

A Case of CD5-Positive Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type Secondary to Chronic Lymphedema

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Abstract: Primary cutaneous lymphoma occurring at the site of lymphedema is a rare complication. A total of 13 cases of primary cutaneous lymphoma associated with chronic lymphedema have been reported in international studies. We reported a case of cutaneous diffuse large B-cell lymphoma (DLBCL) (leg type) secondary to chronic lymphedema of the lower limbs. Histopathology showed hyperkeratosis of epidermis, acanthosis, and significant edema in the superficial dermis, with diffuse mononuclear infiltration in the dermis. Immunohistochemical studies revealed the expression of CD5, CD20, Pax-5, Bcl-2, Bcl-6, MUM-1, c-myc, and Ki-67. Therefore, the diagnosis of cutaneous DLBCL (leg type) was made. The study further confirmed the association between lymphoma and lymphedema. Especially, it showed CD5 expression. CD5-positive DLBCLs is a specific subgroup of DLBCLs, only approximately 10% of DLBCLs express CD5.

Key Words: diffuse large B-cell lymphoma, primary, skin, chronic lymphedema, CD5-positive

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INTRODUCTION

Secondary malignancies are a rare complication of chronic lymphedema and can lead to various malignancies of the skin or subcutaneous tissue. Likewise, the lymphomas secondary to lymphedema are rare. In addition, CD5-positive (CD5⁺) diffuse large B-cell lymphoma (DLBCL) is a peculiar subgroup of DLBCL. Most of the DLBCLs are CD5-negative (CD5⁻), CD5⁺ DLBCL is relatively rare. Here, we reported a case of a 69-year-old woman with CD5⁺ cutaneous DLBCL (leg type) secondary to chronic lymphedema of the lower

limbs for 40 years. The case confirmed the idea that lymphedema can lead to malignant tumors and reported a rare case of CD5⁺ DLBCL.

CASE REPORT

A 69-year-old woman presented with progressive swelling of both lower limbs for 40 years and multiple red nodules on the right lower limb for more than 2 months. The patient developed firm swelling on both lower limbs 40 years ago, without papules, nodules or plaques, pain, or other evident symptoms. The swelling on both lower limbs gradually increased, with thickening and hardening of the skin. Two months ago, multiple nodules of varying sizes appeared on the right lower limb, which were initially red, subsequently turning purplish red and fusing into patches. The surface of some of the lesions showed erosion and exudation, with pain. The patient had no history of hypertension, heart disease, diabetes mellitus, or trauma and denied any family history of similar diseases. Since the onset of the disease, she had a normal appetite, sleep, urination, and defecation and had not lost any weight.

Physical examination showed that the lower limbs were swollen and thickened with nonsunken edema. The skin was hard, with orange peel in the local area. Many irregularly raised lumps were seen on the right thigh, surrounded by scattered raised nodules of varying sizes, smooth, firm, and infiltrated (Fig. 1A). Multiple nodules were seen on the right lower leg, partly in clusters, with a warty, scaly surface, localized erosion, crusting, and pressure pain (Fig. 1B). The other systemic examinations were normal.

The laboratory examination showed abnormal liver function: total protein was 51.3 g/L, albumin was 25.1 g/L, glutamate transaminase was 43 U/L, cholinesterase was 2.90 KU/L, and lactate dehydrogenase was 1533 U/L. The inflammatory parameters showed C-reactive protein was 13.77 mg/L, procalcitonin was 0.121 ng/mL, and addiment C3 was 0.61 g/L. The tumor markers showed ferritin was 303.60 ng/mL. No significant abnormalities were observed in the other laboratory examinations. In situ hybridization for Epstein-Barr virus was negative.

