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CORRESPONDENCE

Does a subset of mature T-cell leukemias with features akin to T-cell prolymphocytic leukemia but lacking rearrangement of the *TCL1* represent peripheral T-cell lymphoma, NOS in a leukemic phase?

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Abstract

In the current WHO classification, a T-cell prolymphocytic leukemia (T-PLL) diagnosis requires lymphocytosis of >5 × 109/L, evidence of monoclonality, and *TCL1A* or *MTCP1* rearrangement. However, the 2019 consensus document suggested that in the absence of rearrangement of *TCL1*-family, the presence of abnormalities involving chromosome 11 (11q22.3; ATM), chromosome 8 (idic(8)(p11), t(8;8), trisomy 8q), 5, 12, 13, 22, or a complex karyotype, as well as involvement specific sites (e.g., splenomegaly, effusions) would suffice for a diagnosis of T-PLL. We present a patient diagnosed with T-PLL with *MTCP1* rearrangement who was successfully treated with alemtuzumab followed by consolidative allogeneic unrelated donor stem cell transplantation. Eight years later, the patient presented with inguinal lymphadenopathy with features more akin to peripheral T-cell lymphoma, NOS (PTCL, NOS) of the GATA3 subtype, and there was no evidence of peripheral blood involvement. However, the lymphoma cells were clonally related to those at presentation. Currently, literature on T-PLL-like cases lacking the rearrangement of *TCL1A* is limited, and the possibility of whether a proportion of such cases could represent PTCL, NOS (with leukemic involvement) needs consideration.

T-cell prolymphocytic leukemia (T-PLL) is a clinically aggressive mature T-cell neoplasm characterized by a lymphocytosis of > 100 × 10^9/L, hepatosplenomegaly, and generalized lymphadenopathy; skin involvement and serous effusions are noted in a minority of cases. It is a rare malignancy, constituting 2% of mature lymphocytic leukemias, and is generally associated with a poor prognosis with a median survival time of 1 year [1, 2]. The leukemic cells frequently co-express CD4 and CD8, express TCL1A, and overexpress CD52 [3, 4]. The most frequent driver abnormality is the chromosomal rearrangement inv(14)(q11q32) or t(14;14)(q11;q32), which juxtaposes *TCL1A* to the enhancer locus of *TRA/TRD*. In about 5% of cases, t(X;14)(q28;q11.2), resulting in *MTCP1::TRA/D* is found [5]. Rarely, *TCL1A* is juxtaposed to the *TRB* locus [6]. In the current 5th Edition World Health Organization (WHO) classification, a diagnosis of T-PLL requires lymphocytosis of > 5 × 10^9/L, evidence of monoclonality, and the presence of *TCL1A* or *MTCP1* rearrangement [7]. However, the 2019 consensus

