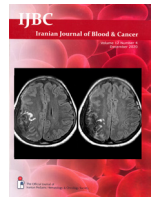
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CASE REPORT

Acute Lymphoblastic Leukemia Switch Lineage upon Relapse to Acute Bilineage Leukemia: A Case Report

Valiollah Mehrzad[1], Pardis Nematollahi[2], Anahita Emami[1], Sayyideh Forough Hosseini[1]

[1]Hematology Division of Internal Medicine Department, Isfahan University of Medical Sciences, Isfahan, Iran
[2]Pathology Department, OMID Professional Hospital, Isfahan University of Medical Science, Isfahan, Iran

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**Corresponding author:*
Sayyideh Forough Hosseini,
Isfahan University of Medical Sciences, Isfahan, Iran
Tel: +98-9131294250
Email: drhosseini.forough@gmail.com

ABSTRACT

Although acute leukemia commonly relapses in adults, the conversion of leukemic cell lineage (lymphoid or myeloid) upon relapse has rarely taken place. "Lineage switch" is a term widely used to define the leukemic lineage transformation as assessed by morphology, cytochemistry, and immunophenotyping from diagnosis to relapse. In most lineage switch cases, B-cell lymphoblastic leukemia/lymphoma relapses as acute myeloid leukemia or vice versa. Here, we report an exceedingly rare case of T-cell acute lymphoblastic leukemia relapsing as mixed-phenotype acute leukemia.

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Introduction

More than 50% of adults with acute lymphoblastic leukemia (ALL) will experience a relapse after the first remission.[1] Most relapsed Leukemia cells present with immunophenotypic and cytogenetic features similar to original leukemia or represent minor acquired additional abnormalities. On the other hand, in rare cases, a "lineage switch" may happen, in which the relapsed leukemia cells lose their defining markers of one lineage and display features of a new lineage.[2] Lineage switch occurs in nearly 6-9% of relapsed cases and is more frequently seen among children and patients receiving immunotherapy with either blinatumomab or chimeric antigen receptor T-cells (CAR-T).[3-5] In most reported cases of lineage switch, patients with B-cell lymphoblastic leukemia/lymphoma (B-ALL) relapsed into acute myeloid or monocytic leukemia (AML).[2]

Occasionally, patients experiencing lineage switch may present with markers compatible with more than a single clone of blasts. According to the latest World Health Organization (WHO) Classification, leukemic cells that do not show discrete evidence of a single-lineage differentiation are considered as acute leukemia of ambiguous lineage. Ambiguous-lineage leukemia accounts for <4% of all acute leukemia cases. It occurs in both children and adults, but it is more frequent in adults. Ambiguous leukemia includes acute undifferentiated leukemias, which express no lineage-specific antigens, and mixed-phenotype acute leukemias (MPALs). In terms of MPALs, leukemic populations may express distinct blasts of more than one lineage or one population with multiple antigens of different lines on the same cells or a combination of both.[6]

Here, we report a rare case of a patient with T-cell lymphoblastic leukemia/lymphoma (T-ALL) who relapsed into MPAL less than 12 months after complete remission. In other words, relapsed leukemia cells did not show evidence of differentiation consistent with single lineage blasts and expressed antigens of more than one lineage to such a degree that it was impossible to assign

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leukemia to one lineage with certainty.

Case Presentation

A 17-year-old boy with a history of fever and malaise was referred to Omid Hematology-oncology Hospital, Shiraz, Iran. On physical examination, generalized lymphadenopathy and splenomegaly were notable. Laboratory tests showed the following results: WBC $54\times10^3/mm^3$, Hb 8.3 g/dL, Platelet $44\times10^3/mm^3$. Mediastinal widening and splenomegaly were remarkable findings on imaging studies. Bone marrow biopsy showed a population of more than 90% lymphoblasts that were compatible with the T-cell phenotype on flow cytometry (figure 1A). Cyctoplastic CD3 was positive in Immunohistochemistry (ICH).

The patient's karyotype analysis was normal, and he did not have any evidence of central nervous system involvement. He received induction chemotherapy for T-ALL with a hyper CVAD regimen,[7] and complete remission was achieved after receiving the first cycle of induction chemotherapy. Although the patient was a candidate for an allogenic stem cell transplant, no suitable donor was identified. Therefore, consolidation chemotherapy (Hyper CVAD, High Dose MTX, and High Dose Cytozar) and then maintenance therapy was continued.[7] Nearly, 12 months after the primary diagnosis, he experienced prolonged fever, splenomegaly, and generalized lymphadenopathy. Laboratory tests revealed WBC $1.5\times10^3/mm^3$, Hb 9.8 g/dL, and Plt $20\times\times10^3/mm^3$.

