Review

Peripheral T-Cell Lymphomas of the T Follicular Helper Type: Clinical, Pathological, and Genetic Attributes

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Abstract: Follicular helper T-cell (TFH) lymphomas comprise a unique group of T-cell lymphomas that represent neoplastic proliferations of follicular helper T-cells and share genetic, immunophenotypic, morphologic, and clinical features. Angioimmunoblastic T-cell lymphoma (AITL) is the prototypical TFH lymphoma; in addition, the 2017 revised World Health Organization (WHO) 4th edition recognizes two other unique subtypes: follicular T-cell lymphoma (FTCL) and nodal peripheral T-cell lymphoma with the T follicular helper phenotype (PTCL-TFH). This review discusses the morphologic spectrum, immunophenotype, diagnostic mimics/pitfalls, and unique genetic attributes of this category of T-cell lymphomas.

1. Introduction

Follicular helper T-cells (TFHs) are a specialized subset of CD4-positive helper T-cells that are essential for germinal center formation, B-cell maturation, and the development of high-affinity antibodies [1,2]. TFH differentiation from naive CD4-positive helper T-cells is a complex multistep process that is initiated by the interaction between dendritic cells (DCs) and T-cells and mediated by interleukin-6 (IL-6), inducible costimulatory (ICOS), and T-cell receptor (TCR) molecules [3]. The second stage of TFH maturation occurs during T-cell interaction with antigen-specific B-cells in the follicle or interfollicular areas. TFH and B-cell maturation in the follicle is a symbiotic process [4] and is mediated by the BCL6-IRF4-BLIMP1 transcriptional axis [5]. TFH maturation is completed in the germinal center (GC), and the majority of GC TFH cells express CD4, CXCR5, PD1, BCL6, CD10, CXCL13, and ICOS [1,6–8]. Mature TFH cells are not confined to the GC; they can exit the follicle and enter a different GC, or return to the same GC, or downregulate BCL6 and become memory TFH cells [1].

The most important function of TFH cells is GC development and function, enabling B-cell maturation and high-affinity antibody production. This critical process is exquisitely regulated and defective TFH function results in suboptimal immune responses to viral infections such as human immunodeficiency virus (HIV) [9]. TFH cells are also implicated in autoimmunity, with increased circulating TFH-like cells seen in some patients with systemic lupus erythematosus (SLE) and Sjögren's syndrome [10]. TFH cells also seem to play a role in cancer immunity, and it is postulated that they may help maintain ectopic lymphoid structures and potentially affect prognosis [11].

Understanding TFH cell maturation has also allowed the identification of these cells in normal lymphoid tissue and in neoplastic lymphoid proliferations, such as lymphomas. It is now understood that a subset of peripheral T-cell lymphomas (PTCL) represents neoplastic

proliferations of TFH cells, the best-characterized of which is angioimmunoblastic T-cell lymphoma (AITL), which has unique clinical and pathologic features [12,13]. Two additional nodal T-cell lymphomas with different morphologic features than AITL, but sharing a TFH cell immunophenotype and genetic and molecular features have been described: follicular T-cell lymphoma (FTCL) and nodal peripheral T-cell lymphoma with the TFH cell phenotype (PTCL-TFH) [14–16]. Additionally, cutaneous T-cell proliferations with the TFH cell phenotype have also been described [17].

To reflect this understanding, the 2017 WHO Classification has removed FTCL and PTCL-TFH from the PTCL, not otherwise specified (PTCL, NOS) category and included them with AITL as subtypes of a new broader category, nodal lymphomas of T-follicular helper (TFH) origin (Table 1) [18]. Cutaneous TFH proliferations are not included in this category, as they do not share clinical or molecular features with nodal TFH lymphomas [19].

Table 1. 2017 WHO classification of T follicular helper cell (TFH) lymphomas.

Angioimmunoblastic T-Cell Lymphoma and Other Nodal Lymphomas of T Follicular Helper (TFH) Cell Origin
Angioimmunoblastic T-cell lymphoma
Follicular T-cell lymphoma
Nodal peripheral T-cell lymphoma with the TFH phenotype

From a practical and diagnostic standpoint, TFH lymphomas share some features. By flow cytometry, many cases show an aberrant CD3 (dim/−)/CD4+ T-cell population [20]. The most commonly used markers for identifying TFH T-cells in paraffin-embedded tissue are CD10, BCL6, PD1, CXCL13, CXCR5, ICOS, SAP, CD200, and MAF, and the recommendations for assigning a TFH phenotype include expression of at least two, ideally three TFH markers [1,6–8,12,13,18,21–24]. Given the varying sensitivities of immunohistochemical stains, utilizing a panel of markers to identify these T-cell lymphomas in routine practice is a prudent approach [25].

2. Angioimmunoblastic T-Cell Lymphoma

Angioimmunoblastic T-cell lymphoma is the prototypical member of the TFH family of PTCLs [26]. AITLs have unique clinicopathologic and pathologic features. Lymph node biopsies are characterized by a polymorphous infiltrate, effaced architecture, and expanded follicular dendritic cell (FDC) meshworks, which especially encircle the proliferating high endothelial venules (HEVs). In addition to cytogenetic abnormalities, AITLs also demonstrate a unique gene expression signature and mutational profile that is partly shared with other TFH lymphomas (discussed in detail later) [13,15,16,27–29].

2.1. Epidemiology and Clinical Features

AITL occurs usually in middle-aged and elderly patients and with a male predominance [30,31]. While it accounts for only 1–2% of non-Hodgkin's lymphoma, it is one of the more common T-cell lymphomas and constitutes 15–20% of non-cutaneous T-cell lymphomas [32,33].

Patients typically have high-stage (III-IV) disease with frequent bone marrow involvement [34]. They present with diffuse lymphadenopathy, hepatosplenomegaly, skin rashes (with or without pruritus), pleural effusion, ascites, and arthritis [30,31,35–37]. Extranodal involvement is usually seen in the liver, spleen, skin, and bone marrow, but other sites such as the lung and gastrointestinal tract can be infrequently involved [31,35,36].

Laboratory studies show polyclonal hypergammaglobulinemia, cold agglutinins, Coombs-positive hemolytic anemia, positive rheumatoid factor, anti-smooth muscle antibodies, and elevated LDH [31,38]. Complete blood counts usually show cytopenia(s) with or without eosinophilia. Patients also demonstrate immune dysfunction, immunodeficiency, and frequent EBV infection. The proliferation of EBV-positive B-cells suggest an etiologic role of EBV in this lymphoma [39,40].

Patients can have a variable clinical course, but the disease tends to be aggressive with a median survival of less than 3 y [41]. Histology or genetics do not influence the outcome [18].

2.2. Morphology and Immunophenotype

Lymph node biopsies are the most common specimens in routine practice that pathologists encounter for AITL diagnosis. An excisional biopsy is the ideal specimen, and diagnoses on small core biopsies might be challenging because of a lack of an architectural context and a paucity of tissue for ancillary tests. A diagnosis of AITL can be especially challenging in extranodal site biopsies.

Lymph node excisional biopsies generally demonstrate effacement of the architecture by a polymorphous infiltrate composed of small, atypical lymphocytes (usually with a clear cytoplasm), plasma cells, macrophages, and scattered larger cells, which appear either immunoblastic or sometimes Hodgkin's-/Reed–Sternberg cell (HRS)-like. The atypical lymphocytes are clustered especially around proliferating high endothelial venules, which are rather prominent in the biopsies. The subcapsular sinuses tend to be distended. Biopsies can also demonstrate tissue eosinophilia.

