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Primary Cutaneous CD4-Positive Small/Medium Pleomorphic T-cell Lymphoma – A Case Report

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Abstract

Primary cutaneous CD4-positive small- to medium-sized pleomorphic T-cell lymphoma is a provisional entity in the 2005 WHO-EORTC classification for cutaneous lymphomas. It is a rare condition and, in most cases, it has a favorable clinical course and prognosis. Primary cutaneous CD4-positive small/medium pleomorphic T-cell lymphoma (PCSM-TCL) is defined as a cutaneous T-cell lymphoma with predominantly small- to medium-sized CD4-positive pleomorphic T-cells without a history of patches and plaques typical of mycosis fungoides. PCSM-TCL usually presents as a solitary plaque or tumor on the head, neck, trunk or upper extremities and it is considered to have indolent clinical behavior. Histologically, it is characterized by a dense infiltration of small/medium-sized pleomorphic T-cells that involves the entire dermal thickness, often with nodular extension into the hypodermis. Using immunohistochemical staining, the majority of the reported cases proved to be CD3, CD4 positive and CD8, CD30 negative. However, due to the rarity and heterogeneity of the PCSM-TCL, precise clinicopathologic characteristics of PCSM-TCL have not been well characterized and the optimal treatment for this group of lymphomas is yet to be defined. Dermatologists and pathologists should be aware of this entity in order to avoid unnecessary aggressive treatments.

Here we present a 30-year-old man with a solitary lesion on the scalp with histopathological features corresponding to PCSM-TCL. After surgical excision, the patient has been disease-free so far, with no additional therapy used to the present day with regular checkups.

Key words

Lymphoma, T-Cell, Cutaneous; Skin Neoplasms; CD4-Positive T-Lymphocytes; Pleomorphic T-cell Cutaneous lymphoma; Treatment Outcome; Case Reports

Primary cutaneous lymphoma represents a heterogeneous group of malignancies with clinical findings that are different from those of systemic lymphoma (1 - 3). The current World Health Organization – European Organization for Research and Treatment of Cancer (WHO – EORTC) classification from 2005, proposed a consensus for a new classification to facilitate more uniformity when diagnosing these cancers (1 – 5). In the new classification, three rare subtypes of primary cutaneous peripheral T-cell lymphomas with particular clinical features have been recognized and marked as "provisional entities": primary cutaneous CD4-positive small/medium T-cell lymphoma (PCSM-TCL), primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma, and primary cutaneous γδ T-cell lymphoma (2, 3).

Primary cutaneous CD4-positive small/medium pleomorphic T-cell lymphoma (PCSM-TCL) is defined as a cutaneous T-cell lymphoma with predominantly small to medium-sized CD4-positive pleomorphic T-cells without a history of patches and plaques typical of mycosis fungoides (MF) and, in most cases, favorable clinical course and prognosis (6). PCSM-TCL usually presents as a solitary plaque or tumor on the head, neck, trunk or upper extremities and it is considered to have indolent clinical behavior. However, due to the rarity and heterogeneity of the PCSM-TCL, the precise clinicopathological characteristics of PCSM-TCL have not been well characterized and the optimal treatment for this group of lymphomas is yet to be defined (7, 8). Here we present a 30-year-old man with a solitary lesion on the scalp with histopathological features corresponding to PCSM-TCL.

Case report

A 30-year-old man was admitted to our department for an asymptomatic tumor on his forehead that appeared in October 2016. During the course of next month, it began growing and changing color, from skin color to red and livid. He was examined by a dermatologist from other healthcare center and was treated with ammonium bituminosulfonate 10% ointment which gave no therapeutic results after 2 weeks, so excision was suggested.

Before excision, the lesion presented on the frontal region as a solitary violaceous nodule 2.5 cm in diameter (Figure 1). There were neither other systemic symptoms, nor palpable lymphadenopathy. The patient was otherwise healthy. There was no family history of malignancies. A surgical excision was performed, and according to the histopathological report the diagnosis of MF tumor stage was given. However, due to the discrepancy between clinical manifestations and the histopathological report, a revision of histopathologic analysis was indicated.

