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Case Report

Idiopathic hypereosinophilic syndrome with
20 years of diagnostic delay



Miguel Pedro de Queiroz Neto*, Fernando Antônio Galvão Gondim Filho

Hospital Metropolitano Norte Miguel Arraes (HMA), Paulista, PE, Brazil

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Introduction

Eosinophils are specialized granulocytes that produce and store diverse biologically active molecules, including cytotoxins, costimulatory proteins, lipid mediators, chemotactic peptides, cytokines, leukotriens and prostaglandins.¹ Eosinophils can also cause direct damage to microorganisms and can activate cells and platelets.^{1,2} The normal count ranges between 0.05 and $0.5 \times 10^9/L$ in the peripheral blood and between 1% and 6% in a myelogram.³

Hypereosinophilia is defined as persistent eosinophilia ($>1.5 \times 10^9/L$) over a minimum of four weeks.^{3,4} Major causes of hypereosinophilia are helminth infections, allergies, atopy and drugs, which are described as secondary hypereosinophilia due to the production of interleukin (IL)-3 and IL-5 that promote eosinophil proliferation. Lymphomas, lymphoblastic leukemia, some solid tumors and some autoimmune diseases are less common causes.³⁻⁵ In primary hypereosinophilia, eosinophils are clonal and are derived from

myeloid lineage. Although rare, the main causes are myelogenous leukemias and myelodysplastic syndromes.^{3,4} The clinical course varies as it may involve single or multiple organs. There are no clear immunophenotypic markers for clonal hypereosinophilia; however, there are highly indicative molecular markers.⁶ The most common are platelet-derived growth factor receptor alpha and beta (PDGFR α and PDGFR β), fibroblast growth factor receptor 1 (FGFR1), the c-abl1 oncogene (ABL1) and Janus kinase 2 (JAK2); the first three are related to t(8;13), t(5;12) and t(9;22) cytogenetic translocations.^{3,4,7}

For a diagnosis of hypereosinophilic syndrome, target organ damage, hypereosinophilia and absence of any other reason for organ damage are needed.⁶ Treatment is based on glucocorticoids and nonsteroidal anti-inflammatory drugs according to symptoms, and tyrosine-kinase inhibitors directed against cytogenetic targets.^{3,7,8}

Herein, we report a case of hypereosinophilic syndrome diagnosed as chronic myeloid leukemia with eosinophilia (CML-eo) in a patient with symptoms over 20 years.

* Corresponding author at: Hospital Metropolitano Norte Miguel Arraes (HMA), Enfermaria de Clínica Médica, Estrada da Fazendinha, S/N, 53413-000 Paulista, PE, Brazil.

E-mail address: miguelqueiroz@outlook.com (M.P. Neto).

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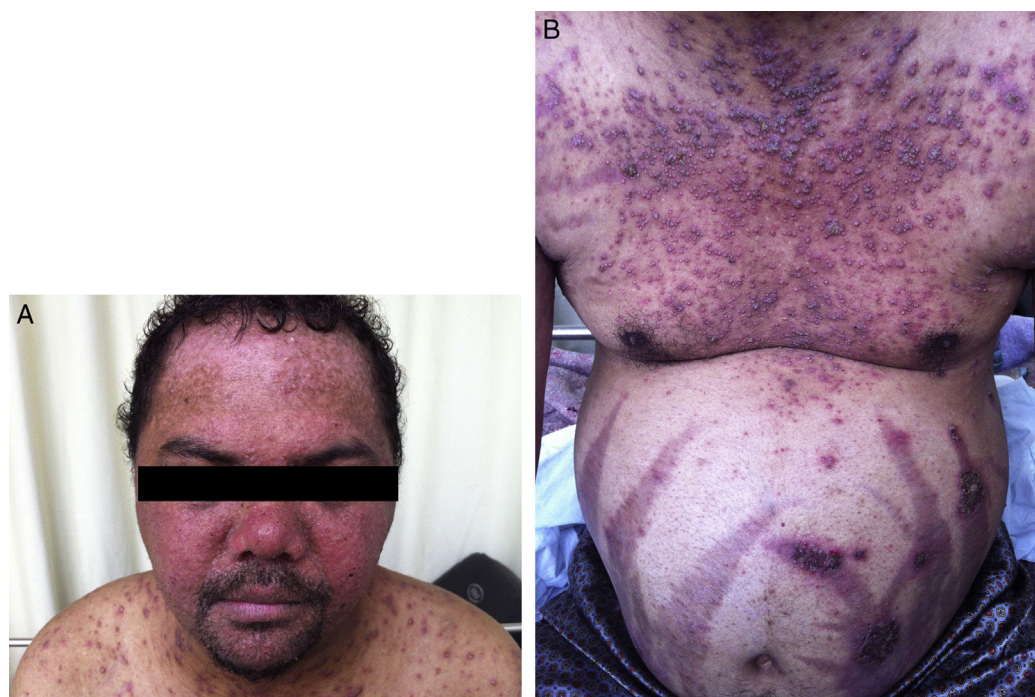


Figure 1 – A and B before Imatinib.