We took a biopsy sample of a nodule from the right lower limb. The histopathology showed hyperkeratosis of the epidermis and acanthosis. The superficial dermis showed significant edema, with no infiltrative zone between the epidermis and the dermis, in which proliferating and dilated lymph vessels and blood vessels were visible. Diffuse infiltration of mononucleated cells was seen in the dermal edematous area and below. At high magnification, some of the infiltrating cells were clearly heterogeneous, large, with lightly stained cytoplasm and irregularly large, vacuolar nuclei. There was either a single nucleolus located in the median nucleus (immunoblast) or multiple nucleoli located in the perinuclear nucleus

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The authors declare no conflicts of interest.

The study was approved by the local Ethics Committee of the First Affiliated Hospital of Zhengzhou University, and the patient and her legal guardians had signed the informed consent documentation.

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FIGURE 1. Skin lesion on the right lower limb of the patient with PCLBCL, LT. A, Many irregularly raised lumps were seen on the right thigh, surrounded by scattered raised nodules of varying sizes, smooth, firm, and infiltrated; B, multiple nodules were seen on the right lower leg, partly in clusters, with a warty, scaly surface, localized erosion and crusting.

(centroblast), showing evident karyokinesis. Below the dermal edema, the collagenous fibers between the infiltrating cells showed proliferation (Fig. 2).

Immunohistochemical studies revealed a strong expression of CD20, Pax-5, and Bcl-2 (positive rate up to 100%) by the neoplastic B cells, whereas some of these cells also expressed Bcl-6 (approximately 60%). Some small lymphocytes throughout the neoplastic cells expressed T-cell antigens such as CD3, CD4, CD8, CD43, CD2, or CD7. Moreover, the expression of MUM-1, c-myc (approximately 30%), and Ki-67 (approximately 90%) was seen in the tumor cells. Additional immunostaining for CD10, CD30, CD56, T-cell intracellular antigen-1, GranB, anaplastic lymphoma kinase, SOX-11, terminal deoxynucleotidyl transferase, and cyclin D1 was negative. (Fig. 3).

Ultrasound showed that the patient had intrahepatic calcification and echogenicity. There were no significant abnormalities in the chest computed tomography and other visceral organs.

Based on these results, the diagnosis of cutaneous DLBCL (leg type), chronic lymphedema, and hypoproteinemia was made. To further establish that the lymphoma is primary to the skin, we recommended the patient to do positron emission tomography computed tomography and bone marrow biopsy, unfortunately the patient and his family declined. However, based on the available test results, we deduced that the patient's lymphoma was more likely primary to the skin.

After the diagnosis was confirmed, the patient was referred to the oncology department. However, the patient and her family refused treatment and were lost to follow-up.

DISCUSSION

Primary cutaneous diffuse large B-cell lymphoma, leg type (PCLBCL, LT) is a rare non-Hodgkin lymphoma that originates in the skin. In 1996, it was first described by Vermeer et al¹ as a special type of cutaneous malignant lymphoma.

PCLBCL, LT mainly affects elderly patients, especially women, and is characterized by skin lesions on one or both lower legs.² The lesions are characterized by single or multiple fast-growing red or bluish-red nodules or masses that are typically not ulcerated but can eventually become ulcerated.³ The histopathology of these lymphomas shows diffuse infiltration of monotonous or confluent centroblasts and immunoblasts in the dermis, often extending into the subcutaneous tissue and occasionally destroying skin appendages. In addition to the B-cell-associated antigens CD20, Pax-5 and CD79a tumor cells are often positive for the germinal center marker Bcl-6 (45%–75%). Bcl-2 is usually overexpressed with a positive rate of as high as 85%–90%.^{4–6} PCLBCL, LT is a more aggressive type of cutaneous B-cell lymphoma with a poor prognosis and a relapse rate of up to 70%.² The location

