Hematological dyspnea: A rare cause with gratifying recovery

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ABSTRACT

A 17-year-old female was referred for evaluation of fever of two-month duration with acute onset of dyspnea since 1 week. Clinical examination revealed tachycardia, tachypnea, elevated jugular venous pressure, bilateral basal crepitations with normal heart sounds, and no murmur. Chest X-ray showed infiltrates in bilateral lung fields. Echocardiography revealed obliteration of biventricular apices along with layered thrombus over the left ventricular endocardium. Doppler studies elicited restrictive physiology with mild mitral and tricuspid regurgitation. Complete hemogram revealed hypereosinophilia with eosinophilic count of 7.4 × 10⁹/L. All secondary causes of elevated eosinophil count were excluded. The patient was started on steroids and anticoagulation. Serial echocardiograms showed clearing of the thrombus with marked symptomatic improvement. We highlight a case of idiopathic hypereosinophilic syndrome with classic cardiac (Loeffler endocarditis) and pulmonary manifestations and prompt recovery with steroids and anticoagulation.

<Learning objective: Idiopathic hypereosinophilic syndrome is a rare entity leading to multi-organ involvement. Cardiac involvement is one of the most common causes of morbidity and mortality. On the basis of this case report, we discuss Loeffler endocarditis in idiopathic hypereosinophilic syndrome; demonstrate classic echocardiographic findings in the intermediate stage, and remarkable symptomatic and echocardiographic recovery after appropriate treatment.>

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Introduction

Hypereosinophilic syndrome (HES) was first described by Hardy and Anderson in 1968, characterized by overproduction of eosinophils and varying degree of organ involvement [1]. Mortality in untreated patients can be as high as 75% at three years [2]. Cardiac involvement (Loeffler endocarditis) is the most common cause of increased morbidity and mortality [3]. Cardiac imaging in the form of echocardiogram and magnetic resonance imaging (MRI) are cornerstones of diagnosis in cases with cardiac involvement. Early recognition of the cardiac disease is of paramount importance to prevent morbidity and mortality associated with the later stages.

Case report

A 17-year-old female was referred to our department for evaluation of fever of two months’ duration and acute onset dyspnea since 1 week. There was no prior history of adverse drug reaction, arthritis, or allergic reactions. Clinical examination revealed tachycardia, tachypnea, raised jugular venous pressure, with normal heart sounds, and no murmur. Chest X-ray revealed bilateral lung infiltrates (Fig. 1a) and electrocardiogram showed non-specific ST-T changes. Two-dimensional transthoracic echocardiogram showed obliteration of biventricular apices with a layered thrombus extending over the left ventricle endocardium (Fig. 2ac; Videos 1a and 2a). Color Doppler echocardiography showed mild mitral and tricuspid regurgitation. Pulse wave Doppler echocardiography and tissue Doppler echocardiography elicited restrictive physiology (Fig. 2e,g). Laboratory investigations revealed increased eosinophil counts (7.4 × 10⁹/L) with no abnormal cells on peripheral smear. All secondary causes of eosinophilia were excluded. The patient’s laboratory investigations revealed negative anti-nuclear antibody (ANA), negative rheumatoid antibody factor, negative cytoplasmic-anti-neutrophil cytoplasmic antibody (ANCA), perinuclear-ANCA, normal IgE levels, normal vitamin B12 levels, normal urine examination with no proteinuria, and normal stool examination with no evidence of parasitic infection (Table 1). Ultrasonography of the abdomen revealed mild splenomegaly with no other abnormality. Bone

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Fig. 1. (a) X-ray chest showing pulmonary infiltrates in bilateral lung fields. (b) Complete resolution of infiltrates after four weeks of therapy.

Fig. 2. (a) Two-dimensional transthoracic echocardiogram, apical four-chamber view, depicting obliteration of apices of both ventricles along with thrombus on the left ventricular endocardium. (b) Significant resolution of thrombus after one month of treatment. (c) Parasternal short-axis view, showing near total obliteration of left ventricular cavity with thrombus. (d) Parasternal short-axis view, showing decrease in the thrombus after 4 weeks of treatment. (e) Pulse wave Doppler echocardiography showing restrictive physiology. (f) Pulse wave Doppler echocardiography, post treatment, showing normal transmirtal flow velocity pattern. (g) Tissue Doppler echocardiography showing low mitral annular velocity ($E'$) and high $E/E'$ ratio suggestive of restrictive physiology. (h) Tissue Doppler echocardiography, after 4 weeks of treatment, showing normal mitral annular velocity ($E'$) reflective normal filling pattern. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.
Table 1: Laboratory work up of the patient.

