Controversies and Considerations in the Diagnosis of Primary Cutaneous CD4+ Small/Medium T-Cell Lymphoma

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The concept of primary cutaneous CD4+ small/medium T-cell lymphoma (PC-SMTCL) began in the early 1990s when the updated Kiel classification system was applied to primary cutaneous T-cell lymphomas that did not meet criteria for mycosis fungoides (MF) or Sézary syndrome. These early studies established that lymphoid infiltrates with predominately small, pleomorphic T-cells had a more favorable prognosis than those with predominantly large, pleomorphic T-cells. Although cases with medium-sized, pleomorphic T-cells were not initially classified consistently, eventually infiltrates with small- to medium-sized, pleomorphic T-cells were grouped together as a single clinicopathologic entity. Because of the association of some CD8+ cases with a significantly worse prognosis, CD8+ cases were excluded, and PC-SMTCL became a provisional lymphoma in the current World Health Organization-European Organization for Research and Treatment of Cancer classification system. Notably, many experts now allow for CD8+ variants of PC-SMTCL.

At approximately the same time, there were immunophenotypic and genetic investigations into a group of cutaneous lesions with a dense lymphoid infiltrate that were classified as reactive lymphoid hyperplasia or cutaneous pseudolymphoma. These pseudolymphomas had a concerning histopathologic appearance but a benign clinical course; no loss of CD2, CD3, or CD5; and no clonal T-cell population, features that were thought to distinguish them from true lymphomas. However, as cases of pseudolymphoma were further examined, examples were identified that showed loss of pan-T-cell markers and a clonal T-cell population (as reviewed in Ploysangam et al). Currently, the distinction between PC-SMTCL and pseudolymphomas, if any, is uncertain, and the precise classification and clinicopathologic features of PC-SMTCL remain topics of ongoing research and debate.

Here, we review the current clinicopathologic features described for PC-SMTCL, and we compare and contrast those features with pseudolymphoma and a variety of other primary cutaneous and systemic lymphomas, many with significantly more-aggressive clinical behavior (Table). Despite its broad differential diagnosis, accurate recognition of
Summary of Features Supporting a Diagnosis of Primary Cutaneous CD4+ Small/Medium T-Cell Lymphoma (PC-SMTCL) or Entities in Its Differential Diagnosis

<table>
<thead>
<tr>
<th>Features</th>
<th>PC-SMTCL</th>
<th>Pseudolymphoma</th>
<th>PCMZL</th>
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<tbody>
<tr>
<td>Skin lesions</td>
<td>Usually solitary</td>
<td>Usually solitary</td>
<td>Solitary to multiple</td>
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<tr>
<td>Cell size</td>
<td>Small/medium</td>
<td>Small/medium</td>
<td>Small/medium</td>
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<td>T cell or B cell predominant</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
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<tr>
<td>Epidermotropism</td>
<td>–</td>
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<tr>
<td>Secondary follicles</td>
<td>–/+</td>
<td>–/+</td>
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<tr>
<td>Loss of pan–T-cell markers</td>
<td>+ –</td>
<td>+ –</td>
<td>+ –</td>
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<tr>
<td>T-cell clone</td>
<td>+ –</td>
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<tr>
<td>B-cell clone</td>
<td>–</td>
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</tr>
<tr>
<td>PD1&lt;sup&gt;+&lt;/sup&gt; cells</td>
<td>Scattered cells and pseudorosettes</td>
<td>Scattered cells and pseudorosettes&lt;sup&gt;2&lt;/sup&gt; or scattered, small cells&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Positive cells within reactive follicles</td>
</tr>
<tr>
<td>Other differentiating features</td>
<td>• No clinical resolution</td>
<td>• Spontaneous resolution or resolution without aggressive/destructive therapy</td>
<td>• Monocytoid B cells</td>
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<tr>
<td></td>
<td>• T&lt;sub&gt;fr&lt;/sub&gt; phenotype, less commonly CD10&lt;sup&gt;+&lt;/sup&gt;</td>
<td></td>
<td>• Sheets of plasma cells</td>
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<td></td>
<td></td>
<td></td>
<td>• Dutcher bodies</td>
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<td></td>
<td></td>
<td></td>
<td>• CD43&lt;sup&gt;+&lt;/sup&gt; mature B cells</td>
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<td></td>
<td></td>
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<td>• Light-chain restriction</td>
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Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; ATLL, adult T-cell leukemia lymphoma; MF, mycosis fungoides; PCFHTCL, primary cutaneous follicular helper T-cell lymphoma; PCMZL, primary cutaneous marginal zone lymphoma; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; T<sub>fr</sub>, follicular helper T-cells.

