Primary Cutaneous Acral CD8+ T-Cell Lymphoma

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- Primary cutaneous acral CD8+ T-cell lymphoma is a new provisional entity in the 2016 revision of the World Health Organization classification of lymphoid neoplasms. This is a challenging diagnosis because of its rarity, as well as its morphologic and immunophenotypic overlap with other CD8 cytotoxic lymphoid proliferations. Appropriate classification of this entity is crucial because of its indolent clinical behavior compared with other CD8+ T-cell lymphomas. Knowledge of the clinical setting, sites of involvement, and morphologic features can aid in correct diagnosis. Here, we review the clinical and pathologic features of primary cutaneous acral CD8+ T-cell lymphoma with an emphasis on the differential diagnosis among other CD8+ T-cell lymphomas.


In 2007, Petrella and colleagues1 described 4 cases of cutaneous lymphomas, localized to the ear, with indolent clinical behavior despite high-grade morphologic findings. Each patient presented with a slow-growing nodule localized to the ear, and all cases demonstrated an indolent clinical course, regardless of treatment modality (surgery, radiation, observation). This newly described entity, referred to as indolent CD8+ lymphoid proliferation of the ear, could not be classified into any existing type of cutaneous T-cell lymphoma, and the clinical behavior was unusual for a primary cutaneous peripheral T-cell lymphoma, unspecified.1 Since the initial report, it is now known that indolent CD8+ lymphoid proliferation may arise at other peripheral sites.2-4 With largely reproducible clinical and pathologic findings, in addition to an invariably indolent clinical course, it seemed inappropriate to classify these lesions as peripheral T-cell lymphoma, unspecified.2,5 Consequently, primary cutaneous acral CD8+ T-cell lymphoma has been added as a provisional entity in the 2016 revision of the World Health Organization classification of lymphoid neoplasms.6 Correct classification of this entity is essential to avoid unnecessary aggressive treatment.

CLINICAL FEATURES

Primary cutaneous acral CD8+ T-cell lymphoma typically occurs in adults older than 50 years, with a slight male predominance.4 Most cases are characterized by a solitary, slow-growing nodule7-9 without preceding patches or plaques,5,9 but bilateral, symmetrical disease and recurrent disease have been reported.2,4 Although most cases arise on the ear, other peripheral locations, particularly the nose, hands, and feet, have also been described as sites of involvement.2-5,8,10 These findings suggest that a local, antigenic stimulus specific to the ear is unlikely.9 Because of the invariably indolent clinical course, there has also been speculation that primary cutaneous acral CD8+ T-cell lymphoma may represent a reactive process; however, the frequent monoclonality and aberrant loss of T-cell antigens supports these lesions being a true lymphoproliferative disorder.9

PATHOLOGIC FEATURES

The original series described by Petrella and colleagues1 showed a diffuse proliferation of monomorphic, intermediate-sized CD8+ T-cells (Figure 1, A and B) involving the dermis and subcutis. Each case exhibited a well-defined grenz zone without epidermotropism. The neoplastic cells had irregular, lymphoblast-like nuclei (Figure 1, C). Immunoperoxidase studies showed expression of CD3, CD8, T-cell receptor–βF1 (Figure 1, D) and T-cell intracytoplasmic antigen-1 (TIA-1; Figure 2, A) with a low proliferation index (<10%) (Figure 2, B).1 CD4, CD30, CD56, granzyme B, and Epstein-Barr virus–encoded small RNA were negative with variable loss of other T-cell antigens.1 Of the 3 cases examined by molecular analysis, all patients demonstrated a monoclonal T-cell γ-gene rearrangement.1

Using the Petrella et al1 series as the prototype, additional cases have amassed in the literature, and it is apparent that the morphologic and immunophenotypic features for the entity indolent CD8+ lymphoid proliferation of acral sites are reproducible.5,7,8,11 Additional features identified in later case studies include the absence of necrosis, ulceration, and angiocentricity.12 Although most cases exhibit similar morphology to those originally described, variant features including a moderate proliferation index (30%-40%), focal epidermotropism, Pautrier collections, and granzyme B expression have been reported.7 Also, although most cases exhibit a monoclonal T-cell γ-gene rearrangement, rare negative cases have been observed.1,2,5,7,9,13

