Primary Cutaneous T-Cell Lymphoma Localized to the Lower Leg

A Distinct, Locally Aggressive Cutaneous T-Cell Lymphoma

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Background: Distinct categories of skin lymphoma with preferential site localization and unique clinical behavior, including leg-type primary cutaneous diffuse large B-cell lymphoma, have recently been described. Although these entities are rare, they exhibit reproducible clinicopathologic features, and their recognition may allow more appropriate treatment protocols.

Observations: We describe the distinctive clinicopathologic features that were observed in 3 patients with an unusual variant of primary cutaneous T-cell lymphoma. All cases originated on the legs of elderly patients and exhibited a locally aggressive clinical behavior with relatively rapid relapses after radiotherapy and resistance to other therapies. Histologically, dense dermal-centered infiltrates of atypical, variably sized mature helper T cells were identified. One patient died of progressive disease.

Conclusions: Rare cases of primary cutaneous lymphomas do not necessarily fit current criteria for a standard diagnostic category but may represent unique clinicopathologic entities, such as primary cutaneous T-cell lymphoma localized to the lower leg. It is important to be able to identify these unusual lymphoma variants for prognosis and adequate treatment. The aggressive nature of lymphomas preferentially localized on the lower extremities may not be restricted to B-cell or cytotoxic neoplasms.

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the term cutaneous T-cell lymphoma (CTCL) was first used in 1975 after the observation was made that mycosis fungoides (MF), Sézary syndrome (SS), and other related cutaneous lymphoid neoplasms had a common T-cell phenotype. Cutaneous T-cell lymphomas are currently classified according to the World Health Organization (WHO) and European Organization for Research and Treatment of Cancer (EORTC) classification system for cutaneous lymphomas. This classification scheme recognizes 2 broad categories of CTCL: MF/SS (including MF variants) and the less common types, which are often referred to as the non-MF CTCLs. The latter group, which is much less common than MF/SS, is classified by histopathologic features and clinical behavior. Among T-cell lymphomas, there are 2 that localize to the lower leg preferentially but not exclusively: the indolent MF variant of localized pagetoid reticulosis (LPR, Woringer-Kolopp type) and the CTCL variant known as subcutaneous panniculitis-like T-cell lymphoma (SPTL). Subcutaneous T-cell lymphomas that localize to the leg have a prognosis that is worse than that of limited patch/plaque-stage MF, and surgical amputation has, in rare cases, been used as a form of therapy. With cutaneous B-cell lymphomas (CBCLs), anatomical localization is often associated with variations in behavior and classification. Primary cutaneous diffuse large B-cell lymphoma of the leg is recognized as a variant with a more aggressive behavior than primary cutaneous follicle center and primary cutaneous marginal zone B-cell lymphomas, which generally present on the head, trunk, or upper extremities.

We describe 3 patients with a variant of CTCL that is distinct from both SPTL and LPR and that stayed localized to the legs, predominantly below the knee. These patients exhibited transient complete responses to radiotherapy, with local recurrences and resistance to many therapies. The aggressive nature of this localized form of CTCL suggests that the

