoma, not otherwise specified
d) Epstein-Barr virus (EBV)-positive nodal T- and natural killer (NK)-cell lymphoma
B) Precursor T-cell neoplasms
• T-cell lymphoblastic leukemia/lymphoma, NOS
C) Tumor-like lesions with T-cell predominance
• Kikuchi-Fujimoto disease
• Indolent T-cell lymphoblastic proliferation
• Autoimmune lymphoproliferative syndrome

and extranodal, comprise only 15% of all non-Hodgkin lymphomas (NHLs).[3] Recently, a new World Health Organization (WHO) classification of lymphomas has listed many distinct entities derived from T-cells.[4] The focus of this review is to provide an inclusive approach to the diagnostic morphological features and clinicopathological features of the most commonly encountered nodal T-cell lymphomas (►**Table 1**).

A) Mature T-cell lymphomas

a) Anaplastic large cell lymphoma

Anaplastic large cell lymphomas (ALCL) are characterized by large pleomorphic cells having a significant amount of cytoplasm, horseshoe to reniform nuclei, and CD30 showing strong uniform expression.[5] Lymphoma cells tend to grow in cohesive sheets and have a predilection for the lymph node sinuses. Anaplastic lymphoma kinase (ALK) expression and their location help in classifying the ALCLs as[6]:

- Nodal ALCL:
  - ALCL, ALK-positive: chromosomal abnormalities involving chromosome 2p23 (*ALK* locus)
  - ALCL, ALK-negative: negative for *ALK* rearrangements, and are heterogeneous at a molecular level
- Extranodal ALCL:
  - Breast implant-associated ALCL
  - Primary cutaneous ALCL (cALCL)

ALK-positive ALCL: It accounts for 10–15% of pediatric and adolescent NHL and approximately 3% of adult NHL.[7] Preferentially affects children and young adults (< 40 years) with a predilection for males and frequent extranodal involvement.[8]

Morphology: In lymph nodes, the lymphoma cells grow in cohesive sheets and disseminate within lymph node sinuses. The prominent involvement of the sinuses mimics metastatic solid tumors. The common variant contained characteristic atypical large hallmark cells that have eccentrically placed horseshoe or reniform or wreath-shaped nuclei, finely clumped chromatin, many distinct basophilic nucleoli, and copious eosinophilic cytoplasm (►**Fig. 1A**). Additionally, multinucleated cells similar to Hodgkin/Reed-Sternberg (HRS) cells of classic Hodgkin lymphoma may be seen. The lymphohistiocytic variant, as the name suggests, is characterized by numerous reactive lymphocytes and histiocytes with admixed few hallmark cells clustered around vessels. The small cell variant lacks hallmark cells and consists of mainly small-sized cells with perivascular aggregation and eosinophilic cytoplasm. ALCL with a Hodgkin's pattern resembles nodular sclerosis classic Hodgkin lymphoma and they are distinguished using an appropriate immunohistochemistry panel.

Immunophenotype: All ALCLs show expression for CD45 (variable) and CD30 (diffuse, strong, membranous, and perinuclear Golgi) (►**Fig. 1B**). Sometimes, it is termed a "null" immunophenotype as the neoplastic cells show a defect in the TCR/ CD3 complex expression and lack expression for T cell antigens. Among pan T cell immunomarkers, more than 75% of cases are negative for CD3. CD5 and CD7 immunostains are not expressed often, whereas CD2 and CD4 expression is noted in some cases. *ALK* rearrangement is pathognomonic for ALK-positive ALCL; 84% cases involve a fusion t(2;5)(p23;q35) *NPM*/*ALK* gene, followed by t(1;2)(q25;p23) with fusion of *TPM3*/*ALK* (13% cases).[9,10] The rare fusion partners are *PurH* gene (*ATIC*), clathrin heavy chain (*CLTC*), *TRK* fused gene (*TFG*), myosin heavy chain 9 (*MYH9*), Moesin (*MSN*), Ring finger protein 213 (*RNF213*/*ALO17*), and tropomyosin 4 (*TPM4*).[6] The immunostaining pattern of ALK protein helps in determining its fusion partner such as nuclear and cytoplasmic ALK expression is seen in cases involving *NPM*/*ALK* fusion (►**Fig. 1C**), strong cytoplasmic and membranous ALK expression corresponds to *TPM3*/*ALK* fusion (►**Fig. 1D**), and the "membranous pattern" uses moesin as a partner. However, the variant translocations do not have prognostic implications.

