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B-cell acute lymphoblastic leukemia associated with hypereosinophilia: a case report and brief literature review

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Abstract

Few cases of B-cell acute lymphoblastic leukemia (B-ALL)-eosinophilia (ALL-eo) association have been reported. The lack or absence of blasts in the peripheral blood smear (PBS) along with urticarial rash, fever, arthralgia, myalgia, sweating, and dyspnea are common features of this condition. Herein, we report a 16-year-old male patient admitted to the emergency department with urticaria and generalized itching. PBS was examined, and eosinophils (90%) were seen in different fields. However, blast cells were not seen in PBS. In a bone marrow examination, terminal deoxynucleotidyl transferase-positive and CD20-positive lymphoid blasts were reported along with eosinophilia. Eventually, the B-ALL diagnosis was confirmed for the patient, and he was started on the Berlin-Frankfurt-Münster chemotherapy regimen. The association of B-ALL with hypereosinophilia is a rare condition. We hope this case report and literature review can help clinicians to manage this rare condition properly.

Keywords

B-cell acute lymphoblastic leukemia, hypereosinophilic syndrome, leukocytosis, urticaria, case report

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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/mm^3), (2) moderate (AEC = 1500–5000/mm^3), and (3) severe (AEC > 5000/mm^3).[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 mm^3) along with evidence of organ damage.[5] It can affect almost all the organs, including the skin, pulmonary and cardiovascular

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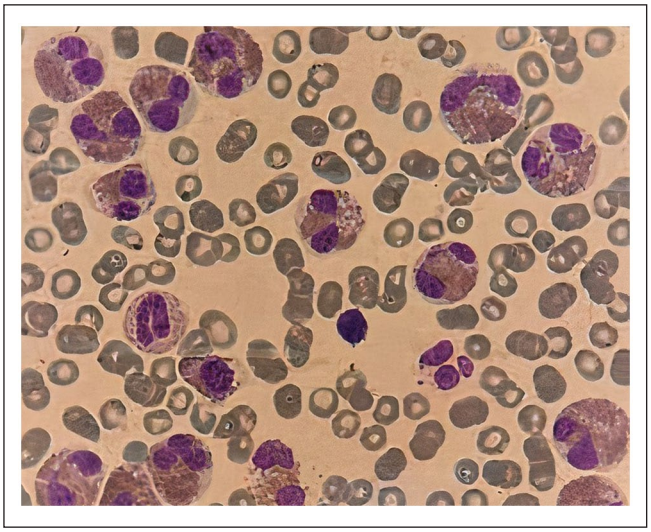

Figure 1. Peripheral blood smear demonstrated eosinophilia with different shapes and hypogranular appearance but with no blasts.

systems, central nervous system, peripheral nervous system, eyes, gastrointestinal tract, and coagulation system.[6] 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. He was referred to our institute with leukocytosis (WBC = 160,000/μL (normal range: 4500–11,000/μL), with 90% eosinophils), anemia (Hb = 9.11 g/dL (normal range: 13.5–17.5 g/dL)), and thrombocytopenia (platelets = 69,000/μL (normal range: 150,000–450,000/μL)). 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). He had no notable past medical, family, or psycho-social history.

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 fluorescence in situ hybridization (FISH) was performed for fibroblast growth factor receptor 1 (FGFR1), platelet-derived growth factor receptor alpha (PDGFRα), and platelet-derived growth factor receptor beta (PDGFRβ). Moreover, breakpoint cluster region (BCR)::Abelson murine leukemia 1 (ABL1) and Janus kinase 2 (JAK2) V617F mutation were also requested. A normal result or a negative result was obtained from these tests (Table 1). Cytogenetic examination of bone marrow showed the patient's karyotype was 47, XY, +mar in half of the analyzed cells and 46, XY in the other half (Figure 2). An examination of the bone marrow at another center revealed a negative translocation of t(5;14). A bone marrow examination showed more than 20% lymphoid blasts, along with eosinophilia and terminal deoxynucleotidyl transferase-positive and CD20-positive lymphoid blasts. 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 FISH staining were in accordance with acute precursor B lymphoblastic leukemia/lymphoma with eosinophilia (Table 2).

