



Clonal eosinophilia with exclusive pulmonary involvement driven by PDGFRA rearrangement treated with imatinib: A case report

Zaineb Mlayah, Inés Ben-Rekaya^{*}, Inaam Bizid, Nader Slama, Sara Boukhris, Mohamed-Adnene Laatiri

Clinical hematology department of Fattouma Bourguiba Hospital, Monastir, Tunisia

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ABSTRACT

Hypereosinophilic syndrome (HES) was first described in 1968 by Hardy and Anderson. It is a group of rare, multisystemic and heterogeneous pathologies, characterized by significant morbidity and mortality. The occurrence of clonal hypereosinophilic syndrome associated with FIP 1L1-PDGFRA+ is estimated to range between 0.31 and 6.3 cases per million individuals. The organs most commonly impacted are the heart and spleen, with the lungs being the next most affected. Clonal hypereosinophilic syndromes with exclusive pulmonary involvement are exceptional. Due to the rarity of clonal HES, this report aims to not only describe the patient's clinical, biological, and radiological manifestations of clonal HES but also enrich the literature to ameliorate the management of this uncommon syndrome.

We report the case of a patient with past medical history of obstructive bronchopneumopathy who was presented with cough and dyspnea. Investigations revealed peripheral blood hypereosinophilia (between 4000 and 9000/mm³) which lead us to suspect clonal hypereosinophilic syndrome (HES). This diagnosis was confirmed by cytogenetics/fluorescence in situ hybridization (FISH) which demonstrated a positive FIP 1L1-PDGFRA rearrangement. The CTAP confirmed isolated lung involvement with interstitial infiltrate of the subpleural territories of both lung bases and the bronchoalveolar lavage showed eosinophil count elevated at 15%. The patient was treated by imatinib at a dose of 100 mg/day was initiated. The patient follow-up showed a reduction in eosinophils count to 7500/mm³ at two months of treatment. A molecular evaluation is scheduled in 3 months to assess the response to imatinib.

1. Introduction

Hypereosinophilic syndromes (HES) constitute a constellation of rare and heterogeneous disorders. Defined by stringent criteria, including a blood eosinophil count surpassing 1500 cells/mm³ and discernible signs of eosinophilic organ involvement, these syndromes arise from a complex interplay of etiological factors, encompassing infectious (parasitic), allergic, rheumatologic, neoplastic, and clonal contributors.

Clonal hypereosinophilic syndromes have been found to be linked with a rare deletion on chromosome 4q12, which leads to the activation of a tyrosine kinase, as observed in the FIP 1L1-PDGFRA rearrangement. The occurrence of clonal hypereosinophilic syndrome associated with FIP 1L1-PDGFRA+ is estimated to range between 0.31 and 6.3 cases per million individuals. The organs most commonly impacted are the heart and spleen, with the lungs being the next most affected. Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFRA,

PDGFRB, or FGFR1, or with PCM1-JAK2 associated with exclusive pulmonary involvement are exceptional.

Herein, we report an uncommon case involving a patient presenting with Myeloid neoplasm with eosinophilia and rearrangement of PDGFRA associated with eosinophilic pulmonary disease, demonstrating successful therapeutic response to imatinib.

2. Case presentation

A 76-year-old Tunisian male patient, presented in december 2023, at the pneumology Department of the Hospital of Fattouma Bourguiba in Monastir, with complaints of cough associated with dyspnea and fatigue on moderate and mild exertion, starting two months earlier and progressively worsening. When describing medical history, the patient reported suffering from obstructive broncho-pneumopathy treated with bronchodilator and budesonide; he refuted the presence of other

^{*} Corresponding author.

E-mail addresses: benrekayaines@gmail.com (I. Ben-Rekaya), adnenelaatiri2@yahoo.fr (M.-A. Laatiri).

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comorbidities or the continuous use of other medication.

Investigations revealed peripheral blood hypereosinophilia (between 4000 and 9000/mm³).

The patient has undergone a thorough infectious and allergic check-up with negative results.