ALK-negative ALCL: This entity represents 5.5 to 15% of mature T cell neoplasms.[11,12] It is similar to ALK-positive ALCL in terms of the hallmark cells, histological patterns, and uniform diffuse CD30 expression but lacks ALK protein expression or *ALK* rearrangement (►**Fig. 1E** and **F**). In comparison to ALK-positive ALCL, it occurs more commonly in the elderly, has a more aggressive clinical behavior, and carries a dismal survival outcome.[11] This group is more heterogeneous at a molecular level and the next-generation sequencing analysis has revealed two subsets of ALK-negative ALCLs.[13,14]

- DUSP22 rearrangements at chromosome 6p25.3 (~30% of cases): most cases had a better prognosis, lack STAT3 activation, and LEF-1 expression, and showed characteristics of "doughnut cells" on morphology (►**Fig. 1G**)
- TP63 rearrangement (8% of cases): associated with aggressive behavior (►**Fig. 1H**)
- Activating mutations of JAK and/or STAT3 pathway in a subset of cases.[15,16]

Differential diagnosis: Breast implant-associated anaplastic large cell lymphoma is present in association with breast implants and is a noninvasive neoplasm characterized by the presence of malignant cells infiltrating the periprosthetic

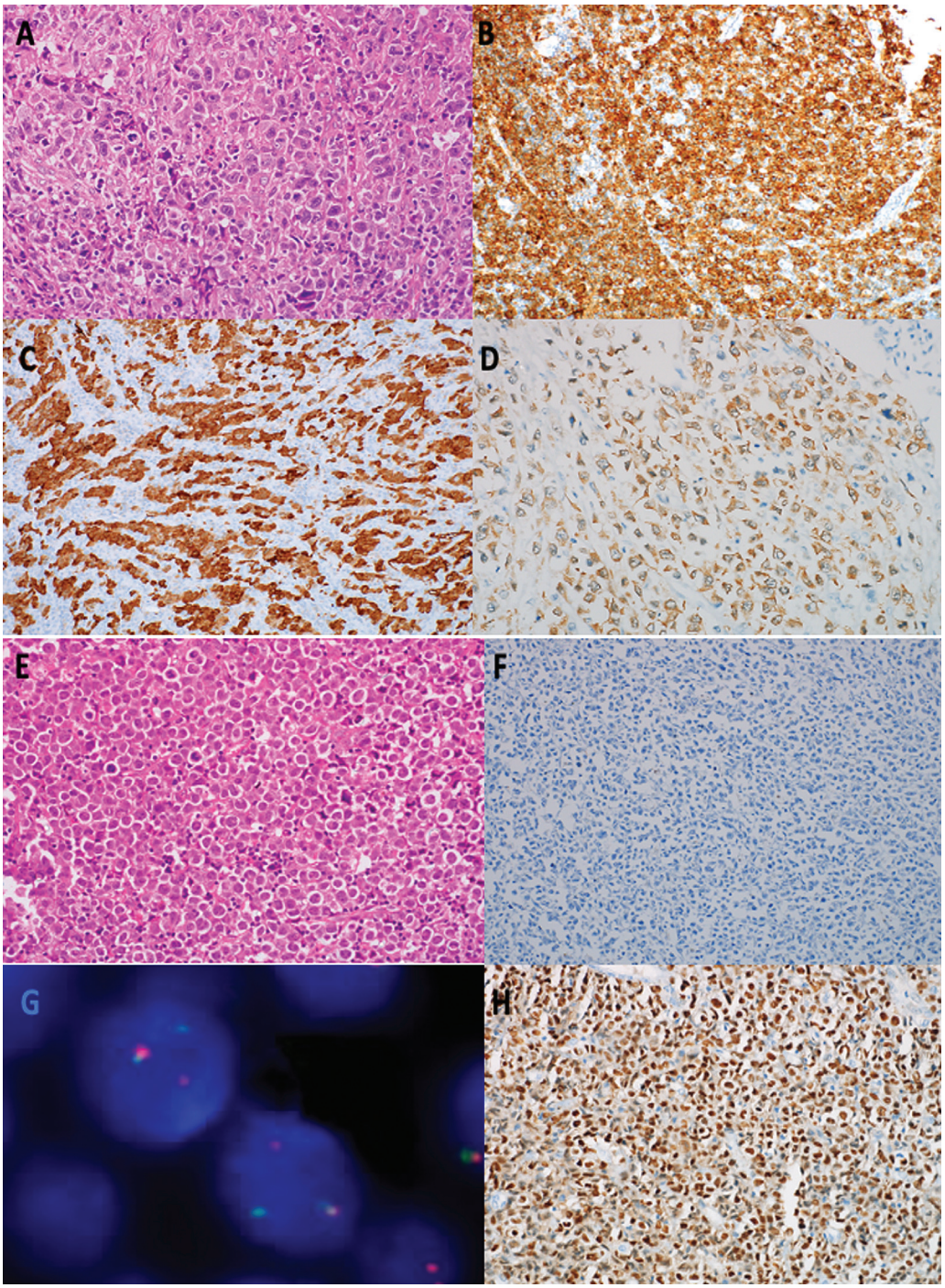

Fig. 1 Anaplastic lymphoma kinase (ALK) positive, anaplastic large cell lymphoma—(**A**) Large hallmark cells with a pleomorphic, horseshoe, or wreath-shaped nucleus and abundant cytoplasm, (**B**) CD30 expression with a membranous and perinuclear (Golgi) pattern, (**C**) Nuclear and cytoplasmic ALK expression, (**D**) cytoplasmic ALK expression. ALK negative, anaplastic large cell lymphoma—(**E**) Hallmark cells along with doughnut cells, (**F**) negative for ALK expression. (**G**) On fluorescence in situ hybridization, the IRF4-DUSP22 dual color break apart probe shows one normal fused signal and one split green-orange signal indicating translocation affecting the DUSP22 locus, (**H**) ALK-ve ALCL showing nuclear expression for P63.

