Case Report

HEMATOLOGY

Paraneoplastic hypereosinophilia in a patient with peripheral T cell lymphoma, not otherwise specified

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Abstract

Under normal physiological conditions, the bone marrow (BM) will have between 1% and 6% eosinophils, translating into a peripheral count of 0.05 – 0.5 x10^9 /L eosinophils in the blood smear. This process is coordinated by transcription factors with specific roles in differentiation and activation. Secondary eosinophilia may be a paraneoplastic syndrome, related to the presence of a subsequent malignancy, as presented in this case report. Such paraneoplastic manifestations should be addressed properly in order for the patient to receive the best treatment of choice. Even if eosinophilia was associated with B-cell malignancies before, this is a report associating this symptom to a peripheral T-cell lymphoma, not other specified, thus emphasizing the importance of a complex approach for the management of the oncological patient.

Keywords: hypereosinophilia, paraneoplastic syndrome, peripheral T cell lymphoma - NOS

Introduction

Eosinophilia is defined as an increased absolute eosinophil count under normal physiological conditions, including in neonates [1]. With age, the number of physiological eosinophils gradually falls. Hypereosinophilia (HE) and the hypereosinophilic syndrome (HES) are defined by an eosinophil count of more than 0.5 x 10^9/L for at least 6 months and for which no primary cause is identified; it is also associated with signs of organ involvement or dysfunction [2]. This definition was later accepted by the World Health Organization (WHO) for chronic eosinophilic leukemia (CEL), not otherwise specified (CEL, NOS) [3]. Physicians should initiate therapy for hypereosinophilia as soon as possible in patients with end-organ damage [4]. Under normal physiological conditions, the bone marrow (BM) has between 1% and 6% eosinophils, translating into a peripheral count of 0.05 – 0.5 x10^9 /L eosinophils in the blood smear [5]. This process is coordinated by transcription factors with key roles in differentiation and activation, such as GATA-1 [6,7]. The same regulatory process plays important roles in reactive eosinophilia. Reactive eosinophilia is different from clonal eosinophilia, with commonly identified tyrosine kinase gene fusions which includes the coding genes for platelet-derived growth factor receptor alpha (PDGFRA), platelet-derived growth factor receptor beta (PDGFRB) or fibroblast growth factor receptor 1 (FGFR1) [8]. This mutational status has a significant clinical importance, as it aids the physician for the differential diagnosis between reactive and clonal eosinophilia. Eosinophils are identified under physiological conditions only in lymphoid organs, mucosa of the gastrointestinal tract and uterus. Prolonged eosinophilia will cause the migration of these cells in non-native tissues and thus cause end-organ damage through local thrombosis and fibrosis. Secondary eosinophilia is a paraneoplastic syndrome linked to an underlying malignancy [9], as presented in the current paper. Paraneoplastic manifestations should be addressed properly in order for the patient to receive the best available treatment.

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Even if eosinophilia associated with B-cell malignancies was previously reported [10], we report here an association of this condition to a peripheral T-cell lymphoma, not other specified (NOS), emphasizing the importance of a complex approach for the management of the oncological patient.

Case report

A 75-year old female with a personal history of paroxystic atrial fibrillation, chronic ischemic heart disease and type II diabetes was referred to the "Prof. Dr. Ion Chiricuta" Oncology Institute - Hematology Department with complaints of fatigability, night sweats, a weight loss of approximately 7 kg in the last month and dysphagia. The clinical examination revealed pale skin and enlarged lymph nodes in the submental, submandibular, bilateral laterocervical and bilateral supraclavicular areas. The peripheral blood count showed a white blood cell (WBC) count of 55.4 x 10^3/µl and eosinophil count of 46.54 x 10^3/µl. The blood tests also showed increased lactate dehydrogenize level of 1191 U/L, high uric acid of 8.12 mg/dL and a normal creatinine at 1.32 mg/dL. The peripheral blood smear revealed 1% basophils, 89% eosinophils, 2% lymphocytes, 2% monocytes, 6% neutrophils and rare pelgeroid eosinophils. Cytologic examination of the bone marrow (Figure 1) was conclusive for hypereosinophilia (with both central and peripheral causes). The bone marrow biopsy (Figures 2 A-J) showed a hypercellular bone marrow, that infiltrates the intraosseous lamellae. All myeloid cells were present, with over 50% of the nucleate cells being eosinophils with cellular atypia, in all differentiation steps. The blast cell population was under 20%. The mutational status for the fusions FIP1L1-PDGFRA, FIP1L1-PDGFRB, FGFR1, PCM1-JAK2, c-KIT and BCR-ABL were negative.

