CASE REPORT

# Chronic eosinophilic leukemia transformation into acute myeloid leukemia with monocytic differentiation

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**Received:** February 6, 2014 **Accepted:** February 26, 2014 **Online Published:** March 11, 2014
**DOI:** 10.5430/crim.v1n2p4 **URL:** http://dx.doi.org/10.5430/crim.v1n2p4

## Abstract

We present a rare case of a patient that presented with a highly elevated total leukocytic count, abnormally high eosinophils and increased number of blasts that was diagnosed as chronic eosinophilic leukemia. The blast cell count did not reach the threshold to diagnose acute leukemia. Over 6 months, the case progressed to acute myeloid leukemia with normal total leukocyte count but high percentage of blast cells and decreased percentage of eosinophils.

## Keywords

Chronic eosinophilic leukemia, Acute myeloid leukemia, Hypereosinophilic syndrome, Targeted therapy

## 1 Introduction

Hypereosinophilia is defined as a persistent (> 6 months) peripheral blood (PB) eosinophil count greater than $1.5 \times 10^9$/L that is associated with tissue damage. The differential diagnosis in a patient with peripheral eosinophilia is extensive and common secondary causes need to be ruled out before considering rarer clonal etiologies. Some such causes include parasitic infections, hypersensitivity conditions, drug reactions, collagen-vascular diseases, and pulmonary eosinophilic diseases [1, 2]. These alterative etiologies were excluded to the best of our ability in the evaluation of this patient via history, physical exam, and laboratory testing.

Chronic eosinophilic leukemia (CEL) is distinguished from hypereosinophilic syndrome (HES) by the evidence of clonal molecular markers or significantly increased numbers of blasts [3]. After the exclusion of secondary causes of eosinophilia, diagnostic evaluation relies on a combination of morphologic review of the PB and bone marrow (BM), characterization of organ infiltration, standard cytogenetics and molecular genetics, flow immunocytometry, and T cell clonality assessment to detect histopathologic or clonal evidence for an acute or chronic myeloid or lymphoproliferative disorder [3]. CEL constitutes a rare entity within the WHO classification [4] defined by unexplained eosinophilia greater than $1.5 \times 10^9$/L with evidence of:

1) Clonal eosinophilia via abnormal cytogenetics (excluding BCR-ABL, PDGFRα, PDGFRβ or FGFR1 rearrangements); or

2) The presence of greater than 2% blasts in the peripheral blood; or

3) 5% blasts (but less than 20%) in the BM.

The estimated age-adjusted incidence rate for HES/CEL is 0.036/100,000 person-years (based on Surveillance Epidemiology and End Results data from 2001 to 2005). The median age at HES diagnosis is 52.5 years, with a male-to-female ratio ranging from 1.47 to 9 [5, 6].The reported 10-year survival rate for patients with HES is less than 50% [7]. While HES and CEL are both characterized by unexplained, persistent hypereosinophilia, there are important differences. Idiopathic HES is a diagnosis of exclusion, whereas CEL requires positive identification of features indicative of leukemia, such as increased blast cells or evidence of clonality. The 2 disorders are mutually exclusive. It is possible that some patients that are currently only classified as having idiopathic HES actually have CEL, but when no evidence to support this suspicion can be found, a diagnosis of idiopathic HES is appropriate. Conversely, when eosinophilia is a feature of a myeloid leukemia, it is not idiopathic and the diagnosis is not idiopathic HES [8].