The histopathologic analysis showed a diffuse lymphocytic infiltration containing small- and medium-sized cells with oval and cut-in nuclei, small nucleoli with moderately extensive transparent cytoplasm. The infiltrate involved the entire dermal thickness, with extension into the hypodermis (Figure 2). Rare, large lymphoid cells were present in less than 20% of lymphoid population. Epidermotropism was present only focally. Amid tumor cells, there was a moderate number of small B-cells, plasma cells and basophil granulocytes. On immunohistochemical analysis, 20% of infiltrated cells were positively stained with CD2, CD3, CD4, CD5, CD7 and Bcl2 (Figure 3). There was no expression for CD8, CD30, CD56 and granzyme B. There was a Ki-67 nuclear expression in approximately 20% of tumor cells. Histopathological features (which show the absence of cerebriform nuclei visible in MF) were consistent with the PCSM-TCL group, rather than MF group. Also, clinical presentation of just one solitary lesion with abrupt onset, and the absence of preexisting patch and plaque stage of MF, led to the diagnosis of PCSM-TCL and not MF, as previously suspected.

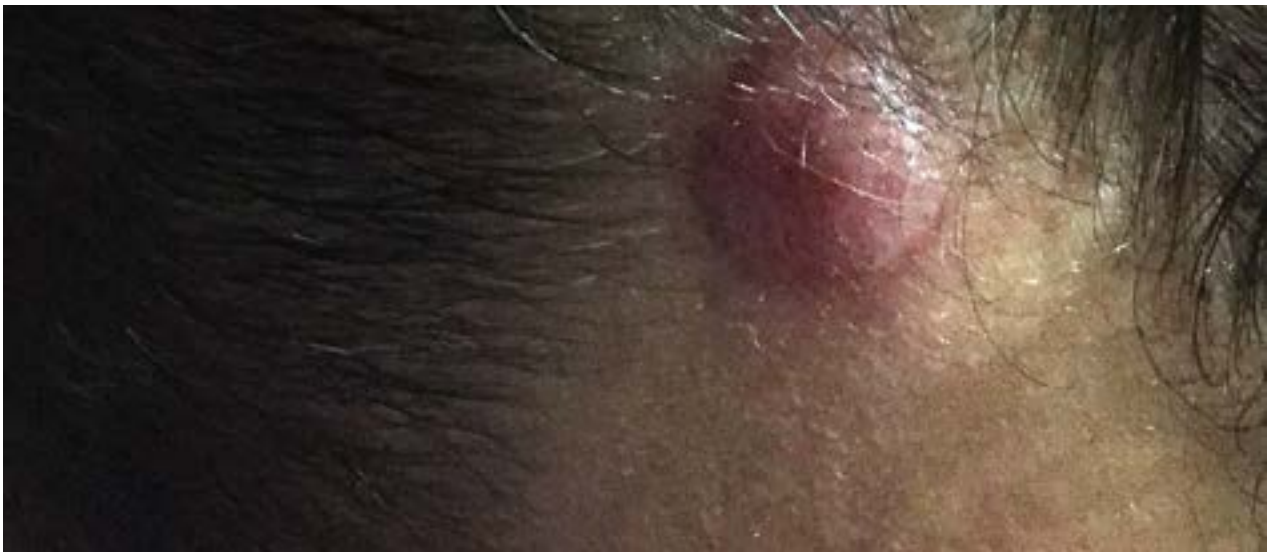

Figure 1. Solitary violaceous nodule, 2.5 cm in diameter, on the frontal region of the scalp

