Acute Lymphoblastic Leukemia With Eosinophilia Lacking Peripheral Blood Leukemic Cell: A Rare Entity

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Abstract We describe a 57-year-old woman who was diagnosed as precursor B-cell acute lymphoblastic leukemia with marked eosinophilia (ALL-eo). She presented with low grade fever and eosinophilia (absolute count $16.5 \times 10^9/l$). Most of eosinophils had hypogranular cytoplasm. Immature cells were absent in her peripheral blood. Since her platelet count was low, bone marrow examination was carried out. 57.2 % of nucleated cells were blastic cells positive for CD10, 19, and 20. Chromosomal analysis revealed a karyotype of 46,XX,t(5;14)(q31;q32). Despite induction chemotherapy, her disease progressed and she died of sepsis a month later. ALL-eo is extremely rare and the diagnosis might be delayed unless leukemic cells are seen in peripheral blood. Therefore, bone marrow should be examined as soon as possible in cases with eosinophilia not only for the differential diagnosis of eosinophilic disorders but also not to overlook ALL-eo.

Keywords Acute lymphoblastic leukemia · Precursor B cell · Eosinophil · t(5;14)

Introduction

Eosinophilia has been known to be associated with B cell acute lymphoblastic leukemia (ALL), but the frequency is very low [1–11]. Reported cases are only about fifty [11] and most of them are pediatric cases [1–4, 6, 8]. Although chromosomal translocation, t(5;14)(q31;q32) [12] resulting in generation of a fusion gene IL3-IgH [13], is most frequently detected in ALL with eosinophilia (ALL-eo), the number is very small and different chromosomal aberrations have also been revealed [6, 8, 9, 11]. Therefore, the pathogenesis of this disease is not fully understood. Various causes of secondary or neoplasm-associated eosinophilia should also be excluded for exact diagnosis. We report an adult case with ALL-eo without appearance of leukemic cells in peripheral blood to accumulate clinical data of this rare disease entity.

Case Report

A 57-year-old woman presented with low grade fever that had continued for a month and eosinophilia. She had no past history of allergic or parasitic disease. Physical examination showed absence of pallor, eruption, lymphadenopathy, or hepatosplenomegaly. Blood examination showed leukocytosis ($28.9 \times 10^9/l$) and marked eosinophilia (57 %, absolute count $16.5 \times 10^9/l$). The eosinophils showed markedly hypogranular feature (Fig. 1a), but the cell size, lobulation of nuclei, and chromatin aggregation were normal. Immature cell was not seen (Table 1). Serum LDH was elevated at 400 IU/l and IgE remained normal (16 IU/ml) (Table 2). No pulmonary infiltration shadow was revealed by chest X-ray examination. As per the recommendations, secondary causes of eosinophilia were

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Fig. 1 **a** Eosinophilia is seen in peripheral blood. Eosinophils are dysplastic with hypogranular cytoplasm. Blastic cells are not present. **b** Bone marrow findings. Immature blastic cells without azurophilic granule are dominantly seen

excluded before entertaining the possibility of primary hematologic eosinophilia disorders [14]. Stool test for parasitic ova was negative. Allergic symptoms, i. e., skin eruption or asthma was not seen. Physical examination and chest and abdominal CT did not reveal lymph node swelling, therefore did not support the co-existence of malignant lymphoma. Her symptoms and the antinuclear test result excluded collagen disease.

Because of thrombocytopenia at $60 \times 10^9/l$, bone marrow was examined. 57.2 % of nucleated cells were blastic cells without azurophilic granules (Fig. 1b) (Table 1). The blastic cells were positive for CD10, 19, 20, and 34 by flowcytometry. Hypogranular eosinophils were seen similarly to peripheral blood. Chromosomal analysis revealed sole abnormality of t(5;14)(q31;q32) (Fig. 2). Other chromosomal aberrations listed as a cause of hematological neoplasm-associated eosinophilia, i. e., abnormality of chromosome 4q

or 8p, t(5;12)(q31-35;p13), and inversion 16 representing a rearrangement of PDGFRA, FGFR1, PDGFRB, or CBFB gene, respectively [14], were not detected. Precursor B cell ALL-eo was diagnosed and induction chemotherapy consisting of vincristine, cyclophosphamide, adriamycin, and prednisolone was given. Unfortunately, the therapy was ineffective and the disease progression with rapid increase of leukemic cells in her peripheral blood was noted. She died of sepsis a month later. Organ failure suggesting infiltration of eosinophils was not observed.