Case report

A 30-year-old male patient presented to the emergency department with dyspnea, fever and productive cough for three days. He had been taking 20 mg of prednisone for 20 years after being admitted to a hospital in Recife. On this occasion, the patient was treated for streptococcal glomerulonephritis. After discharge, he did not return and was lost to follow-up.

The patient also had pruritic skin lesions since ten years of age, which used to erupt, vanish and reappear spontaneously in two-week intervals. After prednisone was started, the frequency of the lesions was related to its intake, as the frequency of lesion reappearance was much higher without prednisone.

At physical examination, the patient's heart rate was 108 beats per minute, respiratory rate was 28 breaths per minute and the blood pressure was 180/100 mmHg. He presented with cushingoid facies, knee arthritis, violet streaks on the abdomen and darkened skin with erythematous and papular lesions on his face, limbs and trunk (Figure 1). He had no kidney injury, hepatomegaly or splenomegaly.

Ceftriaxone and azithromycin were prescribed to treat communitary pneumonia and the prednisone dosage was reduced to 15 mg/day.

On the following days, pustules and erythroderma arose at previous skin lesion sites. Eosinophilia was seen in peripheral blood at levels above $6.0 \times 10^9/L$, which was 30–50% of the total cellularity. Blasts were not seen in peripheral blood.

Anti-neutrophil cytoplasmic antibody (ANCA), skin biopsy, myelogram and human immunodeficiency virus (HIV) tests were examined to investigate secondary hypereosinophilia.

The ANCA and HIV results were negative. The skin biopsy diagnosed eosinophilic pustular folliculitis and the myelogram revealed 20% eosinophils in bone marrow, with normoblastic erythropoiesis, normocellular granulopoiesis, 1% blasts and normoblastic megakaryocytes. Abdomen and thorax computed tomography were also obtained, which revealed axillary, cervical and inguinal lymphadenomegaly.

As an additional workup, no lymphocyte clonality was found by flow cytometry. A subsequent molecular panel for FIP1L1-PDGFR α , breakpoint cluster region-Abelson murine leukemia (BCR-ABL) and JAK2 was obtained, showing only BCR-ABL translocation as positive.

After the recent diagnosis of eosinophilia-associated chronic myeloid leukemia (Eos-CML), hydroxyurea (2 g/day) was given and the peripheral blood eosinophilia was partially controlled. The patient did not tolerate prednisone withdrawal due to an adrenal crisis and he was discharged on 15 mg/day prednisone. During the follow-up, imatinib (400 mg/day) was prescribed and after five days of treatment, the skin lesions receded. Scar spots remained in place of previous lesions (Figure 2).

After four weeks of imatinib, skin lesions relapsed. This time there were pustules and ulcers of the oral mucosa, and on the elbows and back (Figure 3). The patient also complained about dysphagia, intense pruritus and occasional dyspnea, the latter was alleviated with salbutamol and the pruritus was relieved with dexchlorpheniramine. The patient was readmitted due to intense dysphagia. A complete blood count on admission showed $90.0 \times 10^9/L$ leukocytes of which 80% were eosinophils. The dysphagia improved after the prednisone dose was increased to 40 mg/day. However, the skin lesions worsened in the following days and peripheral eosinophilia