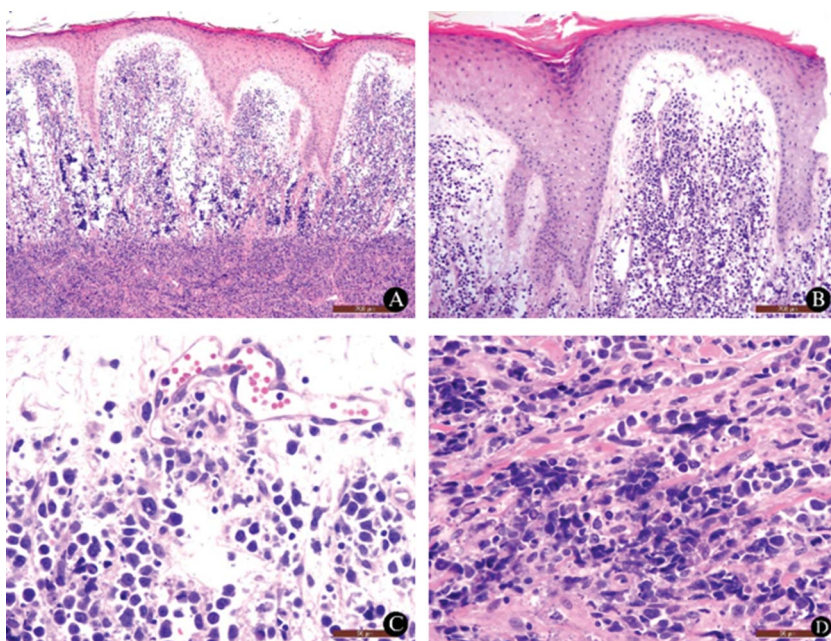


FIGURE 2. Histopathology of the patient with PCLBCL, LT. A, Hyperkeratosis of the epidermis, acanthosis, and diffuse infiltration of mononucleated cells were seen in the dermal edematous area and below [hematoxylin and eosin (HE) $\times 50$]. B, The superficial dermis showed significant edema, with no infiltrative zone between the epidermis and the dermis, in which proliferating and dilated lymph vessels and blood vessels were visible (HE $\times 100$). C and D, Some of the infiltrating cells were clearly heterogeneous, large, with lightly stained cytoplasm and irregularly large, vacuolar nuclei, showing evident karyokinesis. Below the dermal edema, the collagenous fibers between the infiltrating cells showed proliferation (HE $\times 400$).

