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Coexistence of BRAF V600E-Mutated Erdheim-Chester Disease with PDGFRβ- Rearranged Hypereosinophilic Syndrome: Diagnostic and Therapeutic Challenges

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Coexistence of BRAF V600E-Mutated Erdheim-Chester Disease with PDGFRβ-Rearranged Hypereosinophilic Syndrome: Diagnostic and Therapeutic Challenges

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The patient gave written consent for publication.

This study was performed without the involvement of a patient cohort. We describe a single case. Patients were not therefore invited to comment on the study design and were not consulted to in the development of patient-relevant outcomes or interpretation of the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

All methods were performed in accordance with the relevant guidelines and regulations.

Informed consent was obtained from the participant.

Written informed consent for publication of identifiable images was obtained from the participant.

The datasets generated and/or analyzed during the current study are not publicly available due to patient confidentiality but are available from the corresponding author on reasonable request.

Abstract

Erdheim-Chester disease (ECD) is a rare systemic histiocytosis driven by MAPK-pathway mutations, most frequently *BRAF*^{V600E}. Myeloid neoplasms occur in 10-15% of ECD patients. This is the first report of ECD associated with clonal hypereosinophilic syndrome (HES) in the same patient.

A 66-year-old woman was diagnosed with ECD harboring a *BRAF*^{V600E} mutation concomitantly with HES driven by a *TNIP1::PDGFRβ* fusion identified by optical genome mapping (OGM). She presented with cutaneous lesions, lymphadenopathy, hypereosinophilia and pulmonary hypertension. Interferon-alpha was discontinued because of disease progression and worsening pulmonary hypertension. Imatinib was attempted but poorly tolerated, resulting in acute heart failure. Cobimetinib resulted in clinical and metabolic improvement of ECD, with limited effect on eosinophilia. Pulmonary hypertension improved after adding tadalafil and bosentan.

This case illustrates the interplay between histiocytosis and a coexisting myeloproliferative neoplasm, driven by distinct molecular alterations. BRAF inhibition may cause paradoxical MAPK activation and progression in PDGFRβ-rearranged cells, whereas MEK inhibition with cobimetinib provided an effective and well-tolerated alternative for ECD. OGM was essential for identifying *PDGFRβ* rearrangement and guiding therapy.

We report the first reported case *BRAF*^{V600E}-mutated ECD associated with HES due to *PDGFRβ* rearrangement, emphasizing the importance of comprehensive molecular profiling and the therapeutic challenges of managing concurrent clonal hematologic disorders.

To the Editor:

Erdheim-Chester disease (ECD) is a rare adult-onset systemic histiocytosis characterized by tissue infiltration of CD68-positive, CD1a-negative foamy histiocytes (1,2). Its pathogenesis is driven by mutations in BRAF, MAP2K1, and other genes activating MAPK signaling. Myeloid neoplasms (MN) occur in 10-15% of ECD patients (3), with chronic myelomonocytic leukemia (CMML) the most frequently detected. Several mutations implicated in MN are frequently identified in molecular analyses of the bone marrow of ECD patients (with or without associated MN) (3,4).

We present here a case of ECD associated with clonal hypereosinophilic syndrome (HES) linked to a *PDGFRβ* rearrangement.

A 66-year-old woman from Martinique was referred to our center with a constellation of symptoms, including a cutaneous eruption involving the arms, back, and breasts, along with bilateral xanthelasma *(Figure 1a-d)*. Additional findings included lymphadenopathy, marked hypereosinophilia, pulmonary involvement, mesenteric panniculitis, and peripheral paresthesia.

The patient had a history of obesity and obstructive sleep apnea.

Initial laboratory tests showed marked hypereosinophilia (6.05 × 10^9/L), macrocytic anemia (hemoglobin 9 g/dL; mean corpuscular volume 102 fL), monocytosis (1.07 × 10^9/L), elevated IgE (12,486 IU/mL), vitamin B12 (1,766 pg/mL), tryptase (16.1 µg/L), and C-reactive protein (88 mg/L).