PC-SMTCL is important for patient prognosis and treatment options.

**CLINICAL, MORPHOLOGIC, AND IMMUNOPHENOTYPIC FEATURES**

Primary cutaneous CD4<sup>+</sup> small/medium T-cell lymphoma represents approximately 2% to 3% of all cutaneous T-cell lymphomas. Although it affects individuals with a wide age range, including children, most patients are older adults with an average age in the 50s to 60s and without a clear sex predilection. Patients typically present with a solitary, asymptomatic lesion on the face, neck, upper trunk, or upper extremities, which may appear as a violaceous papule, plaque, nodule, or tumor. Some early series, before PC-SMTCL was a well-defined entity, reported a relatively high frequency (50%–74%) of multiple lesions in a localized or generalized distribution. However, recent studies describe a single lesion for most patients. Pain or pruritus has been occasionally noted. The clinical course for these lesions is variable. They may appear suddenly, enlarge rapidly over a few months, slowly grow over years, persist with minimal change, wax and wane over a course of weeks to years, or spontaneously resolve. Ulceration has been described. Unusual clinical presentations include alopecia, poikilodermic plaques, and an association with annular elastolytic giant cell granuloma. By definition, patients should be free of a background of patches and plaques typical of MF.

Lesions of PC-SMTCL are composed of a mixed hematolymphoid infiltrate with a bandlike, nodular, or sheetlike distribution. Frequently, the infiltrate extends into the subcutaneous fibroadipose tissue, and it may also involve skeletal muscle, vessels, and adnexal structures, sometimes with invasion and destruction of vessels and adnexae. Lymphoid cells are most often separated from the epidermis by a grenz zone, but focal epidermotropism may be seen. Notably, prominent epidermotropism should prompt consideration of a diagnosis of MF. As the name implies, most cells in PC-SMTCL are small- to medium-sized, pleomorphic lymphocytes. They are usually found in association with numerous, admixed inflammatory cells, including small lymphocytes, plasma cells, eosinophils, and histiocytes. Granulomatous inflammation may be present. Notably, secondary lymphoid follicles have not been described in association with this lymphoma. A subset of large, atypical, pleomorphic cells may be present, but they make up less than 30% of the infiltrate by definition. Importantly, similar lymphoid proliferations with more than 30% large T-cells are better classified as primary cutaneous peripheral T-cell lymphoma, unspecified/not otherwise specified and have a significantly worse prognosis with a 5-year survival of less than 20%.

Primary cutaneous CD4<sup>+</sup> small/medium T-cell lymphoma is a neoplasm of CD3<sup>+</sup>/CD4<sup>+</sup> T cells that do not express CD30 or cytotoxic markers (Figure 2, A through G). Loss of one or more pan–T-cell markers, most commonly CD7, is noted in 13% to 90% of cases. Intermixed CD20<sup>+</sup> B cells are often numerous (10%–60% of the infiltrate), and intermixed plasma cells are typically polytypic. CD8<sup>+</sup> T cells generally make up a substantial minority of cells (5%–47%). Scattered CD30<sup>+</sup> immunoblasts are usually identified. Thus, immunophenotypic studies confirm the mixed hematolymphoid infiltrate seen morphologically in this lymphoma. Although PC-SMTCL generally has a low Ki-67 proliferation index, usually ranging from 5% to 30%, in some cases it may be as high as 50% to 70%.

