Primary Cutaneous Composite Lymphomas

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• Composite lymphomas have been defined as 2 distinct subtypes of lymphoma occurring at a single anatomic site. Composite lymphomas limited to the skin are a rare occurrence and pose a unique challenge. Many reported cases within the skin are combined B-cell and T-cell lymphomas, typically mycosis fungoides and a low-grade B-cell lymphoma. These cases are challenging to recognize because lymphoid infiltrates within the skin often include a mixed population of B cells and T cells. In particular, reactive lymphoid proliferations (pseudolymphomas), primary cutaneous low-grade B-cell lymphomas, and primary cutaneous CD4+ T-cell lymphoproliferative disorder may show nearly equal numbers of B cells and T cells. In order to exclude these possibilities, overwhelming evidence in support of each lymphoma is helpful, including abnormal architecture, cytology, and immunophenotype, as well as molecular genetic evidence of clonality.

In 1948, Custer and Bernhard described “combined lesions” in which lymphomas with distinct histopathologic appearances were identified in a single patient, either at different anatomic sites or in separate areas of a single lymph node.1 In 1954, Custer designated these cases as “composite” lymphomas.2 In 1977, Kim et al3 refined the definition of composite lymphoma (CL), limiting it to the presence of 2 distinct and well-defined varieties of lymphoma at a single anatomic site. In 1982, the working formulation of non-Hodgkin lymphomas sponsored by the National Cancer Institute continued the definition of CL provided by Kim et al,3 describing CL as the presence of 2 distinct lymphomas within a single organ or tissue.4 This definition of CL was based solely on morphology.4,5 The advent of immunophenotypic and genetic techniques revealed that some lymphomas included as CLs actually represent 2 morphologic manifestations or stages of the same neoplastic clone (eg, follicular lymphoma transforming to diffuse large B-cell lymphoma).5–9 Some authors excluded these latter cases from the term CL, emphasizing the coexistence of 2 “separate and distinct lymphomas” with different cells of origin.5–11 This later definition has gained more support with time.

PRIMARY CUTANEOUS CL

The early series of CLs were predominantly nodal/systemic disease,3,6,7 and most cases included 2 types of B-cell neoplasms. However, cases with B- and T-cell components have been reported.7,10–12,21–24 Cutaneous CLs, although rare, include secondary involvement of the skin by systemic/nodal lymphomas,7,11,14,25,26 or a mixture of primary and secondary cutaneous lymphomas.14,21,27,31 More recently, primary cutaneous CLs in which both lymphoma components are primary cutaneous lymphomas have been described (reviewed in the Table; see Figures 1 and 2).10,16–22,24,33 Although only a handful of these cases have been described, the reported cases are CLs composed of B-cell/T-cell lymphomas. Moreover, most cases are composed of mycosis fungoides (MF) along with a low-grade B-cell lymphoma (Figures 1 through 3; Table).

DIFFERENTIAL DIAGNOSIS

Since its first description, CL has been recognized as a challenge for pathologists.2–5 As stated by Kim et al:2 “The differential diagnosis of these lesions depends, of course, on the particular combination of lymphomas being considered.” Differential diagnostic considerations are consequently quite broad, include differentials for 2 separate lymphomas, and are based on the particular features of the case being considered.34 Cutaneous lesions are especially difficult because skin biopsies are often small and crushed, and many processes within the skin include a mixed population of B cells and T cells. Specifically, reactive lymphoid hyperplasia (pseudolymphoma), primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorders, primary cutaneous marginal zone lymphoma, and primary cutaneous follicle center lymphoma all characteristically include a mixed population of B cells and T cells (reviewed by Lan et al35). Accurate diagnosis often requires a combination of clinical, histopathologic, immunophenotypic, and genetic features.36,37 To complicate matters even more, B-cell lymphomas may display a clonal T-cell receptor gene rearrangement and vice versa.22,27 Some suggest that CLs are really a single lymphoma with an associated atypical, reactive lymphoid hyperplasia,14,22,39 and others have questioned whether the term CL provides any utility.11
### Summary of Reported Primary Cutaneous Composite Lymphomas (CLs)