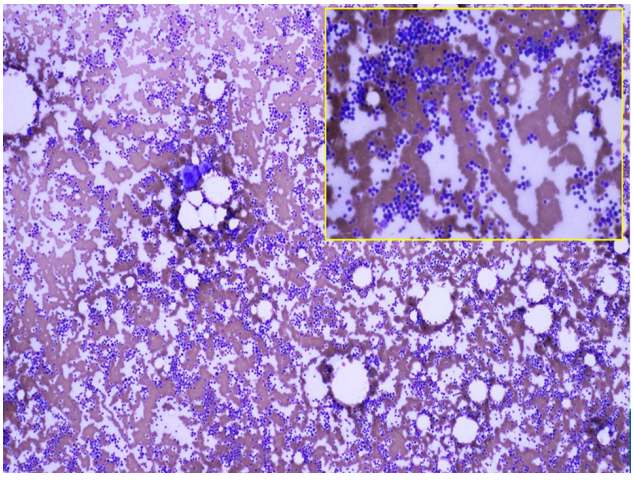

Figure 1. Hypereosinophilia (with both central and peripheral causes). All myeloid lines are present, but with over 50% of nucleate elements being eosinophils in all stages of differentiation. The rest of the nucleate elements were represented by neutrophils (5% blasts, 15% intermediate elements and 20% segmented and unsegmented neutrophils), erythroblasts, mainly oxyphils and polychromatophilic, as well as megakaryocytes.

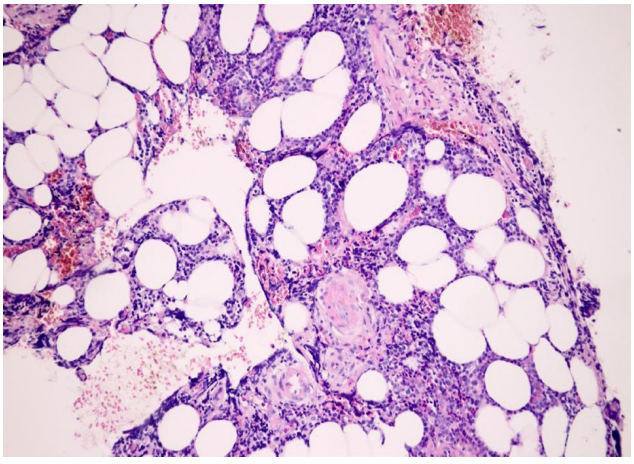

Figure 2 A. Immunohistochemistry staining allowed the diagnosis of a peripheral T cell lymphoma, NOS. The staining was for hematoxylin-eosin.

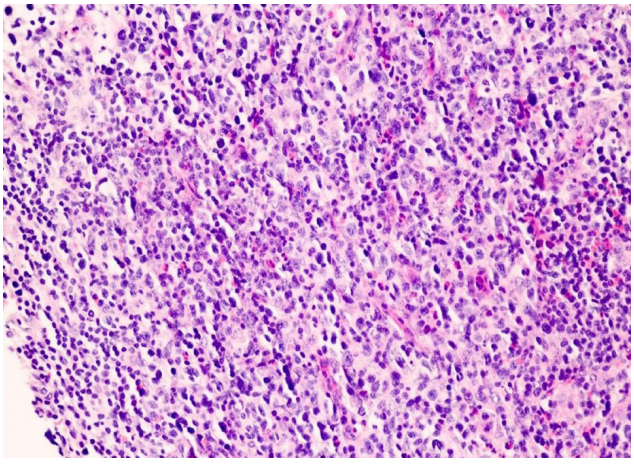

Figure 2 B. Immunohistochemistry staining allowed the diagnosis of a peripheral T cell lymphoma, NOS. The staining was for hematoxylin-eosin.

