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Angioimmunoblastic T-cell lymphoma: a tumor of follicular helper T cells derivation with clinical and pathological relevance

Introduction

Malignancies derived from mature (post-thymic) T cells and NK cells, collectively referred to as peripheral T-cell lymphomas (PTCLs), are a heterogeneous group of diseases, altogether accounting for about 10-15% of all non-Hodgkin lymphomas in most western countries, with a great geographic variation. Irrespective of their pathobiological heterogeneity, PTCLs are, with few exceptions, aggressive diseases with poor prognosis.

According to the WHO classification (Table 1), angioimmunoblastic T-cell lymphoma (AITL) belongs to the group of PTCL with a nodal presentation.[1] The disease, first recognized as a clinico-pathological entity in the mid-seventie's and commonly referred as "angioimmunoblastic lymphadenopathy with dysproteininemia", for a while was felt to be an atypical reactive process or premalignant lesion with an increased risk of progression to lymphoma. At the end of the eighties, cytogenetics and molecular studies for clonality documented that the majority of cases were clonal T-cell proliferations from the onset. Thus, it was concluded to designate this lesion as a peripheral node based T-cell lymphoma, which was included in the updated Kiel classification and has been further recognized as a distinct clinicopathologic entity in the REAL classification and in the current WHO classification as angioimmunoblastic T-cell lymphoma (AITL).[1] Angioimmunoblastic T-cell lymphoma is the second most frequent subtype of peripheral T-cell lymphoma, accounting for up to 2-4% of all lymphomas.[2,3] AITL shows some geographic variation, being more frequent in Europe that in North America.[3]

AITL can be regarded as the paradigm of PTCL in which the microenvironment – likely to be related with its derivation from follicular helper T cells (T_{FH}) – plays a major role in the clinical and pathological features of the disease.[4] Indeed, the properties of T_{FH} cells, through the secretion of cytokines and chemokines as well as cell adhesion molecules may explain several clinicopathologic features associated with AITL.

Clinicopathologic features of angioimmunoblastic T-cell lymphoma

The disease most often arises in the elderly, with a median age around 60 years. AITL discloses a distinct clinical presentation with systemic symptoms including fever and weight loss and

polyadenopathy in most patients. Many patients have concomitant extranodal disease, most frequently involving the spleen, bone marrow, skin, liver and lungs, and the disease is stage III or IV in more than 80% of cases.[5,6] Immunologic abnormalities including hypergammaglobulinemia and hemolytic anemia are frequent. The course is usually aggressive, with occasional spontaneous remissions. The prognosis is dismal with a 5 year overall survival rate of around 30%. However, some patients experience long-term survival.[5] The clinical presentation plays a role in defining AITL although the full-blown expression with B symptoms, polyadenopathy, skin rash and immunologic abnormalities is not found in the majority of patients.

Pathologically, AITL shows distinctive features with (1) a diffuse polymorphous infiltrate containing a variable – often minor – content of medium-sized neoplastic T cells with an abundant clear cytoplasm, admixed with a variable proportion of small lymphocytes, histiocytes or epithelioid cells, immunoblasts, eosinophils and plasma cells; (2) prominent arborizing blood vessels; (3) perivascular proliferation of follicular dendritic cells (FDCs), and (4) the presence of large B-cell blasts often infected by the Epstein-Barr virus (EBV) which may morphologically mimic Reed-Sternberg cells. The neoplastic cells are mature $CD4^+\alpha\beta$ T-cells with a frequent aberrant loss of one or several T-cell markers, most commonly CD7, and a frequent coexpression of BCL6 and CD10 in at least a fraction of the tumor cells.[7-11]

In the absence of accepted specific molecular marker, the precise criteria needed to diagnose a case as AITL are not established and the full morphological spectrum of AITL is not yet fully determined. However, three patterns have been recognized,[10] according to the architectural changes from cases with follicular hyperplasia and neoplastic cells showing a follicular/perifollicular distribution to cases with a diffuse pattern. These histologic patterns are thought to represent successive stages of the disease associated with increasing numbers of neoplastic cells.[9,10,12] Morphologic variants according to the cell content, ie rich in epithelioid cels, rich in clear cells, are also recognized as well as cytological grades,[1,4,8] which do not seem to impact the clinical outcome.[5] The large cells may be neoplastic T-cells, and/or represent an expansion of B-blasts.