The most common genetic abnormality in PDGFR-associated CEL results from a deletion of genetic material from chromosome 4, which brings together part of the PDGFR gene and part of the FIP1L1 gene, creating the FIP1L1-PDGFR fusion. Reports of responses to Imatinib in CEL [9, 10] suggest activation of a tyrosine kinase may be involved in the pathogenesis of these related diseases, and in 2003, Cools et al reported a novel genomic event leading to activation of the PDGFRα tyrosine kinase in a subset of patients with HES [11]. Hematopoietic cells from these patients were demonstrated to possess a gene deletion leading to generation of an in-frame fusion transcript fusing FIP1L1 to the catalytic domain of PDGFRα. The FIP1L1-PDGFRα fusion protein is a constitutively active tyrosine kinase with transforming properties which can be inhibited by Imatinib and other tyrosine kinase inhibitors. Some patients with FIP1L1-PDGFRα negative CEL/HES respond to Imatinib, suggesting that there is another activated tyrosine kinase involved in the pathogenesis of this subset of CEL/HES [12]. When the FIP1L1- PDGFRα fusion gene mutation or point mutations in the PDGFRα gene occur in blood cell precursors, the growth of eosinophils is poorly controlled, leading to PDGFR-associated CEL. It is not clear why eosinophils are preferentially affected by this genetic change.

The Philadelphia-negative ($Ph^-$) myeloproliferative neoplasms (MPNs) are a group of phenotypically-related clonal hematopoietic diseases characterized by the overproduction of mature myeloid blood cells and a prolonged clinical course [13-16]. Transformation to acute myeloid leukemia (AML) occurs in; 5%-10% of cases after 10 years and is associated with exceptionally poor prognosis. Genetic abnormalities are found in most patients with CEL. The most frequent chromosomal abnormality is a deletion on chromosome 4q12 that creates a fusion of FIP1-like 1 protein with platelet-derived growth factor receptor α (FIP1L1-PDGFRα) [17-19]. FIP1L1-PDGFRα is present in only ~10%-20 % of all patients with suspected nonreactive eosinophilia and is associated with increased disease severity due to constitutive tyrosine kinase activity of PDGFRα [20-22]. Recently, several activating mutations in PDGFRα have been identified in FIP1L1-PDGFRα -negative patients [22]. This set of activating mutations induces clonogenic growth, growth factor-independent cell proliferation and constitutive phosphorylation of PDGFRα and signal transducer and activator of transcription 5 (STAT5) and is thought to play a role in the pathogenesis of CEL. Other genetic abnormalities associated with eosinophilia include fusions of fibroblast growth factor receptor 1 (FGFR1) or PDGFRβ, each occurring in <1 % of patients. More than 20 gene fusion partners for PDGFRβ and more than 10 for FGFR1 have been identified [23, 24]. Current understanding of the optimal treatment strategy for patients who undergo leukemic transformation is limited. Since FIP1L1-PDGFRα has been identified as a novel oncogenic fusion tyrosine kinase in cases of HES/CEL and systemic mast cell disease with eosinophilia, the utility of Imatinib (Gleevec®, Novartis Oncology, East Hanover, NJ, USA) in HES/CEL has been investigated. Imatinib responses for the treatment of HES/CEL have been positive. The discovery of the FIP1L1-PDGFRα fusion gene in a significant proportion of patients who would have previously been regarded as having idiopathic HES was very important in advancing our understanding of this group of disorders.

# 2 Case presentation

## 2.1 History

A previously healthy 30 year old male of Middle-Eastern ancestry presented with symptoms that included anemic manifestations, high grade fever and productive cough with prominent bloody sputum. The patient was not taking any medications, had no reported allergies, no history of infectious processes, no recent blood transfusions, no family history consistent with the current symptoms and no other significant events in his past medical history.

## 2.2 Physical examination

On initial presentation, the patient appeared with noticeable pallor and the absence of any organomegaly or adenopathy. On follow-up, he had developed anemic manifestations, hemoptysis, lower limb swelling, fever, bilateral fine crepitation heard throughout the chest and a pan-systolic cardiac murmur located over the apex and tricuspid areas.

## 2.3 Investigations

### 2.3.1 Imaging

Posterior-Anterior chest X-ray indicated the presence of bilateral pulmonary infiltrates. Echocardiogram showed an echogenic mass obliterating the apex of the left ventricle and partially the apex of the right ventricle with thickening of the endocardium especially the lateral and posterior walls.