Table 1. Evaluation of common cellular abnormalities in the bone marrow biopsy.

Abnormality	Specific assay techniques	Finding
8p11.2 (FGFR1 sep)	FISH	Normal
4q12 (PDGFRα translocation/deletion)	FISH	Normal
5q32 (PDGFRβ sep)	FISH	Normal
JAK2 V617F mutation	PCR	Negative
BCR::ABL1*	RT-PCR**	Negative

BCR: breakpoint cluster region; FISH: fluorescence in situ hybridization; RT-PCR: real-time polymerase chain reaction.
*The types of BCR::ABL1 analyzed were p190, p210, and p230.
**It contains translocation t(9;22)(q24;q11).

According to cardiac conditions, glucocorticoid pulse therapy (methylprednisolone 1000 mg IV daily for three consecutive days) was started. Before starting the glucocorticoid pulse, ivermectin (200 μg/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-Münster (BFM) protocol.[7] He was then transferred to another institute to continue his therapy. A 6-month follow-up shows that the patient has been in complete remission without recurrence.

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).[8] 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 marrow.[9]

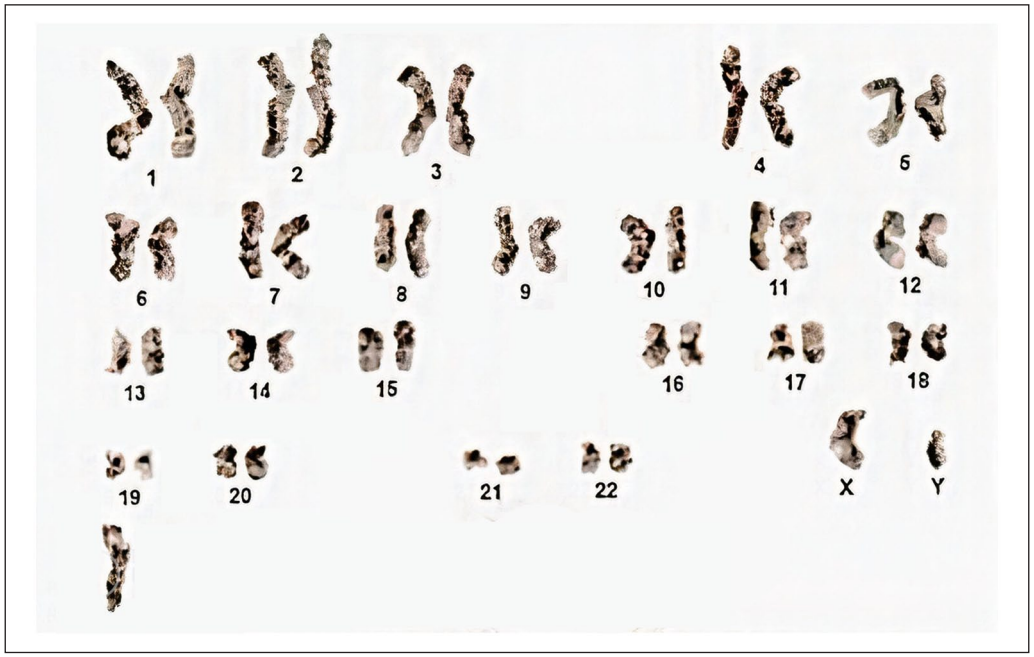

Figure 2. Cytogenetic examination of bone marrow specimens demonstrates the patient's 47, XY, +mar karyotype.

Table 2. Results of immunohistochemical staining of the bone marrow biopsy.

Marker	Finding
CD3	Positive in a few scattered small lymphocytes
CD7	Positive in a few scattered small lymphocytes
CD19	Highlights interstitial infiltration of cells
CD20	Positive
CD34	Positive in blastoid cells in the interstitial pattern
TdT	Positive in blastoid cells
Ckit	Positive in maturing myeloid cells

