Primary Cutaneous Follicular Helper T-cell Lymphoma

A New Subtype of Cutaneous T-cell Lymphoma Reported in a Series of 5 Cases

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Background: Peripheral nodal follicular T-cell lymphomas expressing follicular helper T-cell (T\(_{FH}\)) markers have recently been identified. Such lymphomas are characterized by a nodal neoplastic T-cell proliferation accompanied by numerous reactive B cells and demonstrate some overlap with nodal angioimmunoblastic T-cell lymphoma (AITL). We identified 5 cases of cutaneous T-cell lymphoma with a peculiar pathologic aspect and expression of T\(_{FH}\) markers.

Observations: The mean age of the patients was 61 years (range, 33-78 years). Four patients had multiple papules, plaques, and nodules predominating on the trunk and the head. One had a nodular plaque on the face. Lesional T-cell clonality was found in all 5 patients, and blood T-cell clonality in 4 of the 5. Nodal involvement was never found. Patients had no systemic symptoms and no biological signs of AITL. In 3 cases, findings from skin biopsy specimens were initially misdiagnosed as primary cutaneous follicle B-cell lymphoma due to major B-cell infiltrate and CD10 positivity. Rituximab-containing therapies were ineffective in these cases, and biopsy specimens after treatment with rituximab showed medium- to large-sized atypical T-cell skin infiltrate expressing T\(_{FH}\) markers (CD10, Bcl-6, PD-1, CXCL13, and ICOS). The final diagnosis proposed for all patients was cutaneous T\(_{FH}\) lymphoma. The patient with localized disease was successfully treated with radiotherapy. Patients with diffuse disease showed marked resistance to treatments, with only 1 case of complete remission after allogeneic hematopoietic stem cell transplantation followed by bortezomib and donor-lymphocyte infusion. Bexarotene, methotrexate, thalidomide, interferon alfa, gemcitabine, liposomal doxorubicin, or multiagent chemotherapy with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) were either ineffective or induced transitory partial remission.

Conclusions: We describe an original clinicopathologic series of primary cutaneous lymphomas with T\(_{FH}\) phenotype, suggesting the existence of a new entity among cutaneous T-cell lymphomas. Relations of these lymphomas with the provisional entity of primary cutaneous small to medium CD4\(^+\) pleomorphic T-cell lymphoma need to be further addressed.

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FOLLCULAR HELPER T (T\(_{FH}\)) cells are a specific subset of CD4\(^+\) helper T cells (T\(_{H}\)), normally found in the germinal centers of B-cell follicles.\(^1\) They provide help to B cells and cause them to differentiate into long-lived, antibody-secreting plasma cells or memory B cells.\(^2,3\) T\(_{FH}\) cells have been distinguished from subtypes T\(_{H1}\) and T\(_{H2}\) by several criteria, including a peculiar expression of CXCR5, CXCL13, CD10, Bcl-6, PD-1, and ICOS.\(^4\)

Gene expression profiling of nodal peripheral T-cell lymphoma (PTCL) demonstrated that neoplastic T cells in angioimmunoblastic T-cell lymphoma (AITL) derive from T\(_{FH}\) cells.\(^5\) Neoplastic T-cells in AITL indeed express CD10, Bcl-6, ICOS, CXCL13, and PD-1.\(^6,9\)

More recently, a subset of nodal PTCL with follicular growth (follicular PTCL), derived from T\(_{FH}\) cells, has been identified among PTCL unspecified (PTCL-NOS).\(^10-14\) These lymphomas have been shown to express T\(_{FH}\) markers (CD10, Bcl-6, PD-1, CXCL13, and ICOS) and may show overlapping features with AITL.\(^14\) Twenty-six percent of patients reported to date were said to have systematic nodal involvement and skin involvement. In 2010, 2 cases of primary cutaneous follicular variant of PTCL were reported, in which histopathologic features were reminiscent of those found in nodal follicular PTCL, with no detailed clinical data.\(^15\)

