Angioimmunoblastic T-Cell Lymphoma

Alessandro Broccoli, MD, Pier Luigi Zinzani, MD, PhD*

KEYWORDS

• Angioimmunoblastic T-cell lymphoma • Autologous stem cell transplantation
• Brentuximab vedotin • CHOP • *DNMT3A* • Follicular T-helper • *IDH2*
• Lenalidomide

KEY POINTS

- Angioimmunoblastic T-cell lymphoma is a follicular T-helper–derived neoplasm, sharing many of its features with a proportion of peripheral T-cell lymphomas, not otherwise specified.
- New mutations have been recently described (*TET2*, *DNMT3A*, *IDH2*, *RHOA*), and fresh biological insights into the molecular pathogenesis of the disease are now available.
- Anthracycline-containing regimens represent the most widely adopted first-line option, to be followed by a consolidative autologous transplantation whenever possible.
- Newly approved agents and off-label compounds (romidepsin, belinostat, brentuximab vedotin, lenalidomide) seem active in pretreated patients but response durations are short.
- Innovative induction strategies (CHOP + biologic agent) should be designed to enhance response quality, facilitate autoSCT and prolong survival.

INTRODUCTION AND EPIDEMIOLOGY

An angioimmunoblastic lymphadenopathy with dysproteinemia was first described by the group of Henry Rappaport in the 1970s.[1] At that time, it was not recognized as a malignant condition because some patients seemed to gain long-term benefit from steroid treatment. Some investigators reported, however, that this condition was prone to progression to an overt lymphoma,[2,3] and underscored the difficulty of pathologists in establishing a clear-cut distinction between a "benign" and a "malignant" lesion based on morphology alone. Angioimmunoblastic T-cell lymphoma (AITL) is an acknowledged entity since the 1994 Revised European American Lymphoma (REAL) Classification.[4] Given that a number of recurrent mutations and a peculiar gene

Disclosure Statement: The authors have nothing to disclose.
Institute of Hematology "L. e A. Seràgnoli", University of Bologna, Via Massarenti, 9, Bologna 40138, Italy
* Corresponding author.
E-mail address: pierluigi.zinzani@unibo.it

Hematol Oncol Clin N Am 31 (2017) 223–238
http://dx.doi.org/10.1016/j.hoc.2016.12.001 **hemonc.theclinics.com**

signature characterize a significant proportion of AITL cases (see next paragraph for details), as well as some cases of peripheral T-cell lymphoma (PTCL), not otherwise specified (NOS), which manifest a follicular T-helper (T_{FH}) phenotype, the 2016 revision of the World Health Organization classification unifies under a common heading AITL, follicular T-cell lymphoma, and nodal PTCL with T_{FH} phenotype.[5]

AITL is a rare disease, which accounts for only 1% to 2% of non-Hodgkin lymphomas and 15% to 20% of PTCL.[6,7] Incidence is low, with 0.05 new cases diagnosed per 100,000 patients in the United States per year. Disease incidence is higher in Europe (29% of all cases of PTCL), followed by Asia (18%) and North America (16%): the reasons for this heterogeneity in different parts of the world are unexplained. AITL is generally regarded as the second most common PTCL entity, although it was the prevalent subtype in 2 recently published French datasets, in which it represented 36.1% of all PTCL cases.[8] This may be explained by a geographic heterogeneity of incidence across Europe, but more likely reflects a refined classification of PTCL-NOS cases by the use of novel molecular tools in more recent studies.

The purpose of this article is to provide a brief overview of the new biological insights of AITL, to discuss patients' management, and to review the currently adopted treatment strategies for newly diagnosed, relapsed, and refractory disease.

MORPHOLOGY AND MOLECULAR FEATURES

The architecture of the affected lymph node is completely effaced by a T-cell infiltrate of polymorphous small to medium-sized lymphocytes, usually with clear cytoplasm, which extends beyond the node capsule although characteristically sparing the subcapsular sinus, which appears open and dilated.[9] Regressed follicles may be appreciated, especially in earlier stages of the disease, indicating that the disease arises in association with germinal centers with the extension to extrafollicular regions as it progresses.[10] T-cell–associated antigens are demonstrated by immunohistochemistry, although neoplastic cells may show an aberrant phenotype in many instances. CD3, CD4, CD10, PD1, and sometimes BCL6 are the most frequently encountered antigens, whereas CD5 and CD7 are frequently absent. Using immunohistochemistry, it also has been demonstrated that tumor elements almost invariably express CXCL13,[11] a chemokine characteristic of T_{FH} cells, normally present in germinal centers with a helper function to follicular B-lymphocytes.

Neoplastic cells are admixed with reactive small lymphocytes, eosinophils, plasma cells, and an abundant amount of follicular dendritic cells, which represent the accompanying non-neoplastic populations. Scattered large $CD20^+$ immunoblastic cells, usually staining positively for Epstein-Barr virus (EBV)-encoded RNA (EBNA), are found in most cases (**Fig. 1**). The prominent proliferation of high endothelial venules with a tendency to arborization is a characteristic feature of AITL and reflects the overexpression of the vascular endothelial growth factor (*VEGF*) *A* gene both in lymphoma and endothelial cells.[12]

From the molecular point of view, AITL displays a peculiar signature characterized by a strong microenvironment imprint, made up of the overexpression of genes related to B cells, plasma cells, follicular dendritic cells, extracellular matrix molecules (laminin, collagen, fibronectin), enzymes, and factors involved in extracellular matrix synthesis and remodeling (transforming growth factor-β, fibroblast growth factor, matrix metalloproteinases), cell adhesion molecules (cadherins, integrins), vasculogenesis (*VEGF-A*), and coagulation.[10,12] This particular gene signature distinguishes AITL from PTCL-NOS.