Endomyocardiofibrosis: A Systematic Review

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Abstract: Endomyocardiofibrosis was described first time in Uganda as an infrequent restrictive cardiomyopathy with a poor prognosis, characterized by fibrosis of the ventricular subendocardium and severe restrictive physiology leading to difficult therapeutic management and frequently associated with hypereosinophilic syndrome. Its higher prevalence in the tropics and its relationship in some cases with hypereosinophilic endocarditis has led to the search for genetic, infectious, autoimmune and nutritional causes, but its etiology remains unclear. It is a rare cardiomyopathy, difficult to diagnose and with a nonexistent effective treatment.

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Imaging methods such as echocardiography and cardiac magnetic resonance are essential for the initial diagnosis, although endomyocardial biopsy establishes the definitive diagnosis. Immunosuppressive treatment is only useful in the early stages of the disease and usually ineffective if installed late when signs of heart failure are present. Surgical treatment is generally palliative. (Curr Probl Cardiol 2021;46:100784.)

Introduction

In 1948 the pathologist Jack Davies described endomyocardiofibrosis (EMF) in Uganda, classifying it as a new restrictive cardiomyopathy, with a poor prognosis and an average survival of 2 years after the onset of symptoms.[1,6] Previously, in 1936, Loeffler described the association of hypereosinophilic syndrome with long-term ventricular fibrosis.[1-6] There are multiple probable causes of EMF, all of them insufficient to justify its development. Its higher prevalence in the tropics and its relationship in some cases with hypereosinophilic endocarditis has led to the search for genetic, infectious, autoimmune, and nutritional causes.[1-6] It is an infrequent cardiomyopathy, with a difficult diagnosis and a noneffective treatment.[1-6]

The objective of this review is to summarize the different pathophysiological, clinical, diagnostic, and treatment aspects of this forgotten condition.

Methodology

A systematic review of the literature using the flow diagram of the PRISMA system, was done.[7] We searched MEDLINE and LILACS databases to collect all the information published between 1990 and 2020 on EMF in humans. Discrepancies in selection of articles were resolved by consensus. The initial selection of articles included the following inclusion criteria: randomized clinical trials, case series, observational studies, systematic and nonsystematic reviews, and case reports. All articles were in English. Each manuscript was searched for missing references.

Results

The results of our search can be seen in the PRISMA flowchart indicating the selected articles (Fig 1).

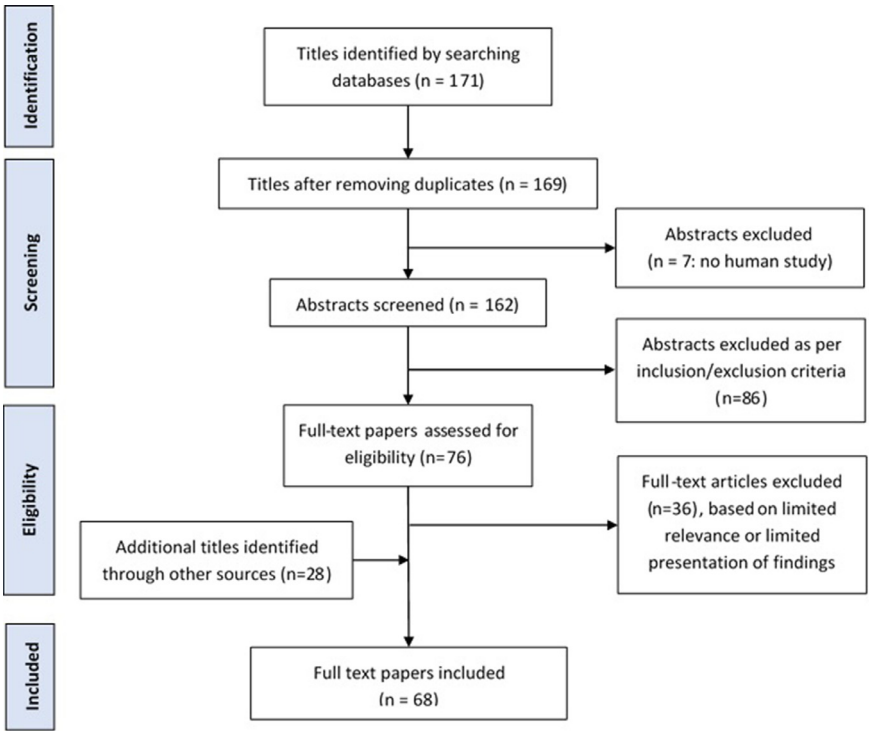

FIG 1. Flow-chart according to PRISMA methodology.

