Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder—clinical and histopathologic features, differential diagnosis, and treatment

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Abstract
Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder usually presents as a slow-growing and asymptomatic solitary lesion in the form of a nodule or tumor in the head and neck region. By definition, it is histologically characterized by small- to medium-sized CD4+ lymphocytes involving the dermis in a dense and either nodular or diffuse pattern. Epidermotropism should be absent or minimal. Tumor cells are accompanied by numerous reactive B cells, plasma cells, histiocytes, and eosinophils. This lymphoproliferative disorder is characterized by the expression of follicular helper T-cell markers, particularly B-cell lymphoma 6 (BCL-6), programmed cell death protein 1 (PD-1), and C-X-C motif chemokine ligand 13 (CXCL-13), while CD10 is usually negative. Molecular studies show a clonal rearrangement of T-cell receptor genes in more than 60% of cases. Management of disease includes surgical excision, radiation therapy, and steroids (topical or intralesional). Patients with this diagnosis have an excellent prognosis, with a clinical course that is invariably indolent.

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Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder (PCS-TCLPD) is, according to the revision of the World Health Organization (WHO) classification of hematopoietic neoplasms, an indolent T-cell lymphoproliferative disorder confined to the skin, with a characteristic population of T cells with a follicular T-helper phenotype. The follicular T-helper phenotype implies that T cells show expression of many common germinal center B-cell antigens (B-cell lymphoma 6 [BCL-6], programmed cell death protein 1 [PD-1], C-X-C motif chemokine ligand 13 [CXCL-13], inducible T-cell costimulator [ICOS], etc.). Despite its original classification of “lymphoma,” it’s now clear that, invariably, all cases have an indolent behavior, do not show extension beyond the skin, and can be easily managed with local therapies (surgery, corticosteroids, local radiation), without the need for systemic chemotherapy. The difficulties that arise with this particular entity are two-fold: first, in the past, many of the so-called T-cell lymphoid hyperplasias with clonal rearrangement of T cells would fall under this category; second, many cases of T-cell lymphomas in the skin (which are now classified as this lymphoma subtype) that do not follow the typically morphologic pattern for mycosis fungoides (MF) or other common cutaneous T-cell lymphomas were diagnosed as peripheral T-cell lymphoma, not otherwise specified. The latter creates a therapeutic dilemma for many clinicians, who will sometimes treat this indolent disease with aggressive regimens, exposing patients to very toxic and potentially harmful chemotherapeutic drugs.

Clinical findings
PCS-TCLPD represents approximately 2% to 3% of all cutaneous lymphomas, although its true incidence may be underscored by clonal T-cell lymphoid hyperplasias. It can occur at any age but most commonly affects individuals in the 6th to 7th decade of life. Many cases have been reported in the pediatric age group. PCS-TCLPD commonly presents as a slow-growing erythematous or violaceous cutaneous lesion in the form of a papule, plaque, nodule, or tumor (Figure 1). Nodules and tumors are the most frequent type of clinical lesions. The original studies from this entity showed multiple lesions in 50% to 74% of cases. However, the most recent large series of cases show that, in the vast majority of patients, a solitary lesion is present. The majority of cases involve the head and neck followed by the trunk and upper extremities. Lower extremity involvement is less common. Lesions are typically asymptomatic, although pain and pruritus have been reported. Some lesions with associated nerve infiltration can show hypoesthesia. There is no gender predilection. Ulceration is rarely present. This lymphoproliferative disorder has a variable clinical course: lesions can start abruptly, enlarged rapidly over the course of several months, slowly grow over years, persist with minimal change, wax and wane over

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*FIGURE 1.* Infiltrative plaque on the right side of the neck, corresponding to a lesion of PCS-TCLPD. PCS-TCLPD, primary cutaneous CD4⁺ small/medium T-cell lymphoproliferative disorder.
the course of weeks, and spontaneously resolve. Very unusual clinical presentations include alopecia, poikilodermatous plaques, and pigmented purpura. A very rare association of this entity with a giant-cell annular elastolytic granuloma has been described. A case of PCS-TCLPD has been reported after treatment with methotrexate and etanercept in a patient with rheumatoid arthritis. Davick et al reported the occurrence of PCS-TCLPD in a patient with metastatic melanoma, previously treated with interleukin 2 (IL-2). Another reported case of this entity in a patient undergoing therapy with vemurafenib for metastatic melanoma was described. A presentation of PCS-TCLPD was described in association with erythema chronicum migrans. A case following heart transplantation was also described. Cases presenting with plaques typical of MF, whether antecedent or current, should not be considered under this diagnostic category. Cases with systemic dissemination have been originally described, but those are now best classified as peripheral T-cell lymphoma or other subtypes of cutaneous T-cell lymphomas.

