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Case report

Primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder: a case report and literature review

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Abstract

Primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder (PCSM-LPD) is characterized by a slow-growing and asymptomatic solitary plaque or tumor, usually involving the head, neck, or upper extremities. The diagnosis is established based on clinical presentation, histopathological features including pleomorphic morphology and CD4-positive immunophenotype of neoplastic T lymphocytes, and molecular analysis showing clonally rearranged T-cell receptor (TCR) genes. Plaques typical of mycosis fungoides are essentially absent. Treatment options include surgical excision, radiotherapy, and topical or intralesional steroids. Because the disease is indolent, aggressive diagnostic tests and systemic treatments are not recommended. We present a case of PCSM-LPD in a previously healthy young man that spontaneously regressed after a biopsy.

Keywords: primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder, primary cutaneous lymphoma, T-cell lymphoma, lymphoproliferative disorder, spontaneous regression

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Introduction

Primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder (PCSM-LPD) is a fairly recently recognized but nonetheless quite frequent entity (second only to mycosis fungoides among T-cell proliferative disorders in the skin) (1). It usually occurs in adults as a solitary nodule or plaque, most commonly in the head and neck region, but it may also appear on the trunk or extremities (1). Histologically, it is defined by the predominance of small to medium-sized CD4-positive pleomorphic T cells without prior or concurrent patches and plaques typical of mycosis fungoides (1). In the 2005 World Health Organization–European Organization for Research and Treatment of Cancer (WHO-EORTC) classification, it was classified as primary cutaneous CD4-positive small/medium pleomorphic T-cell lymphoma. It was considered a rare, poorly defined disease with uncertain malignant potential (2). In the revised WHO-EORTC classification of 2018, the term "lymphoma" was changed to "lymphoproliferative disorder" due to its benign course (3). PCSM-LPD is now considered a relatively common cutaneous T-cell lymphoma (CTCL) with a favorable prognosis and no reported risk of secondary lymphomas (4). Here, we present a case of spontaneous regression of PCSM-LPD after a biopsy in a young man.

Case report

A 22-year-old man presented with a solitary skin lesion on the right upper arm that had been present for 2 months. The family history of skin disease was negative. Physical examination revealed a well-demarcated erythematous plaque with a diameter of 23 mm on the proximal third of the lateral aspect of the right upper arm (Fig. 1a). The patient had no other skin lesions or systemic symptoms.

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The biopsy revealed an unremarkable epidermis and a dense, diffuse, mixed-cell inflammatory infiltrate within the entire thickness of the dermis. The infiltrate was composed predominantly of small to medium-sized $CD3^+$ T lymphocytes, exhibiting somewhat pleomorphic cell morphology (Figs. 2a, b). In the background were less numerous $CD20^+$ B lymphocytes, histiocytes, and eosinophilic granulocytes.

The pleomorphic T lymphocytes showed $CD3^+$ (Fig. 2c), $CD4^+$ (Fig. 2d), $CD8^-$, and $CD30^-$ immunophenotypes and were predominantly positive for CD2, CD5, and CD7, indicating only a slight down-regulation of CD2 and CD7 expression. Programmed cell death protein 1 (PD1) was expressed by a subset of cells (Fig. 2e), focally arranged in small clusters. The Ki-67 proliferation index was low (approximately 5%). Molecular genetic analysis revealed monoclonal rearrangement in the *TcR-gamma* gene. B-lymphocytes were polyclonal.

Laboratory tests, including a complete blood cell count with the differential, liver function tests, lactate dehydrogenase level, and serum protein electrophoresis, were all within the normal limits. Additional immunophenotyping of a peripheral blood sample was performed and showed no abnormalities. Computed tomography (CT) of the thorax and abdomen ruled out the involvement of other organs. Based on the clinical presentation, histomorphological features, and the immunophenotype of the lymphocytic infiltrate as well as monoclonality of T lymphocytes, a diagnosis of PCSM-LPD was made.

About 1 month after the biopsy, partial regression of the lesion was observed (Fig. 1b). After 3 months it had completely disappeared (Fig. 1c). At the time of writing this manuscript, the patient is being monitored every three months and remains in clinical remission.

