

CASE REPORT

Primary cutaneous lymphoplasmacytic lymphoma-like B-cell neoplasm with features of acute inflammation and epidermal atypical cells

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ABSTRACT

Primary cutaneous lymphoplasmacytic lymphoma (LPL) is rare. The author herein reports a case of LPL-like B-cell neoplasm with acute inflammation and epidermal cell atypia. A 69-year-old man presented skin ulcer of neck. The lesion appeared granulation tissue with surface fibrin deposition; an inflammatory process was suggested. Peripheral blood data showed no abnormalities, including the segments of leukocytes. No plasmacytosis was seen. No M-proteins, macroglobulins, or cryoglobulins were noted in serum and urine. The clinical diagnosis was non-specific skin ulcer. A wide biopsy was taken. It showed a destructive proliferation of atypical small lymphocytes, atypical plasmacytoid lymphocytes, and atypical plasma cells in dermis and subcutaneous tissue. The biopsy also showed acute inflammatory features; foci of many neutrophils were scattered in neoplastic cells. Some of them showed microabscesses. In addition, foci of atypical squamous cells were seen in the epidermis. Immunohistochemically, the tumor cell showed B-cell lineage. The tumor cells were diffusely positive for vimentin, CD45, CD20, CD79 α , bcl-2, CD38, and CD138. The tumor cells were only focally positive for CD3 and CD45RO. A few tumor cells were positive for CD30, CD56, and CD10. Some of the tumor cells were positive for p53 and Ki-67 antigen (labeling index = 35%). The tumor cells were negative for pancytokeratin AE1/3, pancytokeratin CAM5.2, CD5, CD23, CD43, and cyclinD1. The tumor cells were positive for κ -chain but negative for λ -chain, indicating that the tumor cells have plasmacytic characteristics and that there was a light chain restriction which indicates monoclonal nature of the tumor plasma cells. The tumor cells were negative for Epstein-Barr virus (EBV) associated molecules such as EBV latent membrane protein-1 (LMP-1) and EBV early RNAs (EBER). A pathological diagnosis made by the author was cutaneous LPL-like B-cell malignant tumor. The author thought that this tumor could not be definitely diagnosed a primary cutaneous LPL, because other small-sized B-cell lymphomas with plasmacytoid differentiation could not be excluded. The current tumor was also characterized by acute inflammatory features and epidermal squamous cell atypia suggestive of squamous cell carcinoma. Imaging modalities including CT identified no other tumors and lymphadenopathy in the body. The systemic bones were free of myeloma features. No bone marrow study was performed after the pathological diagnosis. The tumor cured and the patient discharged from the hospital 3 months after the first presentation.

Key Words: Skin, Lymphoplasmacytic lymphoma, Histopathology, Immunohistochemistry

1. INTRODUCTION

Malignant lymphoma of the skin is relatively rare. Lymphoplasmacytic lymphoma (LPL) of the skin is extremely

rare. LPL is defined as a neoplasm of small B lymphocytes, plasmacytoid lymphocytes, and plasma cells, usually involving bone marrow and sometimes lymph nodes and spleen.

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LPL does not fulfill the criteria for any of the other small B-cell lymphoid neoplasms that may also have plasmacytic differentiation. Because the distinction between LPL and one of these other lymphomas, especially some marginal zone B-cell lymphoma (MALT lymphoma), is not always clear-cut, some cases may need to be diagnosed as a small B-cell lymphoma with plasmacytic differentiation and differential diagnosis provided. Although often associated with a paraprotein usually of IgM type, it is not required as a diagnosis. Waldenstrom macroglobulinemia (WM) is found in a significant subset of patients with LPL and WM is defined as LPL with bone marrow involvement and an IgM monoclonal gammopathy of any concentration.^[1] Recent evidence has suggested that LPL may be associated with hepatitis C virus infection and mast cells.^[1]

