sciendo
Internal Medicine 2018 vol. XV No. 4 - www.srmi.ro 61
10.2478/inmed-2018-0031

HYPEREOSINOPHILIC SYNDROME OF UNDETERMINED SIGNIFICANCE – DIFFICULTIES IN CLINICAL AND THERAPEUTIC APPROACH

Vlad Florin Anton[1], Polliana Mihaela Leru[1,2]
[1]Colentina Clinical Hospital
[2] Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
Correspondence author: Polliana Mihaela Leru, Colentina Clinical Hospital, Internal Medicine Department, Sos. Stefan cel Mare 19-21, District 2, 020125, Bucharest, Romania, email: polianaleru@yahoo.com

Abstract

We report a case of a 69-year-old woman who is followed since seven years for persistent blood hypereosinophilia up to 5100 /mmc. She has been extensively investigated for other diseases known to induce hypereosinophilia, including allergies, parasitic infections and neoplasia. No end-organ dysfunction could be confirmed. We considered a possible primary hypereosinophilic syndrome (HES) and determined the genetic mutation FIP1L1- PDGFRA characteristic for HES, which was negative.

Bone marrow showed reactive eosinophilia with no malignant cells and rare mast cells, less than 15 in aggregates, which is the major criterion for diagnosing mastocytosis. Knowing the association between HES and mastocytosis, we measured and found high serum tryptase levels and positive c-kit D816V genetic mutation, characteristic for systemic mastocytosis. The patient was closely monitored, with regular hematologic and clinical evaluation, mainly for cardiac and neurologic manifestations.

A short trial of high dose corticotherapy induced remission of hypereosinophilia, but this could not be maintained with lower doses. The clinical outcome during follow-up period was rather good, except mild cognitive decline and atrial fibrillation.The reported case is illustrative for versatile presentation and difficulties in management of hypereosinophilia in clinical practice.

Keywords: *blood hypereosinophilia, serum tryptase, systemic mastocytosis*

Rezumat

Prezentăm cazul unei paciente în vârstă de 69 de ani, cunoscută de șapte ani cu hipereozinofilie plasmatică persistentă, cu valori pana la 5100/mm^3. Pacienta a fost multiplu investigată pentru sindrom hipereozinofilic reactiv și nu s-au putut diagnostica boli alergice, parazitare sau neoplazice. Nu s-au putut confirma afectări organice secundare hipereozinofiliei.

Internal Medicine

Clinical cases

Evaluarea hematologică a evidențiat maduvă cu eozinofilie reactivă, iar imunohistochimic nu s-au găsit elemente de clonalitate. Am luat în considerare un posibil sindrom hipereozinofilic primar (HES) și am căutat mutațiile genetice asociate acestuia, care au fost negative. Cunoscând asocierea dintre HES și mastocitoza sistemică, s-a dozat triptaza serică, care a avut valori crescute, iar mutația genetica c-KIT D816V, caracteristică mastocitozei, a fost pozitivă.
S-a efectuat o cură scurtă de corticoterapie cu solumedrol, obținând scădere promptă a eozinofiliei plasmatice, dar aceasta nu s-a menținut după reducerea dozelor. Evoluția clinică a pacientei în ultimii ani a fost relativ bună, exceptând ușor declin cognitiv și fibrilație atrială, tratată cu anticoagulante orale noi. Particularitatea cazului constă în prezentța eozinofiliei cu semnificatie incertă la o pacientă cu posibilă mastocitoză sistemică, greu de încadrat clinic și dificil de tratat.
***Cuvinte cheie**: hipereozinofilie plasmatică, mastocitoză sistemica, triptază serică.*

Introduction

Blood eosinophilia is a frequent condition in medical practice, due to a broad spectrum of diseases, usually reactive to allergies or parasitic infections and more rarely primary or idiopathic. Blood hypereosinophilia is defined as elevation of the absolute eosinophil count (AEC) above the limit of 500/mm3 and has three levels of severity: mild between 500-1500 /mm3, moderate between 1500-5000/mm3 and severe more than 5000/mm3[(1)].

