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How I Diagnose Angioimmunoblastic T-Cell Lymphoma

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ABSTRACT

Objectives: *Angioimmunoblastic T-cell lymphoma (AITL) is a subtype of peripheral T-cell lymphoma derived from T-follicular helper cells. For pathologists, diagnosing AITL may be challenging due to its wide clinical and histopathologic spectrum, which can mimic a variety of reactive and neoplastic processes.*

Methods: *We summarize and discuss the clinicopathologic features of AITL, emphasizing diagnostic tools available to the practicing pathologist. Common diagnostic dilemmas are discussed.*

Results: *AITL exhibits various histologic patterns and is often associated with a prominent microenvironment that can obscure the neoplastic cells. Atypical B-cell proliferations, which can take a number of forms, are common in AITL, and clonal B-cell expansion can be seen. The atypical B cells can closely resemble Hodgkin/Reed-Sternberg cells, leading to misdiagnosis as classic Hodgkin lymphoma. Molecular studies have revealed recurrent genetic alterations, which can aid in differential diagnosis, particularly in problematic cases.*

Conclusions: *Given the complex diagnostic challenges in AITL, an integrated approach, incorporating clinical, morphologic, immunophenotypic, and molecular findings, is helpful to reach an accurate diagnosis.*

Key points

- Angioimmunoblastic T-cell lymphoma (AITL) is a peripheral T-cell lymphoma of T-follicular helper cell origin featuring a broad spectrum of clinical and pathologic manifestations and distinct molecular characteristics.
- B-cell or plasma cell expansion is common in AITL, in some cases leading to misinterpretation as B-cell lymphoma or classic Hodgkin lymphoma.
- The diagnosis of AITL requires careful integration of clinical history, morphologic findings, and immunophenotypic findings, supplemented by molecular/genetic analysis as necessary.

Angioimmunoblastic T-cell lymphoma (AITL) is a subtype of peripheral T-cell lymphoma (PTCL) with unique clinicopathologic and genetic features. While AITL accounts for only 1% to 2% of all non-Hodgkin lymphomas, it is the second most common subtype of PTCL, representing approximately 15% to 20% of all PTCLs.[1-3] When first described, it was considered an abnormal immune reaction or atypical lymphoid hyperplasia.[4,5] Subsequent identification of cytogenetic abnormalities and clonality of the T cells led to the current view of AITL as a T-cell lymphoma.[6-8] Over the past two decades, advances in gene expression profiling and next-generation sequencing technologies have brought tremendous progress in our understanding of AITL. Today, AITL is recognized as a neoplasm derived from T-follicular helper (TFHs) cells, a finding that links together many of its clinical and pathologic features.[9,10] Studies have also identified follicular T-cell lymphoma (FTCL) and other nodal PTCLs with phenotypic and molecular overlap with AITL.[11-13] These lymphomas are now grouped with AITL in the 2016 revised World Health Organization (WHO) classification in the new category of nodal T-cell lymphoma of TFH-cell origin.[14]

Despite these advances, diagnosis of AITL in many instances remains challenging. Due to the functional properties of the neoplastic TFH cells, the lymphoma is polymorphic and contains variable proportions of tumor cells and inflammatory cells. The neoplastic T cells often constitute a minor part of the cellular infiltrate and may be difficult to identify. Moreover, concomitant expansion of B cells or other immune cells may simulate diverse reactive and neoplastic conditions. The histopathologic spectrum of AITL is broad, and sometimes morphologic features can be misleading. Some borderline lesions may pose a challenge to even experienced pathologists. This article summarizes clinical and pathologic features of AITL, with particular emphasis on commonly encountered problems and unique aspects of AITL that may aid in accurate diagnosis.

Case Presentations

Case 1

The patient is a 71-year-old woman with generalized lymphadenopathy. She had a history of polymyalgia rheumatica and had been treated with low-dose steroids for 2 years. A biopsy of an axillary lymph node was performed. Flow cytometry disclosed an atypical T-cell population that was positive for CD2, CD4, CD5, and CD7, with loss of surface CD3, and negative for CD8. Forty-five percent of the T cells were positive for CD10. H&E-stained sections showed a diffuse infiltrate of atypical lymphoid cells, effacing nodal architecture **Figure 1**. Focal follicles with regressive changes were present. The paracortex showed prominent vascularity, with high endothelial venules exhibiting an arborizing pattern. While some cells resembling Hodgkin/Reed-Sternberg (HRS) cells were present, the atypia in the background lymphocytes argued against a diagnosis of classic Hodgkin lymphoma (CHL). As noted, flow cytometry suggested an abnormal phenotype with loss of surface CD3 and expression of CD10. The atypical lymphocytes were also positive for PD1 and ICOS, confirming a TFH phenotype. The HRS-like cells were positive for Epstein-Barr virus (EBV) and were rosetted by the atypical TFH population. A diagnosis of T-cell lymphoma was confirmed by clonal rearrangement of T-cell receptor genes by polymerase chain reaction (PCR). In this case, the differential diagnosis would include nodal PTCL with TFH phenotype vs AITL. Two features favor AITL in the present case: the marked expansion of CD21 dendritic cells enveloping clusters of the atypical lymphocytes and the presence of EBV-positive B cells.

Case 2

The patient is a 63-year-old woman with a several-month history of cervical and submandibular lymphadenopathy with night sweats and fever. The patient had anemia (hematocrit, 22%; hemoglobin, 71 g/L) with normal WBC count and normal platelets. She exhibited polyclonal hypergammaglobulinemia (85 U/L) and moderately elevated lactic dehydrogenase (LDH) (326 U/L). EBV viral load was detected at 420 copies/mL. Chest computed tomography showed bilateral pleural effusions and widespread lymphadenopathy affecting axillary, paratracheal, and para-aortic lymph nodes, as well as hepatosplenomegaly. A cervical lymph node biopsy was performed.

H&E sections of the lymph node **Figure 2** showed numerous follicles with germinal centers displaying a starry sky pattern. The reactive germinal centers appeared to lack well-formed mantle cuffs and instead were surrounded by medium-sized to larger lymphoid cells with clear cytoplasm and vesicular nuclei. Admixed plasma cells were present in the interfollicular region. Increased vascularity was noted in the paracortex. Immunohistochemical stains were performed for CD20, CD79a, CD3, CD4, CD8, CD10, PD1, ICOS, CD21, and IgD. Epstein-Barr virus-encoded small RNAs (EBER) in situ hybridization for EBV was performed. The IgD stain confirmed the absence of a normal mantle cuff. Instead, the germinal centers were encircled by an atypical T-cell population that was positive for PD1, ICOS, and CD10. The atypical T cells were positive for CD3 and CD4. CD21 showed follicular dendritic cell (FDC) meshworks largely confined to the follicles. EBER was positive in scattered cells in the interfollicular region (10-20/high-power field). PCR studies were performed. These confirmed a clonal rearrangement pattern for T-cell receptor γ genes and a polyclonal IG rearrangement pattern.