Bone marrow aspiration revealed hypercellularity with marked granulocytic hyperplasia but no excess of blasts. Myeloid next-generation sequencing (NGS) detected a *U2AF1* mutation with a variant allele frequency (VAF) of 30%, whereas results were negative for *BCR-ABL*,

FIP1L1-PDGFRα and *BRAF*.

Bone-marrow biopsy confirmed isolated eosinophilic hyperplasia. Cytogenetic analysis revealed a translocation t(X;20) and an interstitial deletion of the long arm of chromosome 5, suggesting a PDGFRβ rearrangement due to 5q deletion.
Optical genome mapping identified a 903-kb interstitial deletion on chromosome 5q involving PDGFRβ and TNIP1, predicted to result in an in- frame PDGFRβ::TNIP1 fusion.

Cutaneous biopsy of a breast lesion revealed a dense infiltration of foamy histiocytes ($CD68^+$, $CD163^+$, $CD207^-$, $CD1a^-$, $S100^-$), accompanied by an eosinophil-rich inflammatory infiltrate *(Figure 1e).* Touton giant cells were observed, along with scattered lymphocytes, neutrophils, and plasma cells. Genomic analysis the biopsy specimen led to detection of the $BRAF^{V600E}$ mutation.

A computed tomography scan (CT-scan) revealed multiple lymphadenopathies without hepatosplenomegaly or perirenal/aortic involvement and a marked dilation of the pulmonary artery trunk (*Figure 1f*). Positron emission tomography and computed tomography (PET/CT) showed long-bone osteosclerosis with cutaneous, pulmonary, mesenteric, nodal, and sinus involvement (*Figure 2a*)

Transthoracic echocardiography suggested pulmonary arterial hypertension (PAH) with an estimated systolic pulmonary artery pressure (PAPs) of 43 mmHg. Right-heart catheterization confirmed a precapillary PAH pattern (mean PAP 38 mmHg, pulmonary artery wedge pressure (PAWP) 8 mmHg).

Cardiac and cerebral magnetic resonance imaging (MRI) yielded unremarkable results and electroneuromyography showed no signs of neuropathy.

Interferon-alpha treatment was initiated at a dose of 135 µg/day to address both the histiocytosis and the HES. Four months later, imatinib was added to the treatment regimen due to interferon-alpha intolerance and persistent eosinophilia, but it was rapidly discontinued due to cardiotoxicity leading to acute pulmonary edema.

After six months of follow-up, the patient presented worsening dyspnea and asthenia, persistent eosinophilia (1.6 x 10^9/L), newly developed aortic infiltration, sustained FDG-PET hypermetabolism, and worsening PAH (estimated PAPs of 105 mmHg on echocardiography and PAPm of 62 mmHg on right-heart catheterization). Interferon-alpha treatment was therefore discontinued and cobimetinib (a MEK inhibitor) was introduced.

Four months later, the patient was hospitalized for right heart failure, with an estimated PAPm of 71 mmHg. Tadalafil treatment was initiated and subsequently reinforced by the introduction of bosentan one month later due to a pulmonary vascular resistance of 10.6 Wood Units (WU) and a cardiac output of 1.98 L/min.

After four months of cobimetinib, clinical and metabolic improvement was observed, with near-complete regression of cutaneous, nodal, and bone hypermetabolism on PET/CT (*Figure 2b*). Eosinophilia had decreased to 1.01 x 10^9/L *(Figure 3).*

Two months after the initiation of bosentan treatment, PAH was found to have improved, with a PAPm of 56 mmHg, a decrease in pulmonary vascular resistance to 7.46 WU, and an increase in cardiac output to 3.25 L/min.