Three major patterns have been described in the context of AITL; these are sequentially named Patterns 1, 2, and 3 and are believed to be the histologic progression of the disease (Table 2). A high proportion (up to 17%) of patients present with Pattern 1 [21,42–44], which is especially challenging to diagnose because of retention of the architecture, presence of hyperplastic germinal centers, and lack of overt proliferation of high endothelial venules or polymorphous infiltration. The clues to Pattern 1 diagnosis are the absent/attenuated mantle zones surrounded by clear atypical cells, the PD1 staining pattern (circumferential perifollicular PD1 staining TFH cells as opposed to TFH cells either scattered throughout the germinal center or polarized appearing in reactive lymph nodes), and the slight branching of FDC meshworks outside of the intact germinal centers (Table 1 and Figure 1A,D,G). In addition, closer observation might identify focal expansion of the paracortex and a slight increase in HEVs. Any suspicion of a T-cell lymphoproliferative disorder should trigger a molecular or genetic analysis (see below).

Table 2. Morphologic patterns of angioimmunoblastic T-cell lymphoma.

	Pattern 1	Pattern 2	Pattern 3
Architecture	Preserved	Partially effaced	Totally effaced
Follicles	Hyperplastic germinal centers Absent/attenuated mantle zones	Atretic/regressed Castleman-like follicles	Absent or occasional compressed follicles seen at the periphery (especially highlighted with a CD20 stain)
Paracortex	Focal areas of paracortical expansion and perifollicular polymorphous infiltrate focal slight increase in HEVs	Areas with polymorphous infiltration with immunoblasts and Hodgkin's-like cells Proliferation of HEVs in the expanded areas	Marked polymorphous diffuse infiltration with immunoblasts and Hodgkin's-like cells Marked proliferation of HEVs
TFH cell	Perifollicular with occasional paracortical clustering	Paracortical aggregates spilling out of follicles with grouping around HEVs	Diffuse proliferation of TFH cells with grouping around HEVs
FDC meshworks (CD21 or CD23 IHC)	Intact with slight branching out	Partially intact with areas demonstrating expansion and encircling of HEVs	Marked expansion with encircling around HEVs

FDC, follicular dendritic cells; HEV, high endothelial venule; IHC, immunostain; TFH, follicular helper T-cells.
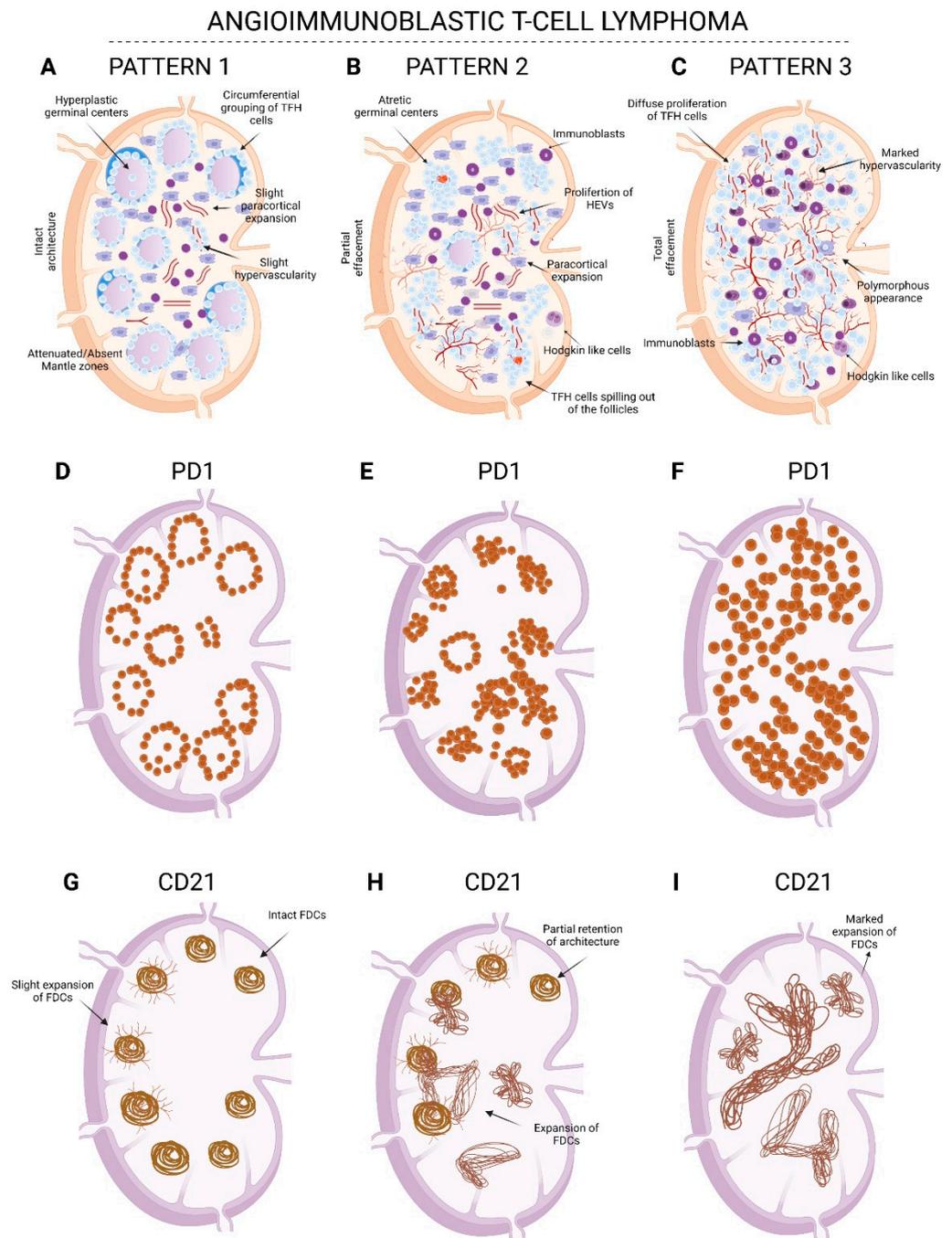
Figure 1. Morphologic patterns of AITL. Pattern 1: (**A**) intact architecture, hyperplastic germinal centers, attenuated/absent mantle zones, slight paracortical expansion, and slight proliferation of high endothelial venules; (**D**) circumferential perifollicular PD1-positive TFH cells with only occasional clustering around vessels; (**G**) intact CD21+ FDC meshworks with only slight expansion into the paracortex. Pattern 2: (**B**) Partial effacement of architecture, proliferation of HEVs, and paracortical expansion by a polymorphous infiltrate with atypical clear cells, small lymphocytes, plasma cells, macrophages, eosinophils, frequent immunoblasts, and rare Hodgkin/Reed–Sternberg-like cells; (**E**) increase in PD1-positive TFH cells extending out of the follicle into the paracortex with accumulation around the HEVs; (**H**) CD21+ FDC meshworks start expanding and encircling the HEVs. Pattern 3: (**C**) Total effacement of architecture, polymorphous infiltration with diffuse neoplastic clear-appearing T-cells, small lymphocytes, macrophages, plasma cells, eosinophils, immunoblasts, and scattered Hodgkin's-/Reed–Sternberg-like cells. Marked proliferation of HEVs is seen with neo-

plastic clear-appearing T-cells clustered around them; (**F**) PD1-positive neoplastic T-cells are diffusely present; (**I**) CD21+ FDC meshworks are markedly expanded and encircle the blood vessels. Image created in Biorender by M.M.