Bone marrow aspiration and biopsy were performed which showed a cellular marrow with more than %90 blasts (figure 1B). However, on morphological reviews, two populations of blastic cells with a proportion of cells >10% were observed. One of the populations were blasts with fine chromatin, scanty cytoplasm, and inconspicuous nucleoli, and the other was comprised of moderate-sized blasts containing cytoplasmic granules.

Flow cytometry revealed two separate populations in the blastic gate. One population showed CD5 (30%), CD7 (T-lymphoblast) (40%), and the other revealed myeloid markers including MPO (90%), CD64, CD33, and HLA-DR (myeloblast) (table 1).

Findings were compatible with MPAL (T/M) or bilineage leukemia (figures 2, 3). Cytogenetic study on bone marrow was normal again. Upon diagnosis of the recurrence, the patient was started on a chemotherapy regimen containing fludarabine, cytarabine, and G-CSF.[8] However, complete remission was not achieved and the patient died due to Sepsis 20 days after the beginning of chemotherapy. (Nothing has been mentioned about obtaining the patient's cnsent to report the case)

Discussion

Most relapsed acute leukemia cases present with minor changes in blastic markers and predominantly feature the phenotype of original lineage. However, a Lineage switch of lymphoid or myeloid leukemia cells rarely happens in the disease course and presents with blasts different from the de novo leukemia.[2]

Previous literature has reported a small number of lineage conversion. In a study by Rossi and colleagues, 9 out of 1,482 (0.6%) pediatric patients with acute leukemia experienced lineage switch, of which seven converted from lymphoid (four Pro-B, two Pre-B, one Common) to myelomonocytic, and two switched from myeloid (bilinear, with myeloid predominance) to Pro-B.

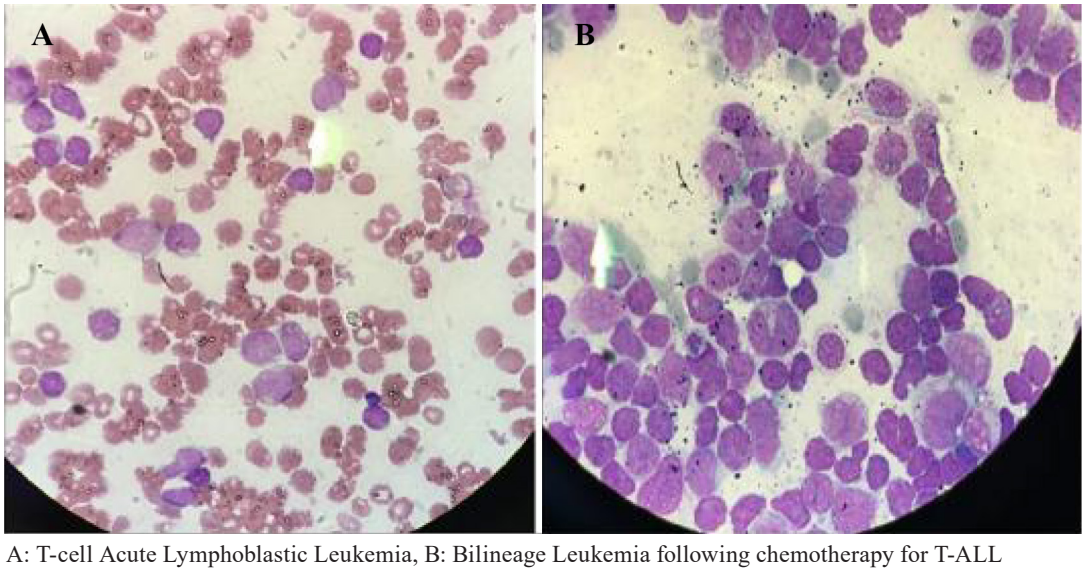


Figure 1: A: T-cell Acute Lymphoblastic Leukemia, B: Bilineage Leukemia following chemotherapy for T-ALL

Table 1: Positive and Negative markers of Leukemic Cells in the first and second presentation

First presentation (T-ALL)		Second presentation (MYE/T Bilineage Acute Leukemia)			
Blast		T-Lymphoblast		Myeloblast	
Positive	Negative	Positive	Negative	Positive	Negative
CD5-CD7	CD2-CD3-CD4-CD8-CD33-MPO-CD13-CD19-CD10-CD20-HLA-DR	CD5-CD7	MPO-CD10-CD19-CD13-CD33-CD64-CD14-CD3-CD2-CD4-CD8-LA-DR	MPO-CD33-CD64-HLA-DR-CD34-CD117	CD10-CD19-CD13-CD14-CD3-CD2-CD5-CD7-CD4-CD8-HLA-DR

