Diagnostic challenges in peripheral T-cell lymphomas

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Hematology Education: the education program for the annual congress of the European Hematology Association

2015;9:265-270

A B S T R A C T

Peripheral T-cell and NK-cell lymphomas pose many challenges to clinicians and pathologists due to their relative rarity, their morphological and immunophenotypic complexity and our still limited understanding of their molecular pathogenesis. In general, the pathological manifestations reflect the functional characteristics of the neoplastic cells. However, it is well known that T cells are able to modulate their function in response to multiple stimuli and to the microenvironment. In addition, some newly discovered genetic defects may lead to the constitutive activation of specific pathways with functional consequences for the neoplastic T cells, modifying their original phenotype. Their remarkable physiological plasticity in conjunction with genetic alterations provides a great challenge in the attempt to identify the normal cellular counterpart of these lymphomas and to develop a biologically relevant and clinically useful classification.

Learning goals

At the conclusion of this activity, participants should be able to:
- discuss the principles of the modern classification of lymphoma;
- understand the diagnostic challenges that pathologists face regarding T-cell lymphoma diagnosis;
- discuss the impact of diagnosis on prognosis and management.

Introduction

Peripheral T-cell and NK-cell lymphomas are uncommon and represent less than 15% of all non-Hodgkin lymphomas. Epidemiologically, they are rare in Western populations and slightly more frequent in Asia and Central-South America.[1] Some entities have a unique distribution reflecting either specific viral infections [such as human T-lymphotropic virus-1 (HTLV-I), Epstein-Barr virus (EBV)] or distinct genetic background (celiac disease).

The WHO classification of T- and NK-cell neoplasms relies on a multiparameter approach, which integrates morphology, immunophenotype, genetics, and clinical features of the disease.[2,3] Clinical features play a critical role in the subclassification of these neoplasms, in part reflecting the normal localization and function of T cells. Therefore, T- and NK-cell lymphomas may present as disseminated (leukemic) disease, predominantly extranodal or cutaneous, or predominantly nodal disease (see Table 1).

Nodal lymphomas represent the most common ones; among them peripheral T-cell lymphomas, not otherwise specified (PTCL-NOS) account for approximately 26%, followed by angioimmunoblastic T-cell lymphomas (AITL) (18.5%) and anaplastic large cell lymphomas (ALCL) (12%). Other types are relatively rare, and include extranodal NK-/T-cell lymphoma, nasal type (10%), enteropathy associated (EATL) T-cell lymphoma (5%), hepatosplenic T-cell lymphoma, and subcutaneous panniculitic-like T-cell lymphomas.[1]

In recent years, the widespread use of new technologies (i.e. next generation sequencing, whole exome sequencing, RNA sequencing, etc.) contributed to the identification of a greater number of genetic defects, which in concert with gene expression profiling have led to a more accurate definition of several entities.[4-9] Nevertheless, in T-cell malignancies the "tumor signature" may be difficult to distinguish from the one provided by the reactive cells abundantly present in the microenvironment. For instance, recently expression of Gata3, in conjunction with a Th2 signature and hypereosinophilia has been identified in a subset of PTCL, NOS and found to be associated with an inferior overall survival.[10] However, it was pointed out that the mere presence of Gata3 by immunohistochemistry was neither sufficient nor entirely specific to identify these cases and that the Th2 expression pattern was most likely derived from the surrounding microenvironment rather than from the neoplastic cells. This study pointed out the need to integrate expression prolife data with the morphological and more functional context.

We also recognize the important role played by the identification of biomarkers, which are highly expressed and/or unique to a neoplastic population. They may aid in the identification of the malignant cells and may shed light on their origin and function, like the expression of *PLS3* in Sezary cells.[11,12] A *PLS3*-restricted pattern of expression may be a useful marker to monitor and assess response to therapy in patients with Sezary syndrome.[13]

Numerous studies have also focused on the identification of key signaling and survival pathways in a variety of T-cell lymphomas. Although they may not be specific for a single

disease entity, they may be relevant for the design of targeted therapy.[14-18]

Pathophysiology of T-cell subsets: is it really helpful? Are we getting there?