A diagnosis of AITL pattern I was made based on these findings. AITL pattern I can be mistaken for atypical follicular hyperplasia. A clue in the current case on H&E was the absence of well-formed mantle cuffs. Cytologic atypia was readily seen on immunohistochemical stains. AITL pattern I often lacks the FDC expansion seen in more advanced cases. Evolution of AITL pattern I to patterns II to III has been shown in patients with sequential biopsies.[15]

Clinical Features

AITL primarily affects middle-aged and elderly adults, with a median age in the fifth to sixth decades.[16] There is a slight male predominance.[17] Most patients have advanced-stage disease (stages III-IV).

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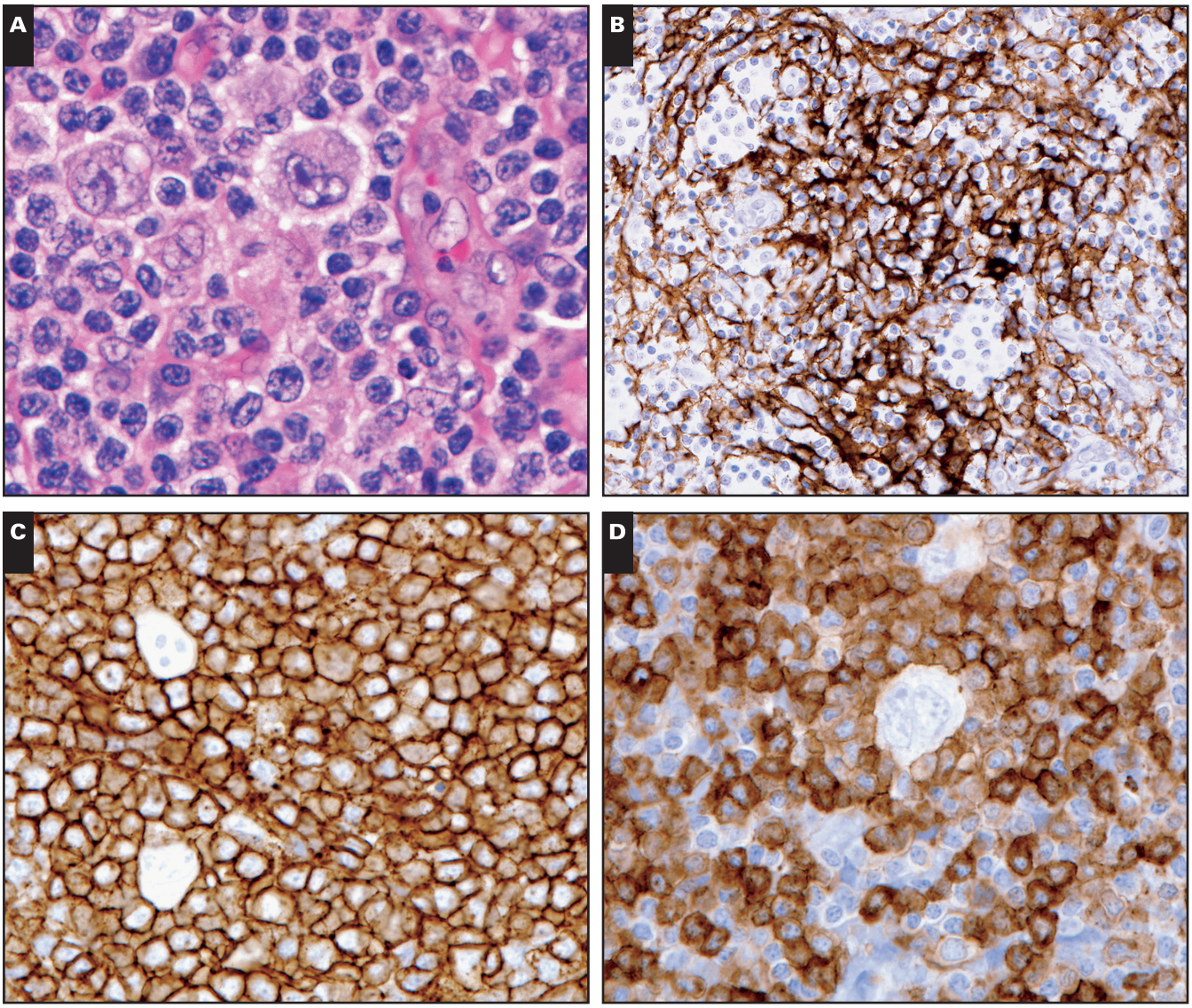

Figure 1 Angioimmunoblastic T-cell lymphoma with Epstein-Barr virus (EBV)–positive Hodgkin/Reed-Sternberg (HRS)–like cells. **A**, H&E shows a diffuse infiltrate of small- to medium-sized lymphoid cells with scattered admixed plasma cells. Prominent high endothelial venules were present. Scattered cells resembling HRS-like cells are present (×400). **B**, CD21 shows expanded dendritic cells that envelope clusters of atypical lymphoid cells (×200). The lymphoid cells are positive for CD4 (**C**, x400) and CD10 (**D**, x400).

Extranodal involvement is common. Characteristic features at presentation include constitutional symptoms, generalized lymphadenopathy (typically <1-3 cm), hepatosplenomegaly, and skin rash.[18] A significant proportion of patients also have pleural effusions and/or ascites. Bone marrow involvement has been reported in up to 70% of the cases.[19] Involvement of other extranodal sites such as lung and gastrointestinal tract can be seen but is less common.[20,21]

In addition to lymphoma-associated symptoms, many patients have immune dysregulation, resulting in autoimmune complications and immunodeficiency. There is usually polyclonal hypergammaglobulinemia and Coombs-positive hemolytic anemia.[22] Polyarthritis, vasculitis, and thyroid abnormalities are common. Laboratory tests frequently reveal circulating immune complexes, autoantibodies, cold agglutinins, elevated LDH, and hematologic abnormalities such as anemia, lymphopenia, thrombocytopenia, or eosinophilia.[23] Some patients may show evidence of immunodeficiency with opportunistic infections.[24] AITL may have a waxing and waning course, but it is generally aggressive, with a

