CASE REPORT

Eosinophilic myocarditis and hypereosinophilic syndrome

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Hypereosinophilic syndrome (HES) is a heterogeneous group of hematological disorders characterized by a chronic, unexplained hypereosinophilia with tissue damage. Cardiac involvement occurs in ~20% of patients with HES and represents a major turning point. Cardiac injuries related to eosinophilia are divided into three chronological phases: eosinophilic infiltration, thrombosis, and fibrosis. We report a case of a 33-year-old woman diagnosed with HES, with pulmonary and gastrointestinal involvement and eosinophilic myocarditis in cardiogenic shock. The evolution was favorable with dobutamine, anticoagulation, corticosteroids, and later, β-blockers and angiotensin-converting enzyme inhibitors. Cardiac involvement in HES is rare but carries a poor prognosis. Corticosteroids are considered by many to be the mainstay of treatment. Although new treatments have been suggested, only a few seem promising.

Keywords: Cardiogenic shock, Corticosteroids, Eosinophilic myocarditis, Hypereosinophilic syndrome, Imatinib

Introduction

Hypereosinophilic syndrome (HES) is a heterogeneous group of hematological disorders characterized by chronic, unexplained hypereosinophilia with tissue damage [1]. Cardiac involvement occurs in ~20% of patients with HES and represents a major turning point [2]. Cardiac injuries related to eosinophilia are divided into three chronological phases: eosinophilic infiltration and myocarditis, thrombosis, and fibrosis. Although major diagnostic and therapeutic advances have been made, HES remains underrecognized and has a poor prognosis [3].

Case report

A 33-year-old woman, with no relevant medical history but a chronic cough, was admitted to our hospital for abdominal pain and vomiting. On admission, vital signs were normal: blood pressure: 125/68 mmHg, heart rate: 75 beats/min, respiratory rate: 18 breaths/min, body temperature: 36.7 °C. Physical examination was normal besides abdominal tenderness. Thoracic and abdominal computed tomography was performed showing interstitial lung disease and thickening of the gastric antrum walls, along with intestinal dilatation (Fig. 1). Esophagogastroduodenoscopy revealed antritis. During the procedure, multiple gastric

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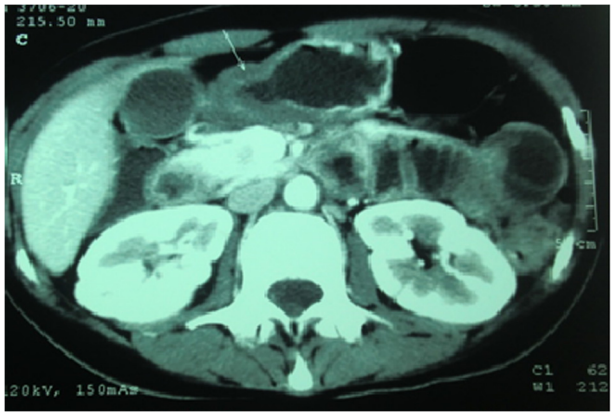

Figure 1. Abdominal computed tomography showing an important thickening of the gastric antrum walls (arrow) along with an intestinal dilatation.

biopsies were performed, which showed inflammatory lesions with eosinophil infiltration. Laboratory tests revealed elevated levels of eosinophil cell count (>2925/mm^3), C-reactive protein (86 mg/l), and immunoglobulin E (>1677 ng/mL). Antineutrophil cytoplasmic antibody and antinuclear antibodies were negative. Bone marrow aspiration found rich marrow filled with eosinophilic myelocytes and mature eosinophils. During her hospital stay, the patient developed shock. Electrocardiography showed atrial fibrillation along with nonspecific T-wave and ST changes on inferior and anterolateral leads. Troponins were positive. Transthoracic echocardiography (TTE) demonstrated dilated cardiac cavities with severe global left ventricular (LV) systolic dysfunction (LV ejection fraction = 29%; Fig. 2). Coronary angiography was normal. In view of the patient's clinical, biological, radiological, and histological findings, we decided that eosinophil myocarditis

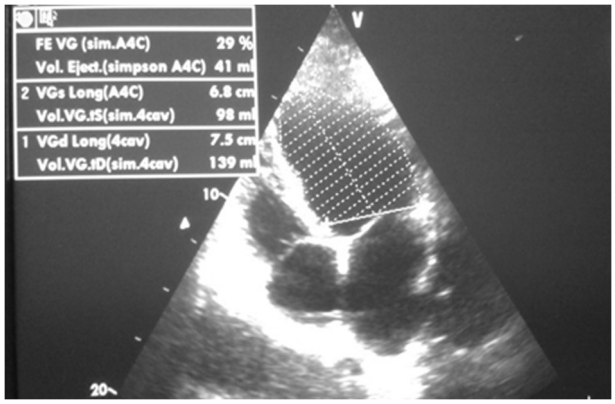

Figure 2. Transthoracic echocardiography: an apical four-chamber view showing a severe impairment of the left ventricular ejection fraction.

