

Successful Treatment for Chronic Eosinophilic Leukemia (CEL) with Imatinib Mesylate

CASE REPORT

Rayane da Silva Souza¹, Nathália de Alencar Cunha Tavares²,
Martina Bragante Fernandes Pimenta¹,
Marcelle Bragante Fernandes Pimenta³,
Matheus Cartaxo Eloy Fialho¹, Ary Serrano Santos²,
Alexandre Rolim da Paz^{1,2}, Flávia Cristina Fernandes Pimenta^{1,2}

- 1 Department of Medicine, Federal University of Paraíba, João Pessoa, Paraíba, Brazil.
- 2 Lauro Wanderley University Hospital, Federal University of Paraíba, João Pessoa, Paraíba, Brazil.
- 3 Department of Medicine, Nova Esperança College, João Pessoa, Paraíba, Brazil.

Abstract

We report a case of a patient with Chronic Eosinophilic Leukemia (CEL) with mutation in alfa PDGFR gene exhibiting a satisfactory response to treatment with imatinib mesylate. A 25-year-old man presented in a hematology service with a persistent cough and hemogram alterations. His blood count showed a hemoglobin level of 12.5 g/dL and a white blood cell count of 94,030/mm³, eosinophils were 68% of all cells. Bone marrow aspiration and biopsy showed hypercellularity with marked eosinophilia (77%) and erythroid differentiation series was hypocellular with normoblast maturation. The immunohistochemically of the bone biopsy was positive for myeloperoxidase and negative for CD34/CD99, consistent with CEL. Fluorescence *in situ* hybridization (FISH) for the beta-fraction of platelet-derived growth factor (PDGFR β) and Philadelphia chromosome (Ph 1) were negative and the alfa PDGFR (Platelet-Derived Growth Factor) was positive and showed heterozygosity in c.2531T>C on 18 Exon and homozygous in C.2562+1G>A at the region of the splicing site at the 18 intron. Treatment was initiated and maintained by administering 400mg/day imatinib mesylate. Laboratory findings returned to normal ranges, with clinical improvement and a hematological response observed after the second month of therapy. Currently, the patient's blood count shows the white blood cell count (5,400 total leukocytes), eosinophils (8.6/mm³), hemoglobin (15.5 g/dl), hematocrit (45.4%) and platelets (298,000/mm³) within normal ranges. The mutation search was negative in peripheral blood one year after the initial treatment. Our work corroborates other studies on the efficacy of imatinib mesylate in the treatment of pa-

Contact information:

Flávia Cristina Fernandes Pimenta.

Address: Centro de Ciências Médicas, Campus I, Jardim Universitário, S/N, Castelo Branco, Cidade Universitária. Zip Code: 58051-900. João Pessoa, Paraíba, Brazil.

Tel: +55 8332167939.

 pimenta.flavia2@gmail.com

tients with CEL PDGFR alpha positive. We emphasize the importance of molecular studies, considering its relevance for the correct staging of the disease. Since CEL is a rare disease, it is important to define its etiology and anticipate its treatment, thus minimizing the damage induced by the disease.

Keywords

Chronic Eosinophilic Leukemia;
imatinib Mesylate;
Chronic Leukemia.

Introduction

Blood and tissue eosinophilia is associated with several conditions. Elevation of eosinophil levels may have different origins, such as helminthic parasitic infection, inflammation, hypersensitive drug reaction, adrenal insufficiency, and collagen diseases, in which cases the eosinophilia is classified as reactive [1, 2, 3]. In reactive eosinophilia, the primary mechanism consists of an increase in interleukin production, especially that specific for eosinophil differentiation, interleukin-5 (IL-5).

Another cause of eosinophilia consists of a primary molecular failure involving hematopoietic stem cells and/or defects in signal transduction from eosinophilopoiesis-mediating receptors, which can cause clonal proliferation; these mechanisms underlie tumor-induced eosinophilia and in these cases eosinophilia is classified as a primary disease [4, 5].

Eosinophilia based hematological disorders, established on the revised World Health Organization (WHO) classification in 2008, revised in 2016 [22], are divided into the following categories: Myeloid and lymphoid neoplasms with eosinophilia and rearrangement of the alpha platelet-derived growth factor receptor (PDGFR α), beta-platelet-derived growth factor receptor (PDGFR β), or fibroblast growth factor receptor-1 (FGFR1) and provisional entity Myeloid/lymphoid neoplasms with PCM1-JAK2; Chronic Eosinophilic Leukemia (CEL) not otherwise specified (NOS) [6, 22].