A thoracic CT scan showed diffuse pulmonary emphysema, a pleural cap with a sequelae-like appearance, bilateral hilobasal bronchiectasis and an interstitial infiltrate of the subpleural territories of both bases.

Bronchoalveolar lavage showed no cells suspicious of malignancy; but the eosinophil count was elevated at 15%, exceeding the normal reference range.

Moreover the patient presented an unexplained persistent normochromic normocytic aregenerative anemia with a hemoglobin level of 9 g/dl with MCV of 85 μ m³, therefore the suspicion arose regarding a potential clonal HES. So the patient was transferred to the hematology department in el Omrane hospital in Monastir for further explorations.

During the clinical examination, his vital signs were as follows: temperature = 37.6 °C; Blood Pressure = 137/84 mm Hg; heart rate =

105 beats/min; respiratory rate = 40 breaths/min; and oxygen saturation = 94% on room air. Chest examination was clear to auscultation of diffuse crepitations bilaterally. Abdomen examination showed normal bowel sounds and no palpable spleen nor liver. Skin examination was normal.

As for the laboratory findings, The WBC count was 12,370/mm³, hemoglobin level was 9 g/dL, and platelet count was 314,000/m L. The WBC differential absolute counts showed 590/mm³ neutrophils, 2000/mm³ lymphocytes, and 9210/mm³ eosinophils. The vitamin B12 level was normal at 520 pg/ml (normal range between 191 and 663pg/ml).

A myelogram was performed and revealed a marrow of normal richness; with an erythroblastic lineage showing many signs of dyserythropoiesis; hyperplasia of the eosinophilic granular lineage at various stages of maturation showing rare dystrophic granulations (Fig. 1).

The search for FIP 1L1-PDGFR α rearrangement by cytogenetics/fluorescence in situ hybridization (FISH) performed on bone marrow was positive, confirming our initial suspicion of diagnosis (Fig. 2).

Regarding the extension assessment of this syndrome, a cardiac

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MONASTIR
Dr. M. Mohsen
Hématologie - Banque du Sang
461 144 Fax 73 460 678

Monastir, le 11.01.2024

MYELOGRAMME N°202401008

NOM ET PRENOM: [REDACTED] AGE : 1948
MATRICULE : SERVICE : PNEUMO.

Prescripteur : Richesse+++
Renseignements Cliniques : Formule sur 200 éléments.....

CELLULES INDIFFERENCIEES

- Cellules réticulaires.....
- Hémoblastes.....

SERIES GRANULOCYTAIRES :

* **Neutrophiles**

- Myéloblastes..... 1%
- Promyélocytes.....
- Myélocytes..... } 18%
- Métamyélocytes..... 12%
- Polynucléaires..... 25%

* **Eosinophiles :**

- Myélocytes.....
- Métamyélocytes..... } 20%
- Polynucléaires.....

* **Basophiles**.....

SERIE MEGACARYOCYTAIRE...
Nombreux mégacaryocytes.

SERIE ROUGE

- Proérythroblastes.....
- Erythroblastes basophiles.....
- Erythroblastes polychromatophiles... } 14%
- Erythroblastes acidophiles.....

SERIE NON MYELOIDE

- Lymphoblastes.....
- Lymphocytes..... 6%
- Monocytes.....
- Histiocytes.....
- Plasmocytes..... 4%
- Mastocytes.....
- Autres Cellules.....

CONCLUSION :
Moelle de richesse normale.
Nombreux mégacaryocytes sur frottis, montrant nombreux signes de dysmégacaryopoïèse (grande taille, noyau fragmenté, noyau bilobé,...)
Lignée érythroblastique montrant nombreux signes de dysérythropoïèse (chromatine mal condensée, cytoplasme feuilleté, ponctuations basophiles).
Hyperplasie de la lignée granuleuse éosinophile à différents stades de maturation, montrant des rares granulations dystrophiques.

Le responsable

Fig. 1. Bone Marrow Aspirate Findings: Hyperplasia of the Eosinophilic Lineage with Dyserythropoiesis and Rare Dystrophic Granulations.



