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Bi-lineage acute leukemia; a case with B-lymphoblasts and myeloid blasts

Esmaeil Shahabi Satlsar[1], Farahnaz Ghahremanfard[2*], Mohammad Mosleh[3], Anahid Nabavi[4]

[1]Takhte Tavous Pathobiology Laboratory, Flow Cytometry Department, Tehran, Iran
[2]Cancer Research Center, Semnan University of Medical Sciences, Semnan, Iran
[3]Rasad Pathobiology Laboratory, Flow cytometry Department, Tehran, Iran
[4]Faculty of Dentistry, Semnan University of Medical Sciences, Semnan, Iran

Correspondence to:
Farahnaz Ghahremanfard, Email: F_ghahremanfard@yahoo.com

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Abstract

Mixed phenotypic acute leukemia (MPAL) is classified under acute leukemia of ambiguous lineage. Most reported cases of acute ambiguous leukemia belong to bi-phenotypic leukemia. However, bi-lineage leukemia is rare. A 57-year-old male was admitted with weakness and weight loss since one month ago. He suffered from anorexia. In admission time he was pale and cachectic. Lymphadenopathy and splenomegaly were not seen. In laboratory tests, the complete blood counts revealed normal limit leukocytes, anemia, and thrombocytopenia. Bone marrow aspiration showed 60% blasts. Immunophenotyping showed a dual population of blasts which expressed CD19, CD10, CD22, TDT and CD13, CD33 and cMPO. Thus, flow cytometric immunophenotyping helped to establish a final diagnosis of MPAL; B/myeloid bi-lineage leukemia.

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Introduction

Acute leukemia of ambiguous lineage comprises up to 5% of acute leukemia cases in both children and adults. Single country studies usually report fewer than 50 cases of children or adults (1). Mixed phenotype acute leukemia (MPAL) can be identified using the recommended panel of the European leukemia net (2) or other comprehensive recommendations (3). All possible combinations can be observed in acute bi-phenotypic or bi-lineage leukemia, including B/myeloid, T/myeloid, B/T, or even rare B/T/myeloid.

Acute bi-phenotypic or bi-lineage leukemia could happen de novo or appear secondary to chemotherapy or radiotherapy. The morphological manifestation of leukemic blasts in patients with acute ambiguous leukemia is heterogeneous (in most cases blastic cells resemble myeloblasts, but without cytoplasmic granulation, and in some cases blastic cells have lymphoblastic morphology), and rarely seen as two distinct populations in one patient. To evaluate the prognosis and appropriate treatment approach, molecular and cytogenetic evaluation is very important. The furthermost usual cytogenetic abnormalities in acute ambiguous leukemia are t(9;22) (q34;q11), (Philadelphia chromosome) or BCR-ABL rearrangements (p190) and the rearrangements of 11q23 (most are seen in children with B-ALL). BCR-ABL translocation leads to the loss of regulatory domain of ABL tyrosine kinase which affects the activity of multiple pathways involved in cellular differentiation. The MLL (mixed lineage leukemia) gene (11q23) encodes a large complex oncoprotein, which maintains HOX gene expression during hematopoiesis (4).

Case Report

A 57-year-old male was admitted with weakness and weight loss. The patient suffered from anorexia and at admission time he was pale and cachectic. Lymphadenopathy and splenomegaly were not seen. His hemoglobin, total leukocyte count and platelets count were 10.2 g/dL, 6.79×10^9/L, and 35×10^9/L, respectively. The patient's peripheral blood smear showed few small to medium sized blasts with different morphology. Bone marrow aspiration showed 60% blasts, some are small sized with scant cytoplasm and others are medium sized with pale blue cytoplasm and rarely showed granular cytoplasm. Myeloperoxidase staining showed positive reaction in about

Core tip

The emergence of bi-lineage or bi-phenotypic leukemia can be as a result of this fact that the cell retains some of its basic characteristics at differentiation. The differentiation of precursor stem cells is accompanied by inhibitory mechanisms such as stop signals. If the stop signals do not work properly, the differentiation continues to operate on different cell lines and thus to a cell clone with the markers that belong to several lines.

4%-5% of blastic cells.

Immunophenotyping was performed in bone marrow aspiration sample prepared in EDTA as anticoagulant by multicolor flow cytometry using coulter FC-500 flow cytometer and MXP software. Gating strategy was performed in two manners; sideward scatter (SSC), versus forward scattered light (FSC) and CD45 versus SSC. In both methods 60% blasts with dim to moderate expression of CD45 was detected in bone marrow aspiration.

Immunophenotyping analysis showed two distinct blastic population with specific marker expression. About half of blastic cells showed expression of HLA-DR, CD19, CD10, CD22, TDT and remaining blasts showed expression of HLA-DR, CD13, CD33, and CMPO (Figure 1). Molecular study was performed for FLT3, NPM1, t(8;21) and t(16;16), which are negative in blastic cells. Final diagnosis according to immunophenotyping finding were acute bi-lineage leukemia (B-ALL/AML).

