Progress in pathology

Follicular T-cell lymphoma: a member of an emerging family of follicular helper T-cell derived T-cell lymphomas

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Summary Unlike B-cell lymphomas, where knowledge of normal B-cell origin and differentiation has greatly contributed to their classification, the current classification of peripheral T-cell lymphomas is limited by a lack of understanding of their cellular origin. In the current World Health Organization classification of lymphomas, follicular T-cell lymphoma was formally recognized as a morphologic variant of peripheral T-cell lymphoma, not otherwise specified. There is growing evidence, however, that follicular T-cell lymphoma may be a unique clinicopathologic entity based on its morphologic features and derivation from follicular helper T-cells. In addition, there are abundant recent data supporting the concept that follicular helper T-cells can give rise to other types of T-cell lymphoma, including angioimmunoblastic T-cell lymphoma, primary cutaneous CD4+ small/medium T-cell lymphoma, and a subset of neoplasms, in addition to follicular T-cell lymphoma, currently classified as peripheral T-cell lymphoma, not otherwise specified. In this review, we focus primarily on the clinicopathologic, immunophenotypic, and molecular features of follicular T-cell lymphoma and discuss its potential relationship with other types of T-cell lymphoma thought to be derived from follicular helper T-cells.

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1. Introduction

The current classification of B-cell lymphomas has been greatly aided by our extensive knowledge of B-cell origin and normal differentiation. In lymph nodes, normal B-cells form unique structures, such as germinal centers, mantle zones, and marginal zones, which can be recognized morphologically. A subset of B-cell lymphomas can exhibit morphologic patterns that correspond to these compartments. A follicular pattern, for example, is a common feature of follicular lymphomas. Assessment of the immunophenotype of normal B-cells in various compartments and correlation with B-cell lymphomas has allowed construction of normal B-cell differentiation stages and a putative cell of origin for most B-cell lymphomas. Recognition of consistent chromosomal translocations in B-cell lymphomas also has been helpful in understanding cell of origin and some chromosomal translocations are defining features of some types of B-cell lymphoma.

In contrast, the current classification of T-cell neoplasms is largely based on a combination of clinical and pathologic features. Cases of T-cell lymphoma are grouped according to their anatomic sites of disease, in particular, leukemic/disseminated, extranodal, cutaneous, and nodal [1]. T-cell lymphomas are further classified according to their morphologic features and the few cytogenetic or molecular abnormalities known to occur in these tumors. This approach has been taken, in part, because we know relatively little about normal T-cell differentiation. In normal lymph nodes,
there are few T-cell compartments that can be recognized morphologically. Most T-cell lymphomas exhibit a diffuse pattern without clues to potential cellular origin or stage of differentiation. Based on what is known about T-cell subsets, others have attempted to classify T-cell lymphomas on the basis on CD4 versus CD8 expression, T<sub>H</sub>1 versus T<sub>H</sub>2 function, or presence or absence of a cytotoxic immunophenotype [1-5]. However, these attempts have failed to delineate clinically meaningful categories.

Approximately 30% of all T-cell lymphomas worldwide, in part by default based on the issues already reviewed, fall into the category of peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) [1,6]. The tumors in this category display a broad spectrum of cytologic features, from highly polymorphous to monomorphic, and with neoplastic cells that can be predominantly small, intermediate-sized, or large and pleomorphic [1]. These tumors can express T-cell markers corresponding to a variety of putative T-cell subsets [5]. Conventional cytogenetic analysis has shown a wide variety of cytogenetic abnormalities, often with complex karyotypes that correlate with inferior outcome [7-9], but very few of these abnormalities are consistent findings that can be used for T-cell lymphoma classification. Comparative genomic hybridization analysis and other high-throughput technologies have shown that virtually all PTCL-NOS cases harbor genetic imbalances, with gains commonly outnumbering losses [10-12]. There are no obvious genetic subgroups of PTCL-NOS that can be appreciated, however, further supporting the heterogeneity of this group of neoplasms. A major challenge for pathologists and researchers, therefore, is to tease out clinically and biologically meaningful subgroups from the category of PTCL-NOS, with the goal perhaps being the eventual elimination of PTCL-NOS all together.

