Intertriginous Mycosis Fungoides

A Distinct Presentation of Cutaneous T-Cell Lymphoma That May Be Caused by Malignant Follicular Helper T Cells

Bryan Gammon, MD; Joan Guitart, MD

Background: Follicular helper T cells are a subset of helper T cells that facilitate B-cell recruitment and maturation. Rare cases of cutaneous T-cell lymphoma manifesting as de novo tumor lesions in intertriginous skin contain an infiltrate rich in B cells. These cases may represent malignant counterparts of skin-homing follicular helper T cells.

Observations: Two men and 1 woman (age range, 35-58 years) were seen with predominantly intertriginous tumor-stage cutaneous T-cell lymphoma lesions characterized by the absence of epidermotropism and the presence of a mixed infiltrate rich in B cells. Two of the patients died of the disease less than 3 years from the initial diagnosis. The surviving patient has aggressive disease and underwent hematopoietic stem cell transplantation. Two of the patients had a prominent CXCL13+, Bcl6/CD3+, and programmed death protein 1–positive follicular helper T-cell population.

Conclusions: The intertriginous tumor variant of cutaneous T-cell lymphoma is heterogeneous but may be associated in some cases with a follicular helper T-cell immunophenotype. These patients may follow an aggressive clinical course. Tumor progression in sanctuary sites on patients receiving phototherapy may manifest as a similar clinical phenotype. Further characterization of the disease process is needed to confirm this observation.

Arch Dermatol. 2012;148(9):1040-1044

FOLLICULAR HELPER T CELLS (Tfh) are a recently described subset of helper T cells that have an important role in B-cell recruitment and maturation. Normally, on close contact with an antigen-primed B cell in the pregerminal center, Tfh promote B-cell expansion, the formation of germinal centers, isotype switching, and plasma cell differentiation.1 The expression signature of this unique subset of helper T cells consists of CXCR5 and its ligands CXCL13, BCL6, SAP, inducible T-cell costimulator, and programmed death protein 1 (PD1).2

A subset of cutaneous T-cell lymphomas (CTCLs) may derive from cells with a Tfh phenotype. In rare cases, CTCLs manifesting as tumor lesions without an antecedent patch stage, the so-called d’emblee presentation, are present within an environment rich in B cells. Angioimmunoblastic T-cell lymphoma (AITL) and CD4+ primary cutaneous small or medium pleomorphic T-cell lymphoma (SMPTL) are T-cell lymphomas that have a similarly brisk B-cell inflammatory infiltrate.3,4 Both AITL and SMPTL have recently been shown to be derived from Tfh.5 It is plausible that the intertriginous presentation of CTCL represents a malignant counterpart of Tfh given its histologic similarity to AITL and SMPTL.

OBSERVATIONS

After obtaining approval from the internal review board at Northwestern University and Northwestern University Lurie Cancer Center, we reviewed the cutaneous lymphoma database at Northwestern University for all the patients with tumor-stage lesions. The clinical medical records of these patients were then reviewed in detail, and patients who had been seen at the Northwestern University Cutaneous T-Cell Lymphoma Clinic with tumor-stage lesions in intertriginous zones without antecedent patch-stage disease were included in the study. Complete staging with the absence of lymph node involvement was required for study inclusion. For patients meeting the aforementioned criteria, clinical and demographic information was recorded, including age, race/ethnicity, disease duration, Sézary cell count, lactate dehydrogenase level, status at the last follow-up visit, and attempted therapies and clinical response.

Histopathological features and immunohistochemistry material were reviewed independently by each of us. If multiple biopsy specimens were avail-
able, the sample with more abundant and preserved lymphoma cells was used for analysis. Reviewers scored each patient for the relative abundance of CD4, CD8, and CD20, as well as the TfH markers PD1, CXCL13, and Bcl6. In an effort to increase the specificity of Bcl6 staining, 2-color immunohistochemistry for CD3 and Bcl6 was performed. The presence of a clonal T-cell population was assessed using fresh skin biopsy specimens and polymerase chain reaction primers (Biomed-2 Concerted Action; Euroclonality) as previously published.7 Patients without a prominent CD20 infiltration were excluded from the study.

Review of the Northwestern University CTCL patient database revealed 4 patients who had been seen with primary cutaneous disease composed of intertriginous tumors as assessed by the presence of CXCL13, Bcl6, and PD1.

Patients 1 and 3 were phototherapy naive at presentation.

