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## T-cell and natural killer-cell lymphomas An update based on the 2008 WHO classification



A B S T R A C T

Mature T-cell and NK-cell neoplasms are relatively uncommon, accounting for less than 10% of all non-Hodgkin's lymphomas on a worldwide basis. The most common subtypes of mature T-cell lymphomas are peripheral T-cell lymphoma, unspecified (PTCL-U) and anaplastic large cell lymphoma (ALCL), ALK<sup>+</sup>. T-cell and NK-cell lymphomas show significant variations in incidence in different geographical regions and racial populations; relative incidence figures are also influenced by variations in B-cell lymphoma prevalence.

Functional approaches to the classification of T-cell lymphomas relate the tumor cells to the innate or adaptive arms of the immune system. The adaptive immune system is functionally complex and includes naïve, effector (regulatory and cytotoxic), and memory T-cells. CD4<sup>+</sup> T-cells are primarily regulatory, acting via cytokine production, while CD8<sup>+</sup> (and double negative) T-cells are primarily cytotoxic. Most lymphomas of the adaptive immune system are nodally-based and occur in adults. The innate immune system is a more primitive type of immune response. Lymphomas with these properties are typically extranodal, affecting mucosal associated sites where the innate defense system plays an important role. T-cell lymphomas in children more closely relate to the innate immune system. Recent studies have begun to dissect out the T-cell lymphomas and relate them to specific cell types. For example, angioimmunoblastic T-cell lymphoma (AITL) has features of the TFH cell of the germinal center, which provides help to B-cells. In contrast, the cells of ATLL express markers of Treg cells, which suppress immune reactions. These observations help to explain the clinical features of these lymphoma subtypes. ALCL, ALK<sup>+</sup>, has many unique features, and despite the dedifferentiated appearance and phenotype of the tumor cells, has a relatively good prognosis. Current concepts consider ALCL, ALK<sup>-</sup> to be unrelated to ALCL, ALK<sup>+</sup>, but also distinct from PTCL, unspecified.

### Incidence and epidemiology of T-cell lymphomas

Mature T cell and NK-cell lymphomas are uncommon, accounting for fewer than 10% of all non Hodgkin's Lymphomas, and show significant variations in incidence in different geographical regions and racial populations (Table 1). HTLV-1 accounts for an increased of adult T-cell leukemia/lymphoma (ATLL) risk in regions

where it is endemic, including southwestern Japan and the Caribbean basin. EBV-associated NK-cell and T-cell lymphomas have an increased incidence in Asians, and in individuals of Native American descent in Central and South America, and Mexico. Genetic factors linked to defective surveillance of EBV have been postulated to play a role in these epidemiological differences. High viral load at the time of initial viral infection may be an

**Table 1.** Mature T-cell and NK-cell neoplasms.

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T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukaemia
Chronic lymphoproliferative disorder of NK-cells <sup>^</sup>
Aggressive NK cell leukemia
Systemic EBV <sup>+</sup> T-cell lymphoproliferative disease of childhood (associated with chronic active EBV infection)
Hydroa vacciniforme-like lymphoma
Adult T-cell leukemia/lymphoma
Extranodal NK/T cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis Fungoides
Sézary syndrome
Primary cutaneous CD30 <sup>+</sup> T-cell lymphoproliferative disorders
Primary cutaneous aggressive epidermotropic CD8 positive cytotoxic T-cell lymphoma <sup>^</sup>
Primary cutaneous gamma-delta T-cell lymphoma
Primary cutaneous small/medium CD4 positive T-cell lymphoma <sup>^</sup>
Peripheral T-cell lymphoma, not otherwise specified
Angioimmunoblastic T-cell lymphoma
Anaplastic large cell lymphoma (ALCL), ALK positive
Anaplastic large cell lymphoma (ALCL), ALK negative <sup>^</sup>

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<sup>^</sup> Provisional entities.

additional risk factor.

$\gamma\delta$  PTCLs occur with increased frequency in the setting of immune suppression, especially following organ transplantation, a finding that is not well understood. Overall, the incidence of T-cell and NK-cell malignancies does not appear to be changing, although long term epidemiological data are not available, as it is only recently with modern immunophenotypic and molecular tools that these neoplasms have been reliably distinguished from B-cell lymphomas.

