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Insights from a patient with chronic lymphocytic leukemia complicating ALK$^+$ anaplastic large cell lymphoma

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SUMMARY Chronic lymphocytic leukemia (CLL) that transforms into a more aggressive lymphoma has been termed Richter syndrome (RS). CLL with T-cell neoplasia is rarely reported; those with ALK$^+$ anaplastic large cell lymphoma (ALCL) are also exceedingly rarely reported. A 63-year-old woman from the south of China presented with generalized lymphadenectasis and fever; she already had a prior diagnosis of CLL 9 years ago. As per her current diagnosis, it was CLL with ALK$^+$ ALCL. The two-lymph node and bone marrow biopsies presented two types of cellular groups: *i*) left cervical lymph node biopsy suggested CLL (Ki67: 10%), along with bone marrow biopsy exhibited enhancement of the small lymphocytes (30%) with scant cytoplasm, round or irregular cell nuclei, and massive amounts of chromatin. Large cells (< 1%) that expressed CD30 and ALK were visible; The results of immunohistochemistry were as follows: CD20 (weak positive); PAX5 (positive); CD23 and CD5 (weak positive); and CD3, CD10, and CyclinD1 (negative); *ii*) left supraclavicular lymph node biopsy suggested ALK$^+$ ALCL (Ki67: 70%). The final diagnosis was CLL with ALCL. The mechanisms of this condition are not fully understood, which might be associated with chronic stimulation of T cells by CLL cells along with immune dysfunction.

Keywords chronic lymphocytic leukemia, Richter syndrome, ALK, anaplastic large cell lymphoma, fludarabine

1. Introduction

Chronic lymphocytic leukemia (CLL) that transforms into a more aggressive lymphoma has been termed Richter syndrome (RS) or Richter transformation (*1*). This occurs approximately in 5-10% of patients with CLL (*2*) and is commonly associated with a worse clinical outcome (*3-5*). Approximately 80-90% of RS cases are clonally related to CLL, whereas only 10-20% are clonally unrelated (*6*). Diffuse large B-cell lymphoma is the most common RS subtype, accounting for 95% of total RS cases, of which less than 5% may develop into classical Hodgkin's lymphoma (*7*). CLL with T-cell neoplasia is rarely reported; those with ALK$^+$ anaplastic large cell lymphoma (ALCL) are also exceedingly rarely reported; however, whether CLL with ALK$^+$ ALCL can be attributed to RS remains controversial (*8*).

2. Clinical manifestation of a rare case

A 63-year-old woman from the south of China was diagnosed with ALK$^+$ ALCL 9 years after she was diagnosed as having CLL (Binet B) in 2011. She complained of lymphadenectasis throughout her body, including in the neck, axilla, and inguinal region. She was untreated (Binet B) as per the National Comprehensive Cancer Network (NCCN) guidelines (*9*) until 2018, when CLL progressed. She underwent six courses of fludarabine, cyclophosphamide, and rituximab chemotherapy and achieved alleviation of the symptoms. In 2020, she felt extreme fatigue with generalized lymphadenectasis. Pathological slices of the left cervical lymph node exhibited the morphological manifestation of CLL/SLL (Figure 1 A1). The results of immunohistochemistry were positive for CD20, CD5, CD23, Bcl-2, Bcl-6, CD21, and Ki67$^+$ cells (10%) and negative for CD3, CD10, Mum1, CyclinD1, and TdT. The results of hybridization in situ were EBER negative. The immunophenotyping data of the bone

