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The spectrum of lymphoblastic, nodal and extranodal T-cell lymphomas: characteristic features and diagnostic dilemmas

Natasha M. Savage MD*, Ryan C. Johnson MD, Yasodha Natkunam MD, PhD

Department of Pathology, L235, Stanford University School of Medicine, 300 Pasteur Dri, Stanford, CA 94305-5324, USA

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Summary T-cell lymphomas represent a heterogeneous group of neoplasms that encompass considerable clinical, morphologic, and immunophenotypic variation. The diagnosis of T-cell lymphoma is challenging because of its relative rarity, the lack of an immunophenotypic marker of clonality, and significant morphologic overlap with infectious/inflammatory processes and neoplasms, including Hodgkin and other non–Hodgkin lymphomas, and even mesenchymal or epithelial lesions. In the current World Health Organization classification of hematopoietic tumors, all except 1 subtype (ie, T-lymphoblastic lymphoma) are recognized as mature neoplasms derived from postthymic T cells. In addition to T-lymphoblastic lymphoma, this review will focus on nodal and extranodal T-cell lymphomas and exclude T-cell lymphomas presenting primarily in the skin. Extranodal natural-killer-cell/T-cell lymphoma, nasal type, will also be discussed because the derivation of this lymphoma from natural killer and natural killer–like T cells shows morphologic and immunophenotypic features that overlap with other T-cell lymphomas. In this review, we discuss the salient clinicopathologic, immunophenotypic, and genetic features, as well as our approaches to the diagnosis of lymphoblastic, nodal, and extranodal T-cell lymphomas.

1. Introduction

The 2008 *World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues* made several important updates to the classification of T-cell and natural killer (NK) cell neoplasms [1]. Unfortunately, because of their relative rarity, our understanding of these entities remains woefully insufficient in comparison with B-cell lymphomas. Nonetheless, recent progress in basic and clinical research has not only improved our knowledge of clinicopathologic features of this category of neoplasms but also furnished important molecules amenable for targeted therapy and better patient outcomes.

The WHO recognizes 1 immature T-cell neoplasm (derived from thymic T cells), T-lymphoblastic lymphoma (T-LBL), and many mature noncutaneous T-cell lymphomas (Table 1). Of these lymphomas, peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS), is the most heterogeneous type, and its diagnosis is considered one of the exclusions, after other subtypes of T-cell lymphomas are excluded during a diagnostic workup. Although many T-cell lymphomas have poor prognoses, few including T-LBL, anaplastic large cell lymphoma (ALCL; anaplastic lymphoma kinase [ALK] positive), and subcutaneous panniculitis-like T-cell lymphoma (SPTCL) have significantly better

* Corresponding author.
E-mail address: nsavage@stanford.edu (N. M. Savage).

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prognoses. In addition, some T-cell lymphomas have well-established therapeutic regimens. Therefore, accurate diagnosis and subclassification of these T-cell lymphomas are of utmost importance for therapeutic and prognostic purposes.

Although accurate diagnosis is critical, this task is often more difficult in T-cell neoplasms than in other malignancies for a number of reasons: (1) their rarity limits familiarity with clinical symptoms and diagnostic expertise; (2) although some patients may initially present with vague or nonspecific symptoms, others may present with acute deterioration secondary to hemophagocytic syndrome, which may cause difficulty in obtaining adequate samples in these fragile patients and may mask the underlying lymphoma if the hemophagocytosis is particularly marked; (3) morphology may be obscured due to a frequently coexistent mixed inflammatory infiltrate, which may result in a reactive appearance, and therefore, a subtle paracortical expansion or an intrasinusoidal pattern of spread may be missed even by an experienced pathologist; (4) T-cell neoplasms may induce an immunodeficiency-like state resulting in a concomitant B-cell proliferation (particularly in angioimmunoblastic T-cell lymphoma [AITL]).

