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Review Article

Tropical endomyocardial fibrosis: an overview

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ABSTRACT

Tropical endomyocardial fibrosis is the commonest form of endemic restrictive cardiomyopathy that affects mainly children and adolescents, and is geographically restricted to some poor areas in the tropical and subtropical regions of the world such as Africa, Latin America and Asia including southern districts of India especially in the coastal belt of Kerala state. Sub-endocardial fibrosis affecting the apices and the inflow tracts of the right or left ventricle, or both; and varying degree of atrioventricular valve regurgitation defines the disease. Chronic systemic venous hypertension and severe pulmonary hypertension are characteristic features of right ventricular and Left ventricular endomyocardial fibrosis respectively. Due to lack of resources for research in the disease endemic areas, the exact epidemiology, etiology and pathogenesis remain unknown, and the natural history is incompletely understood. Various infections and toxic factors were postulated regarding its etiology. During the last few years, incidence of the disease has decreased considerably because of the significant improvement in the living standards of the people with the corresponding decline in the childhood malnutrition, infections, worm infestations and associated eosinophilia. It is a condition with high morbidity and mortality, for which no effective therapy is available. However, surgical management improves the natural history of this disease to some extent. We have conducted a systematic review of the most intriguing aspects of epidemiology, natural history, clinical picture and management of endomyocardial fibrosis, proposing new ways to increase research into this challenging and neglected cardiovascular disease. We relied primarily on articles in the MEDLINE database with either ‘‘endomyocardial fibrosis’’ or ‘‘endomyocardial sclerosis’’ in the title.

Keywords: Endomyocardial fibrosis, Restrictive cardiomyopathy, Eosinophilia, Malnutrition, Endemic disease, Diastolic dysfunction

INTRODUCTION

Endomyocardial fibrosis (EMF) is the commonest form of endemic restrictive cardiomyopathy of unknown origin in the tropical and subtropical regions of the world that is characterized by dense acellular fibro-collagen tissue deposition underneath the endothelial layer of the endocardium and, to a lesser extent, in the myocardium, in the inflow tracts, and the apices of right ventricle, left ventricle, or both resulting in reduced ventricular cavity size leading to restriction of the ventricular filling.[1] The fibrous tethering of the papillary muscles and chordae tendinae of atrioventriclar valves, thereby producing mitral and/or tricuspid regurgitation and superimposed mural thrombosis and calcification as a result of atriomegaly and/or atrial fibrillation further complicate the clinical course of this enigmatic disease.[2] Systolic performance is normal or slightly depressed in patients with EMF; and diastolic dysfunction is mainly responsible for progressive left and/or right-sided heart failure accounting for significant rise in morbidity and mortality in equatorial regions of the globe.[3]

Observed by Arthur Williams as early as 1938, Jack N.P. Davies, a pathologist at Makerere University, Kampala, Uganda, first coined the term endomyocardial fibrosis

(EMF) and delineated the clinico-pathologic features of this new restrictive cardiomyopathy, still called Davies disease by some authors.[4] Since the first descriptions of EMF in the late 1940s, over 2400 cases of this disease have been reported throughout the world.[5] Half of these cases have come from the impoverished children and young adults in sub-Saharan Africa, with a quarter of cases from Uganda alone.[6] Other regions with large case-series of this clinical entity include parts of equatorial Asia and South America[7] (Figure 1).

Figure 1: Distribution by country of published cases of endomyocardial fibrosis between 1950 and 2006. Includes only those cases diagnosed at autopsy, or confirmed by surgery or cardiac imaging.

The nosology of EMF coincides with some related disorders. EMF is sometimes considered part of a spectrum of a single disease process that includes Löeffler endocarditis.[8] Tropical EMF should be distinguished from endocardial fibroelastosis, which is characterized by cartilaginous thickening of the mural endocardium, chiefly of the left ventricle.[9]

Despite uncertainty as to the cause of EMF, the volume of publications on the subject has declined during the past decade. In an effort to rekindle interest in this neglected disease, we have undertaken a systematic review of research on the most intriguing aspects of this clinical entity, both in India and abroad. We have based this review primarily on articles in the MEDLINE database published between January 1, 1950 and January 1, 2014 with either ‘‘endomyocardial fibrosis’’ or ‘‘endomyocardial sclerosis’’ in the title. We limited this search to articles in English only, and did not search other databases. We consulted additional papers and books referenced through this search strategy, and have cited those most focused on epidemiology and etiology.