The patient was treated according to 7+3 chemotherapy regimen (it consists of getting cytarabine continuously for 7 days, along with short infusion of an anthracycline on each of the first 3 days). After 28 days, the patient achieved bone marrow complete remission.

Discussion

A systematic approach is required to diagnose and classify acute leukemias. Most leukemias can satisfactorily be categorized into B/T-lymphoid or myeloid lineage by immunophenotyping. (5) However, a few cases pose a diagnostic dilemma due to the absolute lack or multiple lineage-specific antigen expression. These leukemias have been categorized as acute leukemias of ambiguous lineage by the WHO classification (6). In some patients with acute ambiguous leukemia BCR-ABL, translocation and MLL rearrangement are seen (2). Acute leukemia (AL) of ambiguous lineage (AMBI-L) comprises up to 5% of AL cases in both children and adults (1). Saint Jude's criteria and European Group of Immunological Markers for Leukemias (EGIL) scoring systems were used to assign lineage to leukemia before WHO laid down specific criteria in 2008(2). WHO specifies, MPO to be used as the most specific marker for myeloid lineage demonstrated by cytochemistry, immunophenotyping or immunohistochemistry. Furthermore, monoid lineage can be assigned if blast population is positive for two of the following markers; nonspecific esterase (NSE), CD11c, CD14, CD64, and lysozyme. Cytoplasmic CD3 is lineage specific for T cells. For B cells, multiple antigens are required for lineage confirmation. A strong CD19 expression along with strong expression of CD79a, cytoplasmic CD22 or CD10 is essential for B cell lineage. If the expression of CD19 is weak, then two of the above markers are required to assign B-cell lineage.

In the present case, immunophenotyping data is consistent with presence of two distinct blastic population, which express specific lineage markers; myeloblastic population, that are positive for CD13, CD33, HLA-DR and cMPO and lymphoblastic population which are positive for CD19, CD10, CD22 and TDT.

Few studies have been conducted in patients with MPAL, as a result, it is hard to guess the annual incidence. The pathogenesis of acute ambiguous leukemia is complex, since due to its low incidence, comprehensive studies have not been conducted. Leukemic stem cell transformation occurs at the level of multipotent progenitor.

Conclusion

The emergence of bi-lineage or bi-phenotypic leukemia can be as a result of this fact that the cell retains some of its basic characteristics at differentiation. The differentiation

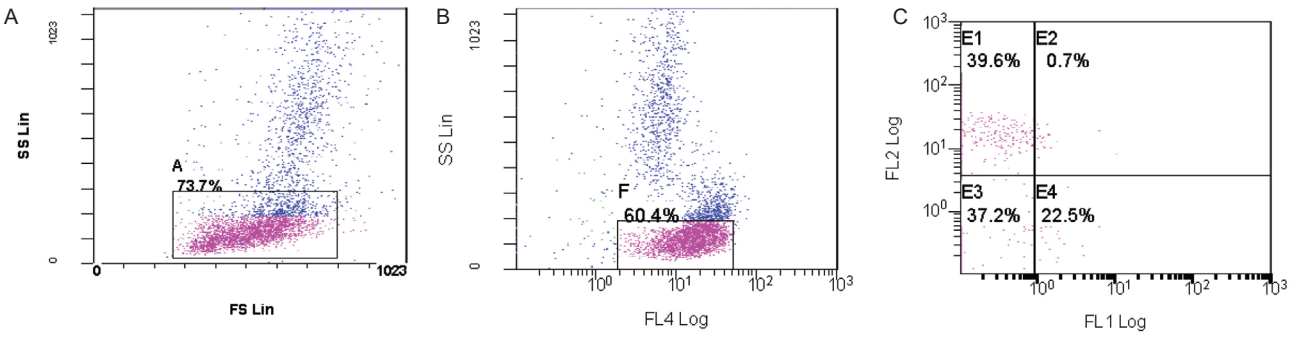

Figure 1. (A) Sideward scatter (SSC), versus forward scattered light (FSC) gating protocol. 73.7% of total cells are mononuclear cells with low SSC. **(B)** CD45 (FL4) vs SSC gating protocol. 60.4% of total cells with low SSC and dim to moderate exoression of CD45. **(C)** FL1 (CD13) vs FL2 (CD10). 0.7% blastic population shows dual expression of CD10 and CD13 and other CD45 dim blastic population shows distinct immunophenotyping

of precursor stem cells is elongated by inhibitory mechanisms such as stop signals. If the stop signals do not work properly, the differentiation continues to act on different cell lines and therefore to a cell clone with the markers that belong to several lines (7).

Authors' contribution

FG, ESS, MM and AN, contributed equally to the manuscript. All authors read and signed the final manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, accuracy of data, double publication) have been completely observed by the authors.

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