Diagnostic evaluation of primary eosinophilia is based on a combination of morphological analysis

of the blood and marrow, cytogenetic evaluation, fluorescence in situ hybridization, flow immunocytometry, and evaluation of T cell clonally to detect histopathological or clonal evidence of an acute myeloid or lymphoproliferative disease or chronic. Screening for structural changes to primary eosinophilia should begin with peripheral blood analysis for fusion of the FIP1L1-PDGFR α gene. The absence of FIP1L1-PDGFR α fusion should stimulate the evaluation of other primary eosinophilia associated with recurrent molecular abnormalities [7].

In the absence of the Philadelphia chromosome, the rearrangement involving PDGFR α -FGFR1/PDGFR β /TEL, and no identification of other acute or chronic marrow neoplasias that present with eosinophilia, we are facing a CEL NOS [7, 8]. Patients with mutations in the platelet-derived growth factor receptor (PDGFR) genes respond well to imatinib mesylate therapy [9]. This drug is a potent inhibitor of alpha and beta growth factors, which stimulate kinase activity [10]. These structural alterations tend to occur predominantly in men, between the second and fifth decade of life [11].

In view of the above, the objective of our study was the diagnostic elucidation of a patient who was admitted with eosinophilic leukemia hypothesis to be clarified. Therefore, we report a case of patient with mutation in gene PDGFR alfa exhibiting a satisfactory response to treatment with imatinib mesylate.

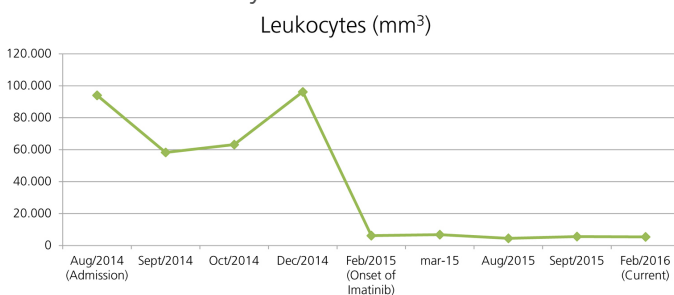
Case report

A 25-year-old man was referred to the hematology service of Napoleão Laureano Hospital for diagnosis of a persistent cough and blood count alterations. Physical examination did not show adenomegaly or visceromegaly. On admission, the patient presented with a hemoglobin level of 12.5 g/dL, and a white blood cell count of 94,030/mm³, 68% of which were eosinophils. Data from laboratory monitoring of the patient, from the time of admission, are described in **Figure 1, 2**.

Laboratory assays testing for human lymphotropic T virus (HTLV), human immunodeficiency virus (HIV), Venereal Disease Research Laboratory (VDRL test), virus hepatitis C and B (HCV and HBsAg B), serum antigen antinuclear factor, C-reactive protein, anti-DNA antibody, and mucoprotein were negative. Protein electrophoresis exhibited a polyclonal hypergammaglobulinemia pattern. Biochemical tests for kidney and liver functions revealed no changes; an echocardiogram revealed discrete right atrial hypertrophy. Computed tomography scans of the chest and abdomen were normal. Parasitic diseases were excluded by laboratory analysis and prophylactic treatment.

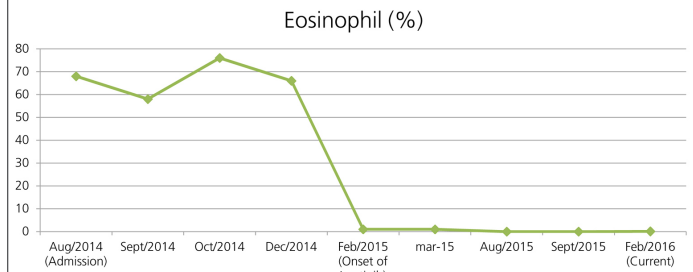
The myelogram and bone marrow biopsy (BMB) showed hypercellular bone marrow with eosinophilic proliferation, respectively, 73% and 95% immature cells, and an absence of fibrosis, suggesting eosinophilic leukemia, as shown in **Figure 3, A**.

Figure 1: Evolution of the patient's white blood cell count during treatment with imatinib mesylate.



