T-cell and NK-cell Lymphomas – An update based on the 2008 WHO Classification

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Bullet Points

• T-cell and NK-cell lymphomas and leukemias are diverse, and in general are more aggressive than B-cell LPD’s.
• The T-cell and NK-cell LPD’s can be related to the innate and adaptive immune systems.
• Tumors of the adaptive immune system are primarily nodal, whereas those of the innate immune system are generally extranodal or systemic (involving bone marrow, liver and spleen).
• EBV + T-cell and NK-cell LPD’s have distinctive epidemiological features.

Key Words
Peripheral T-cell lymphoma, T-zone lymphoma, follicular T-cell lymphoma, anaplastic large cell lymphoma, Epstein Barr virus, celiac disease, chronic active EBV infection

Introduction
Mature T-cell and NK-cell lymphomas are uncommon, accounting for fewer than 10% of all non-Hodgkin's Lymphomas (Table). Functionally, T-cell lymphomas are related to the two major arms of the immune system, the innate and adaptive immune systems. NK-cells and T-cells of the innate immune system recognize antigen in the absence of MHC antigens, and are involved in mucosal immunity. The lymphomas derived from these cells often involve cutaneous and mucosal sites. The expression of cytotoxic molecules in these lymphomas may predispose to apoptosis by tumor cells and normal bystander cells. Hepatosplenic T-cell lymphoma is a systemic disease derived from functionally immature innate effector cells, most often of γδ T-
cell origin. In contrast most nodal T-cell lymphomas belong to the adaptive immune system. Angioimmunoblastic T-cell lymphoma (AILT) is derived from follicular helper T-cells (T<sub>FH</sub>), a finding that explains many of its pathological and clinical features.

The most common subtypes of mature T-cell lymphomas are peripheral T-cell lymphoma, unspecified (PTLU) and anaplastic large cell lymphoma (ALCL). T-cell and NK-cell lymphomas show significant variations in incidence in different geographical regions and racial populations. For example, T/NK-cell lymphomas comprise a higher proportion of non-Hodgkin lymphoma in Asian populations. These differences result from both a true increased incidence, as well as a relative decrease in the frequency of many B-cell lymphomas, such as follicular lymphoma, seen commonly in North America and Europe. 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.

Another major factor affecting the incidence of T-cell and NK-cell lymphomas is racial predisposition. Extranodal NK-cell lymphomas, nasal-type and aggressive NK-cell leukemia are much more common in Asians than they are in other races. Other groups at increased risk for these EBV-associated diseases are individuals of Native American descent in Central and South America, and Mexico. Other rare EBV-positive lymphomas derived from T-cells showing a similar racial and geographic distribution include systemic EBV-positive T-cell lymphoproliferative disorder, which has overlapping features with severe chronic active EBV-infection, and Hydroa vacciniforme-like lymphoma, a form of EBV-positive T-cell or NK-cell lymphoma seen mainly in children. 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 additional risk factor.

γδ 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.

**Pathophysiology of T-cell subsets**

T-cell lymphomas manifest the immunophenotypic features of post-thymic T lymphocytes, being derived from both αβ T-cells and γδ T-cells. This distinction is based on the structure of the T-cell receptor. Gamma-delta T-cells, along with NK-cells are components of the innate immune system, and do not require antigen sensitization to be active. The innate immune system is functional based only on genes encoded in the host genome. It is distinguished from the adaptive or antigen-specific immune system; most T-cells in peripheral blood and peripheral lymphoid organs belong to the latter.

γδ 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 γδ T-cell lymphomas, which otherwise are relatively rare. Gamma-delta T-cells are not MHC restricted in their function, and represent a
first line of defense against bacterial peptides, such as heat shock proteins. They are often involved in responses to mycobacterial infections, and both mucosal and cutaneous immunity.

Cells of the innate immune system represent a first line of defense, a more primitive type of immune response. It is interesting that 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 ($T_{FH}$), 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. $T_{FH}$ 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+ 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.

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. Muco-cutaneous γδ 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 γδ T-cell origin, but an αβ 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.