Consistently, PC-SMTCL is negative for Epstein-Barr virus. A clonal T-cell receptor gene rearrangement

* References 7, 8, 10, 15, 17, 18, 20–23.
† References 7, 8, 10, 12, 15, 17, 20–23.
‡ References 6, 10, 12, 15, 17, 18, 20, 22.
is detected in 54% to 100% of cases, but immunoglobulin heavy-chain (IgH) rearrangements are polyclonal.\textsuperscript{8,17,21,22}

The recent demonstration that the neoplastic CD4+ T-cells in PC-SMTCL coexpress PD1, BCL6, CXCL13, and ICOS has provided valuable insights into the potential derivation of PC-SMTCL and its microenvironment.\textsuperscript{12,22,23}

PD1, or programmed death 1, is expressed on cell membranes of follicular helper T-cells (T\textsubscript{FH}) found in reactive germinal centers, as well as activated T-cells. PD1 appears to negatively regulate T-cell function and immune response, creating an atmosphere of immune tolerance and helping neoplastic cells to evade the host’s immune surveillance.\textsuperscript{12,22,28} BCL6, CXCL13, and ICOS are important mediators of germinal center development.\textsuperscript{28} Although CXCL13 (chemokine [C-X-C motif] ligand 13) has an important role in the homing and entry of B cells into germinal centers, BCL6 is required for the differentiation of T\textsubscript{FH} and germinal-center B cells, and it is involved in B-cell proliferation.\textsuperscript{28–30} ICOS, or inducible T-cell costimulator, is required for germinal-center formation and T\textsubscript{FH} differentiation.\textsuperscript{30} The expression of these markers indicates that the tumor cells in PC-SMTCL show a T\textsubscript{FH} phenotype. Because T\textsubscript{FH} cells are required for germinal-center formation and stimulate B-cell proliferation and differentiation (as reviewed in Crotty\textsuperscript{30}), this phenotype may help to explain the numerous background B cells in this T-cell lymphoma.\textsuperscript{22} In support of this hypothesis, enlarged CD4+ T-cells expressing PD1, BCL6, and CXCL13 form pseudomasses around CD20+ and CD30+ immunoblasts in PC-SMTCL.\textsuperscript{22} These markers highlight a few lymphocytes in PC-SMTCL (usually \textgreek{\textless}30%) as scattered cells, small aggregates, and pseudomas\textsuperscript{22,23}. They also provide additional immunophenotypic support for the diagnosis of PC-SMTCL as they are expressed in PC-SMTCL, but are less common in MF and peripheral T-cell lymphoma, not otherwise specified.\textsuperscript{12,21,22,31,32} In addition, PD1+ cells are infrequent in dermatitis, including drug reactions.\textsuperscript{23} Interestingly, CD10, another T\textsubscript{FH} marker, is uncommonly positive in PC-SMTCL.\textsuperscript{12,22,23}

The prognosis for PC-SMTCL is favorable, with 5-year survival rate of 60% to 100%.\textsuperscript{7,8,10,20,24,26} In particular, patients with one to few localized lesions have an excellent prognosis,\textsuperscript{8} prompting some to consider PC-SMTCL to be a form of reactive lymphoid hyperplasia (T-cell pseudolymphoma) rather than a true lymphoma. Indeed, patients with limited disease are often “cured” with surgical excision or radiation therapy, although recurrences may occur.\textsuperscript{7,8,10,17,20–23} Importantly, however, some studies have reported a subset of patients who meet diagnostic criteria for PC-SMTCL but who follow a significantly more-aggressive course.\textsuperscript{4,6,20} In one such study, Garcia-Herrera et al\textsuperscript{20} reported 5 patients with a fatal outcome and a median survival of 23 months, despite multiagent chemotherapy in 4 patients. However, many of those patients with a worse prognosis have had distinguishing features. In particular, rapidly developing lesions,\textsuperscript{20,21} multifocality,\textsuperscript{3,6,21} larger lesion size (>5 cm),\textsuperscript{20,21} higher proliferation indices,\textsuperscript{20,21} diminished expression of CD4,\textsuperscript{20,20} and more-monotonous infiltrates with significantly decreased numbers of background inflammatory cells, including infiltrating B cells and CD8+ T-cells,\textsuperscript{20,21} have been associated with a poorer outcome.\textsuperscript{8,20} Further studies are needed to more fully understand aggressive cases. Their differing clinical and pathologic features suggest that they may best be categorized separately in the future.