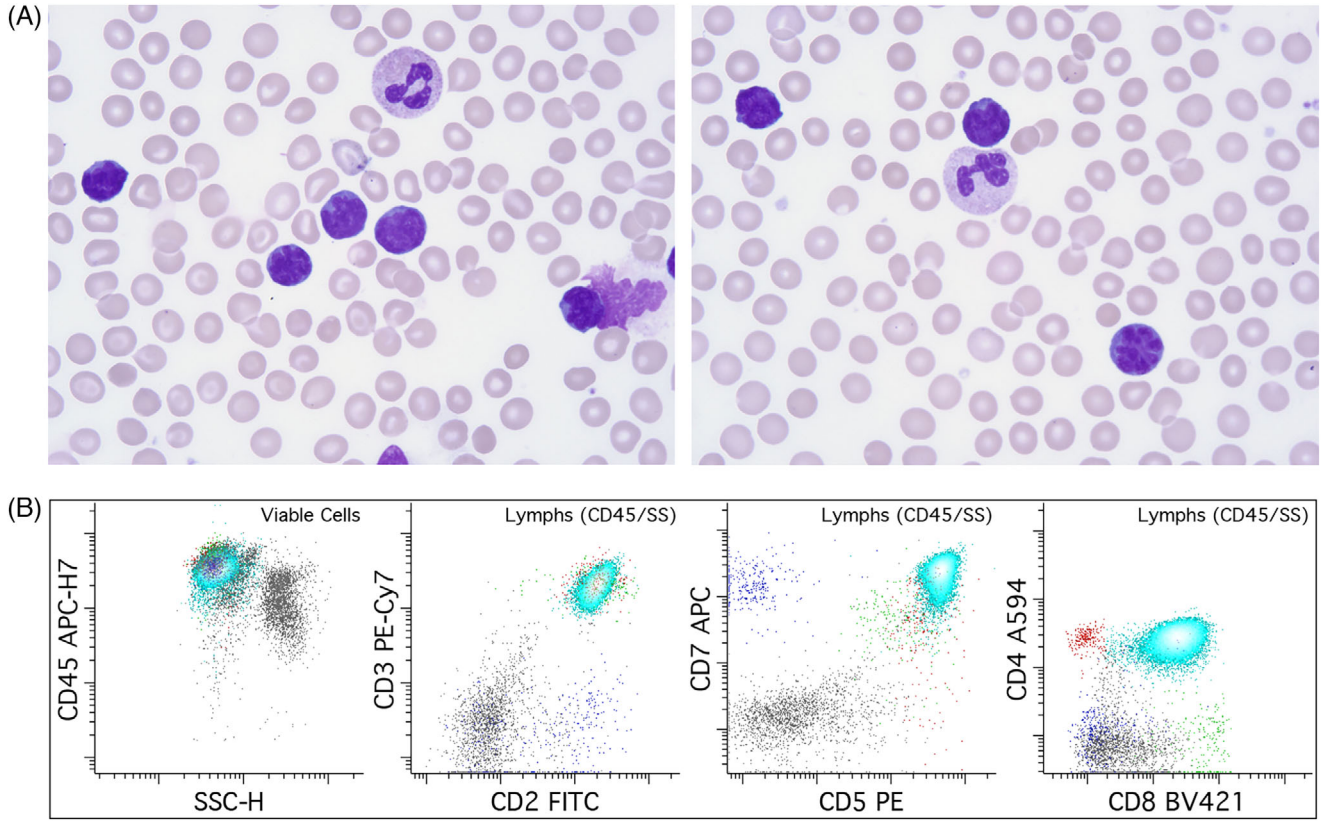

FIGURE 1 Morphologic and flow cytometric features of neoplastic lymphoid cells in the peripheral blood at diagnosis. (A) The atypical lymphocytes in the peripheral blood at diagnosis had irregular nuclear contours, dense, clumped chromatin, and scant basophilic agranular cytoplasm. (B) Flow cytometric analysis of peripheral blood performed at diagnosis revealed an abnormal T cell population (colored in aqua) with low side scatter, and expression of CD45, CD2, CD3, CD5, CD7, and co-expression of CD4 and CD8.

document on the diagnosis of T-PLL suggested that in the absence of rearrangement of the *TCL1*-family, the presence of abnormalities involving chromosome 11 (11q22.3; *ATM*), chromosome 8 (idic(8)(p11), t(8;8), trisomy 8q), 5, 12, 13, 22, or a complex karyotype, as well as involvement of T-PLL specific sites (e.g., splenomegaly and effusions) would suffice for a diagnosis of T-PLL [8]. A recent publication also supports the inclusion of T-PLL-like leukemias without rearrangement of the *TCL1A* family of genes within the T-PLL category [9].