Epidemiology

More than 2400 cases have been reported worldwide,[1-6] mainly in tropical and subtropical underdeveloped countries in Africa, Asia, and South America: half belong to the sub-Saharan Africa, but other regions with large series include Brazil, Colombia, Mozambique, and India (Fig 2).[1-6] The THESUS-HF African Survey, which included 1006 patients with acute heart failure (HF) in 9 countries, detected only 1.3% with EMF.[8] In contrast, a community study using transthoracic echocardiogram (TTE) documented a prevalence of 20% in a rural community in Mozambique.[9] EMF affects children and young adults with a bimodal distribution at 10 years and 30 years, mainly women of childbearing age.[1-9] Its incidence has decreased correlating with the improvement of socioeconomic conditions.[1-6]

Etiology

Although there is not a single explanation, environmental factors that affect genetically susceptible individuals, trigger an acute eosinophilic endomyocardial damage and subsequent fibrosis. A population study report that 60% of the cases of EMF in Uganda had eosinophilia (OR 4.6).[10] Eosinophilic infiltration associated to endemic parasitosis (schistosomiasis, filariasis, malaria, and helminths) could lead to EMF in the long term.[1-6,10-20] Some authors described the presence of autoantibodies against myocardial proteins (anti-myosin antibodies), in some cases secondary to parasitosis such as Malaria.[15-19] A diet poor in magnesium and rich in cerium (present in the tuber *Manihot esculenta Crantz*), or high intake of cyanogenic glucosides (in *cassava linamarin*) frequently consumed in Africa, could generate an eosinophilic activation and EMF.[21-26] The association of EMF with high serum levels of 5-Hydroxyindoleacetic acid, as in carcinoid syndrome or serotonin-releasing drugs chronic consumption (antiparkinsonian drugs), was confirmed in animal studies.[27-29] Genetic susceptibility has also been proposed, especially in children.[30]

Pathophysiology

Olsen et al proposed 3 stages: acute eosinophilic myocarditis, subacute progressive subendocardial necrosis, and EMF with endocardial fibrotic thickening.[20] Type I collagen deposition and fibroblast proliferation leads to focal or diffuse fibrosis.[1-6,31-32] Half of the cases affect both ventricles and 40% only the left ventricle (LV) with severe ventricular distortion, restrictive diastolic dysfunction, and dilation of both atria.[33-35] Fibrosis extends from the apex to the posterior leaflet of the mitral valve