LPL (previously called immunocytoma) usually involve the bone marrow and lymph nodes. Primary cutaneous LPL is extremely rare; only three case reports and one case series have been performed in the world literature.^[2-5] However, previous cases of LPL of the skin may not true LPL of the current era, because the immunohistochemical and molecular techniques have advanced in recent years and also there had been changing definition, nomenclatures and description of malignant lymphomas including Hodgkin's disease. The most series of skin LPL done by Rijlaarsdam et al,^[5] who examined 26 case of cutaneous immunocytoma (LPL) consisting of 16 cases of primary and 10 cases of secondary immunocytomas, demonstrated that primary cutaneous LPLs (immunocytomas) were a distinct type of cutaneous lymphoma, characterized by (a) the presence of solitary or localized skin lesions (13 of 16 cases); (b) preferential localization on arms and legs (15 of 16 cases); (c) excellent response to local treatment (15 of 16 cases), and (d) a favorable prognosis.

The very recent criteria of LPL has been strengthened but the diagnosis of LPL is limited.^[1] It is now stressed that low-grade small size B-cell neoplasms with plasmacytic differentiation should be completely excluded in making the diagnosis of LPL.^[1] That is, small-size low grade B-cell neoplasms including extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma),^[6] small lymphocytic lymphoma/CLL,^[7] follicular lymphoma,^[8] mantle cell lymphoma,^[9] extra-osseous plasmacytoma,^[10] and plasma cell myeloma^[11] should be excluded in making the diagnosis of LPL.

In the current report, the author reports a probable case of primary cutaneous LPL histologically fulfilling the established criteria of LPL. This cutaneous LPL showed peculiar features in addition to LPL. That is, the present case showed acute inflammatory features and atypical squamous cells of

the epidermis in the site of LPL.

2. CASE REPORT

A 69-year-old man consulted our hospital, because of skin ulcer of the neck. Physical examination showed a skin ulcer of the neck. The lesion appeared granulation tissue with surface fibrin deposition; an inflammatory process was suggested. Blood laboratory data were almost within normal ranges, except for the presence of diabetes mellitus (HbA1c = 13.5%, normal 4.6-6.2) and increased C-reactive protein (1.83 mg/dl). Urine test showed high level of glucose. The peripheral blood showed no abnormalities, including the segments of leukocytes. No plasmacytosis was recognized in the blood. No M-proteins, macroglobulins of WM, or cryoglobulins were noted in the serum and urine. No bone marrow studies were performed. The clinical diagnosis was non-specific skin ulcer of the neck. A wide biopsy was taken.

The biopsy showed a destructive proliferation of atypical small lymphocytes, atypical small plasmacytoid lymphocytes, and atypical plasma cells in the dermis and subcutaneous tissue (see Figures 1A-E). The epidermis was rarely involved by these atypical cells (see Figure 1A). No nodular patterns as seen follicular lymphoma were seen. No germinal centers and heterogenous cell populations as seen marginal zone B-cell lymphoma (MALT lymphoma) were recognized. There was no monotonous proliferation of plasma cells as seen in extra-osseous plasmacytoma. There was no monotonous proliferation of small lymphocytes as seen in small lymphocytic lymphoma/CLL. Most of the tumor cells were atypical small lymphocytes. They showed small size, hyperchromatic nuclei, and occasional nucleoli (see Figure 1B-D). Mitotic figures were scant. No nuclear indentations as seen in mantle cell lymphoma were seen. No Dutcher or Russell bodies were seen in the atypical small lymphocytes. The atypical small plasmacytoid cells showed morphologies similar to those of the atypical small lymphocytes, except for the eccentrically located nuclei and relatively ample cytoplasm (see Figure 1B-D). Dutcher bodies and Russell bodies were noted infrequently in this type of tumor cells. The atypical plasma cells showed eccentrically located nuclei, cytoplasmic halo, and relatively ample basophilic cytoplasm (see Figure 1B-E). Dutcher bodies and Russell bodies were also seen in the atypical plasma cells. Larger cells with prominent nucleoli and multinucleated giant cells resembling Reed-Sternberg cells were scattered. The biopsy also showed acute inflammatory features; foci of numerous neutrophils were scattered within the neoplastic cells (see Figure 1F). Some of them showed micro-abscesses (see Figure 1F). In addition, foci of atypical squamous cells were seen in the epidermis (see Figures 1G-H). The atypical

