

An Acute Leukemia Case with B/T-ALL Phenotypes

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Abstract

Biphenotypic acute leukemia is defined as acute undifferentiated leukemia that does not have a single lineage specific antigen and expresses antigens that belong to multiple different lineages in varying degrees. In this study, a case with biphenotypic leukemia is being presented in terms of clinical course and prognosis. As a result, biphenotypic leukemia has different biological characteristics in terms of both immunophenotypic and cytogenetic characteristics.

Keywords: Leukemia; Biphenotypic; Acute myeloid leukemia

Introduction

Acute leukemia (AL), which originates from lymphoid or myeloid stem cells, is classified as acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML) according to morphological, cytochemical, and immunophenotypic features of the blast. Ambiguous lineage acute leukemia, which comprises of less than 4% of all leukemias, does not belong to a single lineage according to WHO classification in 2008 [1]. Biphenotypic acute leukemia is defined as acute undifferentiated leukemia that does not have a single lineage-specific antigen and expresses antigens that belong to multiple different lineages in varying degrees [1]. They could be seen as each blast of two different blast population expressing antigen belonging to different lineage that was formerly called bilineage leukemia, or antigen expression belonging to multiple lineages in the single blast population that is called as biphenotypic acute leukemia [1]. Complex karyotype anomalies, such as t (9:22), gene MLL (mixed lineage leukemia gene) are common in those leukemias. Mixed phenotype acute

leukemias (MPAL) are rare and its incidence that was reported to be less than 2% of all leukemias according to WHO classification in 2008 [2].

In this study, a case with biphenotypic leukemia is being presented in terms of clinical course and prognosis.

Case

A 25-year old male case was admitted with fever, night sweat, and weight loss. Blood smear was performed as cytopenia was in complete blood count (CBC). Bone marrow biopsy was performed as atypical blast was seen in blood smears. Biphenotypic leukemia (B-ALL/T-ALL) was diagnosed with bone marrow biopsy and flow cytometry. Abnormal findings were white blood cell (WBC): 2,400 cells/mm³, hematocrit: 24%, platelet: 24,700 cells/mm³ in CBC; lactate dehydrogenase (LDH): 1382 U/L and INR: 1.2 in biochemistry analysis; hepatosplenomegaly and multiple mesenteric lymph adenomegaly (the largest one was measured in size with 1.5 × 1 cm) in abdomen ultrasonography. Flow cytometry resulted as cCD3: 73%, CD7: 75%, CD34: 51%, CD22: 15%, cCD79a: 58.8%, CD22: 22%, CD38: 72.5%, CD33: 29%, TdT: 57.3%. The findings were compatible with ALL showing aberrant CD79a expression compatible with the european group for the immunological classification of leukemias (EGIL) T-I in T-lymphoid series, but it was less likely to be biphenotypic leukemia, including T and B lymphoid origins (T-ALL was predominating, but there were T and B ALL markers that were considered as biphenotypic leukemia). Conventional cytogenetic analysis revealed complex karyotype abnormalities, including 44-48, XY, +Y {2}, t (6:11) (q12; p14) {7}, +8 {3}, +19 {6}, {cp7} /46, XY {13}. Hyper-CVAD 1A regimen was administered. During febrile neutropenia episode, Meropenem, Tazobactam-Piperacillin, Acyclovir, Caspofungin, Trimethoprim-Sulfamethoxazole and Vancomycin were administered. On day 28, bone marrow aspiration and biopsy were performed for remission control (**Figure 1**).

