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EXPRESSION OF PROGRAMMED DEATH-1 IN PRIMARY CUTANEous CD4-POSITIVE SMALL/medium-sized pleomorphic T-CELL LYMPHOMA, CUTaneous pseuDo-T-CELL LYMPHOMA AND OTHER TYPES OF CUTANEous T-CELL LYMPHOMa

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ABSTRACT

In this study we investigated whether programmed death-1 (PD-1) could serve as useful diagnostic marker to differentiate between primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphomas (PCSM-TCL) and cutaneous pseudo-T-cell lymphomas on the one hand and other types of cutaneous T-cell lymphomas (CTCLs) on the other. Formalin-fixed, paraffin-embedded skin biopsies from 26 patients with PCSM-TCL or pseudo-T-cell lymphoma, including 1 patient with a lymphomatoid drug eruption, and 52 skin biopsies from other types of CTCLs were stained for PD-1. In addition, PD-1 positive cases were stained with antibodies against BCL6, CXCL13 and CD10 to determine a possible relationship with follicular helper T (TFH) cells. In all 26 cases of PCSM-TCL or pseudo-T-cell lymphoma, the medium-sized to large-sized atypical T cells consistently expressed PD-1, BCL6 and CXCL13, but not CD10. PD-1 expression was found in only 2 of 21 cases of mycosis fungoides and in only 2 of 16 cases of cutaneous peripheral T-cell lymphoma, unspecifed. All 4 patients with an aggressive epidermotropic cytotoxic CD8+ CTCL and all 11 cases with a primary cutaneous CD30+ lymphoproliferative disorder were negative for PD-1. In conclusion, PD-1 is typically expressed by the atypical cells in PCSM-TCL and pseudo-T-cell lymphoma, but is not expressed or is rarely expressed in other types of CTCLs. Therefore, it may serve as a suitable adjunct in differential diagnosis. Our results demonstrate that the atypical cells in PCSM-TCL and pseudo-T-cell lymphomas share a common TFH phenotype and support the view that most cases classified nowadays as PCSM-TCL are identical to cutaneous pseudo-T-cell lymphomas described previously.
INTRODUCTION

Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (PCSM-TCL) is a cutaneous T-cell lymphoma (CTCL) that has been included as a provisional entity and rare subtype of primary cutaneous peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), in recent cutaneous lymphoma classifications [World Health Organization–European Organization for Research and Treatment of Cancer (WHO-EORTC) 2005; WHO 2008]. These PCSM-TCLs characteristically present with a solitary plaque or tumor that is generally localized on the face or the upper trunk and rarely present with multiple papules, plaques, or tumors. In particular, patients presenting with a solitary skin lesion have an excellent prognosis. Histologically, these lymphomas show nodular-to-diffuse infiltrates with a predominance of CD3+, CD4+, CD8-, CD30- small-sized to medium-sized pleomorphic T cells and a small proportion (<30%) of large CD4+ pleomorphic T cells. In most cases there is a considerable admixture with small reactive CD8+ T cells and CD20+ B cells, including some blast cells, histiocytes, and in some cases plasma cells and eosinophils. The clinical presentation, the architecture, and cellular composition of these PCSM-TCLs are strikingly similar to those described previously in so-called pseudo-T-cell lymphomas. Demonstration of a T-cell clone (common) and loss of pan-T-cell antigens (rare) are nowadays used as diagnostic criteria for PCSM-TCL, but delineation between PCSM-TCL and pseudo-T-cell lymphomas is arbitrary and a matter of debate.

Recently, Rodriguez-Pinilla et al. reported that the large atypical CD4+ T cells in PCSM-TCL express programmed death-1 (PD-1), BCL6 and CXCL13. PD-1, which is located on chromosome 2q37, is a member of the CD28/CTLA-4 receptor family that regulates cellular immune responses. PD-1 has 2 known ligands called PD-L1and PD-L2. Engagement of PD-1 by its ligands inhibits T-cell activation and induces peripheral tolerance. PD-1 is constitutively expressed by a particular germinal center T-cell subset, called follicular helper T (TFH) cells. These TFH cells, which also highly express CXCL13 and BCL6, play an important role in germinal center formation and plasma cell development. The expression of PD-1, BCL6, and CXCL13 by the large atypical CD4+ T cells in PCSM-TCL suggests that this type of CTCL originates from TFH cells. Previous studies have also demonstrated a high expression of PD-1, CXCL13, BCL6, and CD10 by neoplastic T cells in angioimmunoblastic T-cell lymphoma (AITL), and AITL is now commonly considered as a tumor of TFH cells.