squamous cells showed cellular atypia (see Figure 1G) and pseudo-invasive features with ectopic keratinization suggestive of invasive well differentiated squamous cell carcinoma (see Figure 1H). Histochemical staining showed no amyloid

in the tumor, which are occasionally recognized in small size low grade B-cell neoplasms.^[12-17]

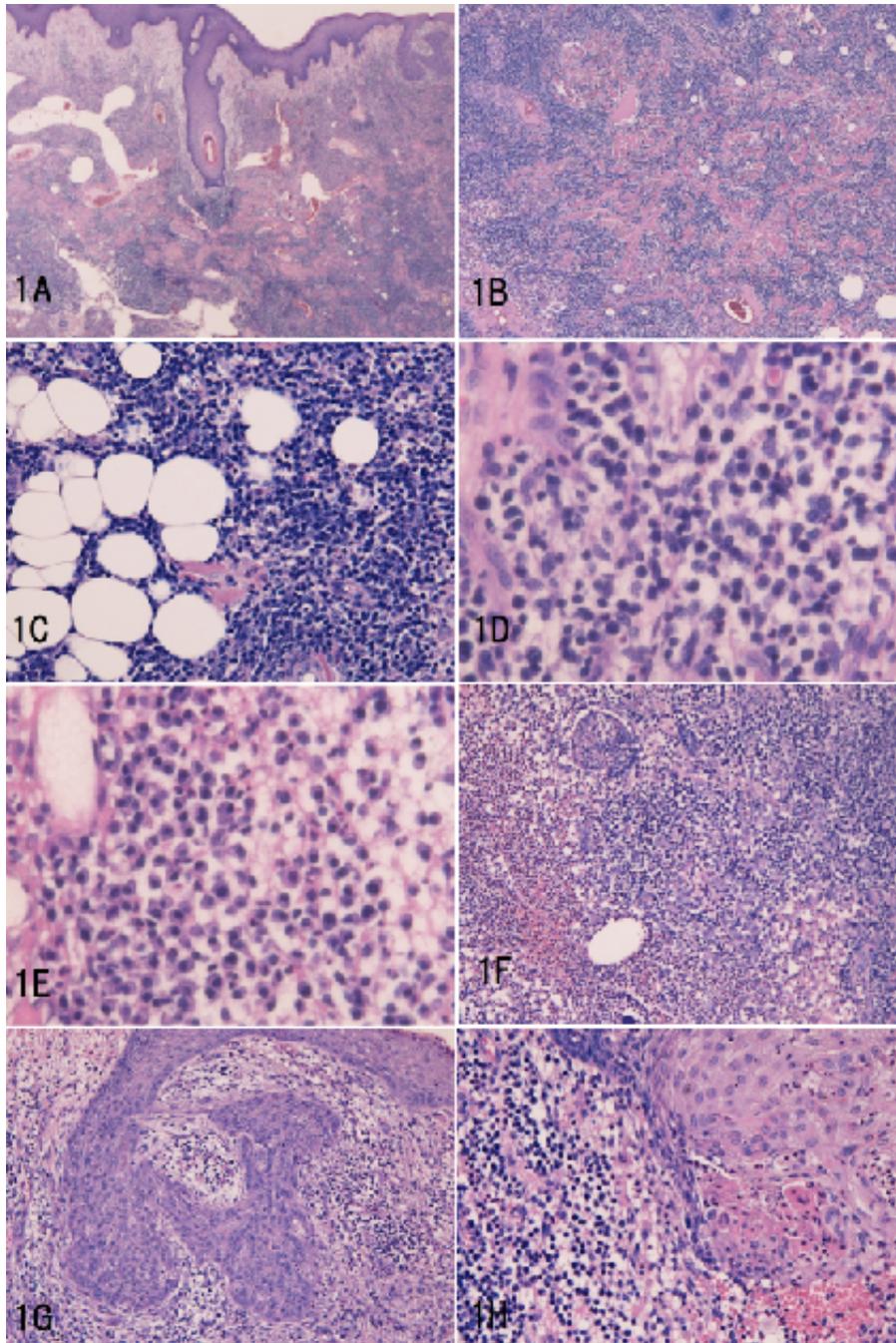


Figure 1. Histological findings of the cutaneous lesion of the neck

A: Very low power view. An intense destructive proliferation of lymphoid cells is seen in the dermis and subcutaneous tissue. Many abscesses are also seen. HE, $\times 20$. B: Low power view of the dermis. The tumor is composed of small atypical lymphocytes. Destructive features of dermal collagen are seen. Abscess formations are also seen. HE, $\times 100$. C: High power view of the tumor cells in the subcutaneous tissue. The tumor is composed of atypical lymphocytes with hyperchromatic nuclei, atypical lymphoplasmic cells, and atypical plasma cells. Large immunoblasts with nucleoli are scattered. HE, $\times 200$. D: Large power view. The proliferating atypical lymphocytes are composed of atypical lymphocytes with hyperchromatic nuclei, atypical lymphoplasmic cells, and atypical plasma cells. Large immunoblasts with nucleoli are scattered. One Russell body is seen (lowermost part). HE, $\times 400$. E: Large power view of the tumor. Plasmacytic differentiation is apparent. HE, $\times 400$. F: Large power view. Foci of numerous neutrophilic infiltration (left) is seen here and there. HE, $\times 200$. G: Atypical squamous cells are seen to project into the dermis. HE, $\times 200$. H: The atypical squamous cells are seen in the dermis. Keratinization is seen (lower), suggesting a squamous cell carcinoma.