EPIDEMIOLOGY

EMF refers to a specific syndrome with characteristic epidemiological features. Though EMF is a disorder found typically in tropical and subtropical Africa, notably in Uganda, southern Nigeria and coastal Mozambique, accounting for 25% of cases of congestive heart failure and death in the equatorial Africa; this disease is increasingly recognized in other tropical and subtropical regions within 15 degrees of the equator, including southern districts of India especially in the coastal belt of Kerala state, Sri Lanka, Brazil, Côte d'Ivoire, Venezuela and Colombia.[10] In fact, more than 90% of the reported cases with EMF have occurred in the same geographical locations that are within 15 degree of the equator[11] (Figure 1). Importantly, it is also recognized in the Middle East, particularly Saudi Arabia.[12] Endomyocardial fibrosis has increased incidence among the Rwanda-Burundi immigrant tribes of Uganda and in individuals of low socioeconomic status.[13] It has a slight male preponderance, is most common in children aged 5-15 years and young adults, but has been described in individuals into the sixth or even seventh decade of life.[14] Although most cases occur in black individuals, there are occasional presentations in white subjects residing in temperate climates. There are rare reports of endomyocardial fibrosis in individuals who have not resided in tropical areas.[15] The highest prevalence of this condition likely remains in regions of sub-Saharan Africa. In a recent screening study in rural area in Mozambique, approximately 20% of a random sample of 1063 subjects of all age groups had echocardiographic evidence of this disease with a male preponderance[16] (Table 1). Reporting bias skews this distribution, and in the absence of population-based studies, worldwide prevalence can only be estimated.[17]

Table 1: Proposed causes of endomyocardial fibrosis.

Causes of EMF	
Infections	Toxoplasmosis
	Rheumatic fever
	Malaria
	Myocarditis
	Helminthic parasites
Allergy	Eosinophilia
	Auto-immunity
Malnutrition	Protein deficiency
	Magnesium deficiency
Toxic agents	Cerium
	Cassava
	Thorium
	Serotonin
	Plant toxins
	Vitamin D

The frequency of EMF cases in Uganda has a bimodal peak at age 10 and age 30.[18] Childhood EMF in this country affects boys and girls equally, while adult EMF affects women twice as often as men.[19] In Nigeria, some studies have found a two to one male preponderance, while others have not shown any difference between the sexes.[20] The majority of EMF cases have come from low-lying, humid parts of tropical countries (Table 1). In East Africa, Uganda has a striking burden of EMF in contrast with Kenya and the Ethiopian highlands. In Tanzania and Mozambique, cases have clustered along the coastal forest.[21] Despite the frequency of EMF in the areas

around the southern cities of Ibadan and Enugu in Nigeria, a review of cardiovascular admissions to a referral center in Zaria's northern savanna during the 1970s found no patients with this disease.[22] In India, Kerala's tropical rain forest has generated one of the largest case series in the world, while other parts of the country have reported relatively few cases.[23] In China, the largest number of case reports has also come from the southern province of Guangxi.[24] In South America, patients with EMF have come from Brazil and Columbia rather than Peru or Ecuador.

ETIOLOGY

Despite several hypotheses regarding cause, no account of the etiology of this disease has yet fully explained its unique geographical distribution. The question of whether all cases of EMF have the same underlying cause still ranks as one of the great mysteries in cardiology.[25] The factors most frequently implicated in the etiopathogenesis of EMF are ethnicity,[26] poverty,[27] cyanogenic glycosides and cerium-mediated toxicity in cassava based diet,[28] serotonin toxicity in a plantain-based diet,[29] malnutrition,[30] magnesium deficiency,[31] cerium and thorium intoxication present in monazite deposits, vitamin D intoxication,[32] chronic beriberi, infections (viral, malarial and parasitic infections), autoimmunity such as rheumatic fever, eosinophil toxicity,[33] other toxic agents (plant toxins such as *Argemone mexicana*), high content of lanthanides in the soil of in the regions with high prevalence of this disease and heredity[34] (Table 2).