We report herein an original series of 5 primary cutaneous T-cell lymphomas with expression of T\(_{FH}\) markers. We pro-
pose calling them primary cutaneous T\textsubscript{FH} lymphomas, and discuss their relationship to the existing entities of the latest World Health Organization (WHO) classification of lymphomas, especially the provisional entity of primary cutaneous CD\textsubscript{4}\textsuperscript{+} small- to medium-sized pleomorphic T-cell lymphoma (PCSMTCL).\textsuperscript{16,17}

REPORT OF CASES

CLINICAL, BIOLOGICAL, AND IMAGING FINDINGS

Clinical data and evaluation of the extension of the disease are shown in Table 1. In brief, patients 1 to 4 had very similar clinical presentation, consisting of multiple papules, plaques, and nodules, distributed on the trunk (in 4 of the 4), the limbs (in 3 of the 4), and the head and neck region (in 3 of the 4). The lesions were erythematous to violaceous and more or less infiltrated (Figure 1). Some of them showed clinical edema. Lesions were not ulcerated. The lesions had appeared progressively over few months, without any history of previous chronic patch or plaque stage. Patient 5 showed a solitary erythematous infiltrated plaque 5 cm in diameter on the right cheek, with nodular reinforcement, evolving over a few months.

Patients 1 and 2 developed palpable regional adenopathies 1 year and 4 years, respectively, after initial skin lesions (axillar or cervical). The patients had no systemic symptoms. Notably, B-cell lymphoma symptoms were absent. Biologic tests showed elevated lactate dehydrogenase in 1 case (patient 3), moderate lymphopenia (700 lymphocytes/µL) in patient 1, and eosinophilia (1800 eosinophils/µL) in patient 4. Other results were in the normal range.

Imaging studies for evaluation of the extension of the disease consisted in thoraco-abdomino-pelvic computed tomography (TAP-CT) in all cases, and positron emission tomography–computed tomography (PET-CT) in patient 3. They did not reveal any visceral involvement nor deep-seated adenopathies. In patient 3, PET-CT showed only diffuse hypermetabolic cutaneous lesions.

The patients’ medical history was nonremarkable, except for non-Langerhans cell cutaneous histiocytosis in patient 4, diagnosed 6 years prior to the cutaneous lymphoma, for which he had been treated with psoralen–UV-A (PUVA) therapy.

Table 1. Clinical, Biological, and Imaging Findings in 5 Patients

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Lesions, No.</th>
<th>Clinical Aspect</th>
<th>T Stage (TNM)</th>
<th>Distribution of Lesions</th>
<th>Palpable Adenopathies\textsuperscript{a}</th>
<th>Serum LDH</th>
<th>Bone Marrow Biopsy Result</th>
<th>Bone Marrow Biopsy, From Imaging Studies\textsuperscript{b}</th>
<th>Successive Treatments</th>
<th>Status at Latest Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/62</td>
<td>&gt;20</td>
<td>Papules, plaques, nodules</td>
<td>T3b</td>
<td>Trunk, cephalic, upper and lower limbs</td>
<td>Axillar (12 mo)</td>
<td>Normal</td>
<td>Negative</td>
<td>Negative (TAP-CT)</td>
<td>Topical steroids, phototherapy, interferon alfa, R-CHOP, bexarotene, gemcitabine, methotrexate, liposomal doxorubicin</td>
<td>Evolutive</td>
</tr>
<tr>
<td>2/M/33</td>
<td>&gt;20</td>
<td>Papules, plaques, nodules</td>
<td>T3b</td>
<td>Trunk, cephalic, susclavicular, (48 mo)</td>
<td>Normal</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative (TAP-CT)</td>
<td>R-CHOP, bexarotene, gemcitabine, rituximab, thalidomide, interferon alfa, CHOP, R-CVP, CHOP, HSC autograft, HSC allograft, bortezomib, DLI, DLI, DL, DLI</td>
<td>Evolutive</td>
</tr>
<tr>
<td>3/M/53</td>
<td>&gt;20</td>
<td>Papules, plaques, nodules</td>
<td>T3b</td>
<td>Trunk, upper and lower limbs</td>
<td>0</td>
<td>Elevated</td>
<td>Moderate lymphocytic infiltration</td>
<td>Negative (TAP-CT, PET)</td>
<td>R-CVP, CHOP, bortezomib, DLI, DLI, DL, DLI</td>
<td>Complete remission</td>
</tr>
<tr>
<td>4/M/77</td>
<td>&gt;20</td>
<td>Papules, plaques, nodules</td>
<td>T3b</td>
<td>Upper and lower limbs, trunk</td>
<td>0</td>
<td>Normal</td>
<td>Negative</td>
<td>Negative (TAP-CT)</td>
<td>Topical chloroquine, topical carmustine, methotrexate, bexarotene, radiotherapy, radiotherapy</td>
<td>Partial remission</td>
</tr>
<tr>
<td>5/F/78</td>
<td>1</td>
<td>Plaque, nodule</td>
<td>T1b</td>
<td>Face</td>
<td>0</td>
<td>Normal</td>
<td>ND</td>
<td>Negative (TAP-CT)</td>
<td>Topical therapy</td>
<td>Complete remission</td>
</tr>
</tbody>
</table>