An immunohistochemical study was performed with the use of Dako Envision method (Dako Corp, Glostrup, Denmark), as previously described.^[18-35] Immunohistochemically, the tumor cell showed B-cell lineage. The tumor cells were diffusely positive for vimentin, CD45, CD20 (see Figure 2A), CD79 α (see Figure 2B), bcl-2 (see Figure 2C), CD38, and

CD138 (see Figure 2D). The tumor cells were only focally positive for CD3 and CD45RO. A few tumor cells were positive for CD30, CD56, and CD10. The CD30-positive cells corresponded to large cells with nucleoli (immunoblasts). Some of the tumor cells were positive for p53 (see Figure 2E) and Ki-67 antigen (labeling index = 35%) (see Figure

2F). The tumor cells were negative for pancytokeratin AE1/3, pancytokeratin CAM5.2, CD5, CD23, CD43, cyclinD1, and Epstein-Barr virus (EBV) associated molecules such as EBV latent membrane protein-1 (LMP-1) and EBV early RNAs (EBER). The tumor plasmacytoid cells were positive for κ -light chain but negative for λ -light chain, indicating that the

tumor cells have plasmacytic characteristics and that there was a light chain restriction that indicates monoclonal nature of the tumor plasma cells. The neutrophils were positive for vimentin and CD45, but negative for other lymphocytic antigens. The Ki-67 labeling of the neutrophils was low (labeling index = 3%).