An understanding of the normal immune system is helpful in classifying lymphomas and it has proven useful and relatively successful in B-cell lymphomas; a similar approach has also been attempted in T-cell and NK-cell lymphomas.[19]

The innate and adaptive immune systems co-operate in an effort to identify and eliminate invading microorganisms and damaged self by activating appropriate immune responses. The innate system represents the first line of defense against foreign pathogens and it is important in barrier immunity (mucosal and skin), providing a rapid, but non-specific response (antigen independent). NK cells are also part of the innate immune system. In contrast, the adaptive arm is antigen dependent; in most instances it requires the presence of class I and II MHC molecules and gives rise to long-lived memory cells. Effective and efficient immune responses depend on the close interaction between the two systems, and γδ T cells and toll-like receptors (TLR) serve as an important link between innate and adaptive responses.

Based on the structure of the T-cell receptor (TCR) that they express, T cells are divided into two major subsets: αβ and γδ T cells. The former, conventional T cells, constitute about 65%-70% of peripheral blood mononuclear cells (PBMCs); they recognize processed peptide antigen in the presence of MHC class I and II, show a broad TCR junctional diversity and express either CD4 or CD8 on the surface. They do not show any tissue tropism and they are the major contributors to the late phase of the immune response. CD4 are the most common T lymphocytes in the body, predominating in peripheral blood and lymphoid tissue, and memory CD4 T cells outnumber memory CD8 T cells in mucosal and other barrier surfaces. Mature naïve T cells constitute the majority of circulating cells in the peripheral blood and lymphoid organs; they express CD45RA and chemokine receptors CCR7 and CD62L (L selectin) that target their traffic from circulation to lymphoid tissue. This process favors their encounter with antigen presenting cells, which are traveling from peripheral site to lymphoid organs. Upon activation, naïve T cells clonally expand and acquire effector properties, during this process they up-regulate integrins and chemokine receptors that will guide them towards sites of inflammation or tissue damage. Each T-cell subtype expresses a different set of transcription factors, cytokine and chemokine receptors to guide trafficking and function (i.e. Th1, Th2, Th17, Treg, and T_{FH}). In the contraction phase, the majority of these cells will die and only a small subset will remain in the memory T-cell compartment as long-lived memory T cells. A variety of subsets exist based on the level of expression of surface markers CD45RO and CCR7, known as central-memory (Tcm) when $CCR7^{high}$ and effector-memory (Tem) when $CCR7^{low}$. Recently, tissue resident (non-circulating) memory T cells (CD8 and CD4) have been recognized in intestine, skin, lung, vaginal mucosa, brain and lymphoid organ[20,21] as clonally expanded populations that are independent from the circulating pool, typically expressing homing receptors such as CD103 together with activation markers CD69, and have the ability to quickly respond to re-exposure to cognate antigens. They have also been reported to constitutively express high levels of cytotoxic molecules, granzyme B and perforin, essential for limiting the spread of infections.

In contrast, γδ T cells represent 1%-10% of nucleated cells in peripheral blood, and show tissue tropism toward epithelial sites such as intestine (25%-60%) and skin. They show a more limited TCR junctional diversity; Vδ1+ cells are found at epithelial surfaces, while Vδ2 + (almost exclusively Vγ9) cells dominate peripheral blood and are found only in humans and high primates. They do not show MHC restriction, but they may require some form of antigen-presenting molecules, lack expression of CD4 and CD8 on the surface, and participate on the early phase of the immune response.

Similar to conventional αβ T cells, expression of CD45RA, CD27 is also used to identify functional subsets, namely naïve CD45RA+, CD27+, Vγ9Vδ2+, which constitute approximately 10%-20% of peripheral blood lymphocytes (PBL). They also represent the major subset in lymph nodes (paracortex), where they also express CCR7 and CD62L and do not secrete IFNγ. After activation γδ T cells become central memory T cells (Tcm) (CD45RA-, CD27+, CD45RO+), they represent 25% Vγ9Vδ2+ in lymph node and 50% in PBL and secrete low levels of IFNγ. After further activation, Tcm generates (CD45RA-, CD27-, Vγ9Vδ2+) effector memory (Tem) that are also CD45RO+, CCR7- and CD26L-, but become tissue chemokine receptor positive for CCR2, CCR5, CCR6 and CXCR3. Tems are rare in lymph nodes, but are present in peripheral blood and inflammation sites. Tcm can also re-express CD45RA+, so called Temra, when activated with IL15. Temra express CCR5 and CXCR3,

Table 1. Current WHO classification of peripheral T-cell and NK-cell lymphomas.