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Recently, CD68 was described as a possible discriminatory marker in distinguishing primary cutaneous acral CD8\(^+\) T-cell lymphoma from aggressive T-cell lymphomas with a cytotoxic CD8\(^+\) phenotype. Wobser and colleagues investigated 44 cases of CD8\(^+\) cutaneous T-cell lymphomas and identified 5 cases of primary cutaneous acral CD8\(^+\) T-cell lymphoma. During immunohistochemical workup, all 5 cases of primary cutaneous acral CD8\(^+\) T-cell lymphoma demonstrated unusual, dotlike perinuclear positivity for CD68 in the Golgi zone of neoplastic cells (Figure 2, C and D). None of the other CD8\(^+\) cutaneous lymphomas expressed CD68, leading the authors to conclude that CD68 with a dotlike pattern may be helpful in identifying primary cutaneous acral CD8\(^+\) T-cell lymphoma. Although the preliminary data are promising, testing with more cases is warranted to substantiate the sensitivity of this marker.

### Differential Diagnosis

Knowledge of the clinical course and distribution of lesions in primary cutaneous acral CD8\(^+\) T-cell lymphoma is instrumental in making the correct diagnosis. The indolent clinical course helps exclude rapidly progressing lymphomas, such as primary cutaneous aggressive epidermotropic CD8\(^+\) cytotoxic T-cell lymphoma, peripheral cutaneous T-cell lymphoma, not otherwise specified, and primary cutaneous \(\gamma\delta\) T-cell lymphoma. The absence of preexisting patches and plaques helps to distinguish primary cutaneous acral CD8\(^+\) T-cell lymphoma from CD8\(^+\) mycosis fungoides. There is no predilection for the subcutaneous tissue, as observed in subcutaneous panniculitis-like T-cell lymphoma. The frequent acral localization and solitary nature of these lesions make lymphomatoid papulosis less likely.

Although some authors describe the infiltrates of primary cutaneous acral CD8\(^+\) T-cell lymphoma as more monomorphic than those of primary cutaneous small/medium-sized pleomorphic cutaneous T-cell lymphoma, the 2 entities may be morphologically indistinguishable. Furthermore, there is striking overlap in clinical features, such as an adult patient population, a predilection for the face and neck, solitary tumors lacking ulceration, and...
indolent clinical behavior.\textsuperscript{8,16} Although it may be reasonable to regard primary cutaneous acral CD8\textsuperscript{+} T-cell lymphoma as a CD8\textsuperscript{+} analogue to CD4\textsuperscript{+} primary cutaneous small/medium-sized pleomorphic cutaneous T-cell lymphoma, studies have shown that the neoplastic CD4\textsuperscript{+} T cells in the latter coexpress programmed death receptor-1 (PD-1), B-cell lymphoma 6 (BCL6), chemokine ligand 13 (CXCL13), and inducible T-cell costimulator (CD278), indicating a follicular helper T-cell phenotype.\textsuperscript{5,7,12,17} These markers have been negative in primary cutaneous acral CD8\textsuperscript{+} T-cell lymphoma.\textsuperscript{2,9} Fortunately, primary cutaneous small/medium-sized pleomorphic cutaneous T-cell lymphoma and primary cutaneous acral CD8\textsuperscript{+} T-cell lymphoma are defined by, and are readily distinguished by, expression of CD4 or CD8, respectively.

The main morphologic clue in distinguishing primary cutaneous acral CD8\textsuperscript{+} T-cell lymphoma from CD8\textsuperscript{+} variants of mycosis fungoides, CD8\textsuperscript{+} aggressive T-cell lymphoma, and type D lymphomatoid papulosis, is epidermotropism.\textsuperscript{8–10} Although rare cases of primary cutaneous acral CD8\textsuperscript{+} T-cell lymphoma have exhibited epidermotropism and single intraepidermal Pautrier collections, most cases demonstrate epidermal sparing with a discrete grenz zone.\textsuperscript{2}

