

# Endomyocardial Fibrosis, Apical Hypertrophy, or Both?



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## INTRODUCTION

Endomyocardial fibrosis (EMF) is characterized by fibrosis of the apical endocardium of the right ventricle (RV) and/or left ventricle (LV), along with a propensity for apical clot formation. While echocardiographic evidence of obliteration of the ventricular apices is suggestive of EMF, the diagnosis based on endomyocardial biopsy has been reported to be conclusive in only about 50% of patients.<sup>1</sup> The differential diagnosis for EMF includes apical hypertrophic cardiomyopathy (HCM), noncompaction of the ventricular myocardium, apical thrombus, and tumors.<sup>1</sup> Cardiovascular magnetic resonance (CMR) imaging may aid in distinguishing apical HCM and EMF, but finding both conditions coexisting is exceedingly rare. It is crucial to have the correct diagnosis, as these 2 conditions are managed in markedly different ways.

## CASE PRESENTATION

A 68-year-old man was referred for assessment of an abnormal electrocardiogram (ECG) performed on routine checkup 2 years before presentation (Figure 1). The patient had a medical history of asthma and hypertension and no family history of cardiac disease. At the time of presentation, they had no symptoms. The cardiovascular physical examination and routine blood work were unremarkable, including the peripheral eosinophil count. A transthoracic echocardiogram (TTE) with ultrasound-enhancing agent suggested obliteration of the LV and RV apices with normal biventricular size and systolic function and no thrombus (Figure 2, Videos 1 and 2). The differential diagnosis included apical HCM and EMF, but the former was favored because of the absence of eosinophilia. The patient was managed expectantly for apical HCM, with periodic determination of the eosinophilic count.

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Two years later, the patient presented with mild cognitive impairment, slurred speech, and gait disturbances. Computed tomography (CT) scan of the brain revealed chronic bilateral cerebellar, left occipital, and left middle frontal gyrus infarcts. A peripheral eosinophil count was elevated at  $1.1 \times 10^9$  (normal,  $0-0.5 \times 10^9$ ). Cardiac CT demonstrated hypodense filling defects at the LV and RV apices, consistent with thrombus. In addition, the LV apex was hypertrophied, measuring up to 13 mm, with attenuation values similar to normal cardiac myocardium (Figure 3). There was moderate calcification in the coronary arteries on cardiac CT; however, no occlusive coronary artery disease was identified. Bone marrow aspirate revealed a mild increase in eosinophils and eosinophilic precursors; however, cytogenetics were normal, with no evidence of a hematological myeloproliferative disorder or malignancy that required treatment. The patient was subsequently initiated on high-dose oral steroid and anticoagulation therapy for EMF with associated apical thrombi.

Cardiovascular magnetic resonance imaging performed a few months later following commencement of treatment, demonstrated a thickened LV apex measuring 15 mm on steady-state free precession CINE sequences with clearly identifiable contraction of the apical segments during systole. Biventricular systolic function was normal, and the RV appeared unremarkable. Mitral and tricuspid valve regurgitation was noted. First-pass perfusion CINE images confirmed normal perfusion in the thickened LV apical segments (Video 3). Late gadolinium enhancement (LGE) images showed 2 distinct patterns of enhancement: subendocardial enhancement in the LV apical region as a V sign consistent with EMF and a small focal area of patchy enhancement in the midmyocardium of the LV apex (Figure 4). Patchy, midwall foci of enhancement in regions of hypertrophy are the usual LGE pattern seen in HCM. Serial echocardiography performed following a course of steroids showed regression in LV apical thickness (Figure 5).

Based on this constellation of findings, the presence of both apical HCM and EMF was diagnosed.

## DISCUSSION

Apical fibrosis and obliteration due to thrombus makes distinguishing EMF from apical HCM difficult on echocardiography. When both diseases are present in the same patient such as in this case, TTE may not be adequate, and other imaging modalities are needed. Furthermore, endomyocardial biopsy may be nondiagnostic or even unnecessary.<sup>1,2</sup> These images demonstrate that CMR can be used to identify both EMF and apical HCM in the same patient, as the former shows typical abnormal subendocardial fibrosis on LGE and apical thrombi formation, while the latter shows LV apical myocardial thickening with heterogeneous enhancement on LGE.<sup>1,3</sup> Cardiovascular magnetic resonance imaging can also be used to estimate valvular regurgitation and ventricular dysfunction in EMF. Serial TTE can be used to assess the response to treatment for EMF with steroids. The patient

## VIDEO HIGHLIGHTS

**Video 1:** Apical 4-chamber view on echocardiography demonstrating obliteration of the left and right ventricular apices, normal biventricular size and systolic function, normal valvular function, and no thrombus.