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An 82-year-old man initially presented with nodular lesions on the right lower extremity. An 8 × 10-cm ulcer with an infiltrated border developed in March 2000 (Figure 1). Several skin biopsy specimens were obtained during the course of the disease and showed a dense nodular and diffuse infiltrate of large atypical lymphocytes in the dermis and subcutaneous tissues, without evidence of epidermotropism. Most of the initial biopsy specimens also showed an inflammatory infiltrate with a histiocytic-rich background and granulomatous features that became less prominent with disease progression (Table). The immunophenotype is shown in Figure 2. Polymerase chain reaction analysis was positive for clonal T-cell receptor gene rearrangement. The patient received trials of phototherapy and topical nitrogen mustard. In July of 2000, he received a course of 36 radiotherapy treatments to the distal aspect of the right lower extremity (36 Gy [to convert to rads, multiply by 100]) via electrons with a 6-field technique and boosts to the sole of the foot (10 Gy) and to the ulcerative lesion at the lateral malleolus (4 Gy in 2-Gy fractions). The superior aspect of the field was just inferior to the patella, with a margin of approximately 20 cm superior to clinically evident disease. However, the patient had a recurrence and, in April of 2003, after topical Carmustine therapy failed, he underwent a second course of radiotherapy to the leg, for a total of 30 Gy in 30 fractions, again using a 6-field electron technique with a boost of 7.5 Gy in 1.5-Gy fractions to the lateral malleolus. Phototherapy and topical clobetasol propionate therapy were initiated to prevent relapse but were unsuccessful. Further radiation therapy was not administered because there was little skin tolerance remaining after the initial 2 rounds. The patient then underwent experimental therapy with CpG-7909 (ProMune) between 2004 and 2005, with no response. He was then given the option of amputation and declined. Instead, he favored infusion therapy with liposomal doxorubicin, which was administered in June 2005 in 5 cycles, with no response. A course of infusional gemcitabine in January 2006 also yielded no response. The patient received an additional short course of radiotherapy in 2006 to a dose of 10 Gy in 1-Gy fractions to the distal aspect of the right lower extremity in addition to 8 Gy via 2-Gy fractions to the skin just inferior to the knee. Before this course of radiotherapy, he was not thought to be a candidate for additional radiation therapy, but he was in need of palliation and was refusing amputation. Hence, the short course was provided. The patient did experience some palliative relief, but his disease persisted and he eventually agreed to amputation in September 2006. The pathology report showed malignant invasion of CTCL into bone. Unfortunately, the CTCL recurred on the distal aspect of the stump, and eventually the patient died of progressive lymphoma. He had lymphoma, isolated to his right leg, for a total of 7 years before his death.

**CASE 2**

A 77-year-old woman presented with an approximately 2-year history of MF localized to the left foot, mainly involving the left heel (Figure 3). Biopsy specimens from the left heel revealed a moderately dense infiltrate of atypical small to medium-sized lymphocytes with epidermotropism, prominent involvement of the dermis, and focal involvement of the panniculus. The immunophenotype is shown in Figure 4. At presentation to our clinic in the fall of 2000, 3 months of treatment with nitrogen mustard ointment, 10 mg/100 g, was not successful. A previous short course of photochemotherapy with psoralen–UV-A also had not helped. The tumors cleared with localized radiotherapy (24 Gy). To prevent a relapse, oral bexarotene (Targretin) therapy was initiated at a dosage of 300 to 375 mg/d with UV-B phototherapy. After a few years, a second relapse occurred, and the patient eventually underwent a trial of denileukin diftitox (Ontak) therapy at a dosage of 9 µg/kg/d for 5 days in 2004. She developed a vascular leak syndrome, and there was no response to therapy, so it was discontinued. A second course of radiotherapy in January of 2005 led to clearance of the tumors in the lower part of the left leg. After a remission of a few months, several 2- to 3-cm scaling plaques appeared on the patient’s foot. Three months of topical bexarotene therapy (2–3 times per day) led to a decrease in scaling, but there were residual plaques, which eventually ulcerated. Therefore, a third course of radiotherapy was initiated in May 2007. The patient’s condition responded, but again the plaques recurred. She is currently being treated with liposomal doxorubicin, with good response. It has been 9 years since the lymphoma on her left leg was diagnosed.

**CASE 3**

An 86-year-old man developed worsening pain over his left heel. Six years earlier, areas of pruritus had initially

Figure 1. Right shin with ulceration and infiltrated plaques and tumors of cutaneous T-cell lymphoma. This picture was taken after recurrence but before amputation.
developed on his left heel and later on the dorsal aspect of his right foot, which were intermittently treated with high-potency topical corticosteroids. Over the past 2 years, these areas had started to ulcerate. A skin biopsy specimen revealed a moderately dense, bandlike, diffuse infiltrate of atypical small to medium-sized lymphocytes with epidermotropism and prominent involvement of the dermis. There were also pustular features with epidermal exocytosis of neutrophils. The immunophenotype is shown in Figure 5. Treatment with an angiotensin-converting enzyme inhibitor had been discontinued to eliminate the possibility of a mimic. The patient presented with disease on both feet.