<table>
<thead>
<tr>
<th>Report of Primary Cutaneous CL</th>
<th>Source, y</th>
<th>Clinical Features</th>
<th>CL Components</th>
<th>Additional Features</th>
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</thead>
<tbody>
<tr>
<td>Barzilai et al,21 2006</td>
<td>Man age 70 y with a 10-y history of papular MF (stage IB) developed a subcutaneous nodule on his right arm that showed a primary cutaneous CL</td>
<td>Papular MF and PCMZL</td>
<td>Indolent course</td>
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<tr>
<td>Huwait et al,22 2010</td>
<td>Woman age 67 y with RA treated for 6 y with MTX and variably with prednisone had a 2-y history of plaques. Biopsies of chin, leg, and auricle revealed CL</td>
<td>Iatrogenic immunodeficiency-associated LPD: MF, tumor stage with large cell transformation, and PCFCL</td>
<td>T-cell and B-cell gene rearrangements with the same amplicon size were identified in the chin and leg</td>
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<tr>
<td>Whitling et al,20 2013</td>
<td>Man age 73 y with a 2-y history of patch/plaque MF developed plaquelike to nodular lesions on his scalp (up to 1.2 cm). Biopsy confirmed a CL</td>
<td>MF, patch/plaque, and primary cutaneous, CD5⁺ small B-cell lymphoma</td>
<td>Flow cytometry of both the peripheral blood and lymph node revealed a small CD5⁺ B-cell population with λ bias</td>
<td></td>
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<tr>
<td>Yang et al,19 2011</td>
<td>Woman age 65 y with diabetes mellitus, hypertension, and hyperlipidemia developed a plaque on her left leg. Biopsy showed a CL</td>
<td>PCPTCL and EBV⁺ large B-cell lymphoma</td>
<td>Per the authors, this case could also be considered an &quot;atypical EBV⁺ lymphoproliferative disorder.&quot; Complete regression occurred</td>
<td></td>
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<tr>
<td>Wang et al,24 2014</td>
<td>Man age 70 y with multiple patch/plaque/nodules on his arm, trunk, and scalp. Biopsies of arm and leg lesions revealed CL</td>
<td>Erythrodermic MF and primary cutaneous CD5⁺ small B-cell lymphoma</td>
<td>T-cell and B-cell gene rearrangements of the same amplicon size were identified in the arm and leg</td>
<td></td>
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<tr>
<td>Julie et al,33 2013</td>
<td>Man age 50 y with patches and tumors. Biopsy revealed a CL</td>
<td>MF, tumor stage, and PCFCL</td>
<td>Flow cytometry revealed 0.7% clonal, CD5⁺ B cells in the bone marrow</td>
<td></td>
</tr>
<tr>
<td>Julie et al,33 2013</td>
<td>Man age 67 y with patches and tumors. Biopsy revealed a CL</td>
<td>MF, tumor stage, and PCFCL</td>
<td>Treated with systemic chemotherapy, including rituximab, then allogenic stem cell transplantation. Although the B-cell lymphoma underwent complete remission, the MF relapsed 4 mo later</td>
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</table>

Abbreviations: EBV, Epstein-Barr virus; LPD, lymphoproliferative disorder; MF, mycosis fungoides; MTX, methotrexate; PCFCL, primary cutaneous follicle center lymphoma; PCMZL, primary cutaneous marginal zone lymphoma; PCPTCL, primary cutaneous peripheral T-cell lymphoma; RA, rheumatoid arthritis.
Figure 1. A 49-year-old woman had a 4-year history of patches and plaques. Biopsy demonstrated mycosis fungoides. There were cytologically atypical lymphoid cells that displayed epidermotropism, Pautrier microabscesses, and a bandlike dermal distribution (A). Immunohistochemical studies showed that these lymphoid cells expressed CD3 (B), with significant loss of CD7 (C) (hematoxylin-eosin, original magnification $\times200$ [A]; original magnification $\times200$ [B and C]).

Figure 2. Four years later, the patient described in Figure 1 developed a forehead mass that enlarged during 4 months. She had no evidence of systemic disease. Biopsy revealed a dense dermal lymphoid infiltrate (A) with 2 populations of cells: medium-sized cells with rounded nuclei, vesicular chromatin, and visible nucleoli (B), and a population of smaller lymphoid cells with irregular nuclear contours and clumped chromatin (C) (hematoxylin-eosin, original magnifications $\times40$ [A] and $\times600$ [B and C]).
Immunohistochemical studies performed on the biopsy in Figure 2 revealed that the larger lymphoid cells were positive for CD3 (A) and CD4 (B) but showed loss of CD2 (C) and CD7 (D). The smaller lymphoid cells were highlighted by CD20 (E) but did not express CD10, BCL6, cyclin D1, CD43, or CD5. Plasma cells were almost exclusively λ positive (F), with a few κ-positive cells intermixed (G). T-cell and B-cell gene rearrangement studies revealed clonal T-cell and B-cell populations, and the patient received a diagnosis of a composite lymphoma: mycosis fungoides and a low-grade B-cell lymphoma with plasmacytic differentiation (immunohistochemistry, original magnifications ×20 [A through E] and ×400 [F and G]).
CLINICAL IMPLICATIONS

Regardless of terminology, recognition of both components of a CL is important for determining prognosis and therapy, and for facilitating interpretation of multiple lesions. Indeed, in CL, prognosis and treatment are determined by the most aggressive component, although consideration of both components is important for the overall treatment strategy. Both components should also be considered in the case of recurrent disease, and staging is often very difficult to determine with certainty, because either or both lymphomas may be present throughout the body. In cases of MF with an associated tumor-forming primary cutaneous B-cell lymphoma, as seen in Figure 1, close clinical-pathologic correlation and follow-up are required to determine whether the patient has tumor-stage MF.

EPIDEMIOLOGY

Given the rarity of CLs and the variability in definition, their incidence is difficult to determine with certainty. It has been estimated at approximately 1% to 5% of systemic/nodal lymphomas, but it may be closer to 10%. In 1 study of MF and B-cell malignancies, of 398 cases of MF, 11 patients (3%) had an associated B-cell malignancy and 2 patients had a CL (1%). Only 1 of these patients had a CL composed of 2 primary cutaneous lymphomas.

PATHOGENESIS

The pathogenesis of CLs is not well understood, and it likely varies depending on the case and types of lymphomas involved. Hypotheses include a coincidence, exposure, such as to a virus or carcinogen, genetic predisposition to lymphoma development, interactions between lymphoma cells and surrounding lymphocytes, immunodeficiency or immune dysregulation, or as biphenotypic manifestations of the same neoplastic clone. Regarding the latter proposal, CLs lent early support to the hypothesis that Hodgkin lymphoma is a B-cell neoplasm. 

CONCLUSIONS

Composite lymphomas are rarely encountered, but they offer a diagnostic challenge to pathologists. Primary cutaneous CLs are a rare subset of CLs that can be difficult to recognize. Nonetheless, accurate characterization of all CLs, including primary cutaneous CLs, is important for staging, prognosis, and treatment.

References