Table 2: Prevalence of EMF.

Region	Authors	Country	Dx	Dates	Pop	n	Ages	Setting	EMF
Sub-Saharan Africa	Freers et al.	Uganda	E	93-94	CV	500	All	O	20%
	Williams et al.	Uganda	N	51-53	HF	231	All	I	15%
	Brockington & Edington	Nigeria	A, N	62	CV	252	All	I	16%
Middle East	Rashwan et al.	Egypt	E	91-93	CV	10000	All	O	0.2%
Latin America	Guimaraes	Brazil	N	90-91	CV	734	All	I	2%
South Asia	Kutty et al.	India	E	78-94	CV	22666	All	O	1.5%
	Datta and Aikat	India	N	64-72	CV	906	All	I	0.9%
China	Yin et al.	China	E	2000	CV	-	All	I	3%

Dx, Diagnostic modality; E, echocardiography; N, necropsy; A, angiography; O, outpatient; I, inpatient; CV, all patients with cardiovascular disease; HF, only heart failure

Since there have been reports of sporadic cases of EMF in foreign people from temperate areas after short stays in endemic regions, and in view of climatic restrictions of the disease, the role of infectious agents appears plausible. Plasmodium species, Schistosoma, Microfilaria, Helminths, Coxsackie B virus, Arboviruses and Toxoplasma gondii, loa loa, etc. have all been considered as possible causes or triggers for disease.[35] Failure to produce typical EMF lesions in a study conducted on plantain-fed guinea pigs, rats and patus monkeys by Mckinny and Crawford culminated the possible role of serotonin in a plantain-based diet.[36]

While the importance of genetic predisposition is less studied, it is supported by the finding of familial cases of EMF in clinical series[37] and demonstration of familial clustering of cases in a community-based study in Mozambique.[38] Both environmental and genetic factors may play a role in determining familial EMF.

Research in African populations has shown evidence of higher prevalence of anti-heart antibodies in EMF patients when compared to those with rheumatic heart disease, dilated cardiomyopathy and healthy controls; it is not clear whether these autoantibodies are the cause or the result of EMF. In a subset of EMF patients from Mozambique who had their serum tested for the presence of anti-myocardial proteins,[39] strong immunoglobulin G (IgG) reactivity against myocardial proteins was found. These patients also had an increase in immunoglobulin M (IgM) reactivity when compared to healthy controls, corroborating previous findings from India.[40]

The role of eosinophils in the pathogenesis of EMF is controversial. Whether the eosinophil actually induces myocardial necrosis and subsequent fibrosis or is attracted to the endocardial surface as a result of the initial insult is unknown. Some authors have argued that in tropical eosinophelia, where the eosinophil count does climb to levels as high as 12500/dl, endomyocardial fibrosis is rarely seen and the cardiac manifestations are limited, while severe eosinophilia is absent in EMF.[41] In general, the eosinophil is not present as frequently in cases of tropical EMF as in löeffler endocarditis especially at later stages of the disease when the patient is symptomatic; thus, the role of the eosinophil in EMF is likely less significant.

EMF is most frequently observed in the socially disadvantaged children and young adults. These groups frequently have malnutrition, and in regions of sub-Saharan Africa, where the disease is most prevalent, the typical diet is high in a tuber called cassava, which contains relatively high concentrations of the rare earth element cerium (Ce). The combination of high cerium levels and hypomagnesemia has been shown to produce EMF-like lesions in laboratory animals.[42] Valiathan and Kartha have speculated that cerium or thorium present in monazite deposits may explain regional variation in EMF prevalence in this region. No empirical studies have yet come forward to support this geochemical hypothesis.[43]

CLINICAL COURSE AND PATHOPHYSIOLOGY

In EMF, the underlying process produces patchy fibrosis of the endocardial surface of the heart, leading to reduced compliance and, ultimately, restrictive physiology as the endomyocardial surface becomes more generally involved. Endocardial fibrosis principally involves the apices and inflow tracts of the right and/or left ventricles and may affect the atrioventricullar valves mainly by tethering the papillary muscles, leading to tricuspid and/or mitral regurgitation.[44]