Peripheral T-cell lymphoma with a nodular/follicular pattern was first reported in 1988 [13]. The unusual morphologic pattern of this type of T-cell lymphoma was the first clue that these neoplasms may be distinctive. It was not until the fourth edition of the World Health Organization (WHO) classification was published in 2008, however, that this type of T-cell lymphoma was formally recognized, and considered as a morphologic variant of PTCL-NOS [1]. This was an important step forward, partly attributable to a flurry of case reports and small case series regarding this type of T-cell lymphoma during the past two decades [13-32]. In the literature, a number of designations have been used for these tumors, including nodular T-cell lymphoma; follicular T-cell lymphoma (FTCL); peripheral T-cell lymphoma with a nodular, follicular, or perifollicular pattern; peripheral T-cell lymphoma with follicular involvement; and follicular variant of PTCL-NOS. Henceforth, we will use the term follicular T-cell lymphoma here to describe these tumors.

Another important step forward is the recent progress in our understanding of the ontogeny of a distinct subset of CD4+ helper T-cells, known as follicular helper T-cells (T<sub>FH</sub>), and their relationship with T-cell lymphomas, including FTCL [23-30,33-44]. Follicular helper T-cells normally have the capacity to home to germinal centers (GCs). This migration is facilitated by the interaction of one of their surface receptors, CXCR5, with the CXCL13 chemokine expressed by follicular dendritic cells in the light zone of GCs, where T<sub>FH</sub> cells support affinity maturation and isotype switching, leading to the generation of memory B-cells and long-lived plasma cells [35-39]. T<sub>FH</sub> cells express an array of molecules serving these functions, including cytokines and cytokine receptors (eg, interleukin-21, CXCL13, CXCR5), immune-modulating receptors/adhesion molecules (eg, programmed death-1 or PD-1, inducible co-stimulator [ICOS], CD57, CD154, CD200, signaling lymphocyte-activation molecule family), cytoplasmic signaling molecules (eg, signaling lymphocyte-activation molecule–associating protein [SAP]), and transcriptional factors (eg, NF-ATc1 and c-Maf) [33-40]. Interestingly, the Bcl-6-MUM1/IRF4-BLIMP1 transcriptional axis, essential for GC B-cell differentiation, is also crucial for T<sub>FH</sub> cell identity [35,39,40]. Deregeneration of T<sub>FH</sub>-cell functions is implicated in a variety of autoimmune disorders in both mouse models and humans [37].

Many of the molecules that support T<sub>FH</sub> cell functions have been used to identify these cells in lymph nodes and other sites using a variety of methods, and identification of T<sub>FH</sub> cells has had practical implications in the diagnosis of lymphomas [33,34,41-62]. These studies have shown that the T<sub>FH</sub> immunophenotype, although characteristic of FTCL, is not specific for this entity. Gene expression profiling studies of cases of angioimmunoblastic T-cell lymphoma (AITL) have shown over-expression of many genes characteristic of normal T<sub>FH</sub> cells, and the results of these studies have been validated at the protein level, suggesting that AITL arises from T<sub>FH</sub> cells [42-44]. These observations also provide a plausible explanation for the autoimmune phenomena and broad range of histopathologic features associated with AITL. In addition, a subset of nodal PTCL-NOS cases other than FTCL have a T<sub>FH</sub>-cell immunophenotype, despite their apparently different morphologic appearances [5,23,29,30,63]. Adding to the complexity is the recent finding that cases of primary cutaneous CD4-positive small/medium T-cell lymphoma also express many T<sub>FH</sub> cell markers [64,65]. These studies support the concept of an emerging family of T<sub>FH</sub>-cell derived PTCLs.

In this review, we focus on FTCL, a rare neoplasm currently considered in the WHO classification to be a morphologic variant of PTCL-NOS. The data are compiled from a total 80 cases from 18 case reports or case series published in the English literature from 1988 to through 2011, as well as one previously unpublished case we have encountered (Figs. 1 and 2) [13-30]. Cases that have been reported more than once in different publications are combined correspondingly [20,24,25]. An additional 20 cases reported in the non-English literature with inadequate clinical data are not included in this review [31,32].
We also discuss the evidence supporting the origin of FTCL from TFH cells and the emerging family of TFH cell-derived lymphomas.

