Case Study

Composite Angioimmunoblastic T-Cell Lymphoma and B-Cell Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Involving Both Lymph Node and Bone Marrow With Digital Gangrene

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Abstract: Composite lymphomas (CLs) containing both T- and B-cell lymphomas are very rare. We describe an unusual case of a CL consisting of angioimmunoblastic T-cell lymphoma (AITL) and B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma (B-CLL/SLL). A 68-year old male presented with skin rash, hand pain and lymphadenopathy. The lymph node contained small lymphocytes intermixed with medium to large-sized atypical cells, and arborizing blood vessels. Flow cytometry, immunohistochemistry, EBER and molecular studies confirmed the presence of CL: predominantly AITL with small portion of B-CLL/SLL. In bone marrow, multiple lymphoid aggregates were identified and proved to be composite B-CLL/SLL and AITL. The patient received R-CHOP (Rituxan, cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy. His skin rash improved but he developed bilateral finger gangrene and nine affected digits were amputated. To the best of our knowledge, this is the first report of CL containing concurrent AITL and B-CLL/SLL involving both lymph node and bone marrow.

Keywords: Composite lymphoma, Angioimmunoblastic T-Cell Lymphoma, Chronic Lymphocytic Leukemia, Small Lymphocytic Lymphoma, Gangrene

Introduction

First introduced by Custer in 1954 [1], the term "composite lymphoma" is defined as the simultaneous presence of two or more morphologically and phenotypically distinct types of lymphomas involving a single anatomical location [2]. These lymphomas can arise synchronously or metachronously, and can be clonally related or unrelated.

Composite lymphoma (CL) accounts for 1% to 4.7% of all lymphomas, and consists of a combination of a Hodgkin lymphoma with a B cell or a T-cell non-Hodgkin lymphoma (NHL), a B-cell NHL with a T-cell NHL, or 2 distinct B-cell or T-cell NHLs [3]. Although a wide variety of CL components have been described, CLs containing both T- and B-cell lymphomas (CTBLs) are very rare.

CLs are mostly identified in one single organ or

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tissue with lymph node being the most commonly involved anatomic site. Although few cases have been reported before [4], it is uncommon to find the same type of CLs in both lymph nodes and extranodal organs. Here we describe a very unusual case of a CL composed of AITL and B-cell CLL/SLL coexisting in both lymph node and bone marrow, which to the best of our knowledge is the first report of such combination simultaneously involving two anatomic sites.

Case Report

A 68-year-old male with a history of 40-year smoking, chronic obstructive pulmonary disease, gastroesophageal reflux disease presented with progressively worsening, pruritic skin rash and bilateral hand pain and numbness. He first noted these symptoms when he was lifting boxes at work when he felt bilateral numbness and tingling at his distal finger tips and found his palms and fingers to be bluish. These symptoms became worse with exposure to cold temperature and direct pressure, and improved with warming and rest. He denied history of similar symptoms. This patient was diagnosed with suspected Raynaud's syndrome and was given nifedipine. Mild symptomatic improvement but failure to completely resolve prompted his presentation to our hospital.

Skin examination showed diffuse papular rash involving trunk, abdomen, groin, and knee with sparing of bilateral distal upper and lower extremities; examination of hands showed midpalmar pallor extending to all ten finger tips with tingling and pain with direct pressure and passive flexion/extension. In addition, many palpable tender lymph nodes were identified in bilateral neck, axillary and groin areas. This patient's complete blood cell count (CBC) showed white blood cells (WBC) count of 16.98 x 10^9/L with a differential of 2% plasma cells, 55% segmented neutrophils, 16% lymphocytes, 20% eosinophils and 7% monocytes, hemoglobin (HGB) 12.7 g/dL, mean corpuscular volume (MCV) 88.4fL, and platelets (PLT) 170 x 10^9/L. Skin biopsy was done which suggested early leukocytoclastic vasculitis and the direct immunofluorescence tests were negative for IgG, IgM, IgA, C3 and fibrinogen. Serology tests were negative for hepatitis C virus (HCV), hepatitis B virus (HBV), cryoglobulin but positive for lupus anticoagulant. CT scan of chest, abdomen and pelvis showed multiple lymphadenopathy all over the body with the biggest lymph node measuring 5.6 x 1.0 cm in the left axillary area. The spleen was mildly enlarged (13.1 x 12.0 cm). There was no evidence of arterial occlusion. Due to the diffuse lymphadenopathy and mild splenomegaly observed in CT scan, a flow cytometry using peripheral blood was done and detected a monotypic lambda-restricted CD5(+) / CD10(-) /CD23(+) B-cell population (4%).

