Hypereosinophilic Syndrome Associated with Simultaneous Intracardiac Thrombi, Cerebral Thromboembolism and Pulmonary Embolism

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Abstract

The hypereosinophilic syndrome (HES) is a subcategory of idiopathic eosinophilia which is characterized by marked unexplained eosinophilia and evidence of tissue eosinophilia which leads to eosinophil-mediated organ damage. Cardiac and thromboembolic complications of HES are the common causes of mortality and morbidity. Here, we report a 54-year-old woman with HES who presented with simultaneously occurring cardiac thrombi, pulmonary embolism, and cerebrovascular thromboembolism.

Key words: hypereosinophilic syndrome, HES, cardiac thrombi, pulmonary embolism


Introduction

Acquired eosinophilia is categorized into three types; secondary, clonal, and idiopathic. Hypereosinophilic syndrome (HES), a subcategory of idiopathic eosinophilia, is defined by the presence of a peripheral blood eosinophil count of 1.5×10^9/L or greater for at least 6 months (a shorter duration is acceptable in the presence of symptoms that require eosinophil-lowering therapy), exclusion of both secondary (including parasitic or viral infections, allergic diseases, drug-induced or chemical-induced eosinophilia, hypoadrenalism) and clonal eosinophilia, evidence of organ involvement, and absence of phenotypically abnormal and/or clonal T lymphocytes (1). The recent classification of HES is associated with the Fip1-like1-platelet-derived growth factor receptor alpha chain (FIP1L1-PDGFRA) mutant kinase (2). It occurs mostly in men and between the ages of 20 and 50. Tissue infiltration with eosinophils usually occurs in multiple organs (3). Cardiac and thromboembolic manifestations of HES are the common causes of mortality and morbidity. Among the patients with HES, the frequency of cardiac manifestations is 40%-50% (4). We describe here a case with HES who presented with cardiac thrombi, pulmonary embolism and cerebrovascular thromboemboli at the same time.

Case Report

A 54-year-old woman was admitted to our department for leukocytosis (23,600/μL) and eosinophilia (8,820/μL) in April 2010. She had a coronary artery bypass graft (CABG) and left ventricular thrombectomy operation in February 2010. The weight of the retrieved thrombectomy material was 19 grams, and the histopathological examination revealed a fibrin mass with no reported eosinophilic infiltration. After the operation, antiplatelet therapy with acetylsalicylic acid (ASA) 150 mg/daily and clopidogrel, and anticoagulation with warfarin sodium were initiated. She had a percutaneous transluminal coronary angioplasty (PTCA) four years previously, and a second PTCA was performed only ten days after the first one due to stent obstruction. She had no clinical history of asthma, allergic diseases, parasitic infections, varicose veins, or hormone replacement therapy.
Figure 1. Thoracic CT revealing embolism in the left pulmonary artery, and thrombi in the left ventricle (arrows).

Figure 2. The echocardiography showing thrombi in the left ventricle and atrium (arrows).