PCSM-TCL should be distinguished histologically not only from pseudo-T-cell lymphomas but also from other types of CTCLs, in particular PTCL-NOS and tumor-stage mycosis fungoides (MF). In rare cases with scattered CD30+ blast cells, a diagnosis of primary cutaneous CD30+ lymphoproliferative disease may even be considered. Finally, cases with a large B-cell component and/or many plasma cells
may be misdiagnosed as cutaneous lymphoid hyperplasia or cutaneous marginal zone B-cell lymphoma. Differentiation between PCSM-TCL and these other types of CTCLs is extremely important, as they have a completely different prognosis and require different types of treatment. Studies on PD-1 expression in PTCL–NOS are few and showed conflicting results, with percentages of PD-1-positive cases varying between 0% and 71%. A recent study reported expression of PD-1 in skin biopsies of 15 of 30 cases (50%) of MF and 8 of 11 cases (73%) of Sézary syndrome. Another study also found increased PD-1 expression by the circulating neoplastic T cells in Sézary syndrome and suggested that PD-1 may contribute to immunosuppression.

The aim of this study was to determine whether PD-1 could serve as a useful diagnostic marker to differentiate between PCSM-TCL and other types of CTCLs. In addition, we also investigated all PD-1-positive cases for expression of BCL6, CXCL13, and CD10 to determine whether these cells have a TFH-cell phenotype.

MATERIALS AND METHODS

Patients
Paraffin-embedded skin biopsies from 26 patients with a PCSM-TCL or with a pseudo-T-cell lymphoma (further collectively termed PCSM-TCL; see Discussion section) were selected from the cutaneous lymphoma database of the Leiden University Medical Center. This group included 1 patient with a lymphomatoid drug eruption reported previously. In addition, 10 patients with patch/plaque-stage MF, 11 patients with tumor-stage MF, 16 patients with a primary (n = 9) or secondary (n = 7) cutaneous PTCL–NOS, 4 patients with an aggressive epidermotropic cytotoxic CD8+ CTCL, which is another rare subtype of PTCL, and 11 with a primary cutaneous CD30+ lymphoproliferative disorder, including 5 patients with lymphomatoid papulosis and 6 cases with a primary cutaneous anaplastic large cell lymphoma (C-ALCL), were studied. In all cases the diagnosis was based on the criteria of the WHO-EORTC classification for primary cutaneous lymphomas and had been confirmed by an expert panel of dermato(patho)logists and hematopathologists of the Dutch Cutaneous Lymphoma group.

Immunohistochemistry
Sections of formalin-fixed, paraffin-embedded tissue were dried overnight (37°C) and subsequently dewaxed and rehydrated. Endogenous peroxidase activity was blocked by incubation with 0.3 % hydrogen peroxide in methanol. After antigen retrieval by boiling for 10 min in 10 mmol/L citrate buffer (pH 6.0), tissue sections were incubated overnight with antibodies against PD-1 (1:200, goat polyclonal
antibody AF1086), CXCL13 (1:400, goat polyclonal antibody AF801), both purchased from R&D Systems (Abingdon, UK), or BCL6 (1:50, monoclonal M-7211) from Dako, Glostrup, Denmark. The PD-1 and CXCL13 sections were then incubated with a Goat HRP-Polmer Kit from Biocare Medical (Concord, CA). The BCL6 sections were incubated with a BrightVision Poly-HRP Kit from Immunologic (Duiven, The Netherlands). Immunoreactivity was detected using diaminobenzidine reagents, and counterstaining was performed with Mayer haematoxylin. Detection of CD3, CD4, CD8, CD10, CD20, CD68, CD79a, and MIB-1 was performed by routine immunostaining. Human tonsil and 3 cases of AITL were used as positive controls for PD-1, BCL6, and CXCL13 stainings. Negative controls were obtained by omitting the primary antibody.

