

Case Report

Cutaneous pseudolymphoma: a case report with an immunohistochemical study

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Abstract: Cutaneous pseudolymphoma (C-PSL) is defined as reactive polyclonal benign lymphoproliferative process predominantly composed of either B-cells or T-cells, localized or disseminated. It heals spontaneously after cessation of the causative factor (e.g. drugs) or after non-aggressive treatment. The author herein presents a case of C-PSL with an immunohistochemical study. A 78-year-old man consulted our hospital because of slightly itching skin swelling on the arm. He denied insect bite and traumatic injury. His usual intake drugs were drugs of hypertension, hyperlipidemia, diabetes mellitus, and emotional disorders. Physical examination showed mildly erosive swelling of the arm. The lesion measured 1 x 1 x 0.2 cm. Biopsy of the lesion was taken, and it revealed excessive proliferation of small lymphoid cells. The lymphoid cells lacked apparent atypical features and appeared matures. Lymphoblastic cells with nucleoli were scattered. Nodular structures were also seen in the lower dermis. Immunohistochemically, the lymphoid cells were positive for vimentin, CD3, CD4, CD5, CD8, CD10, CD15, CD20, CD23, CD30, CD43, CD38, CD138, CD45RO, CD79 α , bcl-2, bcl-6, κ -chain, λ -chain, and Ki-67 (labeling index=7%). No light chain restriction is seen. The lymphoblastic cells were positively labeled for CD15 and CD30. Plasma cells positive for CD38, CK79 α and CD138 were seen in a significant amounts. They were negative for cytokeratin (CK) CAM5.2, CKAE1/3, CK-34BE12, CK5/6, CK7, CK8, CK18, CK19, CK20, EMA, CEA, CD56, CD57, p53, KIT, PDGFRA, and cyclin D1. Because the constituent cells were both B-cells including plasm cells and T-cells, no light-chain restriction was seen, and no histological atypia was seen, a diagnosis of cutaneous pseudolymphoma was made. The low Ki-67 labeling and negative p53 also suggested the diagnosis. The lesion slightly reduced in size (from 1 cm to 0.7 cm), the causative agent was still unknown 11 months after the biopsy.

Keywords: Cutaneous pseudolymphoma, CD, low grade lymphoid neoplasm, immunohistochemistry

Introduction

Cutaneous pseudolymphoma (C-PSL), also called lymphoid infiltrates of the skin mimicking lymphoma, is defined as reactive polyclonal benign lymphoproliferative process predominantly composed of either B-cells or T-cells, localized or disseminated. It heals spontaneously after cessation of the causative factor (e.g. drugs) or after non-aggressive treatment. It has many synonyms such as lymphocytoma cutis and lymphadenosis benigna cutis. According to the dominant patterns, PSL were classified into B-cell PSL (B-PSL) and T-cell PSL (T-PSL). However, there were no significant difference between B-PSL and T-PSL. C-PSL affects all age group with the predilection of Borrelia-induced B-PSL in children and young

adults, while drug induced T-PSL more frequently are seen in adults. Even though Borrelia-induced PSL may be precursor for B-cell neoplasms of the skin, in genera, C-PSLs are self-regressing and do not affect survival. The etiology may involve microbial, physical, chemical, Borrelia burgdorferi infection, insect bite, tattoo, and drugs [1].

Clinically, several variants of C-PSL exist. They include PSL with predominant T-cell infiltrates (T-PSL), PSL with predominant B-cell infiltrates (B-PSL) lymphocytic infiltration (idiopathic or drug induced), palpable migratory arciform erythema, lymphomatoid contact dermatitis, actinic reticuloid, persistent nodular arthropod-bite reactions, and inflammatory molluscum contagiosum. However, these are subclassifications