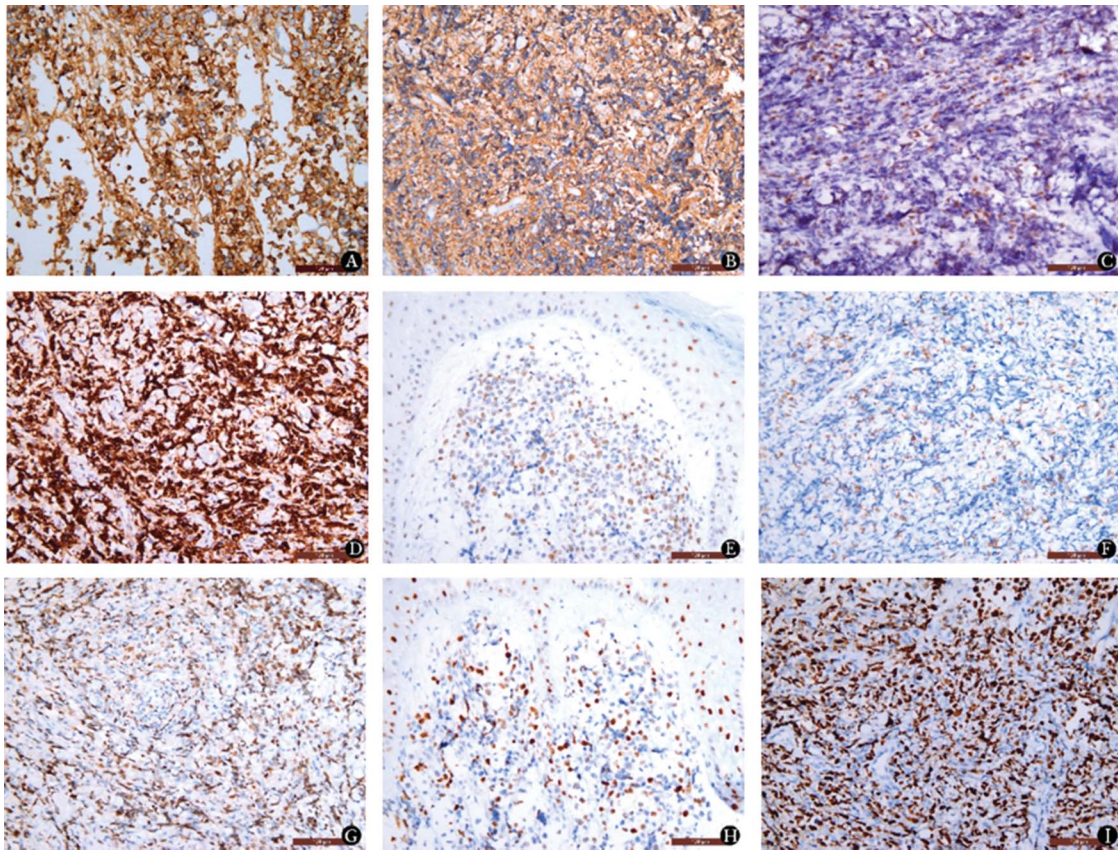


FIGURE 3. Immunohistochemistry of skin lesion of the patient with PCLBCL, LT ($\times 200$). A, CD5 (+). B, CD20 (+). C, Pax-5 (+). D, Bcl-2 (100%+). E, Bcl-6 (40%+). F, CD3 (+). G, MUM-1 (+). H, C-myc (30%+). I, Ki-67 (90%+).

and number of skin lesions and the age of patients are important factors affecting prognosis.^{4,7,8}

Our patient was an elderly woman with skin lesion involving the lower legs. The histopathology was suggestive of B-cell lymphoma, and immunophenotyping showed positive expression of CD5, CD20, Pax-5, MUM-1, Bcl-2 (100% of the cells), Bcl-6 (40%), c-myc (30%), and Ki-67 (90%). Hence, the diagnosis of PCLBCL, LT was made.

This case had 2 distinguishing features. One was that the patient had a long history of chronic lymphedema of both lower legs due to unknown cause and abnormal hepatic function, both of which can cause hypoproteinemia and exacerbate the edema. Primary cutaneous lymphoma occurring at the site of lymphedema is a rare complication. The first case of malignant skin lymphoma with chronic lymphedema was reported in 1984 by Waxman et al⁹ in a 74-year-old woman who developed chronic lymphedema in the corresponding arm after radical mastectomy and postoperative radiotherapy for breast cancer. Sixteen years later, multiple nodules appeared in the arm area with the lymphedema, and B-cell lymphoma was diagnosed. A total of 13 cases of primary cutaneous lymphoma associated with chronic lymphedema have been reported in international studies.^{10–13} In China, Gao et al¹⁴ reported a case of cutaneous nasal NK/T-cell lymphoma of the left lower leg secondary to lymphedema. Shi et al¹⁵ reported a case of CD5⁺ DLBCL of the upper extremity skin in a patient with postoperative breast cancer secondary to

chronic lymphedema at the same site. A review of the literature showed that these lymphomas primarily occurred in the elderly and in distal parts of the body, such as the wrist, back of the hand, and knee, and usually appeared many years after the onset of lymphedema. The clinical presentation, aggressiveness, and prognosis were not significantly different from those of primary cutaneous lymphomas without lymphedema. Most of the tumors were DLBCLs, 5 of which presented as ulcerated nodular lesions on the legs. Scholars believe that the occurrence of these lymphomas was not related to the cause of the lymphedema but more related to the lymphedema itself. The association between lymphomas and lymphedema might not be completely fortuitous.