Disseminated/leukemic
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorders of NK cells*
Aggressive NK-cell leukemia
Systemic EBV-positive T-cell lymphoproliferative disease of childhood
Adult T-cell leukemia/lymphoma
Extranodal
Extranodal NK-/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Hepatosplenic T-cell lymphoma
Cutaneous
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30+ T-cell lymphoproliferative disorders
Primary cutaneous anaplastic large cell lymphoma
Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneousCD8+ aggressive epidermotropic cytotoxic T-cell lymphoma*
Primary cutaneous CD4+ small/medium T-cell lymphoma*
Hydroa vacciniforme-like lymphoma
Nodal
Peripheral T-cell lymphoma, not otherwise specified
Angioimmunoblastic T-cell lymphoma
Anaplastic large-cell lymphoma, ALK-positive
Anaplastic large-cell lymphoma, ALK-negative*

**Provisional entities.*

similar to CD8 αβ T cells, are cytotoxic, have little production of IFNγ, display limited proliferative activity and are considered terminally differentiated.[22] Of interest, both subsets αβ and γδ T cells are capable of inducing immunoglobulin production; therefore, humoral responses can be evoked irrespective of the type of responding T cell. Help to B cell for antibody production is mediated by follicular T-helper cells (T_{FH}), which are localized within germinal centers with high expression of CXCR5, PD-1 and ICOS, CD40L, (which interact with corresponding ligands on B cells CXCL13, PDL-1 PD-L2, ICOS L, CD40, respectively) and signature cytokine IL21. Upon activation via T-cell receptor and co-stimulatory molecule CD28, high expression of CXCL13 is detected in T_{FH} cells; the expression of CXCL13 is not limited to these specialized T cells, since it is also present in follicular dendritic cells.[23] The transcriptional repressor BCL-6 is essential for T_{FH} development. In contrast to CD4 T_{FH}, γδ T_{FH} do not produce IL-21, but they have a Th2 functional aspect with production of IL2, IL4 and IL10; but in contrast to CD4 Th2 cells they lack expression of Gata3 and do not produce IL13. The contribution of γδ T_{FH} to antibody production probably occurs early during microbial infection before the full development of acquired immune responses mediated by CD4 T cells.

In summary, the differentiation and overall complexity of γδ T cells is similar to αβ T cells, and both contribute to the complex cellular elements of the T cell areas in reactive and neoplastic lymphoid organs. In addition, both sets have shown the ability, to a certain degree, to reprogram their function based on the cues that they receive from the microenvironment, further complicating their identification on tissue sections. Therefore, our understanding of mature T-cell differentiation has improved and expanded, but its immediate applicability in lymphoma classification has been limited.[24] Over time, several attempts have been made to create a classification of mature T-cell lymphomas that reflects their differentiation and functional characteristics;[24] however, the lack of a well-defined structure such as the B follicle has made this task much more challenging. It is often difficult to identify the neoplastic T-cell population since its characteristics are similar to the background reactive T cells and may not easily alter the underlying architecture to the same degree as B-cell lymphomas. The neoplastic population may also be a minor component in early lesions and in several instances it has been shown that a shift in the surrounding microenvironment may allow for the clonal expansion of the neoplastic cells. For instance, it is very difficult to identify early involvement by mycosis fungoides (MF), which can precede the diagnosis by several years even in the presence of an accurate clinical history. Frequently, multiple skin biopsies are required before a firm diagnosis is achieved; this is due to the overlapping features with benign chronic inflammatory diseases. It has been shown that between early and late lesions there is a shift between the ratio of atypical CD4+ cells and reactive CD8+ cells, which correlates with a shift in cytokine expression from a Th1 to a Th2 microenvironment from an inflammatory one to a more immune suppressive background that facilitates tumor growth.[25] A similar paradigm with shift of fundamental components of the microenvironment applies to other non-Hodgkin lymphomas and classical Hodgkin lymphomas.[26]