In August 2025, routine blood tests revealed 17% circulating blasts. Bone marrow analysis confirmed B-cell acute lymphoblastic leukemia (ALL). Immunophenotyping showed a $CD34^+/CD19^+/TdT^+$ B-lymphoid profile, and cytogenetics identified t(X;20)(q13;q13) and i(7)(q10), with no detectable fusion transcripts, including PDGFRB rearrangements. Unfortunately, we were unable to perform a new OGM analysis, as the patient was diagnosed and treated for ALL in Martinique, far from any specialized laboratories. The patient was treated under the European Working Group for Adult ALL (EWALL) Backbone protocol, including dexamethasone, vincristine, idarubicin, and rituximab, with a triple intrathecal injection. Complete hematologic remission, but not molecular remission, was achieved after the first induction cycle.

ECD is associated with MN in approximately 10% of cases (3). Reported associations include CMML in half the patients, and various myeloproliferative neoplasms (MPNs) and myelodysplastic syndromes in the other half.

Platelet-derived growth factor receptors (PDGFRs) are receptor tyrosine kinases that play a key role in myeloid neoplasms associated with hypereosinophilia. In such cases, tyrosine kinase inhibitors, particularly imatinib, achieve response rates up to 95% (5).

Germline PDGFRβ mutations have been linked to hereditary progressive mucinous histiocytosis. However, to date, no case of ECD associated with PDGFRβ-mutated hypereosinophilic syndrome has ever been reported.

Interferon-α treatment was initially introduced as the first-line treatment in this case due to its theoretical efficacy against both histiocytosis and hypereosinophilic syndrome (HES).

Interferon treatment has been shown to be effective in ECD (6), with variable responses depending on disease severity and organ involvement, and has also been used as a second-line treatment for HES through direct effects on eosinophils and Th2 cytokine modulation (7). However, interferon therapy is limited by its adverse effects and poor tolerability.

PAH worsened during follow-up. Several clinical studies have reported an association between interferon use and the development of PAH, and experimental data further support this association. Precapillary PAH has also been described in patients with Langerhans cell histiocytosis (LCH), but not in those with Erdheim-Chester disease (8). No published data support an association between PAH and HES.

Given the likelihood of interferon playing a role in the worsening of our patient's condition, we modified her treatment. Despite the presence of a *BRAF*^{V600E} mutation, we decided to introduce cobimetinib (a MEK inhibitor) rather than a BRAF inhibitor, due to the concomitant presence of a myeloproliferative neoplasm. Indeed, the development of cutaneous neoplasms in patients on BRAF inhibitor therapy has been documented, primarily due to paradoxical activation of the ERK signaling pathway in *BRAF*-wild type cells (9). There have also been several case reports describing the progression of myeloproliferative disorders during treatment with BRAF inhibitors (10).

Resistance to BRAF inhibitors in BRAFV600E-mutant melanoma may involve *PDGFRβ* overexpression, promoting proliferation and survival (11,12). PDGFR signaling mimics BRAF activation but acts via an ERK-independent pathway, providing a possible explanation for the failure of MEK inhibition alone or with BRAF inhibitors to reverse resistance in cell models (11). An evaluation after four months of cobimetinib treatment revealed a significant improvement of the patient's ECD, but with only a limited effect on hypereosinophilia and PAH.

More than 20 translocation partners of *PDGFRβ* have been identified in MPNs, *ETV6* being the most frequently reported (13). A fusion of the *TNIP1* and *PDGFRβ* genes has also been documented, with cases responding well to imatinib treatment (14). Given the low incidence of HES and the genetic heterogeneity of the disease, many cases remain cytogenetically or molecularly uncharacterized despite the application of conventional diagnostic approaches. OGM is an emerging genome-wide technology enabling comprehensive detection of clinically relevant genomic rearrangements in a single assay. This technique has already been used to identify gene fusions in MPNs in patients with hypereosinophilia involving *PDGFR*β, as in our patient (15).