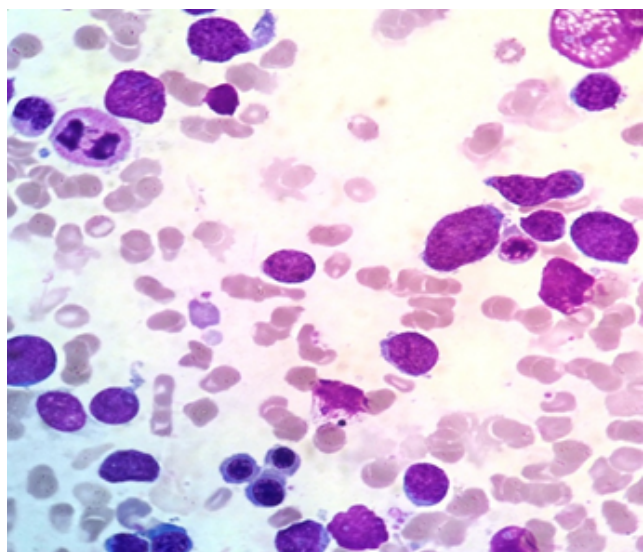


Figure 1: Atypical blast cells (80%) in the bone marrow biopsy after Hyper CVAD-1A chemotherapy (Giemsa: 1×100).

Bone marrow aspirate smears revealed two different sizes (small and large) blast population at the rate of eighty percent and suppression in other series. In addition, flow cytometry results of bone marrow were not consistent with remission. He had the left upper quadrant pain referred in left shoulder and relieved with Tradamol. His pain increased and the long diameter of splenomegaly was measured as 230 mm. Palliative radiotherapy was administered to spleen and then Hyper-CVAD 1B regimen was administered. On day 25, bone marrow aspiration and biopsy control revealed atypical blast cells that some cells had either double or triple nucleus (**Figure 2**).

Salvage FLAG+IDA regimen was administered, but treatment response was not achieved once again (**Figure 3**). The patient died of sepsis.

Discussion

A small subset of acute leukemia, which has both myeloid and lymphoid lineage markers, is defined as mixed lineage or biphenotypic acute leukemia. Biphenotypic acute leukemia (BAL) is quite rare and composes 2% of all acute leukemias originating from common lymphoid progenitor cell [3,4]. Leukemias are generally defined according to the European group for the immunological classification of leukemia (EGIL). This system is based on the number (marker) and specificity (lymphoid or myeloid antigen) of aberrant antigen expression in the blasts. Biphenotypic acute leukemia (BAL) often originates from multipotent progenitor cells and has a poor prognosis. It is unknown exactly treatment is administered targeting AML or ALL. High-dose chemotherapy and stem cell transplantation are recommended for complete eradication of the disease. Blasts are seen as AML or ALL (often in the AML-M1 type), and both rarely can be seen together as it was seen

in our case. Some blasts can be seen either big or small (like lymphoblasts) in a single area of blood smear [5].

A study evaluating clinical and biological characteristics of 22 biphenotypic acute leukemia cases reported that they were older age compared to adult ALL cases, and resistant to chemotherapy (response rates of 65% in BAL; 86% in ALL; $P=0.04$), and cytogenetic analysis resulted abnormal karyotype in 56% of cases. Distinguishing features of BAL were to be seen in elderly, more expression of the CD34 antigen, to have often Philadelphia chromosome, and to be observed spleen, liver, and lymph node infiltration [6]. Biphenotypic acute leukemia is a high-risk acute leukemia and more resistant to chemotherapy than ALL and ALL due to underlying clonal abnormalities; therefore, it should be treated with more intensive chemotherapy. There is no a definitive treatment yet, but treatment recommendation depends on immunophenotyping and gene rearrangement profile [7]. Clonal chromosomal abnormalities were observed in 59-90% of the cases [8]. The complex karyotype anomaly, which is associated with poor prognosis, was seen in our case. Unresponsiveness to hyper-CVAD 1A and 1B and then salvage FLAG-IDA chemotherapies, painful massive splenomegaly that was relieved with tramadol and needed radiotherapy suggested poor prognosis in our case as well.

