Hemophagocytosis by Leukemic Blasts in B Lymphoblastic Leukemia with t(12;21)(p13;q22); TEL-AML1 (ETV6-RUNX1): a Case Report

Jun Eun Park1, Il Joong Park2, Young Ae Lim2, Wee Gyo Lee2, Sung Ran Cho2

Departments of 1Pediatrics, 2Laboratory Medicine, Ajou University School of Medicine, Suwon, Republic of Korea

Abstract. Blasts showing hemophagocytosis have been very rarely reported in acute lymphoblastic leukemia. We report a pediatric case of B lymphoblastic leukemia (BLL) with t(12;21)(p13;q22); TEL-AML1 (ETV6-RUNX1) showing erythrophagocytosis and thrombophagocytosis by leukemic blasts. About 4% of the leukemic blasts in marrow aspirate smears showed phagocytosis of erythrocytes, platelets, or nuclear remnants in a 3-year-old Korean boy with a diagnosis of BLL. Conventional cytogenetics and molecular analysis revealed the presence of t(12;21)(p13;q22); TEL-AML1 (ETV6-RUNX1). The patient responded well to chemotherapy and is in a state of complete remission.

Key words: acute lymphoblastic leukemia; childhood ALL; cell phagocytosis; gene rearrangement; aberration, chromosomal

Introduction

Hemophagocytosis by leukemic blasts is a rare phenomenon observed in approximately 1% of acute leukemia patients, and is mostly associated with acute myeloid leukemia (AML), especially those of a monocytic or monocytic origin [1,2]. Hemophagocytosis by blasts in acute leukemia of ambiguous lineage [1,3,4] and acute lymphoblastic leukemia (ALL) [5,6] is extremely rare. Because the number of cases reported is so few, their outcome is unclear.

To our knowledge, there have been no reported cases of acute leukemia with hemophagocytosis and t(12;21)(p13;q22) or TEL-AML1 gene rearrangements. Here we report a pediatric case of B lymphoblastic leukemia (BLL) with t(12;21)(p13;q22); TEL-AML1 (ETV6-RUNX1) showing erythrophagocytosis and thrombophagocytosis by leukemic blasts at diagnosis.

Materials and Methods

Immunophenotyping. We determined the immunophenotype of the blast cells using a panel of monoclonal antibodies on the Cytomics FC500 (Beckman Coulter Inc., Fullerton, CA, USA). Cell populations with more than 20% that stained above the isotypic cutoff were designated as positive.

Molecular and cytogenetic studies. RNA was extracted from mononuclear cells isolated from bone marrow by the guanidinium isothiocyanate-phenol chloroform method using TRIZOL reagent (Invitrogen, Carlsbad, CA, USA). We measured the RNA concentration with a spectrophotometer and diluted it to 0.1µg/µL in diethylpyrocarbonate (DEPC)-treated water and carried out multiplex reverse transcriptase-polymerase chain reactions (RT-PCR) using the HemaVision kit (Bio-Rad Laboratories, Hercules, CA, USA) as described in a previous study [7]. Chromosome preparations were acquired from a non-stimulated culture of bone marrow aspirate in RPMI1640 medium with 20% fetal calf serum, according to the standard procedures. The subsequent cytogenetic analysis and interpretations were made according to the ISCN 2009 [8].
Case and Discussion

A 3-year-old Korean boy was admitted to a university hospital with complaints of fever and pain at the right hip joint. He had no hepatomegaly or splenomegaly. Laboratory data on admission were: leukocyte count 7,900/µL (blasts 16%, neutrophils 38%), hemoglobin 8.1 g/dL, platelet count 183,000/µL, erythrocyte sedimentation rate 120 mm/hr (reference range 0-20), C-reactive protein 17.62 mg/dL (reference range 0.02-0.80), ferritin 213 ng/mL (reference range 30-400), fibrinogen 449 mg/dL (reference range 220-490), and pro-thrombin time (PT) 15.0 sec (reference range 10.0-12.8). Bone marrow (BM) examination showed a normocellular marrow replaced by blast cells accounting for 72% of nucleated cells. Interestingly, hemophagocytosis or internalization of hematopoietic cells by the blasts was observed in a marrow aspirate smear (Figure 1). About 80% of blasts showed one or more cytoplasmic vacuoles and about 4% of blasts showed phagocytosis of erythrocytes, platelets, or nuclear remnants. Each phagocytic blast usually contained only one erythrocyte, which filled its cytoplasm and compressed and displaced its nucleus. Cytochemical staining showed negativity for Sudan Black B (SBB) and alpha-naphthyl butyrate esterase (ANBE), and positivity for Periodic Acid-Schiff (PAS). Immunophenotyping by flow cytometry revealed the blasts to be positive for CD10, CD13, CD19, CD22, CD33, CD34, HLA-DR, TdT, and cytoplasmic CD79a, and negative for CD3, CD5, CD7, CD20, CD56, surface immunoglobulins, cytoplasmic CD3, and cytoplasmic myeloperoxidase (MPO). Immunohistochemical staining for

