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Review Article

A New Approach to Differentiating Large Granular Lymphocytic Leukemias and Their Mimics in Light of Current Updates in the 5th Edition of the WHO Classification

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Abstract

Background and Objective: Large granular lymphocytic leukemias (LGLLs), including T-cell LGLL and natural kill (NK)-cell LGLL variants, are rare lymphoproliferative disorders characterized by the chronic proliferation of cytotoxic lymphocytes. Despite recent advancements, challenges remain in distinguishing these entities from one another and from related disorders, such as T-cell prolymphocytic leukemia, adult T-cell leukemia/lymphoma, Sézary syndrome, and aggressive NK-cell leukemia, owing to overlapping clinical and morphologic features. This article aims to review the role of molecular and immunophenotypic markers in guiding diagnosis and prognosis of LGLLs, with brief review of their clinical and morphologic features by synthesizing current advances in molecular pathogenesis, immunophenotypic profiling, and updated World Health Organization (WHO) classification criteria in order to enhance diagnostic precision, improve prognostic assessment, and inform personalized treatment strategies for these challenging disorders. ***Methods:*** Literature was searched through Pubmed and the recently published 5th WHO classification criteria. Articles were reviewed and analyzed with emphasis on recent molecular and cytogenetic insights. ***Results:*** A total of 106 publications were reviewed, and the recent molecular insights—focusing on those concerning *STAT3* mutations in T-cell LGLL and *TET2* mutations in NK-cell LGLL which have refined diagnostic frameworks, though gaps persist in understanding their clinical relevance and variability. ***Conclusions:*** By providing a comparative analysis of large granular lymphocytic leukemias and their differential diagnoses in cooperation of the current advances in molecular pathogenesis, immunophenotypic profiling, and updated WHO classification criteria, this work aimed to enhance diagnostic precision, improve prognostic assessment, and inform personalized treatment strategies for these challenging LGLLs.

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Introduction

Large granular lymphocytic leukemias (LGLLs) encompass a spectrum of rare lymphoproliferative disorders that share overlapping diagnostic features but differ in clinical behavior, molecular markers, and therapeutic approaches. These entities pose unique diagnostic challenges due to cytologic similarities and overlapping immunophenotypic markers, often complicating early diagnosis. Misdiagnosis or delayed differentiation among these disorders may lead to inappropriate treatment strategies and impact patient outcomes. In light of recent updates in the World Health Organization's (WHO) fifth edition for hematolymphoid tumors, this review synthesizes advances in the understanding of T-cell LGLL (T-LGLL) and related disorders to provide a practical framework for accurate diagnosis and optimized patient management.

This review explores the distinguishing features of T-LGLL, followed by a comprehensive approach to the differential diagnoses often considered for LGLLs. These include all mature T-cell and natural kill (NK)-cell leukemias, such as T-prolymphocytic leukemia/lymphoma (T-PLL), NK-cell LGLL (NK-LGLL), adult T-cell leukemia/lymphoma (ATLL), and Sézary syndrome (SS), along with brief discussions on aggressive NK-cell leukemia (ANKL). By delving into the molecular and clinical hallmarks, this review aimed to equip practitioners with a nuanced framework for the workup and management of large granular lymphocytic leukemias.

T-LGLL

T-LGLL is a rare lymphoproliferative neoplasm consisting of large granular T cells, often involving peripheral blood, bone marrow, and spleen. Splenomegaly has been reported in a wide range of T-LGLL patients (20–50%) but is usually not prominent. Hepatomegaly is less common, and lymphadenopathy is even more rare.[1,2] T-LGLL accounts for less than 5% of chronic lymphoproliferative disorders and is diagnosed primarily in adults (median age: 60 years) without a predilection for sex.[3]

Approximately one-third of patients are asymptomatic. In

the majority of symptomatic patients, clinical presentations are related to their cytopenia(s).[4,5] Neutropenia is common, affecting as many as 80% of T-LGLL patients and can be defined as an absolute neutrophil count of <1,500 cells/μL. Studies have shown severe neutropenia (<500 cells/μL) in approximately one-fourth of T-LGLL cases. Complications observed with chronic neutropenia include recurrent oral, skin, and perirectal ulcers, and sometimes, severe sepsis or pneumonia.[1] Anemia and thrombocytopenia are less common than neutropenia.[5] Some patients present with transfusion-dependent anemia, and a subset of patients has pure red blood cell aplasia (anemia with low reticulocyte counts and no erythroid precursors in their marrow).[4,6]

T-LGLL is most famously associated with rheumatoid arthritis, but other autoimmune diseases like systemic lupus erythematosus and Sjögren syndrome have been linked as well. At least one-third of the T-LGLL population have serologic abnormalities (detection of rheumatoid factor, antinuclear antibody, polyclonal hypergammaglobulinemia, etc.), which reinforce an immune-activating context in T-LGLL.[1,7]

Monoclonal B-cell lymphocytosis can also coexist with T-LGLL (~25% of cases), and approximately 5% of T-LGLL patients have concurrent hematologic malignancies, mostly B-cell lymphomas.[8,9]

Pathogenesis and molecular abnormalities

Because of T-LGLL's association with autoimmune and hematologic disorders, as well as demonstration of seroreactivity to retroviral proteins (especially human T-cell leukemia virus-1 (HTLV-1)-related proteins), chronic antigenic stimulation is thought to play a key role in the pathogenesis of T-LGLL.[10–12] The proinflammatory cytokine IL-15 and autocrine platelet-derived growth factor stimulate oligoclonal or clonal expansion of T-LGLL memory effector T cells, and these cells resist FAS/FAS ligand-mediated apoptosis.[13–15]

In addition, constitutive STAT3 activation and gene deregulation contribute to T-LGLL cell proliferation and survival.[16,17] More recently, recurrent gain-of-function *STAT5B* mutations have been elucidated in $CD4^+$ T-LGLL cases but are still rare in the $CD8^+$ or γδ subtypes of T-LGLL.[18,19] Other recurrent gene mutations in T-LGLL include *TET2*, *TN-FAIP3*, *BCL11B*, *FLT3*, and *PTPN23*, as well as disturbances in the PI3K/AKT and NF-κB pathways contributing to T-LGLL's pathogenesis.[20–24] Monoclonal or oligoclonal T-cell receptor (TCR) gene rearrangement is a key feature in T-LGLL. Although most cases maintain a consistent monoclonal expansion, changes in the dominant clone can occur.[25]