The liver and spleen show marked sinusoidal infiltration, with sparing of both portal triads and white pulp, respectively. Abnormal cells are usually present in the sinusoids of the bone marrow but may be difficult to identify without immunohistochemical stains. The neoplastic cells have a phenotype that resembles that of immature or resting γδ T-cells, often double-negative for CD4 and CD8, and negative for CD5; CD56 is also positive. The cells express the cytotoxic granule associated protein, TIA-1, but are generally negative for perforin and granzyme B. Isochromosome 7q is a consistent cytogenetic abnormality, usually in association with trisomy 8.
Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is defined as a disease of αβ 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 γδ TCL involving subcutaneous tissue. Panniculitis-like features may be seen in both, but SPTCL has a better prognosis. The neoplastic cells express an activated αβ CD8+ 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 γδ 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 γδ 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+ 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 T_{FH}. 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_{FH}).
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 lymphoma.

**Anaplastic large cell lymphoma (ALCL)**

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.

Cytologically a number of histological variants have been identified, including the small cell and lymphohistiocytic subtypes. These two are closely related, occur mostly in children, and histologically contain a variable component of histiocytes with homogeneous granular eosinophilic cytoplasm. Misdiagnosis as a chronic inflammatory process, or PTLU is a pitfall in diagnosis. Some ALCL have prominent spindle cells in a myxoid stroma. Because ALCL can present as a soft tissue or bone mass, this variant of ALCL may simulate a soft tissue sarcoma or primary bone tumor. Hodgkin’s-like ALCL has proven to be an aggressive variant of classical Hodgkin’s lymphoma in most instances, and shows overlap with mediastinal grey zone lymphomas. These cases present mostly in young males, with a mediastinal mass, and have a prognosis worse than either classical Hodgkin’s lymphoma or primary mediastinal large B-cell lymphoma.
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<th>Table: Mature T-cell and NK-Cell Neoplasms</th>
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<td>T-cell prolymphocytic leukemia</td>
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<td>T-cell large granular lymphocytic leukaemia</td>
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<td>Chronic lymphoproliferative disorder of NK-cells^</td>
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<td>Mycosis Fungoides</td>
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<td>Primary cutaneous gamma-delta T-cell lymphoma</td>
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<td>Primary cutaneous small/medium CD4 positive T-cell lymphoma^</td>
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<td>Peripheral T-cell lymphoma, not otherwise specified</td>
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<td>Angioimmunoblastic T-cell lymphoma</td>
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<td>Anaplastic large cell lymphoma (ALCL), ALK positive</td>
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<td>Anaplastic large cell lymphoma (ALCL), ALK negative^</td>
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^ Provisional entities
References:


Peripheral T-cell & NK-cell Lymphomas
Updates based on the 2008 WHO classification
Mature T-cell And NK-cell Neoplasms (2008)

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukaemia
- *Chronic lymphoproliferative disorder of NK-cells*
- Aggressive NK cell leukemia
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma, *ALK* positive
- *Anaplastic large cell lymphoma, ALK negative*
- Adult T-cell leukemia/lymphoma
- Extranodal NK/T cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Systemic EBV positive T-cell lymphoproliferative disease of childhood
- Hydroa vacciniforme-like lymphoma

*Provisional entities*
Mature T-cell And NK-cell Neoplasms - Cutaneous

Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30 positive T-cell lymphoproliferative disorders
  Lymphomatoid papulosis
  Primary cutaneous anaplastic large cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Primary cutaneous gamma-delta T-cell lymphoma
*Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma*
*Primary cutaneous CD4 positive small/medium T-cell lymphoma*
Peripheral T-cell Lymphoma - NOS 25.9%
Angioimmunoblastic 18.5%
Natural killer/T-cell lymphoma 10.4%
Adult T-cell leukemia/lymphoma 9.6%
Anaplastic large cell lymphoma, ALK+ 6.6%
Anaplastic large cell lymphoma, ALK- 5.5%
Enteropathy-type T-cell 4.7%
Primary cutaneous ALCL 1.7%
Hepatosplenic T-cell 1.4%
Subcutaneous panniculitis-like 0.9%
Unclassifiable PTCL 2.5%
Other disorders 12.2%

Vose et al. International T-cell lymphoma project
Innate Immune System

- γδ T-cells, NK-like T-cells, NK-cells
- Toll like receptors
- Not MHC restricted
- Cytokines, Chemokines, Complement
- Apoptotic & necrotic cell death pathways
- First line of defense with a major role in barrier immunity