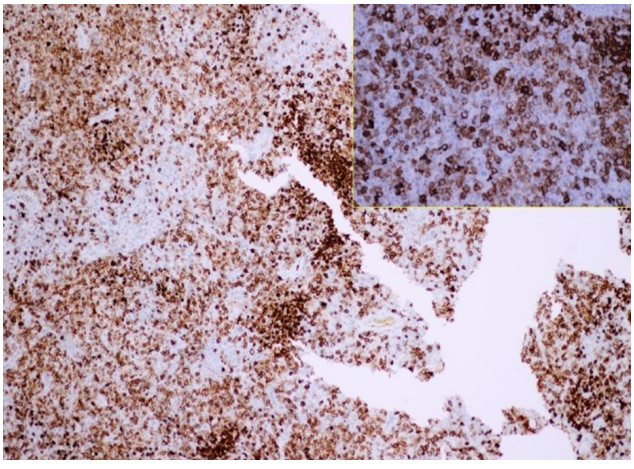

Figure 2 C. Immunohistochemistry staining allowed the diagnosis of a peripheral T cell lymphoma, NOS. The staining was positive for CD20.

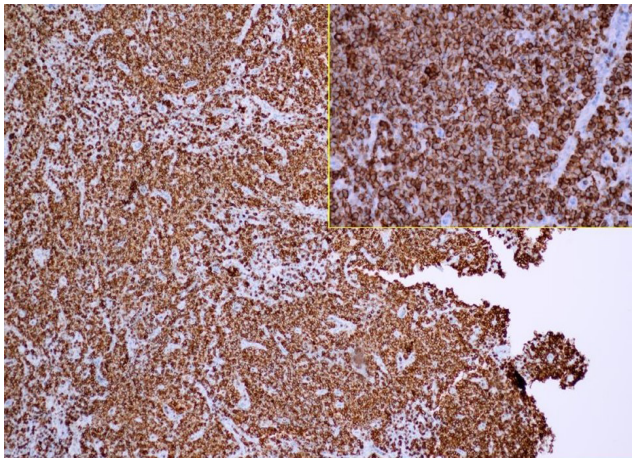

Figure 2 D. Immunohistochemistry staining allowed the diagnosis of a peripheral T cell lymphoma, NOS. The staining was positive for CD3.

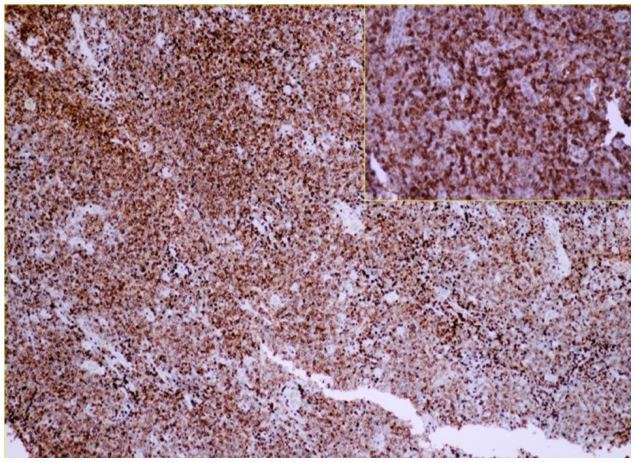

Figure 2 G. Immunohistochemistry staining allowed the diagnosis of a peripheral T cell lymphoma, NOS. The staining was positive for CD4.

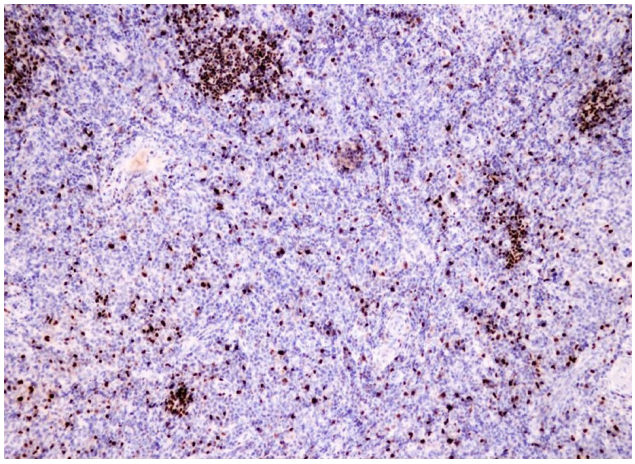

Figure 2 E. Immunohistochemistry staining allowed the diagnosis of a peripheral T cell lymphoma, NOS. The staining was negative for PAX-5.

