

B cell acute lymphoblastic leukemia (B-ALL) associated with hypereosinophilia: A case report and review of the literature

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Abstract

Few cases of eosinophilia associated with B cell acute lymphoblastic leukemia (B-ALL) have been reported. This study reported a 16-year-old male patient diagnosed with B-ALL and hypereosinophilia. He was admitted to the emergency department (ED) with urticaria and generalized itching. On initial examination, the skin was wholly erythematous, and urticarial lesions were scattered throughout the body. Peripheral blood smear (PBS) was examined, and eosinophils were seen in different fields. However, blast cells were not seen in the PBS. In bone marrow examination, terminal deoxynucleotidyl transferase (TdT)-positive and CD20-positive lymphoid blasts were reported along with eosinophilia. In immunohistochemical (IHC) staining, results were within normal limits for the fibroblast growth factor receptor 1 (FGFR1), platelet-derived growth factor receptor alpha (PDGFR α), and platelet-derived growth factor receptor beta (PDGFR β) genes expressions. Moreover, no breakpoint cluster region (BCR)/Abelson murine leukemia 1 (ABL1) mRNA transcripts and no Janus kinase 2 (JAK2) V617F mutation were detected. Eventually, the B-ALL diagnosis was confirmed for the patient, and he was started on the Berlin-Frankfurt-Münster (BFM) chemotherapy regimen. The patient was transferred to another facility and is continuing his treatment there.

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Abbreviations

B-ALL	B cell acute lymphoblastic leukemia
ED	Emergency department
PBS	Peripheral blood smear
TdT	Terminal deoxynucleotidyl transferase
FGFR1	Fibroblast growth factor receptor 1
PDGFR α	Platelet-derived growth factor receptor alpha
PDGFR β	Platelet-derived growth factor receptor beta
JAK2	Janus kinase 2
BFM	Berlin-Frankfurt-Münster
AEC	Absolute eosinophil count
mm	Millimeter
PE	Primary eosinophilia
SE	Secondary eosinophilia
HE	Hypereosinophilia
IL	Interleukin
IGH	Immunoglobulin heavy locus
ALL-eo	ALL with eosinophilia
HES	Hypereosinophilic syndrome
WBC	White blood cells
Hb	Hemoglobin
IHC	Immunohistochemical
BCR	Breakpoint cluster region
ABL1	Abelson murine leukemia 1
CD	Cluster of differentiate
PAPOLA	Poly(A) polymerase alpha
CPSF1	Cleavage and polyadenylation specificity factor 1
FIP1L1	Factor interacting with PAPOLA and CPSF1

Abstract

Few cases of eosinophilia associated with B cell acute lymphoblastic leukemia (B-ALL) have been reported. This study reported a 16-year-old male patient diagnosed with B-ALL and hypereosinophilia. He was admitted to the emergency department (ED) with urticaria and generalized itching. On initial examination, the skin was wholly erythematous, and urticarial lesions were scattered throughout the body. Peripheral blood smear (PBS) was examined, and eosinophils were seen in different fields. However, blast cells were not seen in the PBS. In bone marrow examination, terminal deoxynucleotidyl transferase (TdT)-positive

and CD20-positive lymphoid blasts were reported along with eosinophilia. In immunohistochemical (IHC) staining, results were within normal limits for the fibroblast growth factor receptor 1 (FGFR1), platelet-derived growth factor receptor alpha (PDGFR α), and platelet-derived growth factor receptor beta (PDGFR β) genes expressions. Moreover, no breakpoint cluster region (BCR)/Abelson murine leukemia 1 (ABL1) mRNA transcripts and no Janus kinase 2 (JAK2) V617F mutation were detected. Eventually, the B-ALL diagnosis was confirmed for the patient, and he was started on the Berlin-Frankfurt-Münster (BFM) chemotherapy regimen. The patient was transferred to another facility and is continuing his treatment there.

