Case Report

Diagnosis and prognostic analysis of skin infiltration in chronic lymphocytic leukemia: a case report and literature review

Xiangyu Zhao[1#], Ting Li[2#], Piaoying Wang[1], Xiaoteng Bai[1], Juan Cheng[1,2]

[1]The First Clinical Medical College, Lanzhou University, Lanzhou, China; [2]Department of Hematology, The First Hospital of Lanzhou University, Lanzhou, China

[#]These authors contributed equally to this work.

Correspondence to: Juan Cheng. No. 1 Donggang West Road, Chengguan District, Lanzhou 730000, China. Email: chenggu029@163.com.

Background: Chronic lymphocytic leukemia (CLL) is a malignant lymphoproliferative disorder; excessive aggregation of small mature B cells in peripheral blood, bone marrow, lymph nodes, and spleen is characteristic. Cutaneous involvement of CLL can be classified into specific skin lesions, including skin infiltration by leukemic cells, secondary cutis tumors, nonspecific lesions and associated skin diseases. Uncommonly, skin infiltration in patients who are diagnosed with CLL can be localized or widespread, and it can take various forms, including nodules, plaques, papules, and ulcers.

Case Description: We report a 52-year-old patient diagnosed for CLL with skin infiltration, whose lesions were subcutaneous nodules, widely distributed in the nasal base, right auricle, extremities, and trunk. Lesions are firm, without tenderness and have poor mobility. Spontaneous regression of some skin lesions is the most prominent feature. The pathological biopsy of skin tissue showed that small round cells infiltrated subcutaneous adipose tissue. The immunohistochemical results were consistent with the immunophenotype of neoplastic B cells, and the aberrant co-expression of CD5 and CD23 was the significant marker. The patient is currently being followed up.

Conclusions: Aggressive treatment of the primary disease can alleviate the skin symptoms to a certain extent, and the prognosis of patients is affected by multiple factors such as the extent of the lesions, whether accompanied by epidermal changes, the site of infiltration and the percentage of small B lymphocytes. Long-term follow-up is necessary.

Keywords: Chronic lymphocytic leukemia (CLL); skin infiltration; diagnosis; prognosis; case report

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Introduction

Skin infiltration in chronic lymphocytic leukemia (CLL) is rare, although it occurs in 4% to 20% of patients with CLL (1). The amount of medical literature depicting the manifestation of skin infiltration in patients with CLL is finite. The reported cutaneous infiltration includes nodules, papules, infiltrates, plaques, ulcerations and exfoliative erythroderma (1-4). In the majority of cases described by some researchers, the histopathologic features found in skin infiltration were characterized as a variably dense perivascular and periadnexal infiltrate of small, hyperchromatic lymphocytes throughout the entire dermis and extending into the subcutaneous fat (5). The mechanism of skin infiltration remains unclear. It is commonly believed that the interaction between lymphocyte function-associated antigen-1 (LFA-1) and intercellular adhesion molecule-1 (ICAM-1) mediates lymphocyte migration from the vasculature to the dermis (5). Consequently, we can speculate that skin infiltration may be triggered by the upregulation of LFA-1 and ICAM-1.

At present, there is a lack of optimal therapeutics for specific cutaneous infiltration in CLL (6), and it has been reported that local application of glucocorticoid

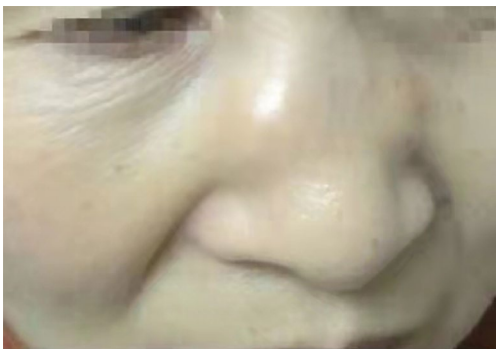

Figure 1 Skin infiltration in the nasal. This image is published with the patient's consent.

is not effective in the treatment, but active treatment of the primary disease can make skin symptoms alleviated to a certain extent (7). Whether the appearance of skin infiltration will have a certain effect on the prognosis of patients with CLL has not been determined yet. Therefore, a deeper investigation of skin infiltration in the course of CLL is crucial. We present the following case according to the CARE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2864/rc).