Pattern 2 demonstrates partial effacement/partial retention of the architecture (Figures 1B and 2A) with paracortical expansion by a polymorphous infiltrate with neoplastic clear TFH cells, small lymphocytes, plasma cells, macrophages, eosinophils, scattered immunoblasts, and Hodgkin's-/Reed-Sternberg-like cells (Figures 1B and 2C). Atretic Castleman-like follicles are also seen (Figures 1B and 2A,B). The neoplastic TFH cells are more pronounced and start spilling out of the follicles into the paracortex (Figure 1B) and encircle the HEVs; this is particularly evident with CD3 (Figure 2D) and TFH marker stains, e.g., PD1 stain (Figures 1E and 2E), CD10 (Figure 2E), and CXCL13 (Figure 2F). CD21 demonstrates partial expansion and distortion of FDC meshworks along with some areas, demonstrating retention of the architecture (Figures 1H and 2G). EBER-ish demonstrates scattered EBV+ cells, demonstrating a size range (Figure 2H).

Pattern 3 is the most recognizable pattern of AITL. Lymph nodes demonstrate complete effacement of the architecture (Figures 1C and 3A) by a polymorphous infiltrate (Figures 1C and 3B) composed of mostly atypical clear-appearing neoplastic TFH cells, macrophages, plasma cells, eosinophils, and numerous larger cells, including Hodgkin's-like cells, representing immunoblasts (Figures 1C and 3B). The neoplastic TFH cells express T-cell markers such as CD3 (Figure 3D) and TFH markers such as PD1 (Figures 1F and 3E) CD10 (Figure 3F), and CXCL13 (Figure 3G). CD21 demonstrates marked expansion and distortion of FDC meshworks (Figures 1I and 3H). CD30 is positive not only in the large HRS-like cells, but also in a subset of the smaller neoplastic TFH cells (Figure 3I). EBER-ish demonstrates scattered EBV-positive cells (Figure 3J).

Immunohistochemical studies are crucial to the diagnosis of AITL, which hinges on the demonstration of a TFH phenotype. An extensive T-cell panel, i.e., CD2, CD3, CD4, CD8, CD5, and CD7, should be used to evaluate immunophenotypic aberrancies. Aberrancies (dimness or loss) of CD3, CD5, and CD7 are most common. The vast majority of the neoplastic TFH cells are CD4-positive. As discussed above, TFH cells express several markers, i.e., CD10, BCL6, PD1, CXCL13, CXCR5, ICOS, SAP, CD200, and MAF, and the recommendations for assigning a TFH phenotype include expression of at least two, ideally three TFH markers [1,6–8,12,13,18,21–24]. Studies have also shown that, while in most cases, a four-marker panel (CD10, PD-1, CXCL13, and BCL6) is adequate, employing ICOS as an additional marker (creating a five-marker panel) greatly improves TFH phenotype detection [25]. An additional consideration is the intensity of these markers, especially PD1 and ICOS, which need to be bright to qualify as TFH markers. In addition, CD10 expression is usually variable and, in most cases, is expressed in a subset of the neoplastic TFH cells. Hence, CD10 needs to be evaluated carefully. Overall, CXCL13 and CD10 are considered most specific, while PD1 and ICOS are considered more sensitive [18]. CD21, CD23, or CD35 can be used to evaluate the FDC meshworks.