Table. Histologic and Immunophenotypic Findings

<table>
<thead>
<tr>
<th>Feature</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell size</td>
<td>Large</td>
<td>Small/medium sized</td>
<td>Small/medium sized</td>
</tr>
<tr>
<td>Degree and pattern of cytologic atypia</td>
<td>Moderate, hyperchromatic lymphocytes with irregular nuclear outlines</td>
<td>Moderate, hyperchromatic lymphocytes with irregular nuclear outlines</td>
<td>Moderate, hyperchromatic lymphocytes with irregular nuclear outlines</td>
</tr>
<tr>
<td>Epidermotropism (presence/absence, degree and features)</td>
<td>Not seen</td>
<td>Present, moderate, with disproportionate exocytosis and occasional Pautrier microabscesses</td>
<td>Present, moderate, with disproportionate exocytosis and occasional Pautrier microabscesses</td>
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<tr>
<td>Prominent adnexotropism (hair follicles and/or eccrine ducts)</td>
<td>Not seen</td>
<td>Not seen</td>
<td>Not seen</td>
</tr>
<tr>
<td>Density and pattern of the infiltrate (diffuse, nodular, band-like)</td>
<td>Dense, nodular and diffuse</td>
<td>Mild to moderately dense, bandlike, and focally nodular + + + + + +</td>
<td></td>
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<tr>
<td>Involvement of epidermis</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Involvement of papillary dermis</td>
<td>+ + +</td>
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<tr>
<td>Involvement of reticular dermis</td>
<td>+ + +</td>
<td>+</td>
<td>+ +</td>
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<td>Involvement of subcutaneous tissue</td>
<td>+ + +</td>
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<td>+</td>
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<tr>
<td>Background inflammatory infiltrate (density and composition)</td>
<td>Abundant background inflammatory infiltrate with epithelioid histiocytes forming granulomas; scattered eosinophils and rare plasma cells</td>
<td>Mild mixed background inflammatory infiltrate with scattered plasma cells, eosinophils, and scattered histiocytes</td>
<td>Mild mixed background inflammatory infiltrate with scattered plasma cells and scattered histiocytes; exocytosis of neutrophils in the epidermis (pustular)</td>
</tr>
<tr>
<td>Dermal fibrosis</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Angiodestruction</td>
<td>Not seen</td>
<td>Not seen</td>
<td>Not seen</td>
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<tr>
<td>Immunophenotype</td>
<td>CD3&lt;sup&gt;+&lt;/sup&gt;, CD4&lt;sup&gt;+&lt;/sup&gt;, CD8&lt;sup&gt;-&lt;/sup&gt;, CD15&lt;sup&gt;-&lt;/sup&gt;, CD20&lt;sup&gt;-&lt;/sup&gt;, CD79a&lt;sup&gt;-&lt;/sup&gt;, CD30&lt;sup&gt;-&lt;/sup&gt;, CD2&lt;sup&gt;-&lt;/sup&gt;, CD5&lt;sup&gt;-&lt;/sup&gt;, CD7&lt;sup&gt;-&lt;/sup&gt;, CD45RA&lt;sup&gt;-&lt;/sup&gt;, CD56&lt;sup&gt;-&lt;/sup&gt;</td>
<td>CD3&lt;sup&gt;+&lt;/sup&gt;, CD4&lt;sup&gt;+&lt;/sup&gt;, CD8&lt;sup&gt;-&lt;/sup&gt;, CD20&lt;sup&gt;-&lt;/sup&gt;, CD30&lt;sup&gt;-&lt;/sup&gt;, CD2&lt;sup&gt;-&lt;/sup&gt;, CD5&lt;sup&gt;-&lt;/sup&gt;, CD45RA&lt;sup&gt;-&lt;/sup&gt;, CD56&lt;sup&gt;-&lt;/sup&gt;, CD56&lt;sup&gt;-&lt;/sup&gt;</td>
<td>CD3&lt;sup&gt;+&lt;/sup&gt;, CD4&lt;sup&gt;-&lt;/sup&gt;, CD8&lt;sup&gt;-&lt;/sup&gt;, CD20&lt;sup&gt;-&lt;/sup&gt;, CD30&lt;sup&gt;-&lt;/sup&gt;, CD45RA&lt;sup&gt;-&lt;/sup&gt;, CD56&lt;sup&gt;-&lt;/sup&gt;, TIA-1&lt;sup&gt;-&lt;/sup&gt;</td>
</tr>
<tr>
<td>Other findings</td>
<td>Granulomatous and histiocyte rich</td>
<td>None</td>
<td>Pustular (exocytosis of neutrophils)</td>
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Abbreviations: −, no involvement; +, mild involvement; + +, moderate involvement; + + + , extensive involvement.