**T-cell Clonality Studies**

Polymerase chain reaction was performed to analyze the clonal expansion of T cells. DNA was extracted from paraffin sections, and T-cell clonality was detected by analysis of T-cell receptor (TCR) β (Vβ-Jβ and Dβ-Jβ) and TCRγ gene rearrangement, as previously described. Appropriate positive and negative controls were included in all experiments.

**RESULTS**

**PCSM-TCL**

**Clinical features**

The study group contained 18 male and 8 female patients with a median age of 55 years at presentation (range, 5 to 88 years). None of the 26 patients had skin lesions or a history suggestive of MF, lymphadenopathy, or B symptoms. One of these patients presented with 3 slightly scaling plaques on the trunk while using carbamazepine. As discontinuation of the antiepileptic drug resulted in complete clearance of the skin lesions, a diagnosis of lymphomatoid drug eruption was considered most likely. The etiology in the other 25 patients is unknown. Altogether, 23 of 26 patients presented with a solitary plaque or tumor (Figures 1A and 2A), which was preferentially localized on the head/neck (n = 7) or upper trunk (n = 14). Only 3 of 26 patients presented with multiple skin lesions. Routine physical and laboratory examinations showed no abnormalities in any case. Additional imaging studies had been conducted in only 4 patients and had not shown any abnormalities. In most cases treatment consisted of topical or intralesional steroids (n = 10) or excision (n = 11), whereas 1 patient was treated with radiotherapy. Spontaneous remission after the diagnostic skin biopsy or after discontinuation of the eliciting drug was observed in 4 patients. Local recurrences after treatment with
topical steroids were observed in 4 patients, 1 of them with multiple skin lesions. After a median follow-up of 10 months (range, 2 to 108 months), 23 patients are in complete remission, and 3 patients are alive with disease. None of the patients have developed extracutaneous disease.

**Histology**

Eleven cases, including the lymphomatoid drug eruption, showed a dense subepidermal band-like infiltrate, which characteristically showed a sharp demarcation at the lower border, which sometimes extended around hair follicles (Figures 1B and C). Fifteen cases showed a nodular-to-diffuse infiltrate throughout the entire dermis, often extending into the subcutaneous fat (Figures 2B and C). In both groups, infiltration of the epidermis or follicular structures was either not present or only focally present. The cellular composition of both groups was also highly similar. In all cases, the infiltrates were predominantly composed of small/medium-sized lymphocytes with variable numbers (5 to 25%) of medium-sized to

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**Figure 1. A PCSM-TCL patient with a superficial band-like pattern.** (A) Patient presenting with a solitary plaque on the upper back. (B) Histologically, there is a subepidermal, band-like infiltrate. Panel C is a higher magnification of the indicated area depicted in panel B, showing medium-sized to large atypical cells (arrowheads). The atypical cells express CD4 (D), PD-1 (E), BCL6 (F), and CXCL13 as perinuclear dots (see inset) (G). The insert at the bottom of E is a higher magnification of the area indicated in the papillary dermis.
Figure 2. A PCSM-TCL patient with a nodular pattern. (A) Patient presenting with a tumor on the left temple (B) Histologically, the lesion shows a non-epidermotropic nodular infiltrate throughout the entire dermis. Panel C is a higher magnification of the marked area in panel B, showing many medium-sized to large atypical cells (arrowheads), which express CD4 (D). There is a considerable admixture with reactive CD8+ T cells (E), CD20+ B cells (F), and CD68+ histiocytes (G). The medium-sized to large atypical T cells express PD-1 (H), BCL6 (I) and CXCL13 (J). The insert at the bottom of H is a higher magnification of the area indicated in the papillary dermis.
large lymphoid cells with hyperchromatic and irregular nuclei and scattered blast cells (Figures 1C and 2C). Scattered mitotic figures were observed. In all cases there was a considerable admixture with histiocytes, and in some cases were accompanied by multinucleated giant cells and/or granulomatous changes. Plasma cells were generally present (in 3 cases even in large numbers), but eosinophils were few or absent.

