Hypereosinophilia in Acute Lymphoblastic Leukemia: Two Cases with Review of Literature

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Abstract Eosinophilia is rare in acute leukemia at presentation. Discrete reports and case studies in recent years have created significant interest in the field of “Acute leukemia with eosinophilia”. We herein present two cases of eosinophilia in association with acute lymphoblastic leukemia with brief review of literature in this field. First case is about 21-year-old female who presented with mediastinal mass along with leukocytosis and hypereosinophilia. On evaluation, she was found to have T cell acute lymphoblastic leukemia. After ruling out benign causes of eosinophilia, she was treated with modified BFM-90 protocol. Her eosinophilia resolved after 4 weeks of induction therapy. Second case is about 32-year-old male who was diagnosed as a case of mixed phenotype leukemia (B cell/myeloid type) along with severe eosinophilia. His hypereosinophilia finally resolved by week 16 of modified BFM-90 protocol. Diagnosing ALL is challenging when eosinophilia is the initial presentation. These two cases emphasize on the importance of considering ALL amongst one of the etiological causes of eosinophilia as delay in diagnosis endangers patient’s life at risk. Also eosinophilia per se is an independent poor risk factor, hence prompt diagnosis and early treatment is the key in all such cases.

Introduction

“Eosinophilic leukemia” is a broad term comprising of all hematological malignancies in which eosinophilia is a

prominent feature. In most of these leukemias, eosinophilia is reactive rather than clonal. ALL associated eosinophilia was first reported by Spitzer et al. [1]. Some studies have reported association of chromosomal anomaly t [5, 14] with eosinophilia associated ALL [2, 3]. Whether reactive or clonal, eosinophilia always endangers vital organs at risk of dysfunction. Although ALL associated eosinophilia is a rare entity, haematologists must be aware of this uncommon initial presentation of ALL, so as to avoid delay in diagnosis and management.

Case -1

A-21-year old female presented with short history of fever and breathlessness for 20 days. She was pale and tachypnoeic at presentation. General physical examination was normal except for D’spine sign suggestive of mediastinal mass. There was no lymphadenopathy or hepatosplenomegaly. Chest X-ray at admission (Fig. 1a) showed a large mediastinal mass of approximately 10 × 10 cm in greatest dimensions. CECT/HRCT chest confirmed the mass to be in anterior mediastinum (Fig. 1e) with bilateral diffuse heterogeneous sheet like parenchymal opacities suggestive of leukemic infiltration (Fig. 1c).

The full blood count showed hemoglobin-101 g/L, total leukocyte count- $155 \times 10^9/L$, platelet count- $43 \times 10^9/L$. The differential leukocyte count showed 90 % eosinophils, 6 % blasts, 3 % lymphocytes and 1 % promyelocytes. The absolute eosinophil count was $135 \times 10^9/L$. Stool examination for parasites(ova and cysts) was negative thrice. Bone marrow examination from iliac spine was markedly hypercellular showing predominant population of cells comprising blasts and eosinophils. The erythropoiesis and thrombopoiesis were suppressed. The differential counts of

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Fig. 1 **a, b** Chest X rays showing mediastinal mass **a** which resolved subsequently after starting chemotherapy; **c, d** HRCT films showing marked improvement in bilateral parenchymal shadows (**d**) as compared from baseline (**c**); CECT films confirming the findings of Chest X ray as evident by marked reduction in dimension of anterior mediastinal mass

all nucleated cells revealed 51 % blasts, 43 % eosinophils, 2 % monocytes, 1 % polymorphs, 1 % basophils & 2 % erythroid precursors. Blasts were two to three times the size of mature lymphocytes with a high nuclear-cytoplasmic ratio, homogenous opened up chromatin and prominent nucleoli in some of the blasts. The cytoplasm was scanty with absence of granules or auer rods. Eosinophils constituted the other large population of cells in bone marrow aspirate. Most were mature with normal morphology, however, some monolobated as well as tri-lobated eosinophils were also noted (Fig. 2).

Immunophenotyping done by multi-parametric flow cytometry revealed surface expression of CD7 & CD5 on the blasts. Blasts also expressed CD45, CD38 and a myeloid marker, namely CD13. Other T-lineage surface markers like CD1a, CD2, CD3, CD4, CD8, and TCR $\alpha\beta$ & TCR $\gamma\delta$ were not expressed. B-lineage surface markers (CD19, CD10, and CD20) and rest of the myeloid lineage markers (CD33, CD117, CD36) as well as HLADR &

CD34 were negative. Intra-cytoplasmic markers showed positivity for cytoplasmic-CD3 with absence of myeloperoxidase (MPO), cytoplasmic-CD79a and terminal deoxynucleotidyl transferase (TdT). The karyotypic analysis did not reveal any abnormality. Molecular/FISH studies for FIP1L1-PDGFR α , FGFR-translocation, BCR-ABL transcripts were negative.

