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Case Report

Biventricular Endomyocardial Fibrosis Due to Hypereosinophilia. About A Case

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Abstract

Endomyocardial fibrosis is a restrictive cardiomyopathy and does not have well-defined accepted diagnostic criteria. In hypereosinophilic endomyocardial fibrosis, two variants of the disease are described: Löffler's and Davies's. The clinical diagnosis is difficult and in most patients it presents as heart failure of unclear origin. It manifests as insidious and progressive heart failure, sudden death, or thromboembolic events. Modern imaging tools, together with clinical and endomyocardial biopsy, allow an accurate diagnosis, but constitute a challenge for cardiovascular specialists. It currently has a poor prognosis and medical treatment is usually not effective. Heart transplantation is the best option in advanced stages. We present the case of a 58-year-old patient who was admitted with symptoms and signs of heart failure, being diagnosed with restrictive cardiomyopathy secondary to endomyocardial fibrosis in which the multidisciplinary approach was decisive for diagnosis and treatment.

Keywords: *Restrictive Cardiomyopathy; Endomyocardial Fibrosis; Echocardiography; Cardiac Magnetic Resonance; Biopsy*

Abbreviations

CMR: Cardiavascular Magnetic Resonance Imaging; EMF: Endomyocardial Fibrosis; HF: Heart Failure; HBP: High Blood Pressure; LGE: Late Gadolinium Enhancement; LA: Left Atria; LV: Left Ventricle; LVEF: Left Ventricular Ejection Fraction; NYHA: New York Heart Association; RA: Right Atria; RV: Right Ventricle; TTE: Transthoracic Echocardiography; TAPSE: Tricuspid Annular Plane Systolic Excursion

Introduction

EMF is still a cardiomyopathy of unknown cause, which is reported to be the first cause of restrictive cardiomyopathy worldwide. The highest prevalence occurs in certain regions of Sub-Saharan Africa and does not have well-defined accepted diagnostic criteria. It responds to a spectrum of pathology with common physiology, but of divergent etiology.

EMF is characterized by LV and RV apical endocardial fibrosis, causing infiltrative restrictive cardiomyopathy. First described in Africa by Bedford and Konstam in 1946, in soldiers of the Second World War, however, Arthur Williams in 1938, made an early description of this pathology. In Uganda in 1948, Jack Davies was the first to coin the term EMF [1].

It has been found in tropical regions of Africa, the South Asian subcontinent and in Brazil, although it is also found in subtropical Africa, and some cases appear infrequently in moderate climates, America. A population prevalence of approximately 20% has been described in rural Mozambique [1,2].

It usually affects mainly children, adolescents and young adults, being more evident in low socioeconomic strata, constituting an entity with idiopathic etiology, or secondary to infectious causes or not, such as medications, autoimmune disease, magnesium and cerium deficiency, atopy or neoplasms hematological diseases such as hypereosinophilic syndrome and eosinophilic leukemia, so their genetic source could be primary or secondary to infiltrative processes.

There are two variants of the disease: Löffler and Davies, the latter being a very infrequent cause of restrictive cardiomyopathy in our environment, but important in equatorial Africa (10 - 20% of cardiac mortality), being the main cause of restrictive heart failure [3].

The clinical diagnosis is difficult, since in most patients it presents as heart failure of unclear origin. Two-dimensional ultrasound is the non-invasive diagnostic method of choice, with the most characteristic findings being normal or small ventricles with obliteration of the apex, which contrast with highly dilated atria and mitral and / or tricuspid regurgitation, with a restrictive filling pattern [3-5].