**Immunohistochemistry**

In all cases, the medium-sized and large atypical cells, varying between 5% and 25% of the total infiltrate, showed a CD3+, CD4+, CD8– T-cell phenotype without loss of CD2 or CD5 (Figures 1D and 2D). In all cases there was a considerable admixture with reactive CD8+ T cells (median, 20%; range, 5% to 30%), scattered or clustered CD20+ and/or CD79a+ B cells, including a few blast cells (median, 15%; range, 5% to 30%), and CD68+ histiocytes (median, 15%; range, 5% to 20%) (Figures 2E–G). Cytotoxic proteins were not expressed. CD30+ blast cells were generally few (< 5%). The proliferation rate varied between < 5% and 20% (median, 10%). MIB-1 was predominantly expressed by the large atypical cells. In all 26 cases the medium-sized to large atypical T cells consistently expressed PD-1, BCL6 and CXCL13 (Figures 1E–G and Figures 2H–J). In all 12 cases the CD10 staining was negative. Serial sections showed that CXCL13 generally stained 50% to 75% of PD-1+ cells, and BCL6 stained 25% to 50% of PD-1+ cells. In addition to the medium-sized to large atypical T cells, a few small reactive T cells showed a positive staining for PD-1, BCL6, and CXCL13. The neoplastic cells of the 3 AITL cases included as a positive control consistently expressed PD-1, BCL6, CXCL13, and CD10.

**Molecular studies**

Multiplex polymerase chain reaction analysis using the BIOMED-2 protocol demonstrated clonal TCR gene rearrangement in 16 cases, including the case with a lymphomatoid drug eruption, an oligoclonal pattern in 1 case, and an absence of clones in 5 cases. In 4 cases, evaluation was impossible because of poor DNA quality or lack of material.

**PD-1 staining in other CTCLs**

PCSM-TCL with a nodular or diffuse pattern resemble cutaneous PTCL–NOS and tumor-stage MF, whereas PCSM-TCL with a band-like pattern resemble patch/plaque-stage MF.1, 16, 17, 21 Skin sections from both plaque-stage and tumor-stage MF and from patients with cutaneous PTCL–NOS were therefore stained for PD-1 to determine whether this molecule is differentially expressed in these lymphomas. Because of the presence of scattered CD30+ cells in most PSCM-TCLs, which may raise suspicion to a cutaneous CD30+ lymphoproliferation, skin biopsies from 5
patients with lymphomatoid papulosis (LyP) and 6 patients with a C-ALCL were selected as well.

The neoplastic cells in all 21 MF lesions had a CD3+, CD4+, CD8– T-cell phenotype with frequent loss of pan-T-cell antigens in tumorous lesions (Figures 3A and B). In only 1 of 10 plaques and 1 of 11 tumorous lesions did virtually all neoplastic cells express PD-1 (Figure 3D). In both cases, BCL6 and CXCL13 were expressed by 25% to 50% of PD-1+ cells (Figures 3E and F), whereas CD10 was strongly expressed by the neoplastic T cells in 1 of these 2 cases (Figure 3C). In the other 19 MF biopsies, PD-1, BCL6, and CXCL13 only stained a few small reactive T cells.

Routine immunophenotypical studies in the PTCL–NOS group showed that 8 cases had a CD3+, CD4+, CD8– T-cell phenotype, 4 cases a CD4–, CD8– T-cell phenotype and 4 cases a CD4+, CD8+ T-cell phenotype. In contrast to the group of PCSM-TCLs, in most cases there was loss of 1 or more pan-T-cell antigens, a minimal admixture with inflammatory cells, and a proliferation rate of more than 50%. In only 2 cases, both secondary cutaneous CD4+ PTCL–NOS, did neoplastic T cells weakly stain for PD-1, BCL6, and CXCL13 but not for CD10. In the other cases, PD-1, BCL6, and CXCL13 only stained a few scattered reactive T cells. The neoplastic CD8+ T cells in 4 patients with an aggressive CD8+ epidermotropic cytotoxic CTCL did not express PD-1.

**Figure 3. Mycosis fungoides.** (A) Haematoxylin-eosin staining of a skin lesion from a patient with plaque-stage MF showing a dense infiltrate in the papillary dermis. The insert at the bottom is a higher magnification of the area indicated in the papillary dermis. There is extensive infiltration in the epidermis with formation of Pautrier microabscesses. The neoplastic cells expressed CD3 (B), CD10 (C), PD-1 (D), BCL6 (E), and CXCL13 (F).
Consistent with previous studies, the large atypical CD30+ cells in skin lesions of 11 patients with LyP (n = 5) or C-ALCL (n = 6) were consistently negative for PD-1. PD-1 expression in the different types of CTCLs are summarized in Table 1.