**Histopathologic features**

Histopathologic features of PCS-TCLPD on standard hematoxylin and eosin sections show a dense infiltrate composed of small- to medium-sized lymphocytes that are arranged in a diffuse or nodular pattern (Figures 2-4). It predominantly involves the dermis, with a tendency to infiltrate the subcutaneous tissue (Figures 5 and 6). Effacement and destruction of structures, including adnexa and vasculature, may be seen due to the density of the infiltrate. Epidermotropism should not be prominent (Figure 7); otherwise, a diagnosis of MF should be considered. Approximately 20% of cases can show epidermotropism and also pilomotropism. Surface ulceration may be present if the lesion is large, but this typically occurs in <10% of cases. Although the majority of the cells are small to medium, large and cytologically atypical may rarely be seen. Additional cells may be associated with the tumor cells, including B cells, plasma cells, histiocytes, and eosinophils (present in 70%-80% of cases). The large cells comprise less than 30% of the cells among the infiltrate. Rare neutrophils and immunoblasts may also be seen. Granulomatous inflammation may accompany the lesion and is mostly perifollicular and periadnexal (Figure 8). Tu- mor necrosis and secondary germinal center formation, while not typical, can be rarely identified in these lesions (authors’ own personal experience).

According to WHO, rare cases presenting with widespread skin lesions and large, rapidly growing tumors with histologic features that include more than 30% large pleomorphic T cells and/or high proliferative fraction should not be included in this diagnosis because they have a more aggressive clinical course and should be classified as peripheral T-cell lymphoma, not otherwise specified. However, Beltraminelli et al reported 4 out of 72 cases in which the Ki67 (MIB1) was greater than 30%.

**Immunophenotype**

The lymphocytes are T cells and consistently express CD3. WHO considers this diagnosis to include cases in which the atypical cells
**FIGURE 3.** PCS-TCLPD—immunohistochemistry. There is a dense infiltrate composed of CD3+ and CD4+ T cells. CD8 stains a minor proportion of T cells. The CD4:CD8 ratio is >20:1. CD20 and PAX5 highlights the very rich background of B cells, which can potentially raise the confusion with a B-cell lymphoma. CD7 shows retained staining in the T-cell infiltrate. PAX5, paired box protein 5; PCS-TCLPD, primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder.

**FIGURE 4.** PCS-TCLPD—immunohistochemistry. This lymphoma subtype shows the characteristic expression of T\(_{FH}\) markers. The lesional cells are positive for PD-1 and BCL-6 (the latter is noted in the larger pleomorphic T cells). MUM1 shows a rich background of plasma cells. The plasma cells are polyclonal by in situ hybridization for kappa and lambda. Ki67 shows a low proliferation index (20%). BCL-6, B-cell lymphoma 6; MUM1, multiple myeloma 1; PCS-TCLPD, primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder; PD-1, programmed cell death protein 1; T\(_{FH}\), follicular helper T cell.
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are positive for CD3 and CD4 and negative for CD8, CD30, and
cytotoxic molecules. It is important to note that, in almost all cases,
the atypical CD4-positive cells are frequently mixed with small,
reactive CD8-positive cells as well as B cells, plasma cells, and
histiocytes. The B cells can constitute up to 10% to 60% of the in-
filtrate and the CD8+ T cells 5% to 47% of the cells.3 Also, if CD30
is present, it should be rare (<1%). However, more recently, Magro
et al reported a series of 15 patients for whom CD30 expression
ranged from 15% to 30% of the infiltrate.41 In 2 of the cases,
the level of CD30 expression approximated 40% of the cells. A loss of
CD5 and CD7 is uncommon but may occasionally be seen. A study
by James et al reviewing 23 cases showed loss of CD5 and CD7 in
52% and 84%, respectively.21 Rare examples of PCS-TCLPD with
CD4+/CD8+ phenotype have been described.10