Institut Pasteur de Tunis
LABORATOIRE D'HEMATOLOGIE
CHEF DE SERVICE Pr. Samia MENIF

Pr. Samia MENIF
Pr. Imen KRAIEM
Pr. Ines SAFRA
Dr Manel KASDALLAH

Dossier N° : 2024/001691 Pvt du: 10/01/2024 15:06

Nom :

EPS FATTOUMA BOURGUIBA M DH :

Code Patient : 733168



Page : 1/1

DIAGNOSTIC MOLECULAIRE DES LEUCÉMIES

Recherche du transcrit FIP1L1-PDGFRa..... Positif

Fig. 2. Molecular biology confirming the FIP 1L1-PDGFRa rearrangement.

ultrasound was conducted, revealing no abnormalities. Additionally, troponin and pro-BNP assays returned negative results. A CTAP scan was ordered, which confirmed isolated lung involvement with interstitial infiltrate of the subpleural territories of both lung bases (Fig. 3).

The patient was diagnosed for Myeloid neoplasm with eosinophilia and rearrangement of PDGFRA with associated exclusive lung involvement.

Treatment with imatinib 100 mg daily was initiated. He tolerated treatment without complications and had a rapid hematologic response with resolution of peripheral hypereosinophilia and anemia within two months. A molecular evaluation is scheduled in 3 months to assess the response to imatinib (Table 1).

3. Discussion

Hypereosinophilia (HE) is defined by eosinophil count $> 1.5 \times 10^9/\text{mm}^3$ on two occasions one month apart and/or tissue eosinophilia. Hypereosinophilic syndrome (HES) is defined by blood HE and organ damage or dysfunction caused by tissue eosinophils and exclusion of other possible causes of organ dysfunction [1].

The severity of hypereosinophilia is conventionally categorized based on the AEC (Absolute Eosinophil Count): mild when it's ranging from the upper limit of normal to $1.5 \times 10^9/\text{mm}^3$, moderate: when it's between 1.5 and $5 \times 10^9/\text{mm}^3$ and severe when the AEC is exceeding $5 \times 10^9/\text{mm}^3$.

3.1. What diagnostic approach should be taken in the case of hypereosinophilia?

The classification of eosinophilic diseases was revised in the 2008 WHO scheme of myeloid neoplasms and reaffirmed in 2016 and 2022 [2].

Our initial evaluation should focus on identifying potential secondary causes of eosinophilia which arises from a wide spectrum of underlying conditions, often necessitating a comprehensive diagnostic workup by specialists from various fields. In developing nations, infectious diseases, especially those caused by tissue-invasive parasites, are the most frequent culprits [3]. Within a germane clinical context, possible causative factors encompass allergic/atopic and hypersensitivity reactions, collagen vascular diseases, eosinophilic gastroenteritis, and even metabolic derangements like adrenal insufficiency [1,4].

Following the exclusion of secondary causes for eosinophilia, the diagnostic workup should shift towards evaluating a possible primary bone marrow disorder:

Initial laboratory evaluation of primary eosinophilia should commence with peripheral blood screening for the FIP 1L1-PDGFRa fusion gene. Fluorescent in situ hybridization (FISH) probes targeting the chromosomal region encompassing the FIP 1L1 and PDGFRA loci can effectively detect the cytogenetically occult 800-kb deletion on chromosome 4q12, which is the underlying driver of the FIP 1L1-PDGFRa fusion event [5,6].

If the FIP 1L1-PDGFRa gene fusion is not detected, further evaluation for other primary eosinophilias linked to recurring genetic abnormalities is recommended. Typically, the presence of a PDGFRA, PDGFRB, FGFR1, JAK2, FLT3 or ETV6 ABL1 fusion gene identified through molecular testing will be accompanied by a corresponding chromosomal abnormality detectable through cytogenetic analysis [7].

These chromosomal abnormalities often involve translocations in specific chromosomal regions: 4q12 (for PDGFRA fusions other than FIP 1L1), 5q31~33 (for PDGFRB fusions), 8p11~12 (for FGFR1 fusions), 9p24 (for JAK2 fusions), 13q12 (for FLT3 fusions), t(9;12)(q34.1;p13.2) (for ETV6::ABL1 fusions) [7,8].