An important point worth mentioning is that AITL can relapse with a follicular T-cell lymphoma (FTCL) morphology (discussed below) and vice versa [15]. Figure 4 illustrates one such case of a patient with a previous history of AITL with a subsequent biopsy demonstrating FTCL.
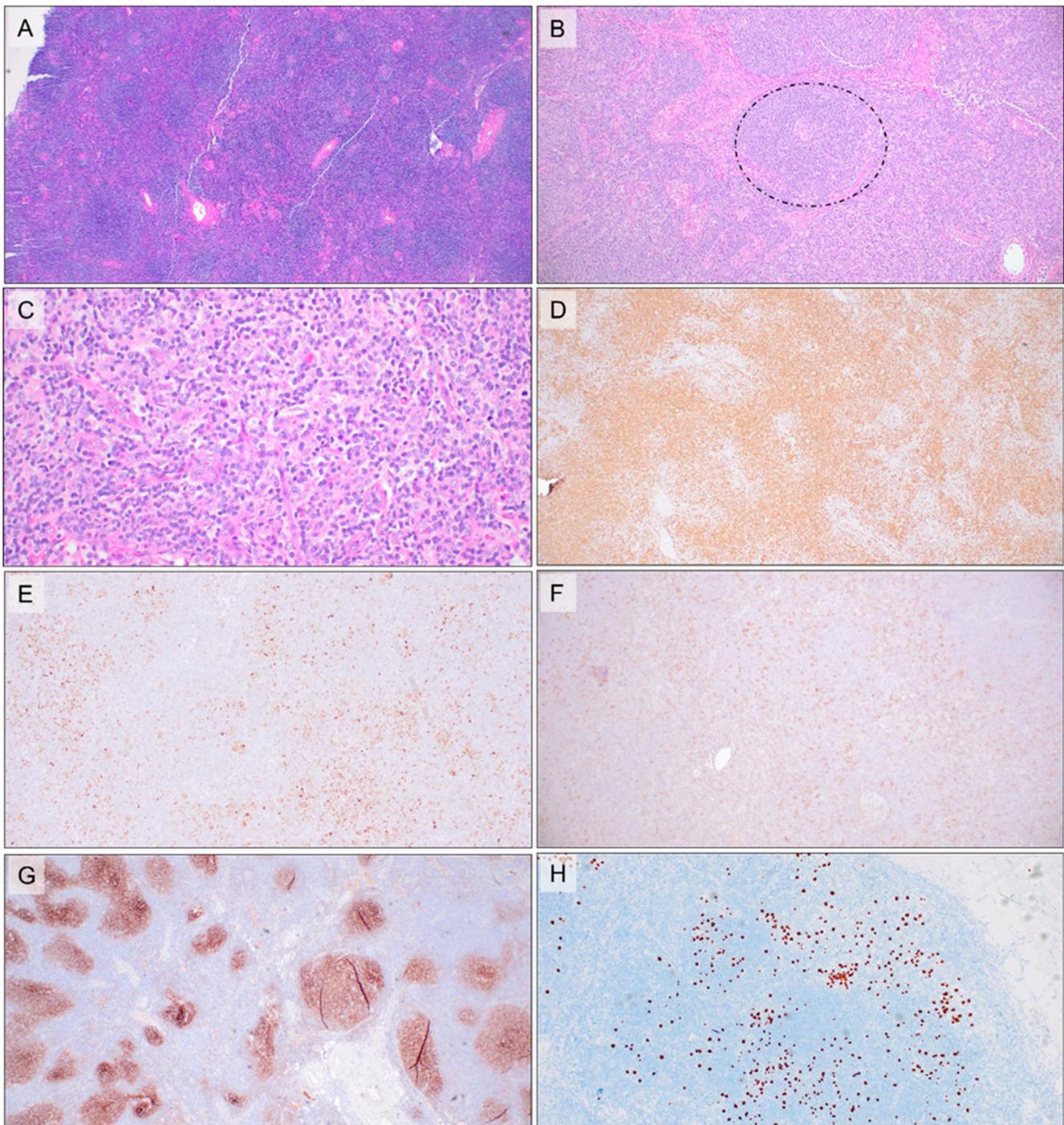
Figure 2. AITL, Pattern 2. (**A**) The lymph node architecture is partially effaced with the presence of atretic follicles, 20×; (**B**) Castleman like-follicles surrounded by atypical TFH cells, 200×; (**C**) partially effaced areas with polymorphous infiltration and the presence of neoplastic T-cells. The neoplastic T-cells are positive for (**D**) CD3, (**E**) PD1, and (**F**) CD10. (**G**) CD21 shows partial FDC meshworks (**right**) and expanded distorted FDC meshworks (**left**). (**H**) EBER-ish demonstrates scattered EBV-positive cells.
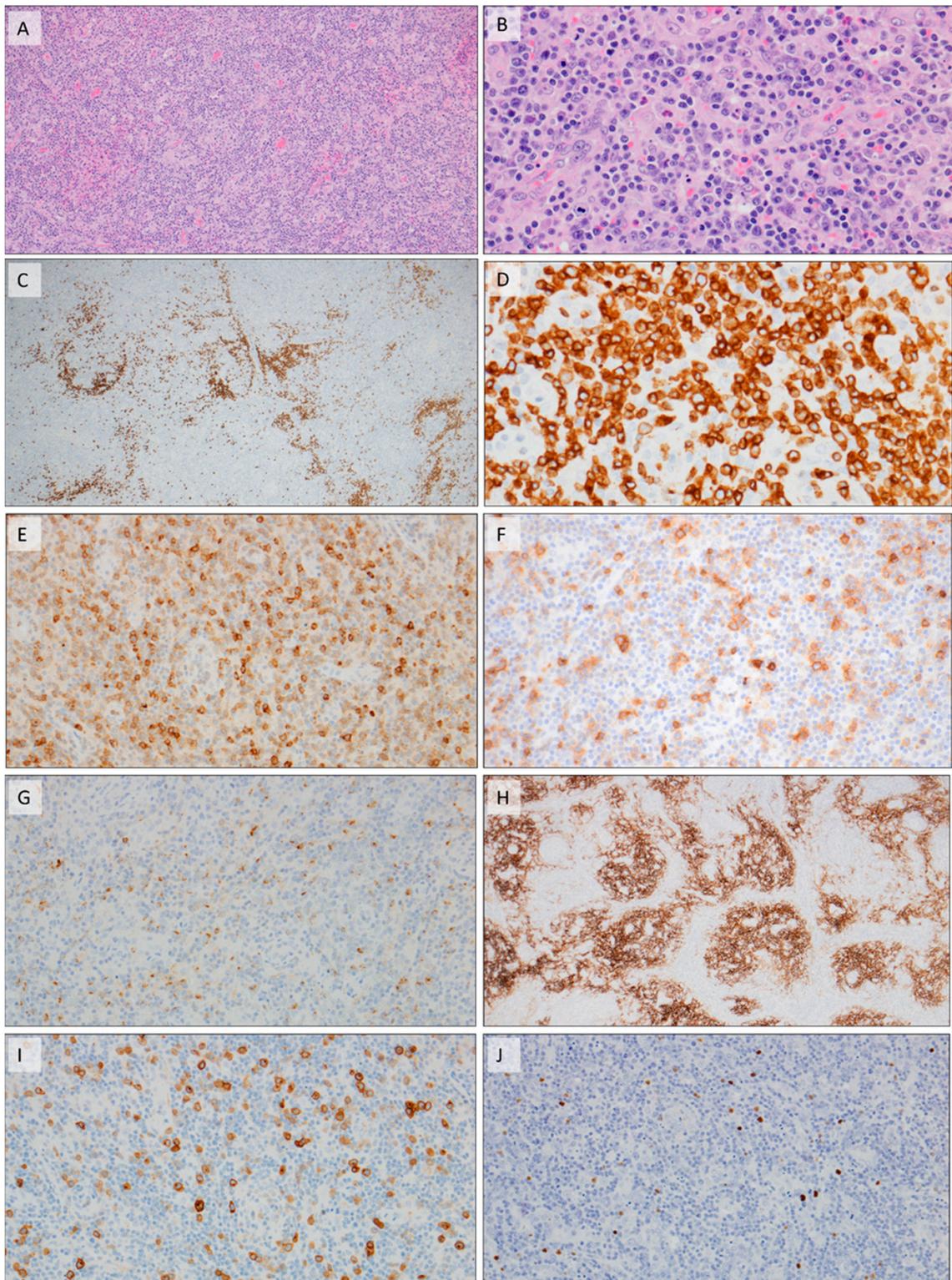
Figure 3. AITL, Pattern 3. (**A**) The lymph node architecture is completely effaced; (**B**) polymorphous infiltrate composed of neoplastic T-cells, macrophages, plasma cells, few eosinophils, and scattered immunoblasts; (**C**) CD20 demonstrates few retained B-cell areas with some follicles compressed at the periphery. The neoplastic T-cells are positive for (**D**) CD3, (**E**) PD1, (**F**) CD10, and (**G**) CXCL13. (**H**) CD21 shows expanded distorted FDC meshworks. (**I**) CD30 demonstrates positivity not only in the larger immunoblastic/Hodgkin's-like cells, but also in the surrounding smaller neoplastic T-cells. (**J**) EBER-ish demonstrates scattered EBV-positive cells.
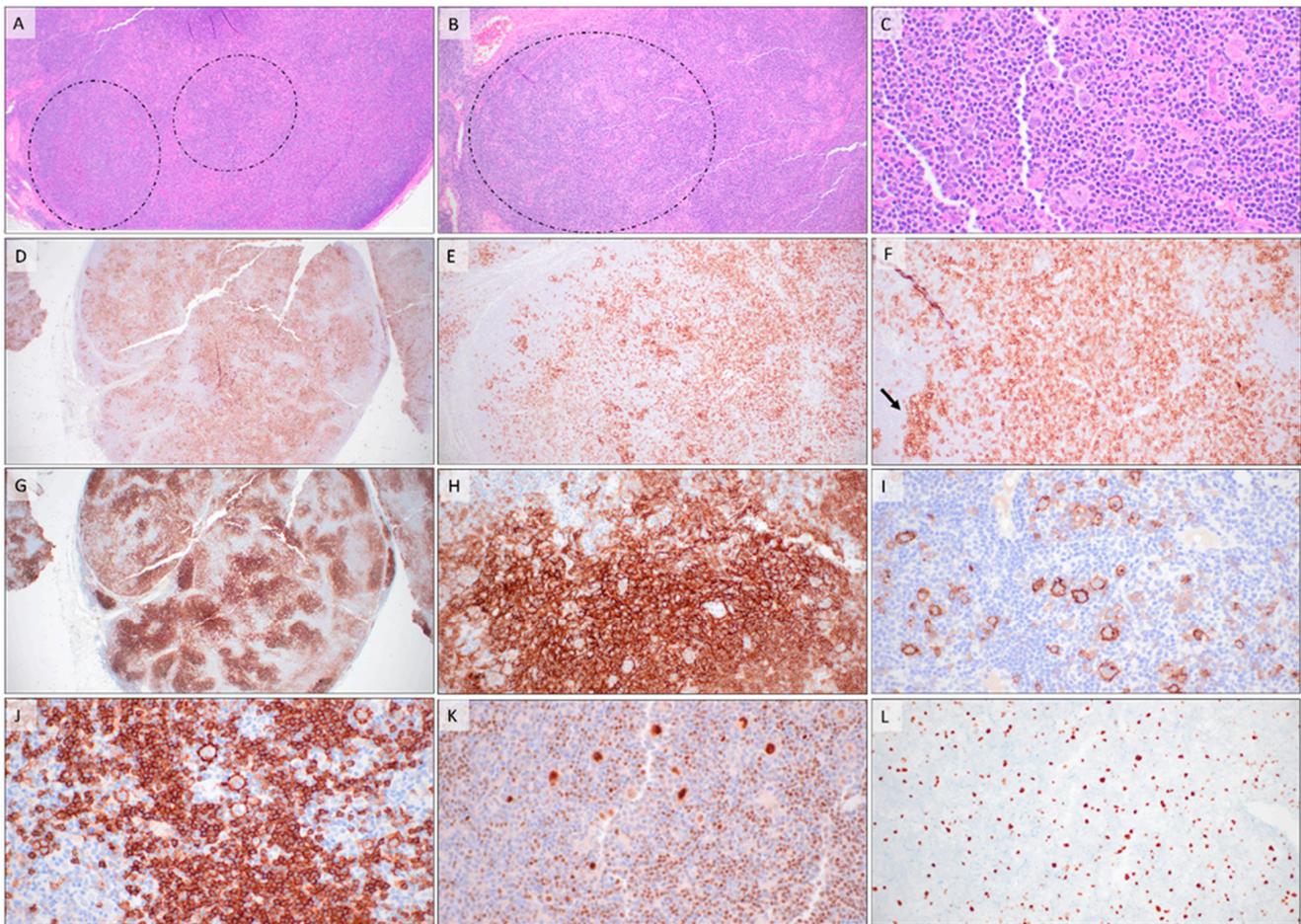
Figure 4. Follicular-T-cell-lymphoma-like relapse of AITL. (**A**) The lymph node demonstrates a nodular architecture. The nodules are composed of mostly small lymphocytes and macrophages (**B**) reminiscent of progressive transformation of germinal centers (PTGCs) and nodular lymphocyte predominant Hodgkin's lymphoma (NLPHL), with scattered larger lymphocyte predominant (LP), Hodgkin's/Reed–Sternberg-like (HRS), and immunoblasts (**C**). PD1-positive neoplastic T-cells are diffusely increased (**D,F**), albeit that in some of the nodules, they form rosettes around the larger cells (**E**). CD21 shows expanded distorted FDC meshworks (**G**), which also surround the HEVs (**H**). The larger HRS and LP-like cells are positive for CD30 (**I**), CD20 (**J**), and OCT2 (**K**). EBER-ish demonstrates scattered EBV-positive cells, both large and small (**L**).

