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Pathobiology of T-cell and NK-cell lymphomas

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Abstract

T-cell and NK-cell lymphomas are uncommon lymphomas with an aggressive clinical course. The causes and precise cellular origin of most T-cell lymphomas are still not well defined. The WHO classification utilizes morphologic and immunophenotypic features in conjunction with clinical aspects and in some instances genetics to delineate a prognostically and therapeutically meaningful categorization. The anatomic localization of neoplastic T-cells and NK-cells parallels in part their proposed normal cellular counterparts and functions. T-cells of the adaptive immune system are mainly based in lymph nodes and peripheral blood, whereas lymphomas derived from T-cells and NK-cells of the innate immune system are mainly extranodal. This approach allows for better understanding of some of the manifestations of the T-cell and NK-cell lymphomas, including their cellular distribution, some aspects of morphology and even associated clinical findings.

Keywords

pathobiology; pathogenesis; anaplastic large cell lymphoma; peripheral T-cell lymphoma; extranodal NK/T-cell lymphoma; enteropathy associated T-cell lymphoma; hepatosplenic T-cell lymphoma; subcutaneous panniculitis-like T-cell lymphoma; primary cutaneous ⊐ λ T-cell lymphoma; cellular origin; nodal; extranodal; innate immune system; adaptive immune system; T-follicular helper cells; αβ T-cell receptor; ⊐ λ T-cell receptor

(A) INTRODUCTION

T-cell and natural killer (NK)-cell lymphomas are uncommon neoplasms comprising fewer than 10% of all non-Hodgkin lymphomas (NHL) [1]. They have complex and often overlapping morphological and immunophenotypic characteristics, with as yet relatively

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None.

little understanding of their molecular pathogenesis. Thus, clinical features play a significant role in the recognition of proposed entities in the WHO classification [2]. The most common of the T-cell and NK-cell lymphomas is peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS) comprising 25% overall. This is closely followed by angioimmunoblastic T-cell lymphoma (AITL) (18.5%) [1]. This review will focus on the most common entities as defined in the current WHO Classification (see Table 1) [3]. Some entities are omitted from this discussion, since they are covered in depth in other articles within this issue.

An understanding of the normal immune system is helpful in categorizing T-cell and NK-cell malignancies. The innate immune system is a primitive defense system important in barrier (mucosal or skin) immunity. It includes NK cells and γδ T-cells[4]. γδ T-cells represent fewer than 5% of normal T-cells and are particularly enriched in certain locations, such as splenic red pulp, intestinal mucosa and other epithelial sites, sites in which γδ T-cell lymphomas often present [4]. Normal γδ T-cells in the spleen, thymus, and intestinal epithelia express the Vγ1 gene. Hepatosplenic T cell lymphoma (HSTL) also shows preferential expression of Vγ1, suggesting that the normal splenic γδ T-cells are counterparts of this lymphoma. Conversely, γδ T-cells in peripheral blood, tonsil, and skin express Vγ2, similar to primary cutaneous gamma-delta T cell lymphoma (PCGD)-TCLs[5].

The adaptive immune system is a more heterogeneous and complex system. Antigen recognition is MHC restricted. Immune memory also is a hallmark feature of the adaptive immune system and results in a more efficient response upon secondary exposure to the same antigen. T cells that are a part of adaptive immune system are quite heterogeneous and functionally complex. Effector T cells include regulatory T cells (Treg), follicular helper T cells (T_{FH}), cytotoxic T cells, and memory T cells. CD4 positive T cells act via cytokine production, while CD8 positive and double negative T-cells are primarily cytotoxic, acting via secretion of cytotoxic molecules directly affecting target cells. Functional counterparts of these T-cell subsets have been recognized among the T-cell lymphomas, as will be discussed below.

A. NODAL T-CELL LYMPHOMAS

B. Peripheral T-cell lymphomas, not otherwise specified (PTCL, NOS)

PTCL, NOS comprises over 25% of all peripheral T-cell lymphomas and NK/T- cell lymphomas and is the most common subtype[1]. It is a diagnosis of exclusion, not corresponding to any of the specific mature T-cell lymphoma entities listed in the current WHO 2008, analogous to diffuse large B-cell lymphoma, not otherwise specified (DLBCL-NOS). Most patients are adults with a median age of 60 and a male to female ratio 2:1 [6]. The majority of cases are nodal in origin. However, extranodal presentations can occur in 13% of patients and most commonly involve skin and gastrointestinal tract.

