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CASE REPORT

INTERMEDIATE

CLINICAL CASE

Tropical Endomyocardial Fibrosis

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ABSTRACT

Tropical endomyocardial fibrosis is a common cause of restrictive cardiomyopathy worldwide, but is relatively rare in developed countries. We present a case of tropical endomyocardial fibrosis with right ventricular involvement initially mistaken as Ebstein's anomaly. We highlight the need for timely and accurate diagnosis to ensure appropriate management. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2020;2:819–22) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

A 42-year-old male immigrant from Kerala, India, with a reported history of Ebstein's anomaly status post-bioprosthetic tricuspid valve replacement presented to cardiology clinic with shortness of breath and abdominal distention. A transthoracic echocardiogram (TTE) demonstrated a normally functioning bioprosthetic tricuspid valve with marked right atrial dilation and prominent right ventricular (RV) apical hypertrophy (**Figure 1A**, Video 1). Contrast-enhanced echocardiography revealed patchy enhancement of the hypertrophied regions, suggesting vascularity (**Figure 1B**, Video 2).

PAST MEDICAL HISTORY

Past medical history was notable for reported Ebstein's anomaly diagnosed 1 year earlier. He initially presented with exertional dyspnea and was found to be in atrial fibrillation. TTE at that time reportedly demonstrated massive right atrial enlargement and an apically displaced septal leaflet of the tricuspid valve along with concomitant tricuspid regurgitation concerning for Ebstein's anomaly (Video 3). He underwent tricuspid valve replacement with a bioprosthetic valve but had persistent symptoms.

LEARNING OBJECTIVES

- To recognize the clinical presentation of EMF.
- To review the imaging modalities and respective findings for EMF.
- To understand the medical and surgical management options for EMF.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for marked RV apical hypertrophy includes variants of Yamaguchi's disease (or apical hypertrophy), Ebstein's anomaly, Loeffler's endocarditis, endomyocardial fibrosis (EMF), and cardiac involvement of Behcet's disease.

INVESTIGATIONS

Cardiac magnetic resonance (CMR) was obtained and demonstrated obliteration of the RV apex with marked apical hypertrophy (Videos 4, 5, and 6). The RV apex was isointense on black-blood fat-suppression imaging, suggesting that the mass was composed of myocardium (**Figure 2A**). On late gadolinium enhancement (LGE) imaging, there was diffuse patchy enhancement of the entire RV apex, suggesting

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ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

EMF = endomyocardial fibrosis

LGE = late gadolinium enhancement

TTE = transthoracic echocardiogram

RV = right ventricular

diffuse myocardial fibrosis (**Figure 2B**). Review of the operative report from his tricuspid valve replacement was notable for "extensive calcification of the RV outflow tract as well as moderator bands with restriction of the anterior and septal leaflets" of the tricuspid valve. His original TTE prior to surgery was reviewed and demonstrated a normally attached septal leaflet of the tricuspid valve without actually meeting diagnostic criteria for Ebstein's anomaly. Based on the distinct surgical and imaging findings as well as the unique demographic portfolio, the patient was diagnosed with tropical EMF.

MANAGEMENT

The patient's persistent symptoms were attributed to the underlying EMF and resultant restrictive physiology leading to symptoms of right heart failure. Owing to his recent surgical intervention, the patient's symptoms were managed medically with diuretics.

DISCUSSION

EMF is believed to be one of the most common causes of restrictive cardiomyopathy in the world, with an estimated global prevalence of 10 to 12 million in 2008. Most cases tend to arise in tropical equatorial regions of Africa, South America, and Asia, including the state of Kerala in India, where our patient was from. EMF tends to affect people with low socioeconomic status with a bimodal incidence in the second and fourth decades of life (1-3).

There are many theorized etiologies for EMF, but the exact cause and mechanism remain unclear. Several infectious organisms have been implicated and appear to elicit an exaggerated immune response. An inflammatory cascade of cytokines is triggered and activates eosinophils, cardiac mast cells, and fibroblasts, which in turn results in collagen deposition within the endomyocardium. Fibrosis extends to the atrioventricular valve with resultant scarring and dysfunction (1,4). It is not known why one ventricle may be affected over the other, or why some patients get biventricular disease and others do not. Eosinophilia has been inconsistently detected in the early stages of the disease process, along with higher levels of autoimmune antibodies, such as anti-myosin antibodies (4).

