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Letter to the Editor

Acute lymphoblastic leukemia presenting with hypereosinophilia: Case report and review of the literature

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Dear Editor:

A 19-year-old woman presented with a 2-week history of dyspnea, fevers, fatigue and generalized body aches. Physical exam was remarkable for splinter hemorrhages in her nailbeds and a purpuric rash on her chest and back. Routine laboratory tests revealed leukocytosis and hypereosinophilia (white blood cells [WBC] 101×10^9/L, 83% eosinophils, 13% neutrophils, no blasts), as well as a normochromic normocytic anemia (hemoglobin [Hb] 11.3 g/dL), and thrombocytopenia (platelets [Plt] 59×10^9/L). She had elevated serum lactate dehydrogenase (703 units/L) and troponin (4.37 ng/mL; normal: 0–0.03) levels. Other laboratory tests including a basic coagulation panel, uric acid, liver and kidney function, IgE, and tryptase were within normal limits. A peripheral blood smear showed marked mature-appearing eosinophilia and few immature cells of unclear lineage morphologically. Fluorescence in situ hybridization (FISH) for *PML/RARA*, *BCR/ABL*, and *PDGFR-A/B* rearrangements was negative.

Intravenous fluids, empiric broad-spectrum antibiotics, and hydroxyurea (2000 mg twice daily) were initiated. However, the patient developed altered mental status and myoclonic seizures, requiring intubation for airway protection. Troponin levels increased to 61 ng/mL and a transthoracic echocardiogram showed impaired left ventricular ejection fraction (40%), significant thickening and irregular left ventricular endocardial surface suggestive of infiltrative cardiomyopathy, and a left ventricular mural thrombus. Magnetic resonance imaging and angiography of the brain showed watershed infarcts in bilateral cerebral hemispheres, basal ganglia and cerebellum, likely due to thromboembolism of cardiac origin. One leukapheresis was performed, and imatinib (400 mg/day) along with methylprednisolone (60 mg twice daily) were started. The bone marrow was markedly hypercellular (>90% cellularity), with 34% eosinophils and 58% small-to-medium sized blasts with a high nucleus-to-cytoplasm ratio, inconspicuous nucleoli, and no Auer rods. These blasts expressed CD10, CD19, CD22, CD34, CD79a, CCD117 and TdT, and were negative for CD5, CD13, CD11B, CD14, CD33, CD56, CD64, CD123 and immunoglobulin light chains. Conventional karyotypic analysis revealed a normal female karyotype. FISH and molecular studies for *PML/RARA*, *BCR/ABL*, *PDGFR-A/B*, and *FGFR1* were negative. A diagnosis of B-cell acute lymphoblastic leukemia (B-ALL) presenting with hypereosniophilic syndrome (HES) was established. Definitive therapy with Hyper-CVAD was started and imatinib was discontinued. Following an initial deterioration with worsening hypoxic respiratory failure (due to diffuse alveolar hemorrhage and eosinophilic infiltrates), subsequent clinical improvement occurred in parallel with normalization of blood counts. *Candida glabrata* fungemia was successfully treated, and the patient achieved a complete remission after one cycle of Hyper-CVAD.

We found a total of 60 previously reported cases of ALL presenting with HES in the literature (Table 1; Supplementary material S1). Patients had a median (range) age of 13 (1–72) years at diagnosis and 43 (69%) were males. B symptoms, lymphadenopathy, neurological dysfunction, and cardiac involvement were present in 46 (77%), 16 (27%), 7 (12%), and 29 (48%) patients, respectively. Pulmonary symptoms, rash and non-specific generalized arthralgia/myalgia were present at diagnosis in 23 (38%), 17 (28%) and 6 (10%) patients, respectively. Among the 36 patients with reported lineage of ALL, 32 (89%) were of B-cell lineage, 3 (8%) were of T-cell lineage, and one case was biphenotypic. The median (range) WBC, Hb, and Plt count at presentation were 46 (6–214) $\times$ 10^9/L, 11 (5–14) g/dL, and 34 ($1-231$) $\times$ 10^9/L, respectively. The median eosinophil percentage in the peripheral blood and marrow was 60% and 30%, respectively. No cytogenetic abnormalities were found in 19 (45%) of the 42 patients for whom this information was obtained and reported. Among those with at least one cytogenetic abnormality ($n = 23$), chromosome 14 abnormalities were most common (39%), and the most common abnormality involving this chromosome was t(5;14)(q31;q32), present in 6 (26%) patients. This translocation, which only rarely occurs in non-eosinophilic B-cell ALL, brings together the genes for immunoglobulin heavy chain and interleukin-3 (IL-3), resulting in increased production of IL-3 by the blasts [1]. As a potent eosinophil growth factor, increased levels of IL-3 can result in marked mature eosinophilia. Survival data were available on 53 cases. With a median follow up of 11 months for survivors, median relapse-free and overall survival (OS) rates for the entire cohort were 11 and 21 months, respectively (Fig. 1). 53% of patients were alive and disease-free at 1 year. In univariate survival analysis, cardiac involvement (HR 2.48, 95% CI 1.12–5.47, $P = 0.02$) and older age (HR 1.03, 95% CI 1.01–1.06, $P = 0.01$) were significant predictors of poor OS. In multivariate analysis, only age remained a significant predictor of survival (HR 1.03, 95% CI 1.00–1.05, $P = 0.04$).

