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Endomyocardial Fibrosis Secondary to Chronic Eosinophilic Leukemia: Case Report

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ABSTRACT

Endomyocardial fibrosis (EMF) is characterized by fibrosis of the endomyocardium of one or both ventricles and atrioventricular valves. Progressive fibrosis leads to irreversible restrictive cardiomyopathy, progressing to heart failure (HF), thromboembolic phenomena, and arrhythmias. It is one of the main complications of chronic eosinophilic leukemia (CEL), resulting from intense eosinophilic infiltration into cardiac tissue. This case is of a 34-year-old male patient with past medical history of CEL, who developed EMF and severe heart failure, NYHA (New York Heart Association) IV, and underwent endocardectomy and mitral and tricuspid valvuloplasty. After the procedure, he improved to NYHA II, initiated cardiovascular rehabilitation, and returned to daily activities.

KEYWORDS: Endomyocardial Fibrosis; Restrictive Cardiomyopathy; Cardiovascular Abnormalities; Hypereosinophilic Syndrome; Leukemia.

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I. INTRODUCTION

Endomyocardial fibrosis (EMF) is a rare and complex restrictive cardiomyopathy whose etiology is not fully understood [1,2,3]. Genetic, environmental, and immunological factors may play a role in its development [1,2]. It is a neglected disease, with an uncertain prognosis and high frequency in subtropical and tropical regions such as Africa, South America, and Asia, affecting populations of lower socioeconomic status. Young adults are most affected, between the ages of 10 and 30, regardless of gender. [1,2,3,4]. It is described by the accumulation of fibrous tissue in the endomyocardium, mainly affecting the apices of the right and/or left ventricle, as well as involvement of the valvular apparatus [5,6].

Structural damage is caused by the chronic inflammatory process resulting from eosinophilic infiltration and cytokine release, leading to local fibrosis, contributing to the development of EMF [7,8]. Clonal proliferation of cells preceding eosinophils, generating lympho- or myeloproliferation persistent in peripheral blood, tissues, and bone marrow, follows the picture of chronic eosinophilic leukemia (CEL). Since this condition usually lacks symptoms, around 10% of the affected population is diagnosed incidentally. The heart is one of the most affected organs, with EMF as the main diagnosis [7].

This study describes a case of endomyocardial fibrosis due to chronic eosinophilic leukemia.

II. CASE REPORT

A 34-year-old male patient reported his first symptom as a feeling of chills while surfing, accompanied by cyanosis of the lips and fingertips. Initial laboratory tests

showed leukocytosis (28,600/mm³) and eosinophilia (7,150/mm³). The diagnosis of chronic eosinophilic leukemia (CEL) was confirmed by the presence of the FIP1L1-PDGFRα rearrangement. The prescription of the tyrosine kinase inhibitor (Imatinib) at a dose of 100mg/day allowed for the remission of leukocytosis and eosinophilia.

During follow-up, a transthoracic echocardiogram (TTE) showed signs of moderate diastolic dysfunction, increased atrial size, moderate mitral insufficiency and preserved left ventricular (LV) systolic function. There were also signs of right ventricle apical obliteration due to fibrosis. Cardiac magnetic resonance (CMR) confirmed the hypothesis of endomyocardial fibrosis (EMF), characterized by apical obliteration of both ventricular chambers due to the fibrotic process (late endocardial enhancement), extending to the mid-basal portion and associated with extensive hypointense formation, which could correspond to thrombus or calcification. Biventricular systolic function was preserved, and signs of indirect restriction, bi-atrial enlargement, and slight pericardial effusion were also observed **(Figure 1A and 1B).**