2. Clinical features and laboratory findings

 Follicular T-cell lymphoma is a rare disease that represents 1%-2% of all PTCL-NOS cases [6]. This frequency may underestimate the overall incidence as this entity is challenging to recognize and cases can be missed [14,15,18,21]. These tumors mainly affect elderly patients, in the seventh decade, with a median and mean age of 62 years (Table 1) [13-29]. There is a wide age range, however, from 27 to 90 years. The male to female ratio is 1.2 to 1. Systemic (B-type) symptoms are observed in less than one-third of patients. Most patients (48/56, 86%) present with systemic lymphadenopathy that most commonly involves the cervical, axillary, or inguinal regions. Extranodal involvement has been reported. Hepatosplenomegaly and bone marrow involvement each occur in approximately one-fourth of patients. The tonsils, salivary glands and hard palate can be rarely involved [18]. A subset of patients (12/51, 23%) has skin lesions, either at time of diagnosis or at relapse, including erythema or papules, and occasionally patients can have isolated skin lesions [21,22,25,27]. Most patients (40/55, 73%) have clinical stage III or IV disease.

 Laboratory tests reveal hematological, immunological, and/or biochemical abnormalities in a subset of patients with FTCL (Table 1). The most common findings include a positive Coombs’ test with or without autoimmune hemolytic anemia or thrombocytopenia (7/14, 50%), elevated serum lactate dehydrogenase level (13/29, 45%), and hypergammaglobulinemia (6/32, 19%). Two patients have been tested for serum soluble interleukin-2 receptor (sIL-2R) and human T-cell leukemia virus (HTLV); both patients had elevated sIL-2R levels and were negative for HTLV-1 [17,28]. Other rare laboratory findings reported in FTCL patients include hypereosinophilia and an elevated serum IgE level, reported in 2 and 1 patients, respectively [13,25].

3. Histopathology

 By definition, FTCL demonstrates a nodular growth pattern in lymph nodes (Fig. 1A). Depending on the morphologic pattern, lymph nodes can display minimal, partial, or total architectural effacement [13-29]. The peripheral sinuses are often spared [13,14,18,19]. Capsular fibrosis can be present [15,17]. Extranodal infiltration by tumor cells, frequently seen in AITL, is uncommon in FTCL [19,22]. In the WHO classification, 3 morphologic patterns in FTCL are recognized: follicular lymphoma (FL)-like, progressive transformation of germinal centers (PTGC)-like (also described
in the literature as nodular lymphocyte predominant Hodgkin lymphoma-like), and marginal zone lymphoma (MZL)–like.

In cases with an FL-like pattern, representing approximately 20% of all FTCL cases, the tumor cells form intrafollicular aggregates or nodules that can closely resemble follicular lymphoma. The nodules can be surrounded by mantle zones, or mantle zones can be absent [19,20,23,26,30]. In cases that are MZL-like, representing approximately 30% of all FTCL cases, the neoplastic lymphoid cells show a perifollicular growth pattern or paracortical involvement that can mimic marginal zone lymphoma [14,15,18,20]. A mixture of FL-like and PTGC-like patterns are frequently seen in the same biopsy specimen.