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### Pathophysiology of T-cell subsets

T-cell lymphomas manifest the immunophenotypic features of post-thymic T lymphocytes, being derived from both  $\alpha\beta$  T-cells and  $\gamma\delta$  T-cells.  $\gamma\delta$  T-cells comprise fewer than 5%

of all normal T-cells, and show a restricted distribution, being found mainly in the splenic red pulp, intestinal epithelium, and other epithelial sites. It is notable that these sites are more commonly affected by  $\gamma\delta$  T-cell lymphomas, which otherwise are relatively rare.

$\gamma\delta$  T-cells, along with NK-cells, and NK-like T-cells comprise the innate immune system. Cells of the innate immune system represent a primitive type of immune response, lacking specificity and memory. Many T-cell and NK-cell lymphomas observed commonly in the pediatric and young adult age group are derived from cells of the innate immune system. These include aggressive NK-cell leukemia, systemic EBV-positive T-cell lymphoproliferative disease of childhood, hepatosplenic T-cell lymphoma, and  $\gamma\delta$  T-cell lymphomas affecting muco-cutaneous sites. ALCL is the most common pediatric T-cell lymphoma, and while it is of cytotoxic origin, is negative for granzyme M, and thus, most likely part of the adaptive immune system.

The T-cells of the adaptive immune system are heterogeneous and functionally complex, and include naïve, effector (regulatory and cytotoxic), and memory T-cells. CD4-positive T-cells are primarily regulatory, acting via cytokine production, while CD8-positive (and double negative) T-cells are primarily cytotoxic. Recently much has been learned about a unique T-cell subset found in the normal germinal center. These cells, termed follicular T-helper cells (TFH), provide help to B-cells in the context of the germinal center reaction. They have a unique phenotype, expressing the germinal center-associated markers BCL6 and CD10, normally found on B-cells. TFH express PD-1, CD4, and CD57, and produce the chemokine CXCR13, which interacts with its ligand CXCL5. CXCL13 causes induction and proliferation of follicular dendritic cells, and facilitates the entry of B-cells and T-cells expressing CXCR5 into the lymph node and germinal center.

A CD4<sup>+</sup> T cell with very different properties is the regulatory T cell (Treg), which functions

to shut off and suppress immune responses. This cell is thought to play an important role in preventing autoimmunity. Tregs express high density CD25, and the transcription factor FOXP3, in combination with CD4. Adult T-cell leukaemia/lymphoma (ATLL) has been linked to Treg cells based on expression of both CD25 and FOXP3, and this finding helps to explain the marked immunosuppression associated with ATLL.

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### Classification of T-cell and NK-cell lymphomas

PTCLs show great morphological diversity, and a spectrum of histological appearances can be seen within individual disease entities. The cellular composition can range from small cells with minimal atypia to large cells with anaplastic features. Such a spectrum is seen in ALCL, ATLL, and extranodal NK/T-cell lymphoma, as selected examples. However, cytological atypia does not necessarily correlate with clinical behavior. The molecular pathogenesis for most T-cell lymphomas is as yet undiscovered. For the above reasons, clinical features historically have played a major role in defining many of the specific entities included in the WHO classification.

EBV-positive T-cell and NK-cell neoplasms include a number of distinct disease entities: Aggressive NK-cell leukemia, Systemic EBV-positive T-cell lymphoproliferative disease of childhood, Hydroa vacciniforme-like lymphoma, and extranodal NK/T-cell lymphoma, nasal type. Systemic EBV-positive T-cell lymphoproliferative disease of childhood and Hydroa vacciniforme-like lymphoma are newly listed in the WHO classification of 2008. They are primarily diseases of childhood, and are often seen in the setting of chronic active EBV infection (CAEBV).

While CAEBV was first described as a persistent EBV infection targeting B cells, the syndrome has come over the years to be primarily associated with EBV infection of T cells, and less often NK cells. It has a strong racial

predisposition, with most cases occurring in Japan and Korea, and some cases in Native American populations in the Western hemisphere from Mexico, Peru, and Central America. It is rare in Caucasians and African Americans. These epidemiological features are shared by all of the EBV-positive T-cell and NK-cell lymphoproliferative disorders. The term T/NK-cell CAEBV has been used in the literature to encompass a very broad spectrum of disease, including a systemic form which may be polyclonal; fulminant and systemic EBV-positive T-cell LPDs that are clonal; hydroa vacciniforme (HV) of T-cell derivation; and severe mosquito bite allergy, usually of NK-cell origin. The 2008 WHO classification has recognized the following disease entities that are considered neoplasms: systemic EBV-positive T-cell LPD of childhood (a clonal T-cell LPD) and hydroa vacciniforme-like T-cell lymphoma.