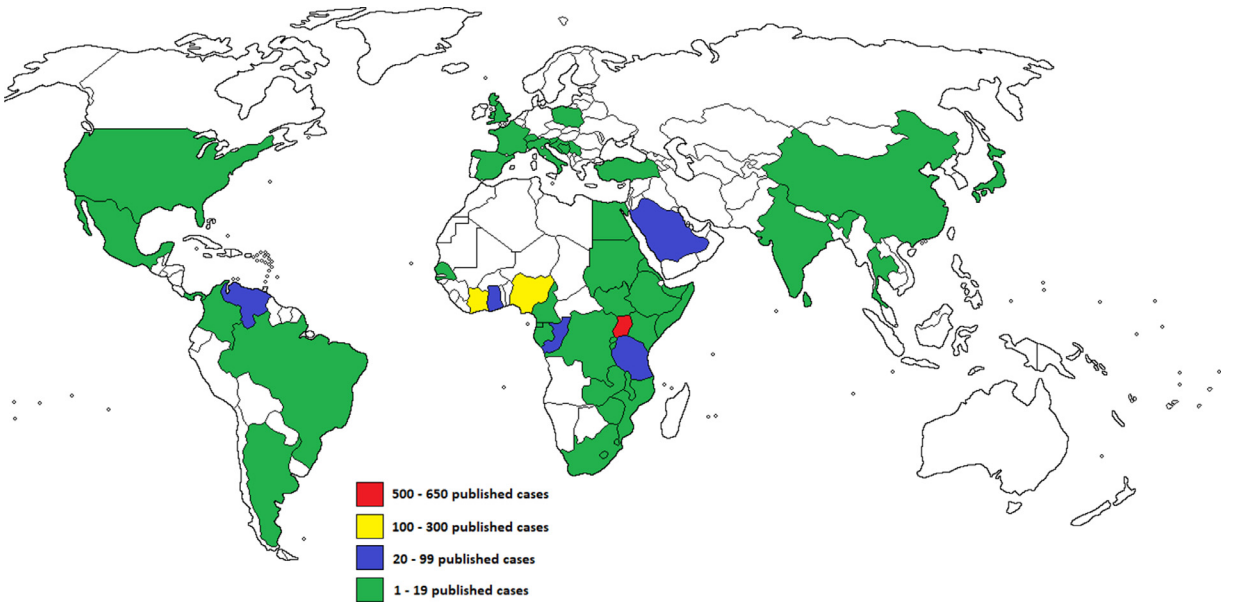

FIG 2. Published cases of EMF by country, between 1950 and 2006. Modified from reference #3.

(preserving LV outflow tract), and it can affect papillary muscles and tendinous chords generating insufficiency and distortion of the atrioventricular (AV) valve.[1-6] In advanced EMF, fibrothrombotic obliteration of the apex[1-6,31-33] can occur.

Clinical manifestations

In the acute phase, eosinophilic pancarditis presents with fever, eosinophilia, acute HF, or cardiogenic shock in some cases.[1-6]

In EMF patients, markers of acute inflammation disappear, and eosinophilia is rare.[1-6] Right HF is the most frequent clinical manifestation: jugular repletion, facial edema, exophthalmos, ascites, hepatomegaly, and congestive splenomegaly.[1-6] In half of the cases, exudative ascites rich in lymphocytes, associated with long-standing disease and poor prognosis, was present.[36] Chronic ascites and intestinal wall edema lead to bacterial translocation and peritonitis.[37-39] Malnutrition and hypoalbuminemia are secondary to a decrease in food intake and the development of a protein losing enteropathy, favoring fluid overload.[40] Paradoxically, lower limb edema is not frequent.[41]

Progressive AV valve regurgitation is also a marker of poor prognosis.[1-6] In advanced EMF, pulmonary embolism (PE) is frequent[42] and LV apical thrombosis can trigger stroke.[43]

Diagnosis

The presence of refractory right HF with or without eosinophilia in endemic countries should alert for a possible EMF diagnosis. A systematic algorithm to the sequential use of diagnostic tools is presented in Figure 3.

Electrocardiogram detect atrial fibrillation in 30% of cases and conduction disorders (first-degree AV block or right bundle branch block), but high-grade blocks are infrequent.[44-46] Right axis deviation and Qr wave in lead V1 are present in right ventricle (RV) dilatation.[44-46] Radiological signs are nonspecific, such as cardiomegaly (RV or biatrial dilation) and linear endocardial calcifications.[1]

TTE is the initial study, and identifies small ventricles with increased endocardial thickness in the inlet tract and apex, ventricular geometry alteration (mushroom or "V" sign), basal hypercontractility ("Merlon's sign"), and fibro-thrombotic obliteration of the apex (Fig 4).[47-51] AV valve regurgitation due to ventricular tenting is usually mild to moderate.[48] A restrictive filling pattern is commonly found, with prominent