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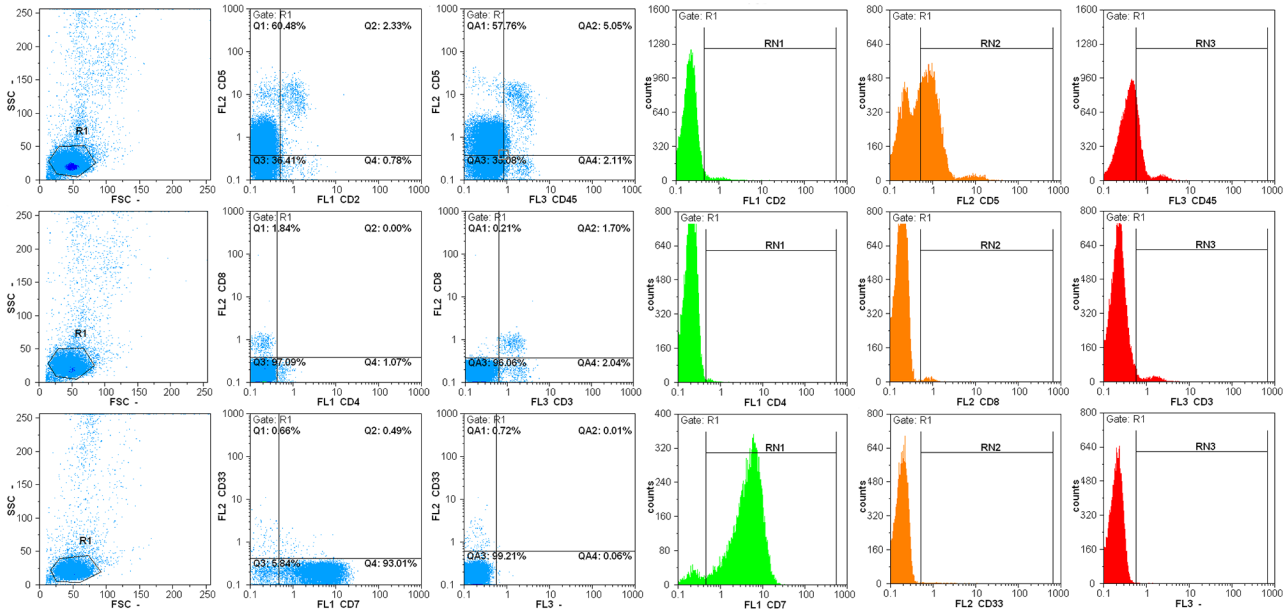