The various morphological aspects of AITL can generate a list of differential diagnoses and AITL can be confused with T-cell/histiocyte-

Table 1. WHO 2008 classification of mature t/nk-cell neoplasms (in press).[2]

Leukemic or disseminated
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorders of NK cells*
Aggressive NK-cell leukemia
Adult T-cell lymphoma/leukemia (HTLV1-positive)
Systemic EBV-positive T-cell lymphoproliferative disorders of childhood
Extranodal
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Hepatosplenic T-cell lymphoma
Extranodal – cutaneous
Mycosis fungoides
Sezary syndrome
Primary cutaneous CD30+ lymphoproliferative disorders
Primary cutaneous anaplastic large cell lymphoma
Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma
Primary cutaneous gamma-delta T-cell lymphoma*
Primary cutaneous aggressive epidermotropic $CD8^+$ cytotoxic T-cell lymphoma*
Primary cutaneous small/medium $CD4^+$ T-cell lymphoma*
Nodal
Angioimmunoblastic T-cell lymphoma (AITL)
Anaplastic large cell lymphoma, ALK-positive
Anaplastic large cell lymphoma, ALK-negative*
Peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS)

**Designates provisional entities*

rich diffuse large B-cell lymphoma, Hodgkin lymphoma, PTCL, NOS or the lymphoepithelioid variant of PTCL/NOS, also referred as Lennert's lymphoma.

Follicular helper T cells cells as the normal cell counterpart of angioimmunoblastic T-cell lymphoma

Importantly, recent studies have provided evidence that AITL is a neoplasm derived from the unique T-cell subset located in the germinal center, designated as follicular helper T-cells (T_{FH}) (review in 4). These normal T_{FH} cells with a $CD4^+/CD57^+/CXCR5^+/CCR7^-$ immuno-phenotype are distributed in the light zone of germinal centers where they provide functional help to B-cells by inducing expression of the activation-induced cytidine deaminase (AID) critical to the follicular B-cell differentiation. These T_{FH} cells express several characteristic markers such as the chemokine CXCL13 and its receptor CXCR5, programmed death-1 (PD-1) and Inducible T-cell Co-Stimulator (ICOS), two members of the CD28 co-stimulatory membrane receptors family, and SLAM-associated protein (SAP), a cytoplasmic adaptor protein involved in cell signalling.[13] Expression of all these molecules, in addition to BCL6 and CD10, has been demonstrated in the majority of AITL cases[9-11,14-18] In addition, the gene signature of AITL has been shown to be enriched in genes of the normal T_{FH} subset (including CXCL13, PD1, ICOS, bcl-6,…), therefore definitively establishing T_{FH} cell as the normal cell counterpart of AITL.[18] Interestingly, the molecular link between T_{FH} cells and AITL has been established in two independent gene expression profiling studies.[19,20]

The cellular derivation of AITL from T_{FH} cells provides a rational model to explain several of the peculiar pathological and biological features inherent to this disease, i.e. the expansion of B cells, the intimate association with germinal centers in early disease stages and the striking proliferation of FDCs.[4] Among the molecular mediators of T_{FH} cells, CXCL13 probably plays a major role. This chemokine critical in B-cell recruitment into germinal centers and for B-cell activation, likely promotes B-cell expansion, plasmacytic differentiation and hypergammaglobulinemia. T_{FH} cells are unique regulatory cells that also suppress conventional T cells in the GC environment through TFG-β and IL-10,[21] a finding that could at least partly explain the immune dysfunctions observed in AITL patients.

These findings also have important diagnostic implications. As mentioned above, in addition to CXCL13, several markers of the T_{FH} signature, including PD-1, ICOS and SAP have been documented by immunohistochemistry in the majority of AITL. These markers represent novel useful tools in diagnostic hematopathology. In addition, the molecular delineation of AITL as a T-cell neoplasm with a T_{FH} signature certainly will help redefining the AITL spectrum. Indeed, by gene expression profiling, we found enrichment of genes of the T_{FH} signature amongst $CD30^-$ PTCL, NOS,[19] and at the protein levels expression of T_{FH} markers has been reported in 30-40% of PTCL,NOS, suggesting that the AITL spectrum may be wider than suspected.[11,17,18] Several studies have shown that at least some of these cases disclose overlapping features with AITL.[11,17-19] Whether the spectrum of AITL should include the recently recognized group of PTCL with a prominent follicular growth pattern, also referred as "follicular PTCL",[23] which have been reported to express T_{FH} markers[24-26] remains questionable. This hypothesis might be supported by the overlapping features with AITL reported in some of these cases, although the association with a translocation t(5;9) involving ITK and SYK seems to be a

characteristic – although inconstant – feature of "follicular PTCL", not found in AITL.[26,27]

