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Updates on Non-B-Lymphoid Neoplasms: A Review of the 5th Edition of the WHO Classification of Hematolymphoid Tumors

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ABSTRACT

The 5th edition of the World Health Organization (WHO) Classification of Hematolymphoid Tumors has recently been published online, marking the first major update since the publication of the 4th edition in 2008. This edition introduces novel scientific data and implements significant changes to disease categories and classifications.

Keywords: World Health Organization (WHO), lymphoid neoplasms, update, lymphoma, classification.

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INTRODUCTION

The 5th edition of the World Health Organization (WHO) Classification of Hematolymphoid Tumors (WHO HAEM5), an update from the revised 4th edition published in 2017, retains the core principles established in the 4th and revised 4th editions. This edition introduces a more hierarchical classification that integrates molecular genetics to predict outcomes, guide management, and accommodate the limitation of access to specialized ancillary testing in many centers. Diseases are sub-grouped based on cell lineage and further subdivided into precursor cells and mature neoplasms. Additionally, this edition features separate chapters for non-neoplastic conditions that closely resemble lymphomas and for germline tumor predisposition syndromes (Table 1).[1]

The WHO HAEM5 also establishes essential and desirable diagnostic criteria for each lymphoma category. The essential criteria specify the minimum requirements for diagnosing a particular entity when resources or samples are limited, primarily utilizing morphology and immunophenotyping. The desirable criteria, while not mandatory for diagnosis, provide additional support for identifying specific entities through morphology, immunophenotyping, genetics (chromosome analysis and Fluorescence In Situ Hybridization [FISH]), genomics (microarray and Next-Generation Sequencing [NGS]), and ribonucleic acid (RNA) expression profiling (Microarray and NGS).

Table 1. The 2022 classification of lymphoid tumors (non-B cell lineages)

T-cell and NK-cell lymphoid proliferations and lymphomas
Tumour-like lesions with T-cell predominance
Kikuchi-Fujimoto disease
Autoimmune lymphoproliferative syndrome
Indolent T-lymphoblastic proliferation
Precursor T-cell neoplasms
T-lymphoblastic leukaemia/lymphoma
T-lymphoblastic leukaemia/lymphoma, NOS
Early T-precursor lymphoblastic leukaemia/lymphoma
Mature T-cell and NK-cell neoplasms
Mature T-cell and NK-cell leukaemias
T-prolymphocytic leukaemia
T-large granular lymphocytic leukaemia
NK-large granular lymphocytic leukaemia
Adult T-cell leukaemia/lymphoma
Sezary syndrome
Aggressive NK-cell leukaemia
Primary cutaneous T-cell lymphoid proliferations and lymphomas
Primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder
Primary cutaneous acral CD8-positive T-cell lymphoproliferative disorder
Mycosis fungoides
Primary cutaneous CD30-positive T-cell lymphoproliferative disorder: Lymphomatoid papulosis
Primary cutaneous CD30-positive T-cell lymphoproliferative disorder: Primary cutaneous anaplastic large cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Primary cutaneous gamma/delta T-cell lymphoma
Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma
Primary cutaneous peripheral T-cell lymphoma, NOS
Intestinal T-cell and NK-cell lymphoid proliferations and lymphomas
Indolent T-cell lymphoma of the gastrointestinal tract
Indolent NK-cell lymphoproliferative disorder of the gastrointestinal tract
Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma
Intestinal T-cell lymphoma, NOS
Hepatosplenic T-cell lymphoma
Anaplastic large cell lymphoma
ALK-positive anaplastic large cell lymphoma
ALK-negative anaplastic large cell lymphoma
Breast implant-associated anaplastic large cell lymphoma
Nodal T-follicular helper (TFH) cell lymphoma
Nodal TFH cell lymphoma, angioimmunoblastic-type
Nodal TFH cell lymphoma, follicular-type
Nodal TFH cell lymphoma, NOS
Other peripheral T-cell lymphomas
Peripheral T-cell lymphoma, NOS
EBV-positive NK-cell and T-cell lymphomas
EBV-positive nodal T- and NK-cell lymphoma
Extranodal NK/T-cell lymphoma
EBV-positive T-cell and NK-cell lymphoid proliferations and lymphomas of childhood
Severe mosquito bite allergy
Hydroa vacciniforme lymphoproliferative disorder
Systemic chronic active EBV disease
Systemic EBV-positive T-cell lymphoma of childhood