In systemic EBV-positive T-cell LPD of childhood patients present with acute onset of fever suggestive of an acute viral respiratory illness. Within a period of weeks patients develop hepatosplenomegaly and liver failure, sometimes accompanied by lymphadenopathy. Laboratory tests showed pancytopenia, abnormal liver function tests and often an abnormal EBV serology with low or absent anti-VCA IgM antibodies. The disease is usually complicated by hemophagocytic syndrome, coagulopathy, multiorgan failure and sepsis. The clinical course is aggressive, with a median survival of less than one year. The infiltrating T cells are usually small and lacked significant cytologic atypia. However, cases with pleomorphic medium-sized to large lymphoid cells with irregular nuclei and frequent mitoses may be seen. The liver and spleen show mild to marked sinusoidal infiltration with striking hemophagocytosis. Bone marrow biopsies show histiocytic hyperplasia with prominent erythrophagocytosis. The cells have a cytotoxic T-cell immunophenotype, CD8 > CD4, with positivity for TIA-1. All cases studied have been monoclonal for TCR genes, and on this

basis as well as the poor clinical outcome, the process has been considered to represent a form of mature T-cell malignancy in the 2008 WHO classification.

Hydroa vacciniforme-like lymphoma affected patients present with fever and malaise. Lesions most commonly involve sun-exposed areas (face and upper limbs). The disease is exacerbated in the summer season, and may abate during the winter months. Lesions show edema, papules, blisters, crusts, ulcers, and heal as vacciniforme scars. Some patients with HV have eventual resolution of their disease in adult life, whereas other patients develop progressive disease with worsening of cutaneous symptoms and eventual systemic dissemination. In addition, some patients with HV-like symptomatology have severe CAEBV early in the course of the disease. An unanswered issue is the distinction of HV from HV-like T-cell lymphoma, if such a distinction exists. Based on the published experience EBV-positivity and T-cell clonality have been found in both types of cases.

The definition of adult T-cell leukemia/lymphoma (ATLL) is largely unchanged in the 2008 WHO classification. New insights stem from the demonstration of FOXP3 in ATLL cells, which suggests that the cells may be derived from Treg cells. Treg's have a mainly immunosuppressive function, and thus this feature helps to explain the immunodeficiency that is so characteristic of ATLL.

Enteropathy-associated T-cell lymphoma (EATL) occurs in adults, the majority of whom have a history of gluten sensitive enteropathy. Patients usually present with abdominal symptoms such as pain, small bowel perforation, and associated peritonitis. The small bowel usually shows ulceration, frequently with perforation. A mass may or may not be present, and the intestinal involvement is often multifocal. The neoplastic cells infiltrate the overlying epithelium, mimicking normal intraepithelial lymphocytes. In refractory celiac disease and ulcerative jejunitis the intraepithelial lymphocytes share clonal identity with the subsequent

lymphomas developing in these patients. The clinical course is aggressive, with poor long-term survival.

The neoplastic cells in EATL have a wide morphological spectrum. The cells are generally medium to large in size, but in a subset they are markedly anaplastic and strongly CD30-positive. A marked tissue eosinophilia may partially mask the neoplastic population. The cells are  $\alpha\beta$  cytotoxic T-cells mimicking the phenotype of IEL. CD56 positivity is seen in a subset of cases, so-called Type II EATL, in which the cells have a monomorphic appearance, are medium in size, and display marked epitheliotropism of the small intestinal epithelium. This variant of EATL has some distinctive genetic features, and may occur in the absence of enteropathy, as a sporadic T-cell lymphoma. All forms of EATL are negative for EBV.

EATL must be distinguished from other T-cell lymphomas presenting with intestinal disease and not all intestinal T-cell lymphomas are EATL. The intestinal tract is a common site of localization of extranodal NK/T-cell lymphoma, nasal-type, which can be distinguished by its EBV-positivity. Mucocutaneous  $\gamma\delta$  T-cell lymphomas may also present with intestinal disease, and may appear similar both clinically and morphologically. They too are of cytotoxic T-cell derivation, and are associated with extensive apoptosis and necrosis.