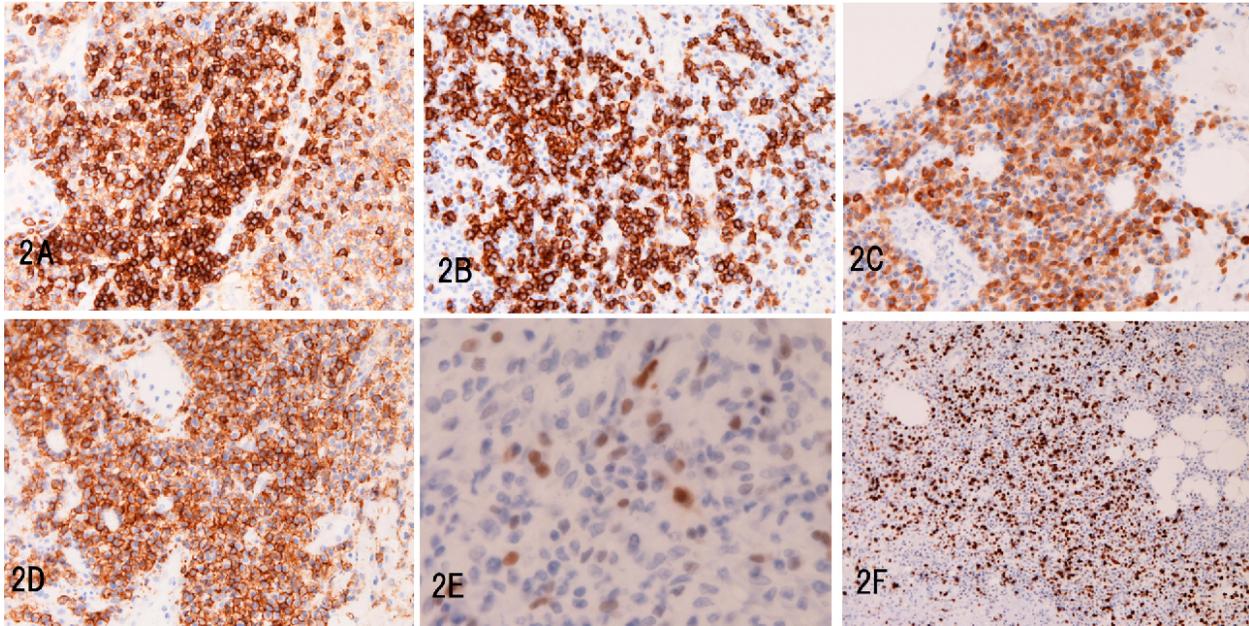


Figure 2. Immunohistochemical findings

The small tumor cells are diffusely positive for CD20 (A), CD79 α (B), *bcl-2* (C), and CD138 (D). Some of the tumor cells were positive for p53 (E) and Ki-67 antigen (labeling index = 35%) (F). Immunostaining, $\times 200$.

A pathological diagnosis made by the author was cutaneous LPL-like B-cell malignant tumor. The author thought that this tumor could not be definitely diagnosed as a primary cutaneous LPL, because other small-sized B-cell lymphomas with plasmacytoid differentiation could not be excluded completely in the author's knowledge, experience, and studies of books and literatures. Of interest is that the current tumor was also characterized by acute inflammatory features and epidermal squamous cell atypia. Imaging modalities including CT identified no other tumors and lymphadenopathy in the body. The systemic bones were free of myeloma features. No bone marrow study was performed after the pathological diagnosis. The tumor cured and the patient discharged from the hospital 3 months after the first presentation.

3. DISCUSSION

In the present case, tumor formation was seen in only the skin. Thus, the skin tumor is primary cutaneous neoplasm. Small atypical lymphoid cells showed destructive proliferations in the dermis and subcutaneous tissue. The cells had cellular atypia such as hyperchromasia and increased nucleo-

cytoplasmic ratio. Mitotic figures were also seen. These histological features highly suggest that the present case is not a reactive non-neoplastic lymphoid cell proliferation but a neoplasm. This is strengthened by the immunohistochemical fact that the present case was composed exclusively of B-cells, and T-cells were very scant; namely the present case is a B-cell neoplasm. Further, light chain restriction seen in the present case implies monoclonal and tumoral nature of the present case. Thus, it can be concluded that the present skin lesion is not reactive lymphoid proliferation, but a lymphoid neoplasm. The positive p53 and high Ki-67 labeling also support this.