We present a case of a male patient in his 60s with absolute lymphocytosis of 116 × 10^9/L and atypical lymphoid cells in the peripheral blood. The atypical lymphoid cells had irregular nuclear contours, dense, clumped chromatin, and scant basophilic agranular cytoplasm (Figure 1A). Clinically, the patient had no appreciable hepatosplenomegaly or lymphadenopathy. Lungs were clear and skin showed no erythema or rashes. Flow cytometric analysis revealed an abnormal, mature T-cell population comprising 89% of the white blood cells with abnormal co-expression of CD4 and CD8, increased CD7 expression, bright CD52, and normal expression of CD2, CD3, CD5, CD38 (variable), CD45, and TCR alpha-beta. CD1a, CD10, CD25, CD34, CD30, CD56, terminal deoxynucleotidyl transferase, and T-cell receptor (TCR) gamma-delta were negative (Figure 1B). Subsequent evaluation of the bone marrow performed at another laboratory raised concern for low-level involvement, while there was no evidence of involvement of the cerebrospinal fluid or other sites. Karyotyping of the peripheral blood sample showed a complex karyotype with t(X;14)(q28;q11.2) and multiple numeric and structural abnormalities. Fluorescent in-situ hybridization (FISH) studies confirmed a TCR gene rearrangement involving chromosomes X and 14. T-cell clonality studies by PCR revealed clonal TCR gamma gene rearrangement (TRGV1-8:TRGJP1/2; 234 bp product) [10]. The FISH study for *TCL1A* gene rearrangement was negative. The patient was successfully treated with alemtuzumab followed by consolidative allogeneic unrelated donor stem cell transplantation.

The patient presented eight years post-transplant with palpable lymphadenopathy in the left femoral groin. Histologic examination of the lymph node showed a diffuse monomorphic infiltrate of small to intermediate-sized atypical lymphoid cells with a scanty to moderate amount of cytoplasm, irregular nuclear contours, coarse chromatin, and variably prominent nucleoli. By immunohistochemistry, the atypical lymphoid cells expressed CD2, CD3, CD5, CD7, CD8, TCR-beta, GATA3 (strong, uniform), and TIA-1 (minor subset) and were negative for CD4, TCL1, CD20, TCR-delta, granzyme B, CD25, CD56, and Epstein-Barr-encoded RNA (Figure 2). Ki-67 proliferation rate varied from 20% to 70%. Flow cytometric analysis performed at another laboratory reported that the atypical lymphoid cells were positive for CD45, CD2, CD3, CD5 (bright), CD7 (moder-