The natural history of EMF is not completely understood because patients usually present late to medical attention and remain asymptomatic for long periods. The early part of the disease is rarely clinically recognized in India and the disease comes to attention in the late stages and isolated endocardial involvement and intracardiac thrombi are the peculiar features.[45] Olsen proposed three phases of the disease in his patients from Uganda. The first necrotic phase involves the eosinophilic infiltration of the myocardium with necrosis of subendocardium with a pathologic picture consistent with acute myocarditis, and characterized by febrile illness and in severe cases with heart failure and shock. This is reportedly present in the first five weeks of the illness.[46] Those who survive this acute illness, progress into the second stage, typically observed after ten months, is associated with thrombus formation over the initial lesions, with a decrement in the amount of inflammatory activity present. Ultimately, after several years of disease activity, the final fibrotic phase is reached, when the endocardium is replaced by collagenous fibrosis. This pathomorphologic schema is not observed uniformly and has not been consistently supported by the other investigators. Most of the patients come to clinical attention in this chronic burnt-out phase. Once clinically diagnosed, the onset of complications like atrial fibrillation, thrombo-embolism, and progressive atrioventricular valve regurgitation abbreviates the natural history.[47]

Myocardial fibrosis consists of collagen deposition and fibroblast proliferation. These changes can potentially explain most of the symptoms in patients with EMF. Fibrosis increases the stiffness of the heart, resulting in the restrictive physiology. Ventricular stiffness along with atrioventricular valvular regurgitation results in atrial enlargement, which has been linked to atrial arrhythmias such as atrial fibrillation. Fibrosis also reduces conduction velocity, impairs activation patterns and may provide substrate for wave breaks and reentry.[48] Atrial fibrillation has been reported in more than 30% of patients with EMF followed by other rhythms or conduction abnormalities like junctional rhythm, heart blocks, and atrioventricular conduction delay.[49]

PATHOLOGY

Endomyocardial fibrosis affects both the right and left ventricles in approximately 50% of patients, purely the left in 40%, and the right ventricle alone in the remaining 10%.[50] The typical gross appearance is that of a normal to slightly enlarged heart. The right atrium may be dilated in proportion to the severity of right ventricular involvement. There is often a pericardial effusion, which may be large. The fibrotic retraction of the right ventricular apex produces the typical apical dimple which is demonstrable with 2-dimensional echocardiography.[51] The hallmark feature of the disorder is fibrotic obliteration of the apex of the affected ventricles (Figure 2). The fibrosis involves the papillary muscles and chordae tendineae, leading to atrioventricular valve distortion and regurgitation. In the left ventricle, the fibrosis extends from the apex to the posterior mitral valve leaflet, usually sparing the anterior mitral leaflet and the ventricular outflow tract. Endocardial calcific deposits can be present involving diffuse areas of the ventricle. The fibrotic tissue often creates a nidus for thrombus formation, which can be extensive. Atrial thrombi also occur. The process usually does not involve the epicardium, and the coronary artery obstruction is distinctly uncommon.

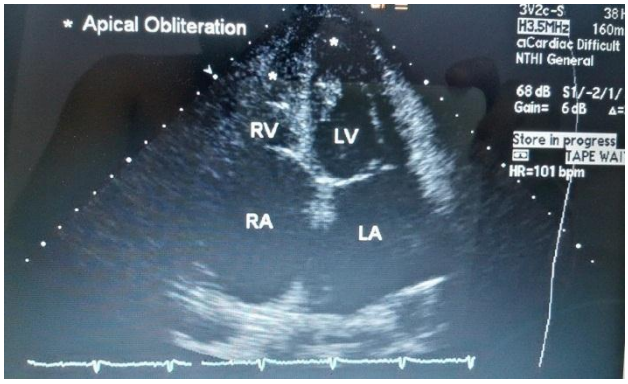

Figure 2: Apical, four-chamber, two-dimensional echocardiogram of a patient with endomyocardial fibrosis showing apical obliteration of both ventricles. RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle.