Immunohistochemistry can help resolve challenging cases but may, at times, further confound the diagnosis. First, staining of intermixed benign lymphocytes may obscure the infrequent neoplastic cells. Second, as mentioned previously, associated B-cell proliferations with appropriate immunohistochemistry may obscure the underlying T-cell lymphoma; a subset of these cases may even (not surprisingly) demonstrate findings of both T-cell and B-cell clonality on polymerase chain reaction (PCR)–based studies. Third, T-cell lymphomas can have occasional CD30-positive cells, mimicking Hodgkin lymphoma, especially when a subset of these cases also show rare CD15-positive cells. Some T-cell neoplasms, especially ALCLs, will have a null cell phenotype requiring extensive staining to substantiate a T-cell lineage. CD20, a typical pan–B-cell marker, is expressed in a small subpopulation of benign T cells and may give rise to aberrant expression of a B-lineage marker on neoplastic T cells (eg, CD3/CD20 positive), causing a diagnostic dilemma with a B-cell neoplasm, typically large B-cell lymphoma. Finally, nuanced panels of rarely used T-cell lymphoma markers such as programmed death-1 (PD-1) and C-X-C motif chemokine 13 may not be readily available at smaller institutions, which necessitates that expert opinions be sought at referral centers.

Flow cytometry may also cause diagnostic dilemmas. Unlike B-cell lymphomas where a well-established marker of clonality exists (ie, restricted expression of immunoglobulin light chains), a similar flow cytometric marker is not routinely available for T-cell neoplasms. In addition, findings commonly associated with malignancy, such as loss of CD7, may also be seen in reactive/infectious conditions. Therefore, flow cytometric and immunohistochemical findings must be interpreted with caution, and markers must be used in appropriate permutations and assessed in the context of morphologic findings.

Finally, because T-cell lymphomas are relatively rare and many pathologists have limited experience with these cases, this lack of exposure may be the largest contributor of misdiagnosis in T-cell neoplasms. Therefore, in this review, we address common pitfalls in diagnosis as well as morphologic mimics of T-cell neoplasms.

2. T-lymphoblastic lymphoma

T-LBL is a neoplasm of lymphoblasts that are committed to the T-cell lineage with a proposed normal counterpart of T-cell progenitor cells or thymic lymphocytes [1]. The distinction between T-lymphoblastic leukemia and T-LBL is solely based on site(s) of involvement. Pure T-lymphoblastic leukemia presenting without a lymphomatous component is quite rare and, thus, will not be discussed further. The morphologic and immunophenotypic findings of the 2 entities are otherwise quite similar, although some differences in gene expression have been reported [1,2]. T-LBL accounts for one third of cases of non–Hodgkin lymphoma in childhood, with adolescent males being the most frequently affected. The most common sites of involvement include mediastinal (thymic), lymph nodes, soft tissue, skin, tonsil, liver, spleen, central nervous system, and testes [1]. Typically, thymic, mediastinal, or nodal involvement is often evident at initial diagnosis. Mediastinal involvement can often lead to adjacent compression of the airway as well as pulmonary effusions causing respiratory compromise at presentation.

T-LBL morphology is variable but is generally composed of medium-sized cells with high nuclear/cytoplasmic ratios, round to irregular nuclear contours, fine (immature) chromatin, and prominent nucleoli (Fig. 1). Occasional deceptive cases may demonstrate more mature morphology similar to that of mature non–Hodgkin lymphomas (Fig. 1). Mitotic figures are typically numerous. In a lymph node, the architecture is usually diffusely effaced in a sheetlike pattern; however, partial paracortical involvement may occur.

Table 1 Noncutaneous T-cell lymphomas recognized by the 2008 WHO

T-LBL
PTCL, NOS
AITL
ALCL, ALK+
ALCL, ALK−
Adult T-cell lymphoma
Extranodal NK-cell/T-cell lymphoma, nasal type
EATL
HSTL
SPTCL
EBV-positive T-cell lymphoproliferative diseases of childhood
(*a*) Systemic EBV-positive T-cell lymphoproliferative disease of childhood.
(*b*) HVLL