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; DLI, donor lymphocyte infusion; HSC, hematopoietic stem cell; LDH, lactate dehydrogenase; ND, not done; PET, positron emission tomography; R-CVP, rituximab–cyclophosphamide, vincristine, and prednisone; R-CHOP, rituximab–cyclophosphamide, doxorubicin, vincristine, and prednisone; TAP-CT, thoraco-abdomino-pelvic computed tomography.

\textsuperscript{a}Delay of onset after the skin lesions.

\textsuperscript{b}Visceral disease extension.
HISTOPATHOLOGIC FINDINGS

In all patients, initial skin biopsies performed either on nodular and/or plaque-type lesions showed similar findings (Figure 2). Findings from biopsy specimens from nodular lesions showed a diffuse dense dermal lymphoid infiltrate, with no epidermotropism. In 2 cases, there was slight pilotropism with focal follicular mucin deposits. Biopsies of plaque-type lesions showed a subepidermal, bandlike lymphoid infiltrate, with no epidermotropism, and a grenz-zone between the infiltrate and the epidermis. The infiltrate was made up of about 50% of CD3+ T cells and 50% of CD20+ B cells. The B- and T-cell populations were admixed without clear B- or T-cell zone (Figure 3). The infiltrate contained a subset of atypical medium to large lymphoid cells showing irregular nuclei with finely dispersed chromatin and small nucleoli, on a background of small lymphocytes and rare eosinophils. Some immunoblast-like cells were also seen. Immunohistochemical stains showed Bcl-6 expression (in all 5 patients) and frequent CD10 expression (in 4 of 5) in the infiltrate. Owing to CD10 and Bcl-6 expression in the lymphoid infiltrate and to the important B-cell population, patients 1 to 3 were initially misdiagnosed as having...
primary cutaneous follicle-center B-cell lymphoma (PCF-BCL). However, they were unresponsive to rituximab-containing (R) chemotherapies (respectively, R-CHOP; rituximab; and rituximab–cyclophosphamide, vincristine, and prednisone). After treatment with rituximab, skin biopsies were performed in these 3 cases, showing a diffuse dermal infiltrate of medium to large atypical CD3+, CD4+, and CD8+ T cells, with no CD20 and no CD79a B-cells, precluding the initially proposed diagnosis of PCFBL, and suggesting T-cell lymphoma. In these biopsy specimens, atypical T cells expressed CD10 and Bcl-6, which was evocative of Tfh phenotype.