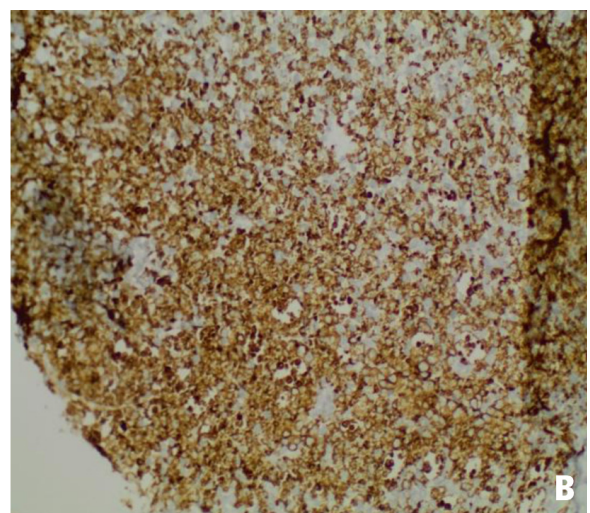
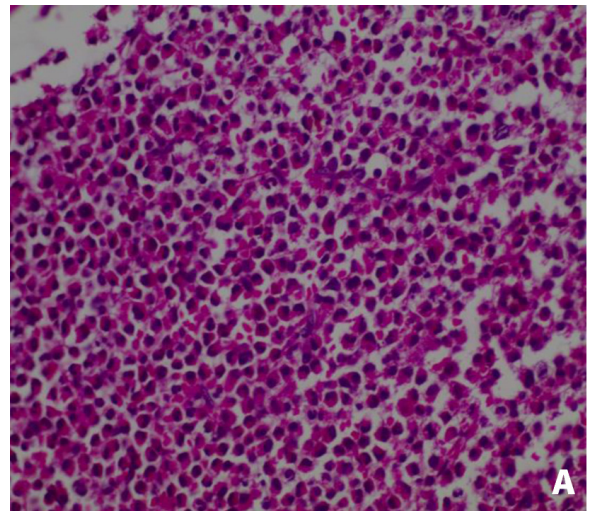
Source: Data collected by the authors.

Figure 2: Evolution of the patient's eosinophil percentage during treatment with imatinib mesylate.



Source: Data collected by the authors.

Figure 3: A) Bone Marrow Biopsy (BMB): numerous eosinophils and bone marrow precursors. B) Immunohistochemistry: positive for myeloperoxidase.



Source: Image captured by authors.

The immunohistochemical study was positive for myeloperoxidase and negative for CD34/CD99, consistent with eosinophilic leukemia, as shown in Figure 3B. Bone marrow aspiration and biopsy showed hypercellularity with marked eosinophilia (77%). An erythroid differentiation series was hypocellular with normoblast maturation. Fluorescence *in situ* hybridization (FISH) for the beta-fraction of platelet-derived growth factor (PDGFR β) and Philadelphia chromosome (Ph 1) were negative.

Genetic analysis of PDGFR alpha was performed using the PCR-DNA technique, with material obtained from the bone marrow, followed by bidirectional sequencing and analysis of exons 10, 12, 14 and 18. The mutations identified were heterozygous in c.2531T>C on 18 exon and homozygous in C.2562+1G>A at the region of the splicing site at the 18 intron.

Treatment was initiated and maintained by administering 400 mg/day imatinib mesylate. The patient became asymptomatic and the laboratory findings returned to normal ranges, with clinical improvement and a hematological response observed after the second month of therapy. Currently, the patient's hemogram shows the white blood cell count (5,400 total leukocytes), eosinophils (8.6/mm³), hemoglobin (15.5 g/dl), hematocrit (45.4%) and platelets (298,000/mm³) within normal ranges.

Discussion

Eosinophilia is defined when blood eosinophilia is greater than $1.5 \times 10^9/L$. There are several causes underlying HE, which can be divided into primary (clonal), secondary (reactive), hereditary (familial) and idiopathic [5, 12].

Under various conditions, eosinophils can produce and release a variety of biologically active substances that can invade target organs and cause dysfunction and/or damage. The harmful role of eosinophils results from their inflammatory, fibrotic, and thrombotic properties [12].

The diagnosis may be incidental due to laboratory findings or clinical manifestations such as pruritus, constitutional symptoms, and symptoms related to multisystem injury [13]. Tissue infiltration occurs in several organs and systems, especially the heart, lungs, skin, central and peripheral nervous system, and gastrointestinal tract. The main mechanism promoting injury is the release of cytokines and the impact of the cytokines on several targets [4, 14].