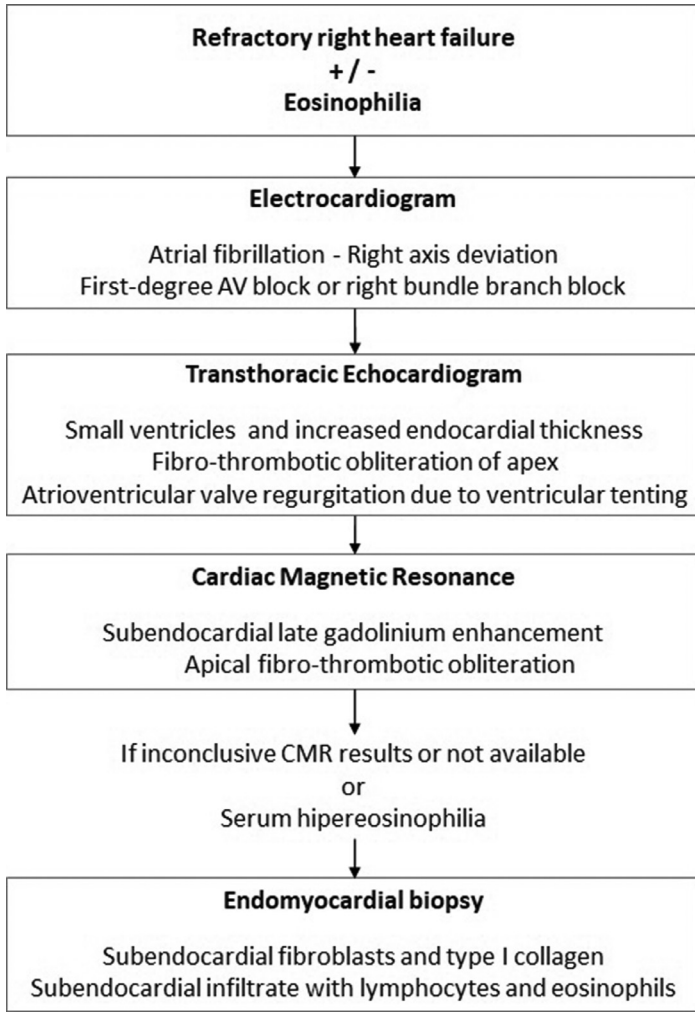

FIG 3. Systematic algorithm for the diagnosis of EMF.

E-wave, short deceleration time of E-wave, and a small A-wave.[54] Pericardial effusion is frequent.[47-51]

Cardiac magnetic resonance imaging, if available, confirms structural and functional findings of TTE, and late gadolinium enhancement technique detect apical fibro-thrombotic obliteration and mild apical hypertrophy better than TTE, useful to guide medical and surgical treatment when TTE is inconclusive (Figs. 5 and 6).[52-56]

Right intracavitary pressures measurement is useful to guide the treatment in cardiogenic shock or to evaluate pulmonary hypertension in

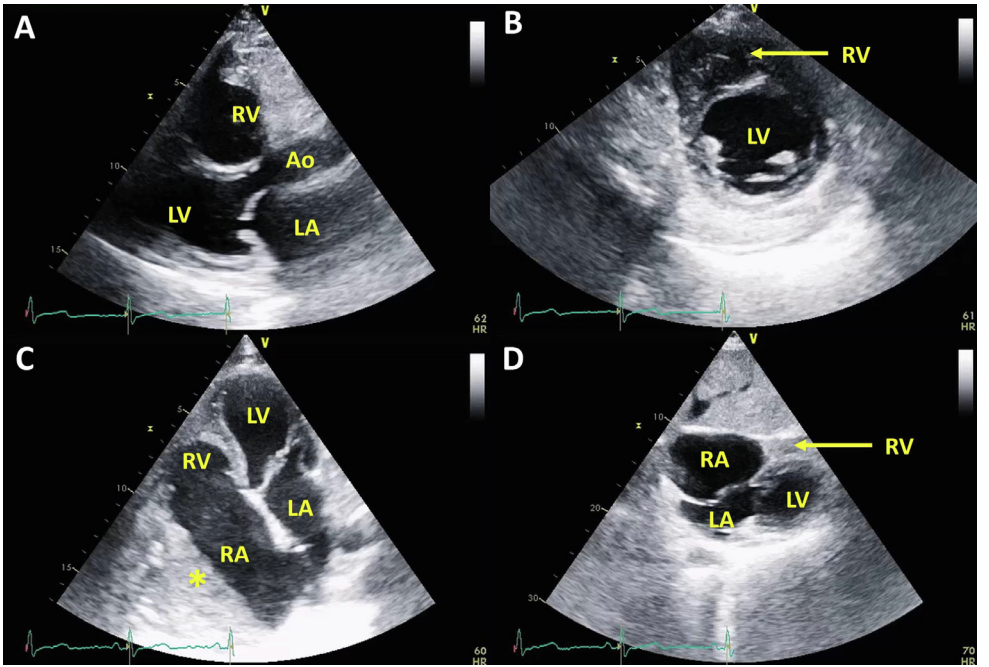

FIG 4. TTE of an EMF case, showing obliterated RV apex and dilated RA with a huge thrombus (*). (A) Parasternal long axis view. (B) Parasternal short axis. (C) Apical 4 chamber view. (D) Subcostal view. Courtesy of Dr. Gabriela Melendez, Magnetic Resonance Imaging Department, National Institute of Cardiology "Ignacio Chavez," Mexico City, Mexico. Ao, aorta; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; TTE, transthoracic echocardiogram.