Additional immunostainings for CXCL-13, PD-1, ICOS, and Ki-67 were performed on all biopsy specimens. The

Figure 2. Histopathologic findings. A, Patient 1: The biopsy of a nodule shows a dense diffuse dermal lymphoid infiltrate with no epidermotropism (hematoxylin-eosin, original magnification ×25; before rituximab). B, Patient 2: The biopsy of a plaque shows a dense diffuse and nodular dermal lymphoid infiltrate with no epidermotropism (hematoxylin-eosin, original magnification ×10; before rituximab). C, Patient 1: Medium and large atypical lymphoid cells admixed with large immunoblast-like cells (hematoxylin-eosin, original magnification ×400; before rituximab). D, Patient 2: Medium and large atypical lymphoid cells (hematoxylin-eosin, original magnification ×400). E, Patient 2: After ineffective treatment with rituximab, a skin biopsy specimen shows atypical lymphoid T cells only (CD3+ cells, but no CD79a+ cells) (hematoxylin-eosin, original magnification ×400).
immunohistochemical results are summarized in Table 2. In brief, at least 2 TFH markers were positive in each case (CD 10, Bcl-6, PD-1, CXCL-13, or ICOS). When present, expression of CXCL-13 was very focal. The Ki-67
proliferative index was moderately high, varying from 30% to 50% in the same patient. Test results for in situ hybridization for Epstein-Barr virus-encoded small RNAs (EBER) were consistently negative. CD30 expression was restricted to rare B immunoblasts.

In patients with palpable adenopathies, lymph node biopsies were performed at least twice. The lymph nodes were hyperplastic, and none showed areas suspect for T-cell lymphoma on morphologic and immunohistochemical analyses, including Bcl-6, CD10, PD-1, CXCL13, and ICOS staining.

Overall, the histopathologic aspect was evocative of T-cell lymphoma, with peculiar important B-cell reactive component, and expression of T<sub>FH</sub> markers. Therefore, we propose classifying these cases as primary cutaneous T<sub>FH</sub> lymphoma.

**CLONALITY ANALYSIS**

The results are shown in Table 2. In brief, T-cell clonality was found in all skin biopsy specimens. The same T-cell clone was found in circulating lymphocytes in the 4 cases with diffuse lesions. When lymph node biopsy was performed, lymph node T-cell clone was either not found (patient 1) or minor (patient 2). Bone marrow T-cell clonality was looked for and found in 2 cases. Interestingly, patient 1 initially showed an associated B-cell clone in the skin and the blood. After R-CHOP therapy, this clone disappeared on following biopsy specimens and blood samples.

**TREATMENTS AND FOLLOW-UP DATA.**

The mean duration of follow-up was 47.8 months (range, 19-85 months). Patient 5, who had local disease, was treated with radiotherapy and is in complete remission to date (19 months). Overall, patients 1 to 4 showed relative resistance to treatments and required systemic chemotherapies. Patient 1 was successfully treated with topical steroids, PUVA therapy, interferon alfa, bexarotene, methotrexate, gemcitabine hydrochloride, and liposomal doxorubicin. Only gemcitabine resulted in partial remission of the disease, with early recurrence after interruption of the treatment. To date, he is still being treated with gemcitabine (as of the 49-month follow-up). Patient 2 was successively treated with thalidomide, interferon alfa, and CHOP (6 cycles). CHOP allowed partial remission, and the patient’s disease has been stabilized for 10 months to date by using bexarotene as maintenance therapy. To date, he too is still being treated with gemcitabine (as of the 85-month follow-up). Patient 3 was successively treated with CHOP; dexamethasone, cytarabine, and cisplatin (DHAP); and autologous hematopoietic stem cell transplantation (HSCT). Both treatments resulted in transitory complete remission with early recurrence. He underwent therapy with allogeneic HSCT, which was followed by an early relapse after 2 months. Bortezomib and donor-lymphocyte infusion resulted in complete and prolonged remission after 20 months of treatment (as of the 61-month follow-up). Patient 4 was successively treated with topical nitrogen mustard, topical Carmustin, methotrexate, bexarotene, and localized radiotherapy on a tumor. He is now in partial remission (as of the 25-month follow-up).