Table 1  Clinical features of patients with FTCL

<table>
<thead>
<tr>
<th>General features</th>
<th>1.2:1 (36:29)</th>
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<tbody>
<tr>
<td>Sex ratio (male:female)</td>
<td>1.2:1 (36:29)</td>
</tr>
<tr>
<td>Age</td>
<td>Mean: 62</td>
</tr>
<tr>
<td>B-type constitutional symptoms</td>
<td>29% (16/55)</td>
</tr>
<tr>
<td>Advanced stages (III/IV)</td>
<td>73% (40/55)</td>
</tr>
<tr>
<td>Organ involvement</td>
<td></td>
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<tr>
<td>Skin lesions</td>
<td>23% (12/51)</td>
</tr>
<tr>
<td>Multiple lymphadenopathies</td>
<td>86% (48/56)</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>23% (6/26)</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>24% (13/54)</td>
</tr>
<tr>
<td>Bone marrow involvement</td>
<td>26% (6/23)</td>
</tr>
<tr>
<td>Laboratory tests</td>
<td></td>
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<tr>
<td>Elevated LDH</td>
<td>45% (13/29)</td>
</tr>
<tr>
<td>Hyper gammaglobulinemia</td>
<td>19% (6/32)</td>
</tr>
<tr>
<td>AIHA/positive Coombs’ test</td>
<td>50% (7/14)</td>
</tr>
</tbody>
</table>

Abbreviations: LDH, lactate dehydrogenase; AIHA, autoimmune hemolytic anemia.
Although these patterns are grouped together in the WHO classification, these patterns are sufficiently different to suggest at least some differences in pathogenesis. In particular, cases of FTCL with a MZL-like pattern have some similarities with early phase AITL, so-called patterns I and II, as summarized by Attiygalle et al. [61]. The overall architecture is often minimally or partially effaced. The lymphoid follicles can be hyperplastic but, more often, are regressed or atretic. In advanced lesions with a perifollicular growth pattern, the neoplastic cells may extend into mantle zones and T-zone regions. Intermodular or intranodular epithelioid histiocytes, rarely prominent, are often encountered [13,15,19,24]. Hodgkin-like cells and eosinophils are sometimes present. Proliferation of high-endothelial venules (HEV), an otherwise uncommon event in FTCL, is often seen in cases with MZL-like morphology [15]. However, in general cases of FTCL differ from AITL in that FTCL cases less often have a polymorphous reactive background, a proliferation of arborizing HEV, or expansion of follicular dendritic cell networks (Fig. 1C) [13,15-17,22,24].

Agostinelli et al reported 4 cases of FTCL involving lymph node in which the tumor nodules were not associated with follicular dendritic cell meshworks [29]. Although we have not reviewed these cases, their description seems similar to the MZL-like pattern of FTCL. All 4 cases expressed 3 to 6 TFH cell markers. However, most other cases of FTCL with MZL-like growth pattern have not been assessed for TFH cell markers because these studies were published before T_FH cells were well-characterized [14,15,18,20]. Therefore, the true frequency of the MZL-like pattern may need to be re-evaluated.

Cytologically, the neoplastic cells of FTCL involving lymph nodes have been described as medium or medium to large in size (58/80, 72.5%), small to medium-sized (16/80, 20%), or large (6/80, 7.5%) (Fig. 1B) [13-29]. The tumor cells tend to have round to slightly irregular or indentated nuclear contours, vesicular to coarsely granular chromatin, and usually moderate or abundant clear or pale eosinophilic cytoplasm with indistinct cell borders. The nuclear features of FTCL cells can resemble centrocytes or centroblasts; the cytoplasm is helpful in their recognition as T-cells.

Follicular T-cell lymphoma also has been reported to involve extranodal sites in a subset of patients, including bone marrow, liver, spleen, skin, tonsils, salivary glands, and hard palate, although as far as we are aware, descriptions of the histologic findings at every one of these sites are not available. The diagnosis of FTCL at an extranodal site can be highly challenging unless the diagnosis already has been established in lymph nodes. The pattern of bone marrow involvement by FTCL has been reported to be paratrabecular and/or interstitial [21,26]. At extranodal mucosal sites, FTCL can be associated with lymphoepithelial lesions similar to those of extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) [18].