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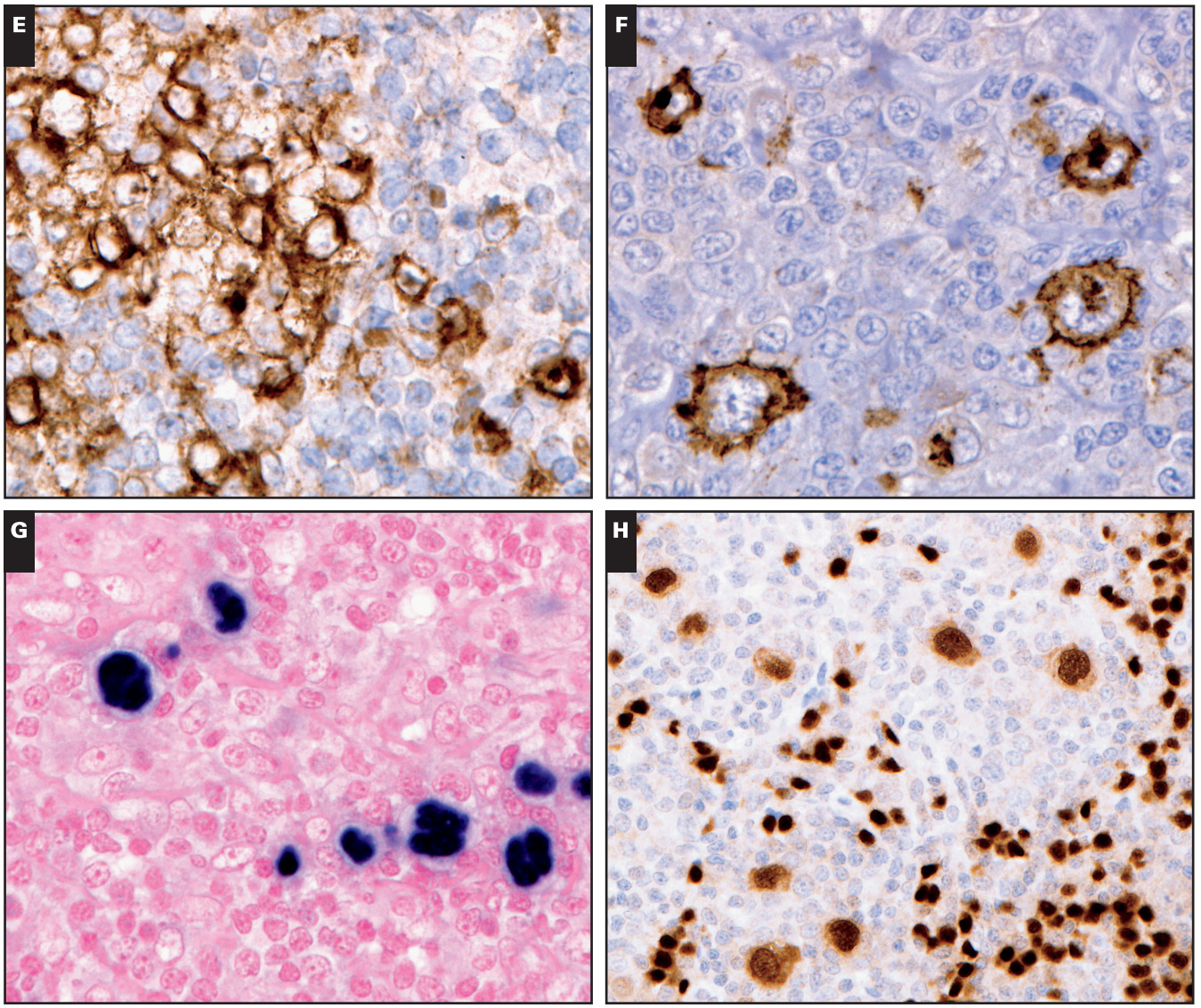

Figure 1 (cont) CD30 is positive in the HRS-like cells (**E**, x400), many of which are also positive for CD15 (**F**, x400). CD30 staining also highlights a subset of atypical lymphoid cells. The HRS-like cells are positive for EBV by EBER in situ hybridization (**G**, x400) and PAX5 (**H**, x200) and exhibit variation in morphology.

median survival of 3 years and a 5-year overall survival rate of approximately 30%.[23]

Morphology and Immunohistochemistry

Lymph nodes involved by AITL typically show partial or complete architectural effacement with perinodal extension, but peripheral cortical sinuses are often spared. The infiltrate is usually diffuse or paracortical, composed of a polymorphous population of small- to medium-sized lymphocytes, scattered immunoblasts, histiocytes, plasma cells, and eosinophils amid prominent networks of arborizing high endothelial venules (HEVs). Follicles are typically regressed or absent, but there is a proliferation of FDCs in extrafollicular regions, often surrounding the HEVs.[25] The neoplastic T cells are usually small to medium in size with clear cytoplasm, clustering around HEVs and enwrapped by FDC meshworks.[26] In some cases, the neoplastic cells may be sparse or lack overt cytologic atypia or distinct clear cell morphology. Some cases may contain numerous large B immunoblasts or abundant plasma cells, obscuring the tumor cell population. Multinucleated HRS-like cells may be seen.[27] There are rare cases rich in epithelioid histiocytes, resembling granulomatous reaction or lymphoepithelioid lymphoma. In other cases, there may be a relatively monotonous proliferation of atypical lymphocytes with