Final diagnosis of T-cell acute lymphoblastic leukaemia with hypereosinophilia and mediastinal mass was made. She was started on pre-induction with dexamethasone followed by induction therapy according to modified BFM-90 protocol. Repeat chest X ray (Fig. 1b) on day 10 of induction therapy showed resolution of mediastinal mass. A repeat CECT/HRCT chest was done on day 21 of induction showed 90 % reduction in the size of mediastinal mass with normal lung parenchyma (Fig. 1d, e). The eosinophil count normalized by day 18 of chemotherapy (Fig. 3a). Presently patient has completed 10 weeks of chemotherapy and there is no recurrence of eosinophilia.

Fig. 2 **a** Peripheral blood film showing eosinophils, occasional one being monolobated (*thick arrow*) accompanied with blasts (*thin arrow*); **b, c** bone marrow aspirate smears showing blasts and eosinophils; **d** bone marrow trephine biopsy showing hypercellular marrow spaces comprising predominantly of blasts and eosinophils

Case-2

A-32-year old male presented with complaints of fever for 1 month. Examination was unremarkable except for pallor. Lab investigations revealed Hb-116 g/L, total leukocyte count- $68.9 \times 10^9/L$, platelet count- $334 \times 10^9/L$. Differential counts were 82 % eosinophils, 14 % polymorphs, 3 % lymphocytes and 1 % monocytes. Bone marrow aspirate was hypercellular with 22 % blasts and 41 % eosinophils. The blasts were two to three times larger than mature lymphocytes, round to irregular nuclear membrane, inconspicuous to prominent 1–2 nucleoli and scanty amount of agranular basophilic cytoplasm. Flowcytometry on bone marrow aspirate revealed expression of B-lineage markers (CD19, CD10 & cytoplasmic-CD79a) along with myeloid markers (CD13 & anti-MPO) on the blasts. In addition, the blasts expressed CD34, CD38, HLADR and TdT. T-lineage markers were not expressed.

Overall immunophenotype was consistent with a mixed phenotypic acute leukemia, B/myeloid type. Similar to case 1, reactive causes of eosinophilia like parasite infestation, drugs were ruled out. Molecular/FISH studies for PDGFRA, FGFR1, BCR-ABL, inversion 16, 11q translocation, NPM, CEBPA, FLT3ITD, and FLT3D835 were negative. He was started on modified BFM-90 protocol. At the end of induction, his total leukocyte count reduced to $9.5 \times 10^9/L$ with 35 % eosinophils. The bone marrow aspirate revealed 3 % blasts. His eosinophil count

normalised finally by the end of week 16 (Fig. 3b). No other complications related to hypereosinophilia were noted.

Discussion

Eosinophilia in hematological malignancies can either be reactive or clonal. Malignancies like hodgkin's lymphoma, myeloproliferative neoplasms, primary cutaneous T-cell lymphoma and solid tumours (colon cancer, ovarian carcinoma etc.) can be associated with severe eosinophilia. Pathophysiologically, eosinophilia in malignancies can occur either due to excessive release of eosinophilopoietic cytokines by neoplastic and T-helper cells (IL-3, IL-5, GM-CSF etc.) or due clonal evolution secondary to various cytogenetic abnormalities [4]. There are various reports of genetic abnormalities in hematological malignancies which have been reported in association with eosinophilia (Table 1). However, the final common cascade is formation of fusion genes leading to constitutive stimulation of tyrosine kinases (commonly PDGFRA, PDGFRB and FGFR1) responsible for eosinophilic proliferation [4]. Considering the importance of co-existence of eosinophilia in hematological malignancies, WHO has created a new entity "Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB and FGFR1" in 2008.

Fig. 3 **a** Depiction of TLC, blast count and eosinophil count during induction therapy (case1). **b** Depiction of TLC, blast count and eosinophil count (Case 2) (24-06-2012 to 10-03-2014)

Lymphoma as compared to leukemia is more commonly associated with eosinophilia. Amongst acute leukemia, hypereosinophilia is more common in AML as compared to ALL [5]. AML with t [16] or inversion 16 are common genetic abnormalities associated with eosinophilia [6, 7]. Most common genetic abnormality detected in case of ALL associated with eosinophilia is t [5, 14] which is otherwise uncommon in classical cases of ALL [2, 3, 8–10]. In general, eosinophilia in association with ALL is rare and that too in T-cell subtype, it is limited to case reports [11–14]. B-cell ALL is commoner subtype than T-cell in association with eosinophilia [15]. The first case described here had T-cell phenotype.