<table>
<thead>
<tr>
<th>Complete haemogram</th>
<th>Liver function tests</th>
<th>Renal function tests</th>
<th>Immunological tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin: 10.0 (g/dl)</td>
<td>Serum bilirubin: (1.1mg/dl)</td>
<td>Blood urea: 18 (mg/dl)</td>
<td>ANA (ELISA): Negative</td>
</tr>
<tr>
<td>TLC: 24,800/mm³</td>
<td>AST: 35 (IU/L)</td>
<td>Serum creatinine: 1.0 (mg/dl)</td>
<td>RA Factor: Negative</td>
</tr>
<tr>
<td>Neutrophils: 42%</td>
<td>ALT: 38 (IU/L)</td>
<td></td>
<td>p-ANCA: Negative</td>
</tr>
<tr>
<td>Lymphocytes: 24%</td>
<td>Alkaline phosphatase: 188 (IU/L)</td>
<td></td>
<td>c-ANCA: Negative</td>
</tr>
<tr>
<td>Monocytes: 4%</td>
<td>Serum proteins: 6.2 (g/dl)</td>
<td></td>
<td>IgE: 0.10 IU/ml</td>
</tr>
<tr>
<td>Eosinophils: 30%</td>
<td>Serum Albumin: 3.4 (g/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basophils: 0–1%</td>
<td>PT INR: 1.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute eosinophil count: 7480/mm³</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets: 1.2 × 10⁹/mm³</td>
<td></td>
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</tbody>
</table>


Table 2: Hematological response to therapy.

<table>
<thead>
<tr>
<th>White blood cells</th>
<th>Admission</th>
<th>4 weeks of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total leucocyte count (cells/mm³)</td>
<td>24,800</td>
<td>12,500</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>42</td>
<td>76</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>Monocytes (%)</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>30</td>
<td>0.5</td>
</tr>
<tr>
<td>Absolute eosinophil count (cells/mm³)</td>
<td>7480</td>
<td>740</td>
</tr>
<tr>
<td>Basophils (%)</td>
<td>0.8</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Discussion

In 1975, Chusid was the first to establish three diagnostic criteria for HES: (a) persistent eosinophilia of 1500 eosinophils/mm³ or more for longer than six months; with (b) lack of evidence for allergic, parasitic, or other known causes of eosinophilia; and (c) symptoms and signs of organ involvement [4]. Over the past 30 years, the heterogeneous group of disorders constituting HES are decreasing, as separate disease entities are recognized. If a patient fulfills Chusid’s criteria and no cause is found for the eosinophilia after thorough investigation, the World Health Organization classifies this patient as having idiopathic HES [5]. Cardiac involvement is found in 50% of the cases of HES [3]. Loeffler endocarditis is used to describe the involvement of the heart in HES [6]. Cardiac disease follows three stages. The first is an acute necrotic stage due to infiltration of eosinophils in the myocardium. The contents of the eosinophilic granules (eosinophilic major basic protein, eosinophilic cationic protein, and eosinophil protein-X) are present within the endocardium and myocardium and are held responsible for initiating the damage [7]. This stage can be asymptomatic in many cases. This is followed by an intermediate phase characterized by mural thrombi and thrombus formation along the damaged endocardium (thrombotic stage) [7]. The left ventricle is more affected and thrombus tends to form at apex where stasis is prominent [8]. The third stage is the fibrotic stage in which the granulation tissue is changed into hyaline fibrosis, sometimes with a small inflammatory zone in deeper layer [7].

Echocardiogram shows endomyocardial thickening in more than 60% of patients [9]. Apical obliteration with thrombus and involvement of posterior mitral leaflet causing mitral regurgitation are classic findings. Doppler echocardiography will usually show restrictive physiology. Pericardial effusion can also be found.

Fig. 3. (a) After four weeks of treatment, cardiac magnetic resonance imaging (MRI) showing mild patchy late gadolinium enhancement of left ventricular (LV) wall. (b) Cardiac MRI on follow-up, showing no significant thrombus in the ventricles with a small apical aneurysm.
Myocardial involvement and thrombus can lead to arrhythmias and systemic embolization. CMR is useful in HES. Hyperintense myocardial area on T2 weighted images is suggestive of edema or necrosis and is usually found at apex in such patients. Delayed gadolinium enhancement of non-ischemic type is characteristic of fibrosis. CMR has high sensitivity and specificity for detecting apical thrombi. Overlying thrombus is identifiable as a low signal mass on the delayed enhancement images, which does not deform on tagged images. Regional areas of hypokinesia or akinesia and estimation of cardiac function can also be determined by CMR.

Treatment at early stage can prevent progression to endocardial fibrocalcific stage in which morbidity and mortality remain highest. Steroids are the cornerstone of treatment. Hydroxyurea and interferon α can be used in steroid-resistant patients. Novel therapies including alemtuzumab, a human monoclonal antibody directed against CD52 on eosinophils, have been reviewed [10]. Patients with fusion protein with tyrosine kinase activity encoded by the FIP1L1-PDGRFA-fusion gene are highly responsive to imatinib. The most important part in treatment is to start the therapy in early stages as once the fibrotic stage sets in, it is irreversible with poor results on medical therapy.

Our patient presented in intermediate stage, which was promptly recognized and appropriate treatment was initiated. We highlight a classic case of idiopathic HES with typical cardiac (Loeffler endocarditis) and pulmonary manifestations.

Conflict of interest

There is no conflict of interest of authors. No financial grant has been received. There is no relationship with industry.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jccase.2015.05.010.

References