**Differential Diagnosis**

**Reactive Lymphoid Hyperplasia/T-Cell Pseudolymphoma**

Reactive lymphoid proliferations in the skin are heterogeneous and, unfortunately, lack precise diagnostic criteria. The term *pseudolymphoma* is not a diagnosis sui generis, but rather refers to a reactive process that clinically and/or pathologically simulates lymphoma.\textsuperscript{14,15,33} It has been defined as a “reactive, polyclonal, benign lymphoproliferative process” and may be localized or disseminated.\textsuperscript{35} It includes a heterogeneous group of bandlike, nodular, or diffuse proliferations of B cells and/or T cells that are...
morphologically worrisome for lymphoma. Despite a concerning histopathologic appearance, pseudolymphomas ultimately behave in a clinically benign fashion: They are not associated with systemic involvement, and they eventually resolve, either spontaneously, after removal of an identified, initiating agent or with nonaggressive therapy (such as topical or intralesional steroids). Common known causes include lymphomatoid drug reaction, lymphomatoid contact dermatitis, and persistent, nodular, arthropod-bite reaction, among others.

Morphologically, reactive lymphoid infiltrates in the skin (pseudolymphomas) may display a marked similarity to PC-SMTCL. Indeed, most consider PC-SMTCL to be indistinguishable clinically and pathologically from pseudolymphoma and have advocated that these proliferations be descriptively termed cutaneous nodular proliferation of pleomorphic T lymphocytes of undetermined significance, solitary small- to medium-sized pleomorphic T-cell nodules of undetermined significance, spectrum of pseudo–T-cell lymphoma/PC-SMTCL, or lymphoid infiltrate of uncertain nature until we more fully understand the nature of these lesions. Pseudolymphomas may be composed of a predominant population of reactive, small to medium CD4+ T cells, often with admixed polyclonal B-cells, plasma cells, eosinophils, and histiocytes (Figure 3, A through E). Unfortunately, there are no precise morphologic criteria to differentiate pseudolymphoma from PC-SMTCL. However, pseudolymphomas may include reactive, secondary follicles, which have not been described for PC-SMTCL.

Given the morphologic similarities, immunohistochemistry and molecular techniques are often used to help support a diagnosis of PC-SMTCL. Loss of pan–T-cell markers, including CD2, CD5, and CD7, and a clonal T-cell receptor gene rearrangement help to favor a diagnosis of PC-SMTCL, although they are not present in every case. Conversely, pseudolymphomas may show loss of CD7 and, less-commonly, CD5, as well as clonal T-cell receptor gene rearrangements. Interestingly, PD1+ and CXCL13+ cells are also present in pseudolymphomas and in inflammatory infiltrates, including dermatitis. However, in many of these inflammatory processes, the TFH cells tend to be small, fewer in number, and do not form pseudosclerotic tissue. In addition, in cases with reactive follicles, these TFH cells tend to be confined to germinal centers. In summary, PC-SMTCL and pseudolymphoma share overlapping features, and the current distinction between the 2 requires the analysis of clinical, morphologic, immunophenotypic, and genetic data.

**References 6–9, 11, 14, 17, 20, 21, 35.**

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**Primary Cutaneous Marginal Zone Lymphoma**

The presence of numerous B cells and plasma cells in PC-SMTCL may prompt consideration of primary cutaneous marginal zone lymphoma (PCMZL) (Figure 4, A through F). Primary cutaneous marginal zone lymphoma, a variant of extranodal marginal zone lymphoma that is limited to the skin at diagnosis, is a low-grade B-cell lymphoma with a favorable prognosis (5-year survival of 90%–100%). Clinically, it presents similar to PC-SMTCL.
Primary cutaneous CD4⁺ small/medium T-cell lymphoma. The lymphoid cells are predominantly CD3⁺ (A) and CD4⁺ (B) T cells and show some loss of CD7 (C). There are few CD8⁺ (D) and CD20⁺ (E) cells. F and G, PD1 marks scattered cells, including rosettes. A T-cell receptor gene rearrangement study revealed a clonal T-cell population (data not shown) (original magnification ×40 [A through G]; original magnification ×400 [G]).
as one to multiple, red to violaceous papules, plaques, or nodules on the trunk or extremities in an older patient.\textsuperscript{7,46} Primary cutaneous marginal zone lymphoma may also show an architecture similar to that of PC-SMTCL, with a dermal to subcutaneous collection of atypical lymphoid cells that are separated from the epidermis by a grenz zone. Cytologically, the neoplastic lymphocytes in PCMZL include variable combinations of centrocyte-like (marginal