Secondary malignancies are a rare complication of chronic lymphedema and can lead to various malignancies of the skin or subcutaneous tissue. The most common tumor is angiosarcoma (Stewart–Treves syndrome), and squamous cell carcinoma, Kaposi sarcoma, melanoma, or lymphoma may also occur. Moreover, fibrosis, infection, and immunosuppression may underlie the pathology of lymphedema secondary to tumors.¹⁶ Severe lymphedema exhibits significant lymph node fibrosis, which may affect the immune function of the lymph node. In addition, inadequate lymphatic drainage because of chronic stagnation may disrupt the flow patterns of lymphocytes and Langerhans cells, which are necessary for immune function, thereby rendering the lymphedema area immunologically vulnerable to infection and neoplasia.^{11–13} Lymphatic dysfunction

leads to elevated levels of interleukin-10, which prevents the maturation of antigen-presenting dendritic cells, which may inactivate dendritic cells in the tumor microenvironment and allow the tumor cells to escape surveillance of the body's immune system. Lymphatic stasis creates a growth factor-rich medium in the tissue interstitium, providing a suitable environment for tumor cell growth.¹⁶ Malignant lymphoma is the most common tumor in the context of immune dysregulation.¹¹ Therefore, abnormal lymphoid hyperplasia may be causally related to lymphatic stasis, and clinicians should be alert to the development of cutaneous malignancies in patients with chronic lymphedema.

Another feature of this case was that the tumor expressed CD5, an antigen expressed mainly on the surface of T cells but also on a small subset of normal B cells. CD5 is closely associated with disease development and is the characteristic antigen of most chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma, and mantle cell lymphoma. Only approximately 10% of DLBCLs express CD5, and this can occur de novo rather than as a manifestation of transformation of CLL or small lymphocytic lymphoma.¹⁷

CD5⁺ DLBCL is a specific subgroup of DLBCLs, which shows a higher age distribution and female predominance compared with CD5⁻ DLBCL, which may be related to the female predominance in autoimmune diseases. CD5⁺ DLBCL is a highly aggressive subtype with a tendency to involve extranodal sites, particularly the bone marrow and spleen. Patients with CD5⁺ DLBCL have a significantly worse prognosis than those with CD5⁻ DLBCL.^{17,18} Primary cutaneous CD5⁺ DLBCL is rare, and the combination of chronic lymphedema is even rarer, with only 2 cases of CD5⁺ DLBCL secondary to chronic lymphedema reported in the literature to date worldwide.^{10,15} This case differs from the previous cases because it occurred in the lower limb, whereas the other 2 cases occurred in the upper limb. Most PCLBCL cases are CD5⁻, with only a few cases expressing CD5. To date, only 6 cases of CD5⁺ PCLBCL have been reported; however, the diagnosis of PCLBCL, LT could not be made in 5 of those cases, so only one case of CD5⁺ PCLBCL, LT has been well documented in the literature to date.¹⁹

In summary, this was the first case of CD5⁺ PCLBCL, LT secondary to chronic lymphedema. The treatment of PCLBCL, LT is the same as DLBCL. The currently accepted first-line treatment regimen is rituximab combined with CHOP regimen, but treatment should be individualized given the complex biology of lymphoma, the clinical susceptibility to recurrence, and the patients' comorbidities.²⁰ Rituximab is only effective in CD5⁻ DLBCL, and rituximab combined with CHOP regimen cannot improve the poor prognosis in refractory CD5⁺ DLBCL. Lenalidomide, an oral immunomodulator targeting CD80 and CD40, has shown strong activity in the treatment of relapsed/refractory indolent or aggressive non-Hodgkin lymphomas, including CLL, mantle cell lymphoma, and DLBCL.²¹ A study of lenalidomide in combination with R-GDP for refractory CD5⁺ DLBCL showed complete tumor remission, followed by the choice of low-dose lenalidomide maintenance therapy, which demonstrated the potential activity of lenalidomide in refractory CD5⁺ DLBCL. However, further

studies are needed to determine whether lenalidomide and its combinations are effective in the treatment of CD5⁺ DLBCL.²²

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