### 4. Immunophenotype

Follicular T-cell lymphoma is composed of lymphoid cells that express a variety of T_FH cell markers (Fig. 2 and Table 2) [22-29]. PD-1/CD279 and ICOS are reported to be most sensitive, positive in all cases tested to date, 38 and 13 cases, respectively. PD-1 is a member of CD28/CTLA-4 co-receptor family that delivers inhibitory signals to T-cells, and ICOS is another member of the same co-receptor family that provides co-stimulation to T-cells. Most cases (35/40, 88%) of FTCL are positive for CXCL13. Cytoplasmic SAP and transcription factor NF-ATc1 have been positive in a few cases tested [23,29]. By contrast, CD10 and Bel-6, 2 markers commonly expressed by both benign and malignant germinal center B-cells, are less sensitive markers of FTCL. CD10 and Bel-6 have been expressed in 37/57 (65%) and 36/46 (78%) of FTCL cases, respectively. Down-regulation of Bel-6 and CD10, which is frequently observed when neoplastic germinal center B-cells migrate out of the follicles in follicular lymphoma, has been observed in small numbers of FTCL cases reported [16,19,21].

It is important to remember that individual T_FH markers can be expressed by other T-cell subsets, other types of T-cell lymphoma (eg, mycosis fungoides) and B-cell lymphoma (eg, chronic lymphocytic leukemia/small lymphocytic lymphoma) as well as in reactive conditions as reported by others [29,30,46,50,51,53,55,57,63,65-69]. Therefore, it has been suggested that a combination of markers be used, with an arbitrary minimum of three markers being positive to define the T_FH immunophenotype [29,35,54]. Thirty-one cases of FTCL reported in the literature have been tested for expression of 4 to 6 T_FH markers, with 29 (94%) positive for at least 3 markers supporting T_FH cell lineage.

The neoplastic cells of FTCL also express pan-T-cell antigens, including CD2, CD3, CD5, or CD7 (Fig. 2 and Table 2).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Immunophenotype of FTCL</th>
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<tr>
<td>CD2—a</td>
<td>100% (56/56) CD10</td>
</tr>
<tr>
<td>CD3—b</td>
<td>99% (74/75) Bel-6</td>
</tr>
<tr>
<td>CD4+CD8+</td>
<td>91% (67/74) PD-1</td>
</tr>
<tr>
<td>CD4+CD8-</td>
<td>1% (1/73) CXCL13</td>
</tr>
<tr>
<td>CD4+CD8-</td>
<td>1% (1/73) ICOS</td>
</tr>
<tr>
<td>CD4+CD8-</td>
<td>7% (5/73) SAP</td>
</tr>
<tr>
<td>CD5</td>
<td>89% (59/66) CD57</td>
</tr>
<tr>
<td>CD7</td>
<td>32% (17/53) NF-ATc1</td>
</tr>
<tr>
<td>CD43</td>
<td>94% (15/16) CD25</td>
</tr>
<tr>
<td>CD45</td>
<td>97% (32/33) CD30</td>
</tr>
<tr>
<td>CD56</td>
<td>0% (0/22) CD31</td>
</tr>
<tr>
<td>TIA1/GraB</td>
<td>0% (0/31) Bel-2</td>
</tr>
</tbody>
</table>

Abbreviations: GraB, granzyme B; PD-1, programmed cell death-1; ICOS, inducible costimulator; SAP, SLAM (signaling lymphocyte-activation molecule)-associated protein.

—a Including 1 case with partial loss of CD2 as positive [19].

—b Including 2 cases with partial loss of CD3 and 4 cases with positive immunohistochemistry but negative flow cytometry as positive [14,18,19].
Table 2) [13-29]. An aberrant T-cell immunophenotype or antigen “loss” is present in many cases. CD7 has been absent in FTCL most often (36/53, 68%), and CD5, in some cases (7/66, 11%). Partial loss of CD2, CD3, or CD4 has been reported in occasional cases. Most (67/74, 91%) of FTCL have a CD4+CD8− helper T-cell immunophenotype. A small subset (7%) of cases reported were CD4−CD8−. Aberrant expression of B-cell markers, such as CD79a or CD20, is rarely encountered (Fig. 2D and E) [22]. T-cell receptor expression has been infrequently assessed in FTCLs.

Other markers seen in a small subset of cases include Bcl-2 (3/9, 33%), CD25 (3/11, 27%), CD57 (7/47, 15%), and dim CD30 (4/34, 12%). CD31 expression has been reported in 2 cases tested [19,22]. They are negative for CD56 and cytotoxic antigens, such as TIA-1 and granzyme B. Scattered Epstein-Barr virus encoded RNA-positive B cells consistent with immunoblasts have been reported in 18 (41%) of 43 cases. Reactive follicular dendritic cell meshworks revealed with immunoblasts have been reported in 18 (41%) of 43 cases tested [19,22]. T-cell receptor expression has been infrequently assessed in FTCLs.