Adaptive Immune System

- Ag specific receptors on B + T-cells
- Antigen presentation to T-cells in the context of MHC
- Immunological defense characterized by specificity & memory
Adaptive Immune System

Much more functionally complex
Includes naïve, memory, and effector T-cells
  – Both regulatory and cytotoxic
CD4+ T-cells are primarily regulatory
  – Act via cytokine/chemokine production
  – Include $T_{FH}$ of GC
CD8+ T-cells are primarily cytotoxic
Lymphomas of the Adaptive Immune System

- Lymphomas of adults >> children
- Lymphomas primary in peripheral lymph nodes >> extranodal sites
- Clinically aggressive
- Morphologically diverse
Nodal Peripheral T-cell Lymphomas

NODAL
PTL, NOS

AILT

PTL variants
T-zone/
Parafollicular
Follicular

PTL variant
Lymphoepithelioid
Cell

CD 4+ CD25 -

CD8+, Epithelioid cells
Peripheral T-cell Lymphoma, Unspecified

A diagnosis of exclusion, by definition a heterogeneous category
Characterized by a broad morphologic spectrum
  T-zone
  Lymphoepithelioid
  Follicular
The “diffuse large B-cell lymphoma” of the PTLs
Mainly nodal lymphomas, generally associated with an aggressive clinical course
T-zone variant of PTCL, NOS
Abnormal karyotype & Clonality by PCR help confirm the diagnosis.

Biphasic pattern for CD5
Follicular Variant of PTCL

de Leval AJSP 2001

- Intrafollicular T-cell lymphomas derived from $T_{FH}$ cells
- Usually CD4+, BCL-6+, CD10+
- Clusters of clear cells within GCs
- May simulate follicular lymphoma
- Lack typical clinical findings of AILT

High incidence of t(5;9)(q33;q22) resulting in fusion of ITK and SYK (Streubel et al, Leukemia, 2006)
Peripheral T-cell lymphoma Vs. Hodgkin’s Lymphoma
Is there a T-cell form of Hodgkin’s Lymphoma?

- > 99% of cases of classical Hodgkin’s lymphoma show phenotypic (PAX-5) or genotypic evidence (IgH genes) of B-cell derivation
- Rare cases of “CHL of T-cell derivation” have been reported
  - Seitz et al. Blood 2003 (2 cases)
  - Muschen et al. J Exp. Med. (2 cases)
Is there a T-cell form of Hodgkin’s Lymphoma? – Probably not

- Some cases of CHL express T-cell ags but lack TCR gene rearrangement *(Tzankov et al)*
  - Aberrant expression of CD4, CD2, CD3
  - RS cells are genotypically B
- Some T-cell lymphomas may simulate CHL and express both CD30 and CD15 *(Barry et al.)*
  - Clinically more closely related to PTCL, nos
Hodgkin’s Lymphoma & T-cell Lymphomas

*Morphological - Immunophenotypic*  “Grey Zones”

- Classical Hodgkin’s Lymphoma
- Peripheral T-cell Lymphoma
- Anaplastic Large Cell Lymphoma
Hodgkin’s Lymphoma & T-cell Lymphomas
- not Biological “Grey Zones”

- Classical Hodgkin’s Lymphoma
- Peripheral T-cell Lymphoma
- Anaplastic Large Cell Lymphoma
Anaplastic Large Cell Lymphoma
ALK+ & ALK-
Overall survival of ALK-positive and negative patients

ALK1+
n= 215

ALK1-
n= 28

P = 0.001

G Delsol
Anaplastic large cell lymphoma - ALK neg
Provisional Entity

Should be similar to ALK+ in terms of morphology, phenotype & genotype

Should be negative for both PAX5 and CD 15

CD30
Angioimmunoblastic T-cell Lymphoma

is a disease of germinal center
derived T-cells ($T_{FH}$ cell)

CD3+, CD10+, BCL6 +/−, PD-1+, CXCL13

EBV pos and neg
B-cells
CD21 dendritic cells
Plasma cells
Angioimmunoblastic T-Cell Lymphoma