Genetics are a potential factor due to ethnic clustering, but it is difficult to tease out the confounding shared environmental exposures that are thought to play a role in the development of EMF (3). Cerium is an element found in higher concentrations in the soil of tropical regions such as Kerala, and can cause subendocardial fibrosis in animal models. Cassava is a tuber with high rates of consumptions in regions with high incidence of EMF, including Kerala. When inadequately prepared, cassava is known to liberate hydrogen cyanide from the gut. Malnutrition impacts the liver's ability to detoxify the cyanide, making the affected individual more susceptible to the toxic effects. In animal models, cassava has been demonstrated to cause EMF (1). Further supporting this theory is the decrease in EMF incidence coinciding with decreased cassava consumption following industrialization of afflicted regions (4).

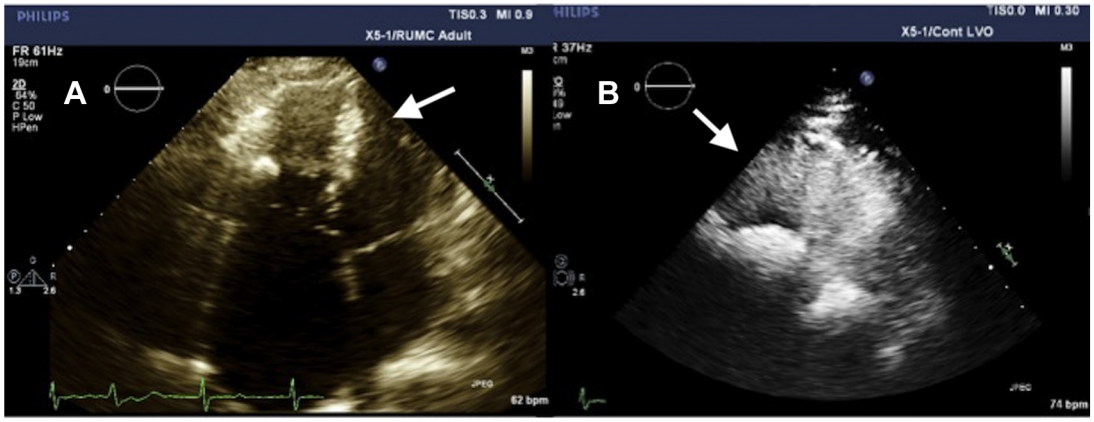
The progression of EMF begins with a pancarditis and progresses to fibrotic hypertrophy of one or both ventricles, with biventricular hypertrophy being most common (1,4). Interestingly, predominant RV hypertrophy is the most common presentation in Kerala, India (5), as was the case in our patient. The disease process is often hallmarked by the development of massive ascites. Initially thought to be related to heart failure, the ascites is actually an exudative process and lymphocyte-predominant, indicating an inflammatory process. This is supported by the absence of concomitant pedal edema (4,6).

The diagnosis of EMF is made primarily by echocardiography. Findings include apical obliteration of the affected ventricle, fibrotic plaques, atrioventricular valve dysfunction, and ipsilateral atrial enlargement. Specific criteria have been outlined, with 2 major criteria or 1 major and 2 minor criteria required to make the diagnosis (3). Our patient met 3 major criteria (obliteration of the RV apex, thrombus without severe ventricular dysfunction, atrioventricular valve dysfunction due to adhesion of the valvular apparatus to the ventricular wall) and 3 minor criteria (thin endomyocardial patches localized to one ventricular wall, enlarged atrium with normal-size ventricle, enhanced density of the moderator band).

CMR will often demonstrate patchy fibrosis on LGE imaging sequences. First-pass perfusion sequences demonstrate perfusion of the hypertrophied areas (Supplemental Figure 1). The affected ventricle will typically appear isointense on T2-weighted imaging, indicating a lack of inflammation seen in the chronic phase (4,7,8) (Supplemental Figure 2).