### 2.3.2 Lab values

The complete blood picture showed hemoglobin of 59g/L, white blood cell count of $55 \times 10^9$/L and platelet count of $109 \times 10^9$/L. MCV was 75.6fL, MCH was 26.3 pg, and the MCHC was 348g/L. The differential count indicated 50% eosinophils and 11% blasts, segmented neutrophils were 12%, bands were 8%, myelocytes were 6%, metamyelocytes were 5% and lymphocytes were 8%. Microscopically the peripheral blood showed a striking elevation in the eosinophil count. Urine and stool were negative for parasites. After 6 months of treatment, the complete blood counts changed to hemoglobin of 66g/L, leukocytic count of $5.3 \times 10^9$/L and $58 \times 10^9$/L platelet count. Microscopically, the eosinophil count had dropped to 11% and the percent blasts had increased to 30%, segmented neutrophils were 8%, bands were 18%, myelocytes were 4%, metamyelocytes were 4% and lymphocytes were 25%.

### 2.3.3 Bone marrow aspirate

At initial presentation the bone marrow aspirate was hypocellular for an individual of the patients' age. The aspirate contained 58% abnormal eosinophils showing dysplastic features and 5% blasts with Auer rods detected, neutrophils were 10%, bands 1%, myelocytes were 4%, promyelocytes were 5%, metamyelocytes were 2%, lymphocytes were 7% and erythroid 8%. At the second presentation 6 months later, the bone marrow aspirate was hypercellular for an individual of his age with 2% eosinophil, 49% blasts, segmented neutrophils were 5%, bands were 3%, myelocytes were 1% and metamyelocytes 2% and lymphocytes were 8% and erythroid 30%. Blasts were negative for myeloperoxidase (MPO) and Periodic acid-Schiff (PAS) staining.

### 2.3.4 Immunophenotyping results

**Table 1. Immunophenotype analysis of blasts at follow-up presentation**

| | Positive Markers | Negative Markers |
|---|---|---|
| Immunophenotype | CD13, CD33, CD117, CD4, CD56, CD45, Cytoplasmic MPO | CD34, CD19, CD10, CD3, CD5, CD14, HLA-DR, , CD61, CD235a, cytoplasmic CD41 |

### 2.3.5 Cytogenetic study

Cytogenetic abnormalities were not detected by conventional karyotyping. BCR/ABL by FISH was negative.

 ISSN 2332-7243 E-ISSN 2332-7251

### 2.3.6 Initial and follow-up treatment

At the 1st presentation the patient received prednisolone (15mg daily) and Hydroxyurea (500 mg twice daily). He did not demonstrate laboratory or clinical improvement within 2 months. Hydroxyurea was discontinued and the patient was commenced on Imatinib, (100 mg po daily) along with prednisolone continued for 4 months. When transformation to AML was confirmed, the patient received 3 + 7 protocol consisting of Adriamycin (45mg/$m^2$) on day 1 to day 3 and Cytarabine (100mg/$m^2$) on days 1 to day 7.

### 2.3.7 Patient outcome

The patient is awaiting bone marrow transplantation but is currently ineligible secondary to heart failure.