The identification of an aberrant phenotype in T-cell populations is also more challenging than in B cells, since often reactive conditions may show a similar spectrum of phenotypic variations like weak CD5 or CD7 expression in chronic inflammatory skin disorders. Although, for instance, we know that the vast majority of MF are CD4 T-helper cells, but based on cytokine pattern and/or transcription factors several studies have assigned a Th1,[27,28] Th2,[29] Treg[30-32] or T_{FH}[33] phenotype to neoplastic cells in MF. This seems to suggest that if each observation is correct, neoplastic T cells may maintain the ability to reprogram or the potential to switch their cytokine profile in response to environmental cues.

Attempts have been made also to classify based on T-cell lineage derivation (αβ vs γδ), and indeed the majority of mature T-cell lymphoma are of αβ derivation, which may just reflect their normal frequency. However, within almost every entity, we can identify cases of both lineages that have either a similar behavior (eg. hepatosplenic: most are γδ, few are αβ, but share a similar clinical outcome; EATL type I: most are αβ and few γδ; both have a dismal prognosis) or different behavior (primary cutaneous γδ T-cell lymphoma *vs*. subcutaneous panniculitic-like T-cell lymphomas αβ).[34] To highlight some additional diagnostic challenges, we would like to focus on a couple of specific entities: T_{FH} related T-cell lymphomas (angioimmunoblastic T-cell lymphoma, PTCL-NOS - follicular variant and primary cutaneous small/medium CD4 positive T-cell lymphoma), and intestinal T-cell lymphomas.

Angioimmunoblastic T-cell lymphoma and related T-cell lymphomas of TFH phenotype

Angioimmunoblastic T-cell lymphoma (AITL) was initially proposed as an abnormal immune reaction or form of atypical lymphoid hyperplasia with a high risk of progression to malignant lymphoma.[35,36] Subsequent studies identifying clonality of the T cells led to the view that AITL was a form of PTCL.[37] It occurs in adults and has not been described in children. Most patients have stage IV disease with generalized lymphadenopathy, hepatosplenomegaly, skin rash, and prominent constitutional symptoms. There are usually polyclonal hypergammaglobulinemia and other hematologic abnormalities, such as circulating immune complexes, cold agglutinin with Coombs-positive hemolytic anemia, or positive rheumatoid factor. Patients may also show evidence of immunodeficiency with recurrent opportunistic infections that may ultimately lead to their demise.

The nodal architecture is generally effaced, but peripheral sinuses are often open and even dilated. At low power there is usually a striking proliferation of post-capillary or high endothelial venules with prominent arborization. Follicles are typically regressed, but there is a proliferation of follicular dendritic cells around high endothelial venules. The atypical T cells have clear cytoplasm, and are associated with a prominent reactive component characterized by small lymphocytes, immunoblasts, plasma cells and histiocytes. The abnormal cells are usually positive for CD3, CD4, CD10, ICOS and CD279 (PD-1), a phenotype characteristic of T_{FH}. A relationship to T_{FH} cells has been confirmed by gene expression profiling data.[4] Strong expression of CD10 and PD-1 in perifollicular lymphocytes can be helpful in the differential diagnosis with reactive hyperplasia of early lymph node involvement by AITL. However, PD-1 is more weakly expressed normally in paracortical T cells, and therefore only strong intense staining is diagnostically useful. CXCL13, a chemokine involved in B-cell trafficking into the germinal centers, is

also expressed in AITL.

B-cell proliferations can complicate the diagnosis of AITL. Expansion of B cells is a hallmark of AITL, likely due to the function of the neoplastic cells as T_{FH}. Polyclonal hypergammaglobulinemia and plasmacytosis were recognized early on as characteristic features, and in some series clonal B-cell populations were identified by molecular techniques.[38] Most frequently the B-cell expansions in AITL are EBV positive. They often show immunoblastic features and are nearly always found scattered in the microenvironment of AITL.[39] Although the hypothesis of defective immune surveillance for EBV related to the underlying T-cell lymphoma has been considered, the exact role of EBV remains uncertain. The number of EBV-positive cells is variable, and progression to EBV-positive DLBCL has been reported in rare cases.[40] Even more rare is the occurrence of an EBV-positive large B-cell lymphoma as a presenting feature that obscures the underlying T-cell process.