Microenvironement in angioimmunoblastic T-cell lymphoma

Non-neoplastic cells – ie B-cells, FDC, eosinophils, histiocytes, endothelial cells,… – typically represent a quantitatively major component of AITL. Accordingly, the molecular profile of AITL is characterized by a strong microenvironment imprint[19,20,28,29] with overexpression of B-cell- and follicular dendritic cell-related genes, chemokines, and genes related to extracellular matrix and vascular biology, with a specific dysregulation of several genes including Vascular Endothelial Growth Factor (VEGF). Clinically, the manifestations of the disease with B symptoms, hypergammaglobulinemia and frequent auto-immune manifestations mostly reflect a dysregulated immune and/or inflammatory response rather than direct complications of tumor growth supporting the concept of a paraneoplastic immunological dysfunction. Moreover, AITL patients have defective T-cell responses, linked to both quantitative and qualitative perturbations of T-cell subsets. The complex pathways and networks as well as the mediators linking the various cellular non-neoplastic and neoplastic components are only partly deciphered. Lymphotoxin beta demonstrated in AITL tumor cells and potentially released by B cells under CXCL13 stimulation, might be involved in inducing FDC proliferation.[30] VEGF is overexpressed in AITL and probably acts as a key mediator of the prominent vascularization observed in the disease.[20,31] By immunostaining, both neoplastic cells and endothelial cells are positive for both VEGF and its receptor, suggesting the possibility of some paracrine and/or autocrine loop.

Among non-neoplastic cells, the presence of B cells including scattered B-immunoblasts and a variable proportion of plasma cells, is a characteristic feature of AITL. These B-blasts are infected by EBV in most cases of AITL.[1,5,32] Although the exact role of EBV in the pathogenesis of AITL remains unknown (review in 32), it is rather suggested that EBV is reactivated within these B cells as a consequence of immunosuppression therefore favouring the expansion of EBV-infected B cells in a primary T-cell disorder. In keeping with this expansion of EBV-infected B-immunoblasts,[33] minor B-cell clones is found in up to one third of AITL patients,[34] which may result in some patients in the development of an EBV-associated B-cell lymphoproliferation, in most instances an EBV-positive diffuse large B-cell lymphoma.[35-37] Interestingly, HHV6B, another herpesvirus with oncogenic and immunosuppressive properties has been found by PCR in almost half of the cases.[38]

Genetic alterations in angioimmunoblastic T-cell lymphoma

The molecular alterations underlying the neoplastic transformation of T_{FH} cells remain unknown. In that respect, genetic studies have provided fairly deceptive information.[39-41] Clonal aberrations which are detected in most cases comprise trisomies of chromosomes 3, 5 and 21, gain of X, and loss of 6q whereas chromosomal breakpoints affecting the T-cell receptor (TCR) gene loci appear to be extremely rare. By matrix-based CGH, the most frequent reported chromosomal imbalances were gains at chromosomes 22q, 19 and 11p11-q14, and losses at chromosome 13q. Despite an absence of SYK-ITK rearrangement, expression of SYK has been reported as a feature common to most AITL as well as other PTCL,NOS, a feature which might represent a potential therapeutic target.[42] A role for the c-maf transcription factor has been sug-

gested, because its overexpression in transgenic mice induces the development of T-cell lymphomas, and high levels of c-maf have been detected in human AITL tissues.[43]

Altogether, the recent identification of T_{FH} as the normal counterpart of AITL may help to understand the clinicopathologic features of AITL which are likely to be mostly contributed by the microenvironment. In addition, T_{FH} markers which are now applicable in routine practice will help to delineate the spectrum of the entity, depict its overlap with PTCL-unspecified and may serve in the future of potential targets for specific therapies.

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