Case presentation

A 52-year-old female patient with a 6-year history of CLL had multiple palpable nodular lesions on both sides of the bridge of the nose, on the edge of the right auricle, on both forearms, and at the root of her fingers. These lumps range from 1 to 2 cm in diameter, with a hard texture and no tenderness. In May 2014, she was first diagnosed with CLL in the hematology department of our hospital due to repeated pain in the right lower abdomen and lymphocytosis. Physical examination showed multiple enlarged lymph nodes in the bilateral cervical region and axilla, which were tough and accompanied by splenomegaly, but no palpable enlargement of the liver. At that time, the blood routine revealed that the leukocyte count was 21.87×10^9/L, the percentage of lymphocytes was 75.9%, the hemoglobin was 154 g/L, and the platelet count was 121×10^9/L. Morphology of bone marrow cells showed that lymphocyte proliferation has significantly accounted for 53%, mainly small mature lymphocytes (47%), occasionally prolymphocytes, larger lymphocytes, and smudge cells. All of these signs supported the diagnosis of CLL. The immunophenotype of the neoplastic cells indicated that abnormal lymphocytes accounted for about 73.3% of the nuclear cells, with complete expression of human leucocyte antigen DR (HLA-DR), CD5 and CD19, partial expression of CD20, CD22 and cytoplasmic CD79a (cCD79a), and no expression of CD3, CD7, CD34 and CD10, which was considered as aberrant lymphocyte expression. In summary, the patient was diagnosed with CLL (RAI stage II; Binet B; low-risk group). Considering the patient's condition, 50 mg of fludarabine was daily given to her for 4 days singly. She was discharged after the blood cell count restored to normal range, and returned to the hospital regularly after discharge.

In 2016, subcutaneous nodules began to appear in the nasal root and fingers of the patient, which were tough, non-tender and with poor activity. In addition, part of the nodules spontaneously subsided was the prominent feature. The patient visited another hospital at that time, and the result showed no significant change after the improvement of relevant examinations, so the original diagnosis of CLL was maintained. For skin infiltration, no special treatment was given, and dynamic observation was recommended.

In August 2020, the patient had recurrent subcutaneous nodules in the nasal base, right auricle, limbs and trunk, and some of them could subside spontaneously. However, the nodules in the nasal root (*Figure 1*) gradually became larger, so the patient revisited our hospital in October 2020. Blood routine at admission indicated that the leukocyte count was 13.16×10^9/L, the percentage of lymphocytes was 77.4%, hemoglobin was 160 g/L, and platelet count was 108×10^9/L. The auto-antibody test showed no obvious abnormality. Biopsy and morphology of bone marrow cells indicated active bone marrow hyperplasia, in which lymphocyte hyperplasia was active, accounting for about 66.0%. Occasionally, prolymphocytes were seen, mainly mature lymphocytes, and the edges of some lymphocytes were irregular. Immunophenotype showed that 71.8% of the cells fully expressed HLA-DR, CD22, CD5, CD19, CD23, CD200, partially expressed CD20, CD25, and did not express CD34, CD3, FMC7 and CD10. According to the Matutes immune marker scoring system, the score was 5 points, which was consistent with the diagnosis of CLL. There was no obvious abnormality in chromosome karyotype. Molecular pathology can detect the immunoglobulin heavy-chain variable region gene (*IGHV*) hypermutation (VH 3-23, homologous proportion 94.93%).

Ultrasound results of the patient indicated that several lymphadenoid tones were detectable in the bilateral cervical region, axilla, and left inguinal area. The largest lymph node was about 20 mm × 5 mm in size. No obvious abnormal