capsule or as a periprosthetic seroma. The clinical behavior is indolent and has excellent outcomes; however, extension to the neighboring structures and contiguous lymph nodes deteriorates the prognosis and also needs to be differentiated from systemic ALCL.[17] Similarly, primary c-ALCL that shares the morphological and immunophenotypic features with the nodal ALCL but exhibits a superior prognosis (5-year overall survival of 90%) needs to be differentiated from cutaneous involvement of systemic ALCL by thorough clinical and radiological examination.[18]

b) Nodal T-follicular helper cell lymphoma

Nodal T-follicular helper cell lymphoma (nTFH) cell family includes three distinct entities that show significant clinical,

immunophenotypic, and TFH gene expression signatures.[19,20] It consists of nTFH cell lymphoma, angioimmunoblastic type (nTFHL-AI), nTFH cell lymphoma, follicular type (nTFHL-F), and nTFH cell lymphoma, not otherwise specified (nTFHL-NOS).[4]

nTFH cell lymphoma, angioimmunoblastic type: It constitutes 15-20% of peripheral T-cell lymphomas (PTCLs) and presents with a median age of 60 years.[21–25] This lymphoma has unique clinical characteristics of generalized lymphadenopathy, hepatosplenomegaly, polyclonal hypergammaglobulinemia, pruritic skin rash, and hematologic abnormalities like Coombs-positive hemolytic anemia.

Morphology: Lymph node in nTFHL-AI usually shows pattern 3 where there is a complete loss of normal architecture with depleted follicles. There is an extensive prominence of arborizing high endothelial venules (HEV) and follicular dendritic cells (FDCs) with a diffuse collection of latter cells surrounding the small vessels (►**Fig. 2A**).[26] The cellularity is variable and composed of small to intermediate neoplastic lymphocytes, clear cytoplasm, and minimal cytologic atypia (►**Fig. 2B**). The background is polymorphous with the admixture of variable numbers of reactive lymphocytes, eosinophils, plasma cells, and histiocytes. The lymphoma cells cluster around HEV and as perifollicular collections. Scattered large B-cell immunoblasts mimicking HRS cells are commonly seen, but sometimes they are plentiful (B-cell-rich nTFHL-AI).[27] In addition, architectural patterns of hyperplastic follicles and depleted /regressive follicles can also be noted.[26,28]