Immunophenotype and morphology

T-LGLL lymphocytes contain small to medium-sized nuclei with condensed chromatin and moderate to abundant pale cytoplasm containing varying amounts of azurophilic granules (Fig. 1). A bone marrow biopsy can be helpful in diagnosing T-LGLL and excluding other causes of cytopenia,[26] although the cytological features can sometimes be difficult to appreciate in bone marrow aspirate specimens. Bone marrow biopsy specimens are usually hypercellular (Fig. 2), although normocellular and hypocellular specimens are also seen. Diffuse interstitial lymphoid infiltrates are present in the majority of cases and may be seen concurrently with non-paratrabecular lymphoid nodules. However, the lymphoid infiltrates may be subtle in some cases.[27,28]

Most atypical cells are $CD8^+$ with a mature memory effector T-cell immunophenotype (positive for CD3, CD8, CD57, CD45RA; negative for CD62L) (Fig. 3). Rare cases may express CD4 with or without CD8.[29] Even rarer (<10%) are the γδ T-cell lineage cases of T-LGLL, which are $CD57^+$ and

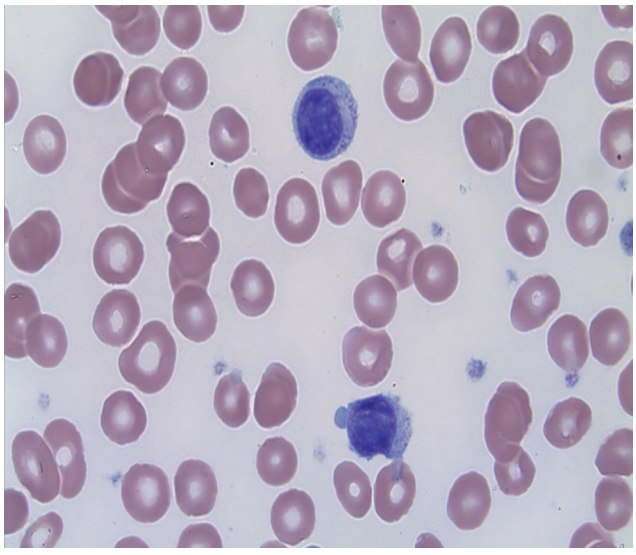

Fig. 1. T-large granular lymphocytic leukemia (T-LGLL) lymphocytes with cytoplasmic azurophilic granules in peripheral blood (Wright-Giemsa stain, original magnification 100×).

$CD16^+$, with partial expression of CD8, and have the Vγ9/Vδ2 profile.[30,31] Immunohistochemistry will generally demonstrate expression of CD2, CD3, CD8, TCRβ, CD7, TIA1, perforin, granzyme B, and granzyme M in these lymphoid cells (Fig. 4). CD56 and CD5 are often negative (Fig. 5).[29] The NK cell-associated antigens CD16 and CD57 are frequently expressed (in 80% and 90%, respectively).[32]

Analysis of the TCRβ constant region and TCRVβ expression by flow cytometry is helpful in highlighting the dominant clone and assessing clonality (Fig. 6). More than one-third of T-LGLL cases will express the NK cell-associated receptors killer cell immunoglobulin-like receptor (KIR) and CD94/NKG2, representing a population of fully differentiated cytotoxic T cells. Another indicator of clonality in T-LGLL is the expression of a single KIR isoform (CD158a, CD158b, or CD158e).[33–35]

The WHO Classification of Haematolymphoid Tumours (5th ed.) lists essential and desirable criteria for T-LGLL. The presence of all three essential criteria, or two essential criteria in addition to one desirable criterion, defines the diagnosis of T-LGLL. The three essential criteria are: 1) increased circulating cytotoxic T cells (no absolute number, but levels are often >2,000 cells/μL), 2) aberrant phenotype of the T-cell population ($CD8^+$ with downregulation of CD5 and/or CD7, and/or abnormal expression of CD16 and NK-cell-associated receptors), and 3) evidence of T-cell monoclonality by demonstrated monoclonal or oligoclonal TCR gene rearrangement. The two desirable criteria are: 1) intrasinusoidal cytotoxic lymphocytic infiltrates in the bone marrow (by immunohistochemistry (IHC)) and 2) *STAT3* or *STAT5B* mutation.[36]

Prognosis

Many treatment modalities have been tested for treating symptomatic cytopenias of T-LGLL, and presently, the first-line therapy consists of a single-agent treatment with methotrexate, ciclosporin, or cyclophosphamide. Corticosteroids may be used as adjunct therapy. Overall, T-LGLL shows a good prognosis and long survival with appropriate treatment. Features such as neutropenia, transfusion-dependent anemia, and *STAT3* mutations have been associated with a poorer prognosis, and there have been a few cases of T-LGLL progressing into an aggressive T-cell lymphoma.[37]