The present tumor had significant cellular atypia. Mitotic figures were also seen. The cellular atypia seen in the current tumor cells highly suggests that the present tumor is malignant. The monoclonal proliferation of B-cells having B-cell antigens and T-cell antigens were very scant in the current tumor highly suggest that the present tumor is B-cell malignant neoplasms. Immunohistochemical demonstration of many p53-positive cells and high ki-67 labeling index (35%) indicate p53 gene mutations and a high cellular proliferation

in the current tumor. These findings also suggest that the tumor is malignant. The atypical lymphocytes in the present case shows small size, and marked cellular atypia as seen in diffuse large B-cell lymphoma (DLBCL) was not seen. Therefore, the present tumor belongs to small size low grade B-cell neoplasm. Thus, it can be concluded that the present tumor is low grade small sized malignant B-cell neoplasms.

The present tumor was histologically composed of atypical small lymphocytes, atypical small plasmacytoid lymphocytes, and atypical plasma cells. The plasma cell characteristics of the present tumor are apparent on histology, only. The presence of Dutcher and Russell bodies also suggest the plasmacytic nature of the tumor cells. These findings strongly suggest that the present B-cell neoplasm is LPL.^[1] The plasmacytoid differentiation and plasma cell characteristics in the present tumor are proved by the positive expression of CD38, CD79 α , CD138, and κ -light chain, all of which are plasma cell antigens. The positive light chain restriction highly suggests the monoclonal plasmacytic nature of the present case. However, these findings do not necessary fulfill the criteria of LPL in the current criteria system,^[1] because the diagnosis of LPL is exclusion one.^[1] Namely, other small-sized low grade malignant B-cell neoplasm with plasmacytoid differentiation should be excluded.

These small-size low grade malignant B-cell neoplasms should be excluded, including extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma),^[6] small lymphocytic lymphoma,^[7] follicular lymphoma,^[8] mantle cell lymphoma,^[9] extra-osseous plasmacytoma,^[10] and plasma cell myeloma.^[11] The most difficult differential diagnosis of LPL is extra-nodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), which may show broad plasmacytic differentiation.^[6] In general, extra-nodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) shows heterogenous proliferation of various types of lymphoid cells. This B-cell neoplasm is characterized by proliferation of centrocytes-like cells (CCL), proliferation of cells resembling lymphocytes of marginal zone outside the mantle zone, presence of monocytoid B-cells, presence of germinal centers, lymphoepithelial lesions (LELs) in epithelial organs, occasional plasma cell differentiation, and follicular colonization.^[6] In the present case, no such heterogeneity of constituent cells were seen. In the current tumor, no CCL, LELs, monocytoid B-cells, germinal centers, or follicular colonization were recognized. These findings strongly suggest that the present tumor is not extra-nodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). However, this is not necessary true because this B-cell neoplasm may show vari-

ous histologies and some cases of this B-cell neoplasm may resemble to LEL.^[1,6] The present tumor seems not small lymphocytic lymphoma, which shows monotonous proliferation of small lymphocytes, and usually lacks plasmacytoid differentiation.^[7] The present tumor seems not to be follicular lymphoma because the present tumor lacked follicular or nodular proliferation of tumor cells.^[8] The immunoreactive bcl-2 pattern is also different from follicular lymphoma. The present case seems not mantle cell lymphoma, which shows characteristic nuclei with nuclear indentation and is positive for cyclin D1,^[9] all of which were not seen in the present tumor. The present case seems not to be extra-osseous plasmacytoma, which is composed only of plasma cells.^[10] In the present case, there were atypical lymphocytes not regarded as plasma cells, being different from plasmacytoma. The present tumor seems not to be plasma cell myeloma, which shows multiple punched out lesions in the bones and the tumor cells are composed only of neoplastic plasma cells.^[11] Negative expression of CD5 as seen in the present study is important in the diagnosis of LPL.^[1]