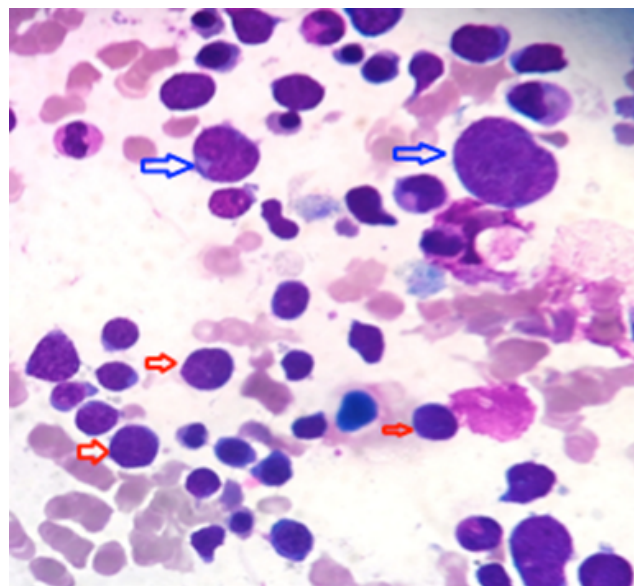


Figure 2: Two different blast cells in the bone marrow preparations (Red arrows point small blast cells; blue arrows point big blast cells, Giemsa: 1×100).

In a study evaluating the immunophenotypic features of 45 patients diagnosed with biphenotypic acute leukemia; cCD79a and cMPO followed by high level CD19 and CD10 expressions; cCD3 and cMPO followed by CD7 and CD5 expression in 18 cases with My/T-ALL; cCD3 and cCD79a co-expression in four cases with T/B-ALL were determined. TdT expression in 30 cases, CD34 expressions in 25 cases, CD117 expression in 31 cases was found as well. CD33 is more expressed than CD13 antigen in My/B-ALL and My/T-ALL patients. Treatment

response rates were reported to be higher in cases with My/B-ALL CD34 (-) than cases with My/B-ALL ile My/T-ALL CD34 (+), and in cases with My/T-ALL CD34 (-) than cases with My/B-ALL CD34 (+). The Co-expression is more observed in My/B-ALL than My/T-ALL. Antigens including cCD3, cCD79a, cMPO are determined in for diagnosis of BAL. The four-color direct immunofluorescence staining with flow cytometry was reported to be very specific for diagnosis of BAL.

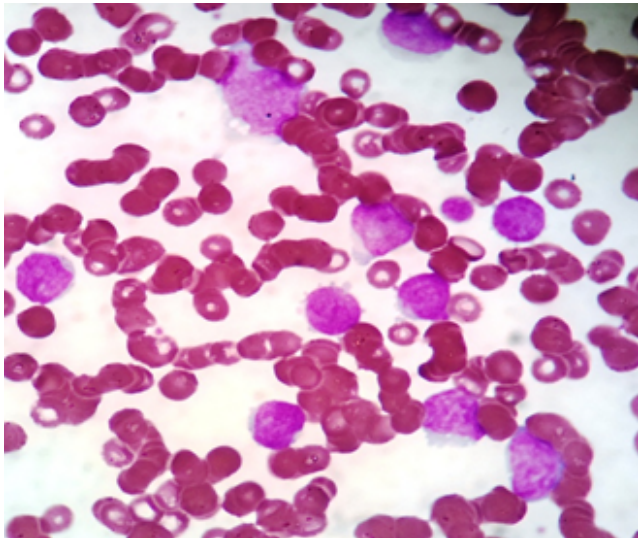


Figure 3: Blast cells after salvage FLAG+IDA chemotherapy in the blood smear.

The most common cytogenetic alterations in mixed phenotypic acute leukemia are t (9,22)(q34;q11) BCR-ABL1, and 11q23 mixed lineage leukemia rearrangement. Using the database of the Surveillance, Epidemiology, and End Results registry (SEER), 313 patients with mixed phenotype acute leukemias were identified and compared them with 14,739 patients with acute lymphoblastic leukemia and 34,326 patients with acute myelogenous leukemias diagnosed between 2001 and 2011. The incidence of mixed phenotype acute leukemias was reported to be 0.35 cases/1,000,000

person-years. In a multivariate analysis, the prognosis was reported to depend strongly on age (as with other leukemias) and it has the worst outcome of all four types of leukemia.

As a result, biphenotypic leukemia has different biological characteristics in terms of both immunophenotypic and cytogenetic characteristics. Subgroup of T/B-ALL leukemia is rarely seen and has the worst prognosis with mixed phenotype.

Conflict of Interest

The author has no conflict of interest.

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