Figure 1. Marrow aspirate smear of the patient. Many leukemic blasts have cytoplasmic vacuoles (A). A subset of blasts contains erythrocytes (B), platelets (C) or nuclear remnants (D). (Wright-Giemsa stains, original magnifications ×1,000 [A through D]).
MPO was also negative. A chromosome study showed the karyotype as 46,XY,t(12;21)(p13;q22) in all of the 20 metaphases analyzed. Multiplex RT-PCR revealed the presence of TEL-AML1 fusion transcripts corresponding to t(12;21)(p13;q22). Based on these findings, we arrived at a diagnosis of BLL with t(12;21)(p13;q22); TEL-AML1, according to the 2008 WHO classification [9]. Although the patient had fever and hemophagocytosis in BM, tests for triglyceride, natural killer cell activity, and soluble CD25 were not performed, and other findings did not fulfill the diagnostic criteria for secondary hemophagocytic lymphohistiocytosis [10].

The patient received induction chemotherapy consisting of vincristine, L-asparaginase, oral prednisolone, and intrathecal methotrexate. He achieved complete remission (showed by a BM study on day 28) after induction chemotherapy and was continuing maintenance chemotherapy without event. RT-PCR for TEL-AML1 gene rearrangements converted to negative a month after the initiation of treatment.

Hemophagocytosis by neoplastic cells has been observed in various diseases including multiple myeloma, malignant lymphoma, chronic myelogenous leukemia in blast crisis, breast cancer, lung cancer, rhabdomyosarcoma, medulloblastoma, hemangioendotheliosarcoma, and AML [11]. More than 30 years ago, Foadi et al. [5] reported four ALL patients, aged between 11 and 17 years, in whom erythrophagocytosis by lymphoblasts was observed. All four patients had only a few lymphoblasts that showed erythrophagocytosis, and this phenomenon was observed only in the later relapses. No cytogenetic results were available. Prolonged chemotherapy may be a contributing factor, and a new clone of more aggressive leukemic cells is perhaps most likely to be the origin of the lymphoblasts with phagocytic features [5]. In addition, Colon-Otero et al. [6] reported a case of erythrophagocytic ALL with B-cell marker and with a 20q- chromosome abnormality in an 87-year-old man, who had striking erythrophagocytosis by lymphoblasts at the time of initial presentation. The present case showed remarkable hemophagocytosis at diagnosis, which is similar to the latter.

The mechanism by which the leukemic blasts phagocytose erythrocytes is still unknown. Phagocytosis is the process that leads to ingestion of the particle. It involves two steps: binding and ingestion. The receptors involved in binding include receptors for complement: CR1 (binding C3b) and CR3; receptors for IgG: Fc receptors, and the receptor for fimbriae: gp150. While these receptors are not normally present on myeloblasts, some investigators observed that leukemic lymphoblasts express Fc receptors [12, 13]. Considering that phagocytosis by leukemic blasts is more unusual in ALL than in AML, it seems that factors more complex than the mere presence of Fc receptors are determining the hemophagocytosis by blasts.

Hemophagocytosis and erythrophagocytosis by leukemic blasts have been linked to certain cytogenetic abnormalities including t(8;16)(p11;p13), inv(8)(p11q13), t(16;21)(p11;q22), t(3;8;7)(q27;p11;q12), del(20)(q11), and t(8;21)(q22;q22). Involved genes are MOZ on 8p11, TIF2 on 8q13, ERG on 21q22, TLS/FUS on 16p11, and RUNXI-RUNX11 on 8q22/21q22 [2, 6]. In addition, a few AML cases with chromosomal translocations between the short arm of chromosome 10 and the long arm of chromosome 17 were reported without elucidation of the involved genes [14]. A more comprehensive cytogenetic and molecular study would be necessary to evaluate the association of certain genes and hemophagocytic features of leukemic blasts.

According to a few case series and case reports, acute leukemias with hemophagocytic activity in
leukemic blasts appear to have dismal clinical outcomes, including frequent extramedullary dissemination, poor response to chemotherapy, early relapse, and short overall survival [6, 14]. On the other hand, BLL with the TEL-AML1 translocation has a very favorable prognosis with cures seen in more than 90% of children [9]. Our case has shown a good response to chemotherapy and supports the new strategy of the WHO classification that regards genetic abnormalities as more important diagnostic and/or prognostic factors than morphologic characteristics.

In conclusion, this study describes a childhood ALL patient with t(12;21)(p13;q22); TEL-AML1 (ETV6-RUNX1), accompanied with hemophagocytosis by blasts and good response to chemotherapy. The peculiar morphologic finding should provoke laboratory personnel to do more meticulous cytogenetic or molecular workup in leukemic patients.

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References