Hepatosplenic T-cell lymphoma presents with marked hepatosplenomegaly in the absence of lymphadenopathy. The great majority of cases are of  $\gamma\delta$  T-cell origin, but an  $\alpha\beta$  origin has been seen in a small subset of cases. The clinical presentation is very homogeneous with most cases presenting in young males, 15-30 years of age. Although patients may respond initially to chemotherapy, relapse has been seen in the vast majority of cases, and the median survival is less than 3 years. Rare long-term survival has been seen following allogeneic bone marrow transplantation. Recent studies have identified an increased risk for hepatosplenic T-cell lymphoma in patients

with Crohn's disease receiving anti-tumor necrosis factor (TNF) therapy.

Subcutaneous panniculitis like T cell lymphoma (SPTCL) is defined as a disease of  $\alpha\beta$  T-cells in the 2008 WHO classification. It usually presents with multiple subcutaneous nodules of varying size, primarily affecting the extremities. It shows a broad age distribution and an equal male: female ratio. The neoplastic cells are generally confined to subcutaneous tissue, and frequently show rimming of fat spaces, a helpful feature in the differential diagnosis with benign panniculitis. Dermal and epidermal involvement are generally absent, a feature which helps to distinguish SPTCL from primary cutaneous  $\gamma\delta$  TCL involving subcutaneous tissue. Panniculitis-like features may be seen in both, but SPTCL has a better prognosis. The neoplastic cells express an activated  $\alpha\beta$  CD8<sup>+</sup> cytotoxic T cell phenotype. In addition, the cells are positive for the cytotoxic associated proteins, granzyme B, perforin and TIA 1. These proteins mediate cytotoxicity and apoptosis by T cells and NK cells, and therefore may be responsible for the cellular destruction characteristic of these lesions. Approximately 20% of patients with SPTCL have an underlying autoimmune disease, most commonly lupus erythematosus.

A hemophagocytic syndrome (HPS) may be seen as a complication of SPTCL, but is much more common in panniculitis-like cutaneous lymphomas of  $\gamma\delta$  T-cell origin. Patients present with fever, pancytopenia, and hepatosplenomegaly. The HPS is most readily diagnosed in bone marrow aspirate smears, which demonstrate histiocytes containing phagocytosed erythrocytes and platelets. The HPS usually precipitates a downhill clinical course, and is an adverse prognostic factor. The HPS appears related to cytokine and chemokine production by the malignant cells, perhaps in a setting of comprised cytolytic function.

Primary cutaneous  $\gamma\delta$  TCL is recognized as a distinct entity in the 2008 WHO classification. Patients may present with plaques, nodules or

tumors. Three major histologic patterns of involvement can be present in the skin: epidermotropic, dermal and subcutaneous. Often more than one histologic pattern is present in the same patient in different biopsy specimens or within a single biopsy specimen. Epidermal infiltration may occur as mild epidermotropism to marked pagetoid reticulosis-like infiltrates. The neoplastic cells are generally medium to large in size with coarsely clumped chromatin. Large blastic cells with vesicular nuclei and prominent nucleoli are infrequent. Apoptosis and necrosis are common, often with angioinvasion. As noted above, a panniculitis-like pattern may be seen, often in combination with other histologies.

Two additional provisional entities were included in the 2008 classification: Primary cutaneous aggressive epidermotropic CD8 positive cytotoxic T-cell lymphoma and Primary cutaneous small/medium CD4 positive T-cell lymphoma. The former is clinically aggressive, whereas the latter entity usually presents with localized disease and has a good prognosis. Rare cases with multiple skin lesions have a poorer prognosis.

Other cutaneous lymphomas, mycosis fungoides, Sezary syndrome, and the primary cutaneous CD30<sup>+</sup> T-cell lymphoproliferative disorders (TLPD) are unchanged in the 2008 classification. Most cases of MF and SS are derived from CD4-positive T-cells showing a loss of CD7 and low levels of activation markers such as CD25 and CD30. However, CD8 expression has been reported in some cases of MF that are pathologically and clinically indistinguishable. The hallmark of MF and SS is epidermotropism, but in fact well formed Pautrier microabscesses are seen in only a minority of cases, and in most skin biopsies the diagnosis of early MF rests of other histological and clinical criteria.

