Indolent Primary Cutaneous γ/δ T-Cell Lymphoma Localized to the Subcutaneous Panniculus and Its Association With Atypical Lymphocytic Lobular Panniculitis

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Key Words: Primary cutaneous γ/δ T-cell lymphoma; Subcutaneous panniculitis-like T-cell lymphoma; Indolent

Abstract

The 2005 classification of lymphoma proposed the designation of subcutaneous panniculitis-like T-cell lymphoma exclusively for those tumors composed of α/β neoplastic cells. Subcutaneous lymphomas that comprised γ/δ T cells are termed primary cutaneous γ/δ T-cell lymphoma. The different clinical outcomes justified this separation; a more indolent course was characteristic of the α/β variants vs the poor 5-year survival of the γ/δ forms. We describe 5 patients with γ/δ T-cell lymphoma localized to the subcutis with a less aggressive clinical course. Two patients were alive 5 years after presentation, and in the remaining 3, the disease is in complete remission after simple intervention. Three patients had a waxing and waning phase, likely representing a prelymphomatous phase, which then progressed to an overt malignant tumor. Therefore, it is important to recognize that not all patients with γ/δ T-cell lymphomas have a poor prognosis.

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) was first described by Gonzalez and coworkers in 1991. Before the recognition of this entity as a form of lymphoma, this condition was reported under the designations of histiocytic cytophagic panniculitis and Weber-Christian disease. In the days before the advent of immunohistochemistry, this condition was assumed to be of histiocytic derivation because of the extent of histiocytic infiltration involving the subcutaneous fat and overlying dermis. Hence, a certain subset of cases reported as histiocytic cytophagic panniculitis and Weber-Christian disease likely represented forms of SPTCL. The first reported case of this form of lymphoma antedated the series by Gonzalez and coworkers. Specifically, Aronson and coworkers described a 36-year-old woman with a 6-year history of recurrent panniculitis followed by a sudden worsening of her condition with skin infiltration by malignant lymphocytes and concomitant hemophagocytic syndrome (HPS). SPTCL has a characteristic presentation both clinically and pathologically, exhibiting a predilection to affect younger females, with many cases occurring in the second to fourth decades of life. Histologically, the infiltrate involves the fat lobule but also extends into the overlying dermis, with the maximum areas of infiltration assuming a peri-eccrine distribution. Fat necrosis, vascular thrombosis, extensive apoptosis, and macrophage infiltration and phagocytosis of other cellular elements, including RBCs and leukocytes, are additional features that add to its distinctive morphologic appearance.

Given the discrepant clinical courses in those cases that exhibit a γ/δ phenotype vs those of the α/β subset, the designation SPTCL has been suggested exclusively for the α/β variant. Although there are arguments to separate...
subcutaneous lymphoma based on the nature of the neoplastic cell populace (ie, α/β vs γ/δ), no substantial histomorphologic differences have been found. The purposes of this report are to describe 5 patients with indolent primary cutaneous γ/δ T-cell lymphoma of the subcutaneous fat and review the literature regarding other forms of γ/δ T-cell lymphoma where the clinical course appears indolent.

Materials and Methods

We studied 5 patients with primary cutaneous γ/δ T-cell lymphoma localized to the subcutis in whom the clinical course appeared indolent. The patients were encountered during a 5-year period in which there were 13 total cases of primary cutaneous γ/δ T-cell lymphoma localized to the subcutaneous fat. In each of the patients, a detailed clinical history and follow-up were obtained. Routine light microscopy, comprehensive phenotypic, and molecular studies were performed on each of the patients. A list of the antibodies studied in each of the patients is listed in Table 1. Light microscopy and selected immunohistochemical studies of patient 3 are shown in Image 1. The molecular technique used was a Biomed (Tampa, FL) T-cell receptor (TCR) gene rearrangement.

Results

Case Histories

Case 1
A 25-year-old woman with an unremarkable medical history developed 4 ulcers in the left, lower medial aspect of the leg in September 2003, with the largest 2 ulcers measuring 6 × 6 cm and 5 × 5 cm. The results of a skin biopsy performed at an outside hospital raised the initial differential diagnosis between a T-cell non-Hodgkin lymphoma and lupus erythematosus profundus (LEP). In April 2004, an additional biopsy specimen taken from one of the lesions established the diagnosis of SPTCL γ/δ type. A subsequent bone marrow biopsy specimen revealed no involvement of lymphoma.