The EBV-positive B cells may resemble Hodgkin/Reed Sternberg (HRS) cells both morphologically and phenotypically.[41,42] In some cases, this may lead to an erroneous diagnosis of classical Hodgkin lymphoma. The underlying AITL may only become apparent over time, at relapse. A clue for correct diagnosis may lie in the detection of the neoplastic T cells through abnormal immunophenotype (strong expression of PD1 and less frequent CD10) and/or clonal TCR by PCR. Less common the HRS cells in AITL can be EBV negative. We recently compiled our experience of T-cell lymphoma cases resembling classical Hodgkin lymphoma. Fifty-seven such cases were identified,[42] from which only 5 cases were EBV negative. Interestingly, most of the T-cell lymphomas had a demonstrable T_{FH} phenotype, including all 5 cases with EBV-negative Hodgkin cells. These observations expand the spectrum of abnormal B-cell proliferations occurring in AITL and related T_{FH} neoplasms, and confirm that the B-cell expansion is not attributable entirely to EBV. Notably, regardless of EBV presence, a prominent rosetting of the Hodgkin cells by the neoplastic T cells expressing PD-1 was noted. This observation suggests the possibility of cooperation between these two populations of different lineages. Studies have shown that PD-L1, the ligand of PD-1, can be up-regulated in Hodgkin lymphoma and EBV-positive post-transplant lymphoproliferative disease.[43,44] The binding of PD-1 positive tumor cells to PD-L1 on abnormal B cells may lead to an immunosuppressive blockade, perhaps allowing continued survival of both populations.[45]

Lastly, clonal plasma cell proliferation EBV negative can dominate the histological picture of AITL, making proper diagnosis difficult.[46,47] Thus, the nature of AITL is more complex than originally thought, with frequent clonal expansions of both B and T cells.

Peripheral T-cell lymphoma-not otherwise specified; follicular variant

Peripheral T-cell lymphoma-NOS follicular variant has been described as another T_{FH}-related lymphoma. The neoplastic T cells are often confined to B-cell follicles, and may mimic follicular lymphoma.[48] The cells typically express BCL-6 and CD4, but are usually negative for CD10. The lesions lack expansion of follicular dendritic cell meshworks outside the follicles, and usually do not have a prominent inflammatory background observed in AITL. Clinically, patients with the follicular variant of PTCL present with localized disease, and lack the prominent constitutional symptoms associated with AITL. However, a morphological, immunophenotypic and genetic overlap of PTCL-NOS follicular variant with AITL has been documented.[4,49-52] A morphological transition between the two entities has been observed in consecutive biopsies.[52] Furthermore, t(5;9)(q33;q22) fusion involving the ITK and SYK genes initially considered to be specific for follicular variant of PTCL has been recently indentified in AITL as well.[49,51] Nevertheless, an overlap between these two T_{FH}-related neoplasms has been observed by gene expression profile studies.[4] Therefore, the current hypothesis is that both AITL and PTCL-NOS follicular variant are part of the same spectrum of disease.[53]

Primary cutaneous CD4 positive small/medium T-cell lymphoma

A third T_{FH}-related lymphoproliferative disorder is represented by primary cutaneous CD4 positive small/medium T-cell lymphoma, which most often presents with slowly growing, localized skin lesions of the head or scalp. It is associated with an excellent prognosis, and requires only limited localized therapy.[54] The presence of rapidly growing or bulky tumors should raise concern for a PTCL-NOS.[55] The lesions are rich in B cells, and the proliferating T cells have a T_{FH} phenotype.[56] PD-1 is the most useful marker for recognition, as CD10 is usually negative, in contrast to AITL.[56,57] Some authors have questioned whether this lymphoid proliferation should be considered a form of "pseudolymphoma", often containing T-cell clones, but having limited potential for progression.[58] Alternative terminologies have been suggested, such as "primary cutaneous CD4+ T-cell lymphoproliferative disease" or cutaneous nodular proliferation of pleomorphic T-lymphocytes of undetermined significance".[58] It is interesting that a T_{FH} phenotype has also been reported in mycosis fungoides,[57,59] and it may not be helpful in the distinction with primary cutaneous small/medium CD4+ T-cell lymphoproliferative disorder; therefore, an integrated approach with detailed clinical history, morphology and phenotype is necessary to achieve an accurate diagnosis.