2.3. EBV, B-Cell, and Plasma Cell Proliferations

B-cell and plasma cell proliferations (clonal and non-clonal) are a frequent occurrence in AITL [31]. The B-cells can appear to be either immunoblastic or HRS-like. While EBV is associated with the majority of B-cell proliferations in AITLs (more than 80%) [31,40,45], EBV-negative cases have also been reported [46]. In most cases, EBV-positive B-cells are scattered or form small clusters; however, in some cases, sheets of large B-cells are seen, which would prompt the consideration of a second diagnosis of a composite diffuse large B-cell lymphoma [45,47]. Plasmacytosis and plasma cell proliferations are a frequent occurrence in AITL, and most of these are EBV-negative. While most are polyclonal, occasional clonal plasma cell proliferations have also been reported [48,49].

2.4. Flow Cytometry

Flow cytometric studies can be a powerful ancillary tool in the diagnosis of AITL [20,50–53]. Neoplastic T-cells in AITL frequently demonstrate the downregulation or the absence of surface CD3 along with absent or diminished surface T-cell receptors

(Figure 5A,B) [53]. However, in these cases, they generally express cytoplasmic CD3 and cytoplasmic TCR-alpha/beta (Figure 5E,F). In addition, most AITL patients (as opposed to PTCL patients) also seem to demonstrate this atypical surface CD3 dim/neg population to varying extents in the peripheral blood [50,52,53]. A simple T-cell panel employing CD3, CD4, CD10, CD14, CD5, and CD45 to evaluate for surface CD3 dim/neg, CD10+, CD4+ population has been suggested to aid in AITL diagnosis, especially in bone marrow and peripheral blood [20]. Bright PD1 expression by flow cytometry has also been shown to be a useful tool for both the diagnosis and monitoring of AITL [54]. Flow cytometry studies might also demonstrate additional immunophenotypic abnormalities described in AITL, e.g., loss of CD5 or CD7.
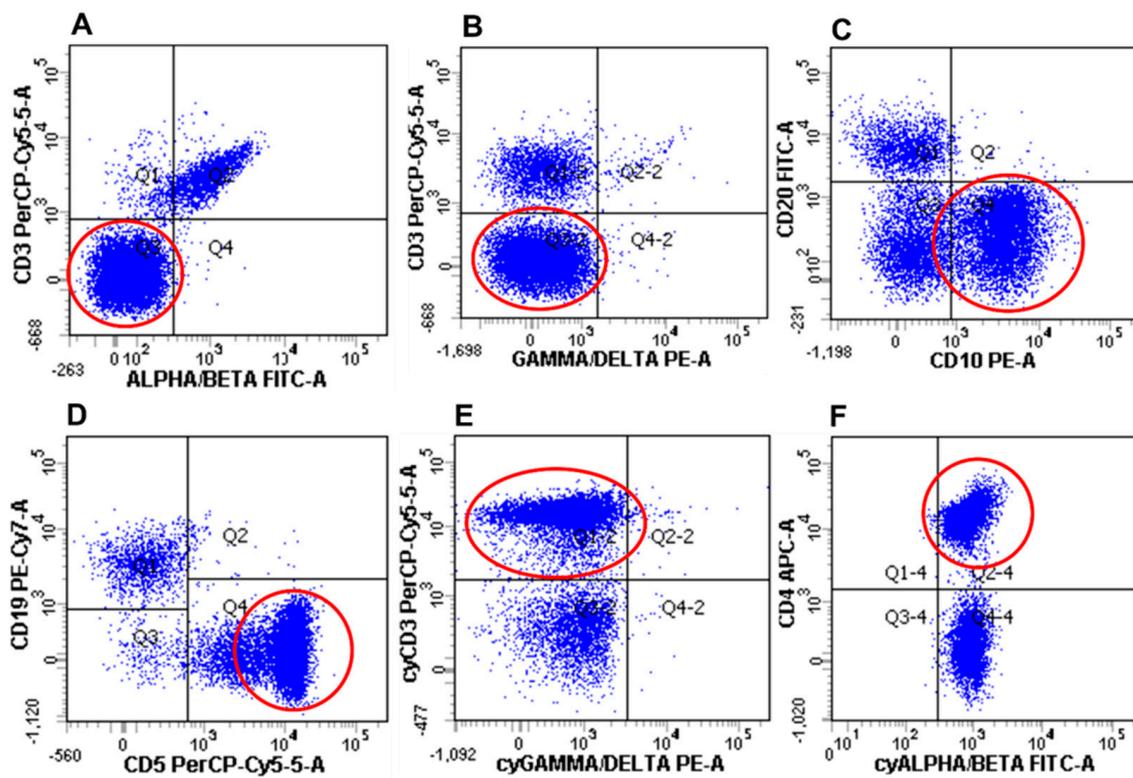
Figure 5. Flow cytometric findings in AITL The neoplastic T-cells are negative for surface CD3 and surface TCRalpha/beta (**A**) and surface TCR gamma/delta (**B**), but positive for CD10 (**C**), CD5 (**D**), cytoplasmic CD3 (**E**), cytoplasmic TCR alpha/beta (**F**), and CD4 (**F**).

2.5. Genetics

Most AITLs demonstrate clonal T-cell receptor rearrangements by PCR; in addition, they also demonstrate clonal immunoglobulin gene rearrangements in 25–30% of cases. The latter usually correspond to EBV-positive B-cell proliferations in most cases [18].

The cytogenetics and mutational spectrum of AITL, as well as the association with clonal hematopoiesis are discussed in detail in a separate section (see below).

2.6. Differential Diagnoses

While other mature T-cell lymphomas including *peripheral T-cell lymphoma NOS* should be considered in the differential diagnosis, the distinction is perhaps less critical from a treatment standpoint. As mentioned above, the diagnosis of AITL hinges on the demonstration of at least two (ideally three) TFH antigens, as well as the presence of other characteristics' findings such as a polymorphous infiltrate, aggregates of TFH cells around proliferating HEVs, and scattered EBV+ cells.