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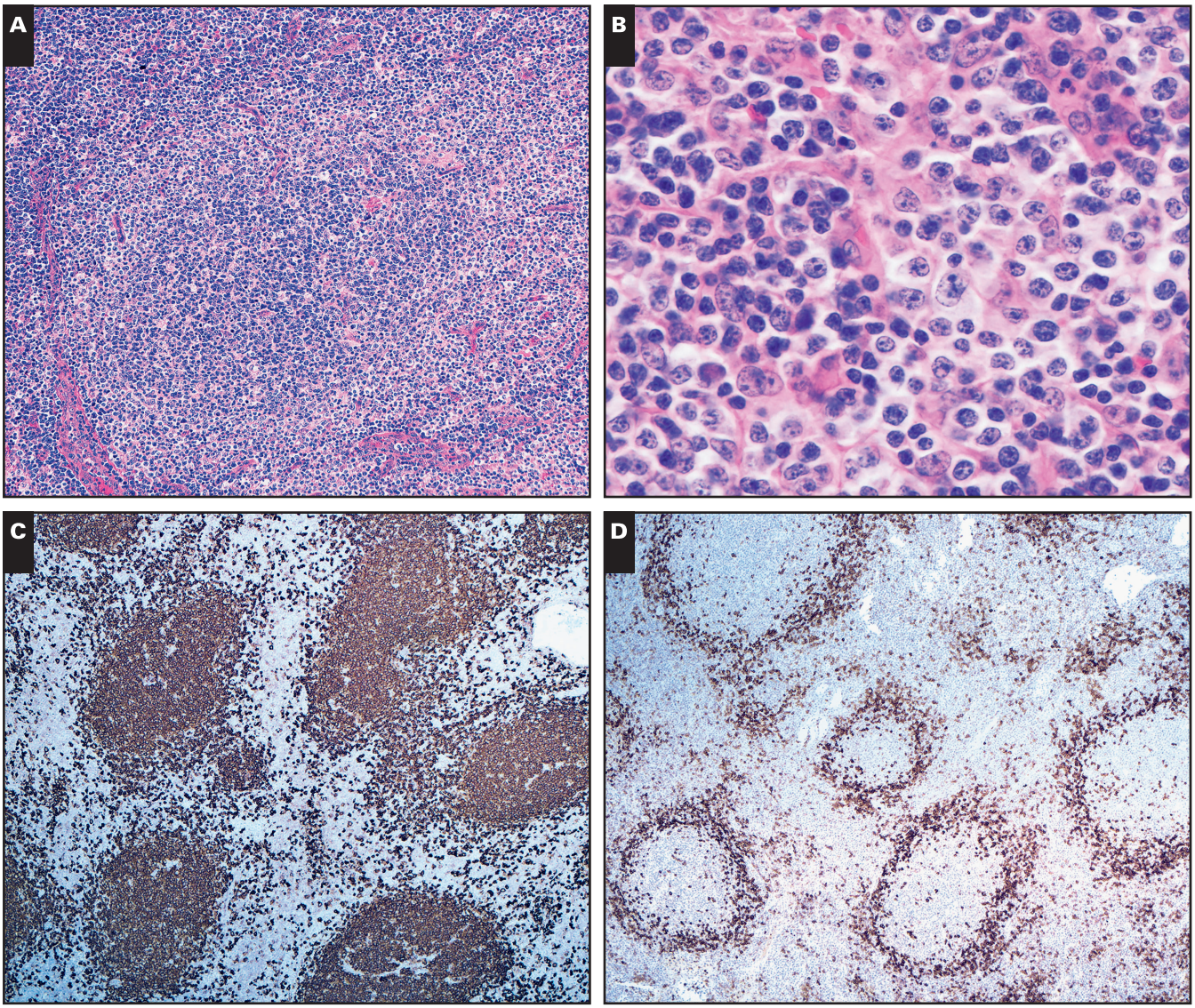

Figure 2 Angioimmunoblastic T-cell lymphoma pattern I. **A**, Reactive germinal center is surrounded by atypical cells with clear cytoplasm and immunoblastic features. High endothelial venules surround the atypical follicular structure (×100). **B**, The perifollicular cells have clear cytoplasm; admixed plasma cells are present (×400). **C**, CD20 highlights the germinal centers and scattered interfollicular B cells (×40). **D**, PD1 is strongly positive in the perifollicular T cells (×40).

sparse inflammatory component, simulating PTCL, not otherwise specified.[28]

Three overlapping histologic patterns have been described in AITL[29] Table 1. Most cases fall into histologic patterns II and III, with the typical morphologic features as described above. In pattern II, there are occasional regressed follicles, while pattern III is characterized by complete architectural effacement with no residual B-cell follicles.[29] The type I pattern is less common but can be particularly difficult to identify. Often, the lymph nodes show largely retained architecture with hyperplastic follicles, imparting an overall reactive appearance.[25,30] The follicles usually have ill-defined borders with attenuated or obliterated mantle zones surrounded by a rim of atypical clear cells. In less obvious cases, the tumor cells may be inconspicuous and are best recognized by immunohistochemical study. Progression of patterns I to III has been documented in sequential biopsy specimens and is thought to represent morphologic evolution rather than clinical progression of the disease.[15,25]

Immunohistochemistry of the lymph node shows expansion of the paracortex by a diffuse infiltrate of T cells. The B-cell areas are often reduced and sometimes compressed in the far cortex of the lymph node, which can be a helpful clue to the diagnosis of AITL. Scattered large B blasts, often CD30+ and EBV+, are frequently found

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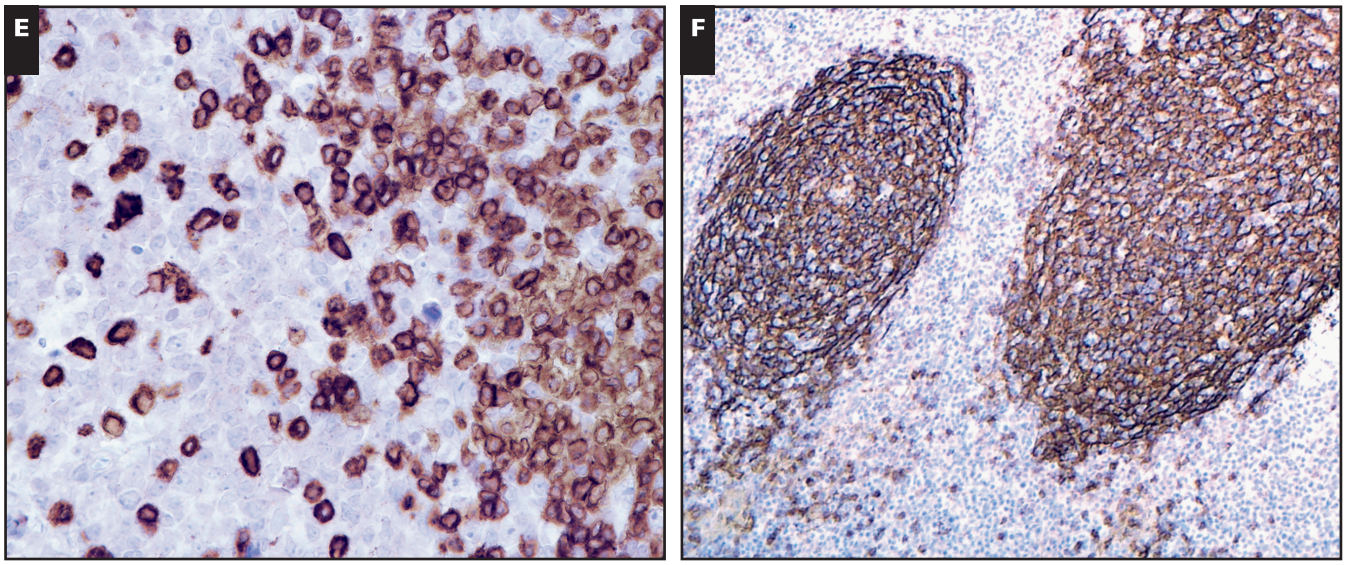