Figure 3.  T-cell–rich reactive lymphoid hyperplasia/pseudolymphoma. Sections show a dense, dermal lymphoid infiltrate with a patchy distribution that is separated from the epidermis by a grenz zone (A) and includes scattered reactive lymphoid follicles (B). Higher magnification reveals mostly small- to medium-sized lymphocytes with irregular nuclear contours and admixed histiocytes, eosinophils, and plasma cells (C). Lymphoid cells include a mixture of CD3\textsuperscript{+} T-cells (D) and CD20\textsuperscript{+} B-cells (E). Gene rearrangement studies for both B-cell and T-cell receptors were polyclonal (data not shown) (hematoxylin-eosin, original magnifications ×40 [A], ×100 [B], and ×600 [C]; original magnification ×100 [D and E]).
zone) B cells; lymphocytes with relatively abundant, pale cytoplasm, imparting a monocytoid appearance (monocytoid B cells); and cells with plasmacytic differentiation. In many cases, the marginal zone cells predominate and are morphologically similar to the neoplastic lymphocytes in PC-SMTCL, showing a small to medium size and irregular nuclear contour. Additionally, there may be background histiocytes and eosinophils. Finally, both lymphocytes and plasmacytoid B cells with Dutcher bodies are present.
phomas may show near-equal mixture of B cells and T cells. Primary cutaneous marginal zone lymphomas typically have numerous, intermixed T cells (50%-75% of cells), whereas PC-SMTCL often includes numerous background B cells (10%-60% of cells; Figure 5, A and B).10,17,20–23

Despite the similarities, several features help to distinguish PC-SMTCL from PCMZL. The presence of sheets of plasma cells, often located at the periphery of the infiltrate, and Dutcher bodies favors PCMZL.7,46 Similarly, reactive lymphoid follicles are often seen in PCMZL and may be colonized by neoplastic lymphocytes, but follicles have not been reported in PC-SMTCL, and follicular colonization is not identified.17,21 In addition, PCMZL frequently shows light-chain restriction (Figure 5, C and D)9 and may show CD43 coexpression by mature B cells.47 Finally, a clonal IgH gene rearrangement also supports a diagnosis of PCMZL.7,9,21,46,47 In contrast, B cells and plasma cells within the reactive background of PC-SMTCL are typically polyclonal by immunohistochemical or in situ hybridization assessment of κ and λ and by B-cell receptor gene rearrangement studies.13,21,22 In addition, PC-SMTCL includes a clonal T-cell population that expresses T_{FH} markers (PD1, BCL6, ICOS, CXCL13, and sometimes CD10). Although PD1- and CXCL13-expressing T cells are present in PCMZL B-cell lymphoma, the cells are largely limited to reactive follicles.22,48

Figure 5. Primary cutaneous marginal zone lymphoma. The lymphoid cells include a near equal mixture of CD3+ T cells (A) and CD79a+ B cells/plasma cells (B). Plasma cells are κ restricted (C) with few λ-positive cells present (D) (original magnification ×40 [A through D]).