Perhaps one of the most challenging differential diagnoses of Pattern 1 AITL is *reactive lymphoid hyperplasia* [21,42–44]. Pattern 1 AITL can often be retrospectively diagnosed in a previous biopsy from a patient with a subsequent Pattern 3 AITL. The main morphologic clues in favor of a Pattern 1 AITL include absent or attenuated mantle zones, the presence of clear atypical cells surrounding the hyperplastic germinal centers (this might not be obvious), focal expansion of the paracortex, and focal increase in HEVs. This should prompt further staining with PD1, which would demonstrate the circumferential grouping of the neoplastic TFH cells and few clusters in the paracortex. CD21 would demonstrate slight branching out of the FDC meshwork. If the findings are suspicious for Pattern 1 AITL, then PCR for T-cell receptor rearrangement and next-generation sequencing studies (NGS) for IDH1, IDH2, DNMT3A, TET2, and RHOA (see below) should be ideally performed. In addition, as discussed above, flow cytometry might demonstrate a CD3dim/neg, CD4+, CD10+ population that is highly suggestive of AITL; if flow cytometry is not available on tissue, it could be attempted on peripheral blood [20,52,53]. Interestingly, several patients present at a clinically advanced stage with a Pattern 1 morphology on a biopsy; this perhaps reflects the morphologic evolution of the disease with the distinct possibility that other lymph nodes in the body might have a more evolved Pattern 3 morphology [42].

Classic Hodgkin lymphoma (CHL) can be a challenging differential diagnosis especially considering the similar polymorphous background and the presence of Hodgkin's-/Reed–Sternberg (HRS)-like cells, which is common in AITL. Adding to the difficulty is the observation that these large cells are usually CD30-positive and occasionally CD15-positive [46,55]. However, the HRS-like cells in AITL generally tend to preserve the B-cell program more often, and an extensive panel of B-cell markers, i.e., CD20, PAX5, OCT2, BOB1, and CD79a, should be employed (albeit that CD20 and PAX5 downregulation can be seen in HRS-like cells in AITL). In addition, an extensive T-cell IHC panel (CD3, CD2, CD5, CD4, CD8, CD7) should be used in challenging cases to evaluate for immunophenotypic aberrancies in T-cells. Fibrosis is unusual in AITL and is more common in CHL. Cytologic atypia in the surrounding T-cells, proliferating HEVs, FDC expansion beyond follicles, morphologic variation, pleomorphism in the larger cells, etc., would favor AITL. In addition, sheets and aggregates of PD1-positive cells beyond rosetting of HRS-like cells should raise suspicion for AITL and prompt further workup including molecular studies (PCR and NGS; see above). In addition, EBV positivity is usually restricted to the large HRS cells in CHL, while there usually is more variation in the cell size of EBV+ cells in AITL. CD30 staining in smaller lymphocytes, in addition to the larger HRS-like cells, should also prompt consideration of AITL [56]. As mentioned above, flow cytometric detection of a CD3 dim/neg, CD4+, CD10+ population can be particularly helpful in the diagnosis of AITL and other TFH lymphomas, as this population is not seen in CHL [20,50–53].
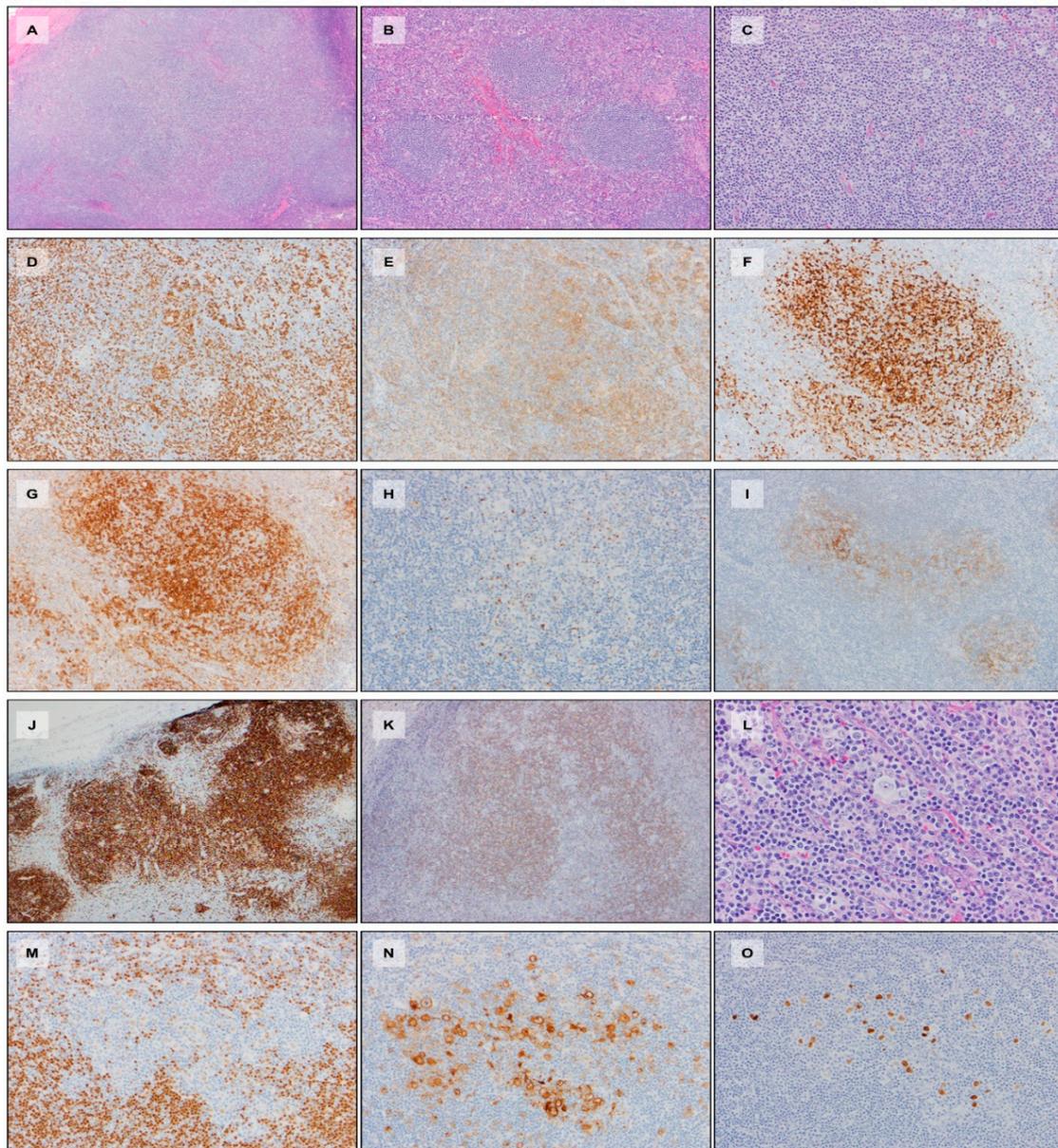
3. Follicular T-Cell Lymphoma

3.1. Epidemiology and Clinical Features

Follicular T-cell lymphoma (FTCL) was first described in 1988 [57] and is a rare entity, representing 1–2% of peripheral T-cell lymphomas. It is a disease of older individuals occurring in the sixth decade of life and slightly more common in males. Patients usually present with diffuse lymphadenopathy, and high-stage disease with extranodal and cutaneous involvement has been reported. Rare patients may show immunological abnormalities on laboratory investigations, including positive direct antibody tests (DATs) and hypergammaglobulinemia [15].