Whether reactive or clonal, eosinophilia remains a potential threat to the life of patient in addition to the risk associated with basic haematological disorder, treatment related complications and opportunistic infections. Major organs at risk due to eosinophilia include heart, lung, kidney, CNS and liver. Various cases of cardiotoxicity/myocarditis [13, 29–31] as well as lung injury [8] secondary to eosinophilia have been reported. Although CSF cytology for

malignant cells or eosinophils were negative in both of presented cases and they did not have any neurological signs or symptoms, it is important to keep in mind that there is increased risk of CNS relapse in cases where CSF is positive for eosinophils [32–34]. Law KL et al. [34] reported CNS relapse in a young girl who was in remission for 3 years, in which eosinophils were found in CSF. Utsunomiya et al. and Sutton et al. proposed that presence of hypereosinophilia should be considered as an independent poor prognostic indicator. Bae et al. [15] reported a case of eosinophilia with biphenotypic acute leukemia similar to our 2nd case.

There have also been rare case reports of parasitic infestation concomitant with acute leukemias [27, 28]. Nesheli et al. [28] reported a case from Iran who had pre-B cell ALL with eosinophilia and whose stool work-up showed larva of *Strongyloides stercoralis*. Similarly Rahman et al. reported a case of newly diagnosed acute myeloid leukemia, in which bancroftian microfilariae was found in peripheral blood as well as bone marrow smears [32]. These two reports suggest that being a curable condition, parasitic infestations need to always be thought of in

Table 1 Reported cases of eosinophilia in association with acute myeloid and lymphoid neoplasms

Author	Age	Sex	Abnormality	Basic disease	Complications associated with eosinophilia
Case 1	20	F	Normal karyotype	T-cell ALL	Eosinophilic pneumonia
Case 2	32	M	Normal karyotype	Biphenotypic leukaemia	None
Sreedhara et al. [7]	48	F	Inv(16)(p13.1;q22)	AML M4	None
Baumgarten et al. [3]	NA	NA	t(5;14) (q31.1;q32.3)	ALL(Type NA)	None
Tan et al. [8]	NA	M	t(5;14) (q31.1;q32.3)	ALL(Type NA)	Pneumonia
Hogan et al. [2]	19	M	t(5;14) (q?,q32)	B cell ALL	None
Tono-oka et al. [9]	8	F	t(5;14) (q31;q32)	B cell ALL	Eosinophilic pneumonia
Amshalom et al. [10]	8	M	t(5;14) (q13;q32)	B cell ALL	None
Bhatti et al. [16]	31	M	t(7;12)(q22;p13)	B cell ALL	None
Li et al. [17]	NA	NA	8p11/FGFR1	T-cell ALL	NA
Nunez et al. [18]	8	M	t(5;9)(q31;p24)	B Cell ALL	None
Trimaldi et al. [19]	64	M	t(8;13)(p11;q12)	B Cell ALL	None
Harisi et al. [20]	0.4	M	t(3;4;6)(q26;q25;q21)	AML M7	None
Park et al. [21]	4	F	t(16;21)(q24;q22)	AML	None
Walz et al. [22]	60	M	ETV6-FLT3 fusion/complex karyotype	T cell Lymphoma	None
Walz et al. [22]	29	M	t(12;13)(p13;q12)/ETV6-FLT3 fusion	T cell lymphoma	None
Fishel et al. [23]	58	F	Complex karyotype	B cell ALL	Eosinophilic myocarditis
Wynn et al. [24]	5	F	5q deletion	B cell ALL	None
Riyami et al. [25]	NA	NA	FIP1L1/PDGFR4	AML	None
Vijay et al. [26]	76	M	Isoschromosome 21 [i(21)(q10)]	AML M4	None
Rahman et al. [27]	NA	NA	Bancroftian microfilariae	AML	None
Nesheli et al. [28]	9	F	Strongyloides stercoralis	B cell ALL	Eosinophilic pneumonia
Bae et al. [15]	46	M	Normal Karyotype	Biphenotypic ALL	Eosinophilic myocarditis

all cases of concomitant eosinophilia especially in tropical countries. Our patients were also worked up and found to be negative for parasitic infection.

Conclusion

Present two cases reinforce on the very fact that eosinophilia can be challenging to deal with especially in conditions of eosinophilia related organ damage. Reactive causes of eosinophilia should be first ruled out in all such cases before considering other possibilities, as being curable, patients can be prevented from bearing pain of unnecessary investigations and procedures. However once reactive causes are ruled out, presence of eosinophilia puts patients to high risk group with greater chances of relapse. Both of our patients achieved remission and are doing well till now.

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