HES can be a primary, clonal stem cell disorder in which the cell of origin can be myeloid or lymphoid (both B and T). In other cases, HES is polyclonal and secondary to increased levels of cytokines such as IL-3 and IL-5 secreted by other cells (usually T cells). Underlying causes for the latter category of HES include parasitic infections, solid tumors, and T-cell lymphoma (i.e. lymphocytic variant). Besides IL-5, T-helper type 2 cytokines such as IL-4, IL-13, and GM-CSF are key players in the development of secondary HES, especially when associated with the lymphocytic variant (T-cell non-Hodgkin lymphoma) [1]. A particular subtype of HES is recognized by the World Health Organization (WHO) as "myeloid or lymphoid neoplasms with rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*, or with *PCM1-JAK2*" [2]. Finally, HES can be

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Table 1
Summary of previous reports of acute lymphoblastic leukemia presenting with eosinophilia.

Reference	Age/sex	Presentation	B/LAP/Neu/heart	WBC/Hb/Plt	PB/BM blasts; PB/BM Eo (%)	B/T	Cyto/Mol. abnl	Induction	Outcome
Spitzer 1973	F/14	CP/DOE/rash	−/−/−/−	132/13/86	3/52; 76/40	NA	Hypodiploid	Daun/VCR/GC	CR, relapse at 11 m, DOD at 2 y
Spitzer 1973	F/16	Fatigue/CP/DOE/rash	−/−/−/+	15/10/58	0/74; 20/17	NA	Hyperdiploid	Ara-C/6TG/GC	CR at 6 m
Blatt 1974	M/9	Fever/rash/abdominal pain	+/+/+/+	17/NA/NA	0/15; 12/60	NA	Hyperdiploid	GC	CR, relapse at 7 m, DOD at 46 m
Nelken 1976	M/12	Fever/fatigue/cough	+/−/−/+	16/10/160	0/6; 62/14	NA	NA	VCR/GC	DOD within days
Rizzo 1976	M/8	Malaise	−/−/−/+	14/11/NA	0/+; 35/+	NA	NA	Daun/VCR/GC	CR
Pereira 1977	M/13	Fever	+/−/−/+	85/8/231	0/38; 64/35	NA	NA	None	DOD within days
Geltner 1978	M/17	Fever/SOB/hemoptysis	+/+/−/+	40/NA/NA	85/>90; 2/NA	NA	NA	Daun/VCR/GC	CR
Wimmer 1978	M/2	Incidental	−/−/−/−	129/10/85	2/42; 63/46	NA	NA	VCR/Asp/GC	CR at 12 m
Parker 1979	M/2	Fever/anorexia/rash	+/+/+/−	28/NA/NA	41/NA; 6/NA	NA	NA	VCR/GC	DOD at 5 y
Catovsky 1980	M/25	Fever, anorexia, jaundice	+/+/−/−	17/12/30	0/>90; 53/+	NA	NA	Ara-C/Daun	CR, relapse at 8 m, DOD at 10 m
Catovsky 1980	M/17	SOB, fatigue	+/+/−/−	25/14/80	3/60; 72/30	NA	NA	TRAMPCO	CR, relapse at 3 m, DOD at 20 m
Catovsky 1980	M/41	Fever, night sweats	+/+/−/−	14/7/81	0/+; 53/+	T	NA	COP	Response, death at 6 m
Catovsky 1980	M/4	LAP	−/+/−/−	111/12/280	90/60; 10/40	T	NA	Daun/VCR/GC/Ara-C/6TG/Asp	PR, relapse at 3 m, DOD at 7 m
Catovsky 1980	M/23	LAP	−/+/−/−	9/12/150	28/>90; 10/0	T	NA	Daun/VCR/GC/6TG/Asp	CR, relapse, DOD at 16 m