In HES with PDGFRβ rearrangements, imatinib mesylate — a tyrosine kinase inhibitor targeting BCR-ABL, KIT, and PDGFRs — has been shown to be highly effective (16). By contrast, limited responses were obtained in six ECD patients treated with imatinib (17), despite PDGFRβ expression on histiocytes in 86.5% of cases (32/37 samples).

Imatinib is generally well tolerated, but cardiotoxicity has been reported in approximately 1.7% of patients, predominantly in older individuals or those with pre-existing cardiac conditions (18). The median time from the initiation of imatinib therapy to the onset of heart failure is 162 days (range: 2–2045 days), consistent with the observations in our patient.

BRAF^{V600E} and *PDGFR*β mutations affect different signaling pathways. A single-agent treatment is therefore unlikely to be sufficient to address both conditions. The combined use of cobimetinib, targeting the MAPK pathway downstream from BRAF, and imatinib, inhibiting PDGFRβ -driven proliferation involving the PI3K pathway, may provide a synergistic treatment option. However, tolerability remains the main limitation of this combined approach.

In this report, we present the first documented case of *BRAF*^{V600E}-mutated ECD associated with clonal HES linked to *PDGFRβ* rearrangement. Cobimetinib has been associated with a complete response in histiocytosis and has a favorable tolerance profile. Optical genome mapping played a key role in precise, cost-effective diagnosis and may contribute to future personalized medicine.

1. Goyal G, Heaney ML, Collin M, Cohen-Aubart F, Vaglio A, Durham BH, et al. Erdheim-Chester disease: consensus recommendations for evaluation, diagnosis, and treatment in the molecular era. Blood. 28 mai 2020;135(22):1929-45.
2. Haroche J, Cohen-Aubart F, Amoura Z. Erdheim-Chester disease. Blood. 16 avr 2020;135(16):1311-8.
3. Papo M, Diamond EL, Cohen-Aubart F, Emile JF, Roos-Weil D, Gupta N, et al. High prevalence of myeloid neoplasms in adults with non-Langerhans cell histiocytosis. Blood. 24 août 2017;130(8):1007-13.
4. Cohen Aubart F, Roos-Weil D, Armand M, Marceau-Renaut A, Emile JF, Duployez N, et al. High frequency of clonal hematopoiesis in Erdheim-Chester disease. Blood. 28 janv 2021;137(4):485-92.
5. Demoulin JB, Essaghir A. PDGF receptor signaling networks in normal and cancer cells. Cytokine Growth Factor Rev. juin 2014;25(3):273-83.
6. Hervier B, Arnaud L, Charlotte F, Wechsler B, Piette JC, Amoura Z, et al. Treatment of Erdheim-Chester disease with long-term high-dose interferon-α. Semin Arthritis Rheum. juin 2012;41(6):907-13.
7. Butterfield JH, Weiler CR. Treatment of hypereosinophilic syndromes--the first 100 years. Semin Hematol. avr 2012;49(2):182-91.
8. Arnaud L, Pierre I, Beigelman-Aubry C, Capron F, Brun AL, Rigolet A, et al. Pulmonary involvement in Erdheim-Chester disease: A single-center study of thirty-four patients and a review of the literature. Arthritis Rheum. 2010;62(11):3504-12.
9. Robert C, Arnault JP, Mateus C. RAF inhibition and induction of cutaneous squamous cell carcinoma. Curr Opin Oncol. mars 2011;23(2):177-82.
10. Callahan MK, Rampal R, Harding JJ, Klimek VM, Chung YR, Merghoub T, et al. Progression of RAS-Mutant Leukemia during RAF Inhibitor Treatment. N Engl J Med. 13 déc 2012;367(24):2316-21.
11. Corcoran RB, Settleman J, Engelman JA. Potential Therapeutic Strategies to Overcome Acquired Resistance to BRAF or MEK Inhibitors in BRAF Mutant Cancers. Oncotarget. 19 avr 2011;2(4):336-46.
12. Nazarian R, Shi H, Wang Q, Kong X, Koya RC, Lee H, et al. Melanomas acquire resistance to B-RAF(V600E) inhibition by RTK or N-RAS upregulation. Nature. 16 déc 2010;468(7326):973-7.
13. Savage N, George TI, Gotlib J. Myeloid neoplasms associated with eosinophilia and rearrangement of PDGFRA, PDGFRB, and FGFR1: a review. Int J Lab Hematol. 2013;35(5):491-500.
14. Ross DM, Altamura HK, Hahn CN, Nicola M, Yeoman AL, Holloway MR, et al. Delayed diagnosis leading to accelerated-phase chronic eosinophilic leukemia due to a cytogenetically cryptic, imatinib-responsive TNIP1–PDFGRB fusion gene. Leukemia. juin 2016;30(6):1402-5.
15. Podvin B, Roynard P, Boudry A, Guermouche H, Daudignon A, Terriou L, et al. Whole-genome optical mapping to elucidate myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions. Leuk Res. déc 2022;123:106972.
16. Apperley JF, Gardembas M, Melo JV, Russell-Jones R, Bain BJ, Baxter EJ, et al. Response to Imatinib Mesylate in Patients with Chronic Myeloproliferative Diseases with Rearrangements of the Platelet-Derived Growth Factor Receptor Beta. N Engl J Med. 15 août 2002;347(7):481-7.
17. Haroche J, Amoura Z, Charlotte F, Salvatierra J, Wechsler B, Graux C, et al. Imatinib mesylate for platelet-derived growth factor receptor-beta–positive Erdheim-Chester histiocytosis. Blood. 1 juin 2008;111(11):5413-5.