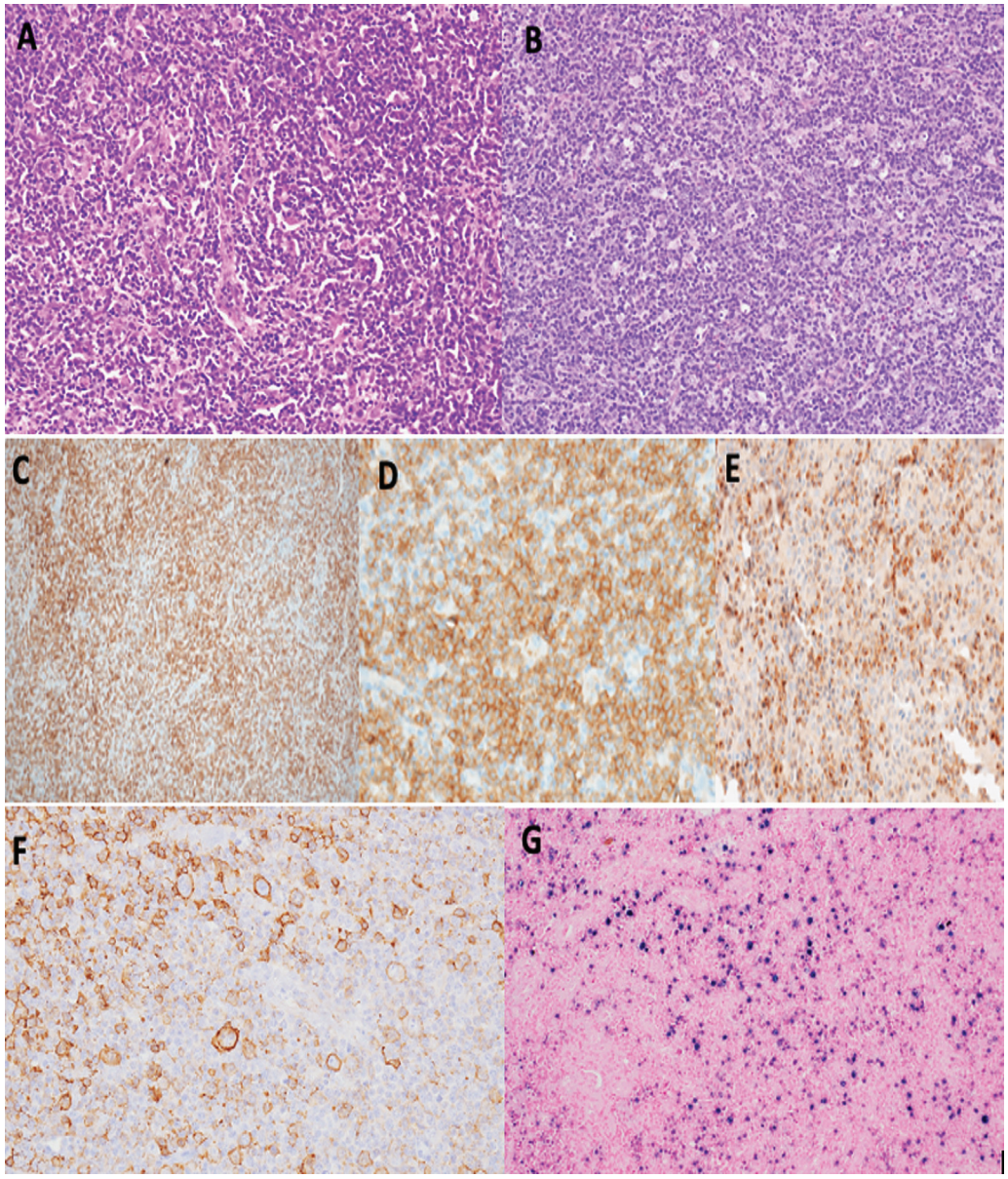

Fig. 2 Angioimmunoblastic T-cell lymphoma—(**A**) normal lymph node architecture is completely effaced with marked proliferation of arborizing high endothelial venules. (**B**) Neoplastic cells are composed of small to medium-sized lymphocytes, with clear to pale cytoplasm, and minimal cytologic atypia. (**C–E**) Neoplastic cells are positive for CD3, programmed cell death protein 1, and CXCL13. (**F**) CD20 highlights the residual follicle center cells as well as many of the large transformed immunoblasts. (**G**) Epstein-Barr encoding region in situ hybridization positivity in CD20-positive immunoblasts.