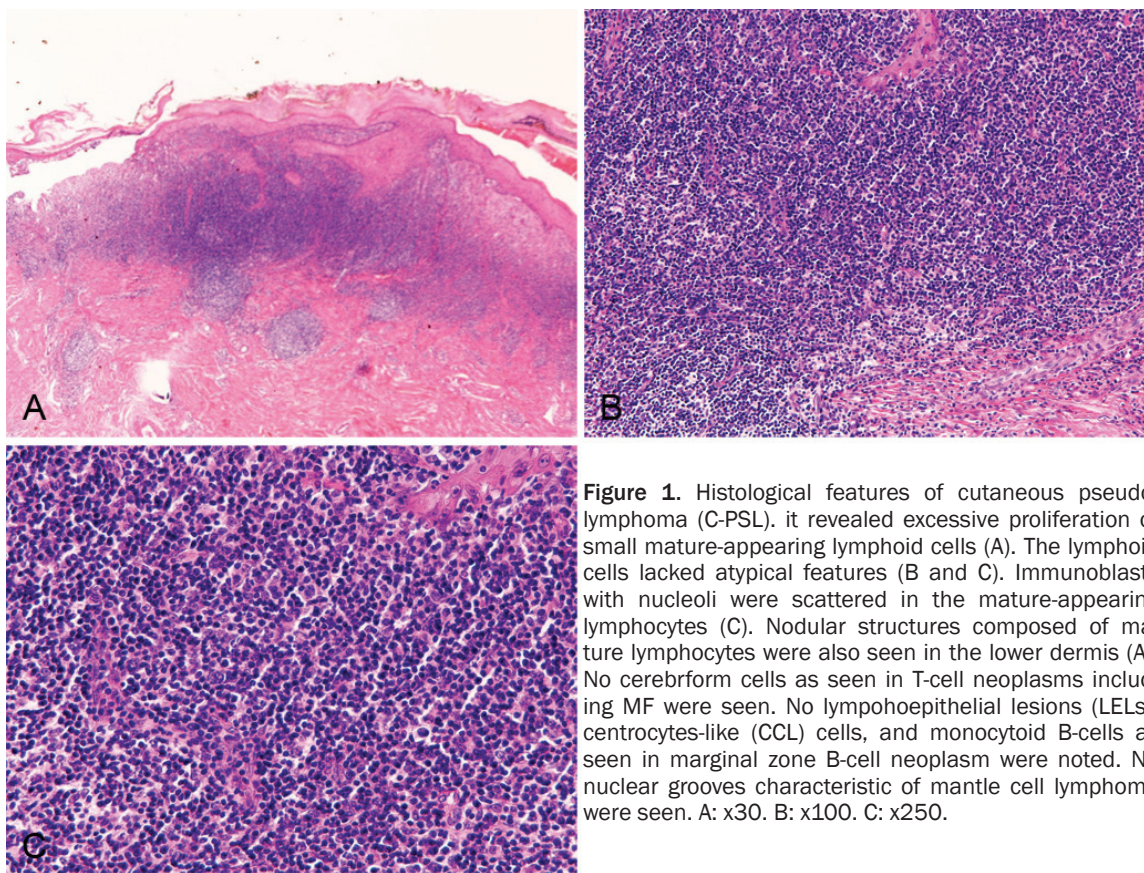


Figure 1. Histological features of cutaneous pseudolymphoma (C-PSL). it revealed excessive proliferation of small mature-appearing lymphoid cells (A). The lymphoid cells lacked atypical features (B and C). Immunoblasts with nucleoli were scattered in the mature-appearing lymphocytes (C). Nodular structures composed of mature lymphocytes were also seen in the lower dermis (A). No cerebriform cells as seen in T-cell neoplasms including MF were seen. No lymphoepithelial lesions (LELs), centrocytes-like (CCL) cells, and monocytoid B-cells as seen in marginal zone B-cell neoplasm were noted. No nuclear grooves characteristic of mantle cell lymphoma were seen. A: x30. B: x100. C: x250.

based on only clinical features. All these variants show the same histopathologies.

Pathologically, C-PSL is classified into ordinary PSL (O-PSL), PSL with predominant B-cell infiltrates (B-PSL), PSL with predominant T-cell infiltrates (T-PSL), and PSL with mixed and unclassified infiltrates.

In the author's lymphoma experience [2-34], the author have experienced several C-PSL, but have not published them because the author had been once concentrated on hepatobiliary pathology. Herein reported is a very interesting case of ordinary C-PSL with main points of differential pathological diagnosis.

Case report

A 78-year-old man consulted our hospital because of slightly itching skin swelling on the arm. He denied insect bite and traumatic injury. His usual in taking drugs were those for hypertension, hyperlipidemia, diabetes mellitus, and emotional disorders. Off course, the patient did not suffered from *Borrelia burgdorferi* infection.