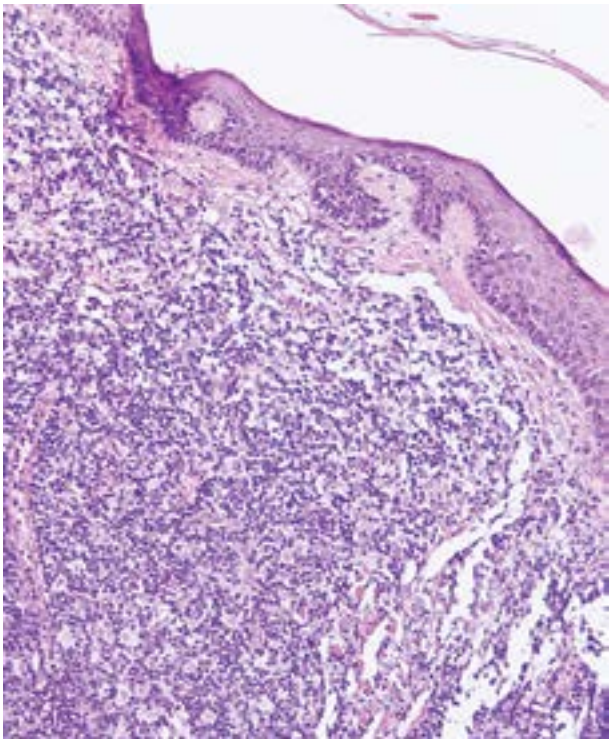

Figure 2. A diffuse lymphocytic infiltration containing small- and medium-sized cells with oval and cut-in nuclei, small nucleoli with moderately extensive transparent cytoplasm. The infiltrate involves the entire dermal thickness, with extension into the hypodermis (hematoxylin and eosin, x 100).

Complete and differential blood cell count, sedimentation rate, glucose, urea, serum creatinine, total proteins, albumins, uric acid, total bilirubin, electrolytes, iron, liver enzymes and C-reactive protein were within physiological limits. The analysis of T-cell clonality from blood sample using polymerase chain reaction (PCR) for the T-cell receptor gamma (TCR-G) gene showed polyclonal rearrangement. There were no signs of central lymphonodopathy or systemic involvement on chest, abdominal and pelvic multislice computed tomography. Peripheral lymph node ultrasound revealed bilaterally enlarged jugulodigastric lymph nodes, measuring 29 x 11 mm and 18 x 11 mm, with features of chronic inflammation. Biopsy of these nodes was performed by a maxillofacial surgeon, and histopathological analysis revealed diffuse reactive lymphadenopathy with no presence of neoplastic cells, neither morphologically or immunohistochemically.

Based on the clinical features, histopathological analysis with immunohistochemistry, laboratory and radiological findings, as well as peripheral blood clonality analysis, a diagnosis of primary cutaneous CD4-positive small/medium pleomorphic T-cell lymphoma, without systemic involvement, was confirmed. No additional diagnostic procedures, including bone marrow biopsy, or any additional treatment were indicated at this point. Follow-up examinations were scheduled every three months, with repeated laboratory tests and ultrasonography.

Discussion

The concept of primary cutaneous CD4+ small/medium T-cell lymphoma began in the early 1990s, when the updated Kiel classification system was applied to primary cutaneous T-cell lymphomas that did not meet criteria for mycosis fungoides or Sezary syndrome. These early studies established that lymphoid infiltrates with predominantly small, pleomorphic T-cells had a more favorable prognosis than those with predominantly large, pleomorphic T-cells, so eventually those cases were grouped together as a single clinicopathologic entity. Because of the association of some CD8+ cases with a significantly worse prognosis, CD8+ cases were excluded, and PCSM-TCL became a provisional lymphoma in the current WHO-EORTC classification system (9).

The largest study was conducted in 2009, by a Research Unit of Dermatopathology, Department of Dermatology, Medical University of Graz. It included 136 patients (male to female ratio 1:1; average age: 53 years, range: 3 - 90 years) with cutaneous lesions that could be classified as small- to medium-sized pleomorphic T-cell lymphomas according to current diagnostic criteria, and its results lead to two major conclusions. Firstly, the disagreement between the indolent clinical course and the worrying histopathologic features poses difficulties in classifying these cases as benign or malignant, and it may be better to refer to them with a descriptive term such as "cutaneous nodular proliferation of pleomorphic T-lymphocytes of undetermined significance", rather than forcing them into one or the other category. Secondly, this study supported the previously published data about nonaggressive therapeutic strategy, particularly in patients presenting with solitary lesions (10).