Immunophenotype: The neoplastic cells are CD3+ T cells, which show downregulation of CD7 and coexpress CD4 (►**Fig. 2C**).[29] Neoplastic cells express characteristic TFH markers, such as CXCL13, programmed cell death protein 1 (PD1) (CD279), and CD10 (►**Fig. 2D** and **E**). The expression of CD10, as compared to other PTCLs, is highly specific. CXCL13 expression is evident in both TFH cells and FDCs. Inducible T-cell costimulator (ICOS) is another sensitive TFH marker. The use of a minimum of two TFH markers is prudent for diagnosis.[30] To summarize, CXCL13 and CD10 are more specific and PD1 and ICOS are more sensitive markers in identifying the neoplastic TFH cells.[31,32] The B-cell markers, such as CD20 and CD79a, highlight the residual follicles and largely transformed immunoblasts in the interfollicular areas (►**Fig. 2F**). Epstein-Barr virus (EBV)-positive B-cells are noted due to reactivation of EBV in the background of a compromised immune system (►**Fig. 2G**).[33] Expansion of the FDC meshworks is highlighted by CD23, especially around the paracortical small vessels.

Genetics: The mutational landscape includes hotspot mutations in *RHOA*, *TET2*, *IDH1*, *IDH2 R172,* and *DNMT3A*.[34] Of these IDH2R172 is specific for the nTFH-AI type, whereas others are also reported in other PTCLs.[35] Cases carrying *RHOAG17V* mutation have classic clinicopathological features, more FDC proliferation, high microvessel density, and pronounced TFH immunophenotype.[36,37] The nTFH-AI type harboring *IDH2* mutations have a distinct morphology in the form of intermediate-to-large sized cells, clear cytoplasm, enhanced TFH phenotype, and strong expression of CD10 and CXCL13.[38]

nTFH cell lymphoma, follicular type: Morphologically, it is typified by follicular pattern and lack of features of nTFHL-AI type, that is, extrafollicular proliferating FDC and HEV.[4,12,39,] CD3 and CD4 are expressed in the neoplastic cells, and also enhanced immunoexpression of TFH markers (PD1 +, CXCL13 +, ICOS +, BCL6 +, and CD10 +/−) is also noted.

nTFHL-NOS: This terminology is used for lymphomas with TFH phenotype and is CD4+ but devoid of features that are characteristics of nTFHL-AI or nTFHL-F. In addition to CD4 positivity, the expression of at least two TFH markers in the neoplastic cells is mandatory for diagnosing nTFHL-NOS. The mere presence of TFH immunophenotype along with some AITL-like features warrants a diagnosis of nTFHL-NOS but not nTFHL-AI. Instead of nTFHL-NOS, the term nTFHL is recommended for small core biopsies to avoid miscategorization as a result of insufficient sampling.[4,39]

Differential diagnosis: Due to diverse histopathologic features of nTFH cell lymphomas, they mimic both benign and malignant lymphoid proliferations.[26] For separating reactive paracortical hyperplasia from early AITL, immunohistochemical staining for PD1 is of utmost importance. In reactive lymph nodes, PD1-expressing cells are limited to the germinal centers, whereas a perifollicular staining pattern is noted in AITL. Prominent EBV-positive B cells, forming confluent foci of large transformed B cells, also pose diagnostic challenges and can mimic large B-cell lymphoma. However, the background of neoplastic T cells with TFH phenotype, FDC meshwork expansion, prominence of HEVs, and monoclonal TCR rearrangement favors the diagnosis of AITL.

c) Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)

Heterogeneous entity comprising nodal and extranodal PTCLs that do not qualify for any specific PTCL subtypes and account for 30% of all PTCLs.[40] The latest WHO edition recommends the omission of nodal PTCLs with a TFH phenotype, before labelling it PTCL-NOS.[4] The COO is activated T-cell, mainly CD4+ of the adaptive immune system.

Morphology: Diffuse nodal architecture effacement or rare cases showing an interfollicular or para-cortical infiltrate can be noted. The cellular infiltrate is polymorphous, with varied cytological features. Most cases have medium-to-large-sized cells with irregular nuclei, prominent nucleoli, and many mitotic figures (►**Fig. 3A**). The milieu shows non-neoplastic lymphocytes, plasma cells, eosinophils, and histiocytes. In the lymphoepithelial variant (Lennert's lymphoma), the atypical lymphoid cells are mainly buried under the confluent sheet of numerous epithelioid histiocytes, and this variant has a superior prognosis compared to other forms of PTCL.[41]