H&E staining of the lymph node biopsy from his left neck showed that the lymph node structure was almost completely effaced by a predominately lymphocytic proliferation intermixed with scattered plasma cells, eosinophils and histiocytes. The subcapsular and trabecular sinuses are patent. Occasionally variably disrupted follicles are noted [Figure 1A]. The lymphocytes are composed of small, mature lymphocytes intermixed with medium to large-sized atypical cells. The atypical cells have oval to irregular nuclei, increased nuclear to cytoplasmic ratios, vesicular to coarse chromatin, occasional prominent nucleoli [Figure 1B]. Occasional, disruptive residual follicles are present and are highlighted by CD21 and CD23 [Figure 1E and 1F]. Mildly increased endothelial venules are noted and there are occasional lymphocytes with clear cytoplasm surrounding the endothelial venules. These atypical cells are positive for T cell markers including CD2, CD3, CD4 and CD5, as well as BCL-2, CD10 [Figure 1C and 1D] and CXCL13 [Figure 1G]. EBER is positive in few cells [Figure 1H]. There is no definite feature suggestive of a Hodgkin lymphoma. However, an unexpected finding was the presence of scattered multiple small lymphoid aggregates consisting of monomorphic lymphocytes with round

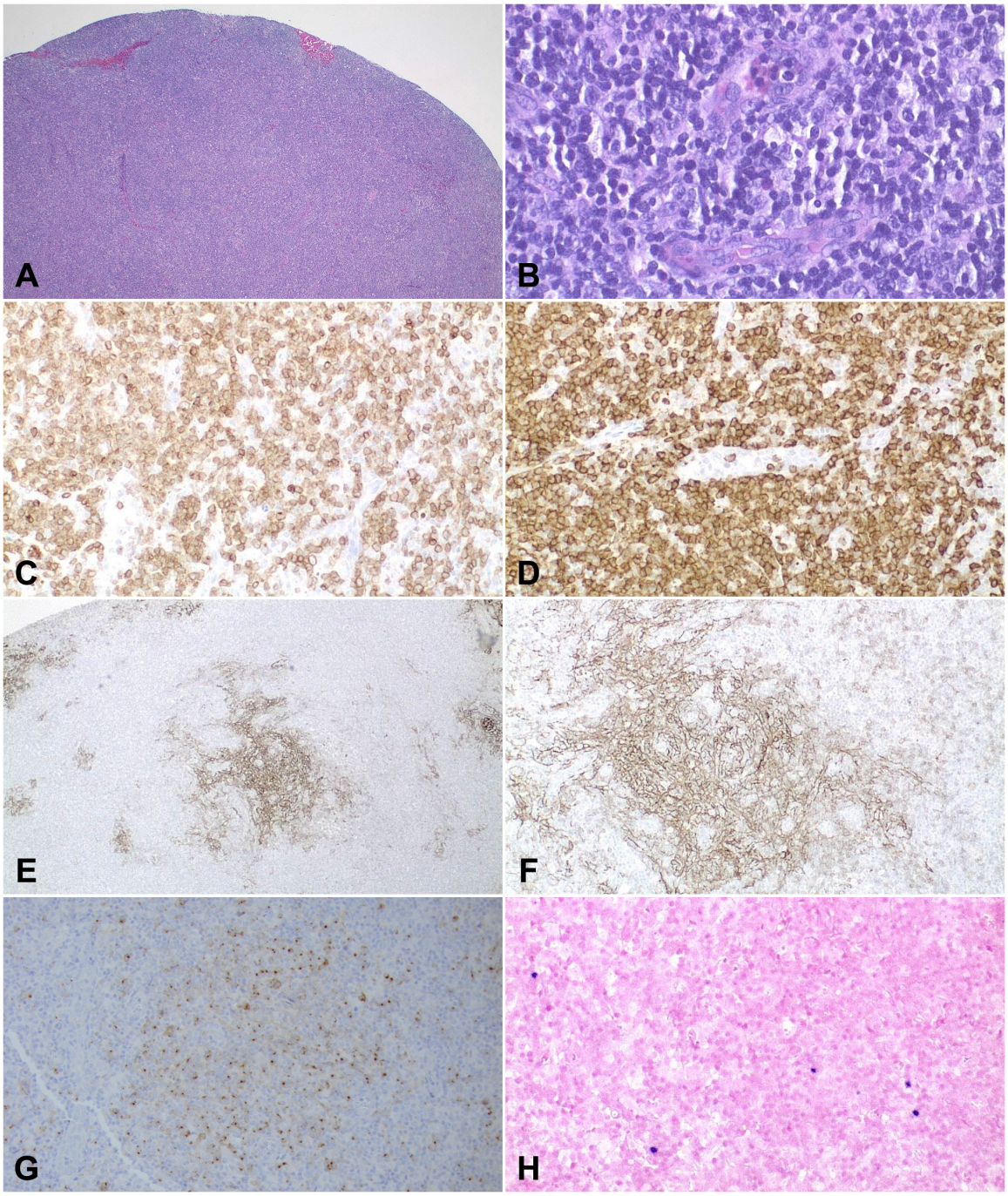

Figure 1: Angioimmunoblastic T-cell lymphoma in the cervical lymph node. A (H&E, X20) and B (H&E, X400) showed the node architecture was effaced by a diffuse infiltrate of small to medium-sized lymphocytes with clear cytoplasm in a background of arborizing endothelial venules. Immunostaining of anti-CD3 (C) revealed their expression in tumor cells (X200), which were positive for CD10 (D, X200); irregular expanded meshwork of follicular dendritic cells were highlighted by CD21 (E, X40) & CD23 (F, X100). Immunostaining of anti-CXCL13 (G, X200) revealed their expression in tumor cells; interspersed immunoblasts showed strong nuclear staining for EBV using in situ hybridization for Epstein-Barr virus encoded nuclear RNA (H, X400).