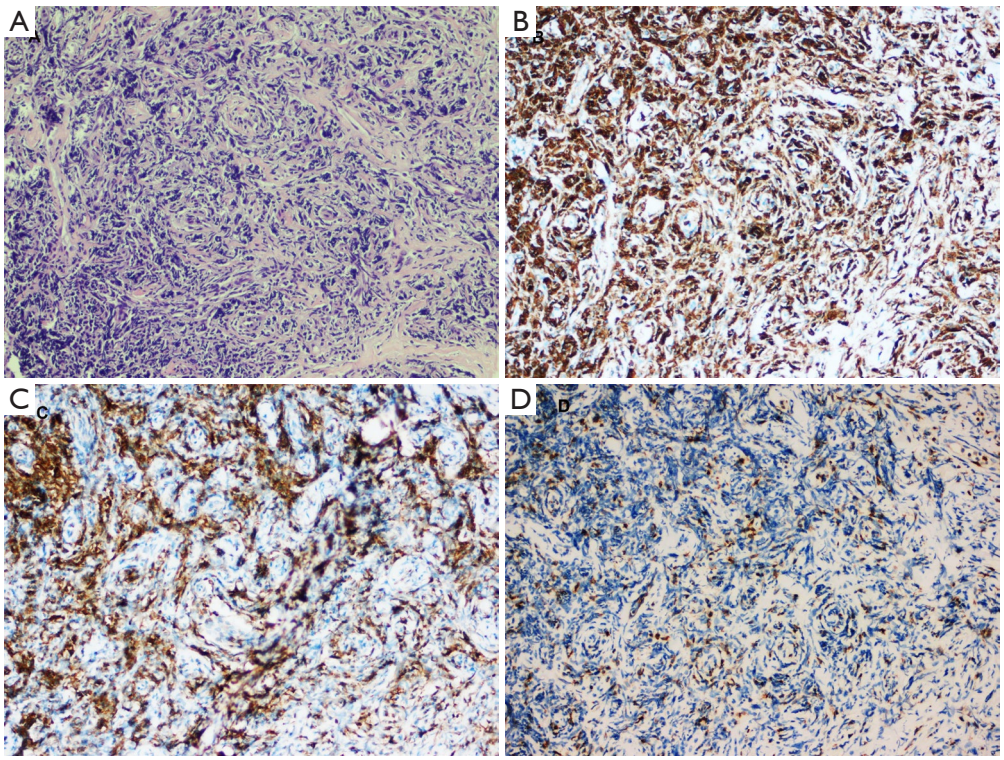

Figure 2 Biopsy results. The subcutaneous nodule of the finger showed atypical lymphoid cells infiltrate adipose tissue (hematoxylin and eosin) (A). Immunohistochemistry revealed $CD20^+$ (B), $BCL2^+$ (C) and $CD5^+$ (D) cells (A-D magnification, ×200).

enlargement of lymph node like echo was detected in right inguinal area, abdominal cavity and bilateral supraclavicular fossa. Subcutaneous low echo area could be explored in the ventral side of the first metacarpal of the left index finger and both sides of the nasal root. Abdominal computed tomography scans showed splenomegaly.

The patient's skin lesions were subcutaneous nodules, widely distributed in the root of the nose, right auricle, limbs and trunk, with a size of 1–2 cm. They were hard in texture, poor in activity, without tenderness, obvious pruritus, skin redness and swelling or other symptoms. Some could regress spontaneously without treatment was its unusual characteristic, the course of disease was easy to repeat. In recent 2 months, the patient noticed that the subcutaneous mass on the right side of the bridge of the nose was larger than before. The pathological biopsy of the infiltrated site showed small round cells were in the fibrous tissue, with deep staining and diffuse arrangement of nuclei, and some infiltrated adipose tissue. The infiltrating sites of the neoplastic cells were consistent with those of the dermal papillary layer, reticular layer and subcutaneous tissue previously reported in the literature. Immunohistochemical investigation revealed CD20 (diffuse +), Bcl-2 (+), CD5 (partial +), CD3 (partial +), CD23 (partial +), Ki67 (10%), and Cyclind-1 (–) (*Figure 2*). The immunophenotype of infiltrated cells in the skin were consistent with that of CLL, and the immunohistochemical results supported the diagnosis of skin infiltration of CLL.

No symptoms of group B, such as fever, night sweats and loss of weight, were found in the patient. Comprehensive evaluation of the physical state, clinical symptoms, signs and auxiliary examination results showed that the patients belonged to the low-risk group. The patient was recommended to be treated with the rituximab + bendamustine regimen or ibrutinib. Due to fear of the side effects of chemotherapy and economic factors, the patient refused and is currently being followed up.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

CLL is a malignant hematologic disease characterized by excessive aggregation of CD5-positive mature small B lymphocytes in peripheral blood, bone marrow, lymph nodes and spleen. Immunoincompetent lymphocytes accumulate progressively, thus affecting normal hematopoiesis and immune function (8). CLL is the adult leukemia with the highest incidence in Western countries such as Europe and the United States. With the change of lifestyle and the aging of the population, the incidence of CLL in China is also increasing. The clinical presentation of most patients with CLL is atypical. Most patients have no clinical symptoms when they are diagnosed with CLL, and their diagnosis is based on a blood routine showing lymphocytosis; others, nevertheless, develop painless enlarged lymph nodes, mainly in the cervical region (9). The most common symptoms include fatigue, fever, night sweats, loss of weight and easy bruising (10). In advanced patients, anemia, granulocytopenia and thrombocytopenia may occur, often accompanied by infection.