18. Atallah E, Durand JB, Kantarjian H, Cortes J. Congestive heart failure is a rare event in patients receiving imatinib therapy. Blood. 15 août 2007;110(4):1233-7.

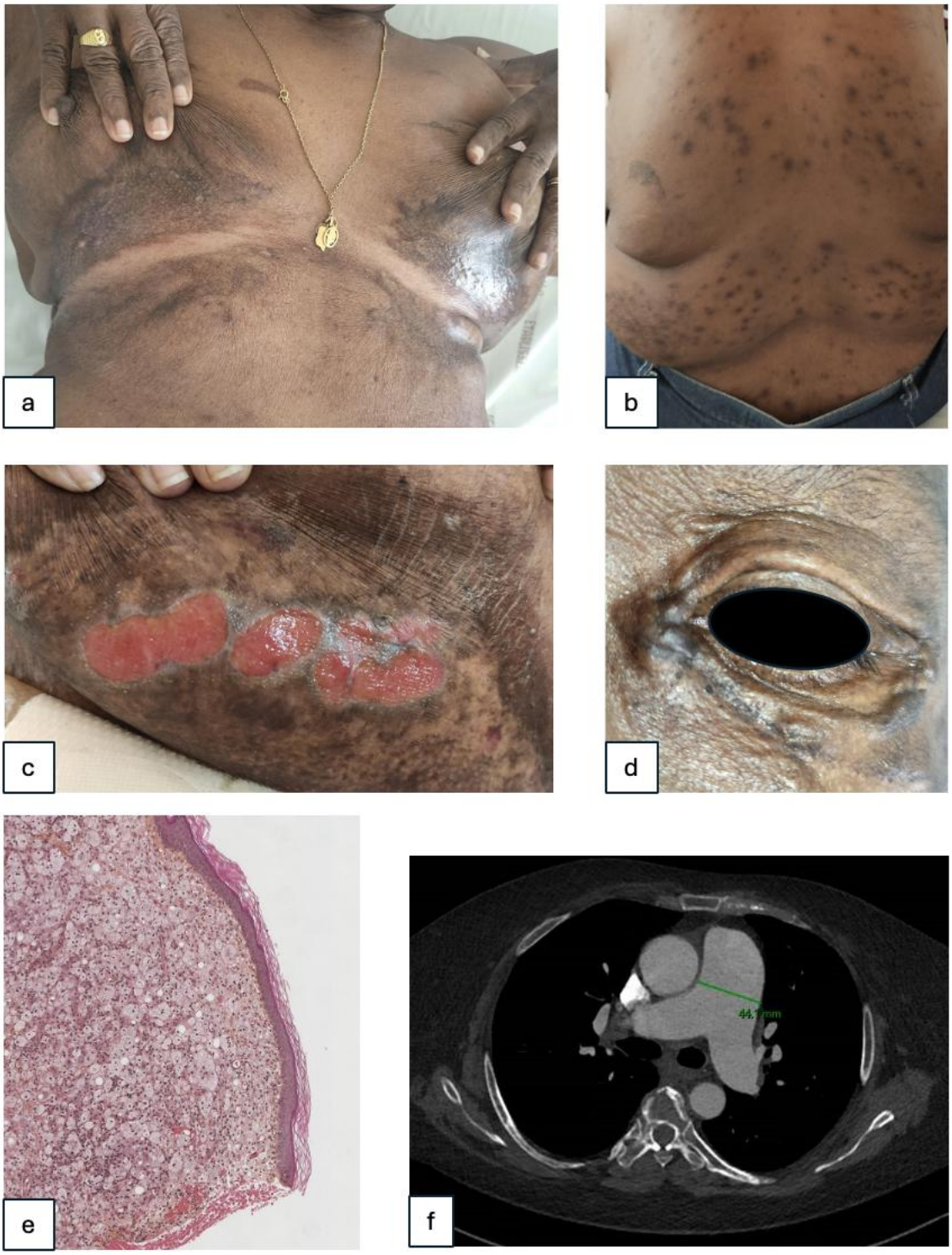


Figure 1 :
a-b-c-d : Initial cutaneous manifestations of Erdheim-Chester disease

a. *Intertriginous brownish infiltrated plaques with ulceration of the left inframammary fold*
b. *Post-bullous ulceration of the left inframammary region on a background of hyperpigmented skin.*
c. *Numerous pigmented nodules scattered across the back.*
d. *Xanthelasma involving the periorbital regions.*

e. *Dermal infiltrate of foamy histiocytes with associated tissue eosinophilia in Erdheim-Chester disease. Hematoxylin and eosin stain of a skin biopsy showing a dense dermal infiltrate composed predominantly of foamy histiocytes with abundant vacuolated cytoplasm and eccentrically located nuclei. Numerous eosinophils are interspersed within the infiltrate, identified by their bilobed nuclei and intensely eosinophilic granular cytoplasm (original magnification ×20). This histological pattern supports the diagnosis of Erdheim-Chester disease with concomitant tissue eosinophilia.*

f. *Pulmonary artery trunk dilatation. Axial computed tomography (CT) scan of the chest demonstrating a markedly dilated pulmonary artery trunk measuring 44.1 mm in diameter. This imaging finding is consistent with pulmonary arterial hypertension (PAH), which was confirmed in this case by right heart catheterization.*



Figure 2 : Metabolic response to cobimetinib in Erdheim-Chester disease as assessed by FDG PET/CT

Whole-body FDG PET/CT scans performed in March 2024 (a) and July 2024 (b) demonstrate a marked metabolic response to cobimetinib therapy. The baseline scan shows intense hypermetabolic activity involving the long bones of the lower limbs, cutaneous tissues, mesentery, and maxillary sinuses. Follow-up imaging after four months of treatment reveals a substantial reduction in FDG uptake in all previously involved sites, consistent with a favorable therapeutic response.