Primary cutaneous CD30-TLPD includes a spectrum of conditions ranging from lymphomatoid papulosis (LYP) to primary cutaneous ALCL (C-ALCL). A common feature in all is a CD30-positive, CD4-positive T-cell,

which in C-ALCL can be shown to be clonal. In LYP the atypical cells are in the minority and are associated with a marked inflammatory background. Lesions regress spontaneously, and dissemination never occurs. C-ALCL lies at the opposite end of the spectrum; large atypical CD30-positive cells predominate, regression often occurs without therapy, and spread to lymph nodes may be seen. However, widespread disease is relatively rare. C-ALCL is consistently negative for ALK although systemic ALCL may present with cutaneous disease. Peripheral T-cell lymphoma, unspecified (PTLU) is the most common category of PTL, and by definition is heterogeneous. PTLU is the “diffuse large B-cell” equivalent of PTL. This subtype includes all cases not readily classified as one of the specific entities in the WHO classification. Three morphological variants are delineated as T-zone lymphoma, lymphoepithelioid cell lymphoma, and the follicular variant of PTLU. The follicular variant is newly included in the 2008 classification. In this variant the neoplastic cells arise in and replace follicular structures. The cells have a phenotype similar to that of TFH. They are typically positive for BCL6 and CD10. This variant has been associated with a distinctive chromosomal translocation in some cases, t(5;9).

As a group, PTLUs are aggressive neoplasms, often present with advanced stage, and are seen mainly in older adults. They are most often nodal, but can present with extranodal disease. They may contain a prominent background of inflammatory cells, be composed of a diverse population of pleomorphic tumor cells, or be monomorphic, resembling diffuse large B-cell lymphomas. For these reasons the diagnosis of PTLU should always be based on confirmatory tests using immunophenotypic or genotypic methods. Using gene expression profiling the proliferation signature has been shown to be of prognostic value.

Angioimmunoblastic T-cell lymphoma (AILT) has emerged as a distinctive subtype of PTL with unique pathobiological features.

This disease is seen mainly in elderly adults with an equal male: female ratio. Originally thought to be a form of abnormal immune response, most patients present with generalized lymphadenopathy, hepatosplenomegaly, skin rash, and marked constitutional symptoms. Polyclonal hypergammaglobulinemia is an almost constant finding and the lymph nodes usually contain polyclonal plasma cells, as well as frequent large B immunoblasts, despite the absence of well-formed follicles with germinal centers. EBV-negative clonal B-cell proliferations also have been reported in AILT. The neoplastic T-cells have clear cytoplasm, and are distributed in a marked inflammatory background. Other features include prominent arborizing high endothelial venules (HEV) and expansion of dendritic meshworks outside the follicle, usually arising from the prominent HEV. The neoplastic T-cells are CD4-positive T-cells that express CD10, PD-1 and sometimes BCL6, features that support an origin from germinal center based T-cells (T<sub>FH</sub>).

Most recently investigators have identified increased expression of CXCL13 in AILT, a finding that helps to link together many of these clinical and pathological features. CXCL13 is associated with expansion of follicular dendritic cells, and facilitates the entry of B-cells into the lymph node, thus helping to clarify the B-cell expansion characteristic of this disease.

Another almost constant finding in AILT is the presence of EBV-positive B-cells. It has been postulated that this finding is secondary to decreased immune surveillance and reactivation of EBV in the setting of a compromised immune system. However, EBV-positive B-cells are found even very early in the course of the disease. In some cases this phenomenon progresses to an EBV-positive B-cell lymphoproliferative disorder resembling post-transplant polymorphic B-cell lymphoma. In other instances the EBV-positive B-cells may resemble Reed-Sternberg cells, leading to an erroneous diagnosis of classical Hodgkin's lym-

phoma. Anaplastic large cell lymphoma (ALCL) is the most common single subtype of PTCL. It is most often nodal, but can present in a variety of extranodal sites. It is most common in children and young adults, but can present at any age. The WHO originally included cases of ALCL positive and negative for the ALCL-associated tyrosinase kinase (ALK) under the heading of ALCL, but ALK-negative cases differ in a number of respects, being seen in an older age group, having a worse prognosis, and generally showing greater nuclear pleomorphism. These findings suggest that ALK-negative ALCL is a separate entity, and ALCL-ALK negative is included in the 2008 classification as a provisional entity. Thus, the diagnostic evaluation of ALCL should always include studies for ALK protein. Besides strong expression of CD30, ALCL are positive for cytotoxic markers, and interestingly often lack CD3, with inconsistent expression of other T-cell associated antigens. These features should be considered in the diagnosis of ALCL, ALK-negative. As CD30 expression is common in many B-cell and T-cell lymphomas, CD30 alone is insufficient.

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