Discussion

PCSM-LPD is the second most common CTCL with indolent behavior. It accounts for approximately 6% of all CTCLs, although the incidence of the disease is probably underestimated (3, 5). PCSM-LPD shows no sex predilection (6). The disease usually begins later in life, with a median age of 59 years, but there are also cases reported in children and even infants (4, 7).

The etiopathogenesis of PCSM-LPD is unclear. There are reports of PCSM-LPD occurring at the site of a melanoma excision scar (8) and of PCSM-LPD coexisting with myelodysplastic syndrome and transforming into chronic myelomonocytic leukemia (9). It can also be drug-induced by methotrexate-etanercept combination (10), vemurafenib (11), interleukin-2 therapy for metastatic melanoma (12), and immunosuppressive therapy (cyclosporine, prednisolone, and azathioprine) after heart transplantation (13). In our case, the patient was previously a healthy young man and was not taking any medication.

Clinically, PCSM-LPD can present with a wide variety of symptoms and signs. Most commonly, it presents as a slow-growing erythematous or violaceous papule, plaque, nodule, or tumor affecting the head, neck, upper extremities, or upper trunk (14). Most lesions are asymptomatic and are rarely associated with pain, pruritus, or ulceration (6). Approximately 7% of patients have multifocal lesions (4).

The diagnosis of PCSM-LPD is based on clinical presentation and histomorphological and immunohistochemical features. Histology usually reveals a dense nodular or diffuse infiltrate of small or medium-sized pleomorphic T lymphocytes with mild to moderate atypia and a low proliferation rate (Ki-67 index < 20%) (3). In addition to T lymphocytes, B lymphocytes, plasma cells, histiocytes, and eosinophils may also be present. Large pleomorphic cells may be present but account for less than 30% of the infiltrate. The infiltrate involves the entire dermis and can extend to the subcutis (3). In most cases, epidermotropism is not present but may occur focally, as was the case in our patient (15). T lymphocytes have a $CD3^+$, $CD4^+$, $CD8^-$, and $CD30^-$ immunophenotype. Partial or complete loss of CD7 and rarely CD5 is possible (16). The T lymphocytes express follicular helper T-cell markers, including PD-1 (CD279), B-cell lymphoma 6 (BCL6), and chemokine (C-X-C motif) ligand 13 (CXCL13) (17), but they lack the expression of chemokine receptor CXCR5 (18). In addition, positive nuclear factor of activated T-cells, cytoplasmic 1 (NFATc1) nuclear staining and clonal rearrangement of T-cell receptor genes are highly characteristic of PCSM-LPD (19, 20).

Basic blood tests should be performed in all patients. In some patients, additional staging with CT scans or positron emission tomography scans, bone marrow biopsy, and immunophenotyping of a peripheral blood sample is performed. However, this is not necessary in all patients, and the extent of staging

investigations should be individualized based on the patient's blood test and physical examination (16, 19). The patient presented had normal laboratory results, normal results of immunophenotyping of the peripheral blood sample, and no abnormalities on the CT scans.

Basal cell carcinoma, adnexal tumors and cysts, and Jessner lymphocytic infiltration may clinically resemble PCSM-LPD (4). Pseudolymphoma, primary cutaneous acral $CD8^+$ T-cell lymphoma, peripheral T-cell lymphoma not otherwise specified (PTCL, NOS), angioimmunoblastic T-cell lymphoma, primary cutaneous follicle center lymphoma, primary cutaneous marginal zone lymphoma, and tumoral stage of mycosis fungoides should also be considered in the differential diagnosis (18, 20-23).

There is no consensus on the optimal treatment for PCSM-LPD. The most commonly used treatment options are surgical excision, radiotherapy, and topical or intralesional steroids. For multiple or recurrent lesions, phototherapy and topical steroids are recommended (15). Oral treatment with doxycycline is also reported to be a safe and effective treatment option (24–26). In the past, aggressive systemic treatments such as chemotherapy were also used. Nowadays, such aggressive systemic treatments are no longer recommended because their risk outweighs the potential benefits (4, 27). In our case, the skin lesion regressed spontaneously after biopsy and the patient required no further treatment. Beltzung et al. reported that complete regression after biopsy occurred in 16.7% of patients and partial regression in 8.3% (28). The exact mechanism of the spontaneous regression is not known. The activation and enhancement of the host immune response, especially the T cell–mediated response, is thought to be involved (29).