A blood laboratory data showed no significant changes. The patient was immunocompetent and free from HIV, HBV, HCV, HTLV. No causative agents such as microbial, physical, chemical, insect bite, and tattoo were recognized. Physical examination showed mildly erosive swelling of the inner side of the arm. The lesion measured 1 x 1 x 0.2 cm. Relatively large biopsy was taken from the lesion, and it revealed excessive proliferation of small lymphoid cells (**Figure 1A**). The lymphoid cells lacked apparent atypia (**Figure 1B** and **1C**). Immunoblasts with nucleoli were scattered in the mature-appearing lymphocytes (**Figure 1C**). Nodular structures composed of mature lymphocytes were also seen in the lower dermis (**Figure 1A**). The epidermis and follicles showed moderate to mild atypical features such as nuclear atypia and cancer pearl formations. No cerebriform cells as seen in T-cell neoplasms including MF were seen. No lymphoepithelial lesions (LELs), centrocytes-like (CCL) cells, and monocytoid B-cells as seen in marginal zone B-cell neoplasm were noted. No nuclear grooves characteristic of mantle cell lymphoma were seen.

Cutaneous pseudolymphoma

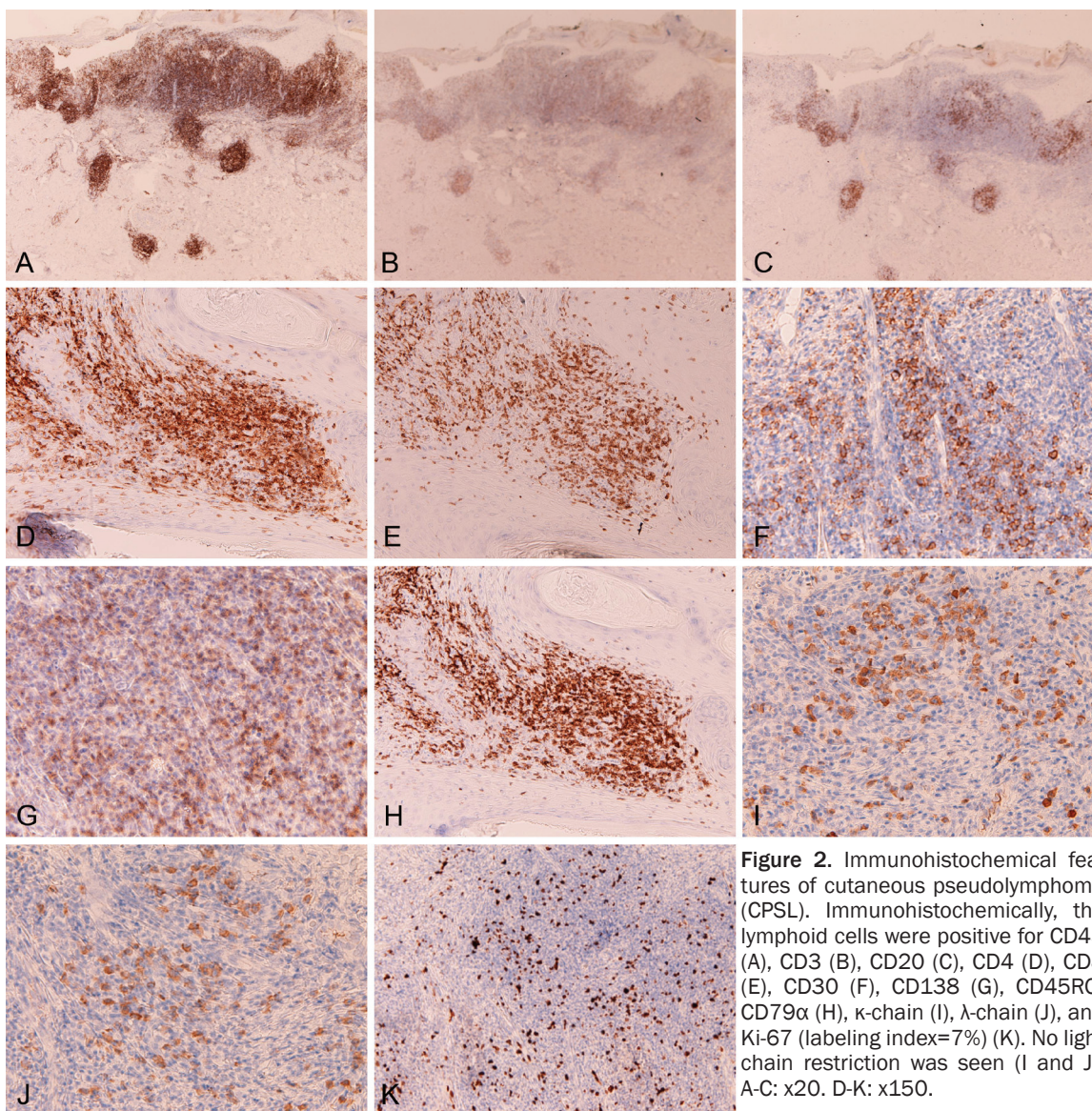


Figure 2. Immunohistochemical features of cutaneous pseudolymphoma (CPSL). Immunohistochemically, the lymphoid cells were positive for CD45 (A), CD3 (B), CD20 (C), CD4 (D), CD8 (E), CD30 (F), CD138 (G), CD45RO, CD79 α (H), κ -chain (I), λ -chain (J), and Ki-67 (labeling index=7%) (K). No light chain restriction was seen (I and J). A-C: x20. D-K: x150.

An immunohistochemical study was performed with the use of Dako's Envision methods as previously reported [35-58]. Immunohistochemically, the lymphoid cells were positive for vimentin, CD45 (**Figure 2A**), CD3 (**Figure 2B**), CD20 (**Figure 2C**), CD4 (**Figure 2D**), CD5, CD8 (**Figure 2E**), CD10, CD15, CD23, CD30 (**Figure 2F**), CD43, CD38, CD138 (**Figure 2G**), CD45RO, CD79 α (**Figure 2H**), bcl-2, bcl-6, κ -chain (**Figure 2I**), λ -chain (**Figure 2J**), and Ki-67 (labeling index=7%) (**Figure 2K**). No light chain restriction was seen (**Figure 2I** and **2J**). The CD15- and CD30-positive cells corresponded to immunoblastic cells. No nodular lymphoid aggregates were positive for bcl-2 and bcl-6. The tumor cells were negative for cytokeratin (CK) CAM5.2,

CKAE1/3, CK34BE12, CK5/6, CK7, CK8, CK18, CK19, CK20, EMA, CEA, CD56, CD57, p53, and cyclin D1.

Because the constituent cells were both B-cells and T-cells, no light-chain restriction was seen, and no histological atypical features were seen, the pathological diagnosis of C-PSL was made. The low Ki-67 labeling (7%) and negative p53 also suggested that diagnosis.