HISTOLOGIC FINDINGS

Endomyocardial fibrosis is clearly apparent histologically, presenting as a thick layer of collagen

overlying loosely arranged connective tissue.[52] In addition, there are fibrous and granular septations extending into the underlying myocardial tissue. Myocyte hypertrophy is common.[53] Whereas cellular infiltration is uncommon, interstitial edema is frequently present. Fibroelastosis that is found in the ventricular outflow tracts beneath the semilunar valves often represents a secondary process caused by local trauma. Examination of intramural coronary arteries may show involvement with medial degeneration, the deposition of fibrin, and fibrosis. Samuel and Anklesaria published initial autopsy series from south India in 1960.[54] CK Gopi, in 1962, from Trivandrum, described the specimen kept in the hospital autopsied in 1950s as a case of right ventricular endomyocardial fibrosis with right atrial thrombi.[55]

CLINICAL MANIFESTATIONS

Typically, EMF has an insidious onset, though the disease may be heralded by an acute febrile illness; and symptomatic status of patients at presentation relates to the specific chambers and/or valves where the disease is most extensive, the duration of disease and the presence of signs of activity.[56] Pulmonary congestion signals left-sided involvement, whereas predominantly right-sided disease may mimic restrictive cardiomyopathy or constrictive pericarditis. Atrioventricular valve regurgitation is common. Endomyocardial fibrosis is a relentless and progressive process, although the time course of decline may vary considerably, with some patients appearing to have periods of stability. Cachexia, malnutrition and hypoalbuminemia are characteristic of advanced disease. Modes of death include progressive heart failure, associated arrhythmias, infection, infarction, sudden cardiac death, and complications of surgery.[57]

Right ventricular endomyocardial fibrosis

In pure or predominant right ventricular involvement, the right ventricular apex is characterized by fibrous obliteration, which may extend to involve the supporting structures of the tricuspid valve, with ensuing tricuspid regurgitation. Patients present with chronic systemic venous hypertension and exhibit exophthalmos, an elevated jugular venous pressure, a prominent *v* wave with rapid *y* descent, and a right-sided S_3 gallop. There is prominent hepatomegaly with a pulsatile liver, ascites, splenomegaly, and peripheral edema, but pulmonary congestion is typically absent because of the lack of left-sided involvement. In this regard, pulmonary artery and pulmonary capillary wedge pressures are normal. A large pericardial effusion is often present, but pleura are spared, yet another noted peculiar feature of this disease.[58] The right atrium may be enormously dilated. Several distinctive features which cannot be explained solely by low cardiac output and retrograde congestion, include central cyanosis, giant ascitis in the absence of pedal edema, hyperpigmentation of lips and gums, proptosis and parotid swelling. Ascitis is not fully explained by congestion since the fluid is an exudate with predominance of lymphocytes and high protein content; it is thought to be due to peritoneal inflammation and reduced reabsorption of peritoneal fluid caused by fibrosis. Cyanosis and clubbing are believed to be due to stretch opening of the foramen ovale, although arterial oxygen desaturation can occur in advanced right EMF even in the absence of atrial septal defect or patent foramen ovale.[59]

The electrocardiogram often has findings consistent with right-atrial enlargement, especially a qR pattern in lead V_1, supraventricular arrhythmias, such as AF in one third of the patients, low QRS voltages, AV blocks, RBBB or LBBB or non-specific IVCD and non-specific ST-T wave changes are common. The chest radiograph often demonstrates obvious right atrial prominence, a pericardial effusion, and calcification in the walls of the right and, less frequently, the left ventricle. Echocardiography demonstrates thickening of the right ventricle with obliteration of the apex, a dilated atrium, hyperechoic endocardial surfaces, and abnormal septal motion in patients with tricuspid regurgitation. Sparing of the outflow tracts is characteristic.

Doppler interrogation yields typical pattern of filling restriction (increased E/A; decreased isovolumic relaxation time (IVRT); and decreased deceleration time) (Figure 2, 4). On angiography, the ‘mushroom sign’ has been used to describe the shape of ventricle when the right ventricular apex is typically not visualized because of fibrous obliteration; tricuspid regurgitation, right atrial enlargement, and filling defects in the right atrium caused by thrombi may be present (Figure 3).