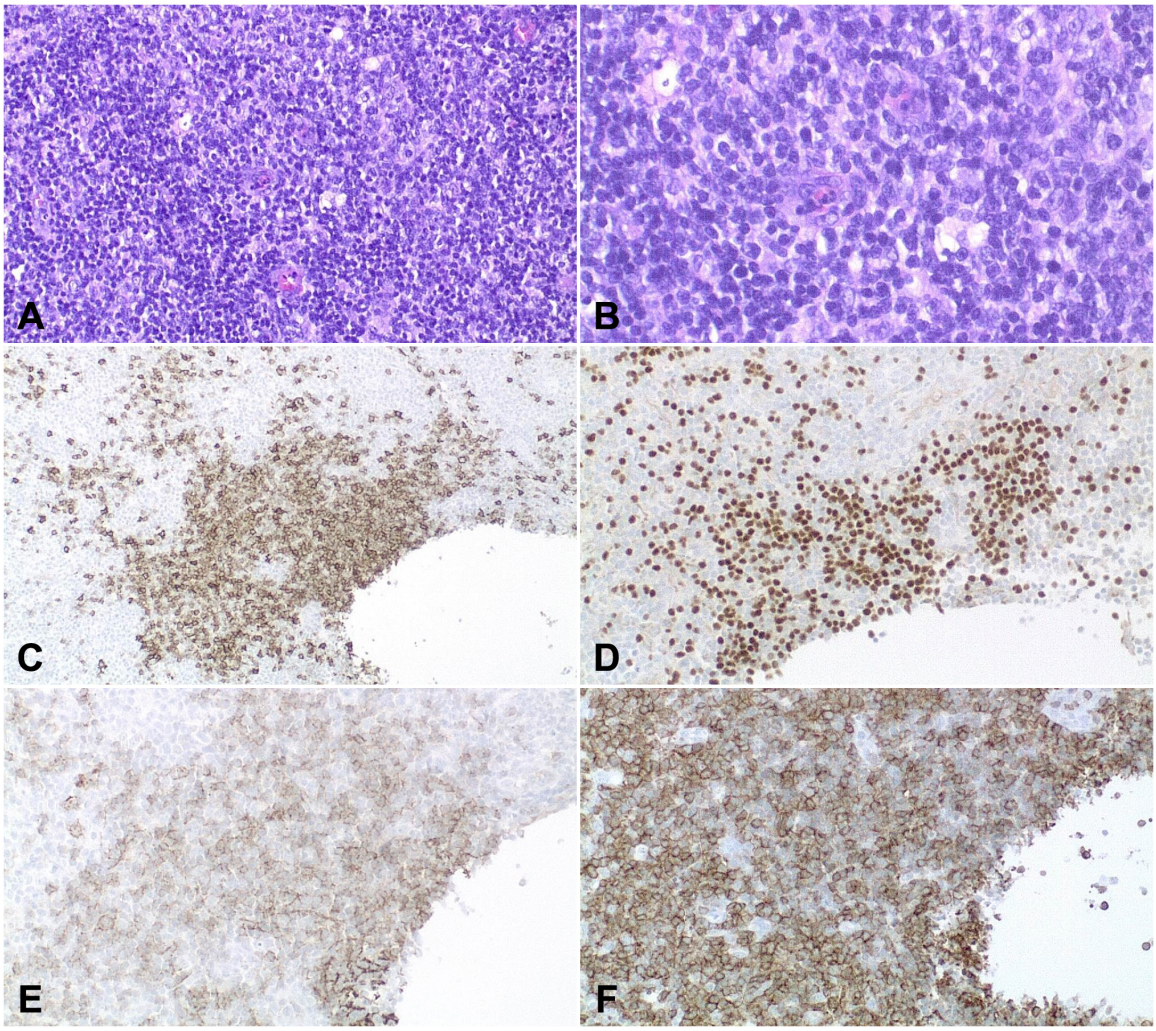

Figure 2: Small B-cell lymphoid aggregates in the cervical lymph node. A (H&E, X200) and B (H&E, X400) showed scattered multiple small lymphoid aggregates consisting of monomorphic lymphocytes with round nuclei, clumped "soccerball-like" chromatin, indistinct nucleoli, and a small amount of cytoplasm. Immunostaining showed that the atypical B cells were positive for CD20 (C), PAX5 (D), CD23 (E) and CD5 (F).

nuclei, clumped "soccerball-like" chromatin, indistinct nucleoli, and a small amount of cytoplasm [Figure 2A and 2B]. These lymphocytes showed positivity for CD5, CD23, CD20, PAX5, CD45 , but are negative for CD2, CD3, CD4, CD8, CD10 and Cyclin D1 [Figure 2C-F]. Flow cytometry of lymph node was done and showed two aberrant populations: 1) CD10(+)/CD4(+)/CD8(-) T-cell, and 2) CD5(+)/CD10(-)/CD23(+) monoclonal B-cell, which is similar to the prior peripheral blood specimen. Cytogenetic studies show normal male karyotype and FISH analysis (CLL panel, including trisomy 12, 13q14/q34, del 11q22.3, del 17p13.1 and t(11;14)) showed no cytogenetic abnormalities. The T-cell receptor (TCR) beta and gamma gene rearrangement by PCR was monoclonal.

