Hypereosinophilic syndrome with severe cardiac involvement and fatal outcome. Case report and review of the literature

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Abstract: We report a case of a 58 years old woman who presented for clinical picture consisting in skin rash, pruritus, astenia, mialgia, with progressive onset during the last month and recently discovered blood hypereosinophilia. The patient was exhaustively investigated and secondary causes for hypereosinophilia were excluded, mainly allergies, parasitic infections, autoimmune and neoplastic diseases. On hospital admission the patient had no symptoms or personal history suggesting cardiac disease. The initial electrocardiography and echocardiography had minimal changes, but cardiac markers such as proBNP and troponin had high values. The clinical evolution was initially good, with moderate dose corticosteroid therapy, but eosinophilia, leukocytosis and cardiac markers continued to increase, followed by progressive cardiac ischemia and ultrasound changes. We considered a rare case of primary hypereosinophilic syndrome with severe cardiac involvement and we switched to high dose corticosteroid followed by add-on therapy with hydroxyurea. Blood eosinophilia decreased, but cardiac markers and ischemia continued to aggravate and unfortunately the patient died due to sudden cardiac arrest, after three weeks from hospital admission. We concluded that hypereosinophilic syndrome with early and progressive cardiac involvement is a severe and difficult to manage disease, with high fatality risk, that requires complex investigations, multidisciplinary approach and prompt therapy.

Key Words: cardiac involvement, fatal outcome, hypereosinophilic syndrome.

Hypereosinophilic syndromes (HES) represent a heterogeneous group of nonhematologic (secondary or reactive) and hematologic (primary, clonal) disorders with potential for end-organ damage [1]. The actual definition of HES is based on diagnosis criteria formulated by Chusid in 1975: blood hypereosinophilia (HE) over 1500/mm³, persisting for at least 6 months, accompanied by one or more organs involvement and without evidence of any other cause of eosinophilia, such as allergic diseases or parasitic infections [2].

The classification of hypereosinophilic diseases is based on 2008 World Health Organization scheme of disease subtypes, including myeloid and lymphoid neoplasms associated with eosinophilia and presence of genetic abnormalities such as activated fusion proteinkinases, mostly FIP1-like 1-platelet –derived growth factor receptor – alfa (PDGFRA)[3]. A new terminology was proposed in 2011 by the Working Conference on Eosinophil Disorders and Syndromes, dividing the eosinophilic syndromes in: familial HE variant, HE of undetermined significance, primary (clonal/neoplastic) HE, and secondary (reactive) HE [4].

Until a primary or secondary cause of eosinophilia is found, HES may be considered a provisional diagnosis. Idiopathic HE is the recommended term when tissue and organ damage is absent. Anderson and Hardy mentioned in the literature the first description of the primary hypereosinophilic syndrome, in 1968 as a severe disease characterized by fever, sweats, weight loss and cardiac failure accompanied by marked hypereosinophilia. Primary HES is a rare and severe disease, more frequent

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in men (sex ratio male/female = 9/1), with onset in adults aged 20-50 years, clinically characterized by systemic symptoms such as fever, rash, marked asthenia, mialgia, complicated with cardiac failure and neurologic signs and symptoms, with high mortality.

Primary HES may be diagnosed after exclusion of a reactive (secondary) hypereosinophilia and based on distinct clinical and laboratory features, such as the presence of genetic mutation of fusion tyrosine kinase FIP1L1/ PDGFRA (F/P). The clinical subtypes of HES described in the literature are: myeloproliferative variant, associated with F/P mutation and usually good response to imatinib and lymphoproliferative variant, generally responsive to corticotherapy or some steroid-sparing agents such as hydroxyurea. About 50% of patients cannot be classified in any of the two subtypes even after comprehensive evaluation. Based on the main clinical manifestations, they can be included in three groups: benign (without evidence of end organ involvement), complex (with evidence of multisystem involvement) and episodic.

Many organ systems are affected in HES, but cardiovascular complications are most prevalent and responsible for high morbidity and mortality (5). The most frequent clinical manifestations of cardiac disease in HES are intracardiac thrombus, heart failure, arrhythmias, embolic events, myocardial ischemia, acute myocardial infarction, rarely pericarditis.