The work-ups for parasitic, malignant, allergic, and rheumatological diseases were negative. A bone marrow aspiration and biopsy was performed, which showed no specific findings for myeloproliferative neoplasms (MPNs); both the aspiration and biopsy were positive for tryptase staining, but there were no specific findings for mastocytosis. The serum tryptase level was also within the normal limits. Janus kinase 2 (JAK-2) V617F and BCR-ABL were found to be negative by polymerase chain reaction (PCR). Flow cytometric evaluation showed no clonality, and FIP1L1-PDGF alpha fusion was negative by fluorescence in situ hybridization (FISH). She was heterozygous for methylene tetrahydrofolate reductase (MTHFR) C677T mutation, but negative for factor V Leiden, and prothrombin G20210A mutations. Anti-thrombin 3 activity, anti-cardiolipin antibodies, anti-beta 2 glycoprotein antibodies, protein C and S levels were normal. Serum vitamin B12 and IgE levels were within the normal limits. She was diagnosed as hypereosinophilic syndrome (HES) since she had an eosinophil count >1.5×10^9/L for more than 6 months, with possible cardiac involvement and no other demonstrated causes of eosinophilia. Corticosteroid treatment was initiated, the eosinophil count decreased to 970/μL after four weeks. There was no thrombi in the control echocardiography. The corticosteroid dosage was tapered due to the side effects of the therapy. During the follow-up her left leg became swollen and she was admitted to the emergency department with dyspnea, cough and hemoptysis in September 2010. The laboratory analysis revealed hypocarbia, and leukocytosis (28,320/μL) with eosinophilia (2,520/μL). D-dimer value was 6.2 mg/L (normal range, 0-0.5 mg/L) and C-reactive protein was 53.1 mg/L (normal range, 0-5 mg/L). Thoracic computed tomography (CT) showed pulmonary embolism in the distal branches of both pulmonary arteries, infarction areas in the lung parenchyma and thrombi in the left atrium, ventricle, thoracic and abdominal aorta (Fig. 1). Doppler ultrasonography of the lower extremities did not reveal deep vein thrombosis (DVT). Due to blurred vision, a fundus examination was performed which was bilaterally normal, and the cranial magnetic resonance imaging (MRI) showed acute infarction areas in the left parietal, subcortical white matter and centrum semiovale. Low molecular weight heparin (LMWH) treatment was initiated and corticosteroid treatment was increased to the maximum dosage. Repeated troponin I levels were normal, and electrocardiogram showed only sinus tachycardia. The echocardiography revealed anteroseptal, apical, anteroapical akinesis and thrombi in the left ventricle (4.5×2.4 cm) and atrium, and mild-moderate mitral regurgitation (Fig. 2). Cardiac MRI showed thinning and fibrosis of the septal and apical left ventricular segments, and thrombi in both the left ventricle and atrium. There was no hyper-enhancement of the left ventricle which is a sign of active inflammation of the myocardium (Fig. 3 and 4). During the follow-up, she developed erythematous, pruritic, papular skin lesions in the posterior side of left cruris and left ankle. The eosinophil count decreased to 770/μL with the corticosteroid treatment, but increased to 4,420/μL although the same corticosteroid dose was administered for two weeks, therefore hydroxyurea (HU) treatment (1,000 mg/day) was added to corticosteroid therapy. After the initiation of HU, the eosinophila was resolved (850/μL) after 4 weeks of treatment. Corticosteroid therapy was gradually withdrawn, and antiplatelet and anticoagulation therapies were recommended lifelong. At the time of this writing, she had received HU for 12 months with a dose of 1,000 mg/daily, and there was no new thromboembolic complications. The leukocyte count was 8,460/μL (eosinophils 780/μL), hemoglobin level was 12.9 g/dL and platelet count was 133,000/μL in September 2011. The course of the disease, the complications and the treatment modalities are displayed in Table 1.

Discussion

HES is characterized by persistent eosinophilia and eosinophil-mediated organ-system damage. Tiredness, cough, breathlessness, muscle pains, angioedema, rash, fever, retinal lesions, sweating, pruritus are the most common presenting
symptoms. The present patient initially presented with ischemic heart disease. Eosinophilia, and elevated leukocyte count are the most common hematologic manifestations in patients with HES. Cardiac involvement and thromboembolic complications are common causes of mortality and morbidity in patients with HES. Congestive heart failure (CHF), and complications of endomyocardial damage are the causes of most deaths in HES patients (3). The cardiac pathology of the disease has been divided into three stages: acute necrosis, thrombosis, and fibrosis. Heart failure, intracardiac thrombus formation, myocardial ischemia, arrhythmias, pericarditis, and syncope are the clinical manifestations of cardiac involvement (4). Chusid et al reported cardiac mural thrombi in 16 of 39 (41%) HES cases as an autopsy finding. Fifteen percent of those patients who died from myocardial infarction and CHF had myocardial necrosis associated with thrombi in the smaller coronary vessels, but pulmonary embolism was rare (5). The present patient had an intracardiac thrombus, and myocardial ischemia as the clinical manifestations of cardiac involvement. Male sex, HLA Bw44 positivity, splenomegaly, thrombocytopenia, elevated serum vitamin B12 level, dysplastic eosinophils, the presence of abnormal early myeloid precursors are regarded as the risk factors for cardiac disease in HES (3). It is predicated that HES patients without cardiac disease tend to be female, and these patients usually present with angioedema or urticaria, hypergammaglobulinemia, elevated serum levels of IgE, and circulating immune complexes (3). Although presenting with cardiac involvement, the present patient is female, she had pruritic papular lesions during the course of her disease, and serum immunoglobulin levels including IgE were normal.

The major goal of treatment in patients with symptomatic HES, is to debulk the blood and tissue eosinophil burden. In patients with organ involvement, the initial treatment is with prednisone (1 mg/kg/day). Glucocorticoids and other immunosuppressive drugs decrease the eosinophil counts and prevent end-organ damage by inhibiting the production of the inflammatory mediators such as eosinophil peroxidase, major basic protein, eosinophil cationic protein, eosinophil derived neurotoxin (1). After continuing glucocorticoids for 1 to 2 weeks, the glucocorticoid dosage is tapered slowly in 2 to 3 months. If symptoms recur with a prednisone dosage of greater than 10 mg/day, either HU (starting dosage, 1,000 mg/daily) or interferon alfa (INF-α) (starting dosage, 1 million units subcutaneously 3 times a week) are used as the corticosteroid sparing agents (1). Vincristine, etoposide, chlorambucil, cladribine, and cyclosporin are the other therapeutic options that can be used in order to debulk the blood and tissue eosinophil burden (3). Imatinib mesylate (IM) and two humanized monoclonal antibody drugs (mepolizumab and alemtuzumab) can be used in the selected treatment resistant cases. Imatinib is the drug of choice for the patients with FIP1L1-PDGFRA(FP) mutation (1, 3). The present patient did not have FIP1L1-PDGFRA(FP) mutation, so IM was not a treatment option, and since she had depression, we did not administer her INF-α.

