T-cell Lymphomas
Updates in Biology and Diagnosis

Sarah L. Ondrejka, DO, Eric D. Hsi, MD*

KEYWORDS

• T-cell lymphoma • Non-Hodgkin lymphoma • T-cell lymphoma subtypes
• Pathobiology • Anaplastic large cell lymphoma • Peripheral T-cell lymphoma
• Angioimmunoblastic T-cell lymphoma • Nodal • T-follicular helper cells

ABSTRACT

Nodal-based peripheral T-cell lymphomas are heterogeneous malignancies with overlapping morphology and clinical features. However, the current World Health Organization classification scheme separates these tumors into prognostically relevant categories. Since its publication, efforts to uncover the gene expression profiles and molecular alterations have subdivided these categories further, and distinct subgroups are emerging with specific profiles that reflect the cell of origin for these tumors and their microenvironment. Identification of the perturbed biologic pathways may prove useful in selecting patients for specific therapies and associating biomarkers with survival and relapse.

Key Features

- Peripheral T-cell lymphomas comprise a diverse group of neoplasms that can present a diagnostic dilemma to clinicians and pathologists.
- Accurate diagnosis usually requires knowledge of clinical data, laboratory test results and an adequate tissue biopsy for routine and ancillary tests.
- The classification scheme for T-cell lymphomas will continue to be updated alongside emerging information about cell(s) of origin, genetic alterations and oncogenesis.
- Many types of peripheral T-cell lymphoma have a poor prognosis and aggressive course, and additional studies are underway to identify the best treatment options.

OVERVIEW AND PRACTICAL CONSIDERATIONS

T-cell lymphomas represent 5% to 10% of non-Hodgkin lymphomas in Western countries and 15% to 20% in the Asian continent, yet are classified in numerous distinct clinicopathologic entities that reflect etiologic factors, morphology, cell of origin, and behavior. Our understanding of the biology and diversity of these tumors has grown progressively in the past several decades, and the classification schemes are continually modified to reflect new information.[1,2] Most types are aggressive neoplasms that demonstrate a poor response to conventional therapies. The T-cell lymphoma subtypes vary in frequency by geographic region, with natural killer (NK)/T-cell lymphoma and adult T-cell leukemia/lymphoma most common in Asia, and peripheral T-cell lymphoma, unspecified (PTCL-NOS), as the most common subtype in both North America and Europe.[1]

The diagnosis of these tumors can be difficult because they are rare and lack certain histologic features that are specific to subtypes of B-cell lymphomas. Most importantly, clinical context is extremely important in classifying T-cell neoplasia and/or generating a differential diagnosis and must be considered in every case. Core needle biopsies are generally suboptimal for diagnosis and

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Department of Laboratory Medicine, Robert J. Tomsich Pathology and Laboratory Medicine Institute, Cleveland Clinic, 9500 Euclid Avenue, L-30, Cleveland, OH 44195, USA
* Corresponding author.
E-mail address: hsie@ccf.org

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are typically useful to heighten suspicion for lymphoma and thereby elicit subsequent procedures. Ideally, tissue samples are excisional biopsies with ample fresh tissue for ancillary diagnostics, including flow cytometry and molecular tests. Immune profiling by immunohistochemistry is helpful but there is much overlap in phenotype among the various entities. Polymerase chain reaction (PCR) studies of T-cell receptor gene rearrangements are often performed to document clonality in T-cell proliferations and aid in separating reactive from neoplastic causes. Even with ample pathologic material, accurate diagnosis is difficult and lacks 100% consensus agreement even by experts in the field. The International Peripheral T-cell and NK/T-cell Lymphoma Study reported an overall agreement of 81%,[1] whereas consistent use of a specified algorithm may improve consensus agreement to 92%.[3] In a comparison of diagnoses made by referring institutions versus central review for patients with T-cell lymphoma in the National Comprehensive Cancer Network, 44% (57/131) had concordant results, 24% were discordant, and 32% were assigned a provisional diagnosis.[4]

Although advanced molecular modalities, such as gene expression profiling and/or genomic sequencing technologies are not currently being used in routine diagnosis of T-cell lymphomas, the information gained from these studies is helping to flesh out the classification of these entities and uncover useful biomarkers that represent important biologic pathways and provide opportunities for tailored treatment regimens.

The current review will discuss the most common nodal types of peripheral T-cell lymphoma, including key features for recognition, immunohistochemistry, and molecular modalities to assist in diagnosis and differential diagnosis, and recent biomarkers and genetic alterations that provide clues to prognosis or classification.

ANAPLASTIC LARGE CELL LYMPHOMA, OVERVIEW

Anaplastic large cell lymphoma (ALCL) is currently classified as being anaplastic lymphoma kinase (ALK) positive, ALK negative, or primary cutaneous, according to the World Health Organization (WHO) 2008 classification.[5] There is also a site-specific form not yet incorporated into this classification scheme; that is, ALCL associated with breast implants, an indolent form when strictly confined to the breast capsule.[6,7] This discussion is limited to the nodal types of ALCL, which represent 3% of non-Hodgkin lymphomas in adults and 30% of childhood non-Hodgkin lymphoma. There is a biphasic age distribution with medians centering on the second and seventh decade, and ALK-positive ALCL is more often seen in the younger age group with a male predominance.[1,5]

ANAPLASTIC LARGE CELL LYMPHOMA, ANAPLASTIC LYMPHOMA KINASE POSITIVE

ALK protein expression defines this specific clinicopathologic entity, and the tumor cells express an ALK fusion protein derived from a rearrangement at the *ALK* 2p23 locus.[8] Both ALK-positive and ALK-negative ALCLs are neoplasms of large CD30-positive cells with pleomorphic, horseshoe-shaped nuclei, a prominent Golgi zone, and eosinophilic cytoplasm. All cases contain the so-called "hallmark cells." Staining for CD30 is strong and diffuse; the quality can be membranous and Golgi, and/or cytoplasmic.[5]

ALK-positive ALCL often presents with B symptoms, peripheral adenopathy, and variable involvement of extranodal sites, including skin, soft tissue, liver, lung, and bone.[9,10] The bone marrow is sometimes involved, and the detection rate is increased with a CD30 immunostain.[11] Rarely, circulating ALCL cells are present in peripheral blood and associated with the small cell variant.[12] The normal counterpart is thought to be a CD4-positive T cell with similarities to the T-helper 17 subset, although not all cases express CD4.[13] ALK-positive ALCL has a favorable prognosis compared with ALK-negative ALCL and many other types of peripheral T-cell lymphoma. The 5-year overall survival rates are in the 70% to 80% range.[14,15]

Lymph node involvement can be sinusoidal or diffuse, and in extranodal sites, ALCL grows in a sheetlike pattern. In addition to the common pattern, there are several histologic variants described in the WHO classification, including lymphohistiocytic, small-cell, and Hodgkinlike. A composite pattern may be seen in few cases.[5] Some cases have rather unusual features and do not fit as one of the recognized variants. These have been described as sarcomatoid, myxoid, round cell, or neutrophil rich.[16] In addition to ALK and CD30 expression, the immunophenotype might include loss of multiple T-cell antigens, with CD2 and CD4 often preserved. Cytotoxic markers (perforin, TIA-1, and granzyme B) are frequently expressed and can be helpful,[17] and sometimes epithelial membrane antigen (EMA) or clusterin is positive. The pattern of ALK staining gives clues to the partner gene, as the *NPM-ALK* fusion (t[2;5][p23;q35]) protein is distributed in both the nucleus and the cytoplasm, whereas many other partners are restricted to the cytoplasm.[18]