Diagnosis of NK and cytotoxic T-cell disorders: a review

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Abstract

A number of NK- and T-cell lymphomas with diverse clinical, histologic, and immunophenotypic features express one or more cytotoxic markers. Because these lymphomas are rare they can be challenging to diagnose for clinicians and pathologists. Though the common theme among the neoplasms discussed in this review is expression of one or more cytotoxic markers, expression of other markers such as cytoplasmic CD3, EBV-associated molecules, CD56, and CD30 tend to provide more important clues to the correct diagnosis. In this review, we discuss NK- and T-cell lymphomas and highlight certain key features that can aid in arriving at the correct diagnosis of these malignancies.

Keywords cytotoxic; EBV; lymphoma; NK cells; T cells

Background

Lymphomas with cytotoxic T-cell or natural killer (NK)-cell phenotypes are rare neoplasms that express one or more cytotoxic markers (e.g. TIA1, granzyme B, or perforin). As is common with rare entities, the precise diagnostic classification of these lymphomas is challenging but improving at a rapid pace due to the ongoing efforts of numerous investigators and technological advances. The aim of this review is to provide a useful resource to guide the practicing pathologist in navigating cases in which cytotoxic NK or T-cell lymphomas enters into the differential diagnosis. In the time since previous reviews of this topic were published, several studies provided novel clinical, histologic, and molecular insight into these diseases and provided have further justification for classification of these entities. The classification system used is that of the revised 4th Edition of the World Health Organization (WHO 2016) Classification of Tumours of Haematopoietic and Lymphoid Tissues.[1] In the WHO classification, cytotoxic NK and T-cell disorders fall under the "Mature T- and NK-cell neoplasms" chapter, which also includes entities that do not typically express cytotoxic markers. Table 1 provides an overview of the entities included in the review and mentions other cytotoxic NK and T-cell disorders that are not covered in this review. Additionally we do not discuss detailed T-cell and NK-cell development or their normal physiologic function as these topics have been extensively reviewed elsewhere.[2] In addition, discussion of certain features that provide insight into the cell of origin, such as TCRαβ or TCRγδ expression, are only discussed if they provide diagnostically useful information. Schematics provided in Figures 1–3 provide useful guides that may aid in understanding how to distinguish these different entities.

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T-cell large granular lymphocyte leukemia

When a patient presents with persistent unexplained neutropenia or severe anemia, the possibility of T-large granular lymphocyte leukemia (T-LGLL) should be entertained. Though the WHO definition of this entity requires a persistent (>6 months) increase in the number of peripheral blood large granular lymphocytes (LGLs), there is not a clear lower limit for the number of circulating LGLs that are necessary for the diagnosis. Patients with T-LGLL usually have a LGL count of $>2 \times 10^9$/L, but a subset of true T-LGLL cases may have LGL counts of $<2 \times 10^9$/L.[3] In the cases that meet all other criteria for T-LGLL but have low LGL counts, close monitoring of LGL counts may be a reasonable management strategy. In addition to identifying circulating LGLs, a clue to the diagnosis may come from an initial CD3 stain performed on a bone marrow biopsy. If there are numerous CD3-positive cells in the bone marrow of a patient with peripheral cytopenias (especially neutropenia), a second round of staining with CD8 and at least two cytotoxic markers such as TIA-1, granzyme, and/or perforin is warranted. In one study, clusters or linear arrays of eight intrasinusoidal CD8-positive or six TIA-1- or granzyme-positive cells were found in approximately 80% of cases of rigorously classified LGL leukemia.[4] In contrast, such clusters or linear arrays are found in only 10–20% (depending on the marker) of patients with reactive causes of large granular lymphocyte proliferation. One important differential diagnostic consideration is hepatosplenic T-cell lymphoma, which typically exhibits more prominent sinusoidal expansion in the bone marrow and can usually be distinguished from T-LGLL based on immunophenotypic and cytogenetic studies (Figure 1). T-LGLL is frequently associated with autoimmune disorders, and this can make it difficult to distinguish from T-LGLL from reactive LGL proliferations such as can be seen in Felty syndrome in the setting of rheumatoid arthritis. The observation that approximately one third of T-LGLL have *STAT3* mutations[5,6] and approximately 10% have *STAT5B*[7] mutations provides molecular abnormalities that may aid in the distinction of T-LGLL from reactive LGL proliferations.

Chronic lymphoproliferative disorder of NK cells (provisional entity)

Chronic lymphoproliferative disorder of NK cells (CLPD-NK) is a provisional entity characterized by a persistent (>6 month) increase in the peripheral blood NK-cell count (usually $>2 \times 10^9$/L). Similar to T-LGLL, patients may present with cytopenias (mainly neutropenia and anemia), but most patients are asymptomatic. The clinical and morphologic features are similar to those of T-LGLL, but the clonal cells in CLPD-NK have an immunophenotype characterized by absence of surface CD3 and expression of cytoplasmic CD3, CD16, and weak CD56. In addition, unlike T-LGLL, CLPD-NK does not have rearrangements of the T-cell receptor genes and thus clonality must be established

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WHO 2016 Mature T- and NK-cell lymphomas with cytotoxic phenotype

T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells (provisional entity)
Aggressive NK-cell leukemia
EBV-positive T-cell and NK-cell lymphoproliferative diseases of childhood
- Systemic EBV-positive T-cell lymphoma of childhood
- Chronic active EBV infection of T- and NK-cell type, systemic form
- Hydroa vacciniforme-like lymphoproliferative disorder
- Severe mosquito bite allergy