Based on the features mentioned above, a diagnosis of composite B-CLL/SLL and AITL was favored and a bone marrow biopsy was performed for staging purpose. In bone marrow, many interstitial and

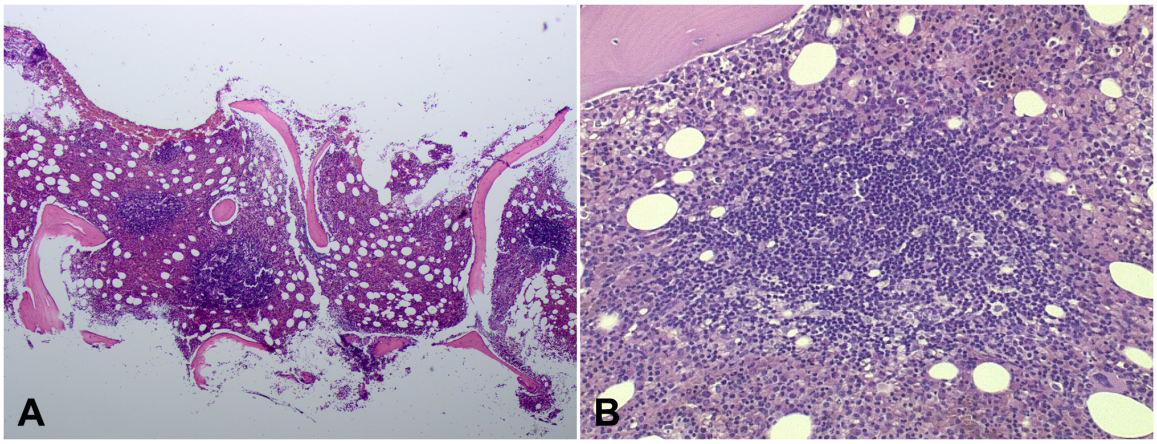

Figure 3: Multiple lymphoid aggregates were noted in bone marrow (A, H&E, X40; B, H&E, X200)

para-trabecular, variably sized lymphoid aggregates were identified, often with prominent blood vessels [Figure 3A and 3B]. These lymphoid aggregates consisted of predominantly B lymphocytes mixed with lesser numbers of T lymphocytes. Immunohistochemistry showed that the lymphocytes comprised about 20-25% of total marrow cells and that the B cell population expressed CD5, CD23, CD20, PAX5, but not CD10. This immunostaining pattern was consistent with of bone marrow involvement of CLL/SLL. In contrast, T cell population is positive for CD2, CD3 and CD10, the pattern of which was consistent with the neoplastic T cells observed in this patient's previous lymph node biopsy [Figure 4A-C]. CD30 only showed occasional positivity within the lymphoid aggregates, and neither the T