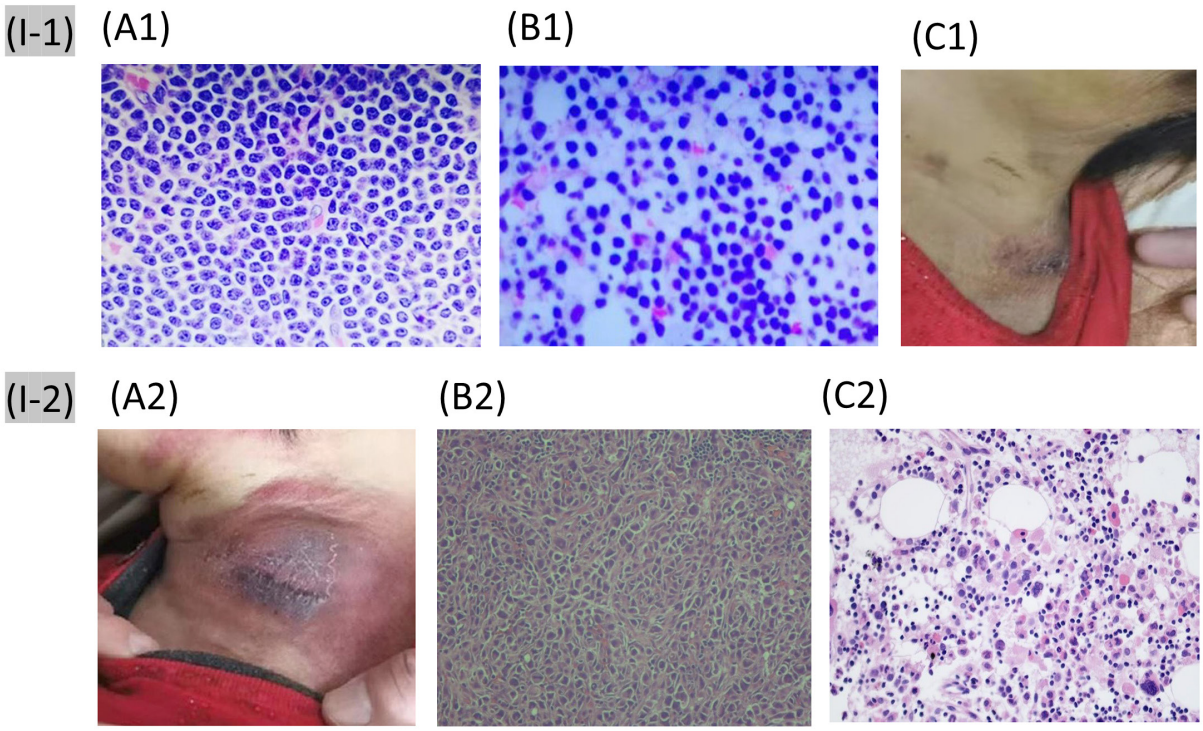

Figure 1. I-1, Images in the first hospitalization (2020); I-2, Images in the second hospitalization (2021). **(A1)** The pathological slices of the left cervical lymph node; **(B1)** The pathological slices of the bone marrow; **(C1)** The skin of the biopsy location of the left cervical lymph node during the first febrile episode; **(A2)** The skin of the biopsy location of the left cervical lymph node at the second febrile episode; **(B2)** The pathological slices of the left supraclavicular lymph node; **(C2)** The pathological slices of the bone marrow. (hematoxylin & eosin staining, 400×).

marrow exhibited increased expression of CD5, CD22, CD19, CD79a, CD23, CD200, IgM, and Kappa and non-expression of CD10, FMC7, CD79b, and Lambda, which indicated that these cells were monoclonal mature B cells (CLL scoring 4-5). Fluorescence in situ hybridization of the marrow revealed the following: CEP12, 68%; D13S319/LAMP1, 85%; ATM/CEP11, P53/CEP17, and IGH/CCND1, negative; TP53 gene mutation, negative; IGH rearrangement, IGHV3-30; and IGH somatic mutation rate, 9.1%. The pathological slice of the bone marrow suggested recurrence of CLL (Figure 1 B1). The patient then underwent treatment with zanubrutinib. After 1 month of zanubrutinib treatment, the biopsy location of the left cervical lymph node began to swell accompanied by tenderness and fever of 39°C (Figure 1 C1).