Extranodal NK/T-cell lymphoma, nasal type
Intestinal T-cell lymphoma
- Enteropathy-associated T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma
- Intestinal T-cell lymphoma, NOS

Indolent NK/T-cell lymphoproliferative disorder of the gastrointestinal tract (provisional entity)
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
ALK-positive anaplastic large cell lymphoma
ALK-negative anaplastic large cell lymphoma
Peripheral T-cell lymphoma, NOS (ones with a cytotoxic phenotype)
Entities not discussed in this review:
- Primary cutaneous CD30+ T-cell lymphoproliferative disorders
- Primary cutaneous γδ T-cell lymphoma
- Primary cutaneous CD8 + aggressive epidermotropic cytotoxic T-cell lymphoma (provisional entity)
- Primary cutaneous acral CD8-positive T-cell lymphoma

Table 1

by other methods such as by demonstration of restricted or absent expression of killer-cell immunoglobulin-like receptors (KIRs). Like in T-LGLL, approximately 30% of CLPD-NK cases have *STAT3* SH2 domain mutations, the detection of which excludes a non-neoplastic NK-cell proliferation.[8]

Hepatosplenic T-cell lymphoma

Hepatosplenic T-cell lymphoma is a neoplasm of cytotoxic T-cells that involves the spleen, liver, and bone marrow. Patients present with hepatosplenomegaly and systemic symptoms and frequently have severe thrombocytopenia as well as anemia and leukopenia. The neoplastic T-cells are medium in size and fill and expand the splenic cords and sinusoids as well as the sinusoids in the liver and bone marrow. It usually expresses TCRγδ but αβ expression is also seen and does not exclude the diagnosis. Almost all patients have bone marrow involvement. One major differential diagnosis to consider together with HSTL is T-LGLL, which usually expresses TCRαβ and only infrequently expresses TCRγδ (Figure 1). T-LGLL more frequently circulates in the peripheral blood, while HSTL usually only involves the peripheral blood late in the disease course. The neoplastic cells of T-LGLL usually infiltrate in an interstitial pattern rather than the more prominent sinusoidal pattern seen in HSTL. In contrast to T-LGLL, which typically expresses CD8, only rare cases of HSTL express CD8 and all HSTL are CD4-negative. Most HSTLs express CD56 but are negative for CD57. T-LGLLs usually express CD57 and only express CD56 in approximately 20% of cases. One cytogenetic abnormality that may be useful in diagnostically challenging cases is isochromosome 7q, which is found in approximately half of HSTLs and is not found in cases of T-LGLL expressing TCRγδ.[9] Mutations in *STAT5B* and *STAT3* are found in approximately 33% and 10%, respectively, of HSTL cases.[10] *STAT3* is also mutated in a significant number of T-LGLL

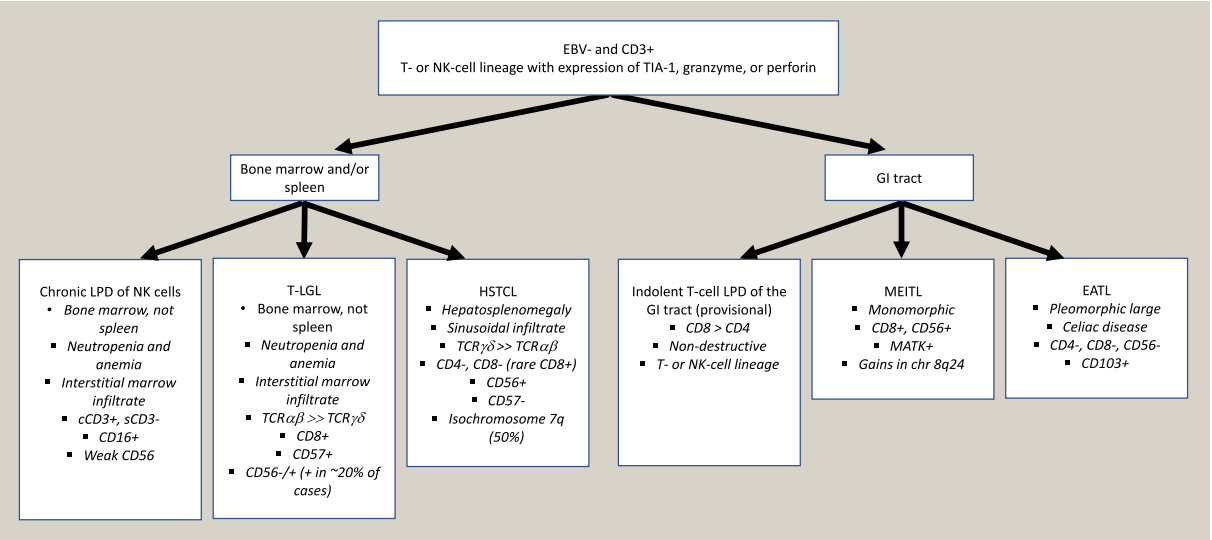

Figure 1 EBV-negative cytotoxic NK- and T-cell proliferations. This figure provides an overview of the EBV-negative cytotoxic NK- and T-cell proliferations and highlights features that can be helpful in arriving at the diagnosis depending on the site(s) of involvement. T-LGL = T-large granular lymphocyte leukemia, HSTCL = hepatosplenic T-cell lymphoma, MEITL = monomorphic epitheliotropic intestinal T-cell lymphoma, EATL = enteropathy associated T-cell lymphoma, LPD = lymphoproliferative disorder.

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