Case Report

Patient CS, 58-year-old female, white skin color, of urban origin with a personal pathological history of essential HBP of 20 years of evolution and type 2 diabetes mellitus for 15 years. Assessed by nephrologist with edemas that reached the anasarca and diagnosed in advanced kidney disease, 2 years before the cardiovascular diagnosis. Her treating doctor found a pansystolic murmur in mitral focus, grade III / VI, with irradiation to the apex and axilla, without thrill. Cardiologist evaluation was requested and TTE to assess cardiovascular function. During interrogation the patient described multiple admissions due to acute HF with superimposed respiratory sepsis, sometimes due to suboptimal treatment, which were accompanied by asthenia, functional class worsening, paroxysmal nocturnal dyspnea, orthopnea, reaching anasarca in a period of no more than 2 years. The antecedent in this patient of confirmed infection by Malaria, Schistosoma or Filariasis is not collected, and in specialized consultations other hematological entities and infiltrative processes were ruled out.

The TTE carried out in February 2019, evidenced the presence of severe mitral regurgitation of possible rheumatic etiology, with moderate tricuspid regurgitation and intermediate probability of pulmonary hypertension secondary to the valve cause, with normal LVEF and mild RV dysfunction. Taking into account the foregoing, it is oriented to assess the patient in her care center, suggesting surgical treatment to replace the mitral valve.

After 8 months, in October 2019, the patient went to emergency room, reporting progressive dyspnea during the last 3 months, with impaired to her functional class IV NYHA, associated with paroxysmal nocturnal dyspnea, asthenia, loss of appetite, decubitus intolerance the last 5 days, without improvement, despite treatment with high-dose diuretics. She was admitted to the emergency service with a diagnosis of exacerbated CHF secondary to rheumatic mitral valve disease, pending surgical treatment, the complementary tests shown in table 1 were performed. Intensive pharmacological treatment for the acute phase started in the emergency room.

HEMOCHEMISTRY		LEUKOGRAM	IONOGRAM	
Hemoglobin	13.4 g/dl	Leukocytes++ 8.1/mm^3	**Na**	139mmol/l
Hematocrit	43.3%	Neutrophils 65%	**K**	3.17 mmol/l
Platelets	112000/mm^3	Lymphocytes 32.5%	**Cl**	103 mmol/l
Glycemia	6.8 mmol/L	Monocytes 2.5%	**Ca**	0.99 mmol/l
ELECTROCARDIOGRAM				
Heart rate:92 sinus	Axis 170 degrees right	**RP:** 160mseg	**P**:2mmx 80mseg	**QRS** 110msg
Isoelectric ST	**Negative and symmetrical T waves** in DII , DIII, AVF and V4-V6	**Left Ventricular Hypertrophy**	**QTc** interval in normal range	
TELECARDIOGRAM				
Heart silhouette :	Regular appearance		**Arches right 2**	Regular appearance
Left bows	Bulging of the middle arch of the pulmonary artery trunk or left atrium		**Hilums**	Congestives
Condensation	Pulmonary		**Redistribution**	Present

Table 1: *Complementary tests performed on the patient immediately upon arrival at the emergency department.*

She was stabilized, and admitted to the hospital ward to update presurgical examinations and definitive treatment. A new TTE was performed and new findings were reported that leaded to a re-discussion by a multi-disciplinary team (Figure 1 and 2 and Table 2).

LA	40mm	**FEVI**	51%	**E/A** 1.8
Septum	9 mm	**FEVI Simpson**	64%	**e' Lateral** 13.6
Posterior wall	8 mm	**TAPSE**	15 mm	**e' Medial** 17
Pulmonary regurgitation limited to the right ventricular outflow tract Fibrosis of the mitral annulus with marked restriction of mobility of the posterior leaflet, practically adhered to the endocardium of the lateral wall, with fibrosis and thickening of the chordae tendineae, close to the insertion of the posterior leaflet. Moderate mitral regurgitation and severe functional tricuspid regurgitation.				
Severe biatrial remodeling. Both ventricles mild remodeling. Obliterated left ventricular apex, with increased echogenicity of the LV apex endocardium, rejected RV apex. Adequate LV systolic function and mild RV dysfunction				
Restrictive pattern in mitral flow chart with increased pulmonary capillary pressures				
Mild pericardial effusion High probability of pulmonary hypertension				