**CASE PRESENTATION**

We report a case of a 58 years old woman who presented to our clinic for skin rash, pruritus, astenia, intermittent fever and mialgia, with progressive onset during the last month and recently discovered blood hypereosinophilia and leukocytosis. She had a personal history of chronic urticaria aggravated by beta lactamic antibiotics and nonsteroidal antiinflammatory drugs, but with no recent use of any of these medication. She was recently diagnosed with hyperthyroidia, not treated due to possible allergic reactions. On hospital admission the patient had no symptoms or personal history suggesting cardiac disease, blood eosinophilia was 13.700/uL and leukocytosis 34.040/uL. The initial electrocardiography (ECG) and echocardiography were almost normal, but cardiac markers such as proBNP (brain natriuretic peptide) and troponin had significant high values. The patient was exhaustively investigated according to international actual algorithm for diagnosis of hypereosinophilic syndromes [1]. Secondary causes for hypereosinophilia were excluded, mainly actual allergies, parasitic infections, autoimmune and neoplastic diseases. Hyperthyroidia was confirmed and antithyroidian therapy with thiamazol 20 mg daily was given for one week, but withdrawn due to thrombocitopenia and not concluent further tests. Bone marrow examination showed mature eosinophils, no atypic cells. Serum tryptase, total serum IgE and vitamin B12 were normal, the genetic mutation FIP1L1/ PDGFRA was negative. Eosinophilic cationic protein (ECP) in plasma, an important marker of activated eosinophils, was very high. The clinical evolution was initially good, with remission of skin lesions and slight improvement of general symptoms, after one week of...
moderate dose corticotherapy. Blood eosinophilia continued to increase at very high values up to 49,980 eosinophils/μL, also did leukocytosis and cardiac markers, followed by progressive cardiac ischemia on ECG and ultrasound changes.

We administered high corticosteroid doses for another one week, with significant reduction of blood eosinophilia. The result was not maintained after dose reduction and cardiac markers and ischemia continued to aggravate. Since immunophenotypically aberrant T-cell population and atypical eosinophils were identified in blood, we considered that it was a case of primary hypereosinophilic syndrome with not typical or overlapped lymphocyte variant and severe cardiac involvement. The clinical evolution was complicated by acute gastric ulcer and melena possibly due to corticotherapy. Cytoreductive therapy with hydroxyurea was later added, with prompt decrease of blood eosinophilia and leukocytosis, but cardiac markers and ischemia continued to aggravate. Unfortunately the patient died due to sudden cardiac arrest, after three weeks from hospital admission. Advanced cardiac investigations such as coronarography, endomiocardial biopsy or cardiac magnetic resonance imaging (CMRI) could not be performed. The medical-legal autopsy was refused by the patient family.

**DISCUSSION**

The acute and severe evolution of the reported HES case, with rapid progression of cardiac involvement and fatal outcome in less than one month rises many problems regarding clinical presentation, laboratory diagnosis and treatment of HES in clinical practice.

The duration of hypereosinophilia persistance for more than 6 months as one of HES criteria is now considered less consistent, mainly due to availability of more advanced tools for rapid evaluation. Data from the literature point out the need for early and adequate treatment in order to minimize the end-organ damage. The new definition of HES does not require a previous 6 months period of hypereosinophilia and also includes...
patients with identified aetiologies and those who have not developed signs and symptoms at the time of diagnosis [4]. It was proven that absolute eosinophil count does not correlate in a consistent fashion with eosinophil-mediated tissue damage [6]. Therapy is usually monitored on the basis of a combination of clinical manifestations and absolute eosinophil count, since no validated markers of disease progression are available. Some of the used markers of hypereosinophilia progression are: serum concentration of cationic eosinophilic proteins (ECP, MBP, EPO, EDN), expression of surface activation markers, presence of abnormal genes (FIP1-L1, PDGFRA), serum tryptase level, presence of T-cell abnormalities [7]. Eosinophilic organopathy due to extensive deposition of cationic proteins, mainly MBP may be confirmed by histopathologic examination of injured organs. The lymphocytic variant of HES is characterized by the presence of clonal populations of abnormal T cells producing interleukin-5, that stimulate the production and activation of eosinophils [8].

Chronic eosinophilic leukemia (CEL) is diagnosed based on the presence of increased blasts cells (but less than in acute leukemia), evidence of clonality or the presence of a fusion gene, particularly the fusion of FIP1L1 and PDGFRA caused by a deletion on chromosome 4q12. This fusion gene encodes for a protein with substantial tyrosine kinase activity which has important implications for therapy [9].