The patient underwent her first cycle of fludarabine chemotherapy without complications. Her skin lesions started improving in June, the largest 2 of which had shrunken to 5 × 4 cm and 5 × 3 cm. She continued to receive cycles of fludarabine, and by July, 3 of her 4 lesions had healed and the fourth one had markedly improved. The patient received 6 cycles of fludarabine in total, which ended in October 2004 with complete resolution of her lesions. She has not had any relapses and is now disease free 7 years after her initial presentation.

Case 2
A 33-year-old woman had a several-year history of waxing and waning skin lesions; she did not undergo skin biopsy until February 2009, when the lesions became persistent and increased in size. A skin biopsy was performed, and the specimen revealed primary γ/δ T-cell lymphoma involving the subcutaneous fat.

The patient underwent ablation chemotherapy using a cyclophosphamide, hydroxydaunorubicin, vincristine (Oncovin), and prednisone (CHOP) regimen followed by allogeneic stem cell transplantation. The patient is currently in remission 2 years since her diagnosis.

Case 3
A 36-year-old white woman had had a longstanding history of what was initially diagnosed as LEP since 2001. She presented in December 2003 with a rash on her left leg of several months’ duration, which on physical examination manifested as an erythematous indurated plaque with central necrosis on her left thigh. She also had developed subcutaneous nodules on her right arm and 4 firm, nontender, subcutaneous nodules on her right calf. Biopsy specimens of the left thigh and right calf nodules were interpreted again as LEP. She was referred to the rheumatology clinic for further evaluation and began hydroxychloroquine treatment, to which she was minimally responsive.

In 2007, she developed constitutional symptoms, including fever, sweats, chills, body ache, and malaise, and had

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Immunophenotypic Studies of 5 Cases of Primary Cutaneous γ/δ T-Cell Lymphoma Localized to the Subcutis*</th>
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</thead>
<tbody>
<tr>
<td>Case No.</td>
<td>CD2</td>
</tr>
<tr>
<td>1</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
</tr>
</tbody>
</table>

EBER, Epstein-Barr virus–encoded small RNA; NA, not available; TIA-1, T-cell intracellular antigen 1.
* + indicates positive; −, negative.
Image 1 Light microscopy and selected immunohistochemical studies in Case 3 (×40). A, H&E; B, βF1; C, CD4; D, CD8; E, CD56; and F, T-cell intracellular antigen 1.
pancytopenia, transaminitis, and splenomegaly. At the same time, her skin lesions worsened. She remained largely unresponsive to hydroxychloroquine. A bone marrow biopsy performed to evaluate her pancytopenia revealed only megakaryocytic and erythroid hyperplasia, with no atypical cells identified. Finally, a skin biopsy specimen of the right medial aspect of the thigh demonstrated a cytotoxic cutaneous γ/δ T-cell lymphoma localized to the subcutaneous fat.

At this point, the patient’s earlier biopsy specimens were reviewed, which were clearly less atypical compared with the most recent specimen. They shared with the recent specimen a lupus-like interstitial mucinosis, a source of diagnostic confusion. The most recent biopsy specimen revealed excessive lymphoid atypia and striking hemophagocytosis. Her earlier, less atypical-appearing biopsy specimens were more within the spectrum of a prelymphomatous phase, described by Magro et al11 as atypical lymphocytic lobular panniculitis (ALLP) and not overt lymphoma.

The patient underwent systemic chemotherapy in 2006. However, she died in November 2008 of complications related directly to her lymphoma.

Case 4

A 76-year-old woman who had a medical history significant for neuropathic pain, hypertension, and diabetes insipidus presented to an outside hospital in early February 2010 for a lump under her right arm. A mammography was performed, the results of which were negative. Chest computed tomography (CT) without contrast revealed a 5-cm mass arising in the inferior aspect of the right breast. On positron emission tomography (PET), the mass demonstrated significant hypermetabolic activity (ie, a standardized uptake value of 20.8). A core biopsy specimen of the axillary mass revealed an atypical lymphoid infiltrate, consistent with peripheral T-cell lymphocytic lobular panniculitis (ALLP) and not overt lymphoma.

After being referred to our hospital, the patient underwent a biopsy, the results of which were compatible with γ/δ T-cell lymphoma involving the subcutaneous fat. The patient refused systemic chemotherapy. She underwent radiation therapy to the axillary region and has been doing well since her radiation treatment.