Figure 2 (cont) Perifollicular T cells show cytologic atypia seen with CD3 (**E**, x400). **F**, A CD21 stain shows well-formed follicular dendritic cell meshworks within the follicles but no expansion in the paracortex (×400).

among the T-cell infiltrate.[31] FDC markers, CD21 and CD23, typically highlight extensive FDC meshworks outside of the follicles. However, in some cases, the abnormal FDC pattern may be focal. In AITL with type I pattern, CD21 and CD23 usually show only subtle sprouts of FDCs extending beyond the germinal centers. The expanded dendritic cells may actually represent fibroblastic reticular cells, which are a lineage closely related to FDC and can upregulate expression of CD21 and CD23. These "pre-FDCs" arise in a perivascular location.[32]

Immunohistochemical assessment of the tumor cell phenotype plays a key role in the diagnosis of AITL. Immunophenotypically, the neoplastic cells are T-cell receptor (TCR) α/β T cells with expression of pan–T-cell markers (eg, CD2, CD3, and CD5), although aberrant loss or downregulation of one or more T-cell markers (commonly CD3, CD5, or CD7) is frequently observed.[33] By flow cytometry, loss of surface CD3 is very commonly seen and can be a clue to the diagnosis.[34] In a subset of the cases, the cells may show partial expression of CD30. The neoplastic cells are usually CD4+ and also express multiple TFH-related antigens, including PD1/CD279, CD10, BCL6, CXCL13, ICOS, SAP, c-MAF, CD200, and CXCR5.[9,29,35-39] It is important to note that these markers are not always specific, and conversely, not all TFH markers can be detected in an otherwise typical case of AITL. Moreover, attention should be paid to the intensity and distribution of TFH markers, and staining pattern should correlate with morphology. Because reactive paracortical T cells with weak and variable expression of PD1 are almost invariably present, only strong staining of PD1 is diagnostically useful.[40,41] CD10 is usually positive in only a small subset of the neoplastic cells and may show variable staining intensity. Among the TFH markers, PD1/CD279 and ICOS are reported to be most sensitive, whereas CXCL13 and CD10 are less sensitive but more specific.[42] As such, the 2016 WHO classification suggests that at least two (ideally three) TFH markers be expressed by the neoplastic cells to diagnose a case of PTCL as having a TFH phenotype.[43] **Table 2** summarizes immunohistochemical markers commonly used to diagnose AITL in routine clinical practice.

Possibly owing to the inherent function of the neoplastic cells as TFH, AITL is frequently accompanied by a proliferation of B cells. Findings that can be seen include polyclonal or clonal proliferation of large B cells, HRS-like cells, and plasma cells, which can be positive or negative for EBV. Studies have reported that more than 80% of AITLs contain a variable number of EBV-positive B cells, ranging from isolated or small clusters of B immunoblasts to focally confluent EBV-positive large B cells.[31,44] This proliferation may be so marked as to suggest a diagnosis of EBV-positive diffuse large B-cell lymphoma (DLBCL), either at initial diagnosis or during disease course.[15,44,45] Alternatively, the EBV-positive B cells may resemble HRS cells both morphologically and phenotypically, leading to a mistaken diagnosis of CHL.[27,46] The expansion of EBV-infected cells was thought to be related to defective immune surveillance for EBV.[24] However, rare cases with EBV-negative HRS-like cells have also been reported, suggesting other mechanisms for the abnormal B-cell proliferation.[46] As discussed below, the B cells in

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Table 1
Comparison of the Three Histologic Patterns of AITL

	Pattern I	Pattern II	Pattern III
Nodal architecture	Largely preserved	Partially or largely effaced	Completely effaced
B-cell follicles	Hyperplastic follicles with attenuated mantle cuffs	Scattered follicles, usually with regressive changes	Largely absent, atretic follicles confined to far cortex
FDC meshwork	No significant expansion or minimal expansion of FDCs around germinal centers	Prominent extrafollicular proliferation of FDCs, usually surrounding HEVs	Irregular proliferation of FDCs, usually surrounding HEVs
Neoplastic cells	Atypical T cells with predominantly perifollicular distribution	Aggregates of atypical T cells within the paracortex	Large aggregates or sheets of atypical T cells
Background	Perifollicular polymorphic infiltrate	Polymorphic paracortical infiltrate, HRS-like cells may be present	Diffuse polymorphic infiltrate, HRS-like cells may be present

AITL, angioimmunoblastic T-cell lymphoma; FDC, follicular dendritic cell; HEV, high endothelial venule; HRS, Hodgkin/Reed-Sternberg.

Table 2
Common Markers Used for Diagnosis of AITL

Markers	Utility	Comment
CD20 and PAX5	Identify B-cell follicles, the distribution, proportion, and cytologic features of B cells in the infiltrate	B immunoblasts and HRS-like cells are variably positive for CD20 and PAX5
CD3	Access the distribution, proportion, and cytologic features of T cells in the infiltrate; identify T cells with cytologic atypia and/or altered expression of pan–T-cell antigens	Dim expression or loss of surface CD3 is found in a subset of AITL
CD2, CD5, and CD7	Identify T cells with cytologic atypia and/or altered expression of pan–T-cell antigens	Loss of CD7 is common in AITL
CD4 and CD8	Access the distribution, proportion, and cytologic features of T-cell subsets	Atypical T cells are CD4+ in >90% of AITLs
CD21 and CD23	Identify FDC meshworks underlying follicles and extrafollicular proliferation of FDC meshworks, usually around HEVs	CD21 is generally more sensitive than CD23
CD10	Highlight reactive germinal centers; help identify atypical T cells with a TFH phenotype	Less sensitive but more specific. CD10 is often weak, heterogeneous, and confined to a small subset of the atypical T cells
BCL6	Highlight reactive germinal centers; help identify atypical T cells with a TFH phenotype	Less sensitive but more specific
PD1	Help identify atypical T cells with a TFH phenotype	Very sensitive but less specific; strong PD1 is more specific than weak staining
ICOS	Help identify atypical T cells with a TFH phenotype	Very sensitive (>90% sensitivity) but less specific
CXCL13	Help identify atypical T cells with a TFH phenotype	Less sensitive but more specific; cytoplasmic staining with a perinuclear dot pattern
CD30	Highlight B immunoblasts and HRS-like cells; may highlight a subset of the atypical T cells	CD30+ atypical T cells can be found in 20% to 30% of AITLs
κ and λ	Evaluate for light chain restriction in plasma cells	Polytypic plasmacytosis is common; monotypic plasma cells can be found in rare cases
EBV ISH	Identify EBV-positive B blasts	Varying numbers of EBV-positive cells can be found in 80% to 90% of AITLs