Table 2: *Description of the TTE performed.*

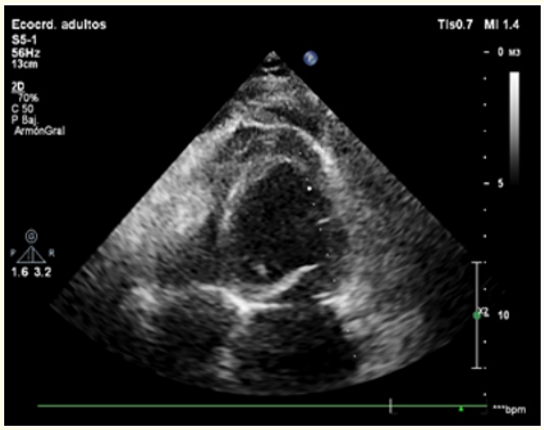

Figure 1: *Obliterated left ventricular apex and fibrotic apical endocardium.*

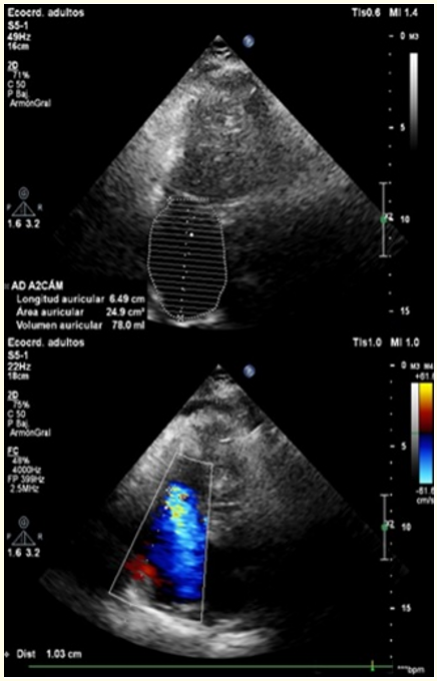

Figure 2: *Rejected right ventricular apex and severe tricuspid insufficiency.*

Subsequently, as a gold standard technique of the cardiomyopathies evaluation, CMR was performed; obliteration of both ventricles apex was observed in the cine sequences and endocardial LGE, compatible with fibrosis at this level; in addition to showing the great dilation of both atria, the inferior vena cava and a marked hepatomegaly, all of this findings are consequence of restrictive ventricular physiology. See images in figure 3 and 4, and the description of the test in table 3.

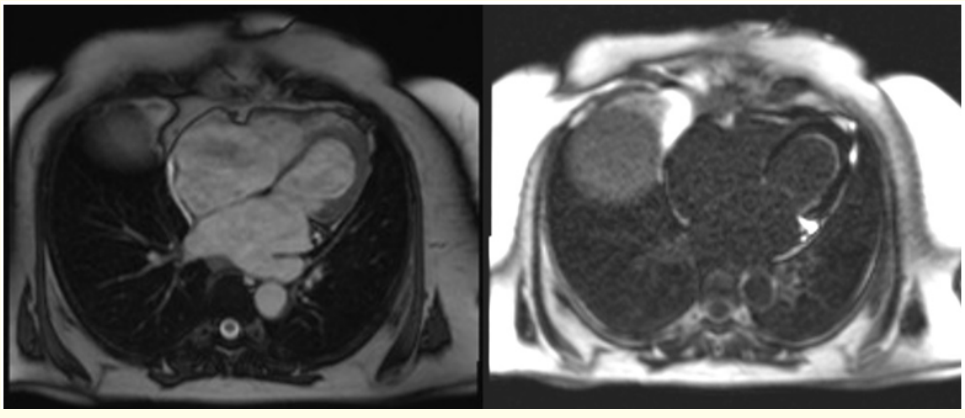

Figure 3: *Views of 4 cardiac chambers: a) Sequence of white blood : apex obliteration of the ventricles and significant enlargement of both atria can be seen. b) T1 segmented inversion-recovery sequence with LGE, hyperintensity at the endocardium level in both ventricles, suggestive of fibrosis.*

