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Review

The microenvironment in T-cell lymphomas: Emerging themes

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ABSTRACT

Peripheral T-cell lymphomas (PTCLs) are heterogeneous and uncommon malignancies characterized by an aggressive clinical course and a mostly poor outcome with current treatment strategies. Despite novel insights into their pathobiology provided by recent genome-wide molecular studies, several entities remain poorly characterized. In addition to the neoplastic cell population, PTCLs have a microenvironment component, composed of non-tumor cells and stroma, which is quantitatively and qualitatively variable, and which may have an effect on their pathological and clinical features. The best example is provided by angioimmunoblastic T-cell lymphoma (AITL), a designation reflecting the typical vascularization and reactive immunoblastic content of the tumor tissues. In this disease, a complex network of interactions between the lymphoma cells and the microenvironment exists, presumably mediated by the neoplastic T cells with follicular helper T-cell properties. A better understanding of the crosstalk between neoplastic T or NK cells and their microenvironment may have important implications for guiding the development of novel therapies.

1. Introduction

Peripheral T-cell lymphomas (PTCLs), which are neoplasms derived from mature T and NK cells, encompass numerous disease entities that collectively account for less than 15% of all non-Hodgkin lymphomas worldwide. Strikingly, their distribution shows important geographic variations, with a higher prevalence in Asia and central/south America than in Europe and North America, which is in part related to the endemic infection by the human T-lymphotropic virus-1 (HTLV1) and the Epstein–Barr virus (EBV) [1]. Most entities are clinically aggressive, with overall poor response to classical treatments and a dismal prognosis.

While the WHO principles of a multiparametric definition of lymphoma entities – based on morphologic, immunophenotypic, genetic and clinical features, and putative normal cellular counterpart – have led to a comprehensive delineation of B-cell lymphoma entities, the classification of NK/T-cell-derived neoplasms remains a challenge [2]. This difficulty is influenced by several factors, including the inherent complexity of the T-cell system, with its numerous functional subsets and probable functional plasticity. Additionally, PTCL entities comprise a broad range of morphologies and exhibit immunophenotypic profiles that tend to overlap across different entities. Only few recurrent genetic alterations have been described in PTCLs that can serve as disease-defining criteria. The clinical presentation, on the other hand, has been critical in defining PTCL entities. Recent findings indicate that the cell of origin is a major determinant of PTCL biology; nevertheless the cellular derivation of many PTCL entities remains poorly characterized or appears heterogeneous [3–5].

There are currently more than 20 PTCL entities listed in the WHO classification; these can be grouped according to their presentation as disseminated (leukemic), predominantly extranodal or cutaneous, or predominantly nodal diseases (Table 1) [2]. Some entities are relatively well defined, while others are more heterogeneous, notably PTCL not otherwise specified (NOS), which is the "default" category for cases not fulfilling criteria for more specific entities. Some entities, for example ALK-negative anaplastic large cell lymphoma (ALCL) are provisional. ALK-positive ALCL is the only one defined by a genetic lesion, and is currently the best-defined entity.

It is remarkable that PTCL entities tend to have a predilection for development in specific anatomical sites, i.e. lymph nodes, skin, intestines, spleen and other extranodal organs. Accordingly, at the molecular level, distinct extranodal PTCL entities have a gene expression signature component that is organ-specific [4,6]. For some entities, the association reflects derivation from a subset of organ-specific lymphocytes, or lymphocytes with peculiar homing properties. For example, enteropathy-associated T-cell lymphoma