Figure 2. Histopathologic features in case 1. Initial skin biopsy specimen of a tumor from the right leg demonstrating absence of epidermotropism (A) and a moderate to dense infiltrate of atypical large lymphocytes (C) admixed with a histiocyte-rich background inflammatory infiltrate with occasional multinucleate giant cells and granulomatous features (B) (hematoxylin-eosin, original magnification ×100 [A], ×200 [B], and ×400 [C]). Sections from the right leg amputation specimen showing prominent ulceration without epidermotropism (D) and a dense infiltrate of large atypical lymphocytes (F) with extensive involvement of the dermis and subcutaneous tissues and extension into bone (E) (hematoxylin-eosin, original magnification ×100 [D], ×200 [E], and ×400 [F]). Immunohistochemical analysis of formalin-fixed, paraffin-embedded tissue sections showed that the infiltrate was immunoreactive with CD3 (G) and CD4 (H) but not with CD8 (I) (original magnification ×200).

Figure 3. Left heel showing annular plaques with ulceration.
in 2007. His lesions all healed after an initial course of 19 Gy of orthovoltage to the sole of his right foot and 20 Gy via electrons to the rest of his right foot and the distal aspect of his ankle, bringing a combined total dose of approximately 27 Gy to the skin of the right foot. He received technically similar treatment with a total dose of 33 Gy to his left foot and a dose of 19 Gy to the sole of his left foot. He had problems related to radiation dermatitis and could not ambulate without significant discomfort for several days. His lesions did clear completely, but a local recurrence developed on his left sole and the medial aspect of his right ankle approximately 6 months later (Figure 6). He was seen in radiotherapy consultation, and a second course of therapy was administered, with localized fields to the sole of the left foot and the right medial aspect of the ankle, to a total of 26 Gy in 2-Gy fractions, with a clinical clearance of disease. It has been 1 year and 4 months since the definitive diagnosis was made.

**COMMENT**

Cutaneous T-cell lymphoma represents a diverse group of skin lymphomas that have a broad clinicopathologic spectrum ranging from those with a good prognosis, such as limited patch/plaque-stage MF, to those with a very poor prognosis, such as cutaneous γ-δ T-cell lymphoma. Although the WHO-EORTC classification system has greatly advanced our ability to classify the variety of CTCLs, some unusual variants of CTCL are rarely observed and are difficult to classify according to current criteria. Also, the heterogeneity and rarity of CTCL variants has led to limited clinical experience and difficulty in proper classification and determination of prognosis and optimal treatment. Indeed, there may be other rare variants of CTCL that may be recognized beyond the category of unspecified primary cutaneous peripheral T-cell lymphoma, as they are provisionally classified by the WHO-EORTC. There are 2 variants of CTCL that may localize preferentially, though not exclusively, to the lower extremity. These are the indolent MF variant of LPR, Woringer-Kolopp type, and the non-MF cytotoxic CTCL variant known as SPTL, which initially included both α-β and γ-δ T-cell infiltrates but is now restricted to α-β T-cell lymphomas primarily involving the subcutaneous tis-
sues. The more aggressive γ-δ infiltrates are now separately classified as cutaneous γ-δ T-cell lymphomas and may show epidermotropic, dermal, and/or subcutaneous infiltrates. We describe 3 patients with a novel variant of CTCL, distinct from SPTL and LPR, that presented in and stayed localized to the lower extremities. However, this localized form of CTCL showed an aggressive clinical behavior and exhibited relatively rapid recurrences after radiotherapy as well as resistance to other therapies. Despite some relatively minor variations in the clinicopathologic findings, the 3 cases shared several similar features. They all consisted of dense cutaneous infiltrates of atypical mature helper T cells involving the legs of elderly patients. The lymphocytic infiltrates exhibited a CD3+/CD4+/CD8+/CD30- immunophenotype and were predominantly centered in the reticular dermis, with variable involvement of the epidermis and the panniculus. Cases 2 and 3 were composed of small to medium-sized atypical lymphocytes with epidermotropism and would currently be classified as tumor-stage MF. Case 1 demonstrated a large-cell infiltrate without significant epidermotropism at the time of diagnosis and would currently be classified as a primary cutaneous peripheral T-cell lymphoma, unspecified according to criteria from the WHO-EORTC Classification for cutaneous lymphomas. However, it is conceivable that case 1 could have represented tumor-stage MF (similar to cases 2 and 3) that underwent large-cell transformation and loss of epidermotropism before the first skin biopsy was performed. Interestingly, cell size does not necessarily have prognostic significance for certain cutaneous lymphomas; eg, in cases of primary cutaneous aggressive epidermotropic cytotoxic T-cell lymphoma, there is no difference in survival between cases with a small- or large-cell morphological appearance.