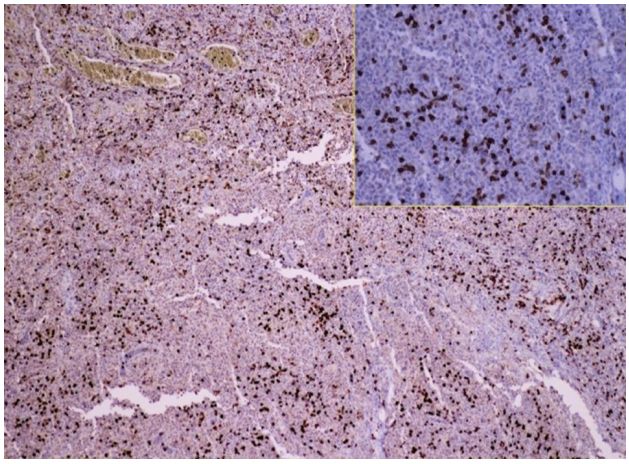

Figure 2 H. Immunohistochemistry staining allowed the diagnosis of a peripheral T cell lymphoma, NOS. The staining was negative for CD8.

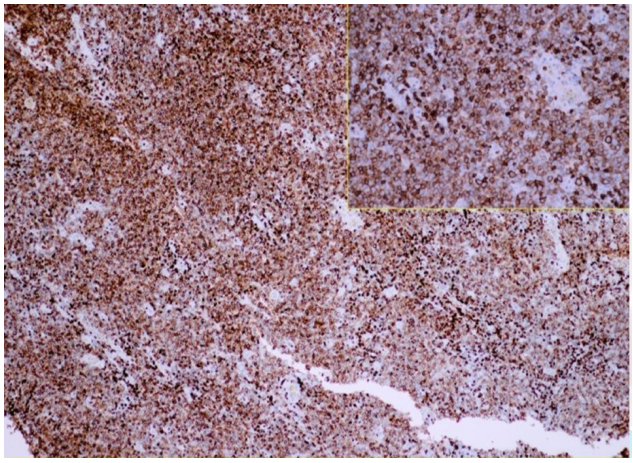

Figure 2 F. Immunohistochemistry staining allowed the diagnosis of a peripheral T cell lymphoma, NOS. The staining was positive for CD5.

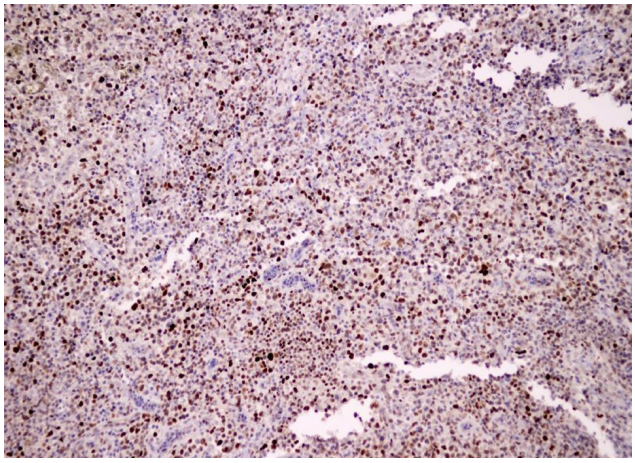

Figure 2 I. Immunohistochemistry staining allowed the diagnosis of a peripheral T cell lymphoma, NOS. The staining was positive for Bcl-6.

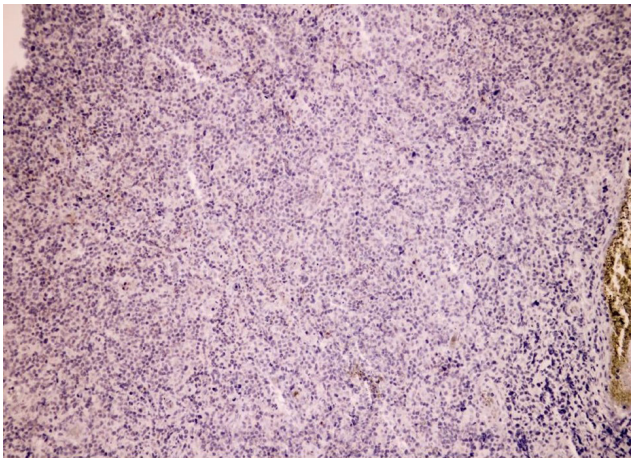

Figure 2 J. Immunohistochemistry staining allowed the diagnosis of a peripheral T cell lymphoma, NOS. The staining was negative for CD10.