However, 1 week after antibiotics administration, fever recurred, which was now accompanied by cough, and the lymph node began to swell again. Antibiotics were again administered, but the symptoms did not improve. The skin in the left neck is shown in Figure 1 A2. Lymphadenectasis was noted at the bilateral neck, axilla, supraclavicular area, and inguinal area. She was then diagnosed with pulmonary infection and underwent several anti-infective treatments, including anti-virals and anti-fungals. The cough improved, but fever persisted. Hence, zanubrutinib treatment was maintained. A second biopsy of the left supraclavicular lymph node was conducted, which revealed heteromorphic cell nests. The cells were large with irregular nuclei and abundant karyokinesis (Figure 1 B2). The results of immunohistochemistry were positive for ALK, CD30, EMA, and $Ki67^+$ cells (70%) and negative for AE1/AE3, Bcl-2, Bcl-6, CD10, CD20, CD21, and CD3. The immunophenotyping data of the peripheral blood revealed that 88.41% of cells expressed CD19, CD200, and Kappa; weakly expressed CD5, CD20, CD23, and CD43; and did not express CD10, FMC7, CD79b, Lambda, CD22, CD103, CD38, and CD138. The results indicate that these cells were monoclonal mature B cells. The values of forward scatter and side scatter were small. The immunophenotyping assay of the bone marrow revealed that 86.15% of the cells expressed CD19 and Kappa; weakly expressed CD5, CD20, CD23, CD43, and CD200; and did not express CD10, FMC7, CD79b, Lambda, CD22, CD103, CD38, and CD138, thus also indicating that these cells were monoclonal mature B cells. The lymphoma gene rearrangement of the marrow fluids showed that TCRD, TCRβ, and TCRγ were negative. Human T-cell leukemia virus type I in the peripheral blood was negative. The pathological slices of the bone marrow revealed 60% bone morrow hyperplasia, enhancement of small lymphocytes (30%) with less cytoplasm, round or irregular nuclei, and massive amounts of chromatin. Large cells (< 1%) were visible and expressed CD30 and ALK (Figure 1 C2). The results of immunohistochemistry were as follows: CD20 (weak positive); $PAX5^+$ (positive); and CD23 and CD5 (weak positive). Meanwhile, CD3,

Table 1. The included literature and patients

Literatures	Age, gender	Time from CLL to ALCL (years)	ALCL location	ALK (+ or −)	ALCL Immunophenotype	Chemotherapy before ALCL	Chemotherapy after ALCL	Outcome
Nai *et al*. 1998 (*3*)	61, F	3	Spleen	UK	CD30 (+), CD3 (+), CD45(+), CD45RO (+), EMA (+); CD15 (+/−); CD20 (−), κ (−), λ (−)	Fludarabine	No	LTF
van den Berg *et al*. 2002 (*4*)	76, M	4	Lymph node	−	CD30 (+), CD45 (+), TIA-1 (+), UCHL-1 (+); EMA (+/−); CD20 (−), CD3 (−), CD15 (−), ALK (−), TARC (−)	UK	UK	UK
Marschalkó *et al*. 2007 (*5*)	75, M	7	Cutis	UK	CD30 (+), TIA-1(+); CD4 (+/−); CD3 (−), CD5 (), CD7 (-), CD8 (-), CD79a (-)	No	UK	MF appeared (1.5 years later)
Liu *et al*. 2008 (*18*)	59, M	8	Lymph node	+	CD30 (+), CD45 (+), CD45RO (+), CD4(+), ALK (+); CD5 (-), CD8 (-), CD20 (-), CD23 (-), CD79a (-), EBER (-)	Chlorambucil/prednisone; fludarabine; fludarabine/ rituximab; pentostatin/ cyclophosphamide/ rituximab; weekly rituximab	ICE	Dead (2 months)
Persad & Pang 2014 (*19*)	47, M	0	Lymph node	−	CD30 (+), granzyme (+), CD43 (+), CD23 (+); CD2 (+/-), CD4 (+/-), CD45 (+/-), Bcl-2 (+/-); CD3 (-), CD5 (-), CD7 (-), CD8 (-), ALK (-), EBER (−), B-F1 (−), CD56 (−), CD57 (−), CD10 (−), CD15 (−), CD20 (−), PAX5 (−)	No	R-EPOCH; Autologous stem cell transplant	CR
Boyel *et al*. 2014 (*8*)								
Case 1	56, F	0	Lymph node	+	CD30 (+), Perforin (+), CD5 (+), EMA (+), ALK (+); granzyme (+/−), CD56 (+/−); CD3 (−), CD4 (−), CD8 (−), CD20 (−), EBER (−), Ki67: 80%	No	R-CHOP	ANED (15 months later)
Case 2	66, F	0.7	Lymph node/bone	+	CD30 (+), Perforin (+), CD5 (+), ALK (+); granzyme (+/−), CD4 (+/−), CD7 (+/−), CD45 (+/−); CD3 (−), CD8 (−), CD20 (−), EBER (−)	Cyclophosphamide, vincristine, prednisone, fludarabine, rituximab	Cisplatin, etoposide, cytarabine	Dead (7 months later)
Mant *et al*. 2015 (*17*)								
Case1	60, F	5	Lymph node/ marrow/blood	−	CD30 (+), Perforin (+), CD2 (+), CD3 (+), CD43 (+); granzyme (+/−); ALK (−), CD4 (−), CD5 (−), CD8 (−), CD56 (−), EBER (−)	FCR	Palliative therapy	Dead (2 months later)
Case 2	44, M	2	Lymph node	−	CD30 (+), CD2 (+); granzyme (−), Perforin (−), ALK (−), CD4 (−), CD5 (−), CD8 (−), CD3 (−), EBER (−)	Fludarabine; CHOP	CHOP	Dead (1 months later)