3.2. Morphology and Immunophenotype

By morphology, two distinct growth patterns are recognized: a follicular growth pattern that mimics B-cell follicular lymphoma (FL-like) and a progressive transformation of a germinal centers-like pattern (PTGC-like) (Figure 6) [18]. In cases with the FL-like pattern, the neoplastic T-cells are arranged in well-defined nodules that lack the morphological features of normal follicles. Mantle zones can either be preserved or absent. In PTGC-

like cases, representing the majority of FTCL, the neoplastic T-cells are seen in small aggregates surrounded by small mantle zone B-cells arranged in large, irregular nodules. Eosinophilic infiltration is uncommon, and unlike in AITL, arborizing high endothelial venules and expanded follicular dendritic cell meshworks are not identified. The neoplastic T-cells range from small to medium with irregular nuclei, coarse to vesicular chromatin, and moderate to abundant pale cytoplasm. While the nuclear features can resemble centrocytes or centroblasts, the pale cytoplasm is a useful distinguishing feature. Scattered B-cell immunoblasts, including some resembling Hodgkin's/Reed–Sternberg cells, usually surrounded by neoplastic T-cells, are seen in a significant subset of cases.

Figure 6. Follicular T-cell lymphoma with a PTGC-like pattern. (**A**) The lymph node architecture is effaced by atypical nodules containing (**B**) small mature lymphocytes resembling mantle zone cells and admixed medium-sized lymphocytes with clear cytoplasm. (**C**) Scattered Hodgkin's/Reed–Sternberg-like cells are noted. The neoplastic T-cells are positive for (**D**) CD3, (**E**) CD4, (**F**) CD10, (**G**) PD1, and (**H**) CXCL13. (**I**) CD21 shows dendritic cell meshworks within the nodules that are composed predominantly of mantle zone B-cells positive for (**J**) CD20 and (**K**) IgD. (**L**) The H/RS-like cells are positive for (**M**) PAX5 (weak), (**N**) CD30, and (**O**) EBER.

The neoplastic T-cells in FTCL express pan T-cell antigens including CD2, CD3, CD5, and CD7. An aberrant immunophenotype is seen in the majority of cases with the loss of CD7 most commonly noted [58]. They are positive for CD4 and express multiple TFH markers, with PD1 and ICOS reportedly the most sensitive, followed by CXCL13. CD10 and BCL6 are less sensitive and are expressed in fewer cases. They are negative for CD8, CD56, cytotoxic markers, and EBV. Follicular dendritic cell meshworks are limited to the nodular areas. The proliferative rate, assessed by Ki-67, is variable, with mean values approaching 50%. The transformed immunoblasts are positive for B-cell markers including CD20 and PAX5. CD30 and EBV can be expressed in a subset of cases [58].

3.3. Molecular Studies

Clonal T-cell receptor gene rearrangements are identified in the vast majority of cases; additionally, a subset of cases may show oligoclonal or clonal IgH gene rearrangements [58].

3.4. Differential Diagnoses

While it is rare, a diagnosis of FTCL should not be overlooked when evaluating a lymph node for involvement by lymphoma. FTCL with an FL-like growth pattern can mimic FL, but can be distinguished from FL by the cytologic features of the neoplastic T-cells and the expression of multiple T-cell markers by the abnormal follicles. The PTGC-like variant raises the differential diagnosis of classic Hodgkin's lymphoma, the lymphocyte-rich variant (CHL-LR), or nodular-lymphocyte-predominant Hodgkin's lymphoma (NLPHL). In cases resembling CHL or NLPHL, careful examination of the T-cells rosetting the H/RS-like cells or LP cells is mandatory, as in most FTCL cases, these T-cells are neoplastic and express multiple TFH markers, most commonly PD1, ICOS, and CD10 [59,60]. A subset of these neoplastic cells can also express CD30, which can help distinguishing them from reactive T-cells [56].

4. Peripheral T-Cell Lymphoma with TFH Phenotype

Multiple studies have shown that a significant subset of peripheral T-cell lymphomas, morphologically classified as peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS), arise from TFH cells and share genomic features, but are not identical to AITL [16,28,61,62]. This relationship has also been confirmed by the evaluation of TFH marker expression in these lymphomas [14,25,63]. In recognition of these findings and to aid in better classification and therapy, the WHO 2017 Classification recommends that nodal CD4+ T-cell lymphomas be evaluated for the expression of TFH antigens and provisionally classified as peripheral T-cell lymphoma with the TFH phenotype (PTCL-TFH) if they express at least two (ideally three) TFH antigens [18]. The rates of classification as PTCL-TFH appear significantly different when using two or three TFH markers, and large-scale studies are required to help develop stringent criteria for reproducible classification [25].

Morphologically, PTCL-TFH shows diffuse effacement of the nodal architecture by neoplastic T-cells that can range in size from small to large (Figure 7). Unlike AITL, PTCL-TFH lacks the clear cell morphology, polymorphous inflammatory background, and expanded dendritic cell meshworks with high endothelial venule proliferation [14,25] (Figure 4).

PTCL-T TFH shares immunophenotypic features with AITL and FTCL with variable expression of TFH markers. PD1 and ICOS remain the most sensitive, while CXCL13, BCL6, and CD10 are expressed in fewer cases [25].
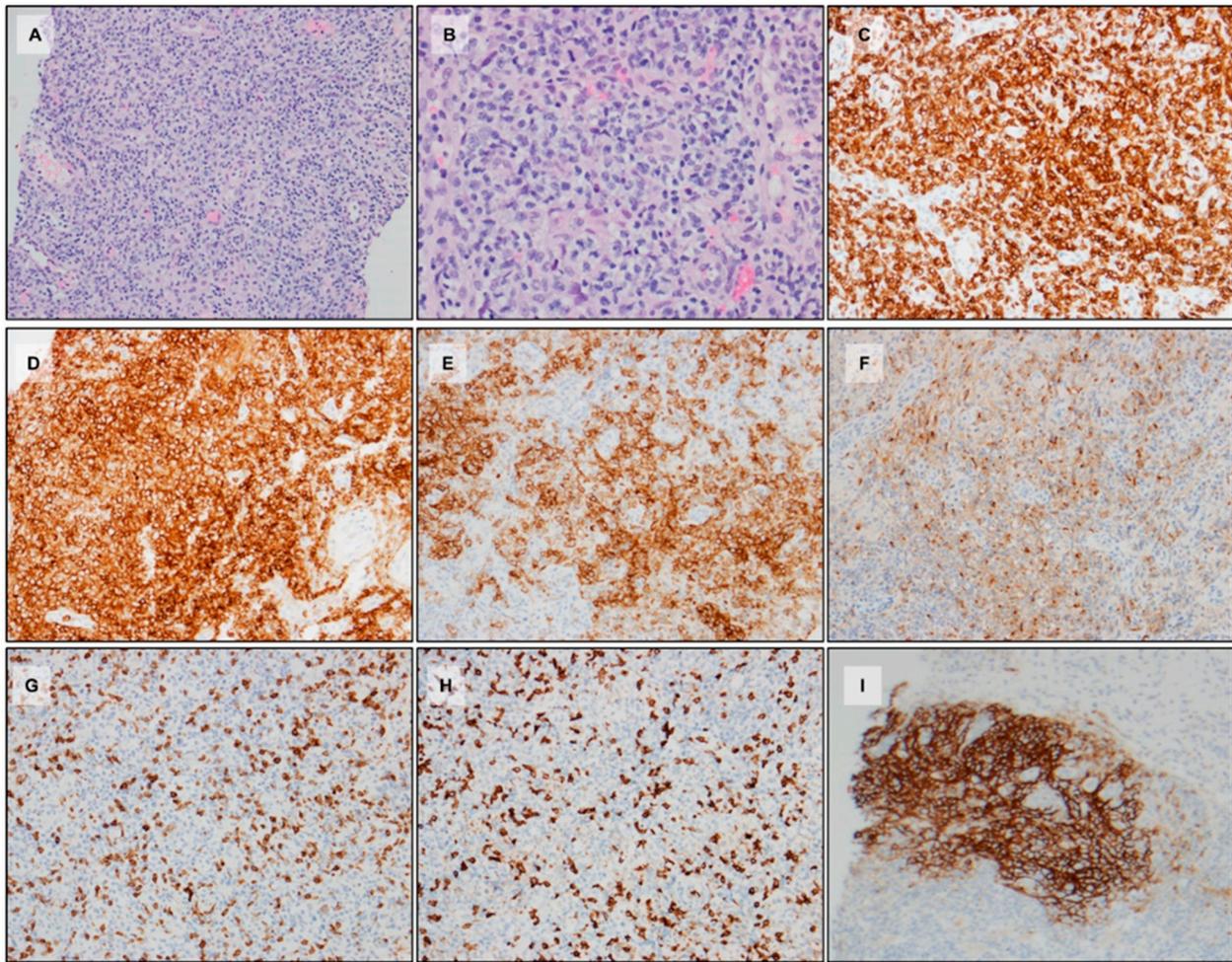
Figure 7. Peripheral T-cell lymphoma with the TFH phenotype. (**A**,**B**) The interfollicular areas are expanded by a diffuse proliferation of predominantly medium-sized cells with irregular nuclei, mature chromatin, and variable amounts of cytoplasm. The atypical cells are positive for (**C**) CD3, (**D**) CD4, (**E**) PD1, and (**F**) CXCL13 and negative for (**G**) CD7 and (**H**) CD8. (**I**) CD21 shows relatively intact dendritic cell meshworks.