Reducing the eosinophil count and optimizing the cardiac function by medical treatment or surgical procedures including valve replacement, thrombectomy, endomyocardectomy and heart transplantation are the treatment options for patients with cardiac involvement. Anticoagulant therapy should be used in patients with intracardiac thrombus and thromboemboli. The activity of the endomyocardial disease designates the duration of the anticoagulant therapy. In the case of an arterial thrombosis, ASA should be used, and venous thrombosis should be treated with anticoagulation (4).

The present patient had 2 PTCAs, and the second one was only 10 days after the first procedure. The repeated coronary thrombi may be due to local eosinophil infiltration or atherosclerotic disease as mentioned in the literature (4, 6, 7). She underwent a CAGB and then she was admitted to our hospital due to leukocytosis and eosinophilia which was noted by the preoperative work-up. If HES with cardiac involvement was considered in the differential diagnosis in the first place, medical treatment with glucocorti-
coids would be more appropriate, since aggressive treatment modalities such as PTCA and/or CABG are not recommended in these patients (1). Another clinical condition that has to be taken into account in our patient is, cholesterol crystal embolization (CCE). It refers to embolization of atheromatous material from ulcerated atherosclerotic plaques, and it is defined by the presence of cholesterol crystals within the lumen of blood vessels (8). CCE is usually a complication of radiology, vascular surgery, and/or anticoagulation, and although frequently involving the kidney and the skin, cholesterol emboli have been identified in almost every organ in the body (9). Most probably in our patient, CCE may not be the explanation of eosinophilia, because the leukocytosis and eosinophilia were present before the coronary angiography and CABG. Also the eosinophilia in our patient persisted for more than 6 months after CABG, which is unlikely in CCE. There was no renal failure in our patient which is a common finding in patients with CCE. Cutaneous involvement is virtually constant in CCE, (i.e. purple toes and/or lower limb livedo reticularis) which also was absent in our patient.

After the diagnosis of HES, our patient developed arterial thrombi in the left atrium, ventricle, pulmonary arteries and aorta during the corticosteroid treatment. The cardiac MRI showed thinning and fibrosis of the septal and apical left ventricle segments, but there was no sign of active endomyocarditis. We could not perform an endomyocardial biopsy however, the diagnosis of HES with cardiac involvement was made on the basis of the imaging, clinical, and laboratory findings.

The present patient was symptomatic, and showed evidence of organ dysfunction. She was in the complex subgroup of the undefined HES category, since she was FIP1L1-PDGFRA negative, and she did not show any evidence of T or B cell clonality. Serum tryptase level was normal and there was no cytopenia(s). The bone marrow biopsy did not show abnormal mast cells, myelofibrosis, or increased bone marrow cellularity. Glucocorticoids and HU are the appropriate treatment modalities in this subgroup of patients, as we administered for our patient.

This case is interesting due to the repeated cardiac thrombi with synchronous detection of pulmonary embolism, multiple mural thrombi in aorta and cerebral thromboembolism developing under corticosteroid treatment. Although she had such serious, multiple thrombi in life-threatening organs, she had no severe complaints during the follow-up.

Physicians should be aware of the thromboembolic complications of HES. The initial evaluation of a patient with eosinophilia should focus on assessment of the target organ (i.e. cardiovascular) damage, and these tests include: complete blood cell count, chest radiography, electrocardiogram, echocardiography, and serum troponin level. Thromboembolic disease associated with HES is difficult to manage. The chronic suppressive treatment for eosinophilia should not be interrupted due to the risk of new thromboembolic events which can be life-threatening.

In conclusion, HES with thromboembolic events and cardiac involvement is usually difficult to manage. Patients should be monitored carefully for the potential complications of the disease and treatment should be managed according to the needs of each individual patient.

The authors state that they have no Conflict of Interest (COI).

References

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| Table 1. The Characteristics of the Patient during the Course of the Disease (ASA: Acetylsalicylic Acid, CABG: Coronary Artery Bypass Graft, HU: Hydroxyurea, LMWH: Low Molecular Weight Heparin) |

<table>
<thead>
<tr>
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<th>On admission (04/16/2010)</th>
<th>At the 4th week of corticosteroid treatment (07/19/2010)</th>
<th>At the beginning of HU treatment (09/15/2010)</th>
<th>At the 12th month of HU treatment (09/05/2011)</th>
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<tr>
<td>Leukocyte count</td>
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<td>Eosinophil count</td>
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<td>780/μL</td>
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