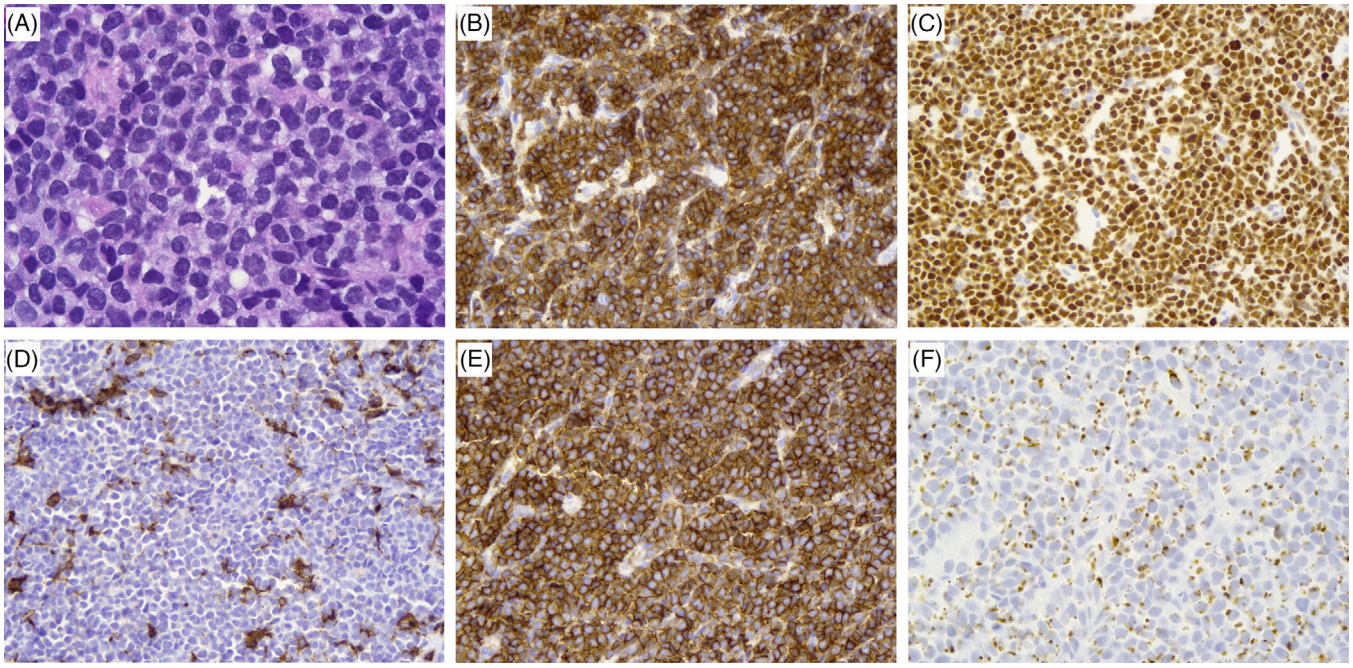

FIGURE 2 Morphologic and immunophenotypic features of neoplastic lymphoid cells in the lymph node at relapse. (A) Morphologic examination of the left femoral groin lymph node at relapse revealed a diffuse infiltrate of medium-sized atypical lymphoid cells with irregular nuclear contours, condensed chromatin, variably prominent nucleoli, and a moderate amount of cytoplasm. (B–F) By immunohistochemistry, the atypical lymphoid cells are positive for CD3 (B), GATA-3 (C), CD8 (E), and TIA-1 (F) while being negative for CD4 (D). This immunophenotype differed from that identified at diagnosis.

ate), CD8 (moderate), and CD38 and negative for CD4, CD16, and CD56. Interphase FISH was negative for *TCL1A* gene rearrangement but revealed a one-copy gain of *TCL1A*. Additionally, next-generation sequencing analysis for genes associated with lymphoid neoplasms revealed the presence of a clinically significant variant involving *ATM* (p.S743*, NM_000051.3:c.2228C > A, VAF 87%). T-cell clonality studies revealed clonal TCR gamma gene rearrangement (TRGV1-8:TRGJP1/2; 234 bp), with the size of the PCR product being identical to that identified at diagnosis, confirming the clonal relationship of the neoplastic lymphoid populations at diagnosis and relapse [10]. Peripheral blood did not reveal any abnormal lymphocytes, and the chimerism study on peripheral blood showed 100% donor origin. A positron emission tomography scan revealed a 13.4 cm hypermetabolic left thigh mass with associated pelvic lymphadenopathy.

We report on an unusual case of mature T-cell leukemia/lymphoma initially presenting with T-PLL-like features (but lacking rearrangement of *TCL1A*) with peripheral blood and bone marrow involvement, and later relapsing in the lymph node and extranodal compartment with features more akin to peripheral T-cell lymphoma, NOS (PTCL, NOS) of the GATA3 subtype. The case highlights the question of whether a subset of T-PLL-like mature T-cell leukemias lacking rearrangement of the *TCL1A* represents PTCL, NOS with a leukemic presentation. Of note, the neoplastic lymphoid population at relapse was CD8 positive, shifted from CD4-/CD8-double positive, and with a strong and uniform expression of GATA3. Immunophenotypic conversion with increased CD8 expression has been described in a small number of T-PLL cases that progress to a more aggressive disease [4, 11]. While pathogenic variants of *ATM* have been reported in a significant proportion of T-PLL, as noted in our case, such aberrations are not specific to T-PLL and are also found in other lymphoid neoplasms, including PTCL, NOS [12, 13]. Leukemic involvement is known in PTCL, NOS. In the study by Kawamoto K et al, 16 of the 91 patients with PTCL, NOS had > 1% tumor cells in the peripheral blood [14]. Circulating neoplastic cells were marginally larger than T-PLL cells in this case series [14, 15].