Case 5

A 45-year-old woman who was otherwise in excellent health presented in 1999 with skin lesions on the inside of her right leg. A biopsy specimen of the lesions demonstrated only necrosis at that time. The lesions persisted, and in 2000, a subsequent biopsy specimen was interpreted as panniculitis, and she was treated with topical steroids. It is unclear whether the lesions followed a waxing and waning course during that period. By September 2004, her skin lesions had spread to include 3 erythematous patches over the right posterior aspect of the neck, a 0.5-cm palpable nodule in the right abdomen, a 1-cm ulcer of the right shin, and multiple flat areas of subcutaneous induration 2 to 3 cm in diameter along both lower extremities without erythema. A biopsy specimen taken at an outside hospital revealed an atypical, mainly panniculitic infiltrate associated with extensive necrosis. Treatment with intralesional triamcinolone in February 2005 was commenced. The results of a bone marrow biopsy and CT performed at the outside hospital were negative, and she received repeated intralesional courses of triamcinolone with reported improvement during the ensuing months.

In July 2005, she was referred to the hematology/oncology service at our hospital for further treatment. A PET/CT scan revealed multiple hypermetabolic subcutaneous nodules predominantly involving the lower extremities, but no associated intrathoracic or intra-abdominal lesions or lymphadenopathy were seen. A biopsy specimen of a left leg nodule was diagnostic of SPTCL of the γ/δ subtype.

In late September, 6 years after her initial presentation, the patient started fludarabine treatment. She received 2 cycles of fludarabine; however, her condition was refractory, and new lesions kept appearing while she was undergoing treatment. A biopsy specimen taken from a 3-cm, rapidly growing, left posterior flank lesion at that time revealed transformed anaplastic CD30+SPTCL. Her chemotherapy was thus changed to CHOP in January 2006, but her skin nodules did not show an obvious response, as confirmed by a follow-up PET/CT scan. Further change of her chemotherapy regimen to dexamethasone, ifosfamide, cisplatin, and etoposide was also not effective. At this point, an autologous stem cell transplantation was considered but not performed because of a low cell count in stem cell collections. In June 2006, her chemotherapy regimen was changed again to include alemtuzumab because of the presence of CD52 on her lymphoma cells. Her large nodules decreased in size, although she continued to develop new nodules.

In July 2006, her chemotherapy was complicated by a cytomegalovirus pneumonia, which resulted in prolonged hospitalization. Her treatment continued being complicated by opportunistic infections, including multiple caseating granulomas with fungal elements in her spleen. In January 2007, the patient died as a consequence of Epstein-Barr virus-associated pneumonitis.

Light Microscopic Findings

All 5 cases exhibited extensive lymphocytic lobular panniculitis with involvement of the lower dermis, the latter condition manifesting adventitial eccrine accentuation. In most cases, the lymphocytes were small and well differentiated. A minor large cell component was noted in most cases. Fat necrosis was a common feature and exhibited 2 distinctive morphologic patterns. One pattern was of the cellular...
necrosis type. In particular, there was infiltration of the interstitial spaces of the fat by lymphocytes, which had undergone necrosis; leukocytoclasia and engulfment of nuclear debris by scavenger macrophages were also prominent. The second pattern was an ischemic one characterized by fibrinoid alteration of the fat lobule accompanied by a pauci-inflammatory thrombogenic vasculopathy. A mixed pattern of fat necrosis could also be seen with cellular necrosis associated with marked apoptosis along with a thrombotic diathesis. In all cases, macrophages were a conspicuous part of the infiltrate. They were disposed singly amid a mucinotic-appearing dermis and within the interlobular septa; the macrophages contained red blood cells and engulfed nuclear debris. The adipocyte rimming was a conspicuous feature in most cases and was characterized by a circumferential encroachment of the lymphocytes around the adipocytes. Although in 4 cases, the dominant infiltrate was a small to intermediate-sized lymphocyte, 1 case had many admixed large cells. The cells exhibited nuclear irregularities and hyperchromasia, although without a cerebriform cytomorphologic pattern. In addition, apoptosis was prominent.

**Phenotypic Studies**

A summary of the phenotypic profile of each of the cases is provided in Table 1. In all cases the cells were determined to be of the γ/δ subset based on a lack of staining for βF1, CD4, and CD8 with proper immunostaining controls. The neoplastic cells expressed T-cell intracellular antigen 1 and granzyme. Four cases showed CD56 expression. All cases had extensive positivity for CD2 and CD3. In 5 of 5 patients tested a striking reduction in CD5 was found, whereas a substantial reduction was found in the expression of CD7 in 2 of 5 patients. In one case, significant positivity for CD30 was seen.

**Molecular Studies**

The TCR gene rearrangement study results are summarized in Table 2. In 2 of 4 patients studied, the TCR gene rearrangement analysis revealed polyclonal TCR rearrangement (cases 2 and 3). These results may be due to nonrepresentative tissue sampling, poor amplification, or failure to detect a small minority of T-cell gene segment rearrangements with the use of consensus polymerase chain reaction primers from an overrepresented but reactive or pre-lymphomatous population.