Introduction

Eosinophilia is a condition determined by an elevated absolute eosinophil count (AEC). In case of severity, it is divided into three grades: 1) mild (AEC = 500-1500/mm³), 2) moderate (AEC = 1500-5000/mm³), and 3) severe (AEC > 5000/mm³)¹. It can also be classified into primary (PE) and secondary (SE) forms. PE is mainly related to clonal abnormalities of myeloid cells, while SE is often reactive to the T cells' cytokine production. Various conditions can cause SE, such as infections (especially parasites), allergic reactions, pulmonary, dermal, renal, or autoimmune diseases, immunodeficiencies, and malignancies. Nevertheless, in very few cases (less than 1%), hypereosinophilia (HE) is associated with acute lymphoblastic leukemia (ALL)². This condition is mainly caused by the translocation t(5;14)(q31;q32), which leads to overexpression of interleukin (IL)-3 through a fusion gene called immunoglobulin heavy locus (IGH)-IL3. Urticarial rash, fever, arthralgia, myalgia, sweating, and dyspnea are the common symptoms in these cases. Notably, the lack or absence of blasts in the peripheral blood smear (PBS) is the characteristic feature in ALL with eosinophilia (ALL-eo)^{3,4}.

Hypereosinophilic syndrome (HES), a rare hematological disorder, occurs when eosinophils invade the vascular system, resulting in multi-organ failure. It is defined as the existence of persistent eosinophilia (AEC >1500 per mm³) along with evidence of organ damage⁵. It can affect almost all the organs, including the skin, pulmonary and cardiovascular systems, central nervous system, peripheral nervous system, eyes, gastrointestinal tract, and coagulation system⁶. In this study, we reported an adolescent case with ALL-eo and HES, with absent blasts in the PBS.

Case presentation

A 16-year-old male patient presented with urticaria and generalized itching to the emergency department (ED). He was referred to our institute with leukocytosis (WBC = 160,000/ μ L [normal range: 4,500-11,000/ μ L], with 90% eosinophils), anemia (Hb = 9.11 g/dL [normal range: 13.5-17.5 g/dL]), and thrombocytopenia (platelets = 69,000/ μ L [normal range: 150,000-450,000/ μ L]). In the initial skin examination, erythematous and urticaria lesions were observed scattered in all parts of his body. Only a splenomegaly was detected about 6-7 cm below the rib edge during the physical examination. PBS showed eosinophilia with different shapes and hypogranular appearances. However, no blast was observed (Figure 1).

Due to hypereosinophilia, cardiac examination and high-sensitivity cardiac troponin check were performed, which were reported positive (15 ng/L [normal range: > 14 ng/L]). Due to leukocytosis and bicytopenia, bone marrow biopsy was performed, and immunohistochemical (IHC) staining was performed for fibroblast growth factor receptor 1 (FGFR1), platelet-derived growth factor receptor alpha (PDGFR α), and platelet-derived growth factor receptor beta (PDGFR β). Moreover, breakpoint cluster region (BCR)/Abelson murine leukemia 1 (ABL1) and Janus kinase 2 (JAK2) V617F mutation were also requested (Table 1). Cytogenetic examination of PBS showed the patient's karyotype was 47, XY, +mar in half of the analyzed cells and 46, XY in the other half (Figure 2). In the bone marrow examination, along with eosinophilia, terminal deoxynucleotidyl transferase (TdT)-positive and CD20-positive lymphoid blasts were reported. Sections of the trephine bone biopsy showed 100% cellularity in which a mixed population of eosinophils precursors and some small blastoid cells were seen. Morphological study and IHC staining were in accordance with acute precursor B lymphoblastic leukemia/lymphoma with eosinophilia (Table 2).

According to cardiac conditions, glucocorticoid pulse therapy (methylprednisolone 1000 mg IV daily for 3 consecutive days) was started. Before starting the glucocorticoid pulse, ivermectin (200 μ g/kg per day)

was also initiated due to the high prevalence of *Strongyloides stercoralis* in the local area. The patient has been diagnosed with B-ALL and was treated with Berlin-Frankfurt-Munich (BFM) protocol. He was then transferred to another institute to continue his therapy.