Immunoperoxidase studies are effective in distinguishing primary cutaneous acral CD8\textsuperscript{+} T-cell lymphoma from morphologic mimickers. Primary cutaneous γδ lymphoma is excluded by the presence of T-cell receptor–βF1 expression and the lack of association with Epstein-Barr virus excludes cutaneous extranodal natural killer/T-cell lymphoma.\textsuperscript{5} The absence of CD30 excludes primary cutaneous CD30\textsuperscript{+} lymphoproliferative disorders, such as cutaneous anaplastic large cell lymphoma and lymphomatoid papulosis.\textsuperscript{4,10}

The morphologic and immunophenotypic overlap between primary cutaneous acral CD8\textsuperscript{+} T-cell lymphoma and subcutaneous panniculitis-like T-cell lymphoma present a formidable diagnostic challenge. Classic features of subcutaneous panniculitis-like T-cell lymphoma, such as lobular infiltration with septal sparing (Figure 3, A) and adipocyte rimming (Figure 3, B), may not be evident in a limited biopsy specimen.\textsuperscript{7,8,10,15} Although CD68 is ex-

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Figure 2. Primary cutaneous acral CD8\textsuperscript{+} T-cell lymphoma. A, T-cell intracytoplasmic antigen–1 (TIA-1) expression in the neoplastic cells. B, Ki-67 showing a low proliferation index. C and D, CD68 highlighting the neoplastic cells with dotlike perinuclear positivity localized to the Golgi zone (original magnification ×500 [A]; original magnification ×100 [B]; original magnifications ×100 [C] and ×500 [D]).
pressed in the neoplastic cells of primary cutaneous acral CD8\(^+\) T-cell lymphoma in an unusual, dotlike perinuclear pattern localized to the Golgi zone, subcutaneous panniculitis-like T-cell lymphoma may have abundant histiocytes, making assessment of the neoplastic cells challenging. Although both entities are known to have a cytotoxic immunophenotype (Figure 3, C) and often show aberrant loss of T-cell markers (Figure 4, A), granzyme B is typically negative in primary cutaneous acral CD8\(^+\) T-cell lymphoma and positive in most subcutaneous panniculitis-like T-cell lymphomas (Figure 4, B). Fat necrosis is frequently a prominent feature in subcutaneous panniculitis-like T-cell lymphoma (Figure 4, C), whereas it is absent in primary cutaneous acral CD8\(^+\) T-cell lymphoma. Possibly, the most helpful distinguishing finding is Ki-67. The proliferation index in subcutaneous panniculitis-like T-cell lymphoma is high (Figure 4, D), whereas primary cutaneous acral CD8\(^+\) T-cell lymphoma typically exhibits a proliferation rate of less than 20%. A clinical history of autoimmune disease, lupus erythematosus panniculitis, and the presence of indurated violaceous plaques or subcutaneous nodules is associated with the diagnosis of subcutaneous panniculitis-like T-cell lymphoma. A summary of clinical, morphologic, and immunophenotypic findings for CD8\(^+\) cutaneous T-cell lymphomas is provided in the Table.

**PROGNOSIS AND TREATMENT**

Despite the high-grade morphologic features and cytotoxic immunophenotype, the clinical course for primary cutaneous acral CD8\(^+\) T-cell lymphoma is invariably indolent. Although there have been cases of cutaneous relapse, there are no reports of extracutaneous disease at diagnosis, and no staging investigations have shown progression to systemic disease during follow-up periods of 3 to 168 months, regardless of treatment modality (topical steroids, radiotherapy, surgical excision, or simple observation). Interferon, psoralen-ultraviolet A phototherapy, and methotrexate have been used in patients with multifocal cutaneous disease to minimize the occurrence of relapse with varying degrees of success.
# Differential Diagnosis of CD8⁺ Cutaneous T-Cell Lymphomas