**Discussion**

We describe 5 cases of primary cutaneous γ/δ T-cell lymphoma localized to the subcutaneous tissue. Four of the 5 patients were younger women with lesions localized to the thigh and arm area, and 3 patients had a long waxing and waning phase. All patients responded to treatment. Complete remission was achieved in 4 patients without any evidence of recurrent disease. However, one patient died of drug-induced immunosuppression, whereas another patient died of complications related to HPS induced by her lymphoma. These findings indicate that there may be a subset of γ/δ T-cell lymphoma of the subcutaneous fat that follows a more indolent clinical course similar to the α/β variant of this lymphoma. Although 2 patients died in this series, their lymphoma was first seen several years before their death.

In the revised World Health Organization–European Organisation for Research and Treatment of Cancer classification, the term *subcutaneous T-cell lymphoma* has been supplanted by *SPTCL*. Clinical and histologic overlap is noted with enigmatic conditions such as LEP, ALLP, Weber-Christian disease, and histiocytic cytophagic panniculitis. Among the many similarities to LEP are a reproducible tendency to involve the proximal aspect of the extremities or trunk; exacerbation during pregnancy; accompanying systemic connective tissue disease symptoms, such as fever, anorexia, and leukopenia; and a baseline histologic pattern of lymphocytic lobular panniculitis. Some cases of panniculitis-like T-cell lymphoma have sufficient clinical and morphologic overlap with LEP that they are initially diagnosed as such. Indeed, 2 of our

**Table 2**

Comprehensive Clinical, Selected Immunophenotypic, and Molecular Studies of the 5 Cases of Primary Cutaneous γ/δ T-Cell Lymphoma Localized to the Subcutis and a Case in the Literature

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age at Onset, y</th>
<th>Sex</th>
<th>Location</th>
<th>Follow-up Period, y</th>
<th>CD4</th>
<th>CD8</th>
<th>CD56</th>
<th>TCR PCR</th>
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<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>F</td>
<td>Leg</td>
<td>7</td>
<td>−</td>
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<td>+</td>
<td>Monoclonal</td>
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<tr>
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<td>33</td>
<td>F</td>
<td>NA</td>
<td>7</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>Polyclonal</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>F</td>
<td>Arm, thigh, leg</td>
<td>7</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>Polyclonal</td>
</tr>
<tr>
<td>4</td>
<td>76</td>
<td>F</td>
<td>Axilla</td>
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<td>−</td>
<td>−</td>
<td>+</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>F</td>
<td>Wrist, leg, chest</td>
<td>8</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>Monoclonal</td>
</tr>
<tr>
<td>Hosler et al(^{12})</td>
<td>37</td>
<td>F</td>
<td>Arms, legs</td>
<td>15</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>Monoclonal</td>
</tr>
</tbody>
</table>

NA, not available; PCR, polymerase chain reaction; TCR, T-cell receptor. * + indicates positive; −, negative.
patients were initially treated with a working diagnosis of LEP. In both of these patients, part of the morphologic confusion was due to the extent of mucin deposition within the skin and subcutaneous fat along with the presence of a subtle interface dermatitis. Neither of the patients had any additional clinical features supportive of lupus erythematosus. Initially, interpreting a case of panniculitis-like T-cell lymphoma as LEP or the converse is a common error. Discriminating light microscopic features separating panniculitis-like T-cell lymphoma from LEP include erythrocyte phagocytosis and the absence of a destructive atrophying interface dermatitis and cell necrosis as opposed to the mucinous hyaline-like acellular degeneration observed in the subcutis as in cases of LEP. Dermal mucin deposition is not a useful morphologic criterion because cases of SPTCL can exhibit dermal and subcuticular mucin deposition. Both conditions are associated with considerable apoptosis of cellular elements. The “bean bag histiocyte” is seen with great regularity in panniculitis-like T-cell lymphoma and LEP and reflects the phagocytosis of cellular debris.