T-CELL AND NATURAL KILLER (NK)-CELL LYMPHOID PROLIFERATIONS AND LYMPHOMAS

Tumor-Like Lesions with T-cell Predominance

The WHO HAEM5 introduces a section detailing non-neoplastic conditions mimicking T-cell lymphomas. Described within this section are Kikuchi-Fujimoto disease (KFD), autoimmune lymphoproliferative syndrome (ALPS), and indolent T-lymphoblastic proliferation (ITLP). KFD, a self-limiting condition, is characterized by lymphadenopathy with paracortical expansion by immunoblasts and histiocytes with characteristic features, necrosis with karyorrhectic debris, plasmacytoid dendritic cell expansion, and the absence of neutrophils. ALPS, often related to germline or somatic defects in the Fas cell surface death receptor-mediated (FAS-mediated) apoptosis pathway, presents with lymphadenopathy, hepatosplenomegaly, autoimmune cytopenias, accumulation of Cluster of Differentiation 4/Cluster of Differentiation 8 (CD4/CD8) double negative αβ-T cells, and an increased risk of lymphoma. Indolent T lymphoblastic proliferation (IT-LBP) is an extrathymic, non-clonal infiltration of T lymphoblasts that occurs alone or in association with other disorders, including Castleman disease, myasthenia gravis, hepatocellular carcinoma, follicular dendritic cell sarcoma, nodal T-cell lymphoma with T follicular helper (TFH) phenotype, angioimmunoblastic-type lymphoma, and acinic cell carcinoma. IT-LBP is not observed in the bone marrow.

Precursor T-Cell Neoplasms

For a comprehensive list of T-cell and NK-cell lymphoid proliferations and lymphomas, please see Table 2. The classification of T-cell acute lymphoblastic leukemia (T-ALL) remains mostly unchanged in the 5th edition of the WHO Classification. Significant progress has been made in understanding the molecular alterations in T-lymphoblastic leukemia/lymphoma (T-ALL); however, currently, there is inadequate evidence to categorize T-ALL based on clinically significant genetic abnormalities alone.[2] In the revised 4th edition of the WHO Classification, NK cell leukemia/lymphoma (Natural Killer cell Acute Lymphoblastic Leukemia/Lymphoblastic Lymphoma [NK-ALL/LBL]) was introduced as a distinct provisional entity. Nevertheless, in the 5th edition of the WHO, it is not treated as an independent category but is included within the T-cell acute lymphoblastic leukemia (T-ALL) section. NK-ALL/LBL is characterized by the absence of sCD3 and commonly expresses CD2 and CD7. Immature subsets may exhibit CD5 and cytoplasmic CD3 (ζ and ε chains). This immunophenotype of NK-ALL/LBL poses a diagnostic challenge because of its similar features with blastic plasmacytoid dendritic cell neoplasm, CD56+T-ALL, CD56+ acute myeloid leukemia, and CD56+ acute undifferentiated leukemia.[3]

Mature T-Cell and NK-Cell Leukemias

This category describes six entities: T-prolymphocytic leukemia, T-large granular lymphocytic leukemia (T-LGLL), NK-large granular lymphocytic leukemia (NK-LGLL), adult T-cell leukemia/lymphoma (ATLL), Sézary syndrome (SS), and aggressive NK-cell leukemia (ANKL). T-PLL is now characterized by a specific genetic alteration, namely the juxtaposition of the *TCL1A* or *MTCP1* gene adjacent to a *TCR* locus, typically the *TRA/TRD* locus. The diagnostic criteria for T-Prolymphocytic Leukemia (T-PLL) have been further defined, requiring the presence of >5x10^9/L cells with a T-PLL immunophenotype in peripheral blood or bone marrow, evidence of T-cell monoclonality, and *TCL1A* or *MTCP1* rearrangement or *TCL1A* protein expression. Large granular lymphocytic (LGL) leukemia is defined by a persistent (>6 months) increase in the number of peripheral blood large granular lymphocytes, accompanied by either an absolute (>2x10^9/L) or relative (>50%) lymphocytosis in the peripheral blood. The most commonly observed gain-of-function mutations in T-LGLLs are in *STAT3* and *STAT5B*.[4,5] Neutropenia, transfusion-dependent anemia, and STAT3 mutations are associated with a poorer prognosis. In the indolent variant of CD4+ T-large granular lymphocytic leukemia (T-LGLL), recurrent STAT5B mutations (primarily p.N642H and p.Y665F; NP_036580.2) are detected in about 30% of cases. However, these mutations are rare in CD8+ T-LGLL or T-γ/δ LGLL and are associated with a more aggressive disease course.[6,7]

The chronic lymphoproliferative disorder of natural killer (NK) cells has been renamed NK large granular lymphocytic leukemia (NK-LGLL) in light of evidence suggesting it is a monoclonal or oligoclonal process. NK-LGLL is characterized by persistently elevated peripheral blood NK cells (typically exceeding 2x10^9/L) without an identifiable cause and exhibits an indolent clinical course.