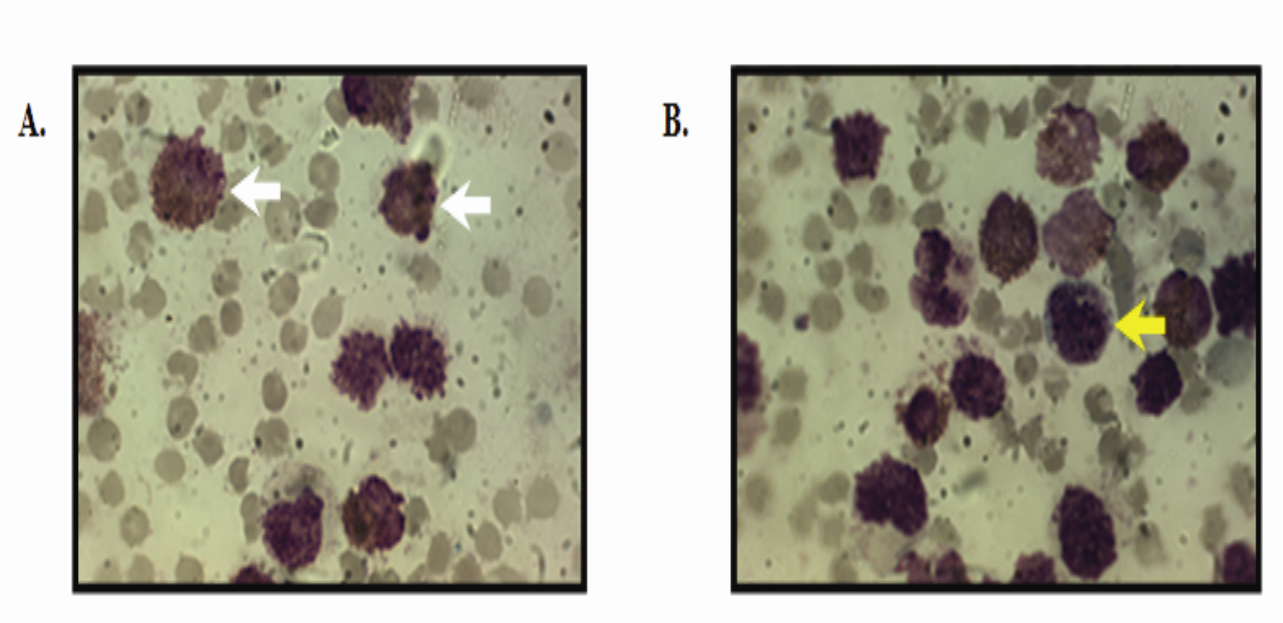


**Figure 1.** The films were Leishman stained and viewed at 100X magnification. Peripheral blood film was performed at initial presentation that showed multiple abnormal eosinophils (A) & blast cells (B).

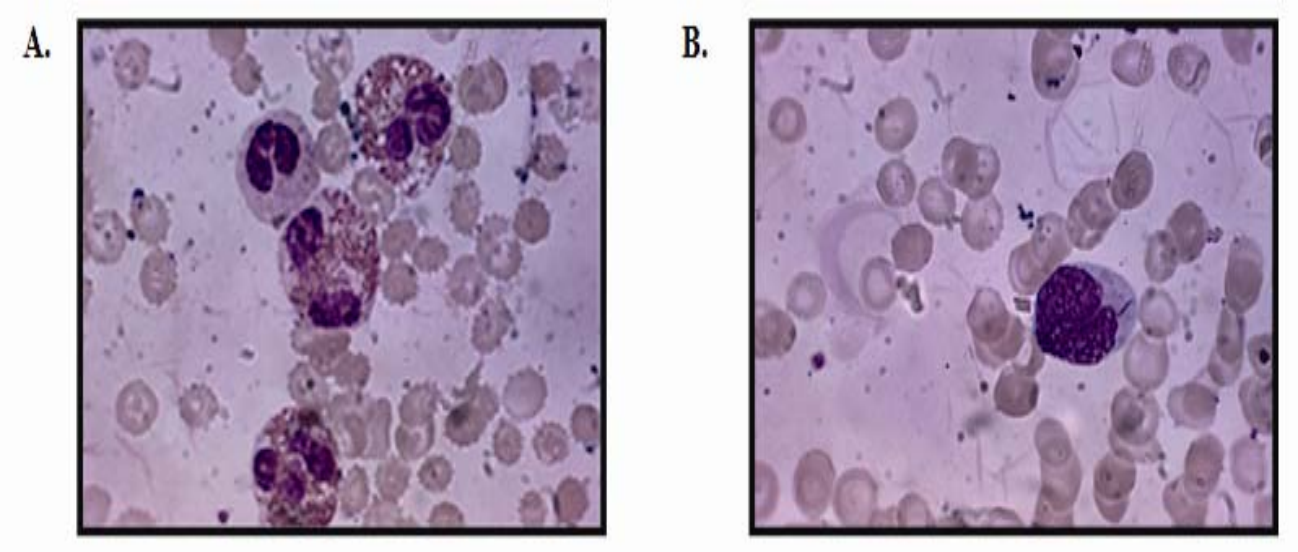


**Figure 2.** Films were Leishman stained and viewed at 100X magnification. Bone marrow aspirate obtained at initial presentation that showed abnormal eosinophils with partial degranulation (A) & blasts which showed Auer rods (B).

