Acute Lymphoblastic Leukemia with Hypereosinophilia

Anwar N. Mohamed

Cytogenetics Laboratory, Pathology Department, Detroit Medical Center, Wayne State University School of Medicine, Detroit, MI USA. amohamed@dmc.org

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Abstract

Acute lymphoblastic leukemia (ALL) with hypereosinophilia is a rare disease, with the majority of reported cases being B-lineage ALL. Although eosinophilia is considered a reactive, non-neoplastic epiphenomenon, it adversely affects patient outcomes, both in children and adults. It is a distinct clinical entity by World Health Organization (WHO) 2008 and commonly associated with a unique cytogenetic abnormality.

Keywords
Acute lymphoblastic leukemia; Hypereosinophilia; t(5;14); deletion 5q

Identity

Marked eosinophilia is an uncommon finding in ALL. It may precede the diagnosis of ALL or occur simultaneously at the time of diagnosis. Eosinophils can mask the underlying or coexisting leukemia. Therefore, comprehensive evaluation for unexplained hypereosinophilia should be carried out to rule out possibility of malignancy including ALL, even in the absence of peripheral circulating blasts.

Clinics and pathology

Epidemiology

ALL with hypereosinophilia is reported in <1% of ALL cases. The disease was first described by Spitzer and Garson in 1973. Subsequently, over 50 adult and pediatric cases have been documented in the literature (Fishel et al, 1990; Parasole et al 2014). The majority of the described cases have B-cell phenotypes. In 1980, Catovscky et al reported two cases of T-cell ALL with eosinophilia. ALL with eosinophilia cases are predominantly male patients, median age at presentation of 15 years with an age range of 2-71 years (Fishel et al, 1990; Wilson & Tefferi, 2005; Parasole et al, 2014).

Clinics

Clinical presentations may be similar to other patients with ALL. Whereas some patients may be presented with signs and symptoms indistinguishable from hypereosinophilic syndrome, and death in some patients appears to have occurred as a complication of eosinophilic tissue damage (Rezamand et al, 2013; Bomken et al 2015). Eosinophilia may precede the diagnosis of leukemia by 1-9 months and during this period, the patients may present with urticarial hyperpigmented plaques and other non-hematological features of HES such as cardiomyopathy, pneumonitis, dermatitis, sinusitis, central nervous system or peripheral neuropathy (Chien et al, 2004; Bomken et al 2015). In patients bearing this association, a significantly increased risk of cardiac and vascular thrombosis exists, and congestive heart failure represents the main cause of mortality in patients with ALL and hypereosinophilia (Nie et al, 2010; Parasole et al, 2014).

Based on the literature review 30% of patients died as a result of congestive heart failure attributed to the eosinophilia (Fishel et al, 1990). Pneumonia or pulmonary infiltrates were present in 50% and chest pain was reported in 20% of
patients. Thrombotic complications may occur in this subset of ALL therefore, prompt heparin prophylaxis or chemotherapeutic modulation of prothrombotic drugs should be planned. Eosinophilic infiltration into endomyocardial, pleural and pulmonary tissue has been documented in those patients (Parasole et al, 2014). Eosinophilia quickly resolved upon achievement of remission, but in most patients reappeared during relapse. Thus, eosinophilia is an important clinical marker to monitor this disease, which disappears with chemotherapy whereas its recurrence following remission is an indication of relapse of ALL.

Cytology
Peripheral blood usually shows leukocytosis and marked eosinophilia. The initial white blood cell count ranged from 4-148x 10^9/L with an average eosinophilia of 55% and rare circulating blast cells. Blasts may be absent in peripheral blood which could lead to delay in the diagnosis, if bone marrow aspiration is not done (Wilson and Tefferi, 2005; D'Angelo et al 2008). Many of the laboratory abnormalities characteristic of hypereosinophilic syndrome (HES), including eosinophil dysplasia, and elevated B12 levels can also be seen in ALL with eosinophilia. Interestingly, elevation of serum tryptase, which is associated with imatinib responsive HES, has not been reported (Robyn et al 2004).