The cytologic spectrum is very broad, ranging from polymorphous to monomorphous. Three morphologically defined variants have been described, including lymphoepithelioid (Lennert) variant, T-zone variant and follicular variant . The lymphoepithelioid variant of PTCL contains abundnant background epithelioid histiocytes and is commonly positive for CD8. It has been associated with a better prognosis [6]. The follicular variant of PTCL, NOS, is emerging as potentially a distinct clinicopathologic entity and will be discussed in the context of other T_{FH} tumors.

The majority of PTCL, NOS have a mature T-cell phenotype with most cases being CD4 positive. 75% of cases show variable loss of at least one pan T-cell marker (CD3, CD2, CD5 or CD7), with CD7 and CD5 being most often downregulated [7]. CD30 and rarely CD15

can be expressed [8],with CD15 being an adverse prognostic feature[7]. CD56 expression, although uncommon, also has negative prognostic impact. Additional adverse pathologic prognostic factors include a proliferation rate greater than 25% based on KI-67 expression, and presence of more than 70% transformed cells. It is possible that in the future, distinct entities will be delineated within this currently heterogeneous category; however, thus far immunophenotypic analysis of these lymphomas offered little insight into their biology.

(B) Angioimmunoblastic T-cell lymphoma (AITL) and other T_{FH} related nodal lymphomas

AITL is a systemic disease characterized by a polymorphous infiltrate involving lymph nodes, prominent high endothelial venules (HEV) and peri-vascular expansion of follicular dendritic cell (FDC) meshworks (Figure 1A–C). AITL was originally termed " lymphadenopathy with dysproteinemia" and was believed to be a condition with a high risk of progression to lymphoma [9, 10].Today AITL is considered a de-novo T-cell lymphoma derived from αβ T-cells of follicular helper type (T_{FH}), normally found in the germinal centers [11–14].

AITL is the second most common entity among peripheral T-cell lymphoma and NK/T-cell lymphomas, comprising about 18.5% of cases [1]. It occurs in middle aged to elderly adults, with a median age of 65 years old. It has not been described in children. The incidence in males and females is approximately equal. Clinically, patients usually have advanced stage disease, with generalized lymphadenopathy, hepatosplenomegaly and prominent constitutional symptoms. Skin rash with associated pruritus is commonly present. There is often polyclonal hypergammaglobulinemia, associated with autoimmune phenomena.

Three different morphologic patterns are described in AITL [11, 15]. The early lesion of AITL (Pattern I) usually shows preserved architecture with characteristic hyperplastic follicles. The neoplastic proliferation is localized to the periphery of the follicles and is better visualized on immunohistochemical stains. In Pattern II the nodal architecture is partially effaced with retention of few regressed follicles, while no residual follicles are present in Pattern III. The subcapsular sinuses are preserved and even dilated. The paracortex contains arborizing HEV and there is a proliferation of FDC beyond the B-cell follicle. The neoplastic cells are small to medium in size, with minimal cytologic atypia. They often have clear to pale cytoplasm, and may show distinct cell membranes. A polymorphous inflammatory background is usually evident.

Although AITL is a T-cell malignancy, there is a characteristic expansion of B-cells and plasma cells, which likely reflects the function of the neoplastic cells as T_{FH} cells. Both EBV-positive and EBV-negative B-cells are present. [16] Occasionally, the atypical B-cells may resemble Hodgkin/Reed-Sternberg like cells morphologically and immunophenotypically, sometimes leading to a diagnostic confusion with that entity [17, 18]. The B-cell proliferation in AITL may be extensive and some patients develop secondary EBV-positive diffuse large B-cell lymphomas (DLBCL) or – more rarely – EBV-negative B-cell tumors, often with plasmacytic differentiation [19–22].

The neoplastic CD4-positive T cells of AITL show strong expression of CD10 and CD279 (PD-1) and are positive for CXCL13 [14, 23, 24]. CXCL13 leads to increased B-cell recruitment to lymph nodes via adherence to the HEV, B-cell activation, plasmacytic differentiation and expansion of the FDC meshworks, all contributing to the morphologic and clinical features of AITL [25]. Intense PD-1-expression in the perifollicular tumor cells is particularly helpful in distinguishing AITL pattern I from reactive follicular and paracortical hyperplasia. EBV positivity within the B-cell component in AITL is seen in up to 97% of cases.