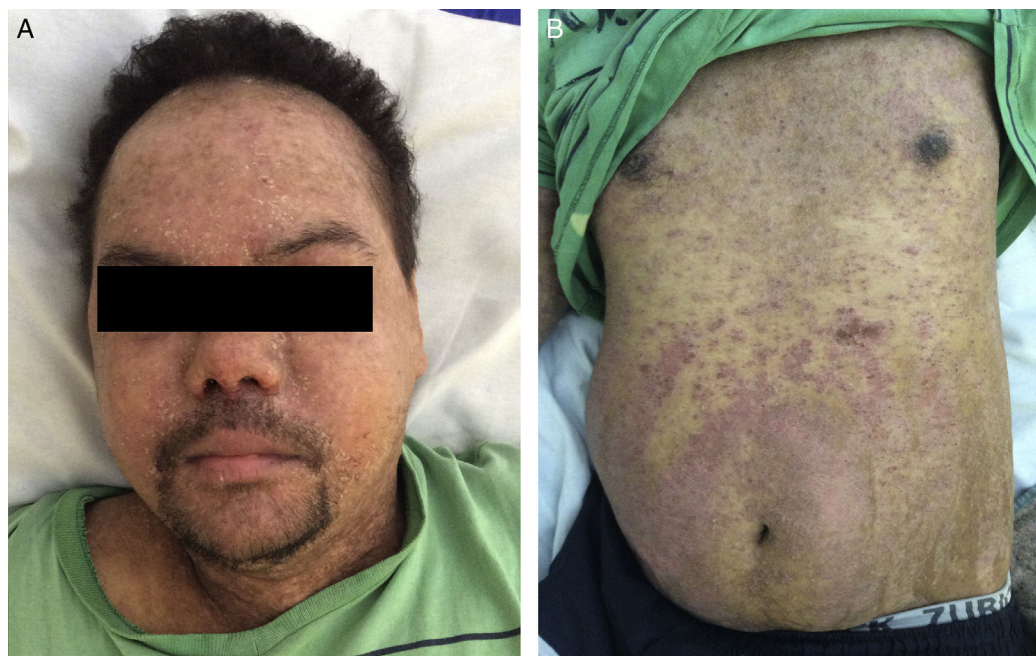


Figure 2 – A and B after Imatinib.

could not be controlled even with a pulse dose of methylprednisolone. A new molecular panel was obtained from tissue and blood exams were repeated.

Skin biopsy revealed hypereosinophilic ulceration and the entire skin molecular panel was negative. TdT, CD89, c-kit, CD20, CD3, CD7, CD2, CD15, CD34, myeloperoxidase and

mutations of PDGFR were tested. The pathologist concluded that the tissue was infiltrated by an undifferentiated myeloproliferative neoplasm. Blood BCR-ABL and mutations of PDGFR were also negative. Another myelogram showed hypercellular bone marrow with 78% of cells being granulocytes (27% eosinophils and 51% eosinophil precursors) of hypoblastic erythroid lineage and hypercellular megakaryocyte lineage, presenting monolobulation and polylobulation. An immunophenotyping panel showed hypercellularity, mature and intermediate eosinophils concluding it was compatible with chronic myeloproliferative neoplasm. No cytogenetic study or bone marrow biopsy was made. As the BCR-ABL results were discrepant, another search for BCR-ABL and PDFGR mutations was made, although the results were negative.

Due to failure of tyrosine kinase inhibitor treatment and the negative BCR-ABL results, imatinib was ceased and hydroxyurea restarted with cellularity control. During the hospital stay, the dyspnea worsening and a new thorax CT was performed, which revealed a 7.0 cm diameter cavity in the right hemithorax. It was decided to start treatment for tuberculosis with rifampicin, isoniazid, pyrazinamide and ethambutol. Despite this therapy, the dyspnea worsened and the patient started with fever. Blood cultures were positive to multidrug resistant *Acinetobacter baumannii* and *Candida albicans*. Subsequently, polymyxin B, gentamicin and micafungin therapy were started.

The patient became septic and later died.



Figure 3 – Skin lesions relapse.

Discussion

Hypereosinophilic syndromes are rare and underdiagnosed diseases. Moreover, there is no published epidemiologic report about their prevalence. Nonetheless, an estimate based on

Table 1 – World Health Organization diagnostic criteria for chronic eosinophilic leukemia.¹⁰

1. Eosinophilia count $\geq 1.5 \times 10^9/L$
2. There is no Philadelphia chromosome or breakpoint cluster region-Abelson murine leukemia (BCR-ABL) fusion gene or other myeloproliferative neoplasm (polycythemia vera, essential thrombocythemia, or primary myelofibrosis) or myelodysplastic/myeloproliferative neoplasms (MDS/MPN) (chronic myelomonocytic leukemia, atypical chronic myeloid leukemia)
3. There is no t(5;12)(q31-35;p13) or any other rearrangement of PDGFR β
4. There is no FIP1L1-PDGFR α fusion gene or any other rearrangement of PDGFR α
5. There is no rearrangement of FGFR1
6. The blast cell count in peripheral blood and bone marrow is $<20\%$ and there is no inv(16)(p13.1;q22) or t(16;16)(p13.1;q22) or other diagnostic feature of acute myeloid leukemia
7. There is a clonal cytogenetic or molecular genetic abnormality or blast cells are $>2\%$ in peripheral blood or $>5\%$ in bone marrow