Molecular analysis of adult T-cell leukemia/lymphoma (ATLL) has identified Cytotoxic T-Lymphocyte Associated Protein 4::CD28 (CTLA4::CD28) and Inducible T-Cell COStimulator::CD28 (ICOS::CD28) fusions, REL C-terminal truncations, recurrent alterations in Human Leukocyte Antigen-A (HLA-A) and HLA-B, and structural variations disrupting the 3'-untranslated region of Programmed Death-Ligand 1 (PD-L1). These findings highlight their role in immune invasion.[8] A correlation was observed between the clinical behavior and the pattern and frequency of somatic alterations. Aggressive subtypes tend to have more genetic alterations, while STAT3 mutations are more commonly found in indolent subtypes. The prognostic subtypes of ATLL[9] have been more thoroughly characterized and are included in the 5th edition of the WHO Classification.

In aggressive NK-cell leukemia (ANKL), growing evidence points to the involvement of various pathways such as the Janus kinase/signal transducer and activator of transcription (JAK/STAT) and RAS/mitogen-activated protein kinase (RAS/MAPK), along with histone modifiers including TET methylcytosine dioxygenase 2 (TET2), CREB binding protein (CREBBP), mixed lineage leukemia 2 (MLL2), and DEAD-box helicase 3 X-linked (DDX3X). Additionally, the immune checkpoint molecules PD-L1/L2 are implicated in the pathogenesis of ANKL.[10]

Intravascular NK/T-cell lymphoma is now provisionally categorized under aggressive NK-cell leukemia rather than as an extranodal NK/T-cell lymphoma, as it was in the revised 4th edition of the WHO Classification. This highly aggressive lymphoma, often associated with Epstein-Barr virus (EBV) positivity, typically does not form mass lesions and shows a predilection for the skin and central nervous system (CNS).[11]

Sézary syndrome, despite its similarities to mycosis fungoides, is included in this category because it presents as a T-cell leukemia and must be differentiated during the evaluation of other entities within this category. Comprehensive genomic analyses have revealed new insights into the roles of cellular aging and ultraviolet (UV) exposure in the development of Sézary syndrome.[12]

Primary Cutaneous T-Cell Lymphoid Proliferations and Lymphomas

CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma, primary cutaneous acral CD8-positive T-cell lymphoproliferative disorder, and primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder, considered provisional entities and listed under "Primary cutaneous T-cell lymphoma rare subtypes" in the earlier edition of the WHO, are now recognized as distinct entities and listed separately in the WHO HAEM5. Primary cutaneous gamma delta T-cell lymphoma is also recognized as a separate entity within the category of cutaneous lymphoma/lymphoid proliferations. The WHO HAEM5 recommends classifying the folliculotropic variant of mycosis fungoides into early and advanced stages due to the varying clinical outcomes observed.[13] A dense dermal interfollicular involvement in mycosis fungoides is associated with an advanced stage.[14] Furthermore, the intermediate plaque stage of mycosis fungoides can be further divided into groups with better or worse outcomes based on several factors, including large cell size, higher Ki67, interfollicular epidermotropism, and the absence of follicular mucinosis.[15] Cases that do not conform to any other recognized categories of cutaneous lymphoma/lymphoid proliferations can be classified as primary cutaneous peripheral T-cell lymphoma, not otherwise specified (NOS).

Intestinal T-Cell and NK-Cell Lymphoid Proliferations and Lymphomas

Compared with the previous edition, there have been changes in the nomenclature of several entities within this category. The term "indolent T-cell lymphoproliferative disorder of the GI tract" has been updated to "indolent T-cell lymphoma of the gastrointestinal (GI) tract. "The adoption of "lymphoma" reflects the morbidity and potential for dissemination associated with this entity, while retaining "indolent" emphasizes its prolonged clinical course.[16]

"Indolent NK-cell lymphoproliferative disorder of the GI tract" (iNKLPD) is a newly introduced entity in WHO HAEM5. Previously known as lymphomatoid gastropathy or NK-cell enteropathy, it was considered a reactive lesion resembling malignancy. However, it has now been reclassified as a lymphoma due to the frequent occurrence of mutations, notably in JAK3, indicating a neoplastic process.[17] This condition typically presents an excellent prognosis, often characterized by spontaneous regression and only occasional development of new lesions over several years, without disease progression or dissemination.[18] The most critical differential diagnosis is extranodal NK/T-cell lymphoma, which shares an identical immunophenotype but is highly aggressive.

The categorization of monomorphic epitheliotropic intestinal T-cell lymphoma as a distinct entity from enteropathy-associated T-cell lymphoma is maintained, as these two entities exhibit different clinicopathological features.

Intestinal T-cell lymphoma, not otherwise specified, continues to serve as a category for primary T-cell lymphomas of the GI tract that do not fit into the other known categories of GI tract T-cell and NK-cell lymphoid proliferations.