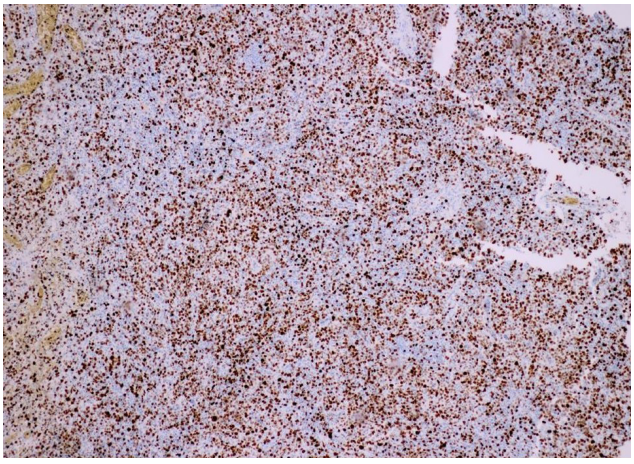

Figure 2 M. Immunohistochemistry staining allowed the diagnosis of a peripheral T cell lymphoma, NOS. The staining was for a 65% Ki67 proliferation index.

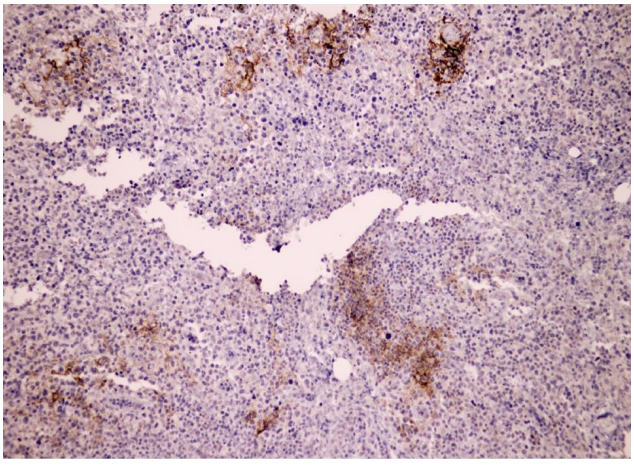

Figure 2 K. Immunohistochemistry staining allowed the diagnosis of a peripheral T cell lymphoma, NOS. The staining was negative for CD21.

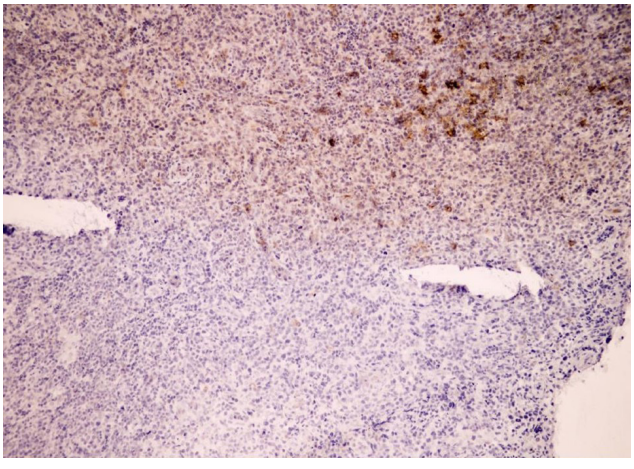

Figure 2 L. Immunohistochemistry staining allowed the diagnosis of a peripheral T cell lymphoma, NOS. The staining was negative for CD30.

The whole-body computer tomography (CT) showed submandibular lymph nodes of 2 cm, a metastatic mass of 3 cm in the right laterocervical area, one of 4 cm in the left laterocervical area, a 5 cm mass in the left retroauricular area, one of 3 cm in the right retroauricular area, a 2 cm mass in the intratracheal area, a 5 cm mass in the right abdominal obturator area, a 3 cm one in the left inguinal canal, a 3 cm mass in the right femoral area and a 2 cm one in the left femoral area.