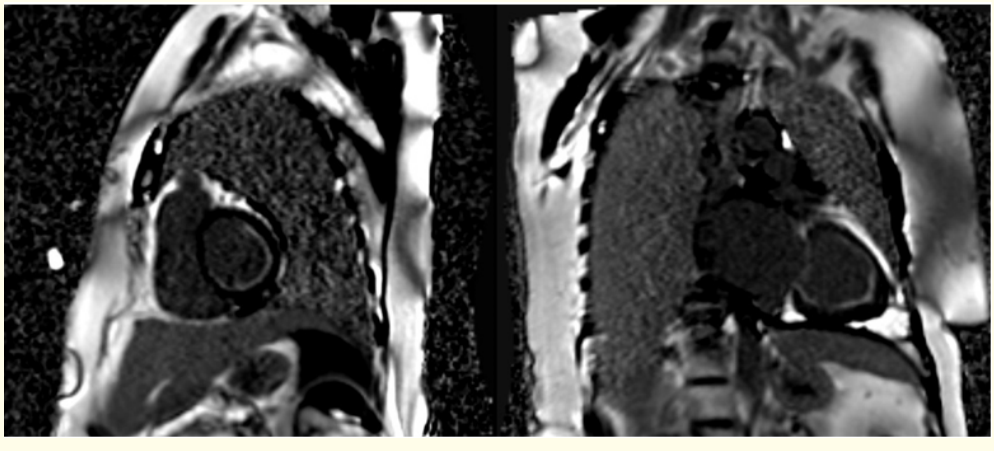

Figure 4: *T1 sequences with inversion-recovery with LGE at sub-endocardium. a) Middle short axis. b) Two-chamber view.*

FEVI 55.6%	**DDVI** 49.5mm	**DSVI** 25.8mm
Perfusion in the first-pass sequence shows an area of hypointensity throughout the subendocardium.		
LA and RA dilation.		
Sequence of inversion-recovery in the sequences of late enhancement after the administration of gadolinium, is observed LGE in the entire sub-endocardium of the LV and RV.		
Non-cardiovascular incidental finding: Hepatomegaly, IVC measures 24.1mm		
Conclusions: Biventricular endomyocardial fibrosis. Moderate mitral regurgitation and tricuspid regurgitation.		

Table 3: *Description of the MRI performed.*

Endomyocardial biopsy was performed for diagnostic purposes. No evidence of parasitosis or eosinophilia was found in the advanced stage of the disease, and enhancement of Masson or trichrome staining was observed, which is specific for type I collagen fibers. Congo red staining was negative, ruling out amyloidosis as a differential diagnosis.

Discussion

Endomyocardial diseases, another cause of restrictive cardiomyopathy, are unified by the finding of endocardial fibrosis. Several diseases share the final pathological phenotype of endocardial fibrosis, but no unifying hypothesis has emerged for this pathology, and each disease may have its own distinctive cause [6]. Various theories have been proposed regarding the pathophysiology of non-eosinophilic EMF, including factors such as foods contaminated with cerium [7], immunological factors where the presence of antibodies against myocardial proteins or genetic factors has been described [8]. However, it has not been demonstrated a direct correlation between these and the development of the disease, so that future studies are required to verify these hypotheses and determine if the cause is purely environmental, genetic or the product of the interaction of genes in the environment.

It is characteristic the impaired ventricular filling and reduction of one or both ventricles diastolic volume, depending on the degree damage. Therefore, the compromise of diastolic function takes precedence over systolic function; the hallmark of EMF is the thickening, fibrosis and coating of the endocardial surface of the ventricles [9].

