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Case Report

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Myeloid/Lymphoid Neoplasm with Eosinophilia and FIP1L1-PDGFRA Rearrangement Associated with T-cell Lymphoma Not Otherwise Specificized (PTCL-NOS): A Case Report in Ecuador

Hector Chiang[1], Alfredo Campoverde[2], Paul Leon-Gomez[3*], Patricio Gonzalez[4], Pablo Farfan[5]

[1]Hematologist Hospital "José Carrasco Arteaga", Cuenca – Ecuador

[2]National Institute of Public Health Research. Dr. Leopoldo Izquieta Pérez (INSPI-LIP), Cuenca – Ecuador, University of Cuenca Faculty of Medical Sciences

[3]National Institute of Public Health Research. Dr. Leopoldo Izquieta Pérez (INSPI-LIP), Cuenca - Ecuador

[4]Clinical Pathologist, Hospital "José Carrasco Arteaga" Cuenca – Ecuador

[5]Head of the Genetic-Molecular Unit, Hospital "José Carrasco Arteaga" of Cuenca

Abstract

Introduction: Myeloid and lymphoid neoplasms with eosinophilia (NLM-eo) and rearrangements are defined by a gene fusion event which gives rise to a constitutively activated tyrosine kinase. This leads to a myeloproliferative neoplasm, myeloproliferative/myelodysplastic neoplasm, lymphoma or primary or secondary acute leukemia.

Case presentation: A 34-year-old man with NLM-eo in blastic phase with a PDGFRA rearrangement. He had previously been diagnosed with idiopathic hypereosinophilia (2011) and T-cell lymphoma not otherwise specificized (PTCL-NOS) (2015).

Conclusion: T lymphomas are rarely associated with PDGFRA rearrangement. Integrated evaluation (cytomorphology, flow cytometry, molecular biology, cytogenetics) is essential for the diagnosis of NLM-eo, particularly because of their pluripotential origin and subsequent lineage differentiation.

Article Highlights

- 34-year-old man with NLM-eo in blastic phase with a PDGFRA rearrangement
- He was previously diagnosed with idiopathic hypereosinophilia in 2011
- Patient also diagnosed with T-cell lymphoma not otherwise specificized
- First reported case of NLM-eo with a PDGFRA rearrangement in Ecuador

Keywords

Myeloid and lymphoid neoplasms; Eosinophilia; PDGFRA rearrangement; T-cell lymphoma

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***Corresponding author:** Paul Leon-Gomez, National Institute of Public Health Research, Dr. Leopoldo Izquieta Pérez (INSPI-LIP), Cuenca - Ecuador, E-mail: pleong@inspi.gob.ec

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Abbreviations

NLM-eo: Myeloid and Lymphoid Neoplasms with Eosinophilia

PTCL-NOS: Peripheral T-cell lymphoma not otherwise specificized

WHO: World Health Organization

MPN: Myeloproliferative Neoplasm

MPN/MDN: Myeloproliferative/Myelodysplastic Neoplasm

FISH: Fluorescence in situ hybridization

MDS: Myelodysplastic Syndromes

CMML: Chronic MyelomonocyticLeukemia

PECCT: Positron Emission Tomography

HES: Hypereosinophilic Syndrome

LV-SHE: Lymphocytic Variant SHE

Introduction

The World Health Organization (WHO) ratified in 2016 to the myeloid and lymphoid neoplasms with eosinophilia (NLM-eo) and rearrangements of FGFR1, PDGFRA or PDGFRB as a subcategory in the classification of tumors of hematopoietic and lymphoid tissues [1,2]. Rearrangements of PCM1/JAK2 have subsequently been introduced in this category as a provisional entity [3].

Its clinical presentation can range from myeloproliferative neoplasm (MPN), myeloproliferative/myelodysplastic neoplasm (MPN/MDN), lymphoma, or primary or secondary acute leukemia [4,5].

(NLM-eo) appears because of gene fusions which results in the overexpression of tyrosine kinases [2]. It is very important to determine which genes are implicated in the aberrations because tyrosine kinases have variable sensitivity reactions to inhibitors. For instance, cases with PDGFRA and PDGFRB abnormalities have shown a remarkable sensitivity to imatinib [1]. However, patients with FGFR1 rearrangements do not respond to this treatment [4].

The most frequent rearrangement within this category of (NLM-eo) is of PDGFRA, specifically the fusion between the FIP1L1 and PDGFRA genes [3]. This abnormality appears from a cryptic deletion at chromosome 4q12 and involves the deletion of CHIC2 [1,2]. Fluorescence in situ hybridization (FISH)is used as a diagnosis method [6].