annual discharges and on a US database for outpatient management has indicated that hypereosinophilic syndromes could represent approximately one-third of chronic myeloid leukemia patients. However, other international reports are related to PDGFR mutations, which are more common and predominantly affect men with an estimated male-to-female ratio between 4:1 and 9:1 with a tendency to occur in people aged from 20 to 50 years old.^{7,8}

The clinical manifestations vary vastly. Any organ or tissue may be affected and myalgia, arthritis, dyspnea, pruritus, skin lesions and other symptoms may develop.^{3,4,6} In this case, the main clinical manifestation was eosinophilic folliculitis, which is characterized by pruritic perifollicular erythematous papules and pustules on the head, neck, limbs and trunk. There is no data regarding its prevalence in hypereosinophilic syndromes or in myeloproliferative neoplasms in the literature. However, skin involvement is common and there can be ulcerations.⁷

The World Health Organization (WHO) proposed a set of criteria to classify myeloproliferative neoplasms, for which molecular and cytogenetic data are required.⁹ Following these criteria rigorously, the above case can only be diagnosed as idiopathic hypereosinophilic syndrome as there is strong evidence of myeloproliferative neoplasm, but eosinophil clonality cannot be proven through molecular studies. Nonetheless, other diagnoses would be possible if there was flexibility in the criteria. Chronic eosinophilic leukemia, for example, would be a strong possibility in this case however, the absence of clonality did not allow this diagnosis (Table 1). Hence, the consensus of the specialists who addressed this case agreed that the WHO criteria are flawed and that new histopathologic and morphologic criteria should be defined to simplify the diagnosis in situations in which clonality cannot be proven.⁴ In the most recent WHO eosinophilia review, no diagnostic criteria were changed.³ It is important to note that no cytogenetic study was done in this case.

Another hypothesis in this case was chronic neutrophilic leukemia. Among the eight criteria for this disease (Table 2), the patient did not have hepatosplenomegaly. The WHO is rigorous in this diagnosis perhaps because this disease is still

Table 2 – The World Health Organization diagnostic criteria for chronic neutrophilic leukemia.¹⁰

1. Peripheral blood leukocytosis $\geq 25.0 \times 10^9/L$, segmented neutrophils and band forms are $>80\%$ of white blood cells, immature granulocytes (promyelocytes, myelocytes, metamyelocytes) are $<10\%$, myeloblasts are $<1\%$ of white blood cells
2. Hypercellular bone marrow biopsy, neutrophilic granulocytes increased in number and percentage, myeloblasts $<5\%$ of nucleated bone marrow cells, neutrophilic maturation pattern normal, megakaryocytes normal or left shifted
3. Hepatosplenomegaly
4. No identifiable cause for physiologic neutrophilia or, if present, demonstration of clonality of myeloid cells by cytogenetic or molecular studies, no infectious or inflammatory process, no underlying tumor
5. No Philadelphia chromosome or breakpoint cluster region-Abelson murine leukemia (BCR-ABL) fusion gene
6. No rearrangement of PDGFR α , PDGFR β or FGFR1
7. No evidence of polycythemia vera, essential thrombocythemia or primary myelofibrosis
8. No evidence of myelodysplastic syndrome or myelodysplastic/myeloproliferative neoplasms (MDS/MPN), no granulocytic dysplasia, no myelodysplastic changes in other myeloid lineages, monocytes $<1.0 \times 10^9/L$

poorly characterized, as it reports that only 40 of the 150 cases described in the literature met the criteria.⁹

In this case, the long duration of symptoms and lack of disease progression should be remembered. The indiscriminate use of prednisone by the patient may also have influenced disease progression. Another possibility that should be taken into consideration is that since childhood, this patient had a hypereosinophilic syndrome that evolved into a myeloproliferative neoplasm.

Conclusion

Initially treated as CML-eo due to the laboratory findings, this case presented the diagnosis of idiopathic hypereosinophilic syndrome with the patient evolving to an unfavorable outcome after presenting symptoms for 20 years prior to diagnosis.

Conflicts of interest

The authors declare no conflicts of interest.

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