The vast majority of cases (up to 90%) have clonal rearrangements of T-cell receptor genes [26, 27]. In addition, immunoglobulin gene rearrangements may be found in up to 25–30% of patients with AITL [26–28]. The B-cell expansion in AILT is attributed to the T_{FH} function of the tumor cells[29]. The relationship between T_{FH} cells and AITL has been recently confirmed by gene expression profiling studies [12].

The follicular variant of PTCL, NOS is another entity with a T_{FH} phenotype [30–32]. In contradistinction to AITL, it does not have prominent HEV or extra-follicular expansion of FDC meshworks. The neoplastic cells may form intrafollicular aggregates, mimicking B-cell follicular lymphoma, but also can have interfollicular growth pattern or involve expanded mantle zones [32–35]. Similar to AITL, this entity occasionally has EBV positive or EBV negative Hodgkin-like cells, mimicking classical Hodgkin lymphoma [18, 36]. Clinically, the follicular variant of PTCL, NOS is distinct from AITL: patients more often present with early stage disease with partial lymph node involvement and may lack the constitutional symptoms associated with AITL.

The recent finding of *TET2* mutations in 47% of AITL and 58% of PTCLs expressing T_{FH} cell markers, suggests overlap between these entities [37] . The relationship between these two neoplasms has also been corroborated by gene expression profiling studies [12]. A subset of PTCL, NOS, follicular variant cases have a t(5;9)(q33;q22) resulting in a fusion of *ITK* and *SYK* and generation of a chimeric protein [38]. This finding was not observed in AITL, but studies of this question are limited. Further studies are necessary to determine the relationship between PTCL, NOS, follicular variant and AITL.

(B) Anaplastic large cell lymphoma, ALK-positive (ALCL, ALK+)

ALCL, ALK+ is one of the best-defined entities within the peripheral T-cell lymphomas, with characteristic “hallmark cells” bearing horseshoe-shaped nuclei and expressing ALK and CD30 (Figure 1D–1F). It accounts for about 7% of all peripheral T-cell and NK-cell lymphomas [1] and is most common in the first three decades of life. There is a slight male predominance. Patients often present with lymphadenopathy, but involvement of extranodal sites (skin, bone, soft tissues, lung, liver) is common and most patients have stage III – IV disease (70% cases). B symptoms are common. Bone marrow involvement is present in 10% of cases on H&E examination, but increases to 30% when immunohistochemistry is employed [39].

ALCL, ALK+ shows a wide morphologic spectrum, with 5 different patterns described, but all variants contain some hallmark cells. Hallmark cells have eccentric horseshoe- or kidney-shaped nuclei, and a prominent perinuclear eosinophilic Golgi region. The tumor cells grow in a cohesive pattern with predilection for sinus involvement [40]. Smaller tumor cells predominate in the small cell variant, and in the lymphohistiocytic variant abundant histiocytes mask the presence of tumor cells, many of which are small.

By definition, all cases show ALK and CD30 positivity, with expression usually weaker in the smaller tumor cells. The majority of cases are also positive for EMA. There is often loss of pan-T cell markers, with 75% of cases lacking surface expression of CD3. CD2 and CD4 are most commonly expressed [41]. In the few “null” cases, T-cell receptor gene rearrangements studies usually confirm the T-cell origin of the neoplastic cells. Most cases are positive for cytotoxic associated markers, such as TIA1, granzyme B and perforin [40].

ALK expression is a result of a characteristic recurrent genetic alteration consisting of a rearrangement of anaplastic lymphoma kinase (*ALK*) gene on chromosome 2p23 to one of many partner genes, resulting in expression of chimeric protein. The most common partner gene, occurring in 75% of cases, is Nucleophosmin (*NPM1*) on chromosome 5q35, resulting

in t(2;5)(p23;q35). The cellular distribution of ALK in different translocation variants may vary depending on the partner gene [42].

ALCL, ALK+ has good prognosis with 5-year survival rate of 70–80% [43]. Relapses are common (30% cases), but the neoplasm remains chemosensitive [44]. Notably, small cell and lymphohistiocytic variants of ALCL, ALK+, often seen in children, may have a more aggressive clinical course [45].