Hypereosinophilia can be secondary or reactive to many diseases, most frequently to allergic diseases and parasitic infections, but also to other viral, bacterial or fungal infections, autoimmune, inflammatory, hematologic or neoplastic diseases[(2)]. Hypereosinophilia is considered primary when is persistent and associated with end-organ eosinophilic infiltration and dysfunction, but no etiology can be identified. The term hypereosinophilic syndrome (HES) is used to describe this condition, which has generally poor prognosis, according to diagnosis criteria established by Chusid in 1975[(3)].

Hypereosinophilia is classified as of undetermined significance or associated when persistent eosinophilia is not accompanied by signs of end-organ dysfunction[(4)]. A subset of patients with HES may be associated or have some features of

systemic mastocytosis, which is another rare disease, characterized by pathologic increase in mast cells in various tissues including skin, bone marrow, liver, spleen, and lymph nodes[4]. Diagnosis of mastocytosis is suspected on clinical picture, which is heterogeneous and confirmed by defined laboratory major and minor criteria, including histopatologic examination of bone marrow. WHO criteria for Systemic Mastocytosis issued in 2016 are[5]:

Major SM criterion - Multifocal dense infiltrates of MCs (≥15 MCs in aggregates) in BM biopsies and/or in sections of other extracutaneous organ(s)

Minor SM criteria

a. >25% of all MCs are atypical cells (type I or type II) on BM smears or are spindle-shaped in MC infiltrates detected on sections of visceral organs
b. *KIT* point mutation at codon 816 in the BM or another extracutaneous organ
c. MCs in BM or blood or another extracutanous organ exhibit CD2 and/or CD25
d. Baseline serum tryptase level >20ng/mL (in case of unrelated myeloid neoplasm, item d is not valid as a SM criterion)

Case presentation

We report a case of a 69-year-old woman who is monitored since 2011 in the Internal Medicine Clinic of our hospital for persistent blood hypereosinophilia, ranging from 2140 /mm3 up to 5100 /mmc, discovered on the occasion of routine medical control. It was first considered due to hepatitis virus C chronic infection, revealed one year before presentation, but with normal hepatic tests and negative HCV-RNA. A detailed history was obtained at first presentation and revealed no familial or personal significant diseases, she took no medication able to induce eosinophilia. No particular signs and symptoms could be found during regular medical examinations. The recommended evaluation of hypereosinophilia was considered according to the most recent data from the literature[6]. The patient has been extensively investigated for diseases known to induce hypereosinophilia, including allergies, parasitic infections, autoimmune diseases and neoplasia. We found normal total serum IgE, moderate increase of eosinophil cationic protein (ECP), which is marker of eosinophils activation, below 200 ng/ml and inconsistent increase of serum vitamin B12. No end-organ dysfunction could be confirmed. We performed bronchoalveolar lavage and biopsies of gastro-intestinal tract and excluded pulmonary and gastrointestinal eosinophilia. Full – body computed tomography and tumoral markers were normal.

Bone marrow examination was performed at two-years intervals and showed reactive eosinophilia, with no malignant cells and rare mast cells. The possibility of HES was considered and we investigated the presence of characteristic genetic mutations – FIP1L1/PDGFRA (F/P), PDGFRB and FGFR1, which were negative. Immunophenotypic findings in peripheral blood identified two abnormal T lymphocytes subpopulations with low CD2 (24%) and CD5 (18%) without clonal proliferation.

A short corticotherapy trial with solumedrol was performed, leading to prompt decrease of blood eosinophilia, but the result could not be maintained with lower doses and no other cytoreductive therapy was approved by hematologist. Due to known association of HES with elevated serum tryptase in a subset of patients, we measured and found increased values of serum tryptase – 27

microg/L (normal range <11microg/L), which is one of the three minor criteria for systemic mastocytosis. The genetic mutation c-kit D816V characteristic for mastocytosis, which is another minor diagnosis criterion, was found positive.

The repeated bone marrow examination confirmed the presence of rare mast cells, less than 15 in aggregates, which is the major criterion for diagnosing mastocytosis. The patient was closely monitored, with regular hematologic and clinical evaluation, mainly for cardiac and neurologic manifestations, which are severe complications of HES. We recently recorded atrial fibrilation and mild cognitive decline, treated with new oral anticoagulant drugs, but causal relation with hypereosinophilia and mastocytosis could not be confirmed, due to relative advanced age.