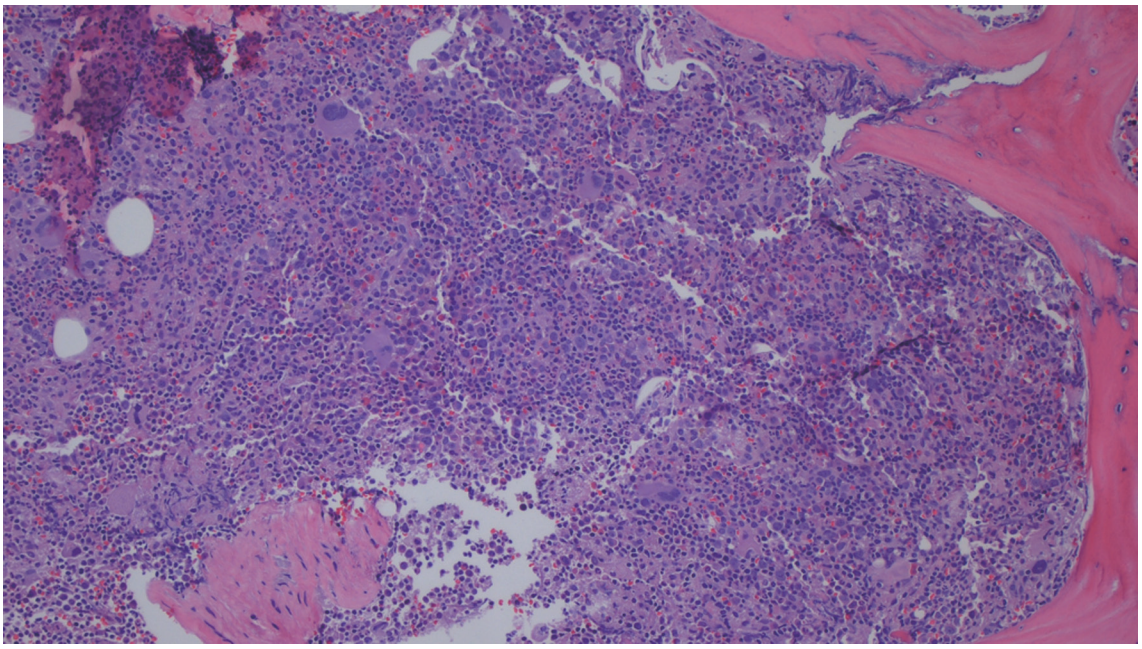

Fig. 2. Hypercellular trephine core bone marrow biopsy with lymphoid infiltrate (Hematoxylin and Eosin stain, original magnification 100×).

NK-LGLL

An important differential diagnosis to consider in the context of T-LGLL is NK-LGLL, a chronic, indolent lymphoproliferative disorder involving the peripheral blood and bone marrow in adults. It can present with cytopenias and occur in the setting of other autoimmune disorders like T-LGLL, but it is not nearly as frequent.[38,39]

Pathogenesis

Although the etiology is unknown, there are suggestions that stimulation of the body's innate immunity may be a contributing factor in NK-LGLL, whether through a viral infection or some other means. It seems less likely that viral infection of NK cells is a direct factor in disease development.[40] *STAT3* mutations are found in ~30% of NK-LGLL patients, *TET2* mutations in ~25–30%, and concurrent *STAT3* and *TET2* mutations in some cases.[16,41,42] *STAT5B* mutations are very rare.[24,43] The possibility of subtypes of NK-LGLL arises because studies have found *CCL22* mutations (21.5% of cases), which appear to be mutually exclusive of mutations in *STAT3* and *STAT5B*, and have a unique mechanism dependent on mutated chemokines driving NK cell tropism and tumor expansion. These mechanisms are still incompletely understood.[44]

Morphology and immunophenotype

The atypical cells are medium to large with abundant pale cytoplasm containing azurophilic granules and small, round nuclei with condensed chromatin. It is important to note that one cannot distinguish between NK-LGLL and T-LGLL by cytologic features alone.[45] These features are difficult to appreciate in the bone marrow, but the lymphocytes will often infiltrate with an intrasinusoidal pattern.[33]

IHC alone is not reliable for distinguishing NK-LGLL from T-LGLL. Flow cytometric evidence must be demonstrated, where abnormal NK-cell receptor expression is the hallmark. KIR should be completely undetectable, or a restricted KIR isoform may be expressed. Other abnormal NK-cell receptor expressions seen include bright CD94/NKG2A heterodimer expression and weak/absent CD161. The atypical cells are positive for CD15, negative for sCD3, and show variable expression of CD3ε. CD56 should be positive, but may be weak or absent in 50% of cases.[46,47] CD7 and CD2 may be diminished or dim; CD8 may or may not be expressed.[48,49] Flow cytometry and IHC can detect expression of cytotoxic granule proteins (TIA-1, granzyme B, granzyme M), with IHC highlighting intrasinusoidal infiltration in bone marrow.[32,33]

Molecular abnormalities

STAT3 mutations and *TET2* mutations define molecular alterations in NK-LGLL. An absence of clonal T-cell populations is seen in T-cell receptor gene rearrangement studies.[16,50]

Prognosis

More than half of NK-LGLL cases tend to be indolent, and treatment is not necessary unless patients have symptomatic cytopenias.

Differentiating features

Although NK-LGLL may show clinical overlap with cytopenias and autoimmune or hematological disorders, its frequency is much lower than that of T-LGLL.[38,39] The most recent recommendations from the WHO are to utilize flow cytometry to demonstrate a restricted pattern of KIR expression to identify clonal expansion. However, clonality can also be determined by evaluating *STAT3* and *TET2* mutations if flow cytometric evaluation for KIR expression is unavailable. Additionally, T-cell receptor gene rearrangement of clonal T-cell populations, a significant finding in T-LGLL,[16,41] should be negative in NK-LGLL.

T-PLL

Another differential diagnosis that must be considered when evaluating T-cell leukemia is T-PLL. T-PLL is a monoclonal peripheral T-cell leukemia with prolymphocytic features,