Discussion

HES is divided into three classifications: 1) idiopathic HES (no evidence for any underlying condition); 2) primary, neoplastic, or clonal HES (including myeloproliferative disorders, chronic myeloid disorders, and acute leukemias); 3) secondary or reactive HES (caused by conditions like infectious diseases, medications, allergic reactions, autoimmune diseases, metastases, and endocrinopathies)⁷. The first step in the classification of HE patients is the assessment of secondary causes. In this regard, providing an excellent medical history, evaluation of clinical manifestations, and paraclinical investigations can make identifying the underlying cause more available. After excluding secondary causes of HE, primary bone marrow disorders must be assessed. It requires analyses over PBS and morphologic, immunophenotypic, and cytogenetic features of bone marrow⁸.

Until now, very few cases of ALL-eo have been reported, mainly in male patients. It shares some similar features with HES. First, they are both more common in males (76%). Second, they are both presented with nonspecific constitutional symptoms. Last, their morbidity rate is mainly related to the site of eosinophilic infiltration and the extent of it. Nonetheless, ALL-eo has been reported to occur at younger ages (mean age of 14 years, with an age range of 2-58 years). HE-related manifestations commonly precede classic ALL signs and symptoms^{2,9}. ALL-eo-related indications are similar to HES and can exacerbate multi-organ damage and thrombocytopenia⁴, as seen in our case, which was referred to the hematology-oncology ward of our institute, with a platelet count of 69,000/ μ L. As mentioned before, due to severe eosinophilia, HES was suspected. Thus, we performed heart monitoring and required paraclinical tests to evaluate cardiac disorders. High-sensitivity cardiac troponin was reported to be positive with a titer of 15 ng/L, suggesting eosinophils infiltrating the heart, causing progressive restrictive cardiomyopathy that may result in Loeffler endocarditis or even death².

Our case also presented skin lesions, including urticaria and generalized itching, reported in the previous studies^{9,10}. Histopathological investigations of the lesions revealed eosinophils, polymorphonuclear leukocytes, and monocytes infiltrating the perivascular area with different numbers¹¹. Urticarial lesions are usually present as a skin manifestation of HES. However, unlike classic urticarial lesions, HES-related lesions are persistent for more than 24 hours. In contrast to urticarial vasculitis, they also demonstrate no vasculitis features in histopathological studies⁹.

The exact mechanism of the association between HE and ALL has not been completely understood. It could be due to neoplastic antigens or exogenous agents (like viral infections), which may stimulate T cells and result in the over-production of eosinophil-stimulating growth factors⁸. Nevertheless, given the development of HE in ALL patients, it appears to be the result of a mixture of reactive and clonal pathways¹². A group of abnormalities such as absent CD3 marker, presence of abnormal and immature T cell, increased expression of CD5 on CD3⁺CD4⁺ cells, and absence of surface CD7 and CD27 marker expression has been frequently reported in these patients. Lymphocytes carrying the mentioned abnormalities can lead to the overproduction of Th2-related cytokines, including IL-3, IL-4, IL-5, and IL-13, leading to the increased production and prolonged survival of eosinophils^{2,13}. ALL-eo has been repeatedly described as associated with translocation t(5;14)(q31;q32), which juxtaposes the IL-3 gene with the IGH enhancer. This will lead to a significant overproduction of IL-3 and, consequently, HE induction¹⁴. Finally, according to WHO, screening tests of the PBS, including factors interacting with PAPOLA and CPSF1 (FIP1L1)/PDGFRA gene fusion and reciprocal translocations that affect 9p24 (e.g., JAK2), 8p11-12 (e.g., FGFR1), 4q12 (e.g., PDGFR α), and 5q31-q33 (e.g., PDGFR β), are recommended and can be helpful to determine the risk-adapted therapy and risk of myeloid malignancies^{2,8}.

Conclusion

The association of B cell ALL with HE is a rare condition. Patients may present with various symptoms,

generally related to the site of eosinophil infiltration. Here, we reported a 16-year-old male patient who was diagnosed with a case of B-ALL along with hypereosinophilia and admitted to the ED with urticaria and generalized itching. Importantly, blast cells were not seen in PBS. The patient has been diagnosed with a case of B-ALL and was treated with BFM protocol.

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Disclosure

The authors have stated that they have no conflict of interest.

Informed Consent

The patient gave informed content for publication.