(EM) was the cause of the cardiogenic shock. Initially, the patient received dobutamine, anticoagulants, and corticosteroids in the intensive care unit. After improvement of the hemodynamic status, β-blockers and angiotensin-converting enzyme inhibitors were started and uptitrated to 12.5 mg carvedilol twice daily and 5 mg/d ramipril. Control transthoracic echocardiography showed significant LV systolic function improvement (LV ejection fraction: 45%).

Discussion

Eosinophilic cardiac disease is a rare condition that was first described in 1936 by Wilhelm Löffler, who called it ''fibroplastic parietal endocarditis with blood eosinophilia''; also known as Löffler's endocarditis [2]. Cardiac injuries related to eosinophilia are divided into three chronological phases: eosinophilic infiltration, as in our patient, thrombosis, and fibrosis. The first stage is characterized by EM with eosinophil and lymphocyte infiltration [1]. The myocardial damage is due to the release by eosinophils of cationic proteins capable of inducing necrosis and apoptosis, namely, major basic protein, eosinophil cationic protein, eosinophil-derived neurotoxin, and eosinophil peroxidase [2].

Several diseases may be responsible for eosinophilia such as drugs, infections, allergies, systemic diseases, malignancies, and HES [1,2]. Our patient had not been taking any medication. No personal or familial allergies were known. After a thorough history taking, physical examination, and oriented workup, we concluded that she had HES.

HES has been defined by Chusid et al. [4] as eosinophilia >1500/mm^3 for >6 months, without any secondary cause and with evidence of tissue damage [4]. It is more common between 20 years and 50 years of age and in men [5]. Two subtypes of HES must be recognized: a lymphocytic variant (L-HES) and a myeloproliferative one. Bone marrow cytogenetic analysis and fluorescent *in-situ* hybridization are mandatory for their diagnosis. The L-HES variant is characterized by an increase in cytokine production, notably interleukin (IL)-5, that plays an essential role in eosinophil production, survival, chemotaxis, and degranulation. The mainstream treatment for L-HES variant is corticosteroids. In the majority of myeloproliferative variant patients, a fusion gene, namely *FIP1L1-PDGFRA* (*FP*), is found. The *FP* gene is responsible for the production of an active protein-tyrosine kinase capable of transforming hematopoietic cells into eosinophil precursors,

which explains why 88% of *FP*-positive patients respond well to imatinib (a tyrosine kinase inhibitor) [1]. Although dermatological, pulmonary, and gastrointestinal involvement seems to be more frequent, cardiac injury is the most redoubtable as it is the major source of morbidity and mortality [6]. Our patient had eosinophilic antritis, interstitial lung disease, and myocarditis. EM may manifest in many forms, ranging from patients without any cardiac complaints to cardiogenic shock, as in the case of our patient. However, it is noteworthy that most patients report an influenza-like syndrome prior to the onset of EM [2]. Electrocardiography usually shows nonspecific ST/T abnormalities and sometimes an S1Q3 aspect [2,3]. Echocardiography is a useful and broadly available tool in assessing patients with EM because it helps to rule out differential diagnosis, but also evaluate and monitor cardiac chamber size, wall thickness, ventricular systolic, and diastolic function, and to detect the presence of pericardial effusion. Cardiac magnetic resonance is currently the gold standard in noninvasive diagnosis of myocarditis [2,7]; however, it remains more often than not burdensome due to its high cost and low availability, especially in developing countries. Endomyocardial biopsy is the only method to definitely make the diagnosis of EM [2]. We did not perform a biopsy because we had all the data that we needed to establish the diagnosis.

Patients with EM manifesting with heart failure or arrhythmias are managed according to current guidelines. Specific treatment of EM is undertaken according to its underlying etiology. In patients with HES, it depends on the variants. In the L-HES variant, corticosteroids, although being controversial, are the first line of treatment. In case of resistance, anti-IL-5 (mepolizumab) is recommended. For the myeloproliferative variants, as explained earlier, imatinib should be initiated [8]. A flood of new treatments for eosinophilic disorders have been suggested but only a few—receptors like benralizumab representing a humanized antibody to IL-5 receptor-α—seem promising [9]. Unfortunately, they have a shortage of evidence from randomized trials.

In conclusion, cardiac involvement in hypereosinophilia, although rare, carries a poor prognosis. It ranges from asymptomatic myocarditis to fibrotic scarring through cardiogenic shock and thromboembolic complications. All etiologies must be ruled out before establishing the diagnosis of HES. Early detection and treatment of myocardial involvement improves prognosis. On this basis, echocardiography must be practiced in moderate (1500/mm^3) to severe eosinophilia (>5000/mm^3) [7]. Specific treatment of EM is undertaken according to its underlying etiology. Immunosuppressive therapy represents the core treatment in the majority of patients with EM.

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