The typical hemodynamic finding on cardiac catheterization is the dip and plateau pattern of restrictive ventricular filling, which does not show pressure equalization between ventricles, unlike constrictive pericarditis.[60]

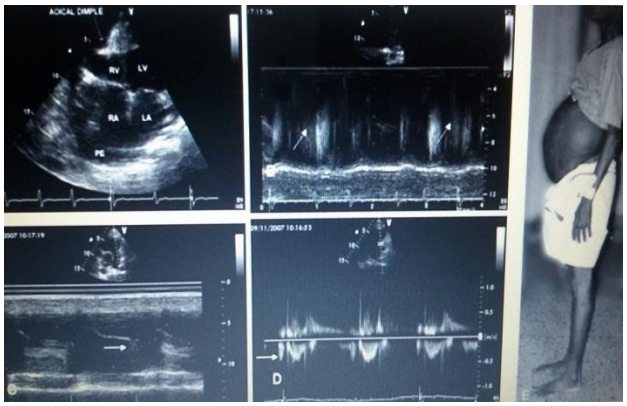

Figure 3: The clinical and echocardiographic features of right ventricular endomyocardial fibrosis. Clinical picture (E) shows the massive ascites with no pedal oedema. Echo pictures A to D show: A. apical 4 chamber view showing the fibrotic obliteration.

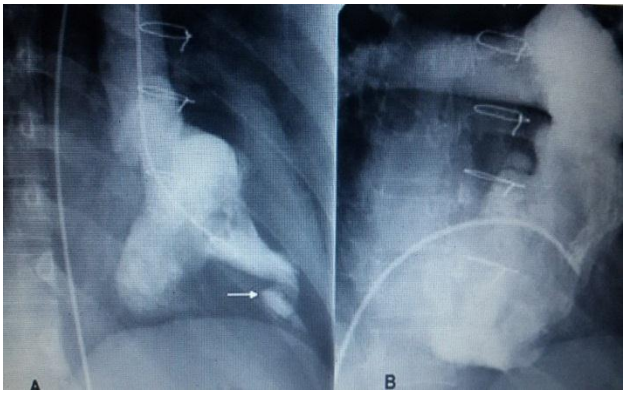

Figure 4: Angiocardiographic features of typical endomyocardial fibrosis showing apical ventricular cavity obliteration. (A) left ventricular angiogram in right anterior oblique view and the arrow points to an apical diverticuation, and (B) shows right vent.

Left ventricular endomyocardial fibrosis

In cases of predominant left-sided disease, fibrosis involves the ventricular apex and often the chordae tendineae or the posterior mitral valve leaflet, producing mitral regurgitation. The associated murmur may be late systolic, characteristic of a papillary muscle dysfunction murmur, or pansystolic. Findings of pulmonary hypertension may be prominent, and an S_3 protodiastolic gallop is frequently present.[61] The electrocardiogram usually shows ST-segment and T wave abnormalities, low-voltage QRS complexes if a pericardial effusion is present, or left ventricular hypertrophy. Left atrial abnormality is often noted. As with right-sided involvement, atrial fibrillation is often present and portends a poor prognosis. Echocardiography reveals increased endocardial echoreflectivity, preserved systolic function, apical obliteration, enlarged atrium, pericardial effusion of varying size, and Doppler ultrasound evidence of mitral regurgitation. Pulmonary hypertension is typically observed during cardiac catheterization, as well as left atrial hypertension and a reduced cardiac index. Left ventriculography shows mitral regurgitation, and ventricular filling defects caused by intracavitary thrombi may be present. Coronary arteriography usually excludes obstructive epicardial vessel stenoses.

Biventricular endomyocardial fibrosis

Biventricular endomyocardial fibrosis is more common than either isolated right- or left-sided disease. The typical clinical presentation of endomyocardial fibrosis resembles right ventricular endomyocardial fibrosis; however, a murmur of mitral regurgitation is indicative of left-sided involvement. Unless left ventricular involvement is extensive, severe pulmonary hypertension is absent and the right-sided findings are the predominant mode of presentation. Approximately 15% of patients will experience systemic embolization, and only 2% will have infective endocarditis.