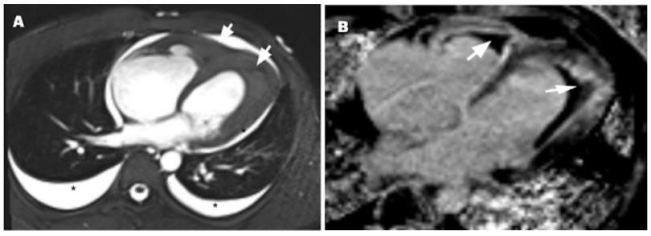

Figure 1: **Cardiac magnetic resonance imaging. A)** Four-chamber cine cardiovascular magnetic resonance imaging. Obliteration of the apex of both ventricular cavities (arrows) in addition to discrete pericardial and pleural effusions (asterisks). **B)** Late enhancement sequence. Presence of diffuse endocardial enhancement involving both cavities in addition to thickening and figure with hypo-signal attached to the apices which may correspond to thrombus or calcification (arrows).

The patient was initially managed with angiotensin-converting enzyme inhibitors, beta blockers, corticosteroids, and uric acid synthesis inhibitors, with doses adjusted over time. He was kept under continuous clinical follow-up with a hematologist and cardiologist due to the CEL and EMF, with heart failure with preserved ejection fraction (HFpEF) NYHA functional class II. During follow-up, a chronic kidney disease (CKD) stage G3a developed.

Three years after symptoms onset, the patient presented acutely with jaundice, jugular venous distension, mitral focus systolic murmur, a third heart sound (B3), and a positive hepatojugular reflux test. Given the worsening of the HFpEF, surgery for endocardectomy and mitral and tricuspid valvuloplasty was indicated. After the surgical procedure, a TTE was performed, showing normal LV systolic function and grade II reduced diastolic function; significant enlargement of the left atrium (LA) and slight enlargement of the right atrium (RA); moderate tricuspid insufficiency, without significant pulmonary hypertension; and slight pericardial effusion. However, the patient continued to experience symptoms with moderate exertion. As a result, cardiopulmonary rehabilitation was prescribed, leading to significant improvement.

Cardiopulmonary exercise test (CPET) after the procedure revealed a slight reduction in aerobic condition (25.6 ml.kg^-1min^-1 - 61.5% of the predicted peak oxygen consumption (VO2)); chronotropic incompetence while using a beta blocker; rare supraventricular arrhythmia; normal behavior of the oxygen pulse curve morphology, VE/VO2 slope at the limit of normal; prolonged recovery time of VO2; and a reduction in peripheral oxygen efficiency **(Figure 2).** The data characterized physical deconditioning as the main cause of the reduced aerobic condition.

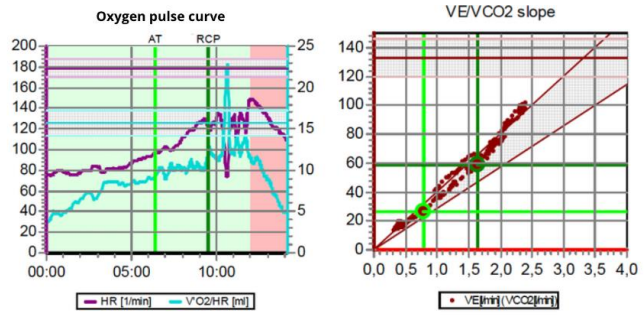

Figure 2. Cardiopulmonary exercise test after the surgical procedure.

Currently 42 years old, the patient is in NYHA functional class II. He is using immunobiologic, anticoagulant, antihypertensive, diuretic, and selective phosphodiesterase-5 inhibitor (PDE-5) medications.

III. DISCUSSION

A 34-year-old man, native to a tropical climate region, was admitted with complaints of lip and fingertip cyanosis after physical exertion. Hematological alteration suggestive of chronic eosinophilic leukemia (CEL) was identified. MRI demonstrated endomyocardial fibrosis (EMF) of both ventricles. He progressed to heart failure with preserved ejection fraction (HFpEF) and stage IIIA chronic kidney disease (CKD).