Mycosis Fungoides

Although the patch and many-plaque stages of MF can be easily distinguished from PC-SMTCL because of the presence of significant epidermotropism, some plaque and many-tumor stage MF lesions may histopathologically be confused with PC-SMTCL when clinical information is lacking because these more-advanced stages often do not include epidermotropism.7,17,21,49 Tumor-stage MF appears clinically as solitary to multiple, discrete lesions of 1 cm or greater (Figure 6, A).50 These lesions are characterized by a dense, dermal infiltrate of small- to medium-sized CD4+ T cells with variable loss of pan–T-cell markers (Figure 6, B and C). Despite the histopathologic similarity, clinical features help to distinguish these 2 processes. Patients with plaque- and/or tumor-stage MF have a long history of patches and plaques characteristic of MF, whereas PC-SMTCL arises de novo.7,21,50 In addition, the neoplastic cells in MF are less likely to express PD1 and tend to show more...
Peripheral T-Cell Lymphoma, Not Otherwise Specified

Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) includes a heterogeneous group of lymphomas that, by definition, do not meet criteria for other categories of T-cell lymphoma. Thus, these lymphomas lack clearly defined clinical, histopathologic, and immunophenotypic characteristics. Peripheral T-cell lymphoma-NOS may be primary to the skin (primary cutaneous PTCL-NOS) or may secondarily involve the skin. Importantly, the prognosis for primary or secondary cutaneous PTCL-NOS is dismal, with a 5-year survival rate less than 20%.

Like PC-SMTCL, primary cutaneous and secondary cutaneous PTCL-NOS usually present in older patients as nodules or tumors. Histopathologically, they are characterized by a nodular or diffuse, dermal to subcutaneous infiltrate of CD4+ T cells, with little or no epidermotropism and a variable, mixed, inflammatory background (Figure 7, A through E). However, primary and secondary cutaneous PTCL-NOS more commonly presents with multiple lesions. In addition, primary cutaneous PTCL-NOS includes more than 30% large T cells and generally does not express PD1, features that distinguish it from PC-SMTCL. Patients with secondary cutaneous involvement by PTCL-NOS have evidence of extracutaneous disease, more commonly have a predominance of large neoplastic cells and less commonly show a Tfh immunophenotype.

Angioimmunoblastic T-Cell Lymphoma

Angioimmunoblastic T-cell lymphoma is a peripheral T-cell lymphoma of follicular helper T cells that is associated with Epstein-Barr virus and frequently includes cutaneous manifestations. Patients are typically older and may present with skin papules or nodules composed of a diffuse dermal infiltrate of small- to medium-sized cells. Like PC-SMTCL, angioimmunoblastic T-cell lymphoma shows a CD4+ Tfh immunophenotype, often with loss of pan–T-cell markers, and includes numerous background B cells, CD8+ T cells, and perivascular eosinophils. However, angioimmunoblastic T-cell lymphoma often presents as a diffuse, pruritic, maculopapular eruption and shows a perivascular infiltrate, vascular proliferation, and/or vasculitis on biopsy, features that are not typical of PC-SMTCL. In addition, angioimmunoblastic T-cell lymphoma may include Epstein-Barr virus–positive cells and commonly expresses CD10, including in extranodal sites. Finally, patients with angioimmunoblastic T-cell lymphoma have evidence of systemic disease and typically follow an aggressive course with a 5-year survival less than 30%.

Adult T-Cell Leukemia/Lymphoma

Adult T-cell leukemia lymphoma (ATLL), a T-cell lymphoma caused by the human T-cell leukemia virus type I, has a broad morphologic, immunophenotypic, and clinical spectrum. Although most patients present with disseminated disease by highly pleomorphic T-cells, ATLL may present similarly to PC-SMTCL as a primary cutaneous, dermal or subcutaneous infiltrate of small- to medium-sized CD4+ T-cells that form a clinical papule, plaque, or tumor. Epidermotropism may be limited or absent and histiocytes and admixed granulomas may be prominent. In addition, the T cells in ATLL
often lack CD7,56,58 and they commonly express PD1.57,59 Although these features overlap with PC-SMTCL, the presence of multiple lesions,58 systemic disease, and human T-cell leukemia virus type I infection help to favor ATLL. Although prognosis depends on clinical subtype/disease extent, patients with ATLL and cutaneous disease generally have a significantly worse prognosis than do those with PC-SMTCL.57