However, in Ecuador due to the lack of accessibility to molecular diagnosis, in some cases these rearrangements are suspected following a negative Philadelphia chromosome result accompanied with eosinophilia, splenomegaly, an increase in mast cells production and after fibrosis is identified following a bone narrow biopsy. In other words, elevated surrogate markers are used (serum tryptase, vitamin B12) [7].

Within the differential diagnosis there are other hematologic diseases that arise along with eosinophilia during their evolution. Those include T lymphomas (including mycosis fungoides, Sézary syndrome), Hodgkin lymphoma, acute lymphoblastic lymphoma/leukemia; acute myeloid leukemias (AML)inv(16), t(16;16), Fab M4Eo); myelodysplastic syndromes (MDS), chronic myelomonocyticleukemia (CMML), systemic mastocytosis[6].

Case Presentation

A 34-years-old man with the following clinical history:

1) Idiopathic hypereosinophilia (2011) and consequently he received hydroxyurea since he did not have a corroborated tissue damage

2) Peripheral T lymphoma NOS (September 2015) His cancer stage was 4 IVB (supra and infragmatic nodal involvement and in bone marrow): He entered in complete morphometabolic remission after 2 lines of treatment (1st line: CHOPx3, 2nd line: ESHAPx4). The complementary examinations results were:

a) Laboratory (9/14/15): Leukocytes: 10980 cells/mm3 (Neutrophils: 1620, eosinophils: 7440 cells/mm3, lymphocytes: 1220 cells/mm3), Hb: 10.4 mg/dl, platelets: 130,000, creatinine: 1.19 mg/dl (0.9-1.2), normal liver profile, LDH: 254 U/L (240-480).

b) Peripheral blood smear: neutrophils 2%, cayates 1%, myelocytes 3%, lymphocytes 8%, eosinophils 83%, basophils 1%, erythroblasts 1%

c) Biopsy (inguinal node): T lymphoma (CD5+, CD3+, CD20-, CD15-, CD79-, CD45+) (Figure 1).

d) Biopsy (bone marrow): CD3+, CD5+, CD20+ lymphoid aggregates in focal form.Grade II reticular weft. Conclusion: Infiltration by non-Hodgkin's lymphoma immunophenotype T

After a second line of treatment an assessment was performed in February 2016:

a) A Positron emission tomography (PEC-CT) performed in May 2016 indicated a complete morphometabolic response (after 4 cycles of ESHAP).

b) Biopsy (bone marrow): increased cellularity (90%), myeloid-erythroid ratio 5:1, fibrosis grade I. Bone marrow hypercellular at the expense of granulocytic series (eosinophils some hypolobulated)

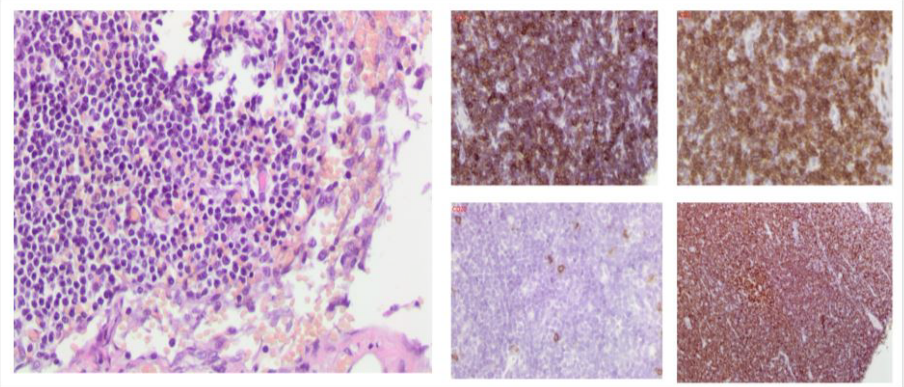

Figure 1: A. inguinal lymph node biopsy (T-lymphoma)