EMF is one of the main consequences of CEL. Patients with CEL present with abnormally elevated eosinophils in peripheral blood and subsequent tissue infiltration, in addition to the presence of the FIP1L1/PDGFRα gene rearrangement [7]. Its pathogenesis involves clonal growth of cells preceding eosinophils, altering fibroblast growth factor receptor (FGFR1) and platelet-derived growth factor alpha (PDGFRα) receptors, leading to fusion of both (FIP1L1/PDGFRα) and encoding the tyrosine kinase protein that regulates gene expression [7,9].

In the heart, inflammation caused by eosinophilic infiltration evolves in three stages: active inflammation, transient progressive, and chronic fibrosis. The patient's signs

and symptoms, along with imaging and laboratory findings, established according to the clinical phases of EMF. In the initial phase, which is the active inflammation phase occurring around five weeks, there is intense eosinophilia and necrosis formation, which until then, due to no increase in ventricular wall thickness, is not noticed on echocardiographic examination. In stage two, with an average duration of 10 months, ischemic symptoms may occur due to thrombus formation on the walls of vital organs such as the heart and brain. After two years of onset, stage three sets in, characterized by established fibrosis, valvular involvement, congestive symptoms, and coronary artery disease [4,7,10,11].

Echocardiographic findings with mild pericardial effusion, mild pulmonary arterial hypertension, moderate mitral regurgitation, preserved left ventricular systolic function, moderate diastolic dysfunction, and right ventricular obliteration by fibrosis were compatible with restrictive fibrotic cardiomyopathy. The apical part of the heart on the right and/or left side may be compromised due to progressive accumulation of fibrous tissue, causing diastolic dysfunction due to endocardial fibrosis [1,2,11].

MRI is an important examination to document the process of endocardial fibrosis through late enhancement sequences, present from the initial phase, with late-phase typically resulting in apical obliteration, often due to thrombus or calcification (or a combination of both), configuring the thrombotic and fibrotic stage of eosinophilic cardiomyopathy [2,11,12]. Involvement of the papillary muscles can cause valve lesions, leading to mitral and tricuspid valve insufficiency, exacerbating congestive symptoms [2,6,11]. Confirmation of eosinophilic myocarditis is achieved through endomyocardial biopsy, when performed early in the disease, and may be repeated during therapeutic follow-up in cases of complicated heart failure [13].

So far, there is no standardized therapy for EMF [10,11]. Pharmacological treatment of EMF is based on controlling symptoms of congestive heart failure and controlling atrial fibrillation (AF) and/or other arrhythmias. High-dose diuretics, sequential nephron blockade, beta-blockers, medications for controlling cardiac remodeling, anticoagulants, and others for symptomatic treatment are indicated as necessary. Paracentesis is part of therapeutic measures due to rapid accumulation of fluid in the abdominal cavity, contributing to short-term symptom improvement [4,11].

In the treatment of CEL with cardiac involvement, high-dose corticosteroids are indicated in the first weeks after CEL diagnosis to reduce inflammation and minimize endomyocardial fibrosis formation. Additionally, the use of tyrosine kinase inhibitor (Imatinib) promotes a good response to treatment and prognosis of CEL, with a high probability of hematological remission. Around 30 days, a large proportion of Imatinib users achieve improvement, with total disappearance of signs and symptoms [14].

The patient progressed to the advanced stage of EMF, with HFpEF, dyspnea on slight exertion, lower limb edema, ascites, and jugular venous distention, posing a clinical challenge [4,6,7]. Because of his HFpEF progression, he underwent endocardectomy and mitral and tricuspid valvuloplasty. Early surgical intervention increases long-term survival [5,15], demonstrating that its effects are superior to drug treatment [4,15]. Cardiac transplantation has been another therapeutic option for patients in the terminal stage of EMF [5]. The prognosis of EMF varies and depends on the clinical presentation and functional class (NYHA) regarding the degree of fibrosis [15].

IV. CONCLUSIONS

It is essential to investigate persistent eosinophilia without apparent cause to achieve early diagnosis and treatment of CEL, avoiding future complications from infiltration into target organs such as the heart. EMF is an irreversible restrictive cardiomyopathy with a reserved prognosis, requiring surgical intervention or even heart transplantation in advanced cases.

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