**Table 1. Clinical Characteristics of Patients With Intertriginous Tumor Phenotype**

<table>
<thead>
<tr>
<th>Patient No./Sex/Race/Age, y</th>
<th>Disease Duration, y</th>
<th>Treatment</th>
<th>Clinical Outcome</th>
<th>Lactate Dehydrogenase Level, U/L</th>
<th>Sézary Cell Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/W/37</td>
<td>2</td>
<td>XRT, PUVA, interferon alfa, interferon alfa monotherapy, NBUVB, pemetrexate, gemcitabine, romidepsin</td>
<td>Dead of disease</td>
<td>207</td>
<td>19</td>
</tr>
<tr>
<td>2/F/B/58</td>
<td>10</td>
<td>NBUVB, oral corticosteroids, interferon alfa + PUVA, gemcitabine, romidepsin, denileukin diftitox, atoligeneic hematopoietic stem cell transplantation</td>
<td>Alive with disease</td>
<td>214</td>
<td>None detected</td>
</tr>
<tr>
<td>3/M/B/35</td>
<td>2</td>
<td>Interferon alfa, PUVA, interleukin 2, bexarotene, gemcitabine, temozolomide, doxorubicin, denileukin diftitox, pentostatin, XRT, CHOP</td>
<td>Dead of disease</td>
<td>190</td>
<td>510</td>
</tr>
</tbody>
</table>

Abbreviations: B, African American; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone combination chemotherapy; NBUVB, narrow-band UV-B phototherapy; PUVA, psoralen–UV-A light therapy; W, white; XRT, radiation therapy.

SI conversion factor: To convert lactate dehydrogenase level to microkatal per liter, multiply by 0.0167.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>T-Cell Receptor</th>
<th>Blood</th>
<th>Tissue</th>
<th>CD4</th>
<th>CD8</th>
<th>CD20</th>
<th>CXCL13</th>
<th>Bcl6/CD3</th>
<th>PD1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>30</td>
<td>10</td>
<td>60</td>
<td>10</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>60</td>
<td>10</td>
<td>30</td>
<td>10</td>
<td>&lt;10</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>60</td>
<td>10</td>
<td>30</td>
<td>20-30</td>
<td>30-40</td>
<td>5-10</td>
</tr>
</tbody>
</table>

Abbreviation: PD1, programmed death protein 1.

**Table 2. Molecular and Immunohistochemical Results**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>T-Cell Receptor</th>
<th>Blood</th>
<th>Tissue</th>
<th>CD4</th>
<th>CD8</th>
<th>CD20</th>
<th>CXCL13</th>
<th>Bcl6/CD3</th>
<th>PD1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>30</td>
<td>10</td>
<td>60</td>
<td>10</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>60</td>
<td>10</td>
<td>30</td>
<td>10</td>
<td>&lt;10</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>60</td>
<td>10</td>
<td>30</td>
<td>20-30</td>
<td>30-40</td>
<td>5-10</td>
</tr>
</tbody>
</table>

Abbreviation: PD1, programmed death protein 1.

**PATHOLOGICAL FINDINGS**

In all 3 patients, biopsy specimens demonstrated a nodular and diffuse lymphocytic infiltrate without significant epidermotropism or adenexotropism extending to a variable degree into the deep reticular dermis (Figure 2). Examination of the cytomorphologic structure revealed aggregates of polymorphous medium atypical lympho-
cytes. Germinal centers were uniformly absent. A variable mixed inflammatory infiltrate composed of eosinophils was present, as well as plasma cells and histiocytes without giant cells or granulomatous aggregates. The inflammatory infiltrate was particularly eosinophil rich in patient 2.

IMMUNOHISTOCHEMISTRY RESULTS

All patients had a significant CD20⁺ B-cell infiltrate, ranging from 30% to 60% of the cells. In patient 1, aggregates of CD3⁺ atypical cells were seen adjacent to aggregates of CD20⁺ cells. Two of the 3 patients had a T-cell population having an immunophenotype consistent with TfHs (Figure 3). Most convincingly, the double-stained Bcl6⁺/CD3⁺ population represented a significant population of the T cells. Taken in aggregate, these results suggest that a large CD20⁺ population correlates with the presence of a neoplastic TfH population in some patients.

The 3 patients described herein illustrate a unique presentation of CTCL. Their clinical manifestation was char-
acterized by rapidly evolving intertriginous tumors composed of malignant T cells with a brisk accompanying predominantly B-cell infiltrate. This is a rare presentation observed in less than 1% of the total population with CTCLs in the Northwestern University Multidisciplinary Cutaneous Lymphoma Group database.