**Video 2:** Apical 4-chamber view on echocardiography with ultrasound-enhancing agent demonstrating perfusion of the thickened apical segments along with cavity obliteration, but no thrombus.

**Video 3:** Four-chamber view on CMR perfusion demonstrating clear perfusion of the apical segments indicating thickened apical myocardium.

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demonstrated characteristics of both EMF and apical HCM, which is highly unusual, although not improbable.<sup>4</sup>

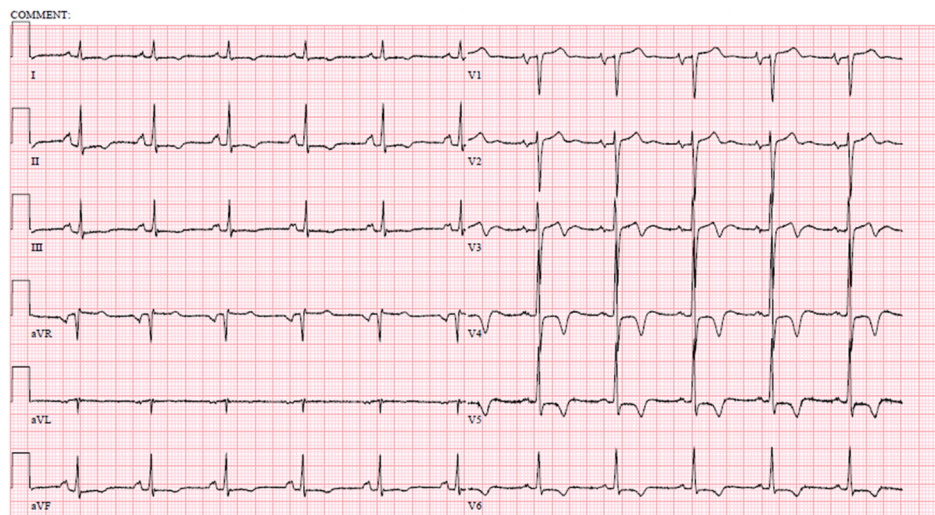
Endomyocardial fibrosis remains a challenging and mysterious disease; the condition is characterized by deposition of fibrous tissue in the endomyocardium, resulting in restrictive physiology.<sup>5,6</sup> Its pathogenesis remains obscure, with dietary, environmental, and infectious factors combining in susceptible individuals and giving rise to an inflammatory process that leads to endomyocardial damage and scar formation.<sup>5</sup> It is endemic in low-income tropical areas and is likely to be the leading cause of restrictive cardiomyopathy in the developing world.<sup>5,6</sup> The condition manifests in relapsing active inflammatory phases that lead to a chronic phase.<sup>5</sup> The active inflammatory phase is characterized by a febrile illness, pancarditis, eosinophilia, itching, and periorbital swelling.<sup>5,7</sup> This leads to myocardial edema, eosinophilic infiltration, subendocardial myofiber necrosis, and vasculitis.<sup>5</sup> Echocardiography remains the first line and most common imaging used given its availability in low-income endemic countries.<sup>5,6</sup>

Changes at this stage show biventricular obliteration, with homogeneous infiltrates filling the myocardium and pericardial effusion. Mural thrombus may occur, and thromboembolic events are frequent.<sup>5,6</sup> As the inflammatory process declines, the eosinophils become undetectable and myocyte hypertrophy develops, leading to myocardial ischemia and fibrosis.<sup>5-7</sup> Early diagnosis of this condition can be challenging due to the limited changes seen on TTE.<sup>5,6</sup>