**DISCUSSION**

In this study, the medium-sized to large atypical CD4+ T cells in all 26 cases of PCSM-TCL consistently showed expression of PD-1, BCL6, and CXCL13, which confirms the results of a previous study and suggests that these cells have a TFH cell phenotype. In contrast to AITL, now commonly considered as a tumor of TFH cells, CD10 was not expressed in any of the 11 PCSM-TCLs studied. In the study by Rodriguez-Pinilla et al., CD10 was expressed by a proportion of the atypical T cells in 3 of 15 cases. Interestingly, in our study PD-1 expression was found in only 2 of 16 PTCL–NOS, both cases with secondary cutaneous involvement, and not in the 4 aggressive epidermotropic cytotoxic CD8+ CTCLs. Our observations are consistent with other studies in PTCL–NOS, in which no or a single case showed PD-1 positivity but are in contrast with another study in which 10 of 14 cases expressed PD-1. Moreover, in our study, PD-1 expression was found in only 2 of 21 cases of MF, including 1 of 10 plaque-stage and 1 of 11 tumor-stage MFs. Both cases also expressed BCL6 and CXCL13, whereas CD10 was strongly expressed in only 1 of them. A recent study reported expression of PD-1 in 6 of 15 (40%) skin biopsies of patch/plaque-stage MF and 9 of 15 (60%) biopsies of tumor-stage MF. An explanation for these discrepant results is currently lacking. Consistent with previous studies, PD-1 was not expressed by the large CD30+ cells in LyP or C-ALCL.

The differences in PD-1 expression between PCSM-TCL on the one hand and cutaneous PTCL–NOS and tumor-stage MF on the other hand indicate that a positive staining of this marker may be used as an additional criterion to differentiate PCSM-TCL from these other types of CTCLs. This is particularly important in cases presenting with a solitary tumor, which was observed in all but 3 cases of PCSM-TCL and also in 4 patients with a primary cutaneous PTCL–NOS, all being negative for PD-1. In contrast to the patients with a PCSM-TCL, 3 of these 4 patients died of their disease 8 to 12 months after diagnosis, whereas 1 recently diagnosed patient is still alive with disease 5 months after diagnosis.

**PCSM-TCL or cutaneous pseudo-T-cell lymphoma?**

In this study, the group of PCSM-TCL contained cases that might be classified either as PCSM-TCL or as pseudo-T-cell lymphoma. The relationship between both conditions is a matter of debate. In the 1990s we and others introduced the term pseudo-T-cell lymphoma for lesions with histologic features suggesting a CTCL...
but with a clinical presentation and clinical course more consistent with a benign condition.\textsuperscript{16, 17, 21} Prototypic patients were those using anti-epileptic drugs and presenting with a solitary plaque or nodule, which showed an atypical band-like subepidermal infiltrate mimicking MF. The correct diagnosis in such patients is a lymphomatoid drug eruption. For skin lesions showing the same atypical band-like infiltrate, but without known cause (most of them), the term pseudo-T-cell lymphoma was used.\textsuperscript{16, 17, 21} In addition to cases with a superficial band-like infiltrate, other patients presenting with a solitary plaque or nodule showed a nodular-to-diffuse infiltrate, which sometimes extended into the subcutaneous fat. Apart from the difference in architecture (band-like versus nodular to diffuse), these pseudo-T-cell lymphomas with a nodular-to-diffuse growth pattern showed the same clinical presentation and clinical course and had the same cellular composition as the cases with a band-like infiltrate: an atypical infiltrate with a predominance of small/medium-sized lymphocytes with variable numbers (but always < 30%) of medium-sized to large CD3\textsuperscript{+}, CD4\textsuperscript{+}, CD8\textsuperscript{−} T cells, a considerable admixture with CD8\textsuperscript{+} T cells, CD20\textsuperscript{+} B cells, and histiocytes, a low proportion of proliferating cells, and no or only focal infiltration of the epidermis or follicular epithelium.\textsuperscript{16}