Hepatosplenic T-Cell Lymphoma

Initially believed to predominantly affect adolescents and young adults, recent research indicates that hepatosplenic T-cell lymphoma affects a broader age range, with 51% of patients being over 60 years old. Mild to moderate dysplasia of bone marrow elements may be present, but this does not have prognostic significance.[19] Approximately 75% of hepatosplenic T-cell lymphoma cases are positive for the T-cell receptor gamma/delta, about 20% exhibit T-cell receptor alpha-beta positivity, and roughly 5% lack T-cell receptors, referred to as having a "silent" or "null" phenotype.[20]

Anaplastic Large Cell Lymphoma

The WHO HAEM5, has retained the entities ALK-positive anaplastic large cell lymphoma (ALK+ ALCL), ALK-negative anaplastic large cell lymphoma (ALK- ALCL), and breast

implant-associated anaplastic large cell lymphoma (BIA-ALCL) as described in the previous edition, now grouped under the category of anaplastic large cell lymphoma. Due to its clinical similarities and favorable prognosis compared to systemic ALCL, cutaneous ALCL has been categorized under cutaneous lymphomas.

Genetic analysis has identified specific gene abnormalities in ALK-negative anaplastic large cell lymphoma (ALK- ALCL) that carry prognostic significance. However, further research is necessary to fully understand and utilize these genetic abnormalities in the diagnosis and management of patients with ALK- ALCL.[21] ALK-negative anaplastic large cell lymphoma (ALK- ALCL) carrying TP63 rearrangements, loss of TP53, and/or overexpression of IL-2Rα are associated with unfavorable outcomes.[22–25] While initial studies linked *DUSP22* rearrangements with a favorable prognosis, more recent research suggests a poor prognosis in cases with *DUSP22* rearrangement.[26] There is a correlation between specific genetic alterations and morphology in ALK-ALCL. *DUSP22* rearrangement is associated with a donut-cell morphology and a sheet-like growth pattern with fewer pleomorphic cells. LEF1 can serve as a surrogate marker for *DUSP22* rearrangement. ERBB4 protein expression is detected in a subset of ALK-negative anaplastic large cell lymphoma (ALK- ALCL) cases exhibiting a Hodgkin-like morphology. *JAK2* rearrangement is correlated with the presence of numerous anaplastic morphology cells.

BIA-ALCL is consistently negative for gene rearrangements involving *ALK*, *DUSP22*, and *TP63*. The WHO HAEM5 also sheds light on the pathogenesis of BIA-ALCL, elaborating on the immunological and molecular events leading to the development of this lymphoma.[27]

Nodal T-Follicular Helper Cell Lymphomas

This family includes lymphomas originating from T-follicular helper cells (TFH) and comprises nodal TFH cell lymphoma, angioimmunoblastic-type (previously known as angioimmunoblastic T-cell lymphoma), nodal TFH cell lymphoma, follicular-type (previously known as follicular T-cell lymphoma), and nodal TFH cell lymphoma, NOS (previously known as peripheral T-cell lymphoma with TFH phenotype). The terminology revision aims to highlight the typical cell of origin, usual clinical presentation, immunophenotype, similar gene expression signature, and mutation profiling.[28] In the WHO HAEM5, the TFH (T-follicular helper) phenotype is defined by the presence of two or more TFH cell markers, such as PD1, ICOS, CXCL13, CD10, and BCL6, alongside CD4 positivity.[29] Nodal TFH lymphomas frequently exhibit the stepwise acquisition of somatic mutations in genes like *TET2* and *DNMT3A*[30] in early hematopoietic stem cells, as well as *RHOA* gene mutations.[31] *IDH2* mutations, when detected, are specifically associated with nodal TFH cell lymphoma, angioimmunoblastic type.[32] Due to the considerable overlap between these entities, cases expressing a TFH phenotype but not meeting the diagnostic criteria for other defined entities should be categorized under nodal TFH cell lymphoma, NOS. When diagnosing these entities using core biopsies, employing the generic term "nodal TFH" is recommended to avoid misclassification due to insufficient sampling.

Peripheral T-Cell Lymphoma NOS (PTCL-NOS)

PTCL-NOS remains a catch-all category for all mature T-cell lymphomas that do not correspond to specific PTCL entities. Gene expression profiling has revealed two molecular subtypes: PTCL-TBX21 and PTCL-GATA3, characterized by the overexpression of TBX21 and GATA3, respectively. These expressions reflect aberrant TH1/2 differentiation and are associated with different prognoses.[33] A potential subgroup of PTCL-*TBX21*, featuring a cytotoxic gene expression program and aggressive behavior, has been described in WHO HAEM5. Further research is needed to fully characterize this subgroup.

