



# A case series of eosinophilic myocarditis: different faces of the same coin

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## Background

Eosinophilic myocarditis (EM) is a rare form of myocarditis with various aetiologies and dire consequences if not diagnosed and treated expeditiously.

## Case summary

We report three cases of EM at different stages of the disease with differing clinical manifestations. We highlight the diagnostic workup including the role of multimodality imaging and endomyocardial biopsy (EMB), and the treatment strategies.

## Discussion

EM is an underdiagnosed and potentially life-threatening disease. Therefore, a high clinical suspicion for EM should arise when patients with signs and symptoms of cardiovascular disease develop hypereosinophilia or vice versa. Early identification of this condition using multimodality imaging and EMB is of paramount importance as the disease may progress to the irreversible late fibrotic stage if treatment is delayed.

## Keywords

Eosinophilic myocarditis • Hypereosinophilia • Heart failure • Case series

## ESC Curriculum

2.1 Imaging modalities • 6.1 Symptoms and signs of heart failure • 6.5 Cardiomyopathy • 2.2 Echocardiography • 2.3 Cardiac magnetic resonance

## Learning objectives

- To illustrate the various clinical presentations of eosinophilic myocarditis (EM) and emphasize the need for timely diagnosis and initiation of appropriate treatment.
- To highlight the importance of cardiac biomarkers and multimodality imaging in patients with hypereosinophilia where cardiac involvement is suspected.
- To emphasize the role of cardiac magnetic resonance imaging in establishing the diagnosis of myocardial involvement and the role of endomyocardial biopsy in establishing a definitive diagnosis of EM.

## Introduction

Eosinophilic myocarditis (EM) is characterized by myocardial eosinophilic infiltration. Although described as a rare disease, it is largely underdiagnosed and is associated with a poor prognosis.<sup>1</sup> The causes may be

classified as primary (clonal or idiopathic) or secondary (parasitic, protozoal or viral infections, allergic or inflammatory conditions and malignancies). The clinical presentation of EM is variable ranging from acute fulminant myocarditis to chronic restrictive cardiomyopathy. Identifying the cause of eosinophilia and initiating appropriate treatment

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is crucial. Although endomyocardial biopsy (EMB) is required to establish definitive diagnosis, whether to initiate therapy based on laboratory and imaging [cardiac magnetic resonance imaging (CMR)] findings without tissue diagnosis, remains controversial.<sup>1,2</sup> In addition to diagnostic challenges, a standardized evidence-based treatment strategy is lacking.

cells/uL (normal reference range: 30–470 cells/uL). High-sensitivity troponin T (hsTnT) was elevated at 373 ng/L (normal reference range: 0–53 ng/L). Electrocardiogram (ECG) and echocardiogram were unremarkable. CMR showed findings suggestive of acute myocarditis (Figure 1). Evaluation for autoimmune diseases and infectious causes was all negative. Peripheral blood smear and bone marrow biopsy did

## Timeline

	Time	Event
<b>Patient 1</b>	Presentation	A 35-year-old male referred to the haematology clinic for evaluation of B symptoms and hyper-eosinophilia.
	February 2021	Thorough investigation for hyper-eosinophilia initiated.
	April 2021	Presents to the ER unit with chest pain and troponin elevation. ECG was unremarkable. CMR suggests acute myocarditis with preserved LV function. Prednisone was initiated.
	May 2021	Admitted to internal medicine ward with worsening laboratory parameters (leucocytosis, eosinophilia). Discharged with prednisone and LMWH (40 mgX1/d).
	July 2021	Re-admitted with chest pain and increasing peripheral eosinophil count. CMR highly suggestive of EM with LV apical thrombus. EMB showed mild EM. Treatment with increased dose of prednisone and LMWH. Treatment with Imatinib (TKI) initiated and steroid tapered off.
September 2021	Eosinophilia resolved and patient asymptomatic. Echocardiography with contrast did not show apical thrombus.	
<b>Patient 2</b>	Presentation and admission course	A 72-year-old woman with signs and symptoms of heart failure, rapid AF, and mild peripheral eosinophilia. Echocardiography demonstrates biventricular failure with significantly reduced LV systolic function (LVEF 25–30%). With the working diagnosis of tachycardia induced cardiomyopathy, rhythm control was attempted. Rapid AF successfully cardioverted but unsuccessful to maintain in sinus rhythm. Discharged with GDMT for HF, digoxin, anticoagulation.
	January 2021	
	March 2021	Echocardiography LVEF 25–30%. EMB demonstrates acute myocarditis with eosinophilic infiltration. Patient readmitted and therapy with prednisone and Imuran initiated.
	April 2021	Clinical improvement but remained symptomatic, NYHA II class, LVEF improved to 40% despite remaining in rapid AF.
	August 2021	Complete resolution of eosinophilia. Her echocardiography shows remarkable improvement of cardiac function (LVEF 60%).
November 2021	Patient doing well overall but remained with symptoms of palpitation and NYHA II.	
January 2022	Patient underwent PVI using cryoablation	
<b>Patient 3</b>	Presentation	A 52-year-old male with exertional dyspnoea, GI symptoms, and peripheral eosinophilia. Mildly elevated troponin and echo shows severely reduced LV and RV function.
	June 2017	EMB shows endocardial fibrosis without inflammation. GDMT initiated.
	July 2017	ICD implantation for primary prevention of SCD.
	August–September 2017	Skin biopsy done from a purpuric skin lesion shows eosinophilic vasculitis. Prednisone therapy initiated.
	May–July 2018	Treatment with Mepolizumab (Anti-IL-5) and Azathioprine initiated
February 2020	Patient in advanced heart failure despite GDMT. LVAD implanted. Awaits heart transplantation	
May 2020	Functional capacity significantly improved.	