The clinical and histopathologic findings in all 3 cases were distinct from those of other well-defined clinicopathologic entities. Localized pagetoid reticulosis is an indolent variant of MF that often has a clinical presentation that is localized to the lower leg. However, the presence of dense tumoral infiltrates and the aggressive clinical behavior seen in our cases would not be compatible with LPR. The presence of partial variable CD30 expression seen in some of the biopsy specimens raised the possibility of cutaneous anaplastic large-cell lymphoma. However, the degree of CD30 expression was always focal and quite limited, ranging from negative to less than one-third of atypical lymphocytes. This variable and limited degree of CD30 expression is well below the cutoff of 75% expression by tumor cells that is currently proposed for anaplastic large-cell lymphoma, and these infiltrates would therefore be considered CD30 negative for classification purposes. Furthermore, the clinical behavior and cytologic features seen in our cases would be unusual for cutaneous anaplastic large-cell lymphoma. Because of the aggressive clinical behavior in our cases, the possibility of other aggressive cutaneous lymphomas was also considered. However, the immunophenotype in our cases was that of mature CD4+ helper T cells and would not be compatible with those entities (ie, γ-δ T cells for cutaneous γ-δ T-cell lymphoma, Epstein-Barr Virus–positive natural killer cells or cytotoxic T-cells for nasal-type extranodal natural killer or T-cell lymphoma, and CD8+ cytotoxic T cells for primary cutaneous aggressive epidermotropic cytotoxic T-cell lymphoma and SPTL T-cell lymphoma). Cases of systemic peripheral T-cell lymphoma with secondary involvement of the skin are usually associated with aggressive clinical behavior. However, all of our cases presented with involvement limited to the skin, and extra-cutaneous involvement was absent or developed late in the course of the disease.

There have been reports of CTCL with tumors localized to the leg. In 1 case, a man was found to have CTCL of the lower extremity at the site of a hematoma after a car crash 3 days earlier. In that unusual case, the tumor recurred after treatment at locations outside the leg, ie, the preauricular area and the brain. Another patient, who was reported to have developed CTCL of the right thigh and later developed a second tumor on the left thigh, died of a fungal infection after 2 cycles of cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone (CHOP)-bleomycin chemotherapy. Subcutaneous variants of CTCL may also preferentially involve the leg and usually have a worse prognosis than that of localized patch/plaque-stage MF, which typically arises elsewhere. Interestingly, amputation was the eventual mode of treatment for this aggressive variant of CTCL in 1 report. Nevertheless, there is currently no consensus regarding the optimal treatment for these unusual CTCL variants and no clear explanation regarding why certain lymphomas localize preferentially to the legs.