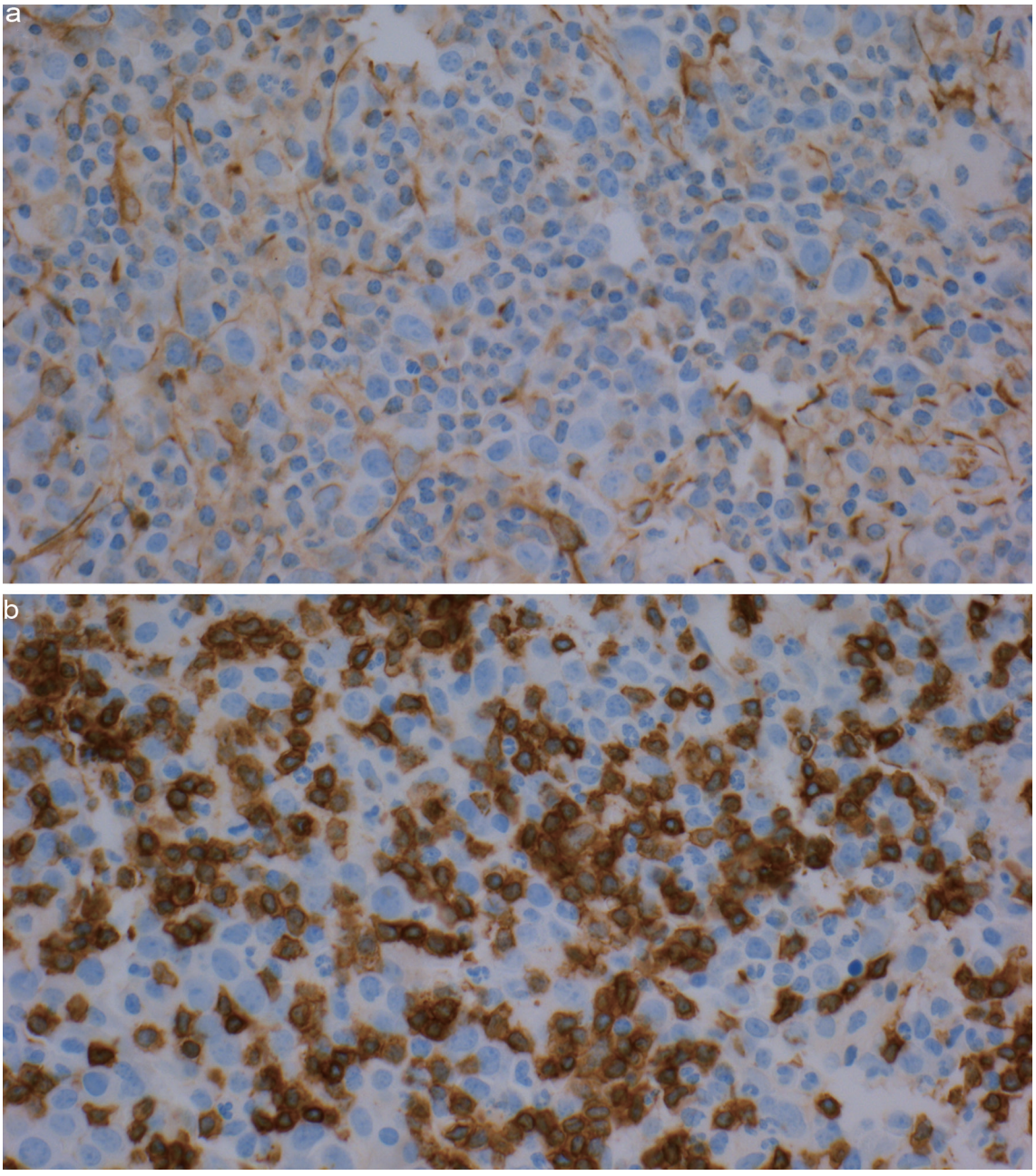

Fig. 3. (a) Negative for PAX-5, a B-cell marker. (b) Positive for CD3 (Immunoperoxidase stain, original magnification 200×).

peripheral blood T-cell lymphocytosis and/or bone marrow involvement, and evidence of *TCL1A* or *MTCP1A* rearrangement in the vast majority of cases.[51]

Clinical findings

T-PLL clinically features, in most frequent order, marked lymphocytosis (>100 × 10^9/L), splenomegaly, lymphadenopathy, thrombocytopenia, hepatomegaly, and anemia.[52] There is also an increased prevalence in patients with ataxia-telangiectasia.[53] Onset generally occurs in older adults, with a median age of 65 years. Patients with ataxia-telangiectasia have been found to develop it as early as adulthood.[54] Approximately 30% of cases may be detected with only subclinical lymphocytosis and no other symptoms, which may later progress to active disease.[52]

Pathogenesis

Chromosomal rearrangements inv(14) (q11q32) and t(14;14) (q11,q32) result in the upregulation of the *TCL1A* gene by the TCR gene enhancer loci of TRA/TRD, or a t(X;14) (q28;q11.2) translocation, which results in *MTCP1* being regulated by T-cell receptor regulatory sequences. Inappropriate expression of these oncogenes is considered the causative factor for T-PLL.[55–57] Additionally, dysfunctional ataxia-telangiectasia mutated (ATM) protein is thought to have a synergistic effect, promoting a leukemogenic pro-

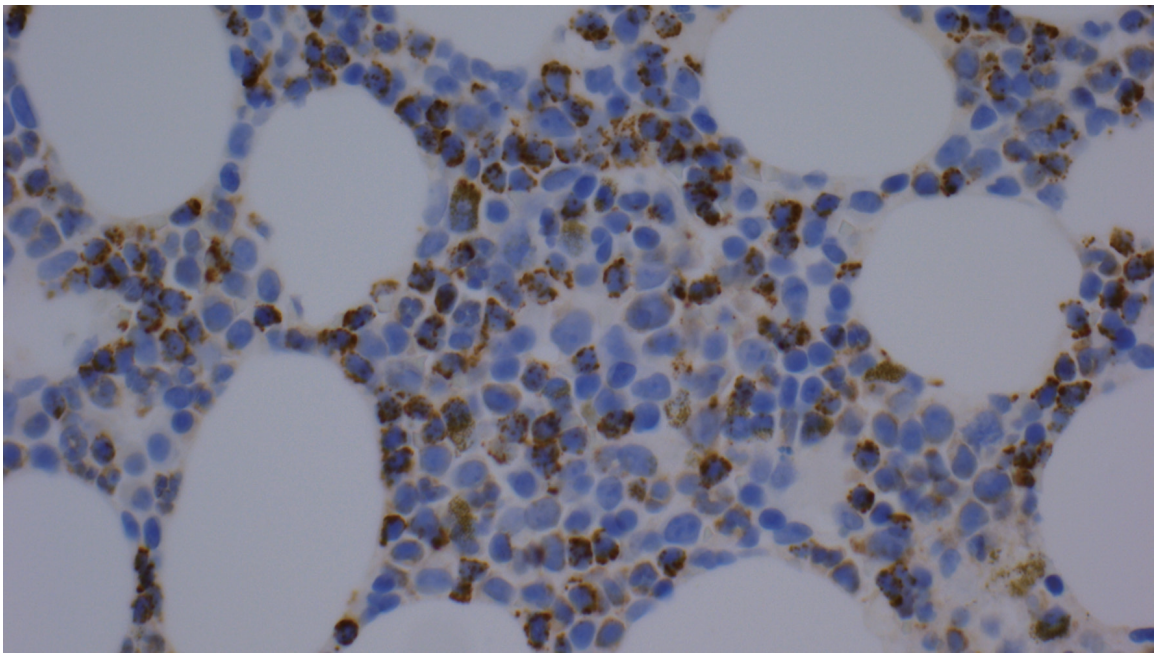

Fig. 4. TIA-1 expression in T-large granular lymphocytic leukemia (T-LGLL) cells (Immunoperoxidase stain, original magnification 400×).