In our initial studies, using Southern blot analysis, no clonality was found, and absence of clonality and absence of marker loss were suggested as useful criteria to differentiate these pseudo-T-cell lymphomas from MF and from primary cutaneous PTCL–NOS.\textsuperscript{1}

With the introduction of new and more sensitive techniques to demonstrate T-cell clonality it has become clear that most cases until then classified as pseudo-T-cell lymphoma contain clonal T cells. In addition, clonal T cells can also be found in lymphomatoid drug eruptions,\textsuperscript{5, 11, 14} as illustrated by the patient with a carbamazepine-associated lymphomatoid drug eruption in this study. In cases

### Table 1. PD-1 Expression in Different Types of Cutaneous T-cell Lymphoma

<table>
<thead>
<tr>
<th>Type of Lymphoma</th>
<th>Number</th>
<th>Neoplastic T cells</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCSM-TCL / cutaneous pseudo-T-cell lymphoma</td>
<td>26</td>
<td>26</td>
<td>100</td>
</tr>
<tr>
<td>MF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patch/plaque stage</td>
<td>10</td>
<td>1</td>
<td>10</td>
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<tr>
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<td>11</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>PTCL–NOS</td>
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<tr>
<td>Primary cutaneous</td>
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<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Secondary cutaneous</td>
<td>7</td>
<td>2</td>
<td>28</td>
</tr>
<tr>
<td>Aggressive CD8\textsuperscript{+} epidermotropic cytotoxic CTCL</td>
<td>4</td>
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<td>0</td>
</tr>
<tr>
<td>Primary Cutaneous CD30\textsuperscript{+} lymphoproliferative disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphomatoid papulosis</td>
<td>5</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Cutaneous anaplastic large cell lymphoma</td>
<td>6</td>
<td>-</td>
<td>0</td>
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in which a cause is known or presumed, and more in general in cases with an atypical band-like infiltrate confined to the papillary dermis, a diagnosis of pseudo-T-cell lymphoma or atypical lymphoid hyperplasia is often preferred, despite the detection of clonal T cells. However, in cases with a nodular-to-diffuse infiltrate, in which generally no causal factor can be detected, demonstration of T-cell clonality, in combination with a sometimes highly atypical morphology, nowadays generally results in a diagnosis of PCSM-TCL.

In this study, using the BIOMED-2 protocol, clonal TCR gene rearrangements were detected in 8 of 10 cases with a band-like pattern and 9 of 12 cases with a nodular-to-diffuse pattern. Both histologic groups had an identical cellular composition and in both groups the medium-sized to large atypical CD4+ T cells consistently expressed PD-1, BCL6, and CXCL13. In our view, there is therefore no reason to classify these two groups separately. Whether all cases should be classified as PCSM-TCL or as pseudo-T-cell lymphoma is a matter of debate. The overlapping features between PCSM-TCL and pseudo-T-cell lymphomas are widely recognized. Since differentiating criteria are lacking, Cerroni suggested the term “cutaneous nodular proliferation of pleomorphic T lymphocytes of undetermined significance”, and emphasized that these cases should not be treated aggressively.3 Most cases in our study were still classified as pseudo-T-cell lymphoma or as “spectrum of pseudo-T-cell lymphoma/PCSM-TCL”. Regardless of the term preferred, there is consensus that patients presenting with a solitary lesion and the characteristic histologic and immunophenotypical features described herein have an excellent prognosis. In our department, staging procedures are generally not performed in these patients, and their skin lesions, if not resolved spontaneously after skin biopsy, are treated with intralesional steroids or surgical excision and only by exception with radiotherapy. As in other pseudolymphomas, we advise a follow-up period of two years. The fact that all patients had an uneventful follow-up and that a skin relapse was observed in only 4 of 26 cases suggest that this is a correct and safe approach.

PCSM-TCLs that do not meet the criteria of the cases described herein are rare and should be fully staged. A recent study suggesting that PCSM-TCLs with rapidly growing bulky tumors, a low percentage of admixed CD8+ T cells, and/or a high proliferative fraction are at risk to develop progressive disease awaits further confirmation.9 Whether such cases have also a TFH phenotype remains to be established.

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