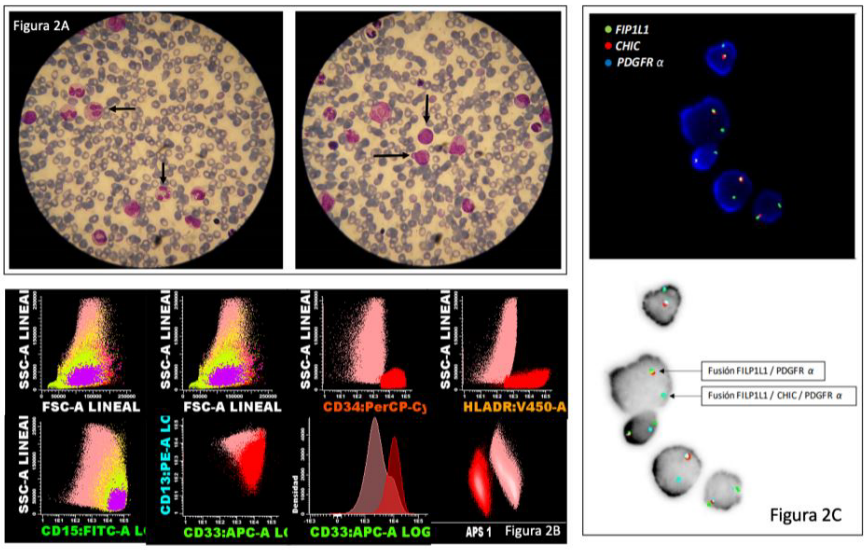

Figure 2: A. Cytomorphology: Eosinophils (28%) with dysplastic signs (degranulated and with cytoplasmic vacuoles) Blasts: 14%). B. Cytomorphology: Eosinophils (28%) with dysplastic signs (degranulated and with cytoplasmic vacuoles) Blasts: 14%. B. Flow cytometry (Phenotype of clonal cells: (14.39%) CD45+; CD34+; HLA DR+; CD33++; CD15-/+(46%); CD16-; CD13+; CD19-; CD3-. C. FISH analysis of the XL 4q12 Translocation Deletion Probe. The normal hybridization pattern has two fusion signals because of the overlap of the three fluorochromes (green, red and blue). While the CHIC2 gene deletion rearrangement pattern has a green-red-blue fusion signal and a green-blue fusion signal.

without increased blasts (<5%). Immunohistochemistry: MPO+ in myeloid series, CD3+ (isolated T lymphocytes), CD79+ (isolated B lymphocytes), CD5+ (isolated T lymphocytes), CD20+ (isolated T lymphocytes), CD34 (focal less than 1%), CD117 (focal less than 5%).

Based on the persistent hypereosinophilia linked to cardiac alterations (mild pulmonary hypertension, mild mitral insufficiency, moderate tricuspid insufficiency), the patient started to receive imatinib (100 mg/day). He took this medicine for 1 year with subsequent suspension due to gastrointestinal intolerance As a result of the health pandemic, medical controls were interrupted.

Current symptoms

His symptoms included a periodic one-month progression of musculoskeletal pain in hip and both extremities with right cellulitis accompanied by a thermal rise of 38.5 degrees. The physical examination showed a distended abdomen, along with pain after deep palpation in both right and left hypochondrium. He also exhibited palpable liver 10cm below the right costal margin and Boyd 4 splenomegaly.

Clinical exams

(a) Laboratory exams (25/3/22): Leukocytes: 37910 cells/mm3 (Neutrophils: 11160, eosinophils: 8200 cells/mm3, monocytes: 2960, lymphocytes: 7040 cells/mm3), Hb: 13.3 mg/dl, platelets: 47. 000, creatinine: 1.51 mg/dl (0.9-1.2), normal liver profile, uric acid: 10.5 mg/dl, LDH: 1420 U/L, vitamin B12 levels: elevated.

(b) The JAK2 mutation study presented a negative result

(c) BCR/ABL study: negative

(d) The BM study indicated that his bone narrow was hypercellular for his age. Whereas the megakaryocytes were of normal aspect, morphology and proportion. Myeloid series (33%): with presence of all mature stages. Monocytes (8%), Eosinophils (28%) with dysplastic signs (degranulated and with cytoplasmic vacuoles). Erythroid series (14%): with predominance of orthochromatic and polychromatic forms.Myeloid-erythroid ratio: 4.9, Lymphoid series (2%): without atypia and without formation of nests. Plasma cells (<1%): without atypia and Blasts: 14% (Figure 1).

(e) The flow cytometry in the bone narrow showed that: Eosinophils were. 27.26%, granulocyte/neutrophils: 23.80%, myeloblasts: 2.13%, myelocyte and promyelocyte: 36.25%, metamyelocytes: 31.%, bands and neutrophils: 30.62%, basophils: 6. 69%, monocyte/dendritic cell series 6.75%, lymphoid series 4.04%, b lymphocytes: 0.50%, CD3+CD4`+ 54.58%, CD3+CD8+ 35.30%, CD4+CD8+ 1.52%, CD4-CD8- 8.60%, CD4/CD8 1.55%, NK cells 1.31%, red series 11.75%, clonal cells1: 14.39%, clonal cells2: 4.98%. Hypercellular BN in which 500,000 events were acquired with a viability of 87%.The eosinophil population is increased, no phenotypic changes are detected in this population. The maturation curve of the granulocyte-neutrophil series is altered with dysplastic features and increased stage II.The basophil population is increased. In the lymphoid series B, T, NK components are detected. The T lymphocyte subpopulation is polyclonal with a normal CD4/CD8 ratio.Two populations of blasts representing 19.37% of the total cellular myeloid phenotype were detected.Phenotype of clonal cells 1: CD45+; CD34+; HLA DR+; CD33++; CD15-/+(46%); CD16-; CD13+; CD19-; CD3. Clonal cell phenotype 2: CD45+; CD34+; HLA DR-; CD33+; CD15-; CD16++; CD13+; CD19-; CD3- (Figure 1).