The Ki67 proliferation index typically ranges from 5% to 30%
in the vast majority of cases.6,10,13,16,17,25-27,42 But on rare occasions
it could be as high as 50% to 70%.25,27 It is frequent to encounter
the atypical T cells to form rosettes around CD30+/organic cation
transporter 2 (OCT2)+ B-cell immunoblasts.26 The neoplastic cells
are positive for T-cell receptor (TCR) alpha beta (beta-F1) and
negative for TCR gamma delta. No evidence of Epstein-Barr virus
(EBV) infection has been detected in these lesions. The so-called
indolent CD8+ proliferation of acral sites, originally believed to be a
variant of this lymphoma with CD8+ phenotype, expression of
cytotoxic markers, and indolent clinical presentations in the ears or
acral skin,15,25,43-46 has now been reclassified as primary cutaneous
acral CD8+ T-cell lymphoma.2

The atypical cells are positive for follicular helper T-cell (T\textsubscript{FH})
markers PD-1, CXCL13, ICOS, and BCL-626,37,47 while negative for
CXCR5.46 CD10-positive staining is not common. In all cases reported
by Rodriguez et al, the atypical CD4-positive cells were also positive
for PD-1, CXCL13, and BCL-6. They were arranged in small clusters
or were seen forming rosettes around CD30- and OCT2-positive B
blast cells. These stains may also highlight the atypical cells forming a
pseudorosette around CD20-positive B cells.26

Genetic and molecular findings
Monoclonal TCR gene rearrangements have been detected in 60%
to 100% of cases.3,10 The largest series from Beltraminelli reported
a prevalence of 60% for TCR-gamma rearrangement among the
124 cases tested,10 while the second largest of 84% (n = 62) was
reported by Alberti-Violetti.8 Some have argued that a positive
clonality study is required to establish this diagnosis, in an attempt
to differentiate this entity from a cutaneous lymphoid hyperplasia.
Immunoglobulin heavy chain rearrangement is typically germline.
However, a diagnosis would be unusual in the absence of a mono-
clonal TCR gene rearrangement. Specific cytogenetic abnormalities
or molecular alterations have not yet been determined, but on
the cases tested, no numerical alterations were seen by array com-
parative genomic hybridization.8

Differential diagnosis
PCS-TCLPD should be differentiated from both B- and T-cell
pseudolymphomas. Among the lymphomas, the differential diag-
nosis includes other lymphoma subtypes that may express PD-1 and other follicular T-cell markers, including primary cutaneous follicular helper T-cell lymphoma (PCFHTL), MF, angioimmunoblastic T-cell lymphoma (AITL), lymphomatoid papulosis, and peripheral T-cell lymphomas not otherwise specified.\(^{26}\) PD1 and CXCL13 expression can also be found in primary cutaneous marginal zone lymphoma (PCMZL) and primary cutaneous follicle center lymphoma (PCFCL),\(^{49,50}\) and thus these diagnoses need to be considered on the differential diagnosis as well. Notoriously, because PCS-TCLPD can have abundant clusters of B cells, a PCMZL is often in the differential diagnosis of this condition. Some of the differential diagnoses are further discussed below.

**T-cell pseudolymphoma\(^{51}\)**

The clinical and histopathological overlap is significant, with a solitary cutaneous lesion consisting of lymphocytes, plasma cells, histiocytes, and eosinophils. However, PCS-TCLPD is less likely to have a spontaneous resolution of the lesion and is more likely to show aberrant loss of T-cell antigens (CD5 or CD7). The CD4:CD8 ratio tends to be relatively high (usually >10:1) in cases of PCS-TCLPD in comparison to T-cell pseudolymphomas. The most helpful finding for the differentiation is a monoclonal TCR rearrangement supporting the diagnosis of PCS-TCLPD\(^{51}\) over a pseudolymphoma, with the caveat that inflammatory dermatoses can sometimes show a clonal population of T cells.\(^{52-55}\) Another caveat of reactive T-cell infiltrates is the fact that pseudolymphomatosus folliculitis can have a high proportion of PD-1+ T cells.\(^{56}\)