cess unique to T-PLL, interfering with DNA damage response, disrupting genomic stability, and leading to chemotherapy resistance.[58,59] Following the rearrangements and interplay with ATM, oncogenic pathways are enhanced, predominantly through AKT signaling and gain-of-function mutations in the JAK/STAT pathway.[59]

Morphology and immunophenotype

T-PLL has three distinct morphologic patterns. The predominant pattern is small to medium-sized cells with a prolymphocytic appearance, non-granular basophilic cytoplasm with visible nucleoli, clumped chromatin, and irregular nuclei (~75%). The small cell variant presents with a lymphocyte appearance, small cells with dense chromatin and an inconspicuous nucleolus (~20%). The last type consists of cells with irregular or cerebriform nuclei, similar to those seen in Sézary syndrome (~5%). Cell morphology cannot be solely used for diagnosis, as there is significant overlap with other

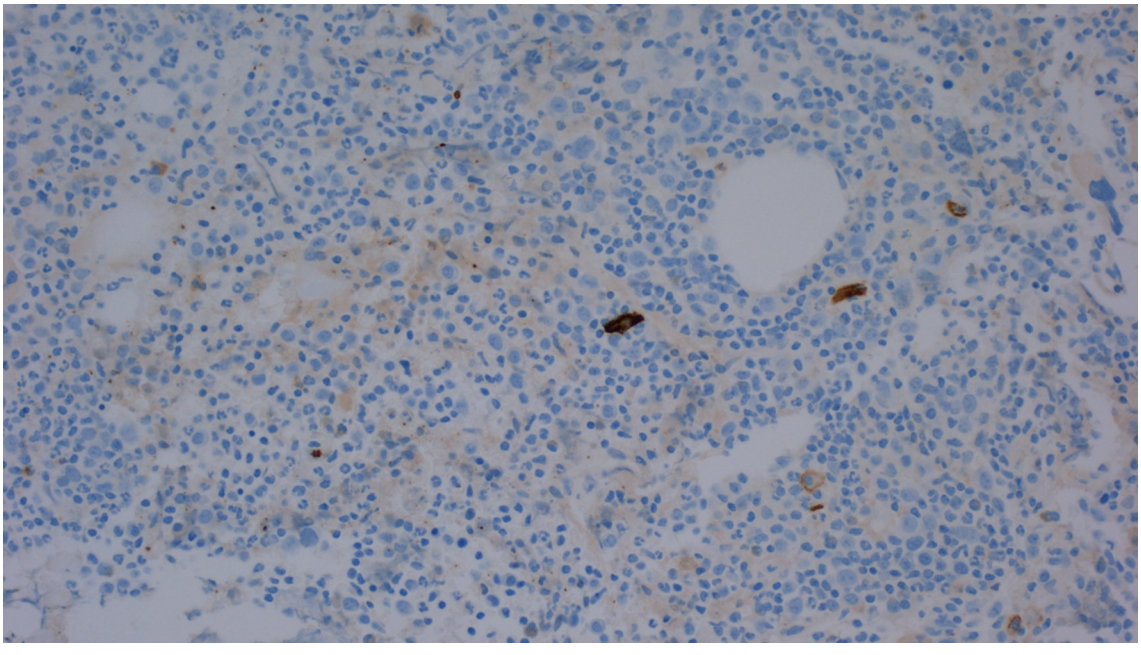

Fig. 5. CD56 is not expressed in the T-large granular lymphocytic leukemia (T-LGLL) lymphocytes in the bone marrow (Immunoperoxidase stain, original magnification 400×).