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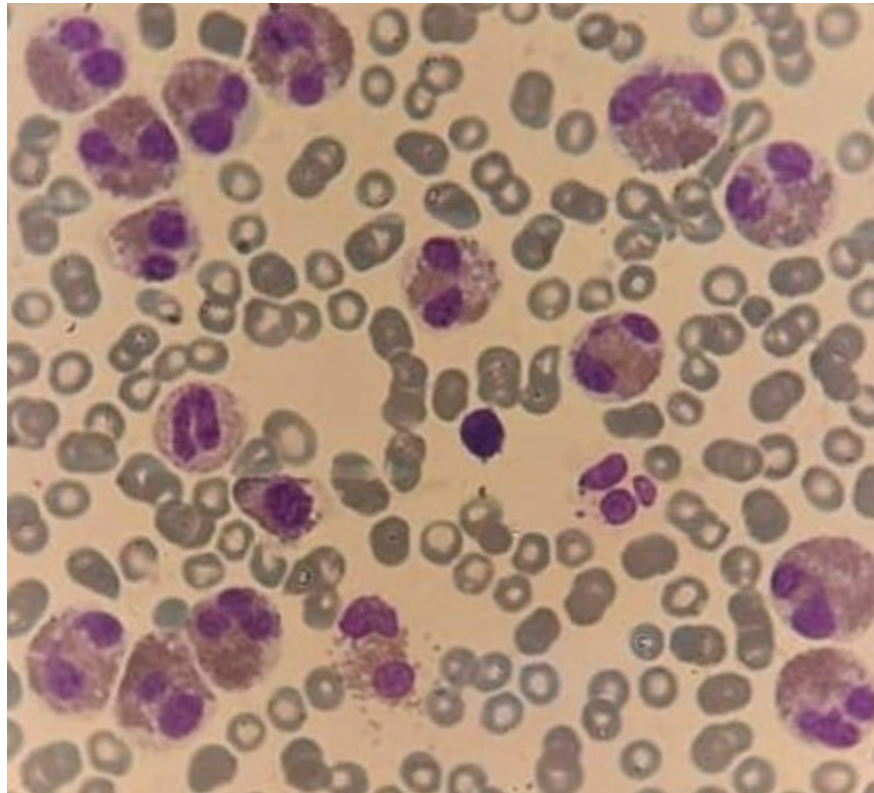
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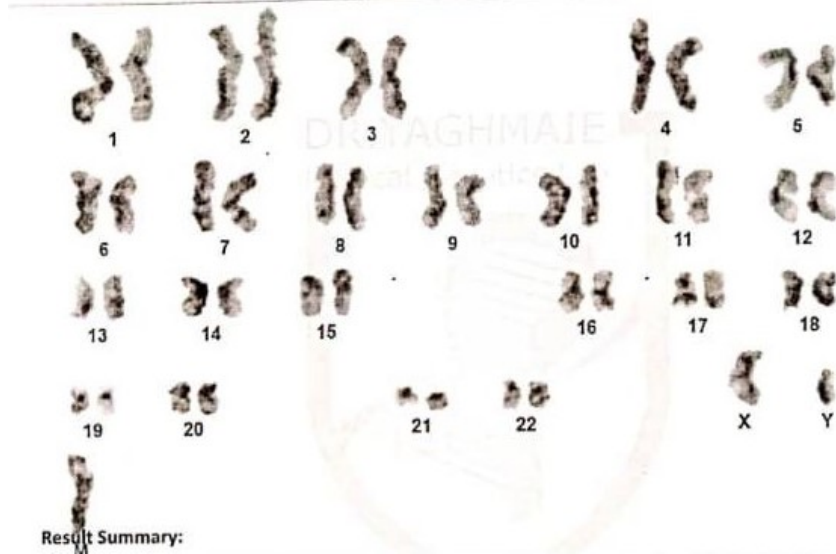
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Figure legends

Figure 1. Peripheral blood smear demonstrated eosinophilia with different shapes and hypogranular appearance but with no blasts.

Figure 2. Cytogenetic examination of peripheral blood specimen demonstrates the patient's 47, XY, +mar karyotype.





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