Catovsky 1980	M/4	Fever, fatigue, weight loss	+/+/−/−	11/8/34	19/94; 11/0	NA	Normal	Dutch protocol ALL II	CR, relapse at 28 m, DOD at 62 m
Catovsky 1980	M/6	Fever	+/+/−/−	19/5/82	0/75; 25/12	NA	Normal	Daun/VCR/GC/Asp	CR, relapse at 7 m, CR at 12 m
Bachhuber 1982	M/23	Rash, arthralgia, weight loss	+/−/−/−	22/13/214	0/+; 75/+	NA	NA	NA	NA
Bottone 1982	M/4	Fatigue, weight loss	+/−/−/−	NA/NA/NA	NA/68; NA/20	NA	NA	VCR/Asp/GC	CR at 20 m
Chilcote 1982	F/11	Fever, CP, lethargy	+/−/−/+	96/10/Nl	0/46; 95/50	NA	+8, 14q marker	VCR/Asp/GC	CR, death of CHF in a few months
Gaynon 1984	F/29 m	Fever, rash	+/−/−/+	144/10/20	0/10; 74/38	NA	Normal	VCR/Asp/GC	CR at 10 m
Troxell 1984	M/21	Cough, fever, DVT	+/−/−/+	29/12/278	0/5; 45/45	NA	+4, +11, +14, +21	VCR/GC	DOD at 100 d
Tono-oka 1984	M/8	Fever, cough	+/−/−/+	148/NA/126	6/20; 70/37	NA	t(5;14)	Cy/VCR/GC	DOD within days
Keene 1987	M/5	Pneumonia, LAP	+/+/−/−	34/11/43	71/24; 1/20	NA	t(12;13)	Daun/VCR/GC/Ara-C/6TG	CR at 2 y
Tan 1987	M/16	Hemoptysis, dyspnea, fatigue, fever, weight loss	+/+/−/−	14/10/22	31/+; 27/+	NA	Normal	Daun/VCR/GC/Asp	CR
Hogan 1987	M/19	Fever, fatigue, weight loss, rash, CP, cough	+/+/−/+	82/11/149	0/40; 57/27	NA	t(5;14)	Daun/VCR/GC/Asp	DOD at 10 m
Baumgarten 1989	M/8	Cough, fever	+/−/−/+	50/NA/NA	15/15; 30/+	B	t(5;14)	BFM-83	DOD at 10 m
Fishel 1990	F/58	Fatigue, fever, CVA	+/−/+/+	206/12/69	57/+; 28/+	B	−8, −12, −20, −5q	Cy/VCR/Dox/GC	CR, relapse at 3 m, DOD at 17 m
Takai 1991	M/37	Fever, DVT	+/−/+/+	36/13/409	0/9; 63/28	B	Normal	NA	DOD at 22 m
Schiff 1992	F/5	Fever, myalgia, chorea	+/−/+/−	59/10/193	0/48; 52/21	B	Normal	Daun/VCR/GC/Asp	CR at 5 m
Knuutila 1993	M/33	Fever	+/−/−/−	28/13/171	0/>90; 67/10	B	+X, t(5;14)	Daun/VCR/GC/Asp and allo-HCT	CR at 2 y
Jain 2000	M/4	Fever, rash, abdominal pain, dyspnea	+/−/−/−	70/10/37	+/45; 80/34	B	Normal	Daun/VCR/GC/Asp	CR, relapse at 20 m, DOD at 21 m
Narayanan 2000	F/7	Fever, rash, dyspnea, arthralgia	+/+/−/+	18/8/75	19/+; 48/NA	B	Normal	Daun/VCR/GC/Asp	DOD at 6 w
Bernasconi 2001	M/18	None	−/−/−/−	19/14/350	0/+; 85/30	B	11p abnormality	NA	NA
Bjerregaard 2002	F/10	Fever, fatigue, weight loss	+/−/−/−	17/6/Nl	0/+; 55/+	B	NA	Daun/VCR/GC	CR, relapsed at 39 m, CR at 61 m
Donahue 2002	F/18	Fever, dyspnea	+/−/−/+	85/NA/NA	NA/NA; 74/NA	NA	NA	NA	DOD at 3 w
Wynn 2003	F/5	Fever, fatigue, rash	+/−/−/−	31/10/109	14/50; 46/14	B	+4, −5q, +6, +7, +9, +21, +21	COG 1991	CR at 12 m
Hill 2003	M/10	Fever, rash	+/−/−/−	98/NA/NA	0/30; 78/+	B	Normal	NA	NA
Nunez 2003	M/9	Fever	+/+/−/−	6/11/42	46/94; 17/1	NA	Normal	VCR/GC/Asp	CR, DOD at 3 y

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