Figure 7. Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS). An 81-year-old man with a history of nodal PTCL-NOS presented with a nodule on his left arm. Biopsy revealed a patchy dermal infiltrate (A) that included numerous small- to medium-sized lymphocytes with irregular nuclear contours, histiocytes forming granulomas, eosinophils, and plasma cells (B and C). D and E, A lymph node biopsy performed a year earlier revealed diffuse effacement by a morphologically similar T-cell infiltrate. T-cell receptor gene rearrangement analysis showed an identical clone in the skin and lymph node (data not shown) (hematoxylin-eosin, original magnifications ×20 [A and D], ×200 [B], and ×400 [C and E]).
Primary Cutaneous Follicular Helper T-Cell Lymphoma

Primary cutaneous follicular helper T-cell lymphoma (PCFHTCL) is a recently proposed lymphoma with few reported cases. This category was suggested by Battistella et al, who described 5 cases of primary cutaneous T-cell lymphoma with follicular helper phenotype. These cases were considered morphologically and immunophenotypically similar to the recently described nodal PTCL showing follicular growth and T<sub>FH</sub> phenotype (follicular PTCL). Similar to PC-SMTCL, most of the patients with PCFHTCL were older than 50 years (4 of 5; 80%) and presented with erythematous to violaceous papules, plaques, and nodules. However, unlike PC-SMTCL these lesions were multiple in most cases (4 of 5, 80%) and rapidly evolved during a few months (5 of 5; 100%). Morphologically both PC-SMTCL and PCFHTCL include a dermal, nonepidermotropic, lymphoid infiltrate with T<sub>FH</sub> immunophenotype and numerous associated B cells, and both lack Epstein-Barr virus and CD30. However, the neoplastic cells in PCFHTCL are described as medium to large, although presence of numerous background, small lymphocytes could cause morphologic overlap with PC-SMTCL. PC-SMTCL also tends to have a higher Ki-67 proliferation index than is typical for PC-SMTCL (30%-50%). PCFHTCL commonly has evidence of extracutaneous disease; many of these patients had a clonal T-cell population in the peripheral blood (4 of 5; 80%), lymph node (1 of 5; 20%), and bone marrow (2 of 5; 40%), in addition to the skin (5 of 5; 100%). In addition, patients with PCFHTCL showed resistance to multiagent chemotherapy, despite an overall indolent course, with no deaths after 5 years.

Interestingly, PCFHTCL and follicular PTCL may mimic follicular B-cell lymphomas. Some have suggested that at least a subset of cases of PCFHTCL share overlapping features with angioimmunoblastic T-cell lymphoma. Given the few reported cases, it seems reasonable that further studies will be necessary to fully establish this proposed primary cutaneous lymphoma and to delineate it from others with a T<sub>FH</sub> phenotype.

Other Considerations

Although subcutaneous panniculitis-like T-cell lymphoma could also be considered in the differential diagnosis, its preferential subcutaneous localization, normally without dermal involvement, and its CD8<sup>+</sup> cytotoxic T-cell phenotype help to distinguish this lymphoma. Similarly, lymphomatoid papulosis and other CD30<sup>+</sup> lymphoproliferative disorders usually have more-numerous CD30<sup>+</sup> cells that are also generally larger and more atypical than those seen in PC-SMTCL. Moreover, the neoplastic cells in CD30<sup>+</sup> lymphoproliferative disorders do not have a T<sub>FH</sub> immunophenotype.

CONCLUSION

Our understanding of PC-SMTCL remains incomplete. Although it shares many overlapping features with cutaneous reactive lymphoid hyperplasia/pseudolymphoma, the extent of the infiltrate, cytologic atypia, and the frequent presence of immunophenotypic abnormalities, T-cell clonality and clinical persistence have led to the provisional classification of this process as a lymphoma. The differential diagnosis for PC-SMTCL includes a variety of other primary cutaneous and systemic lymphomas, some with a significantly worse prognosis. Given its indolent nature, accurate recognition of PC-SMTCL is important for prognostication and to prevent overtreatment.

References

19. Wright DH. Updated Kiel classification for lymphomas.


42. Orbanes A, Diez U, Lozano J, Salazar LC. Lymphomatoid contact dermatitis: a syndrome produced by epicutaneous hypersensitivity with clinical features and a histopathologic picture similar to that of mycosis fungoides. Contact Dermatitis. 1976;2(3):139–143.