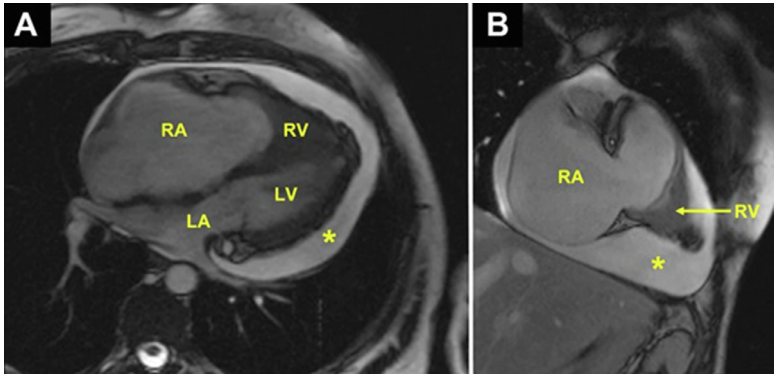

FIG 5. EMF with RV involvement in CMR imaging. Cine images on 4-chambers (A) and 2-chambers (B) views, demonstrating obliterated RV apex, dilated RA, and pericardial effusion (*). Courtesy of Dr. Gabriela Melendez, Magnetic Resonance Imaging Department, National Institute of Cardiology "Ignacio Chavez," Mexico City, Mexico. CRM, cardiac magnetic resonance; LA, left atrium; LV, left ventricle; RV, right ventricle; RA, right atrium; (*) pericardial effusion.

possible heart transplant.[48] Classic "square root" sign is sometimes present (like constrictive pericarditis).[57]

Endomyocardial biopsy shows endocardial thickening rich in fibroblasts and type I collagen, subendocardial infiltrate with lymphocytes and few eosinophils, and decreased capillary density, but with a low diagnostic sensitivity.[58]

In endemic countries, differential diagnoses are other restrictive cardiomyopathies (amyloidosis, hemochromatosis, and sarcoidosis), constrictive pericarditis, Ebstein's anomaly (small RV with low tricuspid valve implant), and rheumatic heart disease (fibrosis of leaflets and fusion of commissures).[1-6,59-61]

Mocumbi et al described some variables to diagnose EMF and predict its mortality (Table 1). The presence of 2 major criteria or 1 major and 2 minor criteria determines the clinical diagnosis; the sum of points determines the severity and prognosis.[9] Mortality causes are progressive HF, PE, and ventricular arrhythmias.[1-6]

Treatment

Symptomatic treatment of HF is based on diuretics, vasodilators, and anticoagulation due to its thromboembolic potential.[1-6] Corticosteroids and immunosuppressive drugs may be useful in severe hypereosinophilia, although there is no evidence to support them.[1-6] In patients with severe ascites and respiratory distress, paracentesis produces short-term symptomatic improvement.[1-6]