A recent systematic review reported that 95.5% of patients recovered completely without relapse, whereas the remaining 4.5% of patients showed partial improvement after treatment. In addition, a 5-year survival rate of 100% was reported without systemic involvement (4). In the case of generalized disease, rapid progression, or resistance to treatment, an alternative diagnosis of peripheral T-cell lymphoma, unspecified, should be considered (3, 6). Histopathology findings associated with unfavorable prognosis are high proliferative index, low CD40 expression, and infiltrates lacking B-cells and CD8-positive T cells (6). There is no consensus on the duration of follow-up for patients with PCSM-LPD. Because the prognosis is excellent and relapses are rare, a follow-up of 2 years is recommended (30, 31).

Conclusions

Currently, PCSM-LPD remains a poorly understood disease with no clear diagnostic or treatment guidelines. In the future, accurate diagnostic criteria and optimal management should be defined to avoid misdiagnosis, potentially unnecessary staging, and unnecessary aggressive treatment. Our case report emphasizes that clinical observation after biopsy could be an initial treatment strategy for PCSM-LPD because spontaneous regression after biopsy is possible.

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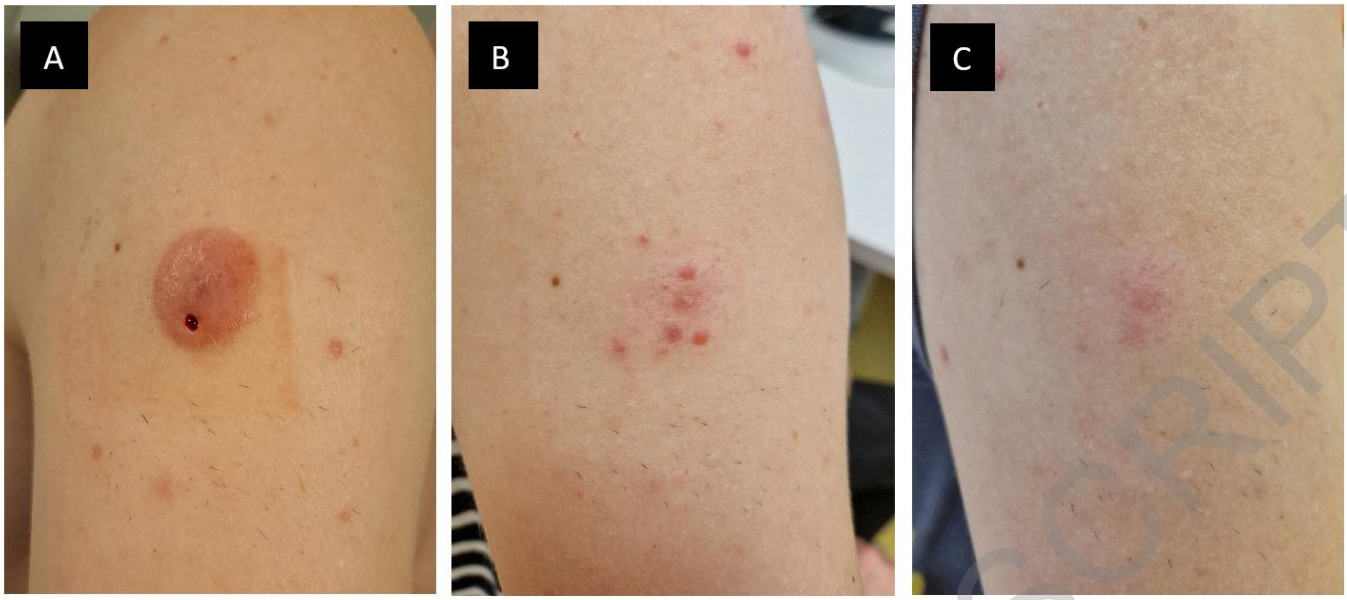

Figure 1. (A) Well-defined erythematous plaque on the upper extremity, (B) partial regression of the lesion, (C) complete regression of the lesion, with two pink scars corresponding to the site of biopsy.