**COMMENT**

We report herein a unique clinicopathologic series of primary cutaneous T-cell lymphomas with expression of T<sub>FH</sub> markers. These cases are characterized by similar histopathologic features, with a diffuse dermal lymphoid infiltrate with admixed T and B cells in relatively equal proportions, the presence of atypical medium-to-large lymphoid cells in variable proportions, absence of epidermotropism, and expression of T<sub>FH</sub> markers. Patients 1 to 4 shared a remarkable clinical picture of multiple diffuse papules, small plaques, and nodules, predominating on the trunk, the limbs, and the head and neck, with no systemic symptoms, and unaltered performance status. Although T-cell clonality was found in the blood and in the bone marrow, and although the lesions were relatively resistant to current therapies for cutaneous T-cell lymphomas, the patients displayed an indolent course, with no deaths after almost 5 years of follow-up.

Neoplastic T cells in our cases expressed at least 2 of the following T<sub>FH</sub> markers: CD10, Bcl-6, CXCL13, PD-1, or ICOS. CXCL13 and Bcl-6 are among the genes whose...
expression is most highly upregulated in $T_{FH}$ cells.48 Programmed cell death 1 (PD-1) is an inhibitory member of the CD28 family, mainly expressed in activated T cells, and especially in $T_{FH}$ cells.4 Expression of PD-1 has been reported in mycosis fungoides, Sézary syndrome and in adult T-cell leukemia and lymphoma.19,20 CD10 expression can be found in some cases with PCFBCL and has been reported in a subset of epithelial and soft-tissue tumors. Bcl-6 is expressed in PCFBCL and in some diffuse large B-cell lymphomas.17 ICOS expression in lymphomas seems restricted to AITL and follicular T-cell lymphoma.21

None of the 5 $T_{FH}$ markers in this study is entirely specific for $T_{FH}$ lineage, and none can be used alone to ascertain a diagnosis of $T_{FH}$ lymphoma. To prove $T_{FH}$ differentiation, the expression of a combination of various $T_{FH}$ markers should be demonstrated, as has been performed in previous studies.14,22

Some differential diagnoses could have been discussed. Mycosis fungoides has been ruled out because of the lack of concordant clinical anamnesis and because of the $T_{FH}$ phenotype of the pleomorphic T cells. The prominent B-cell component and lack of epidermotropism were other arguments against MF, though both may rarely be encountered in MF. PCFBCL can be a diagnosis pitfall, owing to the important B-cell component, to the presence of blastlike B cells, and to the expression of the usual follicular B-cell markers CD10 and Bcl-6. However, careful examination in our cases revealed large, atypical T cells expressing CD10 and Bcl-6, and patients treated with rituximab showed no clinical response.

Nodal follicular PTCL, a variant of PTCL NOS, has overlapping features with AITL (ie, hypergammaglobulinemia, eosinophilia, positive Coombs test result, multiple adenopathies, splenomegaly, B symptoms, and some histopathologic features).14 Classic AITL is characterized by 44% of cutaneous involvement, consisting in a maculopapular eruption, with a waxing and waning course, and a patchy perivascular polymorphic lymphoid infiltrate with expression of CXCL13.6-22 $T_{FH}$-cell clonality has been found in 96% of cases, with possible associated B-cell clonality in 45%.21 AITL is almost always associated with Epstein-Barr virus infection, in contrast with our cases, in which test results for EBER were consistently negative. Clinical presentation in our cases was also different from cutaneous AITL, in that it lacked the waxing and waning course; was mostly papulonodular; and was isolated, without systemic symptoms, multiple adenopathies, effusions, arthritis, or splenomegaly. Although some features were reminiscent of AITL (ie, neoplastic clear cells, scattered B immunoblasts, expression of $T_{FH}$ markers, presence of a B clonality [patient 1], eosinophilia [patient 4], overall clinicopathologic presentation) was not in favor of AITL stricte sensu.