If we confirm the presence of a myeloid (MPN-like or MDS/MPN-like or AML/myeloid sarcoma) and/or lymphoid neoplasm (B- or T-cell ALL), or MPAL, usually with prominent eosinophilia, and sometimes with neutrophilia or monocytosis associated with one gene rearrangement PDGFRA, PDGFRB, FGFR1, JAK 2, FLT3 or ETV6 ABL1 by fish we ascertain the diagnosis of Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusion" (MLN-eo-TK) [8].

If testing for the FIP 1L1-PDGFRa gene fusion isn't available, high blood levels of tryptase and vitamin B12 and an increased number of mast cells can be helpful clues. These markers often appear together in patients with the FIP 1L1-PDGFRa abnormality (found in 79% of patients in one study) and myeloproliferative variants of hypereosinophilic syndrome [9].

If testing for the previously mentioned fusion tyrosine kinases associated with eosinophilia is negative, then chronic eosinophilic leukemia (CEL) becomes a possible diagnosis [10]. This pathology is defined by Sustained hypereosinophilia (eosinophil count $\geq 1.5 \times 10^9/\text{mm}^3$, and $\geq 10\%$ eosinophils^a) for 4 weeks, The presence of a clonal abnormality (by cytogenetics and/or somatic mutation by NGS) (Abnormal bone marrow morphology (e.g., megakaryocytic and/or erythroid dysplasia) Or The presence of increased blasts ($\geq 5\%$ in the bone marrow and/or $\geq 2\%$ in the peripheral blood), Blasts $< 20\%$ in peripheral blood and bone marrow and not meeting WHO criteria for another myeloid neoplasm [8].

After ruling out all potential underlying conditions that might be causing primary or secondary hypereosinophily as well as a specific type