Using conventional cytogenetic analysis, 7 (39%) of 18 cases of FTCL reported had an abnormal and usually complex karyotype (Table 3) [15,20,21,28]. One case reported carried a t(5;9)(q33;q22) involving the fusion of 2 tyrosine kinases, ITK (IL-2-inducible T-cell kinase) and SYK (spleen tyrosine kinase), confirmed by fluorescence in situ hybridization [20]. Fluorescence in situ hybridization analysis for ITK-SYK has shown this fusion in 6 (21%) of 28 cases assessed, including 5 cases with a FL-like pattern and 1 case with a MZL-like pattern [20,25]. Interestingly, t(5;9)(q33;q22) also has been reported in 2 cases of PTCL-NOS with a diffuse growth pattern, one of which was examined for and had TFH cell immunophenotype [5,20]. The translocation was not found inAITL or anaplastic lymphoma kinase (ALK)-negative anaplastic large cell lymphoma [20]. Thus, t(5;9) may be unique to FTCL and rare cases of PTCL-NOS with a TFH cell immunophenotype [5,20]. Expression of ITK-SYK in mice induces lymphoma resembling human PTCL [72,73]. Over-expression of SYK, however, has been shown in a wide variety of T-cell lymphomas that lack t(5;9)/ITK-SYK [74].

The roles of BCL-2 and BC-L6, well known in B-cell lymphomas, are less clear in FTCLs. The Bel-6 protein is known to be important for TFH cell differentiation [35-40]. In one case of FTCL that we observed recently, we showed amplification of both BCL-6 and BCL-2 by fluorescence in situ hybridization analysis (unpublished data). Aberrant somatic mutation of BCL-6 has not been identified in FTCLs [21]. To date, there are no reports of array-based global examination of genetic abnormalities or gene expression profiling in FTCL.

### Table 3

<table>
<thead>
<tr>
<th>Karyotypes of 7 reported cases of FTCL</th>
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<tbody>
<tr>
<td>1. 46,XY,del(6)(q21)[3]/46,idem,add(17)(q25)[7]/46,XY[10]</td>
</tr>
<tr>
<td>2. 46,XX,t(5;9)(q33;q22)[2]/46,XX,t(5;9)(q33;q22),dup(17)(q21q24)[12]/46,XX[18]</td>
</tr>
<tr>
<td>3. 46,XX,del(6)(q15q25)[8]/46,XX,der(11)(3:11)(q13;q25),der(13)t(X;13)(q22:p11)[6]/46,XX,der(9)t(1:9)(q21;p24),der(15;17)(q10;q10),+17[4]</td>
</tr>
<tr>
<td>4. 33-41,der(X)t(X;10)(q28;q24),Y,ins(1;22)[3]/11p15q13,der(2)t(1;2)(q32;37),der(3)t(3;17)(p21;q11),−4,der(5)</td>
</tr>
<tr>
<td>5. 45,XY,der(7)t(17;21)(q21;q22),add(12)(q24),+mar[9]</td>
</tr>
<tr>
<td>6. 47,XY,add(X)(p22),+Y,add(1)(p34),−2,add(3)(q29),</td>
</tr>
<tr>
<td>7. 45,XY,add(1)(q21),add(2)(p11.2),add(7)(p22),add(8)(p11.2),−9,add(10)(q22),−14,add(15)(q22),+mar[18]</td>
</tr>
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</table>

**NOTE.** References [15,20,21,28].
living patients at last follow-up, but only 16 were free of disease after median follow-up of 12 to 35 months (range, 9-124 months) [14-17,20,21,25,27,28].