(f) A CT abdomen performed in March 2022 showed a hepatomegaly of 26 cm and splenomegaly of approximately 25 cm while no adenomegalywas observed. No adenomegalywas observed.

Finally, we performed a peripheral blood Fluorescence in situ hybridization (FISH) analysis using the XL 4q12 Translocation Deletion Probe (Figure 2). All 3 genes are located at the 4q12 locus. The normal hybridization pattern has two fusion signals because of the overlap of the three fluorochromes (green, red, blue). The most frequent PDGFRa rearrangement pattern has a greenred-blue fusion signal, a green-blue fusion signal and a red signal. The rearrangement patternwith deletion of the CHIC2 gene has a green-red-blue fusion signal and a green-blue fusion signal (Figure 2). Two hundred

interphase cells were analyzed. Besides the normal pattern (2.5%), 1greenred-blue fusion signal and 1 green-blue fusion signal were observed in 195 of them, from which it can be deduced that 97.5% of the cells analyzed show the PDGFRa gene rearrangement and deletion of the CHIC2 gene.

We describe a case report of a patient with NLM-eo and PDGFRA rearrangement, preceded by a T NOS lymphoma with idiopathic hyper eosinophilia. Two questions arise from this case:

(a) Were there 2 entities simultaneously from the beginning?

(b) Is this association feasible?

Discussion

We presume is Eosinophilia or primary (clonal) hypereosinophilic syndrome (HES) if the following characteristics are exhibited: elevated tryptase levels, abnormal T-cell population, increased blasts, dysplasia, presence of cytogenetic or molecular alterations, medullary fibrosis, splenomegaly, or lymphadenopathy [7-9].

Eosinophilia is not a prerequisite for NLM-eo, because it is usually marked in NLM with PDGFRA (70-99% of cases), but it can be minimal or absent in patients with PDGFRB, FGFR1, JAK2, FLT3, ABL1 rearrangements [10].

In our patient's case, the progression to blastic phase may have masked to some extent the eosinophilia [11]. It is not fully established whether the evolution of NLM-eo is extrapolable to chronic myeloid leukemia (CML), since in the literature the accelerated phase is omitted [2,3,6].

Regarding the question whether there were 2 diseases happening simultaneously from the beginning? The cytogenetic/molecular clonality of the hypereosinophiliacould not be corroborated in the first instance. Yet, its evolutionary process over time leads us to conjecture it (increase of blasts, splenomegaly, eosinophil dysplasia). Thus, in retrospective it raises the question if the patient could have been favored with Imatinib without the need for chemotherapy.

We also wondered whether it is possible that an association between T NOS lymphoma and NLMeo with a PDGFRA rearrangement exists. The NLM-eo with PDGFRA rearrangement arises in a pluripotential hematopoietic progenitor cell that gives rise to multiple lineages of myeloid and lymphoid differentiation since this fusion gene is found in eosinophils, neutrophils, mast cells, T cells, B cells and monocytes [6,12].

The most frequent clinical presentations of this condition are as chronic eosinophilic leukemia, acute myeloid leukemia and rarely as myeloid sarcoma or acute lymphoblastic T-cell lymphoma [13]. The latter can appear simultaneously with Myeloproliferative neoplasms (MPN) [6]. Yet, there have been reports in which the acute lymphoblastic T-cell lymphoma precedes or develops later [6].

Furthermore, T lymphomas are rarely associated with PDGFRA rearrangement [2,3]. However, there have been evidence of a link between this condition and lymphocytic variant SHE (LV-SHE) as a form of progression (10-20%) [14].

It is also not uncommon to find cases of NLM-eo with PDGFRA after cytotoxic chemotherapy [13].

Based on the patient's molecular and cytogenetic results, we decided to restart Imatinib treatment with a 400 mg dose. Yet, this time without the need to combine it with corticosteroids since his cardiac function troponin levels were normal.

Therapeutic failure or loss of response to Imatinib is unusual. This occurs due to mutations in D842V and T674I and D842V that confer resistance to the patient. Therefore, it is necessary to determine them by allogeneic transplant [11].

Conclusion

Integrated evaluation (cytomorphology, flow cytometry, molecular biology, cytogenetics) is essential for the diagnosis of NLM-eo, particularly because of their pluripotential origin and subsequent lineage differentiation.

Declarations

Ethics approval and consent to participate

We obtained an informed consent from the patient for research purposes of this case report and any accompanying images.

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