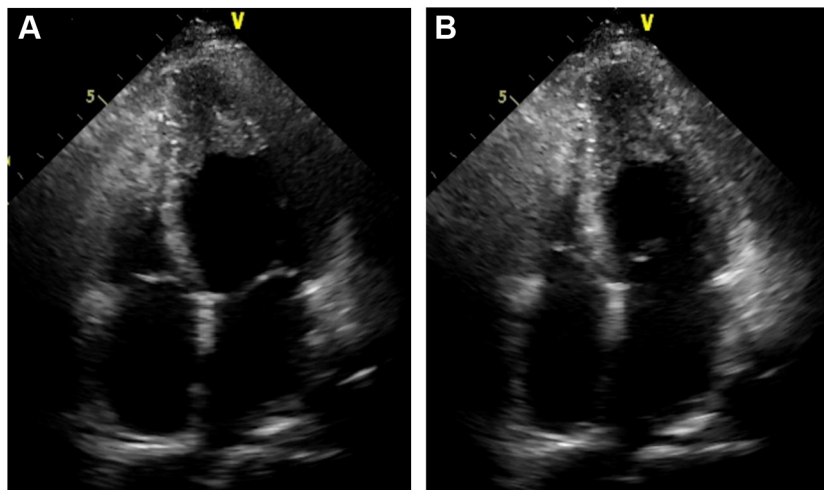
The chronic phase is commonly associated with biventricular involvement followed by isolated right heart involvement, eventually becoming an RV restrictive cardiomyopathy with associated complications, although biventricular restrictive cardiomyopathy can occur.<sup>8</sup> At this stage the ECG typically shows RV hypertrophy, atrial fibrillation is common, and conduction abnormalities such as first-degree heart block and right bundle branch block are often seen.<sup>5</sup> Echocardiographic changes are more pronounced at this stage, with RV EMF showing apical obliteration, reduction of the RV cavity, dilatation of the RV outflow tract, dilatation of the right atrium, tricuspid regurgitation due to adherence of the valve to the endocardium, diastolic opening of the pulmonary valve, features of restrictive cardiomyopathy, and pericardial effusion.<sup>6</sup> The LV EMF echocardiogram typically shows a reduction in the longitudinal diameter of the LV, which becomes spherical or oval, left atrial dilatation, eccentric mitral regurgitation with restriction, and disappearance of the posterior mitral leaflet.<sup>6</sup> Cardiovascular magnetic resonance imaging remains the reference standard for the diagnosis of EMF, showing subendocardial fibrosis with the pathognomonic V sign (apical subendocardial enhancement overlying normal myocardium) and double V sign (3-layered appearance consisting of normal myocardium, subendocardial enhancement, and overlying thrombus).<sup>1,3,9</sup>

Endomyocardial fibrosis shares many similarities with Loeffler's syndrome.<sup>5,10</sup> With respect to imaging, these conditions differ through the pattern of LGE on CMR, with the V sign and double V sign being characteristic of EMF and Loeffler's endocarditis typically having a patchy or diffuse distribution of subendocardial LGE.<sup>9,10</sup>

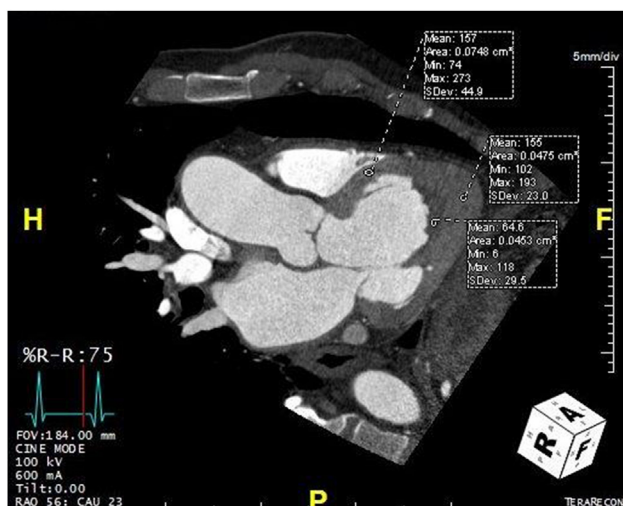
There are limited data on treatment options for EMF, and no randomized clinical trials have been conducted. Current management consists of heart failure management, anticoagulation for thrombus,



**Figure 1** Twelve-lead ECG demonstrates deep inverted T waves in the precordial leads (V3- V6) commonly seen in apical HCM.