Pathology
Bone marrow aspirate and biopsy show hypercellular marrow infiltrated with blasts, and the presence of marked eosinophilia; both precursor and normally maturing eosinophils. The blasts have typical morphology of lymphoblasts and express B-precursor phenotypes classically CD19+ and CD10+.

Prognosis
ALL with eosinophilia is an aggressive form of ALL. Prognosis is poor both in children and adults (Sutton et al 2008; Wilson et al, 2010). Although response to initial chemotherapy was good, relapse occurred in most patients. The prognosis of patients reviewed by Fishel et al was quite poor; 22 of 24 patients died within 5 years of diagnosis, with a median time from diagnosis to death of 7.5 months. Death resulted from either complications of chemotherapy or from organ failure secondary to overwhelming infiltration by eosinophils. Sutton et al described two patients in a cohort of 391 pediatric ALL (Sutton et al 2008). Both patients had a very poor molecular response to initial chemotherapy as measured by high minimal residual disease (MRD) and were stratified to the high-risk group to receive intensive chemotherapy followed by bone marrow transplantation. One patient had subsequently relapsed and the hypereosinophilia, which also recurred, was of donor cell origin.

Cytogenetics
Note
Cytogenetic abnormalities are found only in leukemic blasts whereas eosinophils have normal karyotype indicating not a clonal population. Based on limited reported cases, approximately 2/3 of ALL with eosinophilia cases have chromosomal abnormalities with the most recurrent being:

Cytogenetics morphological

\textbf{t(5;14)(q31;q32)}

this translocation, t(5;14)(q31;q32), has been identified in almost 50% of cases (Hogan et al, 1987; Grimaldi and Meeker 1989; Bomken et al, 2015). The breakpoint of this unique translocation has been cloned and shown to juxtapose the IGH/14q32 enhancer and IL3/5q31 gene, resulting in a constitutive expression of IL3 (Meeker et al, 1990). While IL3 promotes production and survival of eosinophils, high serum levels of IL3 have been postulated to be responsible for the reactive hypereosinophilia. High serum IL3 levels have been demonstrated in one case at diagnosis and seen to recur at leukemic relapse.

\textbf{t(5;9)(q31;p24)}

\textbf{Nuñez et al} reported a novel t(5;9)(q31;p24), in a patient with B-cell ALL associated with eosinophilia. In this case the t(5;9)(q31;p24) possibly led to fusion of the IL3/5q31 and JAK2/9p24 genes that may explain the simultaneous appearance of eosinophilia and ALL (Nuñez et al 2003). Other recurrent chromosome abnormalities reported in ALL with eosinophilia are deletion of 5q, deletion of 7q, deletion of 9p21 with biallelic deletion of CDKN2A (cyclin dependent kinase 2a / p16), t(7;12)(q22;p13) (Wynn et al, 2003; Wilson et al, 2005; Rezk et al 2006; D'Angelo et al, 2008; Parasole et al, 2014; Bhatti et al, 2009). These chromosomal abnormalities are uncommon in ALL without eosinophilia suggesting that this subtype of ALL may represent a unique disease entity.

Genes involved and proteins

IL3

Location
5q31.1

Note
Alternative symbols: showed that the product of the MYC gene has a molecular mass of 65 kD, is located predominantly in the nucleus, and binds to DNAInterleukin 3; Hematopoietic Growth Factor; Multipotential Colony-Stimulating Factor; Multilineage-Colony-Stimulating Factor; Colony-
Stimulating Factor; Multiple; P-Cell Stimulating Factor; Mast-Cell Growth Factor.

**Protein**
The protein encoded by IL3 gene is a potent growth promoting cytokine. It acts by binding to interleukin receptor. This cytokine stimulates the proliferation of a broad range of hematopoietic cell types. It is involved in a variety of cell activities such as cell growth, differentiation and apoptosis.

**JAK2**

**Location**
9p24.1

**Protein**
Protein tyrosine kinase of the non-receptor type.

**IGH**

**Location**
14q32.33

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