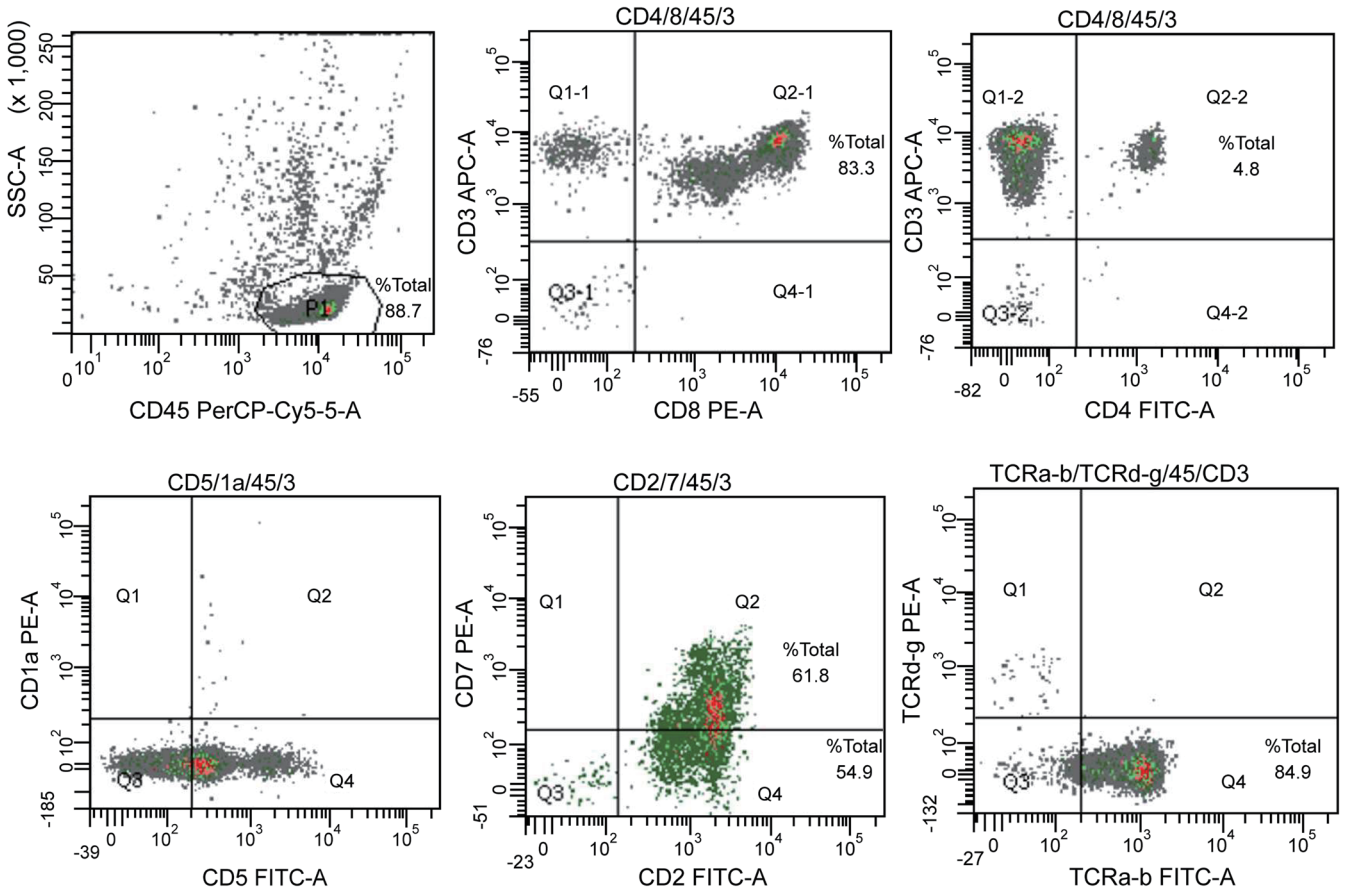

Fig. 6. Immunophenotypic analysis of T-large granular lymphocytic leukemia (T-LGLL) by flow cytometry showing the gated lymphocytes are mostly CD8⁺ T cells with T-cell receptors (TCR alpha/beta clonality).

T-cell neoplasms.[60]

The immunophenotypic expression seen is positive for CD2, CD3, CD5, and CD7, while being negative for TdT and CD1a. Overexpression of TCL1A with nuclear staining is highly sensitive (>80%) for T-PLL and is not generally seen in other mature T-cell lymphomas/leukemias.[61] Additionally, CD4 is usually positive, with varying CD4:CD8 patterns: $CD4^+/CD8^-$ (40–60%), $CD4^+/CD8^+$ (25–41%), and $CD4^-/CD8^-$ (~15%). Coexpression of CD4 and CD8 is distinctive of T-PLL and is rarely seen in adult T-cell leukemia/lymphoma. CD52 is typically expressed and serves as a therapeutic target.[52,61]

Molecular abnormalities

Clonal T-cell receptor gene rearrangements are present in either TCR gamma or beta.[62] Rearrangements involving the TCL1 family genes (*TCL1A*, *MTCP1*) are present in all cases of T-PLL.[51] Rare instances of apparent TCL1-family negative T-PLL are recognized, in which abnormalities in *ATM* are present, with features otherwise similar to T-PLL but without a corresponding TCL1 family genetic abnormality. As of now, this relationship is unclear, and these TCL1-family negative T-PLL entities should be classified as peripheral T-cell lymphoma, not otherwise specified (with leukemic involvement) after excluding all other possible entities.[60] Approximately 75% of T-PLL cases exhibit recurrent activating mutations in *IL2RG*, *JAK1*, *JAK3*, and *STAT5B* genes, leading to constitutive STAT5 signaling.[63] Additional mutations in *EZH2*, *FBXW10*, and *CHEK2* may also contribute to disease development, influencing epigenetic regulation, protein degradation, and DNA repair.[63]

Prognosis

The majority of cases follow an aggressive course, with a subset (20–30%) starting in a stable or slowly progressive state. However, the slowly progressing cases become active within two years, with a median survival time of 21 months. Despite increased success with anti-CD52 monoclonal antibody alemtuzumab and consolidation autologous stem cell transplant, the reported median overall survival only reaches 52 months.[64–66]

Differentiating features

T-PLL does not have the strong association with autoimmune disease like T-LGLL.[4] T-PLL is uniquely defined by *TCL1A* or *MTCP1* rearrangements.[51] CD4 and CD8 co-expression is more frequently seen in T-PLL, while NK-associated antigens CD16 and CD57 are not expressed.[52,67] With respect to clinical outcome, T-PLL has a much more aggressive course, while T-LGLL is often indolent and stable.[37,64] A comparison of some of the key overlapping and differentiating features of each of the large granular lymphocytic leukemias is summarized in Table 1.