B. Anaplastic large cell lymphoma, ALK-negative (ALCL, ALK-)

ALCL, ALK- is included as a provisional category in the 2008 WHO classification. It is defined as a CD30 positive T-cell lymphoma that is morphologically indistinguishable from ALCL, ALK+ with a cohesive growth pattern and presence of hallmark cells, but lacking ALK protein expression. Loss of T-cell markers, a cytotoxic phenotype, EMA expression and sinusoidal growth pattern, although helpful, are not essential for the diagnosis of ALK^{-}ALCL.

Patients are usually adults between the ages of 40 and 65, in contrast to ALCL, ALK+, which is more common in children and young adults. ALCL, ALK- can involve both lymph nodes and extranodal tissues, although the latter is seen less commonly than in ALCL, ALK + [46]. Most cases of ALCL, ALK-demonstrate effacement of lymph node architecture by sheets of cohesive neoplastic cells with typical “hallmark” features. In contrast to the ALCL, ALK+, the small cell morphologic variant is not recognized. Unlike its ALK+ counterpart, ALCL, ALK- shows a greater preservation of surface T – cell marker expression, while the expression of cytotoxic markers and EMA is less likely [43]. CD30 expression should be strong and homogeneous. Caution is advised in the differential diagnosis with CHL, since some cases of CHL can be rich in tumor cells, and negative for CD15 expression. Use of PAX5, nearly always positive in CHL, is a helpful feature.

Gene expression signatures and recurrent chromosomal imbalances are different in ALCL, ALK – and ALCL, ALK+, confirming that they are distinct entities at a molecular and genetic level [47–49]. In addition, recent studies identified a recurrent translocation t(6;9)(p25.3;q32.3) in a subset of ALCL, ALK-cases, which results in down-regulation of DUSP22 phosphatase gene expression located on chromosome 6p25.3, with some data suggesting that DUSP22 might function as a tumor suppressor gene [50].

ALCL, ALK- is clinically distinct from both ALCL, ALK+ and PTCL, NOS, with significant differences in prognosis among these three different entities. The 5 year overall survival of ALCL, ALK- is reported as 49% which is not as good as that of ALCL, ALK+ (at 70%), but at the same time it is significantly better than that of PTCL, NOS (32%)[43]. Thus, both clinical behavior and genetic studies suggest that ALCL, ALK- indeed should be considered as a separate entity. Interestingly, if patients are stratified based on age and disease stage, the prognosis of ALCL, ALK – and ALCL, ALK+ seems to be more similar, suggesting that clinical parameters are important in prognostication[43].

(B) Primary cutaneous ALCL

Primary cutaneous ALCL (C-ALCL) deserves a special mention, as it is often indistinguishable from ALCL, ALK- by morphology. It is defined as a cutaneous tumor of large cells with anaplastic, pleomorphic or immunoblastic morphology with more than 75% of cells expressing CD30. Large cell transformation of MF needs to be excluded on the basis of clinical findings and/or history. Together with lymphomatoid papulosis (LyP), C-ALCL it belongs to the spectrum of primary cutaneous CD30-positive T-cell lymphoproliferative disorders, which as a group comprise the second most common group of cutaneous T-cell lymphoproliferations after mycosis fungoides.

Clinically, C-ALCL usually presents with solitary or localized tumors or nodules. Most patients are adults. Regional lymph node involvement may be seen, which does not appear to mandate a poorer prognosis. In these cases distinction from systemic ALCL, ALK- may be complex [51, 52]. Mucosal presentations have been reported, and are likely part of the same spectrum of the disease [53].

The immunohistochemical staining profile is quite similar to ALCL, ALK- , with a greater proportion of cases staining positive for cytotoxic markers and most cases being negative for EMA. At least 75% of the tumor cells should be positive for CD30. CD15 may also be expressed, and when lymph node involvement occurs, the differential with classical Hodgkin lymphoma can be difficult [54]. Rare cases of ALCL, ALK+ may present with localized cutaneous lesions, and may resemble C-ALCL. [55]. Therefore, staining for ALK is advisable in all CD30+ T-cell neoplasms.

Similar to systemic ALCL, ALK- a subset of cases show translocations of *IRF4/DUSP22* [50, 56, 57].

Despite similarities to systemic ALCL, ALK-, the prognosis in C-ALCL is excellent with 5-year overall survival at 90% [43]. In cases of C-ALCL, a period of observation is warranted since some lesions may regress, similar to LYP. Recurrences, usually confined to the skin, are common and they do not portend a poorer prognosis. Therefore, while systemic ALCL, ALK- is treated with combination chemotherapy, C-ALCL is generally sufficiently treated with local therapies [58].