Discussion

Although ALL-eo was mentioned as a distinct clinical entity of leukemia in recent WHO Classification [15], appropriate therapeutic strategy is not yet established because of lack of clinical data. The prognosis of ALL-eo has been estimated to be similar to that of other cases of ALL [15], while our patient died within a month with resistance to standard induction chemotherapy. However, clinical behavior of ALL-eo is little understood. Its extremely low frequency prevents wide recognition and accumulation of clinical experiences. Moreover, exact diagnosis might be masked if leukemic cells are not observed in peripheral blood as our patient. Clinical manifestation of ALL-eo resembles hypereosinophilic syndrome (HES). Patients with HES often manifest fatal organ damage and thrombocytopenia is also seen in HES [16]. It is likely that diagnosis of ALL-eo might be delayed unless bone marrow examination or recommended work-up for eosinophilic disorders is carried out.

The etiology of eosinophilia in ALL-eo is considered as a benign reaction [1, 9]. A fusion gene generated by t(5;14)(q31;q32) was reported to result in overexpression of IL-3 that is responsible for eosinophilia. However, the contribution of IL-5 that plays a crucial role in the production of eosinophil [17] to ALL-eo remains unclear. It also raises a clinical question whether anti-IL-5 antibodies are effective for organ damage occurring in ALL-eo as observed in HES [18].

In order to expand the clinical experience with this entity, we propose that on encountering a patient with eosinophilia, more attention should be paid to morphological findings of eosinophil. Our patient showed hypogranular eosinophils in peripheral blood and bone marrow as reported previously [3, 5, 9], indicating that bone marrow should be examined to distinguish ALL-eo, HES, and so on. It should be noted that such dysplastic eosinophils are also seen in HES [19]. However, immediate

Fig. 2 Karyotype of bone marrow of the patient. t(5;14)(q31;q32) is seen

Table 1 Laboratory data on admission

Blood cell count (%)		Bone marrow (%)	
WBC	<u>28.9 x 10⁹/l</u>	Blastic cell	<u>57.2</u>
Blast	0 %	Promyelocyte	0.4
Eosinophil	<u>57 %</u>	Myelocyte	1.2
Basophil	1.5 %	Metamyelocyte	2
Stab	19.5 %	Stab	3.2
Segmented	11 %	Segment	1.6
Lymph	9.5 %	Eosinophil	14
Monocyte	1.5 %	Basophil	0
		Monocyte	0.4
RBC	4,650 x 10 ⁹ /l	Lymphocyte	14.4
Hb	13.5 g/dl	Plasma cell	0.8
Ht	40.1 %	Proerythroblast	0
PLT	<u>60 x 10⁹/l</u>	Basophiic erythroblast	0
		Polychromaic erythroblast	4.4
Coagulation test		Orthochromatic erythroblast	0.4
PT	79 %		
FDP	<u>7.7 mg/l</u>		

Abnormal values underlined

Table 2 Biochemical data on admission

LDH	<u>400 IU/l</u>
AST	20 IU/l
ALT	41 IU/l
T-bil	0.6 mg/dl
ALP	<u>311 IU/l</u>
γ-GTP	<u>138 IU/l</u>
BUN	9.9 mg/dl
Cr	0.5 mg/dl
Na	134 mEq/l
K	4.1 mEq/l
Cl	99 mEq/l
CRP	<u>1.72 mg/dl</u>
IgE	16 IU/ml
Anti-nuclear antigen	<×40

Abnormal values underlined

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bone marrow examination might lead to earlier diagnosis of ALL-eo. More accurate frequency and detailed mechanism of this rare type of leukemia remain to be elucidated.

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