The lesion slightly reduced in size (from 1 cm to 0.7 cm), the causative agent was still unknown 11 months after the biopsy. The whole body was examined for nodal lymphoma; the whole body CT, MRI, PET, sonography, endoscopy and

other methods revealed no tumors and no lymphadenopathy.

Discussion

C-PSL is not uncommon conditions. To date about 200 cases have been reported in the literatures [59, 60]. In the present case, the lymphoid infiltrates was composed of both B-cells positive for CD20, CD23, CD10, CD79 α , κ -chain, λ -chain, bcl-2, and bcl-6 and T-cells positive for CD3, CD4, CD5, CD8, CD43, and CD45RO. No NK-cells positive for CD56 and CD57 were seen. Plasma cells positive for CD38, CD79 α , and CD138 were also seen in a significant number. That is, the current tumor is composed of B-cell, T-cell, and plasma cells (B-cell derivatives). No light chain restriction was seen. Histologically, the infiltrates composed of mature lymphocytes with scattered immunoblastic cells positive for CD30 and CD15. The KI-67 labeling was low (labeling index=7%), and p53 was negative. The former represents that the cell proliferation is very low and the latter demonstrates that no p53 mutations are present. In addition, the tumor is slightly reduced in size 11 months after the biopsy. The whole body examination identified no tumors and no lymphadenopathy. All of these findings suggest that the current tumor is C-PSL, and fulfill the WHO criteria of C-PSL [1].

Histologically, C-PSL was classified into ordinary PSL (O-PSL), B-PSL, T-PSL, PSL with mixed and unclassified infiltrates. The current tumor is composed of almost equal amount of B-cells including plasma cells and T-cells. Thus, the present tumor is not B-PSL and T-PSL. The current tumor corresponds to O-PSL or mixed PSL.

Clinically, C-PSL may show several variants in addition to ordinary C-PSL [1]. They include PSL with predominant T-cell infiltrates (T-PSL), PSL with predominant B-cell infiltrates (B-PSL), lymphocytic infiltration (idiopathic or drug induced), palpable migratory arciform erythema, lymphomatoid contact dermatitis, actinic reticuloid, persistent nodular arthropod-bite reactions, and inflammatory molluscum contagiosum. However, these are subclassifications based on only clinical features. All these variants show the same histopathologies. The current case showed no features of these clinical variants,

and the present case clinically belongs to ordinary C-PSL.