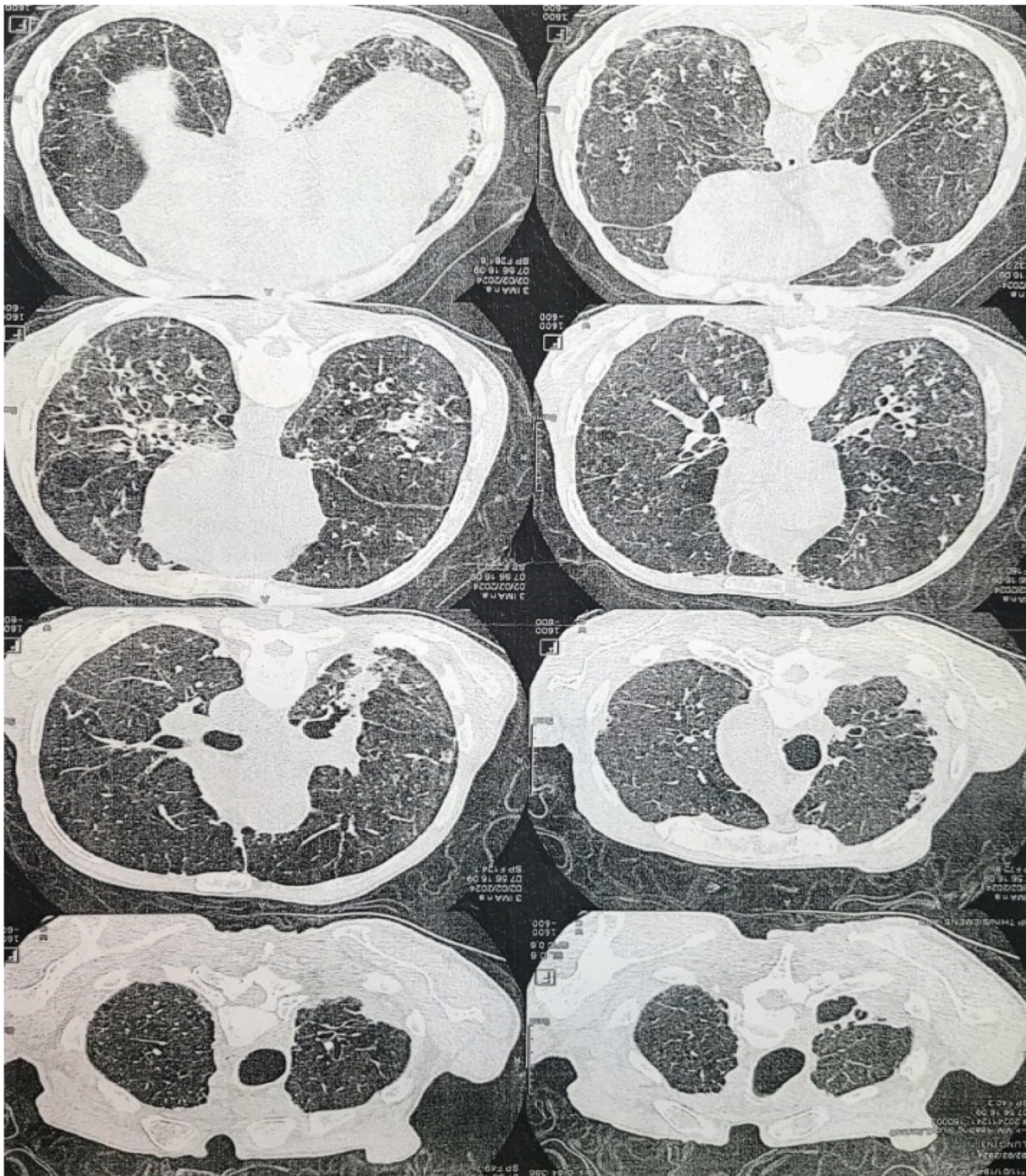


Fig. 3. CTAP scan showing an emphysematous lung with retractive condensations of both upper lobes and sequellar thickening of the right apical cap.

called lymphocyte-variant HE, which involves abnormal immune T-cells producing excessive cytokines, idiopathic hypereosinophilic syndrome (HES) becomes the most likely diagnosis.

3.2. What is the typical management approach for a patient confirmed to have clonal hypereosinophilic syndrome?

Clonal HES can cause a range of tissue damage mediated by eosinophils. This damage can manifest as cardiomyopathy, pneumonitis, dermatitis, sinusitis, central nervous system or peripheral neuropathy, gastrointestinal inflammation, thromboembolic complications, and other organ involvement [11].

The decision to treat hypereosinophilia with medication depends

heavily on whether organ damage is present. Therefore, the initial evaluation prioritizes tests that assess potential damage: a complete blood count checks, a chest X-ray looks for lung abnormalities, echocardiography evaluates heart function and structure for cardiomyopathy, and serum troponin levels, can be particularly helpful in identifying cardiomyopathy in HES patients [12,13].

Additional tests may be tailored to the specific organs involved. These could include pulmonary function tests for respiratory symptoms, gastrointestinal endoscopy for digestive issues, skin biopsy for suggestive skin lesions, sinus radiography for sinusitis, and neuroimaging studies (MRI or CT scan) for neurological concerns [14].

In cases of clonal eosinophilia linked with imatinib mesylate-sensitive molecular markers such as FIP 1L1-PDGFR α , PDGFR β

Table 1
Summary of Laboratory, Radiological and Therapeutic Findings Supporting Bone Marrow and molecular biology Images.