While patients are commonly referred to the competent services with complaints of the respiratory tract, heart disease is the leading cause of morbidity and mortality, occurring in up to 50% of cases [15]. Endomyocardial fibrosis progresses into restrictive cardiomyopathy, apart from the thickening and fibrosis of the atrioventricular valves, with valve regurgitation and formation of intracardiac thrombi [13, 14].

Specific therapies may potentially prevent morbidity and mortality, if started early. When investigating cytogenetic causes involved in the etiology of eosinophilia, the identification of PDGFR α or PDGFR β rearrangements is critical because of the good response to treatment with imatinib mesylate [6]. Among the available therapies, imatinib mesylate is considered the first choice in the treatment of CEL positive for when these mutations are positive [1, 9, 10, 12]. The drug is also used as therapy for the treatment of chronic myeloid leukemia and patients who are treated with the standard dose have favorable outcomes [16].

The first report of treatment with imatinib mesylate for Idiopathic Hypereosinophilia was in 20 January 2017. Cases of hypereosinophilic syndrome patients were published, highlighting rapid and complete hematological responses to imatinib mesylate 100-400 mg per day [18, 19].

The identification of FIP1L1-PDGFR α translocation as a therapeutic target of this drug redefined such cases as a form of chronic eosinophilic leukemia, WHO category of "Myeloid and lymphoid

neoplasms with eosinophilia and Abnormalities of PDGFR α , PDGFR β or FGFR1 [17].

Cytogenetic differences have an impact on the response to treatment with imatinib mesylate when PDGFRA and PDGFRB are compared. The starting dose recommended by the FDA for patients with the FIP1L1-PDGFR A rearrangement is 100 mg per day. Cumulative data with long-term follow-up indicate that this dose is sufficient to cause complete and long-lasting hematological remissions. For patients with rearranged eosinophilia and PDGFRB myeloid neoplasms, the recommended dose is 400 mg per day [7].

There have been reports of patients with CEL NOS or Hypereosinophilic Syndrome who benefited from imatinib mesylate when given at doses higher than 400 mg per day [20]. In our patient, four months elapsed between the diagnosis and the start of treatment; complete hematologic response occurred in the second month of treatment with a dosage of 400 mg/day, In agreement with the results found in the literature when referring to similar cases [21].

It is consensus in the literature on the satisfactory response of CEL with PDGFR α ou PDGFR β B e FGFR1 positive's for mesylate imatinib [16, 17, 19]. Thus, our patient has been undergoing treatment for 25 months and is clinically and laboratory stably in outpatient follow-up.

Conclusion

In our study, the efficacy of imatinib mesylate in the treatment of patients with CEL PDGFR alpha positive, in which we were successful in the treatment was verified. We recommend molecular screening using the PCR technique for future studies and we consider it essential for the correct staging of our case, since the FISH technique did not allow the diagnostic elucidation of the case under study. We highlight that since CEL is a rare disease, it is important to define its etiology and anticipate its

treatment, thus minimizing the damage induced by the disease. The main contribution of our work is because it is a rare form of CEL and is the first case of eosinophilic leukemia with mutations in the PDGFR alpha reported in northeastern Brazil.

Informed Consent

Informed consent was obtained from the patient included in the study

Conflict of interest

None declared.

References

1. Sheikh J, Weller PF: Advances in diagnosis and treatment of eosinophilia. *Curr Opin in Hematol.* 2009 Jan; 16(1):3-8.
2. Spry C: Eosinophilia in Addison's Disease. *Yale J Biol and Med.* 1976 Sep; 49(4): 411-13.
3. Jennette JC, Falk RJ, Bacon PA, N. Basu, M. C. Cid, F. Ferrario et al: 2012 Revised international Chapel Hill consensus conference nomenclature of vasculitides. *Arthritis Rheum.* 2013 Jan; 65(1):1-11.
4. Ackerman SJ, Bochner BS: Mechanisms of eosinophilia in the pathogenesis of hypereosinophilic disorders. *Immunol Allergy Clin of North Am.* 2007 Aug; 27(3):357-75.
5. Valent P, Klion AD, Horny HP, Roufosse F, Gotlib J, Weller PF, et al: Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. *J Allergy Clin Immunol.* 2012 Sep; 130(3):607-12.e9
6. Bain BJ, Gilliland DG, Horny H-P, et al. Chronic eosinophilic leukaemia, not otherwise specified. In: Swerdlow S, Harris NL, Stein H, Jaffe ES, Theile J, Vardiman JW, editors. *World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues.* Lyon, France, IARC Press. 2008. p 51-3.
7. Gotlib, J. World Health Organization-defined eosinophilic disorders: 2015 update on diagnosis, risk stratification, and management. *American Journal of Hematology.* 2015 Nov; 90(11):1077-89
8. Gotlib J, Cools J. Five years since the discovery of FIP1L1-PDGFR A: what we have learned about the fusion and other molecularly defined eosinophilias. *Leukemia.* 2008 Nov; 22(11):1999-2010.