EBV-Positive NK-Cell and T-Cell Lymphomas

Extranodal NK/T-cell lymphoma (ENKTL) has had the qualifier 'nasal-type' removed from its name to reflect its occurrence in sites beyond the nasal cavity. Immune checkpoint inhibitors targeting PD1/PD-L1 have shown promise in treating relapsed/refractory ENKTL. Factors such as PD-L1 expression (both in tumor cells and associated macrophages), immune microenvironment subtypes (classified based on FOXP3, PD-L1, and CD68 immunohistochemistry), or somatic structural rearrangements in the 3'-UTR of *PD-L1* in tumor tissue may predict the response to immune checkpoint inhibitors.[34]

Nodal EBV-positive T- and NK-cell lymphoma, previously described under PTCL NOS in the revised 4th edition of the WHO, is now recognized as a separate entity. EBV+ nodal T- and NK-cell lymphomas have a worse prognosis and lower genomic instability compared to ENKTL.[35] This lymphoma, resembling Diffuse Large B-Cell Lymphoma (DLBCL) in morphology, lacks the coagulative necrosis and angioinvasion typical of ENKTL. It more commonly displays a cytotoxic T-cell immunophenotype rather than an NK-cell phenotype.[36]

EBV-Positive T- and NK-Cell Lymphoid Proliferations and Lymphomas of Childhood

Terminological changes have been made to some entities within this category. Hydroa vacciniforme-like lymphoproliferative disorder (HV-like LPD) has been renamed to hydroa vacciniforme lymphoproliferative disorder (HV-LPD).

Table 2. Highlights of the changes in the T lymphoid neoplasms in the 5th edition of the WHO

Tumour-like lesions with T-cell predominance	Separate sections have been added
T-prolymphocytic leukaemia	Now defined by the characteristic genetic alteration i.e. the juxtaposition of the TCL1A or MTCP1 gene next to a TCR locus mostly the TRA/TRD locus.
T-large granular lymphocytic leukaemia	• neutropenia, transfusion-dependent anemia, and STAT3 mutation are associated with a worse prognosis in LGL. • STAT5B mutations are associated with an aggressive disease course in CD8+ T-LGLL or T-γ/δ LGLL
NK-large granular lymphocytic leukaemia	New name for 'Chronic lymphoproliferative disorder of the NK cells'
Adult T-cell leukaemia/lymphoma	Prognostic subtyping is better characterized in WHO HAEM5
Intravascular NK/T-cell lymphoma	Now described provisionally under aggressive NK-cell leukaemia and not under extranodal NK/T-cell lymphoma
Mycosis fungoides	Recommendation to categorize the folliculotropic variant of mycosis fungoides into early and advanced stages
Indolent T-cell lymphoma of the GI tract	New nomenclature for 'Indolent T-cell lymphoproliferative disorder of the GI'
Indolent NK-cell lymphoproliferative disorder of the GI tract	• Newly introduced entity • Has association with JAK3 mutations
Nodal TFH cell lymphoma, angioimmunoblastic-type	New terminology for 'angioimmunoblastic T-cell lymphoma'
Nodal TFH cell lymphoma, follicular-type	New terminology for 'follicular T-cell lymphoma'
Nodal TFH cell lymphoma, NOS	New terminology for 'peripheral T cell lymphoma with TFH phenotype'
Peripheral T-cell lymphoma NOS	Two molecular subtypes - PTCL-TBX21 and PTCL-GATA3
Extranodal NK/T-cell lymphoma	Has had the qualifier 'nasal type' removed from its name
Nodal EBV-positive T and NK-cell lymphoma	Now described as a separate entity
Hydroa vacciniforme lymphoproliferative disorder (HV-LPD).	New terminology for 'Hydroa vacciniforme-like lymphoproliferative disorder'
Chronic active EBV disease (CAEBV) Severe mosquito bite allergy	• New terminology for 'chronic active EBV infection' • Systemic and localized forms present.
	Now recognized a subset is derived from T cells

The term for chronic active EBV infection has been updated to chronic active EBV disease (CAEBV) to better reflect its unfavorable prognosis.[37]

Two forms of HV-LPD are now recognized: the classic form and the systemic form. Systemic HV-LPD and systemic CAEBV, characterized by systemic involvement and persistent symptoms (often lasting more than 3 months), require differentiation. Systemic HV-LPD, associated with hemophagocytic syndrome and EBV, must be distinguished from systemic CAEBV, which denoted chronic active EBV infection, due to its more aggressive clinical course. Clinicopathologic correlation is vital in making this distinction.[38]

Severe mosquito bite allergy was previously thought to originate from NK cells. However, it is now recognized that a small subset is derived from T cells. Within the category of EBV-positive T- and NK-cell lymphoid proliferations and lymphomas of childhood, all entities, except for systemic EBV-positive T-cell lymphoma of childhood, can originate from either T or NK cells.

All entities within this category are broadly classified as systemic EBV-positive T-cell lymphoma of childhood and chronic active EBV disease (CAEBV). Systemic EBV-positive T-cell lymphoma of childhood typically presents with a rapid and aggressive clinical course, often associated with hemophagocytic lymphohistiocytosis. Localized forms of CAEBV include HV-LPD (associated with hemophagocytic syndrome and EBV), the classic form, and severe mosquito bite allergy. The systemic forms of CAEBV include the systemic form of HV-LPD and systemic CAEBV. While these entities are more commonly observed in childhood, they can also occur in adults.