Immunophenotype and genetics: PTCL-NOS generally shows the expression of pan-T-cell antigens (CD3, CD2, CD5, CD7); however, decreased or absent expression of one or more T-cell markers might be noted (commonly CD5 or CD7) (►**Fig. 3B**). Most of them are CD4 +/CD8-, although certain cases particularly the lymphoepithelial variant are CD4-/CD8 +. Less often, double positive (CD4 +/CD8 +) or double negative (CD4-/CD8-) can be seen. The immunoreactivity of TFH markers (CD10, PD1, CXCL13, or BCL6) is not noted. One or more cytotoxic markers (TIA-1, granzyme) can be expressed in 20 to 35% of cases. Most nodal cases have αβ TCRs, whereas few are either gamma/delta positive or both negative (TCR-silent). Gene expression profiling divides PTCL-NOS into subgroups based on the enhanced expression of GATA3 or TBX21 transcription factors that are chief regulators of T helper 1 (Th1) and 2 (Th2) cells, respectively.[42] In view of their clinical relevance, these subgroups are now considered under the WHO classification. In contrast to TBX21-positive PTCL-NOS with *CXCR3*, *IL2RB*, *CCL3*, and *IFN*-gamma as target genes, GATA-3-positive PTCL-NOS cases with target genes *CXCR7*, *IL18RA*, *CCR4*, *IK* carries a dismal outcome.[43,44]

d) Nodal EBV-positive T- and NK-cell lymphoma

Nodal EBV-positive T- and natural killer (NK)-cell lymphoma, formerly clubbed with PTCL-NOS, is now a definite neoplasm in recent WHO-2022.[4] Patients exhibit advanced stage presentation with or without extranodal involvement. Morphologically, it appears high-grade and lacks classic histopathological findings of extranodal positive T- and NK-cell lymphomas, that is, angioinvasion and necrosis.[45] The cytotoxic immunophenotype is more of a T-cell lineage rather than NK-cell, and in the majority, EBV-encoded small RNA is seen by in situ hybridization.

►**Fig. 4** illustrates the algorithm for diagnosing peripheral T-cell lymphomas.

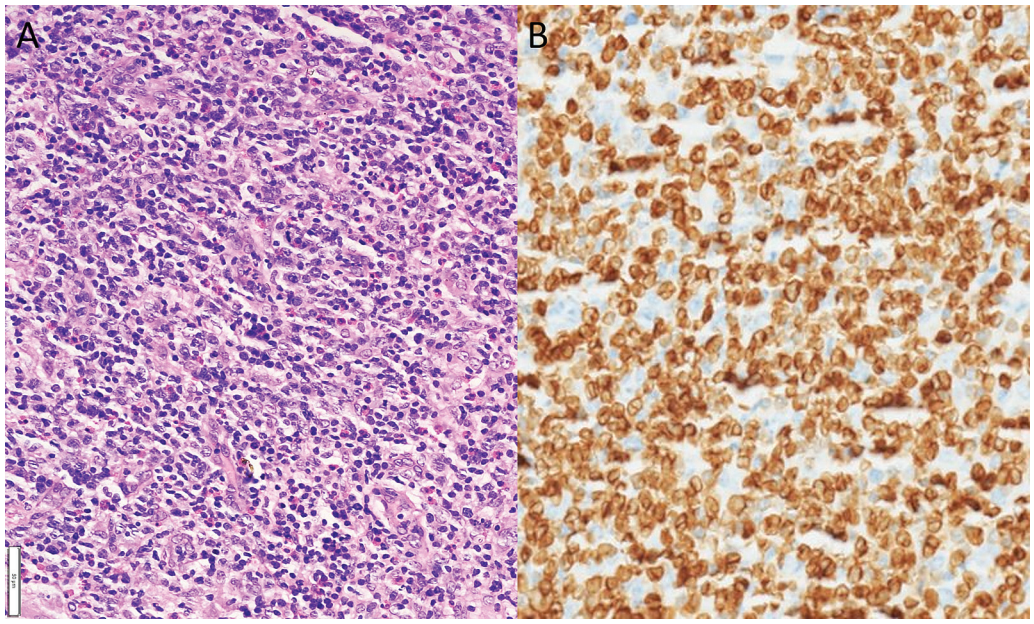

Fig. 3 Peripheral T-cell lymphoma, not otherwise specified—(**A**) shows diffuse effacement of the architecture by polymorphous lymphoid infiltrate with medium to large cells with irregular and hyperchromatic nuclei. (**B**) Lymphoma cells are positive for CD3.