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.[2,10] ALL-eo-related indications are similar to HES and can exacerbate multi-organ damage and thrombocytopenia.[4] 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 death as a possible consequence of HES.[2] Anemia, thrombocytopenia, and hepatomegaly are some of the characteristics associated with ALL-eo. A clonal eosinophilic proliferation, blast crisis, or a soft tissue tumor of myeloblasts (granulocytic sarcoma) can all indicate ALL-eo.[11] According to Rahman[12] a 70-year-old man presented to the emergency room with sudden weakness in the right leg, along with eosinophilia and heart problems. It was determined that HES was an undefined variant in this case. The differential diagnosis of leukemia forms was rejected due to cytogenetic normality, while a normal cytogenetic test did not rule out ALL-eo in our case. In a similar study, Yakoub et al. reported the case of a 10-year-old boy who was diagnosed with childhood ALL after presenting with a high fever and hypereosinophilia in his peripheral blood. Furthermore, no abnormal cytogenetics were found in their evaluations. In these patients who suffered from thrombocytopenia and leukocytosis, Yakoub[13] recommended a bone marrow aspiration. Eosinophilia and blasts count may be revealed by morphologic evaluation of PBS and bone marrow biopsy specimens. Reactive eosinophilia may be caused by B- or T-cell lymphoma, carcinoma, or granulomatous inflammation in the bone marrow examination.[14]

Our case also presented skin lesions, including urticaria and generalized itching, as reported in the previous studies.[10,15] Histopathological investigations of the lesions revealed eosinophils, polymorphonuclear leukocytes, and monocytes infiltrating the perivascular area with different numbers.[16] 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 h. In contrast to urticarial vasculitis, they also demonstrate no vasculitis features in histopathological studies.[10]

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 overproduction of eosinophil-stimulating growth factors.[9] Nevertheless, given the development of HE in ALL patients, it appears to be the result of a mixture of reactive and clonal pathways.[17] A group of abnormalities such as absent CD3 marker, the presence of abnormal and immature T cells, increased expression of CD5 on $CD3^{-}CD4^{+}$ cells, and the 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.[2,18] 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 induction.[19] 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., PDGFRα), and 5q31-q33 (e.g., PDGFRβ), are recommended and can be helpful to determine the risk-adapted therapy and risk of myeloid malignancies.[2,9]

Most ALL patients with hypereosinophilia are treated with corticosteroids first. There has been no study to determine the best initial dose and duration of prednisone therapy in these patients; however, a dose of ⩾40 mg of prednisone is recommended for hypereosinophilia.[12] Generally, this dose is effective for most patients. To achieve the lowest dose possible, the dose should be gradually tapered down while closely monitoring the eosinophil count. Patients undergoing long-term steroid treatment need to be evaluated for bone density and receive adjunctive treatment to prevent bone loss. Based on cardiac conditions, we started glucocorticoid pulse therapy (methylprednisolone 1000 mg IV daily for three consecutive days). After completing the BFM protocol, the patient is currently in remission after 6 months. Based on the study of Narayanan et al.,[20] who presented a case similar to our study including heart disorder, final ALL-eo diagnosis, and corticosteroid treatment, the patient died after 6 weeks of follow-up. It should be noted that their patient died due to treatment failure. This is contrary to our patient's follow-up regarding the completed treatment without recurrence in 6 months. We suggest that complete treatment according to the BFM protocol should be done concerning corticosteroid administration.

Conclusion

There is a clinical importance to be aware of this unique presentation of ALL in the context of hypereosinophilia along with a normal cytogenetic test (negative t(5;14) translocation). There is a high possibility that these patients would be able to benefit from an accurate and timely diagnosis of ALL if this condition were identified as a presenting sign of ALL.

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A preprint has previously been published.[21]

Author contributions

S.K. contributed to the conception and design and provision of study materials or patients; S.K., A.T.P., and M.B. contributed to the collection and assembly of data. All authors contributed to the manuscript writing and final approval of the manuscript.

Data availability statement

The data supporting the findings of this study are available upon request from the corresponding author and with permission from Babol University of Medical Sciences, Babol, Iran.

Declaration of conflicting interests

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Ethical statement

Since the patient was under 18, we obtained written informed consent from the legally authorized representative of the minor subjects prior to study initiation.

Informed consent

Written informed consent was obtained from the legally authorized representative of the minor subjects prior to study initiation for their anonymized information to be published in this article.