**Figure 2** Apical 4-chamber views on TTE during diastole (A) and systole (B) demonstrating obliteration of the left ventricular and right ventricular apices, normal biventricular size, normal systolic function, normal valvular function, and no thrombus.



**Figure 3** Apical 3-chamber view on cardiac CT demonstrating hypodense filling defect consistent with apical thrombus. Apical left ventricular hypertrophy is seen, with attenuation values comparable between the left ventricular apex and septum.

and glucocorticoids to halt the acute inflammatory phase; in severe cases, surgical intervention may be necessary.<sup>5,8,11</sup> Information on prognosis and progression of the condition is also limited; however, one Brazilian case series of 83 patients found that those with EMF who underwent surgery had a 55% probability of survival at 17 years.<sup>12</sup>

Apical HCM is an uncommon variant of HCM, characterized by asymmetric hypertrophy of the LV apex.<sup>13</sup> This is caused by mutations in the sarcomere gene.<sup>13,14</sup> It is prevalent in Asian countries, affecting up to 41% of HCM patients in China.<sup>13</sup> Most patients with this condition are asymptomatic at presentation with the primary concern being an atypical ECG, showing the characteristic “giant” negative T waves and high QRS voltage in the precordial leads.<sup>13,14</sup> Transthoracic echocardiography reveals LV hypertrophy confined to the apex and the hallmark “ace-of-spades” configuration

of the LV cavity during diastole.<sup>13,14</sup> Cardiovascular magnetic resonance imaging typically shows LV apical thickening and heterogeneous subendocardial and apical enhancement on LGE.<sup>13,14</sup> Apical aneurysms can also be seen, which can be detected earlier with CMR.<sup>13,14</sup> With regards to prognosis, recent studies suggest an annual cardiac death rate between 0.5% and 4%.<sup>15</sup> The management differs significantly from EMF, with a primary focus being on beta-blocker therapy to reduce midventricular outflow tract obstruction and reduce the burden of ventricular arrhythmias.<sup>14</sup> Anticoagulation is used if atrial fibrillation is present, and defibrillator device therapies are considered in severe cases.<sup>14</sup>

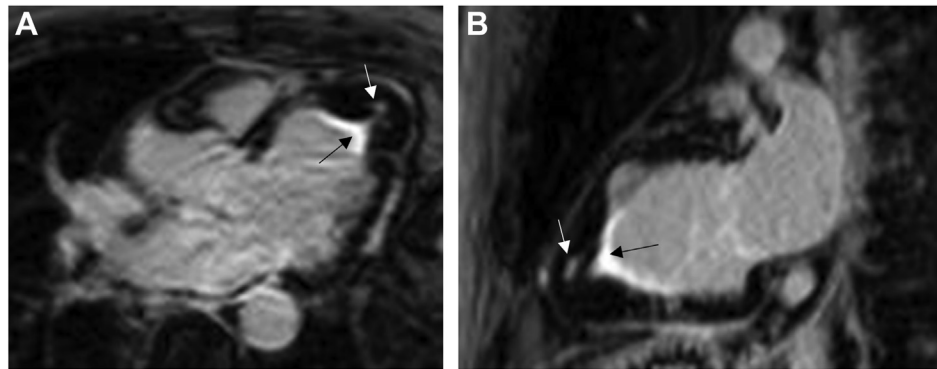
In the present case, the patient’s first echocardiogram and blood tests demonstrated changes consistent with an early stage of EMF, which was not in an active inflammatory state.<sup>5</sup> However, the index presentation, 2 years later, was in keeping with a later-stage EMF in the active inflammatory phase.<sup>5</sup> Concurrently, the apical HCM remained relatively stable throughout the 2 years, exemplifying the more rapid progression of EMF. Recognition of EMF at an early stage would prompt monitoring for the presence of thrombus and other systemic inflammatory changes of this condition, potentially reducing the risk of stroke and minimizing the risk of structural cardiac changes. It is important to recognize the different findings in multimodality imaging for these 2 conditions and the benefit of CMR in this regard (Table 1). Moreover, differentiating these 2 conditions is critical due to the drastic difference in management and prognosis.