(A) EXTRANODAL T-CELL AND NK-CELL LYMPHOMAS

(B) Extranodal NK/T-cell lymphoma, nasal type

Extranodal NK/T-cell lymphoma, nasal type, is an aggressive disease, often with destructive midline lesions. Necrosis is prominent. Most cases are of NK-cell derivation, but some cases are derived from cytotoxic T-cells. It is universally associated with EBV- although technical factors may impede its detection in some cases. This topic will be discussed in detail in Chapter 7 (Nakamura et al).

(B) Enteropathy-associated T-cell lymphoma (EATL)

EATL is an aggressive neoplasm thought to be derived from the intraepithelial T-cells of the intestine. Two morphologically, immunohistochemically and genetically distinct types of EATL are recognized in the 2008 WHO classification: Type I (representing the majority of EATL) and Type II (comprising 10–20% of cases) [2, 59].

C. EATL, Type I—Type I EATL is usually associated with overt or clinically silent gluten-sensitive enteropathy, and is more often seen in patients of Northern European extraction due to high prevalence of coeliac disease in this population[60]. Clinically, patients with EATL type I often have positive serologies for anti-gliadin and anti-transglutaminase antibodies, can have associated dermatitis herpetiformis and hyposplenism [61]. In addition, 90% of patients with EATL type I have coeliac disease-associated human leukocyte antigen haplotypes (HLA-DQ2/8), further strengthening the notion that EATL type I and coeliac disease are related [61]. In a proportion of cases, there is no clear-cut history of coeliac disease; however, the resection specimens reveal histologic features of celiac disease [62]. Patients usually present with abdominal pain or signs of bowel perforation and sepsis.

Most commonly, the lesions of EATL are found in the jejunum or ileum (90% of cases), with rare presentations in duodenum, colon, stomach, or areas outside of the gastrointestinal tract. The intestinal lesions are usually multifocal with mucosal ulceration (Figure 1G, H).

Clinical course of EATL is aggressive with most patients dying of disease or complications of disease within 1 year.

The cytological spectrum of EATL type I is broad, and some cases may contain anaplastic cells. There is a polymorphous inflammatory background, which may obscure the neoplastic component in some cases. The intestinal mucosa in regions adjacent to the tumor often shows features of coeliac disease with blunting of the villi and increased numbers of intraepithelial lymphocytes (IEL), which may represent lesional precursor cells (Figure 1H–I) [62].

By immunohistochemistry, the neoplastic cells are often CD3+CD4-CD8-CD7+CD5-CD56-βF1+, and contain cytotoxic granule-associated proteins (TIA-1, granzyme B, perforin). CD30 is partially expressed in almost all cases. Not surprisingly, CD103, which is a mucosal homing receptor, can be expressed in EATL. Interestingly, the IEL in mucosa adjacent to EATL and in refractory celiac disease (RCD) often show downregulation of CD8, similar to neoplastic cells of EATL [63].

The lymphoma cells show clonal rearrangements of *TCRβ* and *TCRα*. In addition there are frequent gains of 9q31.3, 1q32.2-q41 and 5q34-q35.2 or loss of 16q12.1. Interestingly, in patients with refractory celiac disease (RCD), who subsequently developed EATL, identical TCR gene rearrangements and gain of chromosome 1q are seen in both phenotypically aberrant IEL of RCD as well as in neoplastic cells later on [63]. This suggests that RCD with aberrant IEL is a precursor lesion of EATL. Upregulation of IL-15 in the intestinal epithelia of patients with coeliac disease has been shown to activate antiapoptotic pathways in the IEL, possibly playing a role in malignant transformation of these cells [64, 65].

C. EATL, type II—Type II EATL, also referred to as monomorphic CD56+ intestinal T-cell lymphoma, is defined as an intestinal tumor composed of small to medium-sized monomorphic T-cells that express both CD8 and CD56[59] (Figure 1I). There is often a lateral spread of tumor within the mucosa, and absence of an inflammatory background. The majority of cases express the γδ T-cell receptor [66].

EATL, II has a more world-wide distribution than EATL type I and is often seen in Asians or Hispanic populations, in whom coeliac disease is rare. [60, 67, 68]. In individuals of European descent EATL, II represents about 20% of intestinal T-cell lymphomas, with a history of coeliac disease in at least a subset of cases [60]. The clinical course is aggressive.