Therapy with sodium cromoglycate 400 - 600 mg/day, indicated in systemic mastocytosis for their capacity to reduce mast cells degranulation, was given for few months, with no clear benefit. Blood eosinophilia had variable values between 2680 – 1500/mm.

Based on clinical and hematologic picture plus the presence of genetic mutation, we considered that the positive diagnosis is systemic mastocytosis with hypereosinophilia and we closely monitored the possible organ dysfunction and complications. No other more aggressive treatment could be given, due to lack of organ dysfunction and still unclear hematologic pattern, needing further hematological evaluation.

Discussion

The differentiation between HES associated with high tryptase (HES-tryptase) and systemic mast cell disorder with hypereosinophilia (SMCD-eos) is difficult, but important, due to different clinical outcome and therapeutic approach. Data from the literature showed that patients with HES-tryptase develop end-organ damage due to eosinophilic infiltration, while clinical picture of systemic mastocytosis is related to mast cell tissue infiltration and histamine release[7].

We considered that the most probable diagnosis of reported case is SMCD-eos rather than HES-tryptase, despite missing of typical clinical picture and of dense bone marrow infiltration with dysplastic mast cells. Diagnosis confirmation needs more careful analysis of the bone marrow and performance of more advanced cytogenetic and molecular tests.

Therapeutic approach of hypereosinophilic syndromes depends on degree of eosinophilia, associated end-organ dysfunction, underlying mechanisms and presence of characteristic genetic mutations[8].

Corticosteroids are the most effective therapeutic agents in the majority of

hyperoeosinophilic syndromes, but some HES variants are less responsive and need another cytoreductive therapy, such as hydroxyurea[9]. Tyrosine kinase inhibitor imatinib is recommended as first line therapy in myeloproliferative HES patients with F/P mutation, due to molecular mechanism of hypereosinophilia[10].

Therapeutic choice in undetermined or associated forms of HES may be difficult, depending on clinical picture and availability of more advanced therapies.

Conclusions

The reported case is illustrative for versatile presentations and difficulties in management of hypereosinophilia in clinical practice. Clinicians must be aware of rare diseases such as hypereosinophilic syndromes and mastocytosis and carefull consider associated or overlap forms.

Conflict of interest

The authors declare that they have no conflict of interest in relation with this manuscript.

Patient consent for publication

The patient gave written informed consent for publication of this medical report. A copy of the written consent is available for review by the editor of the journal.

References

1. Gotlib J. World Health Organization-defined eosinophilic disorders: 2014 update on diagnosis,risk stratification and management. Annual Clinical Update in Hematological Malignancies. Am J Hematol. 89; 326-337, 2014.

2. Simon HU, Rothenberg ME, Bochner BS, et al. Refining the definition of hypereosinophilic syndrome. J Allergy Clin Immunol. 2010;126(1):45-49

3. Chusid MJ, Dale DC, West BC, Wolff SM. The hypereosinophilic syndrome: analysis of fourteen cases with review of the literature. Medicine (Baltimore). 1975; 54: 1-27.

4. Escribano L, Akin C, Castells M, Orfao A, Metcalfe DD. Mastocytosis : current concepts in diagnosis and treatment. Ann Hematol 2002, 81: 677-690

5. Valent P, Akin C and Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts, BLOOD, 16 March 2017, Volume 129, Number 11

6. Valent P, Klion AD, Horny HP et al. Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. J Allergy Clin Immunol. 2012; 130: 607-612.

7. Klion AD, Noel P, Akin C et al. Nutman Elevated serum tryptase levels identify a subset of patients with a myeloproliferative variant of idiopathic hypereosinophilic syndrome associated with tissue fibrosis, poor prognosis, and imatinib responsiveness. Blood 2003, Vo.101, Number 12

8. Curtis C, Ogbogu P. Hypereosinophilic Syndrome. Clinic Rev Allerg Immunol. 2015,

9. Klion AD, Bochner BS, Gleich GJ et al. The Hypereosinophilic Syndromes Working Group. Approaches to the treatment of hypereosinophilic syndromes: a workshop summary report. J Allergy Clin Immunol.2006; 117: 1292-1302.

10. Cools J, DeAngelo DJ, Gotlib J et al. A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. N Engl J Med. 2003; 348; 1201-1214.