Category	Details
Laboratory Data	<ul style="list-style-type: none">- WBC count: 12,370/mm³- Neutrophils: 590/mm³- Lymphocytes: 2000/mm³- Eosinophils: 9210/mm³- Hemoglobin: 9 g/dL- Platelets: 314,000/mL- Vitamin B12: 520 pg/mL (normal range: 191–663 pg/mL)- Bronchoalveolar lavage: No cells suspicious for malignancy were observed; however, the eosinophil count was elevated at 15%, exceeding the normal reference range.
Radiological Data	<ul style="list-style-type: none">- CTAP scan: Interstitial infiltrate in the subpleural regions of both lung bases, confirming isolated lung involvement.
Therapeutic Regimen	<ul style="list-style-type: none">- Treatment: Imatinib 100 mg/day- Response: Well-tolerated, rapid hematologic response with resolution of peripheral hypereosinophilia and anemia within two months.- Scheduled molecular evaluation: In 3 months to assess response to imatinib.
Bone Marrow Aspirate	<ul style="list-style-type: none">- Findings: Normal cellularity.- Erythroblastic lineage: Signs of dyserythropoiesis.- Eosinophilic lineage: Hyperplasia with rare dystrophic granulations.
molecular biology	<ul style="list-style-type: none">- FIP 1L1-PDGFRΑ rearrangement: Positive, confirming the suspected diagnosis.

rearrangement, or BCR-ABL, early intervention is prudent. This is because the onset of symptoms or progression to aggressive disease is likely unavoidable, and targeted therapy can lead to both complete clinical and molecular remission, potentially averting complications like leukemic transformation [15,16].

Longitudinal investigations into patient outcomes have demonstrated a robust complete hematological response rate exceeding 90% . Despite the absence of standardized protocols governing the duration and cessation of imatinib treatment, empirical evidence from select studies suggests a median relapse interval ranging between 17 and 30 months post-imatinib discontinuation [17].

4. Clinical course

In this case, the persistent eosinophilia, along with the negative investigation results and the presence of unexplained normochromic normocytic anemia, suggested the likelihood of a clonal marrow disorder. When the marrow findings revealed a primary eosinophilic proliferation, the marrow sample was specifically sent for fluorescence in situ hybridization (FISH) analysis to check for the PDGFRA rearrangement. Following the identification of the FIP 1L1-PDGFRΑ fusion, the patient was promptly started on imatinib at a dosage of 100 mg daily. Within two months of beginning imatinib treatment, the patient experienced a rapid resolution of eosinophilia, with an absolute eosinophil count of 400/mL. His symptoms also improved quickly. Radiological and molecular assessments are planned after three months of ongoing imatinib therapy.

5. Conclusion

In conclusion, persistent hyper eosinophilia may silently lead to substantial and often irreversible tissue damage, making it essential to investigate both primary and secondary causes [18]. Although uncommon, Myeloid/lymphoid neoplasms with eosinophilia can be swiftly diagnosed using FISH on peripheral blood to detect the FIP 1L1-PDGFRΑ gene fusion, and this test should be conducted early in the evaluation of HES [14].

Over time, a clearer understanding has developed regarding various aspects of the fusion, including its incidence, biological characteristics, and the clinical profile of patients with this molecular rearrangement.

Several prospective trials have more precisely outlined the natural history of FIP 1L1–PDGFRA-positive patients treated with imatinib, leading to a few key conclusions: the prognosis is excellent, acquired resistance is extremely rare, but ongoing imatinib therapy is likely necessary to prevent relapse [19].

Informed consent

I, R. Mohamed, hereby give my full and informed consent for the publication of my medical case report in a medical journal. I understand that my anonymized medical information, including diagnosis, treatment, clinical course, and any relevant images or test results, may be used for educational and scientific purposes.

I acknowledge that I have been fully informed about the nature of the publication and the process involved. I approve the use of my anonymized medical data and images for this case report, with the understanding that all personal identifying information will be removed.

I confirm that my participation is entirely voluntary and that I can withdraw my consent at any time without affecting my medical care.

CRedit authorship contribution statement

Zaineb Mlayah: Writing – review & editing, Validation, Supervision, Conceptualization. **Inés Ben-Rekaya:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Inaam Bizid:** Validation, Supervision. **Nader Slama:** Validation, Supervision. **Sara Boukhris:** Validation, Supervision. **Mohamed-Adnene Laatiri:** Validation, Supervision.

Declaration of competing interest

The authors declare no competing interests regarding the publication of this case report and literature review on a rare clonal eosinophilia with exclusive pulmonary involvement driven by PDGFRA rearrangement treated with imatinib.

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