Gain of 9q31.3 or loss of 16q12.1 is found in majority of cases, in common with EATL type I. In contradistinction to the classic form of EATL, monomorphic variant of EATL more often shows amplification of *MYC* oncogene locus at 8q24, while gains in 1q and 5q are less frequent, suggesting that it is a distinct entity [62].

(B) Hepatosplenic T-cell lymphoma (HSTL)

HSTL is an aggressive systemic neoplasm derived from γδ (and rarely αβ) cytotoxic T-cells of the innate immune system [5, 69, 70]. It is one of the rarest T-cell lymphomas, and typically affects adolescents and young adults (median age, 35 years) with a strong male predominance [69, 70]. Up to 20% of cases arise in a background of chronic antigenic stimulation and concomitant immunosuppression. Patients at risk include long term solid organ transplant recipients [70–73] and patients with Crohn's disease treated with azathioprine and infliximab [74, 75]. HSTL often presents with systemic symptom, thrombocytopenia, and marked hepatosplenomegaly in absence of lymphadenopathy [76]. Survival is usually less than 3 years, with rapid relapse and fatal outcome even in those patients who initially might have responded to chemotherapy [70, 71].

The cells are monotonous, medium sized, with narrow rim of cytoplasm. They show characteristic intrasinusoidal involvement of liver and spleen, similar to the normal distribution of γδ T-cells (Figure 1J–L) Neoplastic cells within the sinusoids of the bone marrow are best visualized with immunohistochemistry. Immunophenotypicaly, the neoplastic cells are CD3+, CD5-, CD4-, and variable expression of CD8. They are TIA-1-positive but lack granzyme B and perforin (non-activated phenotype) [69, 77]. In addition, HSTL often shows aberrant expression of multiple killer immunoglobulin-like receptors (KIR) isoforms, normally seen on NK cells, along with dim or absent CD94 [78]. The majority of cases are of γδ T-cell origin; however, there are rare cases expressing αβ T-cell receptor [79]. Most of the γδ cases express the Vδ1 epitope, which is in contrast to PCGD-TCL expressing Vδ2 epitope [70, 73]. At the genetic level, most cases have isochromosome 7q or a ring chromosome leading to 7q amplification. With disease progression, two to five copies of i(7)(q10) in addition to numerical and structural aberrations of the second chromosome 7 have been reported. Gene expression profiling showed that hepatosplenic γδ T-cell lymphoma is distinct from other non-hepatosplenic γδ T-cell lymphomas [80] and revealed similarities in HSTL expressing αβ or γδ T-cell receptor [81].

(B) Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)

SPTCL is a rare T-cell lymphoma with a very wide age distribution (median age35 years) but can be seen in young children [82–84]. The infiltrate is usually confined to the subcutis, with sparing of dermis. (Figure 1M–O). Histologically, the cells surround individual fat cells (rimming) with fat necrosis and karyorrhexis [83, 85]. The infiltrating cells are positive for CD8, and negative for CD56. They express βF1 and cytotoxic markers (TIA1, perforin and granzyme B), consistent with their proposed derivation from activated cytotoxic αβ T-cells. Patients present with subcutaneous nodules on extremities and trunk. The disease has a relatively good prognosis (5 year overall survival of 80%)[82, 86].

SPTCL is associated with autoimmune disease in 20% of cases, most commonly systemic lupus erythematosus (SLE), although it is not clear what role immune dysregulation might play in the genesis of this lymphoma [86]. In some cases, distinction from benign lobular panniculitis may be difficult [82, 85, 87], but lobular pannicultis is not thought to be a predisposing factor. A hemophagocytic syndrome (HPS) is observed in 15–20% of cases and carries a poor prognosis [88]. Patients with HPS exhibit cytopenias and abnormal liver function tests. Dissemination to lymph nodes and other extracutaneous sites is rare.

(B) Primary cutaneous gamma-delta T-cell lymphoma (PCGD-TCL)

PCGD-TCL is composed of a mature activated γδ T cells. Morphologically, three patterns of involvement may be present: epidermotropic, dermal or subcutaneous mimicking SPTCL[89]. In some cases, more than one histologic pattern can be seen. Apoptosis and necrosis are frequent, often with angioinvasion [86].