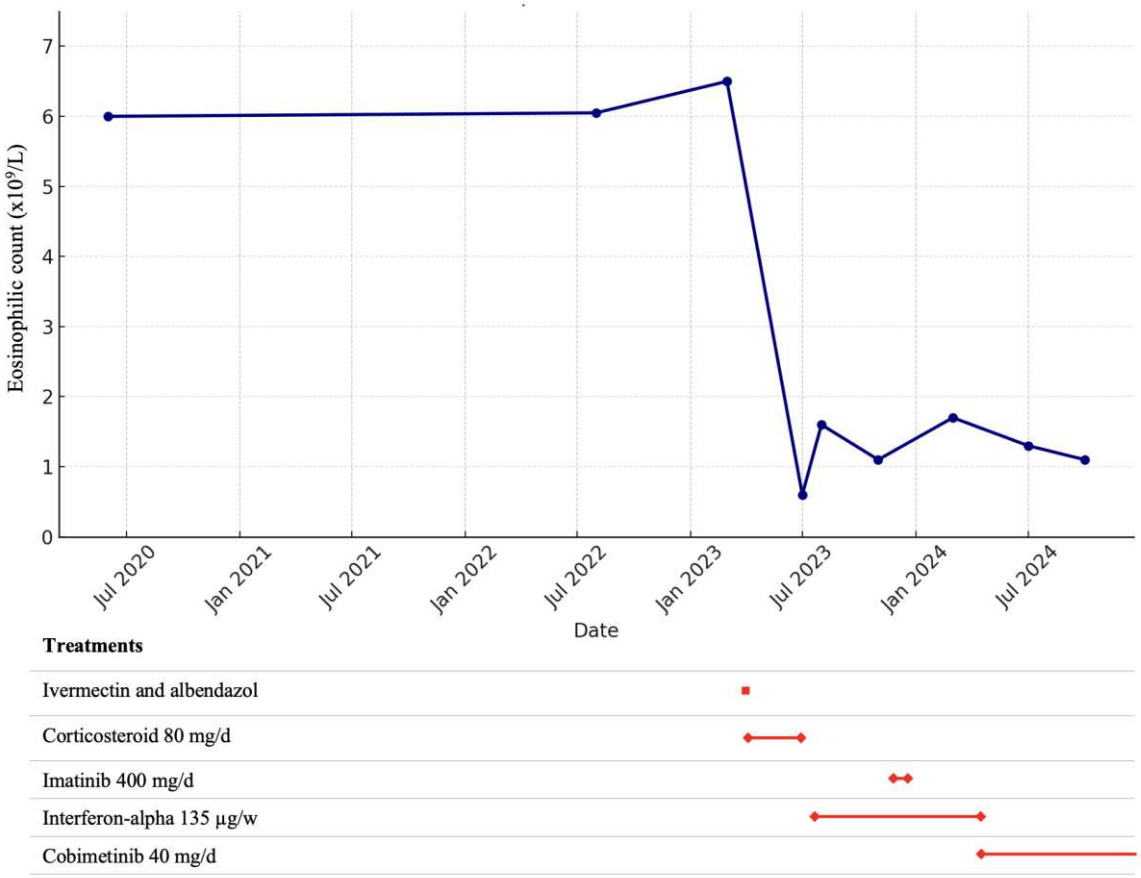


Figure 3 : Eosinophil count over time and therapeutic interventions

Longitudinal evolution of blood eosinophil count (G/L) from June 2020 to October 2024, in relation to administered treatments. A marked decrease in eosinophilia was observed after March 2023. Therapeutic interventions are represented below the graph as horizontal red bars, with red squares marking the start and end of each treatment period.

Treatments include:

- *Ivermectin and albendazole (single dose in March 2023),*
- *Corticosteroids (March–May and June–July 2023),*
- *Imatinib (1 week in December 2023),*
- *Pegylated interferon-alpha (August 2023–April 2024),*
- *Cobimetinib (from April 2024 onwards).*

This visualization highlights the chronological relationship between therapeutic adjustments and fluctuations in eosinophil levels.