Cetinozman et al also found a high proportion of reactive T cells with expression of PD-1, BCL-6, and CXCL-13 in pseudo T-cell lymphomas\(^{57}\) among medium- to large-sized T cells. In a different cohort of patients, they also found that the neoplastic T cells of Sezary syndrome express PD-1, while the reactive T cells in inflammatory dermatoses also do so.\(^{58}\) Therefore, PD-1 by itself seems of limited value in the distinction between reactive and neoplastic proliferations of T cells. Magro et al identified significant levels of nuclear factor of activated T-cell expression in PCS-TCLPD, in comparison to reactive hyperplasias.\(^{59}\) Nihal et al described a series of cases of so-called atypical lymphoid hyperplasias, a process in continuum with lymphoproliferative disorders. It’s likely that many of such cases included examples of PCS-TCLPD.\(^{60}\)

**Primary cutaneous follicular helper T-cell lymphoma\(^{60-68}\)**

PCS-TCLPD, AITL, and PCFHTL have significant histologic and immunophenotypic overlap. Patients with PCFHTL show multiple papules, plaques, and nodules (>20) on the trunk, limbs, and head and neck region. Some patients can have blood cytopenias and elevated lactate dehydrogenase (LDH) levels. Histologically, the lesions are similar to PCS-TCLPD in that the infiltrate has a nodular dermal growth and spares the surface epidermis. Some cases can have limited folliculotropism. A rich background of B cells is noted. Most cases have expression of CD10, as opposed to PCS-TCLPD (the other TFH markers are equally expressed, including BCL-6, CXCL-13, PD-1, and ICOS). As opposed to AITL, Epstein-Barr encoding region (EBER) is negative. Most
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Patients require systemic treatment and/or bone marrow transplant. In contrast to PCFHTL, PCS-TCLPD has as a less aggressive clinical course with a better patient outcome and without disseminated involvement. More recently, cases of nodal variants of follicular T-cell lymphomas have shown the presence of Reed-Sternberg cells, which are positive for CD30 and CD15, have EBER+ B-cell immunoblasts, and were originally misdiagnosed lymphocyte-rich classical Hodgkin lymphoma.66 Two of those patients (n = 5) have skin manifestations upon the diagnosis. RHOA mutations can also be seen in the nodal forms of the disease.69

Mycosis fungoides70

While PCS-TCLPD presents with a solitary lesion predominantly in the head and neck, MF usually presents with a history of multiple erythematous scaly patches and plaques, with the eventual formation of tumors. Histologically, MF will more often than not have epidermotropism (epidermotropism is less prominent in tumoral lesions and folliculotropic forms). Bosio et al have reported cases of MF expressing TFH markers (PD-1, ICOS, CXCL13, BCL-6, CD10), which emphasizes the need for clinicopathologic correlation for diagnosis rather than pathology alone.71 Cases of MF with TFH phenotype were frequently double negative for CD4 and CD8 and show a rich background of B cells.72 Additionally, the expression of PD-1 in MF is often noted during the evolution of the disease.73 Most cases of Sezary syndrome show very high levels of PD-1 expression in the absence of expression of TFH markers.73

Angioimmunoblastic T-cell lymphoma74

Although AITL has a significant histologic and immunophenotypic overlap as the neoplastic cells also express FSH markers (CD10, BCL-6, PD-1, ICOS, CXCL-13),75 the clinical presentation is different. AITL presents with systemic symptoms and involves the skin secondarily. Indeed, the cutaneous rashes associated with AITL can be seen in up to 75% of patients.76,77 The skin manifestations of this disease are very protean. Very frequently, patients with AITL have generalized lymphadenopathy, cytopenias, and hypergammaglobulinemia. B symptoms are often noted (fever, chills, weight loss). Additionally, AITL is commonly positive for EBV, while PCS-TCLPD has not shown any association with this virus. In AITL, the proliferation of B-cell immunoblasts is positive for EBER. AITL is also more frequently positive for CD10, while PCS-TCLPD is not. AITL shows frequent mutations in IDH2,78,79 RHOA, and TET2.80 Such mutations can be identified in cutaneous lesions of AITL while not in cases of PCS-TCLPD. AITL on the skin can have an abundance of B cells, which has led to presentations that mimic PCMZL.82,83 Another complication of AITL in the skin includes the transformation into a diffuse large B-cell lymphoma, which is typically EBV+.84