Cardiovascular involvement has an overall prevalence in HES of more than 50%, being rare in the lymphocytic variant, but often occurs in the myeloproliferative forms [10]. Three stages of cardiac pathology in HES has been described: acute necrosis, thrombosis and fibrosis [11]. It was mentioned in the literature that the acute necrotic stage is observed when the duration of illness is short, with a mean duration of 5.5 weeks, while the thrombotic stage occurs when the mean duration of eosinophilia is 10 months. The late fibrotic stage is described after approximately 24.5 months of disease duration [11]. The acute necrotic stage is characterised by eosinophilic infiltration of the myocardium associated with myocardial necrosis due to release of toxic cationic proteins from degranulating eosinophils [12]. Since the patient may have no cardiac symptoms and electrocardiography and echocardiography are not changed, it is often difficult to diagnose cardiac disease at early stage [5]. Endomyocardial biopsy may be required for early diagnosis, although cardiac magnetic resonance (CMR) imaging is considered useful in demonstrating preclinical involvement. The acute myonecrosis is followed by formation of mural thrombi, often involving both ventricles, the ventricular outflow tracts and the subvalvular regions, leading to atrioventricular valvular incompetence [13]. The intermediate phase, called thrombotic stage, is characterised by mural thrombi and thrombus formation along the damaged endocardium and formation of granulation tissue that replaces the normal endocardium. The third stage is characterized by fibrotic changes, in which the granulation tissue is changed into hyaline fibrosis. It is mentioned that patients with HES may not be diagnosed with cardiac involvement until this final stage of their disease, when they present with scarring of the chordae tendinae and endocardium, leading to a restrictive or dilated cardiomyopathy and progressive valvular incompetence [14]. The fibroplastic parietal endocarditis with blood eosinophilia was first mentioned and described by Loeffler in 1936 [15]. The term Loeffler’s endomyocarditis is used now to describe the cardiac involvement in HES, especially in the thrombotic and fibrotic stage. Some authors consider this cardiac involvement to be secondary to hypereosinophilia itself, irrespective of the underlying condition, [16].

Possible risk factors for cardiac disease in HES are: male sex, HLA-Bw44 positivity, thrombocytopenia, elevated serum vitamin B12, dysplastic eosinophils and the presence of abnormal early myeloid precursors [11]. Data from the literature suggest that these features are characteristic of a myeloproliferative variant of HES that includes chronic eosinophilic leukemia (CEL) associated with the FIP1L1-PDGFRα (FP) fusion tyrosine kinase [17]. Differential diagnosis of cardiac disease with peripheral eosinophilia includes HES, Churg-Strauss syndrome (CSS), early giant-cell myocarditis, hypersensitivity reactions to drugs or other agents, parasitic infections, Loeffler or tropical endomyocardial fibrosis and malignancy. Laboratory diagnosis of HES-associated cardiac disease includes electrocardiography, echocardiography, CMR imaging and endomyocardial biopsy, which remains the diagnostic gold standard [18]. The increase of serum troponin level may indicate the initial phase of acute myocarditis or the necrotic stage, with normalization after initiation of high dose corticosteroids, suggesting that troponin is a possible sensitive marker for the cardiac damage and cardiac decompensation [19].

The management of HES with cardiac involvement should consider first the presence of FP mutation, since most of the positive cases have good response to imatinib therapy, which should be started before the occurrence of irreversible structural changes.

**CONCLUSION**

We reported a case of hypereosinophilic syndrome with severe cardiac involvement and fatal outcome, that could not be included in one of the well defined subtypes of HES, based on available investigation tools. Some aspects consistent with lymphocytic variant of HES were identified, such as history of atopy, early cutaneous manifestations and phenotypically aberrant T cell population, but cardiac involvement is more frequent in the myeloproliferative subtype of HES. The acute evolution
and severe cardiac involvement led to fatal outcome, despite initial good hematologic response to cytodestructive therapy, showing the need for early aggressive therapy, irrespective the cause or subtype of HES. We concluded that severe cardiac involvement in hypereosinophilic syndromes is a very difficult to manage pathology, with significant fatality risk, that requires trained staff, complex investigations and prompt therapy. Management of patients with hypereosinophilic disorders in clinical practice need multidisciplinary approach, requiring specialized medical centers and availability of advanced diagnostic technologies.

Conflict of interest. The authors declare that they have no conflict of interest relating to this work and manuscript.

References

Authors’ contribution. PML is the allergist who diagnosed and treated the patient during the first two weeks, collected the data, obtained the informed consent, drafted and approved the manuscript and choose the journal for publication. VFA is the specialist in training who participated to the medical care of the patient and contributed to collecting the data. CB is the internal medicine specialist who coordinated the medical assistance during the last week of hospitalization and approved the manuscript.

Patient consent for publication. The patient agreed and signed written informed consent for publication of this case report. A copy of the patient written informed consent is available for review by the chief Editor of this journal.