Clinical presentation is insidious, without gender predilection, it usually affects children and young adults in Africa. The absence of eosinophilia is the norm and if it exists, it is usually secondary to associated parasitosis (90%). The involvement can be biventricular (50% of cases), left ventricle (40%) or right (10% of cases). Atrial ventricular (AV) valve regurgitation, embolism, and atrial fibrillation are common [10,11].

Two variants of the disease are described: Löffler's and Davis's. Löffler's hypereosinophilic syndrome is more common in temperate countries, is rapidly progressive, affects mainly men, and is associated with hypereosinophilia, generalized arteritis, and thromboembolic phenomena. In contrast, Davis disease has a higher incidence in tropical countries, affects younger patients, and has an inconsistent association with hypereosinophilia [12].

Oslen described 3 stages of the disease: necrotic, thrombotic necrotic, and fibrotic [13]. The necrotic phase consists of an intense myocarditis rich in eosinophils, associated with arteritis.

The thrombotic stage occurs when the disease has lasted at least 10 months, the myocardial process tends to regress and some nonspecific changes in endocardial hypertrophy are already present. Various degrees of thrombi, often extensive, are superimposed; at this stage, arteritis also tends to regress and thrombi are frequently found occluding the small intramyocardial vessels. Fibrotic phase is reached after an average time of 24.5 months and resembles endomyocardial fibrosis in every detail. Fibrosis is due to an abnormal stimulation of the cardiac fibroblast that leads it to increase its production of collagen, representing a reactive stromal change.

The clinical characteristic of these patients depends on the affected ventricle, the duration of the disease, the presence of active disease or not. Although the clinical signs can develop within three months of the onset of hypereosinophilia, most patients with hypereosinophilic syndrome take several years for the heart disease to progress to a fibrotic stage. Large intracavitary thrombi can develop in the left ventricle in early stages and compromise ventricular filling or promote systemic embolism.

It is an entity in which a large participation of eosinophils has been shown, with properties that predispose to causing myocardial injury: the ability to secrete eosinophilic cationic protein and major basic protein in the areas of inflammation, production of free radicals and lipid peroxidation mediators that lead to cardiac injury [14].

Even though modern imaging tools together with clinical and endomyocardial biopsy allow an accurate diagnosis, this represents a challenge for cardiovascular specialists.

TTE plays an essential role in the diagnostic suspicion. Hyperechoic endocardium can be observed in the vertex, associated with the reduction in the longitudinal diameter of the ventricle, which is oval in shape, enlargement and hypercontractility of the basal portion, papillary muscles retraction and giant atria.

Obliterated apex observed in EMF should be differentiated from that described in hypertrophic cardiomyopathy where this only occurs during systole [15]. On Doppler evaluation, a restrictive filling pattern is observed and there is a rapid deceleration of the E wave with an inconspicuous A wave. Additionally, it is possible to observe retraction of the posterior leaflet of the mitral valve and very dilated atria [16].

Mocumbi., *et al*. Classified the entity according to the findings in the echocardiogram. The diagnosis is made with two major criteria or one major and two minor; Less than 8 points indicate a mild compromise, 8 - 15 moderate and more than 15 is a severe compromise. These criteria are useful in asymptomatic patients in the early stages, since making a rapid diagnosis improves the prognosis [17]. (Table 4) Applying these, the patient presented a total of 12 points.