The prominence of the CD20$^+$ population may be a clue that these lesions are composed of TfHs. Recently, TfHs have been implicated in other lymphomas that are rich in B cells, namely, AITL and SMPTL.\(^5\,6\) Typical mycosis fungoides, on the other hand, rarely manifests with a prominent CD20$^+$ infiltrate.\(^8\) We occasionally observe sparse CD20$^+$ cells in tumor-stage mycosis fungoides, but these rarely comprise more than 10% of the infiltrate (J.G., unpublished data). A prominent CD20$^+$ population seems to be associated with a TfH manifestation in some lymphomas with cutaneous involvement.

A thorough history of prior therapy, particularly phototherapy, seems to be important to differentiate the intertriginous tumor presentation from its clinical mimics. Two of 3 patients described herein were young men who were phototherapy naïve. These patients were shown to have a significant population of PD1$^+$, CXCL13$^+$, and Bcl6/CD3$^+$ TfHs in proximity to CD20$^+$ aggregates. On the other hand, patient 2 had previously been exposed to phototherapy. The CTCL tumor lesions may occur at intertriginous sites in patients receiving phototherapy because these sites are protected from UV radiation. Response to phototherapy before presentation could have caused patient 2 to recapitulate the intertriginous de novo tumor phenotype due to tumor progression in photo-sanctuary sites. Patient 2 was negative for TfH markers. The pathogenesis of the prominent CD20$^+$ infiltrate in patient 2 remains unclear.

While the intertriginous tumor phenotype may show some immunohistochemistry features seen in AITL and SMPTL, the characteristics of the patients described herein can be easily clinically distinguished from those entities. Notably, Bcl6, CXCL13, and PD1 are frequently expressed in AITL\(^6\) and SMPTL\(^5\,9\) and are infrequently expressed in mycosis fungoides and unspecified peripheral T-cell lymphomas.\(^9\) However, SMPTL characteristically is seen as an isolated head and neck lesion that typically follows an indolent course.\(^10\) On the other hand, AITL is a peripheral T-cell lymphoma that manifests as lymphadenopathy, dysproteinemia, and constitutional symptoms, with cutaneous involvement in only 50% of cases.\(^11\) Together, the evidence suggests that the characteristics of the patients described herein may be distinct from recognized World Health Organization–European Organization for Research and Treatment of Cancer\(^12\) cutaneous lymphoma entities.

The results of this study shed light on prior work suggesting that SMPTL is a heterogeneous entity with variable clinical outcomes. In 2008, Garcia-Herrera et al described 24 patients with SMPTL and reported that cases with isolated lesions, a large CD8+ population, and a low proliferative index followed an indolent clinical course, while those with rapidly expanding ulcerated tumors, a small CD8+ population, and a high proliferative index were aggressive and often fatal. We would argue that SMPTL invariably manifests as a single lesion, often on the head or neck. The progression in these patients follows an indolent clinical course. The observations herein reinforce that patients seen with multiple rapidly enlarging tumors follow a distinctly aggressive clinical course, and while their disease may show some histologic similarity to SMPTL, it represents a distinct entity. The present study reinforces the need for aggressive management in bulky tumor lesions composed of a mixed infiltrate with prominent TfHs. Notably, the authors report 3 additional cases of SMPTL characterized by abdominal and extremity lesions with prominent eosinophilia and clusters of B cells. These cases manifest histologic similarities to patient 2 in the present study, whose disease was also characterized by tissue eosinophilia and clusters of B cells. Further study of this rare clinical and histopathological presentation is needed.

The intertriginous tumor phenotype is heterogeneous, but a subset of patients with this rare presentation may have neoplasms of TfH origin. These patients may follow an aggressive clinical course and be recalcitrant to standard therapies. Patients with extensive phototherapy history may similarly manifest intertriginous tumors. Phototherapy-naive patients having CTCL lesions with a prominent B-cell component in intertriginous zones seem most likely to have a significant population of TfHs. Further characterization of the disease process is needed to confirm these observations.

Accepted for Publication: April 14, 2012.

Correspondence: Bryan Gammon, MD, Department of Dermatology, Northwestern University, 676 N St Clair, Ste 1600, Chicago, IL 60611 (bryan.gammon@gmail.com).

Author Contributions: Drs Gammon and Guitart had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Gammon and Guitart. Acquisition of data: Gammon and Guitart. Analysis and interpretation of data: Gammon and Guitart. Drafting of the manuscript: Gammon. Critical revision of the manuscript for important intellectual content: Gammon and Guitart. Study supervision: Guitart.

Financial Disclosure: None reported.

Additional Contributions: Thomas N. Traczyk, BS, performed the immunohistochemistry.

REFERENCES