Intestinal T-cell lymphomas

The intestinal mucosa, as a major interface with environmental antigens, commensal microorganisms and dangerous pathogens, is well equipped with specialized populations of the innate and adaptive immune systems.[60] Gut T cells are distributed through the organized lymphoid tissue including Peyers patches, gut-associated lymphoid tissue (GALT), and isolated lymphoid follicles. T lymphocytes are also found throughout the mucosa both in the lamina propria and within the intraepithelial compartment (IEL). Normal IEL are CD3, CD8, $\alpha\beta$, (75%), and $\gamma\delta$ double negative (15%). The majority of IEL are CD8+ T cells ($\alpha\beta > \gamma\delta$) that also express CD103.[20]

Enteropathy associated T-cell lymphomas (EATLs) are intestinal tumors derived from intraepithelial T cells (IEL). Two variants of EATLs were included in the 2008 WHO classification, referred to as Type I and Type II. Type I is associated with either overt or clinically silent gluten-sensitive enteropathy and HLA phenotype (HLADQ in 90% of celiac patients), and is largely seen in patients of European extraction. By contrast, the Type II form has a more worldwide distribution (it is the dominant type in Asians and Hispanics), it is not clearly linked to celiac disease and, therefore, it should be considered a separate entity. Patients with both types usually present

with abdominal symptoms, including pain, small bowel perforation, and associated peritonitis. The clinical course is aggressive, and most patients have multifocal intestinal disease.[61]

In Type I the cytological composition is somewhat varied, and more polymorphous than Type II lymphomas. The neoplastic cells show prominent invasion of the mucosa and are cytotoxic T cells (CD3+, CD5-, CD4-, CD8-/+, CD56-, TIA+, granzyme B+, MATK-) most often of αβ origin. The cells also express the homing receptor CD103 (HML-1). Cells with anaplastic features positive for CD30 may be present. The adjacent small bowel usually shows enteropathy-type changes; the immunophenotype of the IEL is often aberrant and is usually concordant with the lymphomatous component.

In Type II, the infiltrate is monomorphic, composed of medium-sized cells with clear cytoplasm showing prominent epitheliotropism. Spread of tumor cells in the epithelium distal to the main lesion may be seen, mimicking the changes of celiac disease. The cells are CD56+, CD8+, MATK+ with a subset expressing CD103 and tend to be CD30-. EATL type II can be both αβ[62] and γδ.[63] Both Type I and II share some genetic aberrations, including chromosomal gains on 9q33–34.[2] (2). Other T-cell lymphomas can present with intestinal disease, and should be distinguished from EATL. These include the EBV-positive extranodal T-/NK-cell lymphomas of nasal type, and other γδ T-cell lymphoma lacking epitheliotropism.[34]

Rare cases of gastrointestinal T-cell lymphomas with indolent behavior[64,65] and NK enteropathy[66] have been described. It is important to be aware of their existence in order to avoid misdiagnosis with celiac disease or EATL. Indolent CD4 positive cases show villous atrophy with T-cell infiltrating the lamina propria, but lack intraepithelial T cells and cytotoxic markers.

Conclusions

For a correct diagnosis of mature T-cell lymphomas, a multiparametric approach is essential due to the degree of variability of morphology, phenotype and clinical characteristics within each entity. Although most are aggressive neoplasms, the presence of some indolent forms needs to be recognized, because these cases require a different therapeutic approach. The frequency of αβ and γδ positive cases by phenotype or gene expression profiling varies between different lymphoma types, and so its clinical relevance. In the light of the plasticity of reactive and malignant T cells and their response to the microenvironment, more studies are needed to better understand their pathogenetic mechanisms, which will allow us to design better therapies.

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