Lymphomatoid papulosis

LyP is characterized by a self-resolving eruption composed of multiple papules that usually self-resolve over the course of 3 to 6 weeks. On microscopy, there is a wedge-shaped lymphocytic infiltrate with the base at the epidermis and the tips in the reticular dermis. There is variable epidermotropism, unlike PCS-TCLPD,
which should not have any. The atypical T cells are positive for CD3, CD4, and CD30 and will show a clonal TCR rearrangement. This condition can be distinguished from PCS-TCLPD by the clinical presentation.

Primary cutaneous marginal lymphoma
Cutaneous marginal lymphoma typically presents in the trunk and extremities in the form of solitary or multiple papules or plaques. Histologically, the lesions show a rich background of T cells and can have a nodular appearance. Frequently, the atypical infiltrate follows the adnexal structures, and atrophic germinal centers are often found. The infiltrate consists of a mixture of monocytoid B cells, lymphoplasmacytic cells, and plasma cells, which often show light chain restriction with the use of in situ hybridization or immunohistochemistry. The neoplastic B cells lack expression of germinal center markers (CD10, BCL-6) and are negative for CD43. The plasma cell component can be demonstrated with CD138 or CD38. Follicular dendritic networks are distorted and expanded, as shown by CD21, CD23, or D2-40 immunostains. Additionally, a high proportion of immunoglobulin G (IgG)4+ plasma cells is frequently encountered.

Primary cutaneous follicle center lymphoma
PCFCL typically presents in the head and neck region, in the forms of indurated plaques or tumors, without ulceration. Histologically, the lesions show a combination of nodular, nodular and diffuse, or predominantly diffuse growth patterns. Similar to PCMZL, a rich background of T cells is evident in most cases. The neoplastic follicles lack well-defined polarity, a mantle zone, have a lower proliferation rate, and lack tingible body macrophages (as opposed to normal germinal centers). The neoplastic B cells show expression of CD10 (less frequently in the cases with diffuse growth), BCL-6, and have variable expression of BCL-2. The background T cells show a rich number of PD-1-positive T-cell cells, as opposed to PCMZL.

Treatment
PCS-TCLPD has an excellent prognosis. It has an indolent clinical behavior with a 5-year survival rate of 100%. It is very likely that the original case series of PCS-TCLPD included examples of peripheral T-cell lymphomas and cutaneous follicular T-helper lymphomas, which accounted for the reduced survival in patients with multiple cutaneous lesions. It wasn’t until the most recent WHO edition (Revised 4th Edition; 2017) that the term “primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder” was chosen, rather than “primary cutaneous CD4+ small/medium T-cell lymphoma.” This was largely due to the fact that cases of PCS-TCLPD have similar clinicopathological features as well as an indolent clinical course as cutaneous pseudo-T-cell lymphomas.

Patients with limited disease are usually treated successfully with local surgical excision, radiation therapy, and/or topical or intralesional steroids. Case reports have shown spontaneous remission after biopsy of these lesions, and, in such cases, close clinical monitoring of the biopsy site without additional treatment.
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is sometimes considered. Local recurrences are rare. A case underlying resolution following the administration of doxycycline has been reported.92

In summary, PCS-TCCLPD usually presents as a plaque or nodule in the head and neck region. Histologically, this condition is characterized by CD4+ lymphocytes that are mostly small to medium in size and that involve the dermis in a dense and either nodular or diffuse pattern. The lesional lymphocytes typically express Tfh markers, particularly BCL-6, PD-1, and CXCL13, while CD10 is usually negative. The condition is associated with an excellent prognosis and a clinical course that is invariably indolent. Management of disease includes surgical excision, radiation therapy, corticosteroids, and close clinical monitoring.

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