As mentioned before, PCSM-TCL was included as a provisional entity in the new WHO-EORTC classification for cutaneous lymphomas, and it accounts for 2 ~ 3% of all cutaneous lymphomas (1 – 5). This classification of PCSM-TCL is restricted to the cases with predominance of the small/medium-sized

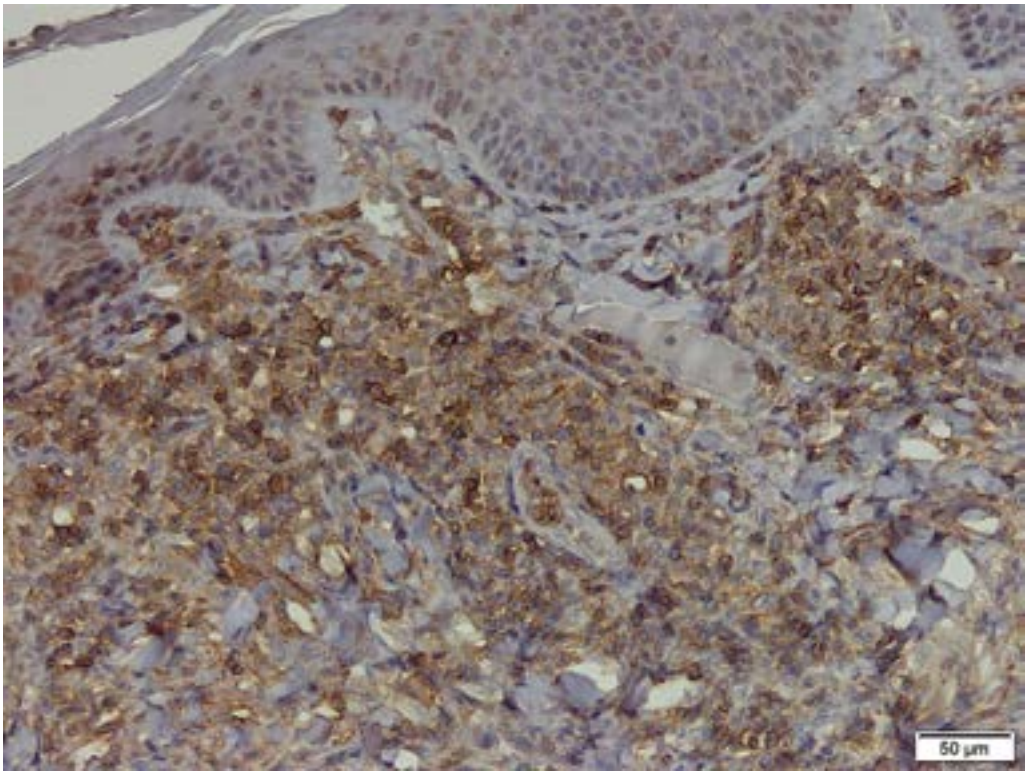

Figure 3a. Tumor immunohistochemistry, CD43 positive cells in the infiltrate (x20)