ATLL

ATLL is a mature $CD4^+$ T-cell neoplasm that is associated

Table 1. Comparison of large granular lymphocytic leukemias

Key features	T-large granular lymphocytic leukemia (T-LGLL)	NK-large granular lymphocytic leukemia (NK-LGLL)	T-prolymphocytic leukemia (T-PLL)	Adult T-cell leukemia/lymphoma (ATLL)	Sézary syndrome (SS)
Morphology	Small to medium sized nuclei, cytoplasmic azurophilic granules	Medium to large with azurophilic granules	Three patterns: 1) Small to medium sized cells with prolymphocytic appearance; 2) Small cell variant; 3) Sézary-like appearance	Variable, pleomorphic sizes. Acute variant-flower cells	Medium to large cells with irregular grooved nuclei
Immunophenotype	$CD2^+$, $CD3^+$, $CD8^+$, $CD18^+$, $CD57^+$, $CD45RA^+TCR\beta$, CD7, TIA, perforin, granzyme B and granzyme M	Indistinguishable from T-LGLL. Flow cytometry studies: $sCD3^-$, $CD16^+$ NK cells. Restricted pattern of KIR expression	$CD2^+$, $CD3^+$, $CD5^+$, $CD7^+$, TdT^-, $CD1a^-$, $CD4^+$, varying $CD8^{+/-}$, $CD52^+$, TCL1A overexpression	$CD2^+$, $CD3^+$, $CD5^+$, $CD25^+$, $CD7^-$, $CD4^+/CD8^-$, $CD4^-/CD8^+$	$C3^+$, $CD4^+$, $PD1^+$ (CD279); CLA^+, $CCR4^+$, $CCR7^+$, $CXCL13^{+/-}$; Variable pan T-cell marker loss ($CD8^-$, $CD2^-$, $CD5^-$, $CD7^-$)
Cytogenetic/Molecular	Mono/oligoclonal TCR gene rearrangement. *STAT3, STAT5B* most common mutations	*STAT3*, *TET2*: No T-cell gene rearrangement	*TCL1A or MTCP1A* rearrangement. Clonal TCR rearrangements (TRG or TRB)	Monoclonal integration of proviral HTLV-1 DNA	Clonal TCR gene rearrangement
Clinical presentation	Absolute neutropenia, strong autoimmune association	Cytopenias, slight autoimmune association	Marked lymphocytosis, hepatosplenomegaly, LAD, cytopenias	Variable presentation: LAD, varied organ involvement	Skin involvement, LAD
Prognosis	Good prognosis, responsive to therapy	Very good with mostly indolent disease process	Poor (median 21–52 months with therapy)	Varies based on clinical subtype	Poor, significant mortality to opportunistic infection (median survival 32 months)

KIR, killer cell immunoglobulin-like receptor; LAD, lymphadenopathy; NK, natural killer; TCR, T-cell receptor; TRG, T-cell receptor gamma; TRB, T-cell receptor beta.

with HTLV-1 and is another differential that should be considered with T-LGLL. ATLL occurs mostly in regions (in particular southwestern Japan, the Caribbean, intertropical Africa, the Middle East, South America, and Papua New Guinea) endemic for the retrovirus HTLV-1, especially in immunodeficient patients.[50,68] The clinical presentation of ATLL is diverse, including general lymphadenopathy, cutaneous lesions, hepatosplenomegaly, and organ infiltration, such as in the central nervous system, gastrointestinal tract, bone, and lungs. Leukocytosis is common, with increased atypical lymphocytes that have cerebriform/flower-like nuclei.[69] There are four clinically defined forms of ATLL: 1) acute, 2) lymphomatous, 3) smoldering, and 4) chronic. These variants are defined by the type of organ involvement, degree of leukemic manifestation, and LDH/calcium laboratory values.[70]

Pathogenesis

In patients with HTLV-1 infection, approximately 3–5% go on to develop ATLL.[71] Patients are usually infected at a very young age with a long latent viral period, which is why the onset of ATLL usually occurs in adults.[72] HTLV-1 infects cells and changes their immunophenotype, promoting viral and cell proliferation and anti-apoptosis through two crucial genes, *Tax* and *HBZ*.[73,74] The efficacy and quality of the cytotoxic T lymphocyte response to HTLV-1-infected cells essentially determine the proviral load and are associated with progression to ATLL.[67,75] Significant alterations seen in ATLL include clonally rearranged T-cell receptor genes and one or more HTLV-1 integration into the host genome by a series of accumulating molecular and genetic alterations/mutations (of which the specifics will not be addressed here).[76,77]

Morphology and immunophenotype

The histologic presentation of ATLL depends on the organ involved. In lymph nodes, a diffuse or paracortical pattern of neoplastic cell infiltration, or rarely, preserved/dilated sinuses containing the neoplastic cells, is seen.[78] The cytologic morphology of ATLL T-cells is diverse. The atypical cells can range from small to large pleomorphic cells, with anaplastic forms also present. The lymphoid cells tend to have condensed chromatin with a prominent nucleolus. In the acute variant, cells with irregular multilobulated nuclei and basophilic cytoplasm are called "flower cells," while the cells are less atypical and smaller in the smoldering or chronic variant.[79,80]

Tumor cells are mostly positive for CD2, CD3, CD5 but negative for CD7. $CD4^+$ $CD8^-$ is the most common immunophenotype seen, but some can be $CD4^-$ $CD8^+$, double-positive, or double-negative. Most cases will be CD25 positive, and in larger cells, CD30 can be variably positive. CCR4 is frequently positive in tumor cells, and FOXP3 is variably expressed.[81,82]

Molecular abnormalities

Molecular studies will show neoplastic T cells with monoclonal integration of proviral HTLV-1 DNA. The previous gold stand-

ard for detection was Southern blot hybridization; however, this method has high tissue requirements that small tissue samples cannot typically satisfy. A more feasible recent approach for FFPE samples uses RNA *in situ* hybridization with RNA scope analysis to detect the incorporation of the viral *HBZ* gene and quantitative PCR to detect the viral *tax* gene. An algorithmic combination of these two techniques demonstrates exceptional sensitivity and specificity.[83,84] Demonstrating proviral integration or detecting HTLV-1 antibodies confirms an ATLL diagnosis.[83]

Prognosis

Clinical outcomes correlate with the clinical subtype of ATLL, with prognosis from worst to best in the acute, lymphoma, chronic, and smoldering subtypes, respectively.[70,85]

Differentiating features

The atypical cells of ATLL display cerebriform/flower nuclei, a clear difference from the more conventional lymphocytic T-LGLL neoplastic cell appearance with cytoplasmic azurophilic granules.[79,80] It is essential to prove HTLV-1 involvement and/or monoclonal integration of HTLV-1 in ATLL to distinguish it from other LGTLLs.[83]

SS

SS is a rare, generalized disease with a leukemic presentation and the classic skin manifestation of erythroderma. It is composed of mature T lymphocytes with three definitive findings: 1) erythroderma, 2) generalized lymphadenopathy, and 3) clonally related neoplastic T cells with cerebriform nuclei (Sézary cells) in the skin, lymph nodes, and peripheral blood.[86,87] SS accounts for only 2–3% of all cutaneous T-cell lymphomas.[88]