STAGING

Mocumbi and colleagues provided a set of echocardiographic criteria that is useful in staging the disease, studying its progression, and comparing the results of different epidemiological studies.[62] In this classification, there are six major and seven minor criteria. The diagnosis is considered when two major; or one major and two minor criteria are present. A score has been assigned to each criteria and the severity of the disease is assessed by this scoring system; a total score of less than 8 indicates mild EMF; a score of 8-15 indicates moderate disease, and a score of more than 15 indicates severe disease.

Major criteria

1. Endomyocardial plaque more than 2mm in thickness; score: 2
2. Thin (≤1 mm) endomyocardial patches affecting more than one ventricular wall; score: 3
3. Obliteration of the right and/or left ventricular apex; score:4
4. Thrombi or spontaneous echo contrast without severe ventricular dysfunction; score: 4
5. Retraction of the RV apex (RV apical notch); score: 4
6. Atrioventricular valve dysfunction due to adhesion of valve apparatus to the ventricular wall; score: 1-4 depending on the severity of regurgitant lesion.

Minor criteria

1. Thin endomyocardial patches localized to single ventricular wall; score: 1
2. Restrictive flow pattern across atrioventricular valves; score: 2
3. Pulmonary valve diastolic opening; score: 2
4. Diffuse thickening of anterior mitral leaflet; score; 1
5. Enlarged atria with normal sized ventricles; score: 2
6. M movement of the IVS and flat posterior wall; score: 1
7. Enhanced density of the moderator or other intraventricular bands; score: 1

DIAGNOSIS

The clinical manifestations of EMF of either ventricle overlap with other conditions that cause heart failure or ascites. For this reason, a conclusive diagnosis of EMF depends on imaging or surgical visualization of the heart during life, or on autopsy after death.[63] Detection of endomyocardial fibrosis in individuals from the appropriate geographic area requires typical clinical and laboratory findings as well as angiography. Eosinophilia is variably present and may result from parasitic infection.[64]

Endomyocardial biopsy is diagnostic, but false negatives can occur because of the patchy nature of the disease.

Insofar as myocardial biopsy may be complicated by systemic emboli, left-sided myocardial biopsy is contraindicated.

DIFFERENTIAL DIAGNOSIS

In areas endemic for EMF, distinction should be made from RHD, dilated cardiomyopathy, tuberculous pericarditis and constructive pericarditis, hence the need for echocardiography. Past history of rheumatic fever, evidence of mitral stenosis or involvement of the aortic valve favors RHD, but pure mitral insufficiency may be particularly difficult to differentiate from left EMF when fibrosis and endocardial thickening affects predominantly the valve tissue. Of notice is the concurrence of RHD and EMF in some patients.[65] Dilated cardiomyopathy is a diagnosis by exclusion of other possible causes of cardiac failure. Finally, right EMF may mimic Ebstein malformation.[66]

MANAGEMENT

The medical management of endomyocardial fibrosis remains challenging. The medical management of EMF consists of ameliorating acute disease, as well as preventing and treating heart failure, arrhythmias and thromboembolism. In poor settings, where the disease is endemic, this is usually achieved with the use of diuretics, vasodilators, digitalis, beta-blockers and anticoagulants. Patients with advanced disease need large doses of drugs and frequent admissions to hospital for invasive procedures to alleviate effusions and control arrhythmias. The use of oral corticosteroids in patients with EMF and hypereosinophilia is not supported by clinical trials or longitudinal studies on the effects of this therapy. Indeed, several reports show that they have no or little influence on the natural course of EMF.[67] Management of ascitis relies on frequent evacuation of fluid by paracentesis; sometimes intravenous replacement of albumin at the time of the procedure is used to compensate protein loss.[68]

Patients with AF and/or thrombus on echocardiography warrant standard anticoagulation therapy. Heart failure is difficult to control, and diuretics are effective only in early stages of the disease, losing efficacy with advanced ascites. Once endomyocardial fibrosis progresses to severe form, surgical decortication with atrioventricular valve replacement on affected sides is the treatment of choice[69] (Figure 5). Surgery increases survival and quality of life, when compared to medical therapy, but must be performed before irreversible cardiac and hepatic damage occurs.[70] Surgical therapy consisting of conservative endocardiectomy and valve replacement or repair usually results in hemodynamic improvement with reductions in ventricular filling pressures, increased cardiac output, and normalized angiographic appearance. Operative mortality is high, between 15% and 25% and may be lower if valve replacement is not necessary.[71] Relative contra-indications for surgery in poor-settings are large long-standing ascitis, extreme cachexia, chronic pulmonary thromboembolism, extensive endocardial fibrosis or calcification, impaired myocardial function and extreme shortening of leaflets when valve replacement being anticipated.Fibrosis may recur, although there are case reports of excellent long-term survival.[72]