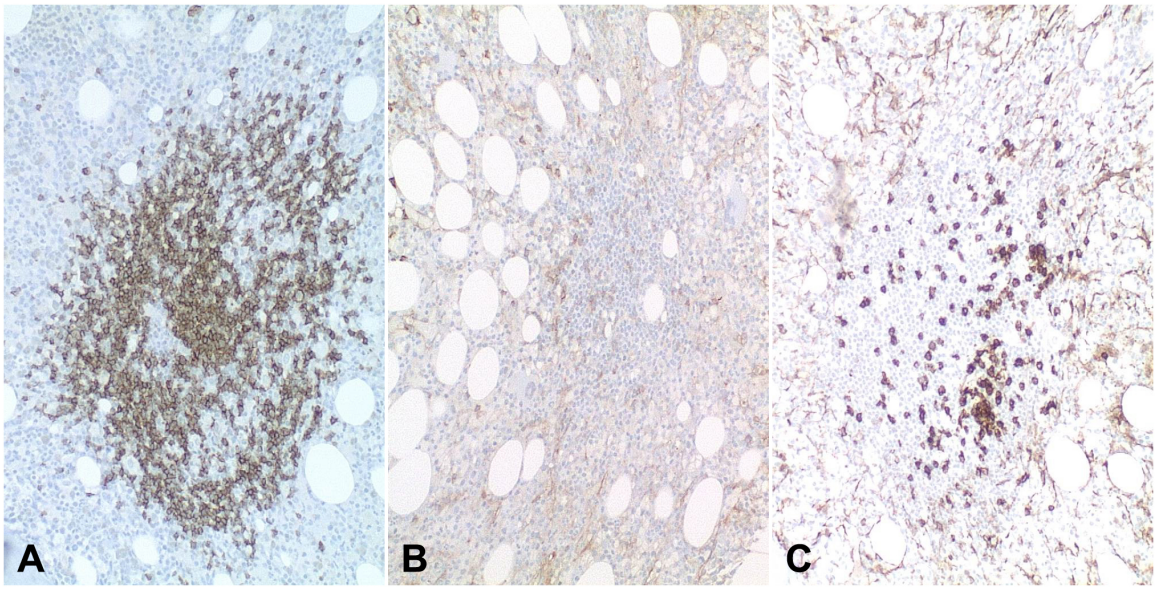

Figure 4: These lymphoid aggregates identified in the bone marrow consisted of predominantly B lymphocytes that are CD20 positive (A), mixed with lesser numbers of T lymphocytes that are CD4 positive (B) and CD10 positive (C).

nor B cells were positive for CD30. These two B and T cell populations were also identified by flow cytometry. Monoclonal T cell population was further identified by the TCR beta and gamma gene rearrangement study (same peak size as those seen in the lymph node). In conclusion, immunohistochemistry, flow cytometry and molecular studies of the bone marrow confirmed that the CL in the lymphoid aggregates similar to that identified in the lymph node: B-CLL/SLL and AITL.

After the diagnosis of composite lymphoma in both the lymph node and the bone marrow, this patient received three cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy. His skin rash mildly improved but he gradually developed bilateral fingers gangrene and infection. Eventually nine affected digits were amputated.

Three months post-chemotherapy, a repeat bone marrow biopsy was performed and identified multiple atypical lymphoid aggregates, which consisted of predominantly T lymphocytes mixed with lesser numbers of B lymphocytes. Immunohistochemistry showed that these B lymphocytes coexpress CD5 and CD23, suggesting low level bone marrow involvement by this patient's known CLL/SLL. In contrast, T lymphocytes were positive for T-cell markers (CD2, CD3, CD5, and CD7) but appeared to be negative for CD10. Moreover, TCR gene rearrangement was not detected, and cytogenetic studies showed normal male karyotype and FISH analysis (CLL panel) showed no cytogenetic abnormalities. Therefore, residual AITL was not identified in the post-chemotherapy bone marrow biopsy.

Discussion

CTBL is very rare and the estimated incidence is lower than 1% of all lymphoid malignancies. So far, less than 100 cases of CTBL have been reported [5, 6]. The B-cell lymphomas in CTBL include CLL, nodular lymphocyte predominant Hodgkin lymphoma (NLPHL), diffuse large B-cell lymphoma (DLBCL), and plasma cell neoplasia, whereas the T-cell non-Hodgkin lymphoma are angioimmunoblastic T-cell lymphoma (AITL), anaplastic large cell lymphoma, and peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS) [7]. In the case series study of Suefuji et al, the combination of DLBCL and AITL was the most common CTBLs (21 out of 29 cases) in the investigated Japanese population [8]. In contrast, Wang et al in the United States reported that PTCL, NOS was the most common T-cell neoplasms (7/14 cases) with DLBCL being the most common coexisting B-cell neoplasms (6/14 cases) [5]. This difference in term of the CTBLs component frequencies in these two studies might be associated with different populations (Japanese vs. Americans). In the present case, CLs containing B-CLL/SLL and AITL was identified in both the lymph nodes and bone marrow. Moreover, monotypic lambda-restricted CD5(+) / CD10(-) /CD23(+) B-cell population was detected in peripheral blood flow cytometry. To the best of our knowledge, no CTBL case with such specific T and B cell components involving two anatomic sites has ever been reported before. Our case likely represents the first description of this entity.