AD: Alive with disease; ANED: alive with no evidence of disease; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CR: complete remission; FCR: fludarabine, cyclophosphamide, rituximab; ICE: ifosfamide, carboplatin, and etoposide; LTF: loss to follow-up; MF: mycosis fungoides; R-EPOCH: rituximab, etoposide, prednisone, vincristine, doxorubicin, and cyclophosphamide; UK: unknown.

Table 1. The included literature and patients (continued)

Literatures	Age, gender	Time from CLL to ALCL (years)	ALCL location	ALK (+ or −)	ALCL Immunophenotype	Chemotherapy before ALCL	Chemotherapy after ALCL	Outcome
Case 3	86, M	1	SNose	−	CD30 (+), CD43 (+); CD4 (+/−), granzyme (+/−); ALK (−), CD5 (−), CD8 (−), CD3 (−), CD45 (−), CD15 (−), CD56 (−), EBER (−)	UK	No	AD (3 months later)
Case 4	64, M	8	Lymph node/ Ascitic fluid/CNS	+	CD30 (+), CD4 (+), granzyme (+), Perforin (+), ALK (+), EMA (+); CD43 (+/−), CD45 (+/−); CD2 (−), CD5 (−), CD8 (-), CD3 (-), EBER (-)	FCR	CHOP; High dose methotrexate; intrathecal chemotherapy	ANED (16 months later)
Case 5	63, F	8	Lymph node	+	CD30 (+), CD43 (+), Perforin (+), ALK (+); CD4 (+/-); CD45 (-), CD56 (-), CD5 (-), CD8 (-), CD3 (-), granzyme (-), EBER (−)	Chlorambucil and prednisone	CHOP	ANED (10 months later)
Thakra & Konoplev. 2017 (*6*)	56, M	UK	Marrow	+	CD30 (+), ALK (+), CD4(+), CD5 (+), CD45 (+), CD43 (+); CD2 (+/−); CD3 (−), CD7 (−), CD8 (−), CD15 (−), Pax-5 (−)	UK	UK	UK
Van Der Nest *et al*. 2019 (*11*)								
Case 1	77, F	4	Lymph node	+	CD30 (+), MUM1 (+), granzyme (+), perforin (+), ALK1 (+); CD4 (+/−), CD45 (+/−); CD20 (−), PAX5 (−), CD79a (−), BOB1 (−), OCT2 (−), CD3(−), CD5 (−), CD138 (−), BCL2 (−), EBER (−), CD15 (−), C-MYC (−), CD34(−), CD117(−), TIA1(−)	UK	Mini-CHOP	A high-grade neuroendocrine tumor occurred
Case 2	74, M	8	Cutis	−	CD30 (+), CD3 (+), CD4 (+), granzyme (+); CD2 (+/−), CD5 (+/−), CD7 (+/−); CD20 (−), ALK (−), EBER (−), CD8 (−), BF1 (−)	No	CHOP, R-CHOP, dexamethasone, cytarabine, carboplatin, gemcitabine/vinorelbine, high dose methotrexate	Dead (3 years later)
Case 3	66, M	16	Cutis/Lymph node/Bone	−	CD30 (+), CD 4(+), CD43 (+), CD2 (+), CD7 (+), TIA (+), granzyme B (+), (focal) and EMA (+), (patchy); CD20 (−), CD45RO (−), CD3 (−), CD5 (−), CD8 (−), CD56 (−), ALK1 (−), CD163 (−), CD123 (−), BCL11A (−), CD2AP (−), CD303 (−), EBER (−), HHV8 (−)	No	Cyclophosphamide; vincristine/gemcitabine and brentuximab vedotin.	Dead (4 years)

AD: Alive with disease; ANED: alive with no evidence of disease; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CR: complete remission; FCR: fludarabine, cyclophosphamide, rituximab; ICE: ifosfamide, carboplatin, and etoposide; LTF: loss to follow-up; MF: mycosis fungoides; R-EPOCH: rituximab, etoposide, prednisone, vincristine, doxorubicin, and cyclophosphamide; UK: unknown.