## CONCLUSION

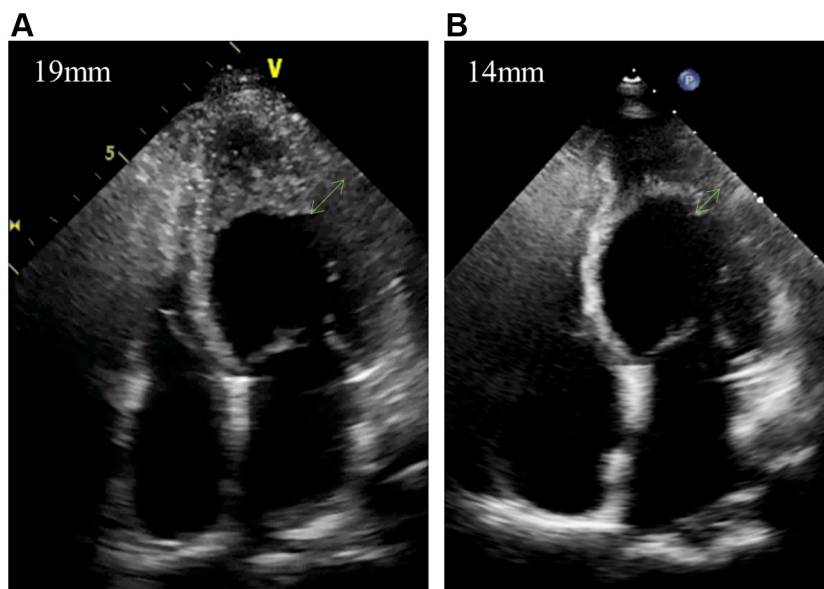
Cardiovascular magnetic resonance imaging may aid in distinguishing HCM and EMF. Finding both conditions coexisting is exceedingly rare. It is crucial to have the correct diagnosis, as these 2 conditions are managed in markedly different ways.

## SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.case.2022.08.001>.



**Figure 4** Apical 4-chamber (A) and apical 2-chamber (B) LGE images on CMR show V- shaped subendocardial enhancement in the left ventricular apical region (denoted with *black arrow*) and a small focal area of heterogenous enhancement in the left ventricular apex (denoted with *white arrow*).



**Figure 5** Apical 4-chamber view on TTE prior to the administration of steroids where apical left ventricular thickness measures 19 mm (A) compared to the study following treatment with a course of steroids where apical left ventricular thickness measures 14 mm (B).

**Table 1** Key imaging features of EMF and apical HCM on TTE and CMR

Imaging modality	EMF <sup>1,3,5,6,9</sup>	Apical HCM <sup>13,14</sup>
TTE	<ul style="list-style-type: none"> <li>• Obliterated LV and/or RV apex</li> <li>• Severely dilated atria</li> <li>• Endomyocardial plaques</li> <li>• Presence of thrombus in LV or RV</li> <li>• Severe mitral regurgitation</li> <li>• Severe tricuspid regurgitation</li> <li>• Restrictive flow pattern across mitral or tricuspid valves</li> </ul>	<ul style="list-style-type: none"> <li>• Apical LV systolic cavity obliteration</li> <li>• “Ace-of-spades” deformity of LV cavity during diastole</li> <li>• Apical aneurysm</li> <li>• LV hypertrophy confined predominantly to LV apex</li> <li>• Typically, no mitral regurgitation or tricuspid regurgitation.</li> </ul>
CMR	<ul style="list-style-type: none"> <li>• Apical obliteration of LV and/or RV apex</li> <li>• Severely dilated atria</li> <li>• V sign: apical subendocardial enhancement overlying normal myocardium</li> <li>• Double V sign: 3-layered appearance consisting of normal myocardium, subendocardial enhancement and overlying thrombus</li> <li>• Severe mitral regurgitation</li> <li>• Severe tricuspid regurgitation</li> </ul>	<ul style="list-style-type: none"> <li>• LV apical myocardial thickening</li> <li>• Spade-like deformity of LV cavity during diastole</li> <li>• Apical aneurysm (often detected earlier than TTE)</li> <li>• Heterogenous enhancement on LGE, characteristically apical and subendocardial</li> </ul>

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