Clinical Features:
- Older adults, generalized lymphadenopathy
- Hepatosplenomegaly
- Skin rash, effusions, fever,
- Polyclonal hypergammaglobulinemia, hemolytic anemia
- Aggressive clinical course, high risk of infectious complications with treatment
- Secondary EBV+ and EBV- B-cell LPD’s reported
CXCL13 expression explains many aspects of AILT pathology

- CXCL 13 causes induction and proliferation of follicular dendritic cells
- CXCL 13 is involved in B-cell recruitment to LN’s and activation of B-cells
  - CXCL13 is required for the adhesion and arrest of B-cells on HEV’s
- Explains expansion of B-cells in a T-cell lymphoma
Model of AILT, Dunleavy et al. 2007

- Germinal Center
- B Cell Recruitment & Activation
- Polyclonal Gammaglobulinemia
- HEV
- Paracortex
- CD21
- TFH Activation
- B7
- EBV
- CD28
- TCR
- CXCL13
- CXCR5
- T_{FH}
- Polyclonal Gammaglobulinemia
Increased B-cells in AILT: EBV+ and EBV-

• EBV+ B-cell blasts in PTL may assume RS-cell morphology and immunophenotype
  – RS-like cells seen in many EBV+ B-cell lymphoproliferations
    • Infectious mononucleosis
    • Methotrexate associated LPD
    • PTLD
• EBV+ RS-like cells described in
  – AILT, ATLL, and PTL-NOS
Diffuse large B-cell lymphomas, EBV+, may arise in the setting of AILT
Persistent questions regarding the role of B-cells in AILT (EBV+/EBV-)

• Does EBV play a fundamental role in AILT-like T-cell lymphomas, or is it merely a passenger, secondary to defective immune surveillance?

• If EBV negative B-cells are passively acquired by chemokine/ cytokine expression, why do they appear so atypical, or evolve to a clonal proliferation in some cases?
Innate Immune System

- \(\gamma\delta\) T-cells, NK-like T-cells, NK-cells
- Toll like receptors
  - Not MHC restricted
- Cytokines
  - Chemokines
  - Complement
- Apoptotic & necrotic cell death pathways
- First line of defense with a major role in barrier immunity

Adaptive Immune System

- B-cell
- T-cell
- APC
- Antigen presentation to T-cells in the context of MHC
- Ag specific receptors on B + T-cells
- Immunological defense characterized by specificity & memory
Innate Immune System

- Does not require antigen sensitization
- Not MHC restricted
- Involved in mucosal and cutaneous immunity - barriers against invasion
- Comprised of NK-cells, NK/T-cells, and $\gamma\delta$ T-cells
- A primitive type of immune response
Pediatric vs. Adult T-cell Lymphomas

- Most pediatric T-cell lymphomas relate to the innate immune system
  - Cytotoxic
  - T-cells and NK-cells
  - Extranodal or systemic (bm, spleen, liver)
- Most adult T-cell lymphomas relate to the adaptive immune system
  - Frequently nodal
Gamma Delta T-cells
Frequency and Distribution

< 5% of mature T-cells
Restricted distribution
  – Splenic red pulp
  – Intestinal epithelium
  – Skin, other epithelial sites
• Sites of involvement of gamma delta T-cell lymphoma reflect those of normal counterparts
Hepatosplenic T-cell lymphoma

- Children and young adults
- Males >> Females
- Immature cytotoxic T-cell ($\gamma\delta > \alpha\beta$)
- Systemic disease
  - Liver, Spleen, BM
  - Aggressive course
Role of Immune Perturbations in γδ T-cell lymphomas (Belhadj, Blood 2003)

- Combination of chronic immune suppression and antigenic stimulation
  - Post solid organ transplant
  - Late occurring, not associated with EBV
- Other chronic immune disorders associated with antigenic stimulation and immune defects
  - Crohn’s disease (mucosal barrier defects), combination of antigenic challenge & secondary immunosuppression
  - SLE, Hodgkin’s, malaria
Primary Cutaneous $\gamma\delta$ T-cell lymphoma

- Mainly adults, Males = Females
- Variety of patterns in the skin
  - Plaques, nodules, tumors
- May be panniculitis-like
  - Must distinguish from subcutaneous panniculitis-like T-cell lymphoma of $\alpha\beta$ origin
- Activated cytotoxic T-cell phenotype
- Clinically aggressive, OS 11%
  - Increased risk of hemophagocytic syndrome
T-cell Lymphoma: Alpha Beta vs. Gamma Delta (all patients)
Survival, $P < 0.0001$