Figure 2: Flow Cytometry Analysis T-ALL

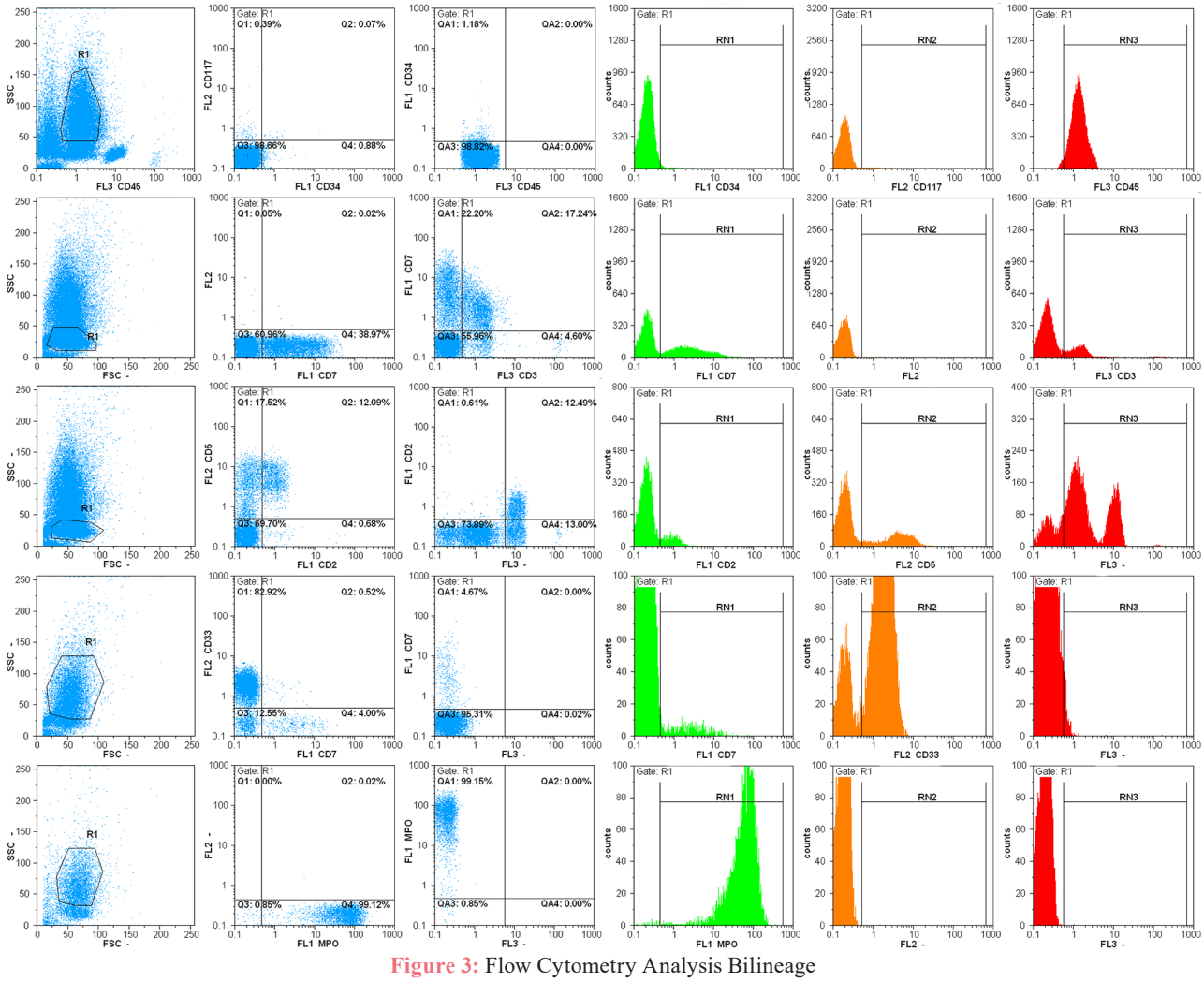


Figure 3: Flow Cytometry Analysis Bilineage

Switches were confirmed with morphology and occurred within 8 days to 6 months from initiation of chemotherapy. Interestingly, in the stability evaluation of clonal abnormalities by cytogenetic RT-PCR/Ig-TCR rearrangement, seven cases had abnormalities in the 11q23/MLL gene.[2]

In another study, Aujla and colleagues reported a pregnant patient who presented with T-ALL, relapsing as AML and then returning as T-ALL again while taking therapy during the third trimester of pregnancy. The patient retained the same cytogenetic and next-generation molecular findings in both leukemias.[9]

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Moreover, Ruiz-Delgado et al. reported a 60-year-old male with lineage switch from pre-B lymphoblastic acute leukemia, BCR ABL negative, hyperdiploid 46 XY to AML.[10]

The current report is an unusual case in which a patient initially diagnosed with T-ALL, immunophenotypically and morphologically, relapsed into MPAL.

The term acute bilineage leukemia has been applied to MPALs containing separate populations of blasts of more than one lineage. The present case meets the criteria for bilineage leukemia with two distinct populations, T lymphoblast with positive cytoplasmic CD3 on IHC and myeloblasts with more than 90% positive MPO on flow cytometry.

Although the precise underlying mechanism of linear switch remains unestablished, some hypotheses have been proposed.[10] The most consistent theory suggests that both lineages are derived from the same precursor stem cells. The well-differentiated leukemic cells respond to the chemotherapy, and the poorly differentiated stem cells can then proliferate through other pathways that are unrecognizable for the given chemotherapy.[11-13]

Another hypothesis suggests the presence of a selection of smaller chemotherapy-insensitive subset displaying different lineage among the dominant phenotype of leukemic blasts, which results in the development of antigen-resistant sub-clone.[14]

Looking at another hypothesis examined by Fujisaki et al., the environment that leukemic stem cells grow plays a crucial role in the differentiation process. In their study, when the myeloid cells of a lineage-switched T-ALL to AML was engrafted in the severe combined immunodeficient (SCID) mice receiving GM-CSF, T-ALL emerged in the mice instead of AML.[12]

In our patient, karyotype was normal at the time of diagnosis and relapse. However, the molecular profile was not analyzed. It seems that the leukemic clone has achieved the ability to produce lymphoid and myeloid blasts, or probably chemotherapy has had a role in leukemic phenotype change. However, the role of chemotherapy in primary clone suppression or reprogramming is not yet well understood.

Conflict of Interest: None declared.

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