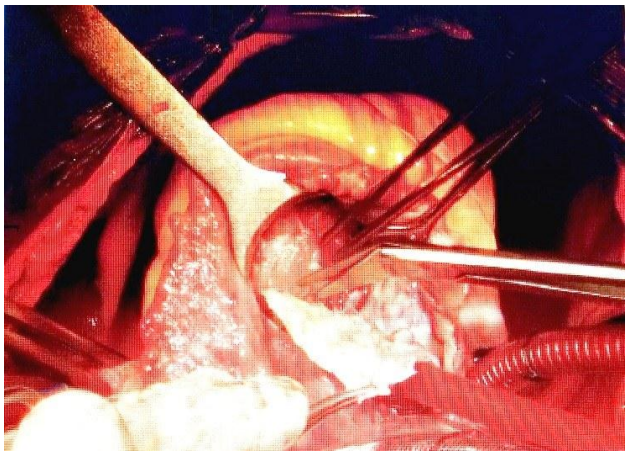

Figure 5: Intraoperative image of the surgical procedure to excise the thickened endocardium. Myocardium with healthy appearance is seen underneath the excised endocardium.

PROGNOSIS

Overall prognosis of patients with EMF is poor and depends on the extent and distribution of the disease within the various chambers and valves of the heart. The disease is usually progressive but the time course of decline varies.[73] Since most patients have extensive disease at the time of presentation; therefore, survival after diagnosis is relatively brief, averaging approximately two years after symptom onset.[74] In one study, 95% of a group of patients had died at two years.[75] In a second study, 44% of patients died within one year after the onset of symptoms, and another 40% of patients died 1-3 years after onset of symptoms. Gupta and colleagues[76] defined the natural history of the disease in Kerala in the late 1980s. Follow up of the initial 200 patients showed a 10 year survival of only 37 per cent. Patients with right-sided disease present better tolerance to exercise and may remain relatively asymptomatic for several years, despite severe disease associated with cardiomegaly and intermittent pericardial effusion. Their lack of disability and relative longevity seems to be associated with the capacity to increase cardiac output and slightly decrease the right atrial pressure.[77] Ascites, atrial fibrillation and New York Heart Association (NYHA) class IV were the poor prognostic indicators.[78]

FUTURE DIRECTIONS

Irrespective of intense multi-faceted research, endomyocardial fibrosis continues to be an enigmatic

disorder. The specific endocardial involvements, localization to certain geographical pockets, propensity to affect the poor and typical endocardial calcification are the peculiarities of this disease. Advanced evaluation like extending to genomics and proteomics is likely to throw light on the final common pathway which leads to endocardial damage and fibrosis. At the same time, molecular techniques could bring new life to old ideas. The fusion protein FIP1L1-PDGFRa, a constitutively activated tyrosine kinase found in as many as half of those with the idiopathic hypereosinophilic syndrome, has emerged as a therapeutic target for imatinib. The prevalence of FIP1L1-PDGFRa among those with EMF could give another important clue about the etiology and treatment of this disease.[79] Studies that measure levels of inflammatory markers, such as C-reactive peptide or inflammatory cytokines such as tumor necrosis factor alpha, could help explore the role of inflammation in EMF and suggest therapeutic strategies in early forms of the disease.[80] Echocardiographic studies of patients with hyper-reactive malarial splenomegaly could shed light on the prevalence of early endocardial disorders in this population. The recent finding that serotonin acts as a chemotactic factor for eosinophils may reignite inquiries into the role of this pathway in EMF.[81] Zanettini and colleagues have found that some anti-Parkinson medications induce valvular fibrosis via their action on 5HT2B receptors and polymorphisms in this receptor could influence susceptibility to EMF in the presence of intermittent eosinophilia.[82]

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