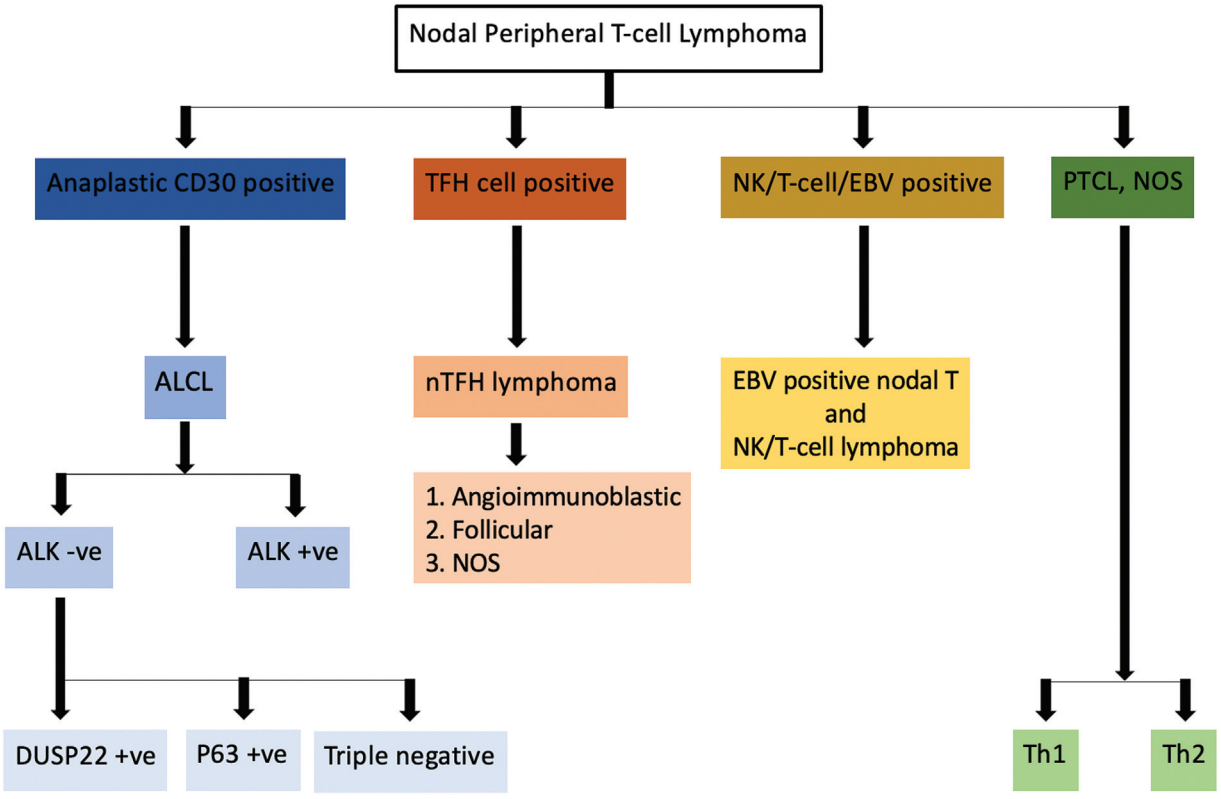

Fig. 4 The algorithm for diagnosing nodal peripheral T-cell lymphomas. ALCL, Anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; EBV, Epstein-Barr virus; NK, natural killer; NOS, not otherwise specified; PTCL, peripheral T-cell lymphomas; TFH, T-follicular helper.

B) Precursor T-cell Neoplasms

T-cell lymphoblastic leukemia/lymphoma, NOS: T-lymphoblastic leukemia/lymphoma, NOS, is a neoplasm arising from immature T-cells. It mainly develops in children and adolescents as an aggressive disease with extensive peripheral blood and bone marrow involvement (acute T- lymphoblastic leukemia T-ALL).[46] It is termed as T- lymphoblastic lymphoma (T-LBL) when primary involvement is the thymus, lymph node, or extranodal sites with blasts count in the marrow $\leq$25%.

Morphology: Characterized by small-sized lymphoid cells, finely granular chromatin, and small pinpoint nucleoli in a diffuse growth pattern. Cells may sometimes expand only