Up to this point, the differential diagnosis for hypereosinophilia was ranging between primary hypereosinophilia (with a differential diagnosis between chronic myeloproliferative disorders/myelodysplastic syndrome and acute myeloid leukemia/acute lymphoblastic leukemia with B/T cells), and secondary/reactive hypereosinophilia (secondary to a paraneoplastic syndrome, infection, autoimmune disease or iatrogenic disease), according to the consensus group definitions for HE and HES and to the WHO classification for myeloid neoplasms. The surgical excision of a lymph node, followed by its evaluation by two independent certified pathologists allowed the diagnosis of peripheral T-cell lymphoma, NOS. Thus, hypereosinophilia was a paraneoplastic syndrome, as the aberrant T cell malignant clones secreted an excess of eosinopoietic cytokines.

Discussion

The present clinical case brings forward a complex diagnostic scenario, of great importance for medical oncologists and hematologists. The differential diagnosis ranges from HE or HES to secondary eosinophilia due to a paraneoplastic syndrome and is elucidated by the lymph node biopsy. The diagnosis procedure is complex and is built around the histology of the lymphoma and of the aberrant expression of CD20. Thus, the differential diagnosis for

lymphoma was established taking into consideration angioimmunoblastic lymphoma, Lennert's lymphoma and a peripheral T cell lymphoma, NOS [11-13]. The diagnosis of a peripheral T-cell lymphoma, NOS is confirmed by the absence of a more prominent network of vascular structures, with thick hyaline fibers, as well as due to the negative staining of the malignant cells for CD10, corroborated with the paucity of hyperplastic follicular dendritic cells.

Hypereosinophilia develops as the malignant lymphoma cells secrete various cytokines and growth factors which stimulate the bone marrow to induce the differentiation of granulocyte precursors toward eosinophils as confirmed for NK lymphomas, T-cell/histiocyte-rich B cell lymphomas or anaplastic large cell lymphomas [14].

In the clinical settings, the assessment of eosinophilia relies on the investigation of the underlying cause, as well as whether any end-organ damage or dysfunctions are present. Physicians start with a detailed medical history and evaluate the presence of allergic disorders like asthma, eczema or urticaria, in parallel with any cardiovascular or gastrointestinal symptoms. A detailed travel history is taken, to exclude any tropical infections or parasites, as well as a thorough drug history. HE and HES are defined as eosinophil counts greater than 0.5 x 10^9/L, for at least 6 months and for which no primary cause is identified, associated with signs of organ involvement and dysfunction. The peripheral blood smear may identify a central or peripheral cause of hypereosinophilia, as well as a morphologic evidence of an underlying hematological malignancy: blast cells, circulating lymphoma cells, neutrophilia or left shift of the cellular subpopulation. Unfortunately, up to this diagnostic step, this was not the case for our patient, for whom a biopsy of a lymph node was required.

Elevated eosinophils count has been associated with cancer before; Montgomery et al. (2013) identified this paraneoplastic syndrome in 0.5-7% of cancers [15], even if it is usually present in a more advanced metastatic disease. Workup of a suspicion of persistent eosinophilia as a paraneoplastic syndrome requires thorough clinical investigation, including radiologic surveys, as it was the case for our patient. Even if hypereosinophilia was identified in malignancies before, its association with T-cell lymphomas was rarely reported before and is probably linked to the eosinophils connection with the neoplastic clone. This is the case of unexplained isolated hypereosinophilia, chronic eosinophilic leukemia, chronic myelomonocytic leukemia with eosinophilia or atypical chronic myeloid leukemia with eosinophilia. No relevant genetic aberrations were present in our patient, thus clonality could not be proven and hypereosinophilia is most probably a paraneoplastic syndrome, associated with various cytokine secreted by the malignant T lymphoma cell. In such cases, therapy should be directed at the underlying case immediately after the emergency end-organ damage or managed using steroids for HES.

Conclusion

There is no absolute consensus for the number of eosinophils in the peripheral blood at which treatment is required, as the number of eosinophils does not correlate with the severity of end-organ damage. However, immediate treatment should be initiated in such cases using corticosteroids, followed by a detailed investigation of the case and treatment of the underlying cause. The case we reported is relevant for the clinical hematology setting. Our patient presented with hypereosinophilia as a paraneoplastic syndrome, for which the differential diagnosis was difficult; correct diagnosis, as well as appropriate therapy and follow-up is of utmost importance for the patient outcome.

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