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References

1. Curtis C and Ogbogu P. Hypereosinophilic syndrome. *Clin Rev Allergy Immunol* 2016; 50: 240–251.
2. Ferruzzi V, Santi E, Gurdo G, et al. Acute lymphoblastic leukemia with hypereosinophilia in a child: case report and literature review. *Int J Environ Res Public Health* 2018; 15: 1169.
3. Song G, Liu H, Sun F, et al. Acute lymphocytic leukemia with eosinophilia: a case report and review of the literature. *Aging Clin Exp Res* 2012; 24: 555–558.
4. Kaneko H, Shimura K, Yoshida M, et al. Acute lymphoblastic leukemia with eosinophilia lacking peripheral blood leukemic cell: a rare entity. *Indian J Hematol Blood Transfus* 2014; 30: 80–83.

5. Ono R, Iwahana T, Kato H, et al. Literature reviews of stroke with hypereosinophilic syndrome. *Int J Cardiol Heart Vasc* 2021; 37: 100915.
6. Hsieh FH. Hypereosinophilic syndrome. *Ann Allergy Asthma Immunol* 2014; 112: 484–488.
7. Henze G, Langermann HJ, Brämswig J, et al. [The BFM 76/79 acute lymphoblastic leukemia therapy study (author's transl)]. *Klin Padiatr* 1981; 193: 145–154.
8. Valent P, Klion AD, Horny H-P, et al. Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. *J Allergy Clin Immunol* 2012; 130: 607–612.e609.
9. Gotlib J. World Health Organization-defined eosinophilic disorders: 2017 update on diagnosis, risk stratification, and management. *Am J Hematol* 2017; 92: 1243–1259.
10. Hill A and Metry D. Urticarial lesions in a child with acute lymphoblastic leukemia and eosinophilia. *Pediatr Dermatol* 2003; 20: 502–505.
11. Smith KJ, Jacobson E, Hamza S, et al. Unexplained hypereosinophilia and the need for cytogenetic and molecular genetic analyses. *Arch Dermatol* 2004; 140: 584–588.
12. Rehman HU. Hypereosinophilia: a diagnostic dilemma. *J Clin Med Res* 2010; 2: 233–238.
13. Yakoub AI. A rare presentation of childhood acute lymphoblastic leukemia with hypereosinophilia lacking peripheral blood smear leukemic cells. *J Appl Hematol* 2021; 12(1).
14. Kelemen K, Saft L, Craig FE, et al. Eosinophilia/hypereosinophilia in the setting of reactive and idiopathic causes, well-defined myeloid or lymphoid leukemias, or germline disorders. *Am J Clin Pathol* 2021; 155: 179–210.
15. Chien AJ, Argenyi ZB, Colven RM, et al. Acute lymphoblastic leukemia presenting with urticarial plaques and hypereosinophilia in a child. *J Am Acad Dermatol* 2004; 51: S151–S155.
16. Fauci AS, Harley JB, Roberts WC, et al. NIH conference. The idiopathic hypereosinophilic syndrome. Clinical, pathophysiologic, and therapeutic considerations. *Ann Intern Med* 1982; 97: 78–92.DOI: 10.7326/0003-4819-97-1-78.
17. Kahn JE, Groh M and Lefèvre G. (A Critical Appraisal of) classification of hypereosinophilic disorders. *Front Med (Lausanne)* 2017; 4: 216.
18. Roufosse F. Hypereosinophilic syndrome variants: diagnostic and therapeutic considerations. *Haematologica* 2009; 94: 1188–1193.
19. Guenzel AJ, Smadbeck JB, Golden CL, et al. Clinical utility of next generation sequencing to detect IGH/IL3 rearrangements [t(5;14)(q31.1;q32.1)] in B-lymphoblastic leukemia/lymphoma. *Ann Diagn Pathol* 2021; 53: 151761.
20. Narayanan G, Hussain BM, Chandralekha B, et al. Hypereosinophilic syndrome in acute lymphoblastic leukaemia–case report and literature review. *Acta Oncol* 2000; 39: 241–243.
21. Barary M, Pirzaman AT, Mousavi-Fatemi K, et al. B cell acute lymphoblastic leukemia (B-ALL) associated with hypereosinophilia: a case report and review of the literature. *Authorea* 2022.