AITL, angioimmunoblastic T-cell lymphoma; EBV, Epstein-Barr virus; FDC, follicular dendritic cell; HEV, high endothelial venule; HRS, Hodgkin/Reed-Sternberg; ISH, in situ hybridization; TFH, T follicular helper.

AITL may harbor mutations in *TET2*, similar to the neoplastic T cells, suggesting possibly common mutational events in a hematopoietic stem cell.[47,48]

AITL is also often associated with plasmacytosis.[49,50] Sometimes the plasma cells may be abundant, obscuring the underlying neoplastic T cells.[50] In rare instances, patients may have marked peripheral blood and/or bone marrow plasmacytosis.[19,51,52] The plasma cell expansions in AITL are thought to result from the increased release of cytokines such as interleukin (IL)–6 or IL-10.[53] The plasma cells in most cases are polyclonal and EBV negative, but clonal plasma cell proliferations also have been reported.[49,50]

Skin and Bone Marrow Involvement

In addition to lymph nodes, skin and bone marrow involvement by AITL is also frequent. The histologic findings of AITL involving skin are subtle histologically.[54] Skin biopsy specimens often show mild perivascular or periadnexal lymphoid infiltrates that may be difficult to

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differentiate from inflammatory conditions. Characteristic features of nodal AITLs, such as clear cells, vascular hyperplasia, and EBV-positive cells, are seen in only a minority of cases.[55] Immunohistochemistry for TFH markers may be helpful to identify the neoplastic cells, and PCR studies have identified a monoclonal T-cell population in more than 80% of cases.[54,56] However, it is important to note that a TFH immunophenotype is not entirely specific for AITL, and it can also be seen in primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder and other cutaneous T-cell lymphomas.[54] Correlation with clinical history and lymph node pathology is essential in these cases, as the skin biopsy specimen alone is usually not definitive.

In bone marrow, AITL usually shows single or multiple loose nodular lymphoid infiltrates with a paratrabecular or interstitial distribution pattern.[19,51,57] The infiltrate is often polymorphic, composed of many small or scattered larger lymphocytes, histiocytes, variable eosinophils, and, occasionally, aggregates of clear cells. Various secondary changes such as trilineage hematopoietic hyperplasia, polyclonal plasmacytosis, and myelofibrosis may be present. Immunohistochemical studies have shown a more subtle expression of the TFH markers in the bone marrow than lymph node. Nevertheless, immunohistochemical staining of the TFH markers, such as PD1, BCL6, and CXCL13, can still be helpful for detecting lymphomatous infiltrates. In addition, it has been recognized that most cases of AITL display a unique sCD3(–/dim)/CD4+/CD10 variable phenotype by flow cytometry.[34,58,59] Thus, flow cytometry is an effective tool in identifying small populations of aberrant T cells and can assist in diagnosis and monitoring of AITL, particularly in fluid specimens such as peripheral blood and bone marrow.[34,58]

Molecular and Genetic Features

Most AITLs show clonal or oligoclonal rearrangement of the T-cell receptor genes. In addition, clonal and oligoclonal rearrangements of the B-cell receptor genes are found in up to 50% of cases, in part due to the expansion of EBV+ B cells.[60] By conventional cytogenetic analysis, clonal abnormalities, most commonly trisomy 3, trisomy 5, trisomy 21, additional X chromosome, and loss of 6q, are detected in approximately 70% of AITL cases.[61,62] The t(5;9)(q33;q22);*ITK-SYK*, which is reported in around 20% of follicular T-cell lymphomas, has been identified infrequently in AITL.[12,63,64]

In the past two decades, significant progress has been made in understanding the pathobiology and pathogenesis of AITL. The tumor cells in AITL are recognized to originate from TFH cells based on gene expression profiling.[9,10] Whole-exome sequencing and targeted sequencing studies have identified a group of recurrent mutations, including genes encoding the epigenetic regulators, *TET2* (50%-80%), *DNMT3A* (20%-30%) and *IDH2* (20%-45%), the small GTPase, *RHOA* (50%-70%), and the components of the TCR signaling pathways such as *PLCG1* (14%), *CD28* (9%-11%), *FYN* (3%-4%), and *VAV1* (5%).[65-71] Among these mutations, the $RHOA^{G17V}$ mutation, present in up to 70% of AITLs, is also commonly observed in other T-cell lymphomas with the TFH phenotype but is seldom detected in other cancers.[48,69,71,72] Therefore, it is considered a hallmark and genetic indicator for TFH lymphoma. In contrast, the $IDH2^{R172}$ mutation, occurring at a frequency of 20% to 30%, is found in AITL and is rare in other PTCLs with the TFH phenotype.[70,72]

Importantly, studies have shown that *TET2* and *DNMT3A* mutations are not restricted to T cells but can also be identified in the admixed mature B cells in the lymph nodes and the hematopoietic stem cells of patients with AITL, whereas *RHOA* and *IDH2* mutations appear confined to the neoplastic T cells.[66,73,74] In light of these and some other findings, a multistep and multilineal tumorigenesis has been suggested, in which initial epigenetic deregulation (*TET2*, *DNMT3A*) occurring in hematopoietic stem cells in cooperation with subsequent mutations in genes important for T-cell function (*RHOA*, *VAV1*, *PLCG1*, *CD28*, and others) leads to AITL.[72] Interestingly, previous studies have shown that clonal hematopoiesis (CH) and myeloid neoplasms such as chronic myelomonocytic leukemia and acute myeloid leukemia are more frequent in patients with AITL than in the general population.[75] In some patients, the myeloid neoplasms and AITL share common ancestral mutations in *TET2* and/or *DNMT3A*, suggesting that they arise from divergent evolution of a common CH clone.[76,77] Moreover, Nguyen et al[74] recently reported that in addition to *TET2* and *DNMT3A* mutations, the B cells in AITL lymph nodes can acquire additional B-cell–specific mutations in *NOTCH1* and other genes, which may account for the frequent occurrence of clonal B-cell expansion in AITL.