7. Other T<sub>FH</sub> cell–derived T-cell lymphomas

Other types of T-cell lymphoma that have a T<sub>FH</sub> cell immunophenotype are known, the best known of which is AITL, the first type of T-cell lymphoma shown to have a T<sub>FH</sub> cell immunophenotype. The morphologic findings of AITL have been divided into 3 patterns, arbitrarily designated as patterns I, II, and III, which correlate with disease progression and loosely correlate with clinical progression and prognosis [61,75-77]. Cases of FTCL with an MZL-like pattern share some histological and clinicopathologic features with patterns I and II of AITL. It seems possible that FTCL with a MZL-like pattern and AITL are closely related or represent a spectrum of the same disease. Supporting this concept, rare cases of FTCL with coexistent AITL also have been reported [30]. In addition, Huang and colleagues reported that 4 patients were initially diagnosed with AITL but relapsed with biopsy specimens that resembled FTCL [25]. However, relapse of AITL as FTCL is rare as Attygalle et al followed up 30 patients with AITL and relapse as FTCL was not reported [75].

A subset of cases currently classified as PTCL-NOS also have been shown to express T<sub>FH</sub> cell markers suggesting a possible relationship with FTCL [5,29,30,42-44,46,50,53,55,63]. These cases have been identified by gene expression profiling or immunohistochemical analysis using T<sub>FH</sub>-associated markers. In gene expression profiling studies, approximately 20% to 25% of PTCL-NOS cases have a T<sub>FH</sub> gene signature [42-44]. Using immunohistochemistry, Rodriguez-Pinilla and colleagues [63] assessed for expression of CD10, Bcl-6, PD-1, and CXCL13 in 81 cases of PTCL-NOS; 16 cases (20%) expressed at least three TFH markers supporting a TFH cell immunophenotype. Zhan et al [30] also studied the same set of T<sub>FH</sub> cell markers in 81 cases of PTCL-NOS and found 4 cases (5%) that expressed 3 or more T<sub>FH</sub> markers. The explanation for the discrepancy between these 2 studies is unknown, but the results of Rodriguez-Pinilla and colleagues are more in line with the results of gene expression profiling studies [42-44].

It also appears that there are morphologic correlates associated with expression of T<sub>FH</sub> markers in PTCL-NOS. A subset of cases have some histologic features suggestive, although not diagnostic, of AITL [30,42,63]. It therefore seems likely that some cases of PTCL-NOS may be early cases of AITL, at a stage before the characteristic clinical or histologic features of AITL are present. In addition, cases of the lymphoepithelioid variant of PTCL (so-called Lennert lymphoma), T-zone variant PTCL, and rare cases of ALK-anaplastic large cell lymphoma, and truly unclassified cases of PTCL-NOS can express multiple T<sub>FH</sub> markers [29,30,63]. Importantly, there are definitional issues involved in classification. Is a T<sub>FH</sub> cell immunophenotype adequate evidence to remove a tumor from the PTCL-NOS category and suggest another diagnosis, such as AITL?

Primary cutaneous CD4-positive small/medium T-cell lymphoma (PCSMTCL) is another type of T-cell lymphoma recently shown to have a T<sub>FH</sub> cell immunophenotype [64,65]. PCSMTCL is a rare and indolent disease, currently listed as a provisional entity in the 2008 WHO classification [1,78]. These neoplasms have a predilection for the head/neck and upper trunk regions. Morphologically, PCSMTCL shows a diffuse or nodular dermal infiltrate that has a tendency to infiltrate the subcutis and can exhibit a minor component of epidermotropism. A reactive background is common. Aberrant T-cell immunophenotypes are uncommon and EBV infection is rare [64,78]. The T<sub>FH</sub> cell markers Bcl-6, PD-1 and CXCL13, but not CD10, are consistently expressed which help distinguish PCSMTCL from other types of cutaneous T-cell lymphoma and reactive conditions [64,65]. Le Tourneau et al reported 2 cases of FTCL occurring in head/neck and upper trunk [27]. These tumors exhibited a follicular dendritic cell (FDC) meshwork and were positive for CD10. It is not known whether these cases represent cutaneous FTCL or PCSMTCL with follicular pattern. Alternatively, PCSMTCL may represent a diffuse variant of FTCL. However, the indolent clinical behavior of PCSMTCL distinguishes this neoplasm from FTCL which is clinically more aggressive.