Surgical resection of the fibrotic endomyocardium is the mainstay of treatment, with replacement of any affected valves at the time of surgery (9). Immediate post-surgical mortality remains high at 30%, but 10-year survival following surgical intervention has been reported as high as 70% in some studies

FIGURE 1 Transthoracic Echocardiogram Images

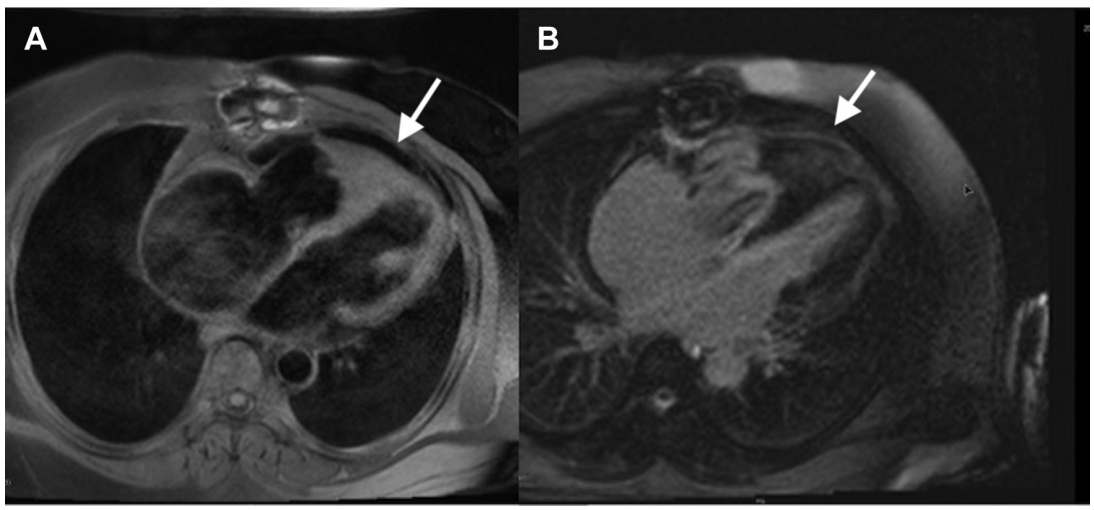


(A) Transthoracic echocardiogram without echo-enhancing contrast demonstrates right atrial dilation and right ventricular apical hypertrophy. **(B)** Contrast-enhanced echocardiography demonstrates perfusion of hypertrophied regions, suggesting vascularity.

(2,10). Heart failure symptoms are managed with diuretic therapy. Spironolactone has been recommended for its known antifibrotic properties, though evidence supporting its use in EMF specifically remains limited (8).

Prognosis for patients with EMF is overall poor, with initial observational studies estimating a life expectancy at diagnosis of 2 years (2,3,5). This was often attributed to late presentation and lack of viable treatment options. However, with advances in surgical intervention, prognosis has improved, with recent data estimating 90% survival at 3 years (10). Causes of death are most often related to progressive heart failure, acute thromboembolism, complications of cirrhosis from right heart failure, and fatal arrhythmias.

FIGURE 2 Cardiac Magnetic Resonance Images



(A) Black-blood fat-suppression phase imaging demonstrates signal intensity of the right ventricular apex similar to that of myocardium. **(B)** Late gadolinium enhancement phase imaging demonstrates diffuse patchy enhancement of the hypertrophied right ventricular apex, suggesting fibrosis.

FOLLOW UP

Our patient was referred to a specialized transplant program for consideration of advanced heart failure therapies.

CONCLUSIONS

Although EMF remains relatively uncommon, the number of cases encountered in the United States is increasing with immigration of populations from endemic areas. The diagnosis of EMF can be made by echocardiographic findings alone, though history and CMR can be helpful in distinguishing the disease entity from other processes on the differential. The overall prognosis remains poor and treatment options remain limited, with surgical endocardectomy being the only viable strategy for improving survival. Prompt and accurate diagnosis with appropriate referral to experienced surgical centers gives patients the best chance at improving their quality, and quantity, of life.

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APPENDIX For supplemental figures and videos, please see the online version of this paper.