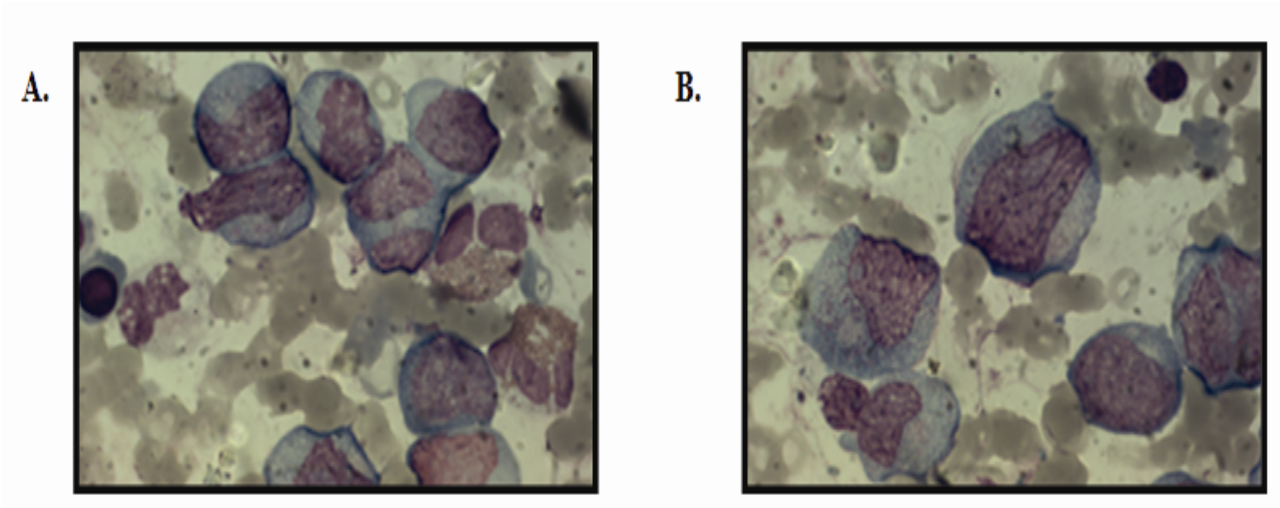


**Figure 3.** The films were Leishman stained and viewed at 100X magnification. Bone marrow aspirate at follow-up presentation that showed abnormal eosinophils with partial degranulation (A) & blasts (A, B).

## 3 Discussion

CEL is a rare MPN that presents with a highly variable clinical course. Transformation to AML is a complication of MPNs associated with short-lived response to induction chemotherapy and poor survival. The disease may remain stable for many years, perhaps decades, or may rapidly progress and transform to acute leukemia. Hence, the most appropriate treatment should be determined on an individualized basis. Treatment may include corticosteroids, chemotherapy, Hydroxyurea or interferon therapy. Stem cell transplantation is also considered in selected cases. High-dose chemotherapy combined with stem cell transplant holds some potential for cure in the treatment of $Ph^-$ leukemic myeloproliferative disorders, but these studies are limited by low patient enrollment, heterogeneity in the biology of initial disease, patient variability at remission and the lack of a control arm to fully ascertain benefit [25].