8. Conclusions

There appears to be an emerging consensus that FTCL is a rare but distinctive type of T-cell lymphoma that arises from T<sub>FH</sub> cells, a normal T-cell subset located in the germinal centers of lymphoid follicles. A variety of morphologic patterns have been accepted in the WHO classification, but in our opinion, this heterogeneity raises the possibility that the criteria for diagnosis of FTCL need further refinement. A subset of FTCL is associated with a distinctive molecular abnormality, t(5;9)(q33;q22), involving SYK and TYK, further suggesting heterogeneity that will need to be addressed. Follicular T-cell lymphomas are clinically aggressive and often refractory to standard chemotherapy regimens such as CHOP.

There is also emerging evidence that there is a family of T-cell lymphomas that have a T<sub>FH</sub> cell immunophenotype, including FTCL, AITL, the lymphoepithelioid (Lennert lymphoma) and T-zone variants of PTCL-NOS, and PCSMTCL. There are also case reports and small series of patients who have had FTCL and AITL or PTCL-NOS with a T<sub>FH</sub> immunophenotype, simultaneously or in sequential fashion. Whether these are examples of transformation from FTCL into another tumor type, or represent plasticity of T<sub>FH</sub> cell differentiation is unknown. It is essential to remember that many of these widely used T<sub>FH</sub> cell–associated markers are not entirely specific for T<sub>FH</sub> cells. As a result, the use of a single T<sub>FH</sub> cell marker for defining
TFH cell immunophenotype is inadequate. There appears to be an emerging consensus that at least 3 TFH cell–associated markers being positive are needed to support a TFH cell immunophenotype[29,35,54].

Many questions remain to be answered. The paraclonal or perifollicular location of the neoplastic cells in cases of FTCL with MZL-like pattern is difficult to reconcile with the GC location of TFH cells, the postulated cell of origin. As many cases of MZL-like FTCL were not assessed for TFH cells at the time they were published, perhaps considering these cases as FTCL needs to be evaluated. Alternatively, a recent study has identified a subset of non–germinal center T-cells with TFH cell immunophenotype [79]. These non-GC TFH cells induce the proliferation and differentiation of native, but not GC, B cells. There is also a qualitative difference in the expression of some of the TFH cell markers between these 2 subsets of TH cells [35,79,80]. Another recent development is the identification of TFH cell counterparts in the peripheral blood [81,82]. It is unknown whether these non-GC TFH cells are a completely different subset of TH cells, or they may represent a non-GC stage (precursor or memory stage) of GC TFH cells [35,36].

The identification of a family of T-cell lymphomas that arise from TFH cells or show TFH cell differentiation may have practical implications. Others have suggested that TFH cell–derived lymphomas have a broad spectrum and this raises the possibility of defining these neoplasms as a group in future lymphoma classification schemes. Although there are similarities between FTCL and AITL, the relationship between FTCL, AITL, PCSMTCL, and some cases of the lymphoepithelioid and T-zone variants of PTCL-NOS is unclear [25,29,30,62,63]. Should all of these lymphomas be classified as subtypes under the same umbrella term of TFH cell-derived lymphoma? In some ways, an analogy can be made with B-cell lymphomas that have a germinal center B-cell immunophenotype, a group that includes clinically indolent low-grade follicular lymphomas and clinically aggressive diffuse large B-cell lymphomas as well as Burkitt lymphoma. The umbrella term germinal center B-cell derived lymphoma has some academic value but certainly does not convey practical information in terms of guiding therapeutic decisions or predicting prognosis. At least for now, it may be premature to redefine T-cell lymphomas purely on the basis of a TFH cell immunophenotype.

9. Note in added proof

After acceptance of this manuscript, Miyoshi et al reported 17 cases of FTCL [83]. In their study, the authors emphasize that FTCL shares many clinical and pathologic characteristics with AITL, as well as a TFH cell immunophenotype. The authors further suggest that FTCL and AITL belong to the same disease spectrum. The findings presented in this study are in keeping with some of the data we have presented in this review.

References