Most cases occur in adults with equal prevalence in males and females. Extremities are most commonly involved, particularly thighs and buttocks. B symptoms are common. Patients may present with ulcers, plaques, or dermal / subcutaneous nodules. HPS is often present in patients with SPTCL-like involvement [86], a finding leading to a poor outcome[90]. Elevated liver enzymes and leucopenia are seen in 50% of patients, and are associated with poor prognosis [91]. Lymph nodes, spleen and bone marrow are usually spared. PCGD-TCL is resistant to multiagent chemotherapy and radiation. It is aggressive, with median survival of about 15 months.

Immunohistochemically, PCGD-TCL has an activated cytotoxic phenotype; CD8 is variably expressed and CD56 is usually positive. The cells express the γδ T-cell receptor [73].

There are rare T-cell lymphomas of γδ T-cell derivation that present in non-cutaneous extranodal sites, including nasal mucosa, intestine, lung, orbit and tongue [92]. Their relationship PCGD-TCL is uncertain.

Summary

Peripheral T-cell and NK-cell lymphomas are heterogeneous neoplasms, often with overlapping morphological features. Broadly speaking, T-cell and NK-cell lymphomas can be categorized as primarily nodal or extranodal with parallels to the adaptive and innate immune systems. The current WHO 2008 classification uses a multi-modality approach to define prognostically distinct entities. Attempts to better define the normal cellular counterparts of the T-cell/NK-cell lymphomas has resulted in better understanding of some entities such as AITL and the follicular variant of PTCL, NOS. Other categories, such as PTCL, NOS, lack clear defining characteristics and are quite heterogeneous, similar to DLBCL. Unlike B-cell lymphomas, few peripheral T-cell/NK-cell lymphomas are defined by recurrent genetic alterations, but with the implementation of new genomic sequencing strategies, the number is likely to increase. These techniques have yielded new insights into ALCL, ALK-, and the T_{FH} malignancies in particular. In addition, effort should be expanded to identify pathologic predictors of prognosis and potential therapeutic targets within different categories of peripheral T-cell/NK-cell lymphomas. To date most treatment protocols are applied across all the T-cell lymphomas, with few exceptions. However, new drugs directed at the ALK kinase, or at CD30 expression point the way towards targeted therapies [93, 94].

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Research Agenda

- The elucidation of the genomic changes associated with the specific forms of peripheral T-cell lymphoma is in its early stages.
- Both exome sequencing and whole genome sequencing offer great promise to illuminate the nature of mature T-cell lymphomas, and the relationship between the histological subtypes.
- Identification of relevant pathways of neoplastic transformation will have relevance for more targeted therapy of these tumors in the future.