Other Nodal Peripheral T-Cell Lymphoma With TFH Phenotype

In addition to AITL, the 2016 revised WHO classification included two provisional entities of PTCL-TFH, namely, FTCL and nodal PTCL with a TFH phenotype. In FTCL, lymph nodes typically show a

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predominantly nodular/follicular growth pattern, mimicking follicular lymphoma. The neoplastic T cells tend to form small aggregates dispersed in the B-cell nodules.[12] These lesions may contain EBV-positive or EBV-negative HRS-like cells but usually do not have a prominent inflammatory background and lack proliferation of HEVs or extrafollicular expansion of FDC meshworks.[46] Despite morphologic differences, the immunophenotypic and molecular features overlap with AITL.[11] Furthermore, there are a few reports of patients with typical features of AITL at initial presentation but FTCL in subsequent biopsy specimens or vice versa, suggesting that these entities may represent variations along the spectrum of a common disease.[12]

Diagnostic Challenges

Accurate diagnosis of AITL can be difficult due to its diverse clinical symptoms and wide histopathologic changes, which can mimic a variety of benign and malignant lymphoid proliferations ▮Table 3▮. One of the common challenges is identifying "early" AITL cases (type I pattern) and separating them from reactive paracortical hyperplasia. In addition, B-cell proliferations that accompany AITL may also pose a challenge in the differential diagnosis. In particular, the presence of HRS-like cells may lead to misdiagnosis as CHL. Distinguishing AITL from other nodal PTCL-TFHs can be particularly difficult, although it currently has no impact on clinical management. Given the complex heterogeneous nature of AITL, a multiparameter approach with careful integration of clinical history, morphology, and immunophenotypic findings, supplemented by molecular/genetic analysis as necessary, is essential to make an accurate diagnosis. In the next section, we discuss some of the most common questions about the diagnosis and differential diagnosis of AITL.

Questions for the Experts

1. How do we distinguish AITL with a type I pattern from reactive paracortical hyperplasia?

A significant proportion of AITL cases (up to 17%) present histologically with the type I pattern (also called "early" pattern).[29,30] The distinction between type I AITL and reactive paracortical (T-zone) hyperplasia can be challenging due to their overlapping morphologic features.[29] As mentioned earlier, AITL pattern I usually comprises hyperplastic follicles with ill-defined borders and attenuated mantle zones. While the presence of atypical clear cells at the outer rim of the germinal centers favors AITL, in many cases, the atypical cells may be inconspicuous, and morphologic findings alone are insufficient to signify a correct diagnosis.

Immunohistochemical staining for the TFH cell markers, particularly PD1, is of great value in distinguishing AITL type I with reactive paracortical hyperplasia. In paracortical hyperplasia, strong PD1-positive cells are confined to the germinal centers (primarily to the light zone at the periphery of germinal centers), although there may be scattered or sometimes numerous extrafollicular T cells with variable and weak PD1 positivity.[40] In contrast, PD1 demonstrates a strong perifollicular staining pattern in AITL, corresponding to the "perifollicular" distribution of neoplastic TFH cells. Markers such as CD10, if strongly expressed in perifollicular T cells, are a helpful clue. Expansion of CD21+ meshworks with a perivascular distribution, seen in pattern II or III, is usually not evident in pattern I. The presence of interfollicular EBV-positive B blasts is also helpful but may not be a distinguishing feature, as it can also be seen in acute and chronic EBV infection as well as other lymphoproliferative disorders.

Clinical features have particular importance in the diagnosis of AITL. Interestingly, despite early involvement (pattern I) histologically, many patients reportedly had clinically advanced disease.[15] Caution should be exercised in cases that lack characteristic clinical symptoms. If an early AITL is suspected, clonality studies should be obtained. The findings of clonal T-cell gene rearrangement, with or without concurrent B-cell gene rearrangement, are helpful in confirming a diagnosis of AITL. As always, the final diagnosis should be based on both the clinical and pathologic features as well as the molecular findings. In equivocal cases, close follow-up and repeat biopsy are recommended to establish a definitive diagnosis.

2. Where should we draw the line between B-cell proliferation in AITL and so-called composite lymphoma?

As mentioned previously, the presence of large B cells, often with immunoblastic features, usually but not always infected by EBV, is a characteristic feature of AITL.[46] These cells are typically scattered in the interfollicular zone, sometimes showing an HRS-like appearance.[27] However, in some cases, there may be prominent expansion of EBV-positive B cells, forming large clusters to confluent foci of large transformed B cells, focally obscuring the coexisting T-cell component.[44] B-cell proliferation may progress, and so-called secondary large B-cell lymphomas have been reported in a few cases, occurring simultaneously or before the initial diagnosis of AITL or, more commonly, at relapse.[44,45]

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Table 3
Differential Diagnosis of AITL

Entity	Confusing Features	Features Favoring Diagnosis of Entity	Features Favoring Diagnosis of AITL
Reactive paracortical hyperplasia	Paracortical expansion Immunoblastic proliferation Extrafollicular T cells with variable and weak PD1 positivity Increased vascularity	No definite cytologic atypia Strong CD10 or PD1-positive cells are confined to the germinal centers No FDC meshwork outside germinal centers No clonal rearrangement	Atypical clear cells at the outer rim of the germinal centers or around HEVs TFH markers such as CD10 and PD1 are strongly expressed on interfollicular or perifollicular atypical T cells FDC meshwork outside germinal centers EBV-positive immunoblasts and HRS-like cells Oligoclonal or monoclonal TCR rearrangement Monoclonal IG rearrangement sometimes present
Classic Hodgkin lymphoma	HRS-like cells, frequently EBV positive Polymorphic background	Bands of fibrosis Nodular growth pattern No atypical T-cell population TFH markers highlight a single layer of reactive T cells forming rosettes around HRS cells CD30 staining restricted to the HRS cells No clonal TCR rearrangement	Open peripheral sinuses; prominent arborizing HEVs TFH markers highlight aggregates of atypical T cells surrounding the HRS-like cells The neoplastic T cells may express variable CD30 Monoclonal TCR rearrangement
Peripheral T-cell lymphoma, NOS	Atypical T-cell population with frequent loss of T-cell antigens	Lack of characteristic TFH phenotype Lack of extrafollicular FDC meshwork or prominent arborizing HEVs	Polymorphous infiltrate; Extrafollicular FDC meshwork Prominent arborizing HEVs Expression of at least two (ideally three) TFH markers Occasional EBV-positive immunoblasts
Diffuse large B-cell lymphoma	Large B-cell proliferation Monoclonal IG rearrangement	Cohesive sheets of large B cells No atypical T-cell population in the background No clonal TCR rearrangement	Atypical T cells with TFH phenotype in the background Extrafollicular FDC meshwork Prominent arborizing HEVs Monoclonal TCR rearrangement
Nodal marginal zone lymphoma	B-cell proliferation Monoclonal plasma cells may be present Extrafollicular T cells with variable and weak PD1 positivity Monoclonal IG rearrangement	No atypical T-cell population in the background No clonal TCR rearrangement	Atypical T cells with TFH phenotype in the background Extrafollicular FDC meshwork Monoclonal TCR rearrangement EBV-positive immunoblasts and HRS-like cells