Another differential diagnosis in these cases is primary cutaneous small to medium CD4$^+$ T-cell lymphoma (PCSMCTL), considered as a provisional entity in the 2008 WHO classification of lymphomas.16,17 Histopathologically, PCSMCTL is primarily a diagnosis of exclusion. It shows a dense, diffuse, or nodular infiltrate within the dermis, with a predominance of small- to medium-sized pleomorphic T cells. A considerable admixture with small reactive lymphocytes, CD20$^+$ blasts, eosinophils, plasma cells, and histiocytes may be observed. By definition, the cells have a CD3$^+$, CD4$^+$, CD8$^-$, and CD30$^-$ phenotype, without cytotoxic granules, and show clonal rearrangement of T-cell receptor gene. Recent studies have shown that PCSMCTL is clinically highly heterogeneous, encompassing many cases with localized disease and benign evolution, and rarer diffuse cases with poor prognosis.23 Contradictory results have been published regarding the expression of $T_{FH}$ markers in PCSMCTL. $T_{FH}$ markers were positive in the study by Rodríguez Pinilla et al.,24 whereas CD10 and Bcl-6 were consistently negative in the study by Grogg et al.20 Altogether, it seems that the provisional entity of PCSMCTL may encompass different subtypes of T-cell lymphomas, not yet recognized. The PCSMCTL entity should be rethought in the next few years. Cases described herein as primary cutaneous $T_{FH}$ lymphoma may represent a part of PCSMCTL or may have partial overlap with this provisional entity. In particular, patient 5 had a clinical presentation close to the classic one of PCSMCTL, differing only by the prominence of medium to large T cells and by their $T_{FH}$ phenotype. The presentation of our patients with diffuse disease may better fit in the category of PTCL NOS.

In conclusion, we describe herein an original series of 5 primary cutaneous T-cell lymphomas with expression of $T_{FH}$ markers, which could be called primary cutaneous $T_{FH}$ lymphomas. Table 3 shows provisional criteria that we propose for these lymphomas, which could represent the cutaneous counterpart of the nodal follicular PTCLs, a variant of PTCL NOS.

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**Table 3. Proposed Provisional Criteria for Primary Cutaneous Follicular Helper T-cell ($T_{FH}$) Lymphoma**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>Papules, plaques, and nodules, often multiple</td>
</tr>
<tr>
<td></td>
<td>Trunk, head, and neck involvement</td>
</tr>
<tr>
<td></td>
<td>No patch stage</td>
</tr>
<tr>
<td></td>
<td>No adenopathies at onset of the disease</td>
</tr>
<tr>
<td></td>
<td>No B-cell lymphoma systemic signs of AITL</td>
</tr>
<tr>
<td></td>
<td>The resistance of previously diagnosed PCFBCL to rituximab may raise suspicion for this entity</td>
</tr>
<tr>
<td>Histopathologic</td>
<td>Diffuse dermal infiltrate of pleomorphic medium to large CD4$^+$ T cells</td>
</tr>
<tr>
<td></td>
<td>Prominent B-cell component with some immunoblasts</td>
</tr>
<tr>
<td></td>
<td>$T_{FH}$ phenotype of neoplastic T cells (ie, $&gt;$2 positive markers among CD10, Bcl6, PD-1, CXCL13, or ICOS)</td>
</tr>
<tr>
<td></td>
<td>No epidermotropism</td>
</tr>
<tr>
<td>Molecular biology</td>
<td>T-cell clone (skin)</td>
</tr>
<tr>
<td></td>
<td>T-cell clone may also be found in the blood and the bone marrow</td>
</tr>
</tbody>
</table>

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; PCFBCL, primary cutaneous follicle-center B-cell lymphoma.
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Author Contributions: All authors had full access to all of the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Bachelez, Bagot, and Battistella. Acquisition of data: Beylot-Barry, Bachelez, Rivet, Vergier, Bagot, and Battistella. Analysis and interpretation of data: Beylot-Barry, Bachelez, Rivet, Vergier, and Bagot. Drafting of the manuscript: Battistella. Critical revision of the manuscript for important intellectual content: Beylot-Barry, Bachelez, Rivet, Vergier, and Bagot. Administrative, technical, and material support: Beylot-Barry. Study supervision: Bachelez, Rivet, Vergier, and Bagot.

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REFERENCES