MAJOR CRITERIA	**SCORE**
Plaques greater than 2 mm thick in the endomyocardium.	2 points
Patches smaller than 1mm in the endomyocardium, affecting more than one wall of the ventricle.	3 points
Obliteration of the ventricular apex.	4 points
Spontaneous thrombus or echo contrast without the presence of ventricular dysfunction.	4 points
Retraction of the apex of the right ventricle.	4 points
Dysfunction of atrioventricular valves due to adhesion of the subvalvular apparatus to the wall of the ventricle. According to the degree of valvular insufficiency, the score is given.	1 - 4 points
MINOR CRITERIA	**SCORE**
Thin patches of endomyocardium located in a ventricular wall	1 point
Restrictive pattern across the atrioventricular valves	2 points
Diastolic opening of the pulmonary valve	2 points
Diffuse thickening of the anterior mitral leaflet	1 point
Enlarged atria with normal ventricles	2 points
Enhancement in the density of the moderator band or trabeculae	1 point
In M-mode: movement of the interventricular septum and the posterior wall	1 point

Table 4: *Criteria for the diagnosis and evaluation of the severity of EMF, obtained from the publication of the cardiology service, Fundación Universitaria de Ciencias de la Salud, Bogotá, Colombia, available online since October 22, 2016 [2].*

CMR is a powerful diagnostic tool to characterize myocardial pathologies; is a non-invasive imaging modality capable of providing high-resolution images of the heart in any desired plane [18], it allows the implementation of early treatment strategies and timely referral to specialized sites in order to improve clinical outcomes.

With the evaluation of LGE, it is possible to differentiate between ischemic and non-ischemic forms of cardiomyopathies, providing information on the exact amount of irreversible myocardial damage, a relevant characteristic as a prognostic factor [19].

It is also very useful for determining myocardial fibrosis extension and can distinguish endomyocardial fibrosis from other restrictive cardiomyopathies because it presents a typical pattern of abnormal subendocardial fibrosis and apical obliteration, and occasionally apical thrombus [20]. The ' 'V sign' at the apex, characterized by the appearance of a three-layer formation (dark-appearing thrombus, shiny-appearing fibrous endomyocardium, followed by dark myocardium) [21].

In a study by Chaosuwannakit., *et al,* in which the usefulness of CMR as a non-invasive diagnostic tool was evaluated, EMF was diagnosed in 25% of patients, of which 71.4% had compromise of both ventricles. All patients had LGE, mainly in the apex and, eventually, in the subvalvular region [22].

With regard to the histological study by biopsy, there is evidence of fibrous thickening of the endocardium, which is more pronounced in the apex [23]. Three stages are evident: the first is a phase of acute necrosis that is difficult to diagnose and that, generally, goes unnoticed; the next phase is the formation of thrombi adjacent to the compromised endocardium, which can produce thromboembolic events, and the last phase is fibrosis, which is characterized by progressive endocardial scarring, resulting in a restrictive pattern with atrial ventricular dysfunction and valve dysfunction [24].

Patients with isolated LV involvement predominate in functional class I and II, and can receive medical treatment for a longer time. Those with biventricular involvement or only RV involvement predominate in functional class III and IV, and tend to deteriorate faster. EMF has a poor prognosis, and medical treatment is usually ineffective.

Corrective surgery with endocardial resection in Schneider's study shows 70% survival after surgery at 10 years, with good quality of life [25-27]. Although initial surgical mortality can be high (15 - 20%) [28]. Currently, there is no effective medical treatment, with the surgical "corrective".

The clinical course varies depending on the underlying pathology and treatment. Heart transplantation remains a viable therapeutic option for selected patients with terminal heart failure and limiting symptoms. The prognosis is poor, with a 10-year survival of less than 50%. The causes of death are generally: heart failure, sudden death or thromboembolic events.

The low prevalence of this pathology, its insidious and progressive presentation usually determine errors in diagnosis and delays in dealing with it, as occurred with this patient.

At the time of this presentation, the patient continued with standard pharmacological treatment for heart failure, with a slight improvement in functional class. She has been rejected for surgical treatment.

Conclusions

EMF is the cardiomyopathy that constitutes the main cause of restrictive HF in tropical and subtropical countries of Africa and in some regions of South America. This entity, due to its low prevalence in practice and diagnostic approach, is a challenge for cardiologists.

We presented a patient who met the clinical, imaging and histological requirements for the diagnosis of hypereosinophilic endomyocardial fibrosis.

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