Table 3. Stroma-derived neoplasms of lymphoid tissues

Mesenchymal dendritic cell neoplasms
Follicular dendritic cell neoplasms
• Follicular dendritic cell sarcoma
• EBV-positive inflammatory follicular dendritic cell sarcoma
• Fibroblastic reticular cell tumour
Myofibroblastic tumours
Myofibroblastic tumour
Intranodal palisaded myofibroblastoma
Spleen-specific vascular-stromal tumours
Splenic vascular-stromal tumours
• Littoral cell angioma
• Splenic hamartoma
• Sclerosing angiomatoid nodular transformation (SANT) of spleen

STROMA-DERIVED NEOPLASMS OF LYMPHOID TISSUES

A new category added to the WHO HAEM5, encompasses mesenchymal tumors specific to the lymph nodes (including intranodal palisaded myofibroblastoma) and spleen (including littoral cell angioma, splenic hamartoma, and sclerosing angiomatoid nodular transformation) (Table 3). Mesenchymal tumors that may occur in, but are not limited to, the lymph nodes or spleen are briefly described in the WHO HAEM5. Moreover, neoplasms originating from follicular dendritic cells and fibroblastic reticular cells have been transferred from the "histiocytic and dendritic cell neoplasms" category to this new category. This change is based on the understanding that follicular dendritic cells and fibroblastic reticular cells originate from mesenchymal rather than hematopoietic stem cells.[39] Additionally, the entity previously known as inflammatory pseudotumor-like follicular/fibroblastic dendritic cell sarcoma has been renamed to EBV-positive inflammatory follicular dendritic cell sarcoma. It has been designated as a separate entity distinct from follicular dendritic cell sarcoma,[40] a change first introduced in the WHO Classification of Digestive Tract Tumors (5th edition, 2019).

GENETIC TUMOR SYNDROMES

The WHO HAEM5 has introduced a dedicated chapter on genetic tumor syndromes, reflecting advancements in molecular techniques that have improved the identification of these conditions (Table 4). Recognizing germline predisposition syndromes is essential for diagnostic purposes, treatment planning, surveillance, and family counseling. Notable germline mutations associated with lymphoid neoplasms include mutations in Ataxia Telangiectasia Mutated (ATM) and Nibrin (NBN), which lead to Ataxia Telangiectasia and Nijmegen-Breakage Syndrome, respectively. It is crucial to designate neoplasms occurring in the context of genetic tumor syndromes by the name of the syndrome followed by the tumor entity (e.g., Ataxia Telangiectasia–related classic Hodgkin lymphoma).

Table 4. Genetic tumour syndromes

Fanconi anaemia
Bloom syndrome
Ataxia-telangiectasia syndrome
RASopathies

CONCLUSION

The WHO HAEM5 acknowledges the complexities involved in classifying lymphoid tumors, given that many tumors fall within a diagnostic spectrum. The understanding of lymphoid neoplasms is continually evolving, presenting ongoing challenges in classification. In light of this, the WHO HAEM5 has allowed for further evolution in its framework. The modifications in terminology aim to integrate crucial characteristics that enhance the accuracy of diagnostic categorization in routine clinical practice.