A panel of antibodies has been proposed for differential diagnosis of these small size low-grade B-cell lymphomas.^[1,6-11] The antigens include CD5, CD10, CD23, CD43, and cyclin D1.^[1,6-11] In small lymphocytic lymphoma, the expression pattern is CD5 -, CD10 -, CD23 +, CD43 +, and cyclinD1 -. In follicular lymphoma, the expression pattern is CD5 -, CD10 +, CD23 -, CD43 -, and cyclinD1 -. In extra-nodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), the expression pattern is CD5 -, CD10 -, CD23 -, CD43 +/-, and cyclinD1 -. In mantle cell lymphoma, the expression pattern is CD5 +, CD10 +/-, CD23 -, CD43 +/-, and cyclinD1 +.^[1,6-11] In the present tumor, the expression pattern was CD5 -, CD10 +, CD23 -, CD43 -, and cyclinD1 -. The expression pattern of these antigens of the present skin tumor is consistent with follicular lymphoma. However, the present skin tumor is absolutely not follicular lymphoma histologically and immunohistochemically. Therefore, this procedure of the expression pattern cannot identify the nature in the current skin tumor.

Although the author believes that the current tumor is LPL, the author titled the present case as primary cutaneous lymphoplasmacytic lymphoma-like B-cell neoplasm. Because the author is not a specialist of lymphoma and the author has no experience of this type of skin tumors. In addition, the location of the present LPL is unusual; only four reports of LPL have been present in the skin location.^[2-5] Furthermore, the clinical features are somewhat different from typical LPL; i.e. the lack of M-protein, cryoglobulins, and macroglobulin of WM are not typical for LPL in the current case. Moreover, the current case seem not involve the bones, being atypical

for LPL in this skin tumor. From overall these reason, the author diagnosed the lesion as primary cutaneous LPL-like B-cell neoplasm, although the author believes that this case is real LPL.

It is well known that EBV infection may be associated with several B-cell neoplasms such as Burkitt lymphoma and pyothorax-associated lymphoma as well as carcinomas such as nasopharyngeal carcinoma and lymphoepithelial carcinoma. In the current tumor, the lymphoid cells were negative for LMP-1 and EBV early RNAs in situ hybridization (EBER), suggesting that the present B-cell tumor is not associated with EBV.

Of interest is that the present tumor showed acute inflammation within LPL-like B-cell neoplasm. Numerous neutrophils were seen in the cutaneous tumor and many abscess formations were seen within the tumor. The clinical findings also indicated that the lesion is granulation tissue with infection. In general, infection or acute inflammation in malignant lymphoma seems exceptional. The neutrophils had no p53 immunoreactivity and Ki-67 labeling is very low (3%), suggesting that the neutrophils are not tumor cells. These findings indicate that infection and acute inflammation can occur in the lymphoma tumor, although a PubMed search

did not found such a case of lymphoma.

Also of interest is that the present case showed atypical squamous cells in the site of the cutaneous lymphoma. The author thinks that the atypical cells are authentic squamous cell carcinoma in situ or micro-invasive. A PubMed search did not identify such a case. These findings imply that squamous cell carcinoma may arise in the site of cutaneous lymphoma.

LPL is an indolent tumor, and the prognosis of LPL is relatively good.^[1,5] The tumor of the present patient cured completely, suggesting that the prognosis of LPL is good. However, periodical follow-up is needed in the present patient.

In summary, the author reported an extraordinary rare case of primary cutaneous LPL or LPL-like low grade malignant B-cell neoplasm. A broad immunohistochemical study was done. Differential diagnosis of low grade small size B-cell neoplasms was discussed. In addition, the author indicated that acute inflammation and squamous cell carcinoma may develop in the site of cutaneous lymphoma.

CONFLICTS OF INTEREST DISCLOSURE

The author declares no conflict of interest.

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