The etiology of the present C-PSL is unclear. The patient did not suffer from *Borrelia burgdorferi* infection. The patient denied insect bite, tattoo, and injection of chemicals. The patient did not suffer from microbial disease, and not from physical agents. The remaining are drugs. The patient was suffered from hypertension, hyperlipidemia, diabetes mellitus, and emotional disorders, and the patient was taking many drugs for these disorders. Identification of the causative agent (drugs) in the present C-PSL was difficult, because of lack of drug injured the patient. However, the identification of the causative agent is necessary to completely cure the patient.

The C-PSL should be differentiated from true malignant lymphoma, in particular small cell T cell neoplasms including mycosis fungoides (MF) and low grade B-cell neoplasm including small lymphocytic lymphoma (SLL)/CML, lymphoplasmacytic lymphoma (LPL), follicular lymphoma (FL), extranodal marginal zone B-cell neoplasm (MALT lymphoma) and mantle cell lymphoma (MCL).

The present case is composed of B- cells and T-cells. Therefore, low grade T-cell neoplasms (MF) are unlikely, because these T-cell neoplasms are usually composed of T cells and their nuclei are cerebriform, both of which were not seen in the present case. T-cell-rich B cell lymphoma is unlikely because the B cells did not so much atypia as seen in T-cell rich B-cell lymphoma.

Low grade B-cell lymphoma can contain reactive T-cells. Therefore, the current tumor should be differentiated from these B-cell neoplasms including SLL, LPL, FL, MALT lymphoma, and MCL. The present tumor is difficult to differentiate from SLL, in which small B-cells proliferate neoplastically. No T-cell elements were seen basically in SLL, thus the current tumor seem not to be SLL because the current tumor contained significant number of T-cells. The current tumor is not LPL because the current tumor showed T-cell phenotype. In the current tumor, the nodular areas in the lower parts showed bcl-2 and bcl-6 immunoreactivity, thus complicating the distinction of C-PSL and FL. However, in general, FL is free from T-cell element. Only

this point is the differential diagnosis favoring C-PSL. The most worrisome diagnosis is MALT lymphoma. However, in the present case no apparent lymphoepithelial lesions and no apparent centrocytes-like monocyte-like B-cells were seen. Thus, the present tumor is not MALT lymphoma. The present tumor is not MCL because of lack of characteristic nuclear grooves and cyclin D1 immunoreactivity.

A panel of antibodies has been proposed for differential diagnosis of these low-grade B-cell lymphomas [61-66]. The antigens include CD5, CD10, CD23, CD43, and cyclin D1. In SLL, the expression pattern is CD5 -, CD10 -, CD23 +, CD43 +, and cyclin D1 -. In FL, the expression pattern is CD5 -, CD10 +, CD23 -, CD43 -, and cyclinD1 -. In MALT lymphoma, the expression pattern is CD5 -, CD10 -, CD23 -, CD43 +/-, and cyclinD1 -. In MCL, the expression pattern is CD5 +, CD10 +/-, CD23 -, CD43 +/-, and cyclinD1 +. [61-66]. In the present tumor, the expression pattern was CD5 +, CD10 +, CD23 +, CD43 +, cyclin D1 -. Thus, the expression pattern in the current cutaneous tumor does not fit any low grade small cell B-cell lymphomas. The positive CD5 and CD23 in the current case may favor the expression pattern of small lymphocytic lymphoma. However, the author excludes small lymphocytic lymphoma because of above described reasons. The positive expression of CD5 in the present case may suggest mantle cell lymphoma, but the current tumor was negative for cyclin D1. From the overall appearances including HE histology, clinical features, and immunohistochemical findings, the author believes that the present cutaneous tumor is C-PSL.

In the present tumor, both CD4 (helper/inducer) and CD8 (cytotoxic) were positive. This double positivity is extremely rare, and is thought to be associated with immunodeficiency [58, 60-66]. However, the present patient showed normal immunity and free from HIV.

The present CPSL showed atypical features of epidermis. The atypical epithelial features are frequently seen in cutaneous lymphoma. The atypical features are so pronounced in some cases, and they may be diagnosed from well differentiated squamous cell carcinoma. In the present case, the atypical epithelial features are present, but weak. Probably, cytokines released from the lymphoid infiltrates cause epithelial atypical features.

Declaration

The author has no conflict of interest.

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