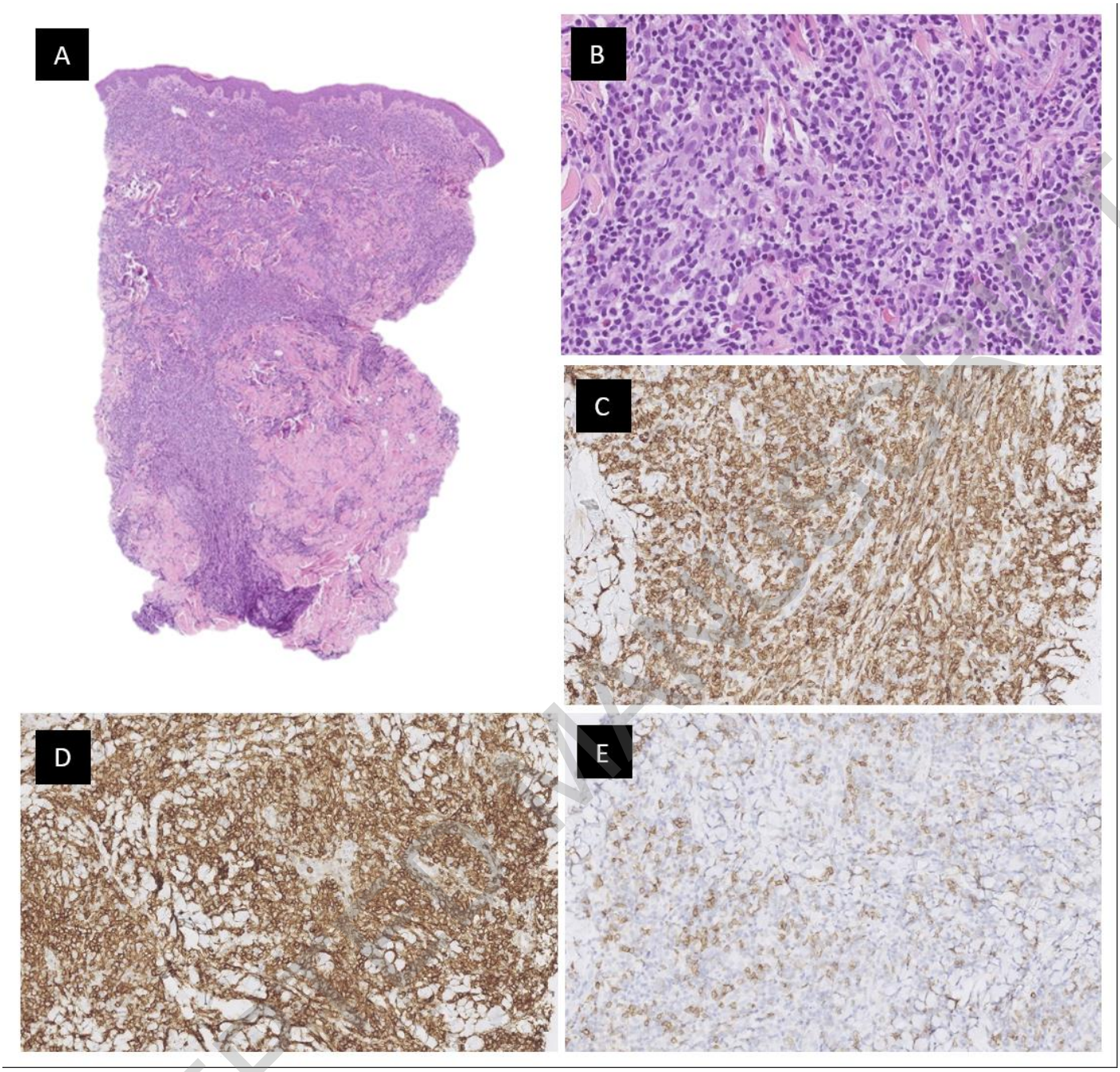

Figure 2. (A) Scanning magnification of a dense intradermal infiltrate (hematoxylin&eosin, 2.5×), which is composed predominantly of (B) small to medium-sized pleomorphic T cells with a mixed cellular background (hematoxylin&eosin, 40×); neoplastic T cells express (C) CD3 (20×), (D) CD4 (20×), and (E) programmed cell death protein 1 (PD1) (20×).