* Alpha Beta
  21/71 failed

o Gamma Delta
  24/33 failed

Toro et al Blood 2003
Clinical Spectrum of Cutaneous $\gamma\delta$ T-cell lymphomas
Primarily Dermal $\gamma\delta$ T-cell lymphoma
Primary Cutaneous $\gamma\delta$ TCL - “panniculitis-like”

Often both dermal & epidermal involvement
Subcutaneous Panniculitis-like TCL is a disease of $\alpha\beta$ T-cells

- Very broad age range, children & adults
  - Median age 35 yrs, F > M
- Multiple lesions, extremities > trunk
- OS 82% at 5 yrs
  - 91% without HPS; 46% with HPS
- 19% of patients had history of autoimmune disorder
  - SLE, RA, ITP,
- Mature cytotoxic CD8+, EBV negative

WHO/EORTC 2005; Willemze Blood 2008
Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma (Provisional)
Similar to some primary cutaneous $\gamma\delta$ lymphoma
Primary cutaneous CD4 positive small/medium T-cell lymphoma (Provisional)
Enteropathy Associated T-cell Lymphoma (EATL)

- Broad morphological spectrum
  Adjacent mucosa shows villous atrophy
- CD3+, CD103+, Cytotoxic markers, TCR $\alpha\beta$
  often double negative for CD4/CD8, CD56 +/-
- Often presents with intestinal perforation
  aggressive clinical course with poor prognosis
Epidemiology of EATL

- Risk is closely associated with HLA DQ2 & celiac disease, overt or silent
- Largely a European disease
- EBV+ “intestinal T-cell lymphomas” from endemic regions (Mexico, SA, Asia) are primarily nasal-type NK/T-cell lymphomas (Quintanilla-Martinez, 1999)

– And not EATL
Intestinal T-cell Lymphomas

• Not all T-cell or NK-cell lymphomas presenting with intestinal disease are EATL
  – Mucocutaneous gamma-delta TCL
  – Nasal type T/NK-cell lymphoma
  – Anaplastic large cell lymphoma

• All may present as “intestinal T-cell lymphomas”
Most EBV-associated T-cell and NK-cell neoplasms share a similar epidemiology

- Aggressive NK-cell leukemia
- Extranodal NK/T-cell lymphoma, nasal type
- Hydroa vacciniforme-like lymphoma (T>NK)
- Mosquito-bite allergy (NK > T)
- Systemic EBV+ T-cell lymphoproliferative disease of childhood
  - Chronic Active EBV-infection
Systemic EBV+ T-cell LPD of Childhood

Asian or Hispanic children

Acute systemic illness with hemophagocytic syndrome

Follows acute EBV infection high viral loads

EBV+ T-cells are clonal

May follow chronic active EBV infection (CAEBV)

Overlaps with what has been termed severe CAEBV
- Hydroa-vacciniforme-like lymphoma
- Asian or Hispanic children
- Lesions in sun exposed areas
- Chronic course but may progress to acute phase with systemic disease

Cells of T-cells or less often NK cell origin

EBER
Peripheral T-cell & NK-cell Lymphomas (2008)

Peripheral T-cell lymphoma, not otherwise specified
Angioimmunoblastic T-cell lymphoma
Anaplastic large cell lymphoma – **ALK positive**
Anaplastic large cell lymphoma – **ALK negative**
Hepatosplenic T-cell lymphoma
Extranodal NK/Tcell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
**Systemic EBV+ LPD of childhood**
**Hydroa vacciniforme-like lymphoma**
Mycosis fungoides & Sezary syndrome
Primary cutaneous CD30+ T-cell LPD
  LYP and primary cutaneous ALC
Subcutaneous panniculitis-like T-cell lymphoma
  \((\alpha\beta \text{ only})\)
Primary cutaneous \(\gamma\delta\) T-cell lymphoma
Small/med CD4+ cutaneous lymphoma
  (provisional)
Aggressive CD8+ epidermotropic cutaneous T-cell lymphoma (provisional)
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Indolent large granular NK-cell lymphoproliferative disorder (provisional)
Aggressive NK-cell leukemia
Adult T-cell leukemia/lymphoma