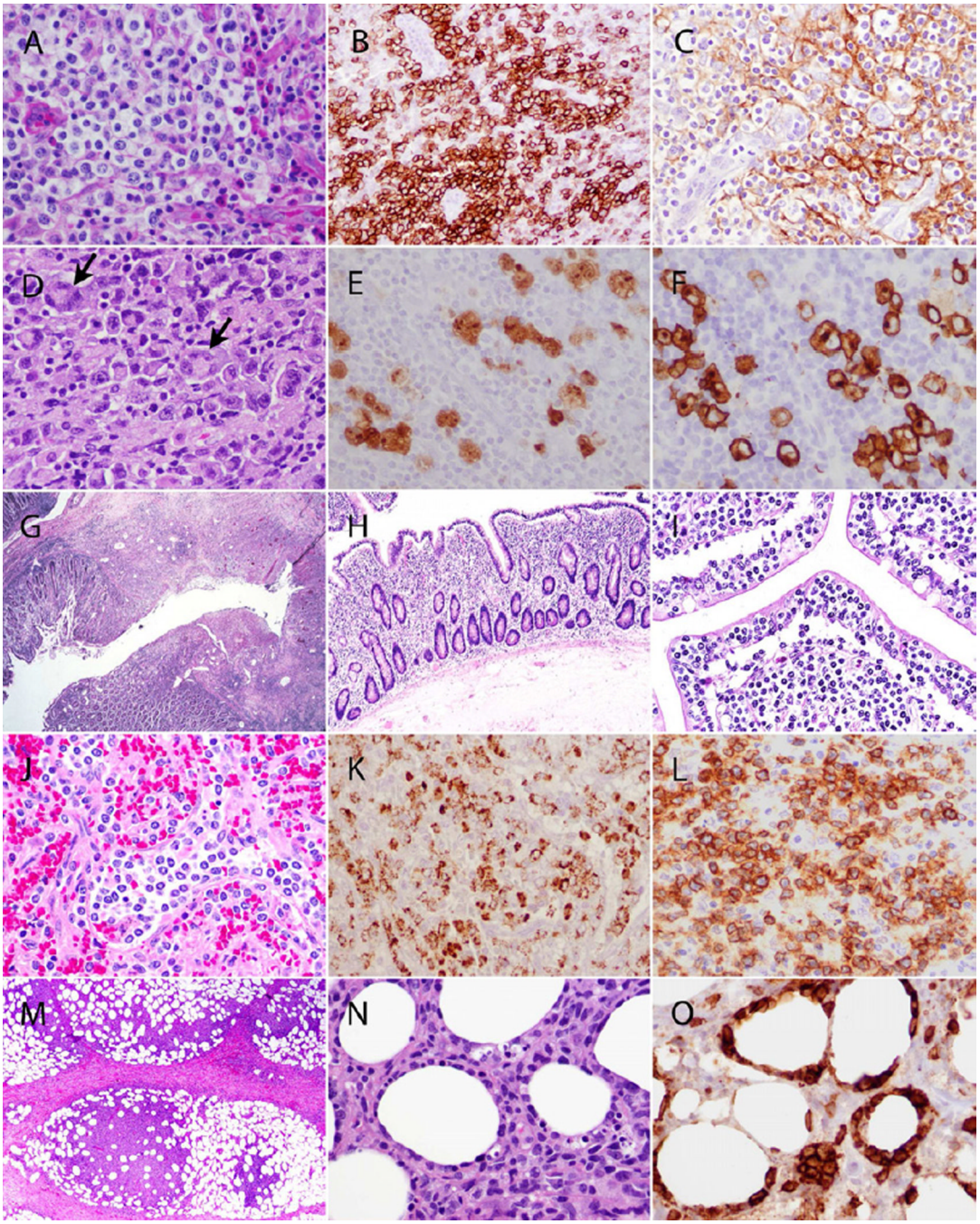

Figure 1. Pathological spectrum of T-cell lymphomas

(A–C) **Angioimmunoblastic T-cell lymphoma, lymph node**. A. H&E stained section shows prominent clusters of atypical lymphocytes with clear cytoplasm surrounding the HEV. B. PD-1 positivity within the neoplastic cells clustered around the HEV. C. CD21 immunohistochemical stain demonstrating expanded perivascular FDC meshworks .

(D–F) **Anaplastic large cell lymphoma, ALK positive, lymph node**. D. Characteristic "hallmark" cells (examples indicated by arrows) with eccentric horseshoe-shaped nuclei and prominent perinuclear eosinophilic Golgi regions. E. Cytoplasmic and nuclear ALK

expression in the neoplastic cells. F. Strong CD30 expression with a membranous and perinuclear dot-like staining pattern (highlighting Golgi region).
(G–I) **Enteropathy-associated T-cell lymphoma, Types I and II, small intestine**. G. EATL, type I. Low-power view of small intestinal lesion with a penetraing mucosal ulcer. Atypical lymphoid cells infiltrate the intestinal wall. H. EATL, Type I. Adjacent mucosa shows marked villous blunting. I. EATL, Type II. There is marked infiltration of the mucosa by monomorphic medium-sized cells with clear cytoplasm.
(J–L) **Hepatosplenic T-cell lymphoma, spleen**. J. H&E stained section of spleen demonstrating red pulp involvement by monotonous population of neoplastic cells. K. TIA-1 positivity within the neoplastic cells. L. The neoplastic cells express the T-cell receptor gamma chain, indicating a gamma-delta phenotype.
(M–O) **Subcutaneous panniculitis-like T-cell lymphoma, skin**. M. Subcutaneous tissue involvement predominantly affecting the fat lobules with sparing of the septa. N. High-power view demonstrating rimming of the individual fat cells by neoplastic cells. O. Neoplastic cells surrounding the fat cells are strongly CD8 positive.

Table 1

WHO classification of tumors of haematopoietic and lymphoid tissues (2008).

Mature T-cell and NK-cell neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK-cells
Aggressive NK leukemia
Systemic EBV positive T-cell lymphoproliferative disease of childhood
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
Sezary syndrome
Primary cutaneous CD30 positive T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large 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
Angioimmunoblastic T-cell lymphoma
Anaplastic large cell lymphoma, ALK positive
Anaplastic large cell lymphoma, ALK negative
Proviional entities are in italics. Entities discussed in this article are underlined.