Diagnosing T-PLL is particularly challenging due to its heterogeneous clinical presentation and morphologic variation. In addition to the classic prolymphocytic morphology (~75%), cases with small cell and cerebriform variants are described. The 5th Edition WHO classification mandates the detection of *TCL1A* family rearrangement by FISH studies or karyotyping, or TCL1A protein expression for diagnosis [7]. The WHO definition characterizes T-PLL as an entity defined by the presence of 'relatively unique' genetic drivers for the disease in the context of appropriate secondary genetic abnormalities or a characteristic clinical presentation. The WHO definition requires all three major criteria to be met—lymphocytosis of $> 5 \times 10^9$/L or bone marrow infiltrate with T-PLL immunophenotype, evidence of T-cell monoclonality, and the presence of *TCL1A* or *MTCP1* rearrangement or TCL1A protein expression. In addition, one of the four minor diagnostic criteria needs to be met—abnormalities involving chromosome 11 (11q22.3, *ATM*); abnormalities in chromosome 8: idic(8)(p11), t(8;8), trisomy 8q; abnormalities in chromosome 5, 12, 13, or 22, or complex karyotype; involvement of specific sites (e.g. splenomegaly, effusions). A less stringent definition, as suggested by the 2019 consensus docu-

ment, may inadvertently include other T-cell malignancies. According to this document, a diagnosis of T-PLL can be made if either all three major criteria or two major criteria (lymphocytosis of $> 5 \times 10^9$/L or bone marrow infiltrate with T-PLL immunophenotype, evidence of T-cell monoclonality) along with one minor criterion are met. However, this definition as per the 2019 consensus document excludes the requirement for the unifying genetic driver. Such a 'loose' definition may compromise our efforts to effectively treat the disease, potentially affecting cure rates and increasing the risk of morbidity [8]. Further clinical, immunophenotypic, genomic, and transcriptomic studies on a larger cohort of such T-PLL-like cases are essential for understanding the biology of these neoplasms and improving diagnostic accuracy. The case we present also questions whether it is appropriate to include cases with *MTCP1* rearrangement within the category of T-PLL, as the subsequent follow-up data were different from that of conventional T-PLL. Studies on *MTCP1*-rearranged T-PLL are scarce. Hu et al reported 15 cases of *MTCP1*-rearranged T-PLL, highlighting some significant differences from conventional T-PLL [5]. In this series, the male-to-female ratio was 1:2 (in contrast, conventional T-PLL shows mild male predominance); 10 patients were identified incidentally without any B symptoms; and only five had splenomegaly. Similarly, the patient we presented had no appreciable splenomegaly.

In conclusion, as the available data on clinicopathological and molecular aspects of T-PLL-like cases lacking rearrangements of *TCL1A* and *MTCP1* are insufficient, and the relationship to T-PLL is currently not clear, such cases should preferably be classified as PTCL, NOS (with leukemic involvement) after exclusion of other leukemic T-cell entities. If classifying these cases as leukemic PTCL, NOS does not seem appropriate, the "umbrella/family" category, mature T-cell leukemia may be used. Furthermore, a large cohort study comparing T-PLL cases with *TCL1A* rearrangement to those with *MTCP1* rearrangement is essential.

AUTHOR CONTRIBUTIONS

David C. Gajzer wrote and edited the manuscript. Xueyan Chen edited and critically evaluated the manuscript. Daniel E. Sabath edited and critically evaluated the manuscript. Christina Poh edited and critically evaluated the manuscript. Kikkeri N. Naresh wrote, edited, and critically evaluated the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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