<table>
<thead>
<tr>
<th>Differential Diagnosis</th>
<th>Skin Lesions</th>
<th>Cell Size</th>
<th>Epidermotropism</th>
<th>Loss of T-Cell Markers</th>
<th>Cytotoxic Markers</th>
<th>PD-1⁺ Cells</th>
<th>Potentially Distinguishing Features</th>
<th>Ki-67</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD8⁺ cutaneous lymphomas</td>
<td>Primary cutaneous acral CD8⁺ T-cell lymphoma</td>
<td>Solitary, slow-growing erythematos nodules; head and neck (especially ear), hands, feet</td>
<td>Small–medium</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Monotonous infiltration of the dermis with a grenz zone below the unaffected epidermis; CD68 localized to Golgi zone</td>
</tr>
<tr>
<td></td>
<td>Primary cutaneous aggressive epidermotropic CD8⁺ cytotoxic T-cell lymphoma</td>
<td>Rapidly growing, generalized, and ulcerated papules, plaques, nodules; trunk, extremities, face; rapidly disseminated lesions to visceral sites</td>
<td>Medium</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>N/A</td>
<td>Prominent epidermotropism, folliculotropism common</td>
</tr>
<tr>
<td></td>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
<td>Solitary or multiple, deeply seated plaques or subcutaneous nodules; often extremities</td>
<td>Small–medium, rarely large</td>
<td>–</td>
<td>+/−</td>
<td>+</td>
<td>+</td>
<td>Only subcutis involved; associated with autoimmune disorders (nearly 20%); lobular infiltration with septal sparing, adipocyte rimming; necrosis and granulomas common</td>
</tr>
<tr>
<td>CD8 variants of CD4 or null cutaneous lymphomas</td>
<td>Mycosis fungoides, cytotoxic</td>
<td>Generalized, scaly patches and plaques, ulcerated nodules; predilection for buttocks and sun-protected areas</td>
<td>Variable</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–/+</td>
<td>Pautrier microabscesses, intraepidermal vesiculation, cerebriform nuclei, haloed lymphocytes</td>
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<tr>
<td></td>
<td>Cutaneous anaplastic large cell lymphoma</td>
<td>Solitary or grouped ulcerating nodules that can regress but often recur; head, extremities</td>
<td>Large</td>
<td>–/+</td>
<td>+</td>
<td>+</td>
<td>N/A</td>
<td>Markedly atypical CD30⁺ cells</td>
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<tr>
<td></td>
<td>Peripheral cutaneous T-cell lymphoma, not otherwise specified</td>
<td>Scattered or diffuse, ulcerating nodules with rapid dissemination and systemic involvement; no specific site</td>
<td>Medium–large</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–/+</td>
<td>Advanced clinical stage at presentation; significant immuno-phenotypic aberrations</td>
</tr>
<tr>
<td></td>
<td>Primary cutaneous small/medium-sized pleomorphic cutaneous T-cell lymphoma</td>
<td>Usually solitary, erythematous nodules on face, neck, or upper trunk</td>
<td>Small–medium</td>
<td>–</td>
<td>+/−</td>
<td>+</td>
<td>–</td>
<td>CD4⁺, follicular helper T-cell phenotype</td>
</tr>
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</table>

Abbreviations: +, positive; −, negative; +/−, variable but more frequently positive; −/+, variable but more frequently negative; N/A, not available; PD-1, programmed death-1; TCR, T-cell receptor.
CONCLUSIONS

Correct diagnosis of primary cutaneous acral CD8+ T-cell lymphoma is essential because the prognostic and therapeutic implications are distinct among other CD8+ cytotoxic lymphoid proliferations. Aggressive epidermotropic cutaneous CD8+ lymphoma and primary cutaneous peripheral T-cell lymphoma, not otherwise specified (NOS) warrant staging investigations and aggressive therapy.3 In contrast, primary cutaneous acral CD8+ T-cell lymphoma can be managed conservatively and tends to follow an indolent clinical course regardless of treatment modality.4 Knowledge of the clinical setting and morphologic and immunophenotypic features can aid in correct diagnosis.

References

Figure 4. Subcutaneous panniculitis-like T-cell lymphoma. A, CD5 showing diminished expression within the neoplastic cells. B, Granzyme highlighting a subset of the neoplastic cells. C, lysozyme highlighting abundant histiocytes within areas of fat necrosis. D, Ki-67 showing a high proliferation index (original magnification ×200 [A]; original magnification ×200 [B]; original magnification ×200 [C]; original magnification ×100 [D]).