Although the exact pathogenesis of CL remains unclear, several possible theories were proposed for the simultaneous occurrence of AITL and B cell lymphomas in CTBLs. First, the origin of the neoplastic cells in AITL is follicular T helper cell, which could produce B-cell stimulatory factors leading to a continuous stimulation of B cells and promoting their malignant transformation. Second, Epstein-Barr virus (EBV) is known to be associated with AITL, and this specific microenvironment might be associated with the increasing risk of development of an EBV-positive B-cell lymphoma. Third, TET2 mutations are commonly seen in AITL T-cell tumor clones, and these mutations have been identified in some monocytes and hematopoietic precursor cells, and might also be shared by the B cell clones. As such, this genetic lesion might cause the simultaneous development of both T- and B- cell lymphoma [7]. Other proposed theories include chronic expo-

sure to common antigens or carcinogens which simultaneously stimulate or transform B- and T- cells lineages [5]. Our study indicates there is an association between these two lymphomas. The fact that the composite B-CLL/SLL and AITL was found in two different anatomic locations and detected in the same lymphoid aggregates in the bone marrow argue against coincidence or the possibility of incidental collision of these two neoplasms.

The diagnosis of CTBLs can be challenging because on the biopsy sections one lymphoma component often overshadows the other component [5]. Some ancillary studies, such as flow cytometry, immunohistochemistry, oncogenic virus tests such as EBV, cytogenetic study, and molecular tests, can be very helpful in detection of masked neoplastic components. In our case, there are only scattered small to medium-sized lymphoid aggregates on the lymph node sections. Immunostaining, flow cytometry, TCR gene rearrangement study and EBER test greatly help us make the final diagnosis.

AITL patients typically present with generalized peripheral lymphadenopathy, hepatosplenomegaly, and prominent systemic symptoms including fever, weight loss, and rash. Skin biopsy of the rash may demonstrate lymphohistiocytic vasculitis and about 90 percent of patients present with advanced disease. The bone marrow involvement is seen in 30-60% AITL cases [9]. Laboratory abnormalities include polyclonal hypergammaglobulinemia, autoimmune hemolytic anemia, eosinophilia, thrombocytopenia, lymphopenia, elevated lactate dehydrogenase serum levels, elevated erythrocyte sedimentation rate, cryoglobulins, cold agglutinins, and an array of autoantibodies (rheumatoid factor, antinuclear antibody, anti-smooth muscle antibody) [10]. So far, digital gangrene has only been reported once in AITL patients [11] and is rarely seen in patients with Hodgkin, B- cell non-Hodgkin lymphomas and other types of T- cell lymphomas [12, 13]. The patient in our case initially presented with skin rash, hand pain, lymphadenopathy and his skin biopsy suggested leukocytoclastic vasculitis. Eventually he developed digital gangrene and underwent finger amputation. The digital gangrene in this patient is likely associated with thrombosis of vessels secondary to a vasculitis, although the etiology is not completely clear.

The prognosis of CL patients is still very unknown and different literatures show conflicting conclusions [5, 14, 15]. The overall prognosis usually depends on the more aggressive component of CL and should be treated accordingly. The survival of CL patients is mainly defined by the response of the more aggressive component to chemotherapy [16]. In the current case, after three cycles of R-CHOP chemotherapy, although there still low level bone marrow involvement by CLL/SLL, the AITL component was not identified by morphology, immunohistochemistry and molecular testing in the post-chemotherapy bone marrow biopsy. These findings demonstrates that R-CHOP is likely effective in eliminating the AITL instead of the CLL/SLL component in the composite lymphoma.

In conclusion, we presented here a rare case of CL composed of AITL and B-cell CLL/SLL coexisting in both lymph node and bone marrow. This case illustrates the importance of recognization of classic morphologic feature of different lymphomas in conjugation with ancillary studies in the diagnosis of CTBL. The detection of a second clonally unrelated lymphoma may be helpful for therapeutic decisions or prognostic stratification [14]. Further study of such cases may provide useful information for clarifying the etiology and inter-relationship of clonal evolution in lymphoma.

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