Although a distinct clinicopathologic variant of CTCL localized exclusively to the leg has not been previously proposed, CBCLs do have a variant that is characteristically localized to the leg. It is uncertain why localization of CBCLs to the leg is associated with a distinctly worse prognosis than that of non-leg CBCLs. Primary cutaneous diffuse large B-cell lymphoma, leg type, has been shown to express abnormal levels of Fas, Fas ligand, and bcl-2, which could alter apoptotic pathways. However, in a recent large study of 60 patients with primary cutaneous diffuse large B-cell lymphoma, leg type, bcl-2 expression had no independent effect on survival. In multivariate analysis, disease-related death was statistically significantly associated with location on the leg, and cases located on the leg had a worse prognosis independently of any other prognostic factor, including bcl-2 expression. It is unclear whether antiapoptotic pathways would lead to preferential localization on the legs or would be specifically involved in cases of CTCL of the lower leg (CTCL-LL). However, there is growing evidence that lymphomatous localization on the legs may be independently associated with more aggressive clinical behavior.

It is not only cutaneous lymphomas that can localize to the legs. The affinity of malignancy for a swollen extremity has been recognized in 2 vascular-based tumors: Kaposi sarcoma and Stewart-Treves–type angiosarcoma. In each of these, angiogenesis is a key component. Moreover, a posttransplantation lymphoproliferative disorder localized to the lower leg has also been reported. We have considered several possibilities for this increased risk: (1) The lower leg often has associated edema due to vascular insufficiency, with resultant increased vascular pressure and decreased oxygen tension, which are unique to this dependent and distal part of the body. These changes may affect proper
immune function, which could lead to a quasi–immuno-
privileged site that could more easily allow clonal ex-
pansion of a mutant cell. Moreover, the damage to the leg
caused by radiotherapy could actually be worsening
the normal leg architecture, thereby hastening disease pro-
gression or recurrence. (2) It is possible that these leg-
specific diseases represent an intrinsic defect in the sig-
naling of the endothelial and lymphatic cell compartment,
leading to inappropriate interaction between the skin and
the immune system. (3) Finally, abnormalities in angio-
genesis that arise as a compensatory mechanism to in-
creased edema and decreased oxygen tension may lead to
an increased susceptibility to malignancy.

One major dilemma in the workup of a patient with
possible primary CTCL-LL is whether a particular case
represents an aggressive variant of CTCL that is local-
ized preferentially to the leg and not simply an indolent
form of CTCL that occurs sporadically on the leg. Cur-
rently, there are no universally accepted clinicopatho-
logic features to consistently differentiate these types.
However, our cases suggest that after recurrence of a
treated CTCL that is localized to the leg, the possibility of
CTCL-LL should be considered. Moreover, as addi-
tional treatments fail and no new lesions develop out-
side the lower extremities, treatment should be geared
toward a more aggressive type of CTCL.

Equally difficult is the optimal treatment of patients
with CTCL-LL. We propose that initial treatment should
entail an adequate dose of irradiation. The first chal-
lenge is to try maintenance therapies that in some way
can reverse the milieu of the leg that fosters this type of
aggressive lymphoma. Compression therapy for leg swell-
ing would be reasonable. It could be conjectured that an-
tiangiogenic therapy should also be considered. Also,
maintenance therapy could be considered with sys-
temic agents that are well tolerated over long periods, such as
methotrexate, oral bexarotene, interferon, vorino-
stat, and denileukin difitox. Once maintenance fails, re-
peated radiotherapy is often needed; yet other therapies
should also be considered, such as those used (albeit in-
effectively) in our cases: liposomal doxorubicin and de-
niluekin difitox. Furthermore, with regard to toxic thera-
pies, the possibility of surgically removing or controlling
the CTCL-LL by amputation may be addressed and given
some consideration, but generally not until other poten-
tially successful nonsurgical options have failed. Over-
all, CTCL-LL represents a therapeutic problem for the
patient and the physician. The cases presented herein
have had less than successful therapeutic outcomes, and it is
hoped that by recognizing and discussing further cases of
this distinct clinical entity the optimal care of those
afflicted can be discovered.

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Poligone, Wilson, Subtil, and Heald. Analysis and inter-
pretation of data: Poligone, Wilson, Subtil, and Heald.
Drafting of the manuscript: Poligone, Wilson, Subtil, and
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