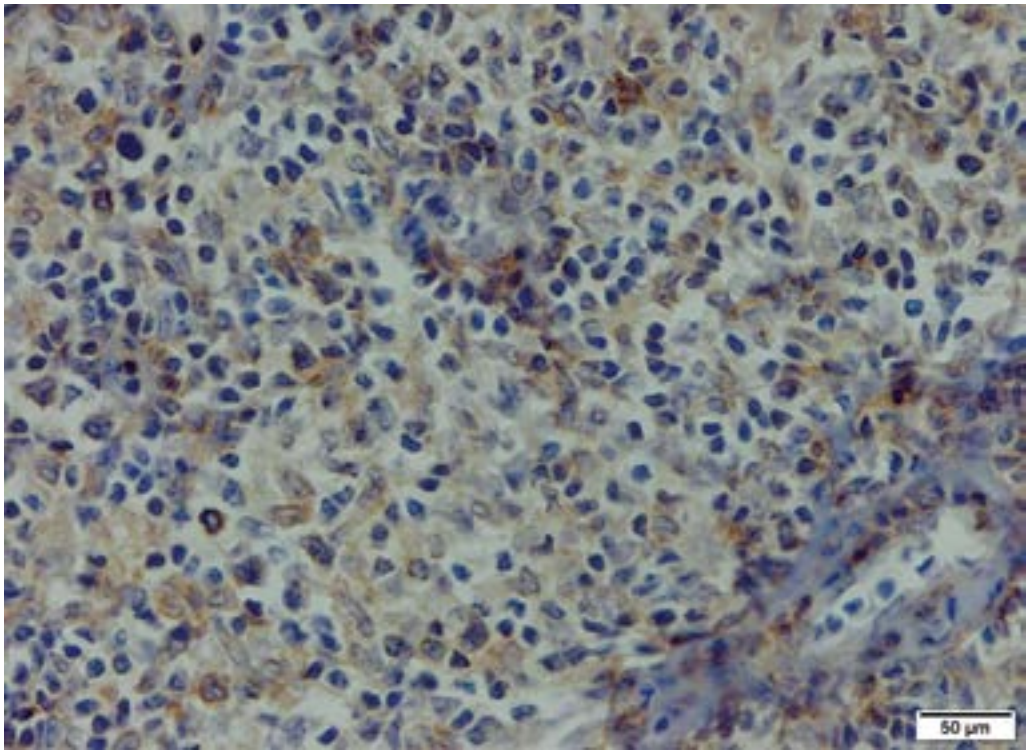

Figure 3b. Tumor immunohistochemistry, CD4 positive small to medium-sized tumor cells in lymphoid tumor infiltrate (x40)

pleomorphic CD4-positive T-cell phenotype, without features of MF (1 – 5). In our case, the patient met restrictive criteria for classification as a PCSM-TCL.

Single lesions were the most common clinical presentations in the majority of reported cases (10, 11, 12). They are mostly located on the head and neck, upper extremities or trunk. They range in size from 1 to 2.5 cm in diameter (12). Multifocal lesions have been less commonly described (10, 13 – 15). Although patients' age ranges from 3 to 90 years, the median age at the onset of the PCSM-TCL was reported to be 53 years (10). Our patient was 30 years old at the disease onset and he presented with one solitary lesion on the scalp that was 2.5 cm in diameter.

Histologically, PCSM-TCL is characterized by a dense infiltration of small/medium sized pleomorphic T-cells (12 – 15). There is no evident epidermotropism and the infiltrate involves the entire dermal thickness, often with nodular extension into the hypodermis. Variable numbers of scattered large lymphoid cells are present, comprising less than 30% of the infiltrate (12). In our case, a diffuse lymphocyte infiltration, containing small and medium-sized cells with oval and cut-in nuclei were found throughout the whole dermis and focally in hypodermis. Also, epidermotropism was present focally and there were rare large lymphoid cells in less than 20% of lymphoid population, which again proves the histological heterogeneity of these lymphomas.

Using immunohistochemical staining, the majority of the reported cases were CD3, CD4 positive and CD8, CD30 negative (1, 5, 12 – 14). Nevertheless, many studies have also reported tumors that were CD8 positive or even CD4 negative (1, 5, 10, 13, 15). Moreover, many PCSM-TCL cases have shown a rich infiltrate of reactive B cells (14). Our patient belongs to the majority of reported cases so far, with immunohistochemically CD3, CD4 positive, and CD8, CD30 negative.

PCSM-TCL has a favorable prognosis with a 5-year survival rate being approximately 60~80% (1 – 4). The median survival was significantly longer in patients with localized lesion than in patients with multifocal skin lesions (5, 16). Moreover, indolent clinical behavior was associated with stable small lesions (<3 cm), low proliferative activity and an intense CD8 positive lymphocyte infiltration, whereas an aggressive course was associated with rapidly evolving large skin lesions (>5 cm), high levels of proliferation markers and rare CD8 lymphocytes (15).