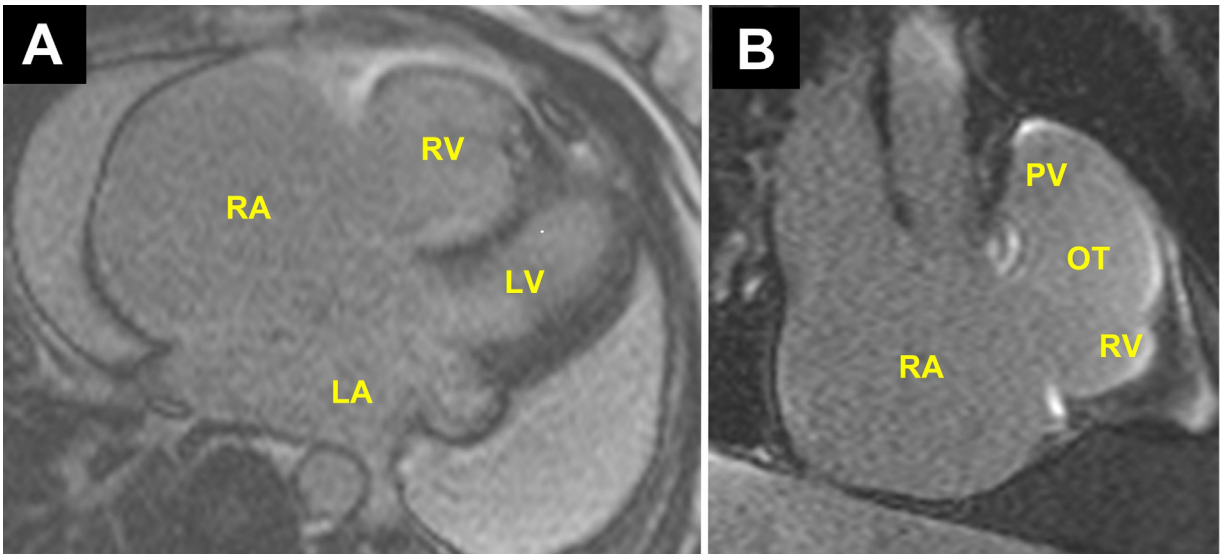

FIG 6. EMF with RV involvement in CMR imaging with subendocardial nonischemic patron LGE. (A) Four-chambers view. (B) Three-chambers view. Courtesy of Dr. Gabriela Melendez, Magnetic Resonance Imaging Department, National Institute of Cardiology "Ignacio Chavez," Mexico City, Mexico. CRM, cardiac magnetic resonance; LGE, late gadolinium enhancement; LA, left atrium; LV, left ventricle; OT, RV outflow; PV, pulmonary valve; RA, right atrium; RV, right ventricle.

Table 1. Diagnostic and prognostic criteria of EMF

Major criteria	Score
Endomyocardial plaques >2 mm in thickness	2
Thin (1 mm) endomyocardial patches affecting more than 1 ventricular wall	3
Obliteration of the right ventricle or left ventricular apex	4
Thrombi or spontaneous Echo contrast without severe ventricular dysfunction	4
Retraction of the right ventricular apex (right ventricular apical notch)	4
Atrioventricular valve dysfunction due to adhesion to ventricular wall	1–4
Minor criteria	Score
Thin endomyocardial patches localized to a ventricular wall	1
Restrictive flow pattern through mitral or tricuspid valves	2
Diastolic opening of the pulmonary valve	2
Diffuse thickening of the anterior mitral valve leaflets	1
Enlarged atrium with normal sized ventricle	2
Paradoxical motion of interventricular septum and flattening of the posterior wall	1
Increased density of the moderator band or other interventricular bands	1

Modified from reference #9.

Surgical resection of subendocardial fibrosis in centers of expertise increases survival but is not curative.[1-6,62-65] Surgical valve replacement in severe AV regurgitation cases usually does not have good results, especially in tricuspid regurgitation, with a postoperative mortality of 20%.[65] Surgical adverse outcomes predictors are prolonged ascites, PE, extensive endocardial fibrosis, RV hypoplasia, or cachexia, so the early diagnosis appear to be the key to the any treatment success.[1-6,62-65] Cavopulmonary connection in EMF with RV hypoplasia, and cardiac transplantation, are options in advanced cases, but evidence of benefit is insufficient.[1-6,66,67]

Some molecules that block different pathways of eosinophilic inflammation are under investigation. Imatinib is a monoclonal antibody that blocks FIP1L1-PDGFR tyrosine kinase, an essential enzyme in the pathophysiology of idiopathic hypereosinophilic syndromes, which could be useful in treatment of early stages of EMF.[68]

Discussion

EMF is a restrictive cardiomyopathy characterized by ventricular subendocardial fibrosis and restrictive physiology, which is usually late diagnosed and whose treatment is therefore often ineffective.[1-6]

Epidemiological studies that seek to describe the prevalence of EMF in the sub-Saharan Africa have focused on the presence of clinical manifestations, mainly HF, which has probably provided erroneous data. We must focus on subclinical disease detection to assess the real prevalence and create an early management strategy in endemic countries. Furthermore, these

studies have been conducted in hospital settings or in urban areas, so they may not really reflect its prevalence in the general population.

International multicenter studies are needed to identify genetic or environmental predisposing factors, leading to effective treatment of the disease.

The diagnosis of right HF and eosinophilia in patients residing in endemic countries should alert the cardiologist about possible EMF, although symptomatic cases are usually advanced, and their treatment is ineffective. Imaging methods such as TTE and cardiac magnetic resonance imaging, if available, are essential for diagnosis,[47-56] although only the endomyocardial biopsy establishes the definitive diagnosis.[58] The spread of TTE in tropical countries should allow the development of epidemiological surveillance and early diagnosis.

Finally, surgical treatment is generally palliative[1-6,62-65] and molecular techniques could shed light on the development of new effective options.[68]

Conclusions

EMF is a rare restrictive cardiomyopathy, prevalent in underdeveloped countries with a tropical climate, and its etiology remains uncertain. Early diagnosis and treatment in endemic areas reduce its morbidity and mortality. A better understanding of the etiology of EMF may allow us to offer the best possible treatment for this serious disease.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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