Certain patients respond to Imatinib which is most often used for the treatment of chronic myeloid leukemia (CML). The optimal dose of Imatinib for the treatment of FIP1L1/PDGFRα positive CEL patients remains unknown since systematic dose comparison studies have not been performed. Klion et al. determined that the dose necessary to suppress the presence of the fusion gene below the level of detection by nested RT-PCR was 100 to 400 mg daily [26]. Our patient was treated with Imatinib at 100 mg daily which may have contributed to the rapid disease progression. In addition, the high variability in effective dosing may arise from differences in drug absorption and metabolism, patient noncompliance, level of disease burden and the susceptibility of different fusion breakpoints to Imatinib. It is likely that genetic evolution of CEL to a malignant clone independent of FIP1L1/PDGFRα or FIP1L1/PDGFRα dependent event that was Imatinib-resistant also contributed to rapid disease progression. Acquired drug resistance may account for the lack of treatment response. The first case of Imatinib resistance in a patient with advanced AML arising from CEL was reported by Gotlib and Cools [27]. The patient exhibited the FIP1L1–PDGFRα fusion in addition to a complex karyotype. Despite a complete hematologic remission, he relapsed after 5 months of therapy, coinciding with the identification of a T674I mutation within the ATP-binding domain of PDGFRα. The observed acquired resistance in this CEL patient also confirmed that the FIP1L1–PDGFRα fusion protein was indeed the therapeutic target of Imatinib. Additional cases of molecular resistance were similarly due to the PDGFR T674I mutation, one in a patient with CEL evolving to myeloid blast crisis and one in a patient with Langerhans histiocytosis with eosinophilia treated with multi-agent chemotherapy [28, 29]. Most HES/CEL patients reported thus far have responded to Imatinib doses of 100 mg per day. However, Imatinib at 800 mg per day resulted in higher rates of complete cytogenetic and molecular remissions in previously untreated, chronic phase CML, compared to the standard dose of 400 mg daily. Suboptimal dosing may lead to reduced response rates, accelerate the emergence of

 ISSN 2332-7243 E-ISSN 2332-7251

drug resistance and promote transformation to acute blast crisis. Suboptimal dosing and the potential to accelerate the emergence of drug-resistance may account, at least in part, for the rapid progression of the patient described here. Future studies are needed to determine whether treatment of CEL with Imatinib at doses higher than 100mg per day translates into a higher proportion of hematologic, cytogenetic and molecular remissions and lower rates of acquired resistance.

# 4 Conclusion

Based upon the clinical presentation, laboratory studies and immunophenotyping, the patient was diagnosed with CEL that then transformed to AML with monocytic differentiation. CEL can be treated with a variety of modalities, including glucocorticoids, Hydroxyurea, Interferon-α, allogeneic stem cell transplantation and tyrosine kinase inhibitors (TKIs); however, with the exception of TKIs, responses to many of these agents are typically short-lived [30-32].For reasons that are not completely clear, some patients rapidly progress to AML even though Imatinib is initiated at 100 mg/day. Rapid disease progression may be due to insufficient dosing since the optimal Imatinib dose for CEL that has transformed to AML has not been defined. Also, genetic instability of the malignant clone may generate point mutations that inhibit Imatinib binding to targets and thus reconstitutes active FIP1L1-PDGFRα and generates drug resistance. This is similar to $Ph^+$ leukemia where point mutations within the BCR-ABL kinase domain constitute the major cause of acquired resistance in CML patients treated with Imatinib.

CEL represents a recent addition to the list of molecularly defined chronic myeloproliferative disorders. Imatinib elicits a rapid hematologic remission in a small proportion of patients with HES. The empiric use of Imatinib in CEL treatment provides a dramatic example of how the development of targeted therapeutics can provide tremendous insight into the molecular etiology of what appear to be a diverse and otherwise indecipherable collection of diseases. . Because of the marked sensitivity of this condition to Imatinib therapy, identifying these patients is now of considerable clinical importance. Unfortunately, it has to be noted that the majority (80%-90%) of CEL patients are, in fact, FIP1L1-PDGFRα negative. Although Imatinib displays high rates of response in patients with the FIP1L1-PDGFRα mutation, the response is less robust in patients without this abnormality. Because of the rare responses observed in FIP1L1-PDGFRα-negative patients, it is also possible that FIP1L1-PDGFRα is not the only molecular target of Imatinib in patients with HES [33-36]. The probability that empiric use of Imatinib will generate a positive response is low. Our case illustrates the need for further investigation of the genetics responsible for CEL, to define the events that promote the rapid emergence of drug resistance and to identify novel therapeutics that inhibit these targets. Eventually, an array of different mutations should emerge to reveal new molecular targets and novel agents that improve patient outcome.

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