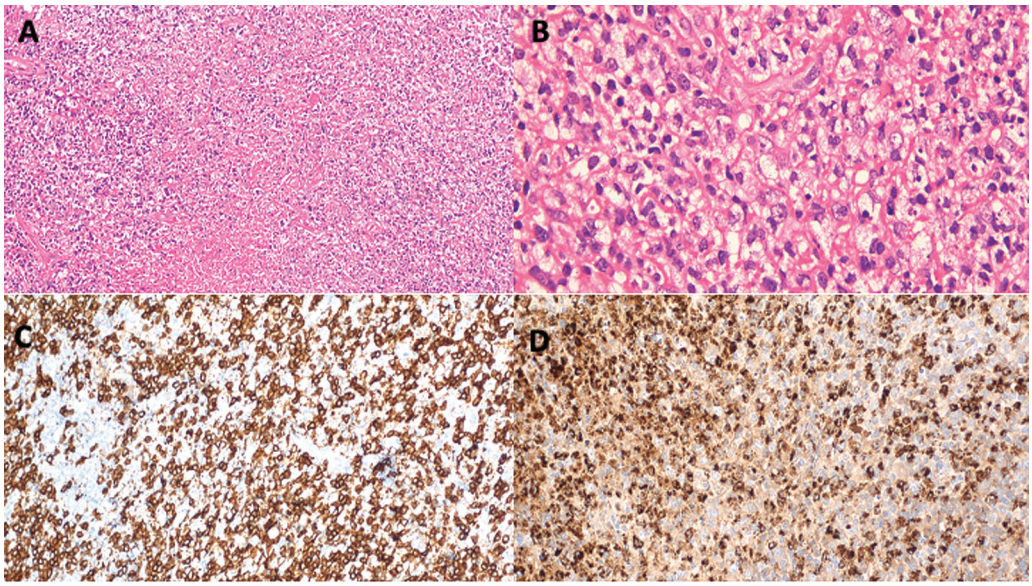

Fig. 5 Kikuchi lymphadenitis—(**A**) showing partial preservation of the lymph node architecture with necrosis, apoptotic cells and nuclear debris; (**B**) admixed histiocytes and large transformed lymphocytes; (**C**) CD3 expression in large, transformed cells; (**D**) Myeloperoxidase expression in crescentic histiocytes.

the interfollicular area in subtotally replaced lymphoid organs and occasionally may have prominent nucleoli (such as in the L2 subtype).

Immunophenotype: Lymphoma cells express markers of T-lineage (CD2, CD3, CD4, CD8, CD5, CD7) and markers of immaturity (CD34, CD99, HLA-DR, and TdT). Like normal cortical thymocytes, they often have a double-positive (CD4+, CD8+) immunophenotype along with CD1a positivity or can express either CD4 or CD8 resembling medullary thymocytes.

C) Tumor-Like Lesions with T-cell Predominance

The fifth edition of WHO (WHO-HAEM-5) incorporated the new family of tumor-like lesions with T-cell predominance.[4] This includes Kikuchi-Fujimoto disease (KFD), autoimmune lymphoproliferative syndrome (ALPS) and indolent T-lymphoblastic proliferation (IT-LBP).

a) Kikuchi-Fujimoto disease

KFD comprises three phases: the proliferative, necrotizing, and xanthomatous phases. It is characterized by paracortical expansion of activated cytotoxic T cells that appear morphologically atypical along with histiocytes and apoptotic debris that may be confused with PTCL (►**Fig. 5A-B**).[47] However, KFD in comparison to lymphoma shows preserved overall lymph node architecture and lacks the diffuse monotonous population of neoplastic cells. The myeloperoxidase-positive histiocytes with crescent-shaped nuclei are typical of KFD. KFD contains essentially CD8+ proliferating T-cells and may have numerous plasmacytoid dendritic cells, whereas PTCLs are CD3+/CD4+ in most cases (►**Fig. 5C–D**).

b) Indolent T-lymphoblastic Proliferation

Indolent T-lymphoblastic proliferation occurring as tiny clusters or confluent sheets of lymphoid cells morphologically consistent with thymocytes has been noted by itself or in association with other benign and malignant lesions.[4,48] These thymocyte-like cells express TdT and may be misdiagnosed as T-lymphoblastic leukemia/lymphoma. However, IT-LBP does not obscure the architecture of nodes and is devoid of monoclonal TCR gene rearrangement.

c) Autoimmune Lymphoproliferative Syndrome

Autoimmune lymphoproliferative syndrome (ALPS) is a lymphoproliferative disorder with heterozygous mutations noted within the first apoptosis signal (FAS) receptor signaling pathway.[49] Clinically, it is characterized by cytopenia, splenomegaly, lymphadenopathy, and autoimmune disorders. Morphologically, it shows florid paracortical expansion by small proliferative lymphocytes that are double negative (CD4-/CD8-) T-cells, immunoblasts, and plasma cells. Overall, the preserved nodal architecture and expression of the pan–T-cell antigens (CD2, CD5, CD7) help to differentiate it from T-cell lymphoma.

Conflict of Interest
None declared.

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