AITL, angioimmunoblastic T-cell lymphoma; EBV, Epstein-Barr virus; FDC, follicular dendritic cell; HEV, high endothelial venules; HRS, Hodgkin/Reed-Sternberg; IG, immunoglobulin; NOS, not otherwise specified; TCR, T-cell receptor; TFH, T follicular helper.

Moreover, there are rare reports of AITL and DLBCL in the same anatomic site, so-called composite AITL and large B-cell lymphoma.[78,79] Our own clinical experience suggests that that prognosis is dominated by AITL and that the EBV-positive B-cell expansions are less significant clinically. Given the B-cell expansion in AITL, rituximab had been incorporated into clinical treatment protocols, but long-term clinical benefit was not shown for this approach.[80] Therefore, a diagnosis of "composite" lymphoma is generally not made in these cases. Recent data have found shared mutations within the B cells and T cells in some cases of AITL, raising the possibility that AITL arises in a pluripotential stem cell. These observations are provocative but require further investigation to decipher the clonal relationship of the B cells and T cells within AITL.

3. How many TFH markers are needed for the diagnosis of AITL, and which ones need to be done routinely?

Since being recognized in the 1970s, several immunohistochemical and flow cytometric markers have been reported that could aid in the identification of neoplastic TFH cells in AITL. These include surface markers PD1, CD10, CD200, ICOS, and cytoplasmic SAP; transcription factor BCL6 and c-MAF; the chemokine CXCL13 and its receptor CXCR5; and so on.[9,29,35-39]

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Among TFH markers, PD1 and ICOS are more sensitive for identifying the neoplastic TFH cells, whereas CXCL13 and CD10 are more specific.[42] However, none of the TFH markers in isolation is 100% sensitive or specific for the TFH phenotype. For this reason, the 2016 WHO requires demonstrating expression of at least two but ideally three TFH markers to establish a diagnosis of TFH lymphoma.[14] We routinely perform CD10, BCL6, ICOS, and PD1 stains on all cases and additional TFH markers such as CXCL13 when necessary. Basha et al[81] recently evaluated the utility of a five-marker TFH panel (CD10, BCL6, PD1, CXCL13, and ICOS) for the diagnosis of AILT and PTCL-TFH. They showed that while a four-marker panel (CD10, BCL6, PD1, CXCL13) was adequate to diagnose most AITLs, a five-marker panel with the addition of ICOS significantly increased the ability to identify PTCL-TFH. A significant issue is intensity, since many of these markers (PD1, ICOS) can be dimly positive, a feature with less specificity. With CD10, the number of positive cells may be only few, but if they are cytologically atypical, even few positive cells are relevant. It is important to bear in mind that AITL is based on a constellation of clinical and pathologic features. In a classic case, with expansion of FDCs around the HEVs, arborizing vascular proliferation, and increased EBV-positive cells, fewer TFH markers may be required to reach a confident diagnosis of AITL.

4. How do we differentiate AITL and other PTCL of TFH derivation with HRS-like cells from classic Hodgkin lymphoma?

As mentioned earlier, HRS-like cells are common findings in lymphomas of TFH derivation, such as AITL and FTCL, and can assume both the morphology and immunophenotype of classic Reed-Sternberg cells of Hodgkin lymphoma.[46] As atypia in the background T-cell population may be minimal, a potential pitfall in the differential diagnosis of the lymphomas of TFH derivation is misdiagnosing CHL. This is especially so in FTCL, in which HRS-like cells are present in a background of small lymphocytes with a nodular growth pattern, closely mimicking lymphocyte-rich CHL.[82]

Like CHL, the HRS-like cells in PTCL-TFH are consistently positive for CD30 and show weak PAX5, often with coexpression of CD15, negative or variably positive for CD20. In PTCL-TFH, the HRS-like cells are commonly EBV infected, and in situ hybridization for EBER most often highlights a wider range of positive cells than seen in EBV-positive CHL; however, this is not always the case. The key to the correct diagnosis lies in the recognition of a background atypical T-cell component with appropriate immunophenotypic and molecular studies. In FTCL, immunostaining characteristically highlights aggregates of small- to medium-sized, mildly atypical T cells with a TFH immunophenotype, surrounding the HRS-like cell. In contrast, TFH markers usually identify a single layer of reactive T cells forming rosettes around HRS cells in lymphocyte-rich CHL.[46,82] Accordingly, immunophenotyping by flow cytometry frequently detects a distinct CD3−/dim CD4+ T-cell population in AITL and FTCL but not in CHL, which may also provide a clue in the differential diagnosis.[34] In some cases of PTCL-TFH, the neoplastic T cells may also express variable CD30, whereas CD30 staining is typically restricted to the HRS cells in CHL. A common finding is clusters of atypical CD30+ or MUM1+ T cells surrounding the HRS-like cells. The findings of open peripheral sinuses, prominent arborizing HEVs, and extrafollicular FDC expansions are helpful features to suggest a diagnosis of AITL rather than CHL. While the correct diagnosis can generally be made based on morphologic and immunophenotypic findings, in difficult cases, molecular studies may be necessary to confirm the diagnosis.

Conclusions

AITL is a neoplasm of TFH cells with a constellation of clinical symptoms and pathologic characteristics that can pose diagnostic challenges. An integrated approach, incorporating clinical, histologic, immunophenotypic, and molecular findings, is essential to reach an accurate diagnosis. The growing knowledge of the molecular underpinnings of TFH lymphoma has improved our understanding of its pathobiology and will continue to aid in the diagnosis, especially of problematic cases, leading to a more precise classification and, eventually, better therapeutic strategies for patients with PTCL-TFH.

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