5. G. Genetics of TFH Lymphomas

T-cell lymphomas of T follicular helper origin show some distinct differences from other peripheral T-cell lymphomas. Angioimmunoblastic T-cell lymphomas have a distinct gene expression profile relating to the unique microenvironment that includes a B-cell signature, angiogenesis/vascular endothelial signature, cytokine signature, and T follicular helper signature [16,29,64]. While PTCL-TFH also shares the TFH signature, it lacks the characteristic microenvironment signature of AITL. Nevertheless, the gene expression profiles of AITL, FTCL, and PTCL-TFH are similar and distinct enough to support the argument that they likely represent a continuum of a single disease [16]. Rodriguez also demonstrated that AITL, but not PTCL-TFH cases that were enriched for the B-cell signature had a more favorable prognosis [61].

Among the genetic mutations identified in T-cell lymphomas, IDH2 R172 mutations seem to be specific for AITL and have only rarely been reported in other PTCL-NOS, while they have been reported in 20–40% of AITL cases [16,29,64,65]. In one study, this mutation was significantly associated with chromosome 5 gains and upregulation of IL4, IL13, and MAPK9 [66].

TET2 mutations and, less frequently, DNMT3A mutations are also enriched in TFH lymphomas (TET2 mutations are seen in approximately 50–75% of cases). Interestingly,

these mutations are not only seen in tumor cells, but are present in non-tumor hematopoietic cells as well, suggesting that these lymphomas may have a pre-malignant mutant clone (clonal hematopoiesis of indeterminate potential), much as what has been extensively described and investigated in myeloid malignancies such as myelodysplastic syndrome [16,64]. TET2 mutations have been associated with advanced-stage disease, high IPI scores, and shorter progression-free survival [67].

RHOA mutations, almost always at the G17V hotspot, are frequently identified in AITL and FTCL (60–70%) and essentially always co-occur with TET2 mutations [61,64,68]. While the TET2 mutation is found in the non-tumor hematopoietic cells, the RHOA mutation appears restricted to the tumor cells and likely occurs as a later event. The combination of the two mutations may contribute to AITL-specific pathogenesis. RHOA T19I mutations, albeit less common, have also been reported [69].

Genotype/phenotype correlations have also been described, with AITL carrying RHOA G17V mutations showing increased vasculature and prominent follicular dendritic cell meshworks [70], while those with IDH2 R172 mutations having more prominent large, clear cells and strong TFH marker expression [71].

The cytogenetic profile of AITL is considerably less abnormal than other PTCLs [66]. Chromosome 5 gains are seen in about 40% of AITL and are distinct among hematologic malignancies, which more typically show losses in chromosome 5. Cases that do not have chromosome 5 gains show enrichment of NF-KB and PI3K-AKT pathways and may have a distinct pathogenesis [66]. Additionally, ~20% of FTCL carry a recurrent translocation t(5;9)(q33;q22)(*ITK-SYK*). This rearrangement is not specific for FTCL and has been described in other peripheral T-cell lymphomas, including AITL [72,73].

6. TFH Lymphomas, Clonal Hematopoiesis of Indeterminate Potential, and Myeloid Neoplasms

TET2 and DNMT3A mutations are frequently noted in clonal hematopoiesis of indeterminate potential (CHIP) [74,75] and myeloid malignancies [76–78]. The subsequent discovery of TET2 and DNMT3A mutations in TFH lymphomas has prompted the investigation of the relationship between these seemingly disparate categories of hematologic malignancies. Interestingly, studies have shown that TFH lymphomas can arise from divergent clonal evolution from TET2 and DNMT3A-mutant progenitor cells upon acquisition of RHO and/or IDH2 mutations [79]. Supporting this hypothesis are reports of TFH lymphomas and myeloid malignancies (both de novo and therapy-related) co-occurring in patients and arising from TET2 and DNMT3A-mutated clonal progenitor cells [80,81]. Furthermore, the presence of two or more TET2 mutations and a mutant allele fraction > 15% appears to confer a higher risk for myeloid neoplasms in patients with TFH lymphomas [81,82]. These studies have elucidated the unique biology of TFH lymphomas and highlight the importance of the evaluation for clonal hematopoiesis in these patients, which can have important diagnostic and therapeutic implications.

7. Treatment and Conclusions

TFH lymphomas are an important subtype of peripheral T-cell lymphomas, and the last decade has seen significant advances in understanding their biology and molecular pathogenesis. The identification of shared recurrent mutations in AITL, FTCL, and PTCL-TFH has justified classifying these morphologically unique lymphomas as a single biological category. These discoveries have also provided a wealth of biomarkers for diagnosis and targets for therapy [83]. Currently, the distinction between TFH lymphomas and PTCL, NOS, has no impact on current clinical management, with most patients treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like upfront therapy, but with less-than-optimal response rates. Recent studies have shown improved progression-free survival (PFS) and overall survival (OS) in patients with systemic CD30-positive T-cell lymphomas treated with CHOP-like chemotherapy regimens that replace vincristine with brentuximab vedotin, an anti-CD30 antibody drug conjugate. The majority

of these patients had anaplastic large cell lymphoma (ALCL), which is characterized by diffuse and strong CD30 expression. Patients with other T-cell lymphoma subtypes expressing CD30, including AITL, were included; however, due to small sample sizes, efficacy in the non-ALCL subgroups could not be evaluated [84]. Studies evaluating the efficacy of romidepsin, a histone deacetylase inhibitor, in the treatment of TFH lymphomas have shown interesting results. Romidepsin in addition to CHOP showed marginal, but not significant beneficial effects when compared to CHOP in previously untreated patients with TFH lymphoma [85]; however, romidepsin, either alone or in combination with other drugs, had significant benefits in patients with relapsed/refractory TFH lymphoma [86]. These incongruous results warrant further investigation with larger patient cohorts. Finally, the identification of TET2, DNMT3A, and IDH mutations in TFH lymphomas has created opportunities for targeted therapy with hypomethylating agents, such as azacytidine, in combination with current therapy regimens with promising results [87,88].

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