CD10, CyclinD1 were negative. Hence, the patient was finally diagnosed as CLL with ALK^+ ALCL. She then underwent cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) plus zanubrutinib chemotherapy. After 4 days of treatment, fever abated. After two courses of treatment, generalized lymphadenectasis was resolved, and efficacy was evaluated as "partial remission". The patient is well and alive after the last follow-up (2022 August).

This study was approved by the ethics committee of the First Hospital of Putian City, and informed consent was signed to present her agreement reported in this study.

3. Experience and insights

CLL with ALCL is rarely reported. By far, only 16 cases have been reported in the literature (Table 1); of those, 10 are males and 6 are females. The median age of patients was 63.5 years (range, 47-86 years). The average time from CLL to diagnosis of ALCL was 4 years (range, 0-16 years). With respect to ALK expression, seven cases were ALK^+, seven cases were ALK^-, and two cases were unknown. In this case, the patient was 63 years old, and the time from CLL to diagnosis of ALK^+ ALCL was 9 years.

To date, mechanisms of the CLL complicating aggressive T lymphoma remain unclear. Some authors believe that it is associated with the chronic stimulation of T cells by CLL cells along with immune dysfunction (*10-12*). In addition, abnormal proliferation of T cells might cause new mutations that may develop into aggressive T-cell lymphoma (*12*). This theory is also supported by a previous report that the cytotoxic T-cell expansions in the peripheral blood are closely associated with the occurrence of T-cell lymphoma (*13*). In total, 12 of 16 CLL patients that developed ALCL expressed cytotoxic T lymphocyte-related genes such as TIA-1, granzyme, and perforin (Table 1). Unfortunately, the expression of these genes was not investigated in the patient in this study. The immune dysregulation inherent to CLL also contributes to T-cell oncogenesis due to its capacity to induce mixed neoplastic clones (*10*). A high occurrence of lymphoma is also observed in other diseases with immune dysregulation, such as sicca syndrome, rheumatoid arthritis, and chronic lymphocytic thyroiditis. All of this evidence indicates that immune dysregulation plays a role in the occurrence of lymphoma. Moreover, T cells from patients with CLL (*vs*. healthy subjects) seem to be more resistant against cellular apoptosis (*14*). All these factors might have contributed to the development of aggressive T lymphomas. Another factor that must be seriously considered is that whether the treatment for CLL has secondarily induced the occurrence of ALCL. Indeed, this is a controversial issue. The present case underwent six courses of fludarabine treatment before the occurrence of ALK^+ ALCL. Of all the 16 patients included in the literature review, 5 underwent treatment with fludarabine. Gassner *et al*. reported that the administration of fludarabine continuously reduced the number of $CD4^+$ and $CD8^+$ T cells, which then correlates with the cytotoxic effects of fludarabine on T cells *in vitro*. Moreover, fludarabine plays a role in immune modulation, which might be a double-edged sword to T-cell oncogenesis (*15*). The role of CLL treatment in T-cell oncogenesis requires further investigation.

Before this patient could be diagnosed with ALCL, fever was a predominant symptom, and lymph node swelling recurred after zanubrutinib treatment, which we considered as both being due to the skin and soft tissue infections. Unfortunately, the subsequent anti-infective therapy was ineffective. We had to determine the final diagnosis by performing lymph node and bone marrow biopsies. When the patient had fever and recurrence was considered, the lymph node biopsy exhibited ALK^+ cells. Moreover, the bone marrow biopsy found that there were < 1% large cells (Figure 1 C2). These results suggested that the lymph nodes and bone marrow were involved.

Generalized ALCL has a poor clinical outcome. Patients with ALK^+ may have better outcomes than those of ALK^- with the development of treatments such as brentuximab vedotin (BV) and crizotinib. The 5-year survival rate of ALK^+ ALCL is 70-80%; in contrast, those with ALK^- ALCL is only 40-60% (*16*). Our case is well and alive. However, due to the small sample size and the heterogeneity of the included studies, the effects of ALK expression on the prognosis of CLL complicating ALCL as well as the efficacy of the related treatments require further investigation.

Taken together, CLL with ALCL is rare, and the mechanisms involved are not fully understood. Chronic stimulation of T cells by CLL cells, along with immune dysfunction in CLL, might play a role. Several clinical problems, such as whether fludarabine treatment will increase the risk of CLL developing ALCL and the difference in the prognosis between idiopathic ALCL and ALCL complicated from CLL, have not been elucidated. Further investigation is required in the future.

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