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REFERENCES

1. Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IBO, Berti E, et al. The 5th edition of the world health organization classification of haematolymphoid tumours: lymphoid neoplasms. Leukemia 2022; 36(7): 1720–48.
2. Bardelli V, Arniani S, Pierini V, Di Giacomo D, Pierini T, Gorello P, et al. T-Cell acute lymphoblastic leukemia: biomarkers and their clinical usefulness. Genes (Basel) 2021; 12(8): 1118. [CrossRef]
3. Weinberg OK, Chisholm KM, Ok CY, Fedoriw Y, Grzywacz B, Kurzer JH, et al. Clinical, immunophenotypic and genomic findings of NK lymphoblastic leukemia: a study from the Bone Marrow Pathology Group. Mod Pathol 2021; 34(7): 1358–66. [CrossRef]
4. Jerez A, Clemente MJ, Makishima H, Koskela H, Leblanc F, Peng Ng K, et al. STAT3 mutations unify the pathogenesis of chronic lymphoproliferative disorders of NK cells and T-cell large granular lymphocyte leukemia. Blood 2012; 120(15): 3048–57. [CrossRef]
5. Rajala HLM, Eldfors S, Kuusanmäki H, van Adrichem AJ, Olson T, Lagström S, et al. Discovery of somatic STAT5b mutations in large granular lymphocytic leukemia. Blood 2013; 121(22): 4541–50. [CrossRef]
6. Yamane T, Kawakami T, Sekiguchi N, Kobayashi J, Ueki T, Kobayashi H, Kawakami F, et al. High frequency of STAT3 gene mutations in T-cell receptor (TCR)γδ-type T-cell large granular lymphocytic leukaemia: implications for molecular diagnostics. Br J Haematol 2020; 190(5): e301–4. [CrossRef]
7. Andersson EI, Tanahashi T, Sekiguchi N, Gasparini VR, Bortoluzzi S, Kawakami T, et al. High incidence of activating STAT5B mutations in CD4-positive T-cell large granular lymphocyte leukemia. Blood 2016; 128(20): 2465–68.
8. Kataoka K, Nagata Y, Kitanaka A, Shiraishi Y, Shimamura T, Yasunaga J, et al. Integrated molecular analysis of adult T cell leukemia/lymphoma. Nat Genet 2015; 47(11): 1304–15. [CrossRef]
9. Kataoka K, Iwanaga M, Yasunaga JI, Nagata Y, Kitanaka A, Kameda T, et al. Prognostic relevance of integrated genetic profiling in adult T-cell leukemia/lymphoma. Blood 2018; 131(2): 215–25. [CrossRef]
10. Tang YT, Wang D, Luo H, Xiao M, Zhou HS, Liu D, et al. Aggressive NK-cell leukemia: clinical subtypes, molecular features, and treatment outcomes. Blood Cancer J 2017; 7(12): 660. [CrossRef]
11. Kuo TT, Chen MJ, Kuo MC. Cutaneous intravascular NK-cell lymphoma: report of a rare variant associated with Epstein-Barr virus. Am J Surg Pathol 2006; 30(9): 1197–201.
12. Jones CL, Degasperi A, Grandi V, Amarante TD; Genomics England Research Consortium. Spectrum of mutational signatures in T-cell lymphoma reveals a key role for UV radiation in cutaneous T-cell lymphoma. Sci Rep 2021;11(1): 3962. [CrossRef]
13. Willemze R. Mycosis fungoides variants-clinicopathologic features, differential diagnosis, and treatment. Semin Cutan Med Surg 2018; 37(1): 11–7. [CrossRef]
14. Charli-Joseph Y, Kashani-Sabet M, McCalmont TH, Kornak J, Allen I, Ai WZ, et al. Association of a proposed new staging system for folliculotropic mycosis fungoides with prognostic variables in a US cohort. JAMA Dermatol 2021; 157(2): 157–65. [CrossRef]
15. van Santen S, Jansen PM, Quint KD, Vermeer MH, Willemze R. Plaque stage folliculotropic mycosis fungoides: histopathologic features and prognostic factors in a series of 40 patients. J Cutan Pathol 2020; 47(3): 241–50. [CrossRef]
16. Margolskee E, Jobanputra V, Lewis SK, Alobeid B, Green PH, Bhagat G. Indolent small intestinal CD4+ T-cell lymphoma is a distinct entity with unique biologic and clinical features. PLoS One 2013; 8(7):e68343. [CrossRef]
17. Xiao W, Gupta GK, Yao J, Jang YJ, Xi L, Baik J, et al. Recurrent somatic JAK3 mutations in NK-cell enteropathy. Blood 2019; 134(12): 986–91. [CrossRef]
18. Mansoor A, Pittaluga S, Beck PL, Wilson WH, Ferry JA, Jaffe ES. NK-cell enteropathy: a benign NK-cell lymphoproliferative disease mimicking intestinal lymphoma: clinicopathologic features and follow-up in a unique case series. Blood 2011; 117(5): 1447–52. [CrossRef]
19. Yabe M, Medeiros LJ, Tang G, Wang SA, P Patel K, Routbort M, et al. Dyspoietic changes associated with hepatosplenic T-cell lymphoma are not a manifestation of a myelodysplastic syndrome: analysis of 25 patients. Hum Pathol 2016; 50: 109–117. [CrossRef]
20. Yabe M, Medeiros LJ, Tang G, et al. Prognostic factors of hepatosplenic T-cell Lymphoma: clinicopathologic study of 28 cases. Am J Surg Pathol 2016; 40(5): 676–88. [CrossRef]
21. Crescenzo R, Abate F, Lasorsa E, Tabbo' F, Gaudiano M, Chiesa N, et al. Convergent mutations and kinase fusions lead to oncogenic STAT3 activation in anaplastic large cell lymphoma. Cancer Cell 2015; 27(4): 516–32. [CrossRef]
22. Boi M, Rinaldi A, Kwee I, Bonetti P, Todaro M, Tabbò F, et al. PRDM1/BLIMP1 is commonly inactivated in anaplastic large T-cell lymphoma. Blood 2013; 122(15): 2683–93. [CrossRef]
23. Lobello C, Tichy B, Bystry V, Radova L, Filip D, Mraz M, et al. STAT3 and TP53 mutations associate with poor prognosis in anaplastic large cell lymphoma. Leukemia 2021; 35(5): 1500–5. [CrossRef]