9. Valent P: Pathogenesis, classification, and therapy of eosinophilia and eosinophil disorders. *Blood Reviews*. 2009 Jul; 23(4):157-65.
10. Cool J, Stover EH, Włodarska I Marynen P, Gilliland DG: The FIP1L1- PDGFR α kinase in hypereosinophilic syndrome and chronic eosinophilic leukemia. *Current Opinion in Hematology* 2004 Jan; 11(1):51-7.
11. Weller PF, Bubley J: The Idiopathic hypereosinophilic syndrome. *Blood* 1994 May 15; 83(10):2759-79.
12. Helbig G, Hus M, Francuz T, Dziaczkowska-Suszek J, Soja A, Kyrzcz-Krzemień S: Characteristics and clinical outcome of patients with hypereosinophilia of undetermined significance. *Med Oncol*. 2014 Jan; 31(1):815.
13. Arruda MMAS, Sandes AF, Borges NM, Chauffaille MLLF: Chronic eosinophilic leukemia with expression of FIP1L1-PDGFR rearrangement - case report and literature review. *J Hematol* 2010 May; 32(2):177-80.
14. Akuthota P, Weller PF: Eosinophils and disease pathogenesis. *Seminars in Hematology* 2012 Apr; 49(2): 113-119.
15. Shin SY1, Jung CW2, Choi DC2, Lee BJ2, Kim HJ1, Kim SH1.: Chronic eosinophilic leukemia with a FIP1L1-PDGFRFA rearrangement: Two case reports and a review of Korean cases. *Blood Reviews*. 2015 Mar; 50(1):58-61.
16. Cortes J, Hochhaus A, Hughes T, Kantarjian, H: Front-line and salvage therapies with tyrosine kinase inhibitors and other treatments in chronic myeloid leukemia. *Journal of Clinical Oncology*. 2011 Feb 10; 29(5): 524-531.
17. Schaller JL, Burkland GA. Case report: rapid and complete control of idiopathic hypereosinophilia with imatinib mesylate. *Medscape General Medicine*. 2001 Sep 7; 3(5):9.
18. Brito-Babapulle F. The eosinophilias, including the idiopathic hypereosinophilic syndrome. *British Journal of Haematology* 2003 Apr; 121(2):203-23.
19. Gleich GJ, Leiferman KM, Pardanani A, Tefferi A, Butterfield JH.. Treatment of hypereosinophilic syndrome with imatinib mesilate. *Lancet*. 2002 May 4; 359(9317):1577-8.
20. Helbig G, Hus M, Hałasz M, Dudziński M, Więclawek A, Stachowicz M, et al. Imatinib mesylate may induce long-term clinical response in FIP1L1-PDGFR α -negative hypereosinophilic syndrome. *Medical Oncology*. 2012 Jun; 29(2):1073-6.
21. Iurlo A, Fracchiolla NS, Ferla V, Cassin R, Gottardi E, Beghini A, et al. Successful Treatment With Imatinib in a Patient With Chronic Eosinophilic Leukemia Not Otherwise Specified. *Journal Of Clinical Oncology*. 2014 Apr 1; 32(10):e37-9.
22. Arber, Daniel A, Orazi, Attilio, Hasserjian, Robert, Thiele, Jürgen, Borowitz, Michael J, Le Beau, Michelle M. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia (The Updated Who Classification of Hematological Malignancies). *BLOOD*, 2016 19 May; 127(20): 2391-2405.

Publish in International Archives of Medicine

International Archives of Medicine is an open access journal publishing articles encompassing all aspects of medical science and clinical practice. IAM is considered a megajournal with independent sections on all areas of medicine. IAM is a really international journal with authors and board members from all around the world. The journal is widely indexed and classified Q2 in category Medicine.