Pathogenesis

Mutational signatures 1 and 7 have been identified as key players in SS. Signature 1 is associated with age-related spontaneous deamination of methylated cytosines, while signature 7 implicates UV exposure in the pathology of SS and other cutaneous T-cell lymphomas, such as mycosis fungoides (MF), though it should not be present in other mature T-cell lymphomas/leukemias.[89] The difference in the cell origin of SS and MF is that SS is a malignancy of central memory T cells or skin-homing $CD4^+$ T cells, while MF arises from skin-resident effector memory T cells.[90] Gross chromosomal instability, with recurrent gains and losses, is noted in SS, with isochromosome 17q being a recurrent feature.[91] SS and MF generate type-2 T-cell cytokines that suppress Th helper 1 activity, creating a state of immunosuppression thought to contribute to tumor cell survival.[92] SS, like MF, exhibits complex karyotypes with numerous abnormalities.[93] A hallmark of SS is a high mutation burden, precipitated by UV radiation exposure.[89] Recurrent gain-of-function mutations in *PLCG1*, *CARD11*, *CD28*, and *CARMIL2* genes are frequently identified, leading to dysregulation of T-cell receptor signaling pathways and increased NF-κB activity.[94] Numerous driver mutations in regulatory and repair pathways, including DNA repair (*TP53*, *POT1*, *ATM*), JAK/STAT signaling (*STAT5B*, *JAK3*), and chromatin regulation (*ARID1A*, *TRRAP*, *DNMT3A*, *TET2*), contribute to SS pathogenesis by disrupting cellular homeostasis and promoting oncogenesis.[94,95]

Morphology and immunophenotype

Characteristic Sézary cells are atypical lymphocytes of intermediate to large size with irregular, deeply grooved, or infolded nuclei with delicate convolutions (cerebriform nuclei). Lymph nodes are partially or completely effaced by a dense infiltration of Sézary cells. In the skin, the infiltrate is often monotonous and perivascular. Although SS presentation is distinct, as many as one-third of patients may show nonspecific histology in their biopsies.[96,97]

The malignant cells are typically $CD3^+$, $CD4^+$, and $CD8^-$, with an aberrant loss of pan T-cell antigens (CD2, CD5, CD7, and/or CD26). Sézary cells in the skin and blood will almost always express PD1 (CD279). The neoplastic cells also express cutaneous lymphocyte antigen, the skin-homing receptor (CCR4), and CCR7, with variable expression of CXCL13. They are also typically positive for TCRαβ, CD25, and ICOS. NK cell markers, such as CD158k/KIR3DL2 and NKp46, may or may not be expressed.[98–102]

Molecular abnormalities

T-cell receptor gene rearrangement analysis demonstrates clonality in the neoplastic Sézary cells.[102–104]

Prognosis

SS is very aggressive, and most patients die due to opportunistic infections. The survival rate varies depending on the stage of the disease, but the overall median survival time is reported as 32 months, with a five-year survival rate of 10–30%.[88]

Differentiating features

Although the classic presentation of Sézary Syndrome involves erythroderma, there may be cases of solely leukemic presentation where a thorough differential diagnosis is necessary.[97] Cytologic differences, such as the classic cerebriform nuclei in Sézary versus the abundant cytoplasm, azurophilic granules, and round nuclei in T-LGLL, can be helpful.[96] The neoplastic cells of Sézary Syndrome will distinctly express PD1, cutaneous lymphocyte antigen, CCR4, and CCR7, and have aberrant loss of pan T-cell antigens (CD2, CD5, CD7, and/or CD26).[98,99] They will not express the NK cell-associated antigens CD16 and CD57, which are seen in T-LGLL.[100,101]

ANKL

Worthy of brief discussion is ANKL, which can exhibit a similar morphologic appearance to T-LGLL and NK-LGLL. It may present with neoplastic lymphocytes containing azurophilic cytoplasmic granules.[105] Beyond the morphologic appearance, however, this entity diverges significantly with an aggressive and symptomatic clinical course, EBV association, and greater atypical morphologic variation. It is otherwise characterized by a typical NK-cell origin immunophenotype with no T-cell receptor expression or clonal T-cell receptor gene rearrangement.[105] While it is relatively easily differentiated from the more indolent possibilities, the initial presentation of neoplastic lymphocytes with azurophilic granules should prompt consideration of this entity, as it has a severely fulminant clinical course and short survival time.[106]

Conclusions

This review offers a comprehensive comparative analysis of T-LGLL and related lymphoproliferative disorders, emphasizing critical diagnostic and molecular markers essential for accurate differentiation. It highlights significant advancements in the understanding of large granular lymphocytic leukemias; however, the rarity of these neoplasms poses inherent challenges. Much of the current knowledge is derived from

small cohort studies, which may limit the generalizability and statistical power of conclusions regarding diagnostic criteria, molecular markers, and prognostic implications. Additionally, the overlap of clinical features among LGLLs and related disorders underscores the need for further research to refine and validate diagnostic and therapeutic approaches. These limitations highlight the ongoing necessity for larger, multi-institutional studies to strengthen the evidence base and improve clinical outcomes.

As overlapping features often blur diagnostic boundaries, precise identification of LGLLs is increasingly important for guiding optimal treatment strategies and improving patient outcomes. Recent advancements in understanding molecular alterations—such as mutations affecting pathways like *STAT3* and *TET2*—along with updated WHO classification criteria, contribute to refining diagnostic and prognostic frameworks. These classification updates reflect an ongoing effort to clarify a complex category of lymphoproliferative diseases that remains only partially understood. Continued research into these and other molecular markers is crucial for identifying novel diagnostic tools, enhancing prognostic accuracy, and developing targeted therapies. By improving diagnostic precision, clinicians can better tailor treatments to individual patients, advancing patient care and potentially transforming outcomes for those affected by these rare and challenging hematologic disorders.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

Study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content (DWP, IEL, DX, JW). All authors have made significant contributions to this study and have approved the final manuscript.

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