24. Richardson AI, Yin CC, Cui W, Li N, Medeiros LJ, Li L, et al. p53 and β-Catenin expression predict poorer prognosis in patients with anaplastic large-cell lymphoma. Clin Lymphoma Myeloma Leuk 2019; 19(7): e385–92. [CrossRef]
25. Liang HC, Costanza M, Prutsch N, Zimmerman MW, Gurnhofer E, Montes-Mojarro IA, et al. Super-enhancer-based identification of a BATF3/IL-2R-module reveals vulnerabilities in anaplastic large cell lymphoma. Nat Commun 2021; 12(1); 5577. [CrossRef]
26. Hapgood G, Ben-Neriah S, Mottok A, Lee DG, Robert K, Villa D, Sehn LH, et al. Identification of high-risk DUSP22-rearranged ALK-negative anaplastic large cell lymphoma. Br J Haematol 2019; 186(3): e28–e31. [CrossRef]
27. Miranda RN, Aladily TN, Prince HM, Kanagal-Shamanna R, de Jong D, Fayad LE, et al. Breast implant-associated anaplastic large-cell lymphoma: long-term follow-up of 60 patients. J Clin Oncol 2014; 32(2): 114–20. [CrossRef]
28. Kim CH, Lim HW, Kim JR, Rott L, Hillsamer P, Butcher EC. Unique gene expression program of human germinal center T helper cells. Blood 2004; 104(7): 1952–60. [CrossRef]
29. Basha BM, Bryant SC, Rech KL, Feldman AL, Vrana JA, Shi M, et al. Application of a 5 marker panel to the routine diagnosis of peripheral T-cell lymphoma with T-follicular helper phenotype. Am J Surg Pathol 2019; 43(9): 1282–90.
30. Ko M, An J, Pastor WA, Koralov SB, Rajewsky K, Rao A. TET proteins and 5-methylcytosine oxidation in hematological cancers. Immunol Rev 2015; 263(1): 6–21. [CrossRef]
31. Dobson R, Du PY, Rásó-Barnett L, Yao WQ, Chen Z, Casa C, et al. Early detection of T-cell lymphoma with T follicular helper phenotype by RHOA mutation analysis. Haematologica 2022; 107(2): 489–99. [CrossRef]
32. Wang C, McKeithan TW, Gong Q, Zhang W, Bouska A, Rosenwald A, et al. IDH2R172 mutations define a unique subgroup of patients with angioimmunoblastic T-cell lymphoma. Blood 2015; 126(15): 1741–52. [CrossRef]
33. Iqbal J, Wright G, Wang C, Rosenwald A, Gascoyne RD, Weisenburger DD, et al. Gene expression signatures delineate biological and prognostic subgroups in peripheral T-cell lymphoma. Blood 2014; 123(19): 2915–23. [CrossRef]
34. Lim JQ, Huang D, Tang T, Tan D, Laurensia Y, Peng RJ, et al. Whole-genome sequencing identifies responders to Pembrolizumab in relapse/refractory natural-killer/T cell lymphoma. Leukemia 2020; 34(12): 3413–19. [CrossRef]
35. Wai CMM, Chen S, Phyu T, Fan S, Leong SM, Zheng W, et al. Immune pathway upregulation and lower genomic instability distinguish EBV-positive nodal T/NK-cell lymphoma from ENKTL and PTCL-NOS. Haematologica 2022; 107(8): 1864–79. [CrossRef]
36. Attygalle AD, Cabeçadas J, Gaulard P, Jaffe ES, de Jong D, Ko YH, et al. Peripheral T-cell and NK-cell lymphomas and their mimics; taking a step forward - report on the lymphoma workshop of the XVIth meeting of the European Association for Haematopathology and the Society for Hematopathology. Histopathology 2014; 64(2): 171–99. [CrossRef]
37. Kimura H, Ito Y, Kawabe S, Gotoh K, Takahashi Y, Kojima S, et al. EBV-associated T/NK-cell lymphoproliferative diseases in nonimmunocompromised hosts: prospective analysis of 108 cases. Blood 2012; 119(3): 673–86. [CrossRef]
38. Cohen JI, Manoli I, Dowdell K, Krogmann TA, Tamura D, Radecki P, et al. Hydroa vacciniforme-like lymphoproliferative disorder: an EBV disease with a low risk of systemic illness in whites. Blood 2019; 133(26): 2753–64. [CrossRef]
39. van Nierop K, de Groot C. Human follicular dendritic cells: function, origin and development. Semin Immunol 2002; 14(4): 251–7. [CrossRef]
40. Jiang XN, Zhang Y, Xue T, Chen JY, Chan ACL, Cheuk W, et al. New clinicopathologic scenarios of EBV+ Inflammatory follicular dendritic cell sarcoma: report of 9 extrahepatosplenic cases. Am J Surg Pathol 2021; 45(6): 765–72. [CrossRef]