Three of the 5 patients had reported a waxing and waning phase, likely representing ALLP. We previously designated ALLP as a distinctive form of cutaneous lymphoid dyscrasia, which could represent the waxing and waning phase that may presage panniculitis-like T-cell lymphoma in some cases but does not necessarily eventuate into malignant lymphoma. Other forms of T-cell dyscrasia can include pityriasis lichenoides chronica, pigmented purpuric dermatosis, alopecia mucinosa, syringolymphoid hyperplasia with alopecia, and large plaque parapsoriasis. In all cases, there were areas in the current biopsy specimens that were reminiscent of this entity, including foci of infiltration of the fat lobule by a relatively modest interstitial lymphocytic infiltrate. Atypia was mild, such foci were devoid of fat necrosis, and adipocyte internalization was not observed. All of these features are characteristic of ALLP. In 1 patient, we were able to document morphologic progression, whereby the earlier biopsy specimen was within the morphologic spectrum of ALLP. Phenotyping had not been conducted on this biopsy specimen when it was first reviewed in 2003 because it was assumed to represent LEP. Retrospective assessment of the infiltrate revealed an identical phenotypic profile to the current biopsy specimen. In general, the changes in ALLP are not as notable as those observed in LEP, SPTCL, or γδ T-cell lymphoma involving the subcutaneous fat. The infiltrates are modest and unaccompanied by necrosis, apoptosis is minimal, and vascular injury and tissue ischemia are unusual. The main abnormality is mild ALLP. In 2 patients, the diagnosis of LEP was brought into question based on the lack of responsiveness to hydroxychloroquine. In our experience, constitutional symptoms are uncommon in most cases of LEP and ALLP and should be an important clinical clue to a diagnosis of panniculitis-like T-cell lymphoma.

There is substantial literature on panniculitis-like T-cell lymphoma of the γδ subset, most of which follows an aggressive clinical course. In one study by Salhany and coworkers of 11 patients, 2 patients had SPTCL of the γδ subtype and both died of their disease within 3 to 25 months. In a comprehensive study addressing SPTCL, Willemze and coworkers examined clinicopathologic features, immunophenotype, treatment, and survival in patients with SPTCL. In this study they subdivided the cases into 63 of the αβ subset and 20 of the γδ form. The αβ form was generally confined to the subcutis; had a CD4+, CD8+, CD56−, βF1+ phenotype; was uncommonly associated with HPS (17%); and had a favorable prognosis (5-year overall survival, 82%). Patients with this variant of SPTCL without HPS had a significantly better survival than patients with HPS (5-year overall survival, 91% vs 46%; P < .001). The γδ form often showed (epi)dermal involvement and/or ulceration; a CD4+, CD8−, CD56+/−, βF1− T-cell phenotype; and poor prognosis (5-year overall survival, 11%), irrespective of the presence of HPS or type of treatment. These results indicate that the αβ vs γδ forms of SPTCL are distinct entities and justify that the term SPTCL be used only for the αβ variant. However, in that same series, 3 of 14 patients with the γδ form of SPTCL treated with multiagent chemotherapy achieved complete remission, including the patients treated with additional autologous stem cell transplantation. Another patient not responding to chemotherapy reached complete remission after an allogeneic stem cell transplantation. Among the responsive patients, 2 were still in complete remission at 38 and 108 months after initial diagnosis. In addition, there is 1 prior report of a patient with a 15-year history of panniculitis. After several years of indolent behavior, the disease underwent an aggressive turn, and she was diagnosed as having γδ T-cell lymphoma. Molecular analysis identified a T-cell clone, which through retrospective analysis was also to be present in the patient’s original biopsy material. This case is remarkably similar to patient 3 of our series. A summary of 6 cases of primary cutaneous γδ T-cell lymphoma localized to the subcutaneous fat after an indolent course is presented in Table 2.

The γδ T-cell lymphomas define a heterogeneous group of lymphomas whereby the subtype of neoplastic γδ T cell is site-dependent. In 1 study, all cases of hepatosplenic γδ T-cell lymphoma are derived from the Fγδγ gene in contradistinction to SPTCL, which expresses the Fδδ2 gene. The pattern of Fδ gene expression reflects the normal γδ T-lymphocytes that reside in the affected tissues.

In conclusion, this study emphasizes that a subset of primary cutaneous γδ T-cell lymphoma of the subcutaneous fat follows a more indolent course analogous to SPTCL. A characteristic feature is the presence of a long prodromal phase over years possibly representing a prelymphomatous phase defined by ALLP. In the 6 patients with detailed clinical
courses, an ALLP-like presentation was observed in 4. Furthermore, we documented morphologic progression into a more aggressive morphologic pattern in 2 of the 4 patients, indicating that these lymphomas do not arise in a de novo fashion as an explosive aggressive lymphoma. Physicians must have a high index of suspicion in patients who develop waxing and waning lesions that exhibit a morphologic pattern compatible with ALLP despite the lack of overt features of malignant tumors. The fact that there is a subset of the γδ lymphomas with a more indolent course might argue for the reclassification of all primary subcutaneous T-cell lymphomas as SPTCL because the clinical course is not one that is universally aggressive.

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References