The optimal treatment for PCSM-TCL is yet to be defined (4, 8). Cases of localized disease are usually treated with surgical excision or local radiation therapy, whereas more aggressive treatments, such as chemotherapy, are not required (1, 10, 12, 17). However, careful monitoring with regular follow-up visits is recommended (10). In patients with more generalized skin lesions or those who are unresponsive to topical therapy, multi-agent chemotherapy that includes cyclophosphamide may be effective (4, 5). During the short follow-up of our patient, no disease relapse was evident, but careful monitoring is planned.

In conclusion, PCSM-TCL represents a rare entity which should be acknowledged as a diagnostic category separate from other primary cutaneous T-cell lymphomas. In patients with solitary lesions limited to the skin, indolent clinical course can be expected. Given the fact that precise clinicopathologic features of PCSM-TCL are not well established, further studies are needed to define the precise diagnosis and optimal treatment. Dermatologists and pathologists should be aware of this entity in order to avoid unnecessary aggressive treatments, especially in cases like ours, where the lesion was localized.

Abbreviations

PCSM-TCL - Primary cutaneous CD4-positive small/medium pleomorphic T-cell lymphoma
WHO-EORTC - World Health Organization - European Organization for Research and Treatment of Cancer
MF - Mycosis fungoides
PCR - Polymerase Chain Reaction
TCRG - T-cell receptor gamma

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Primarni kutani pleomorfni T-ćelijski limfom malih i srednjih CD4 pozitivnih ćelija – prikaz slučaja

Sažetak

Uvod. Primarni kutani pleomorfni T-ćelijski limfom malih i srednjih CD4+ ćelija privremeni je entitet u važećoj klasifikaciji Svetske zdravstvene organizacije i Evropske organizacije za istraživanje i lečenje kancera iz 2005. godine. To je redak entitet i, u većini slučajeva, ima povoljan klinički tok i prognozu. Primarni kutani pleomorfni T-ćelijski limfom malih i srednjih CD4+ ćelija (PKTL-MSĆ) definiše se kao neoplastična proliferacija malih i srednje velikih, pleomorfnih T-limfocita u koži bez kliničke prezentacije infiltrovanih plakova karakterističnih za *mycosis fungoides*. Klinički se manifestuje kao solitarni tumor ili plak na glavi, vratu, trupu ili gornjim ekstremitetima i smatra se da ima indolentno kliničko ponašanje. Histološki, karakteriše ga gusta infiltracija malih i srednjih pleomorfnih T-ćelija; zahvata celu debljinu derma, sa čestim nodularnim produžecima u hipodemis. Imunohistohemijskim bojenjem, većina slučajeva je CD3 i CD4 pozitivna, a CD8 i CD30 negativna. Međutim, uzevši u obzir raritet i heterogenost ovih limfoma, precizne kliničke i histopatološke karakteristike još uvek nisu jasno definisane.

Prikaz slučaja. U radu je opisan slučaj tridesetogodišnjeg muškarca sa solitarnim tumorom na koži poglavine čije histopatološke karakteristike odgovaraju primarnom kutanom pleomorfnom T-ćelijskom limfomu malih i srednjih CD4+ ćelija. Kratkotrajno praćenje pacijenta pokazalo je da, nakon hiruške ekcizije solitarnog tumora, nema znakova relapsa bolesti. Nisu korišćene dodatne metode lečenja do danas, ali su neophodne redovne tromesečne kontrole.

Zaključak. Dermatolozi i patolozi bi trebalo da imaju u vidu ovaj entitet da bi se izbegle nepotrebne agresivne metode lečenja. Redovno praćenje pacijenata sa ovim limfomom neophodno je radi rane detekcije relapsa bolesti.

Ključne reči

T-ćelijski kutani limfom; Kožne neoplazme; CD4 pozitivni T-limfociti; Pleomorfni kutani T-ćelijski limfom; Ishod terapije; Prikazi slučajeva