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

PTCL entities	Frequency (%)**	Cellular derivation	Phenotype
Disseminated/leukemic			
T-cell prolymphocytic leukemia	ND	Tαβ	Non-cytotoxic
T-cell large granular lymphocytic leukemia	ND	Tαβ (more rarely Tγδ)	Cytotoxic (A)
Chronic lymphoproliferative disorders of NK cells*	ND	NK	Cytotoxic (A)
Aggressive NK-cell leukemia	ND	NK	Cytotoxic (A)
Systemic EBV-positive T-cell lymphoproliferative disease of childhood	ND	Tαβ	Cytotoxic (A)
Adult T-cell leukemia/lymphoma	9.6	Tαβ	T regulatory
Extranodal			
Extranodal NK/T-cell lymphoma, nasal type (ENKTCL)	10.4	NK (more rarely Tγδ or Tαβ)	Cytotoxic (A)
Enteropathy-associated T-cell lymphoma (EATL)	4.7	IEL, Tαβ (more rarely Tγδ)	Cytotoxic (A)
Hepatosplenic T-cell lymphoma (HSTL)	1.4	Tγδ (Vδ1) (more rarely Tαβ)	Cytotoxic (NA)
Cutaneous			
Mycosis fungoides	ND	Tαβ (mostly CD4)	Non-cytotoxic
Sézary syndrome	ND	Tαβ (mostly CD4)	Non-cytotoxic
Primary cutaneous CD30+ T-cell lymphoproliferative disorders		Tαβ (mostly CD4)	
Primary cutaneous anaplastic large cell lymphoma	1.7	Tαβ (CD4)	Cytotoxic (A)
Lymphomatoid papulosis	ND	Tαβ (CD4)	Cytotoxic (A)
Subcutaneous panniculitis-like T-cell lymphoma	0.9	Tαβ (CD8)	Cytotoxic (A)
Primary cutaneous γδ T-cell lymphoma	ND	Tγδ (Vδ2)	Cytotoxic (A)
Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma*	ND	Tαβ (CD8)	Cytotoxic (A)
Primary cutaneous CD4+ small/medium T-cell lymphoma*	ND	Tαβ (CD4, T_{FH})	T_{FH}
Hydroa vacciniforme-like lymphoma	ND	Tαβ (rarely NK)	Cytotoxic (A)
Nodal			
Peripheral T-cell lymphoma, not otherwise specified	25.9	Tαβ (CD4 > CD8), rarely Tγδ	Variable, a subset T_{FH}, a subset cytotoxic (A)
Angioimmunoblastic T-cell lymphoma	18.5	Tαβ (CD4, T_{FH})	T_{FH}
Anaplastic large-cell lymphoma, ALK-positive	6.6	Tαβ (likely Th2)	Cytotoxic (A)
Anaplastic large-cell lymphoma, ALK-negative*	5.5	Tαβ (Th2)	Cytotoxic (A)

Adapted from Swerdlow et al. [2].
ALK, anaplastic lymphoma kinase; EBV, Epstein–Barr virus; NK, natural killer.
Cytotoxic (NA), non activated (expression of TIA-1 only); (A), activated (expression of perforin and/or granzyme B in addition to TIA-1).
* Provisional entities.
** Statistics are based on pathologic anatomy registries, according to Armitage et al [1], with under-representation of leukaemic and cutaneous entities. ND, not determined

(EATL) which typically presents as a single or multiple jejunal lesion(s), is derived from intraepithelial lymphocytes of the intestinal mucosa. Most cases of hepatosplenic T-cell lymphoma (HSTL) are thought to derive from functionally immature cytotoxic γδ T cells of the splenic pool with vδ1 gene usage. Epidermotropic mycosis fungoides (MF), which is the most common cutaneous lymphoma, is associated with an expansion of lymphoid cells with homing properties to the skin. Altogether, this suggests the importance of tissue-specific factors in sustaining or promoting tumor growth. Interestingly, a feature common to extranodal PTCL entities is the rarity of dissemination to the bone marrow and the lymph nodes.

In addition to the neoplastic cell population PTCLs have a microenvironment component, composed of non-tumor cells and stroma, which may exhibit quantitative and qualitative variance (Fig. 1). In certain PTCL entities, the non-neoplastic component is itself a defining feature. For example, in angioimmunoblastic T-cell lymphoma (AITL), the typical vascularization and immunoblastic content of the tumor tissues are among the defining criteria of the disease (Fig. 2A). Other examples include the follicular variant of PTCL, NOS, which is named after a growth pattern of the lymphoma cells in association with follicles and follicular dendritic cells; and the lymphoepithelioid variant (Lennert's lymphoma) defined by the presence of an abundant histiocytic infiltrate (Fig. 1A). In PTCL, NOS and in ALK-positive ALCL in particular, the microenvironment component can vary significantly in individual cases, and in some instances, the abundance of the non-neoplastic component may obscure the neoplastic cell population (Fig. 1B and 1C).

The characterization of the microenvironment in PTCL remains largely unexplored and the functional interactions between the microenvironment and neoplastic components poorly understood. In this section we will focus our review on AITL, emphasize the potential contribution of the germinal center milieu to T-cell lymphomagenesis and summarize the literature on distinct environmental components in other PTCL subtypes.

2. Microenvironment in T-cell lymphomas: the paradigm of angioimmunoblastic T-cell lymphoma

2.1. From angioimmunoblastic lymphadenopathy to lymphoma

AITL, originally described in the 1970s as "angioimmunoblastic lymphadenopathy (AILD) with dysproteinemia" [7], "immunoblastic lymphadenopathy" [8] or "lymphogranulomatosis X" [9], was initially reported as a nonneoplastic lymphoproliferation and believed to represent an abnormal "hyperimmune" reaction of the B-cell system or an atypical lymphoid process, despite a clinical course characterized by multiple relapses and a fatal outcome in the majority of patients [8]. The successive designations of the disease referring to immunoblasts, granulomatous infiltrate and angiogenesis underlined the importance of the microenvironment in disease definition. Subsequently, the identification of morphologic features of malignancy in cases with features of AILD led to the designation "immunoblastic T-cell lymphoma" [10]. In the 1980s, the discovery of clonal cytogenetic abnormalities and of clonal T-cell receptor (TCR) gene rearrangements definitively established the neoplastic nature of the disease [11–14].