Fifty percent of CLL patients will develop skin manifestations such as pruritus, pigmentation, erythema, papules, nodules and mosquito bite reactions. Cutaneous involvement in CLL can be divided into specific lesions and nonspecific lesions, depending on the clinical and histopathological features (11). However, what is noteworthy is that the vast majority of lesions that occur are nonspecific (12,13). Specific lesions due to leukemic cells infiltration are rare in CLL cutaneous lesions, with an incidence of 4–20% (1). That's why we reported this case. Specific skin lesions include leukemia cutis (LC) and Richter syndrome. The reported cutaneous infiltration includes nodules, papules, infiltrates, plaques and ulcerations. Aberrant co-expression of CD5 and CD23 in neoplastic B lymphocytes in the infiltrated skin was a significant feature. Aggressive treatment of the primary disease can alleviate the skin symptoms to a certain extent.

The patient in our case report was found to have lymphocytosis during blood routine examination due to right lower abdominal pain in 2014, and multiple enlarged lymph nodes could be found in the bilateral cervical region and axilla. She did not have group B symptoms, such as fever, night sweats and loss of weight. The patient was diagnosed with CLL after complete examination. Since 2016, she has had recurrent subcutaneous masses, and some of them could remit spontaneously, which is the remarkable feature and the special feature of this case. In recent half a year, the skin symptoms have become progressively worse. The immunohistochemistry results of skin infiltrated tissue supported the diagnosis of CLL.

The median survival of CLL patients is about 10 years, but the prognosis is highly heterogeneous among different patients. The prognosis of skin infiltration in the course of CLL is controversial. While most authors agree that skin infiltration is associated with a worse prognosis (14,15), others have claimed the opposite (2).

A retrospective study including 42 patients with skin infiltration of CLL suggested that cutaneous lesions may have no influence on prognosis (16). Colburn and other scholars described 2 cases with the appearance of lymphocytic skin lesions in the course of CLL correlating with a favorable prognosis (16). However, it has been observed that unfavorable prognosis usually occurred in patients who had LC lesions in the course of Richter's syndrome or who developed skin lesions after being diagnosed with CLL (2). Some authors observed that 12 out of 16 patients with CLL died an average of 16 months after the presence of LC lesions, leading them to speculate that LC may be an unfavorable prognostic factor (17). Several histological features are associated with an unfavorable prognosis: the presence of epidermal changes (especially acanthosis and ulcerations), more than 5% of medium and large B lymphocytes, massive diffuse or striped infiltration, and the presence of reactive cells in the infiltrate (such as neutrophils, plasma cells and eosinophils) (6). In addition, conversion to Richter syndrome and the appearance of skin infiltration following the diagnosis of CLL suggest a poor prognosis.

In this case report, the skin infiltration was limited and did not involve the epidermis. The infiltration was deep, mainly located in the lower layers of the dermis and the subcutaneous tissue. The infiltrating cells were mainly small B lymphocytes, without reactive cells, and there was no tendency to transform into Richter syndrome. Of these adverse factors, the only consistent one is that skin infiltration appeared after the diagnosis of CLL. So, we predict that may be a good prognosis for her.

Some literature has shown that active treatment of the primary disease can alleviate the skin symptoms to a certain extent. Therefore, we recommended bendamustine + rituximab regimen or ibrutinib, but unfortunately, both of them were refused by the patient. As a result, it is impossible to evaluate the efficacy of each regimen in alleviating the symptoms of skin infiltration, or to compare the differences and advantages between them. This is the limitation of our case. The patient is currently being followed up and we will

continue to follow up on her disease progress.

In clinical practice, early and accurate diagnosis of skin infiltration in CLL is essential, however, until now, detailed descriptions of cutaneous lesions have been lacking in the medical literature. Many challenges remain in diagnosing and treating these skin lesions. For instance, it is difficult to differentiate specific skin lesions from non-specific skin lesions clinically and morphologically in CLL, and there is a lack of optimal treatment strategies for specific skin lesions, etc. To sum up, it is of great scientific significance and practical value to further research the skin infiltration of CLL, which will deepen our understanding of the disease.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2864/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2864/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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