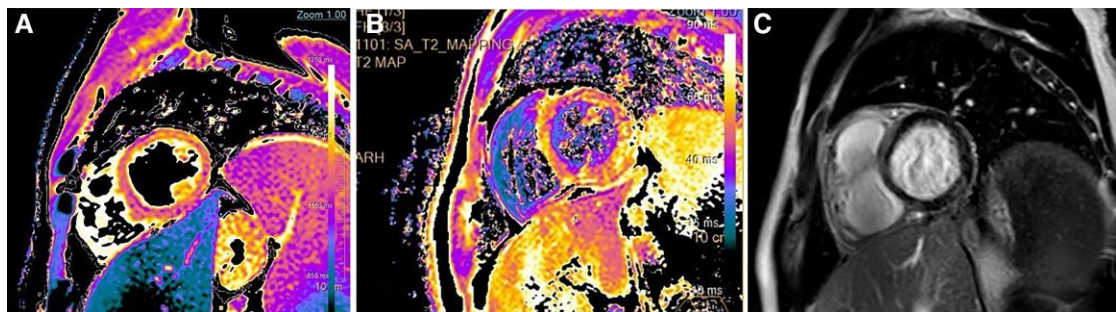
AF, atrial fibrillation; CMR, cardiac magnetic resonance imaging; ECG, electrocardiogram; EM, eosinophilic myocarditis; EMB, endomyocardial biopsy; ER, emergency department; GDMT, guideline directed medical therapy; GI, gastrointestinal; ICD, implantable cardiac defibrillator; LMWH, low molecular weight heparin; LV, left ventricle; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PVI, pulmonary vein isolation; RV, right ventricle; SCD, sudden cardiac death; and TKI, tyrosine kinase inhibitor.

## Case presentation

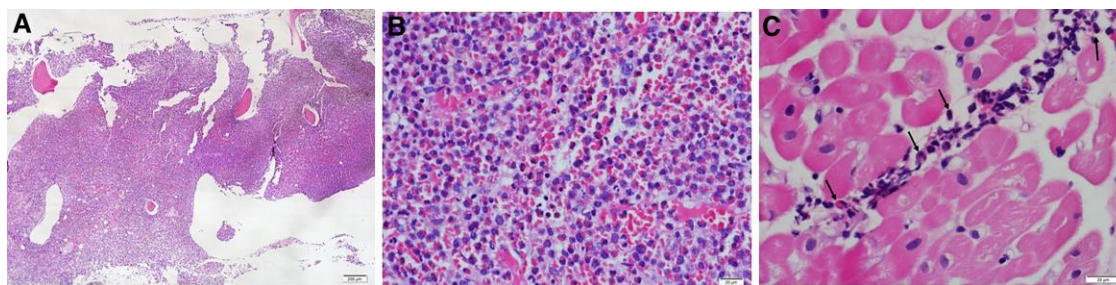
### Case 1

A 35-year-old previously healthy male patient, presented to the outpatient clinic with night sweats, significant weight loss, and pleuritic chest pain of 8 months duration. Complete blood cell count showed remarkable leucocytosis of 58 000 cells/uL (normal reference range: 3 800–10 300 cells/uL) with an absolute eosinophilic count of 22 000

not demonstrate blasts (Figure 2A and 2B). Genetic testing, including platelet-derived growth factor receptor-alpha mutation, was negative. A total body computed tomography (CT) demonstrated hepatosplenomegaly and a (18)F-fluorodeoxyglucose (FDG) positron emission tomography (PET) scan showed no pathological FDG uptake. With a working diagnosis of hypereosinophilia with possible EM, steroid therapy and a prophylactic dose of low-molecular-weight heparin (LMWH) therapy were initiated. Subsequently, a myeloproliferative disease was



**Figure 1** Cardiac magnetic resonance imaging (3T). Native T1 (A) and native T2 (B) mapping in the short-axis view show increased T1 and T2 values (1342 and 68 ms, respectively). (C) A short axis phase-sensitive inversion recovery image shows a mid-wall late gadolinium enhancement in the inferolateral and septal region.



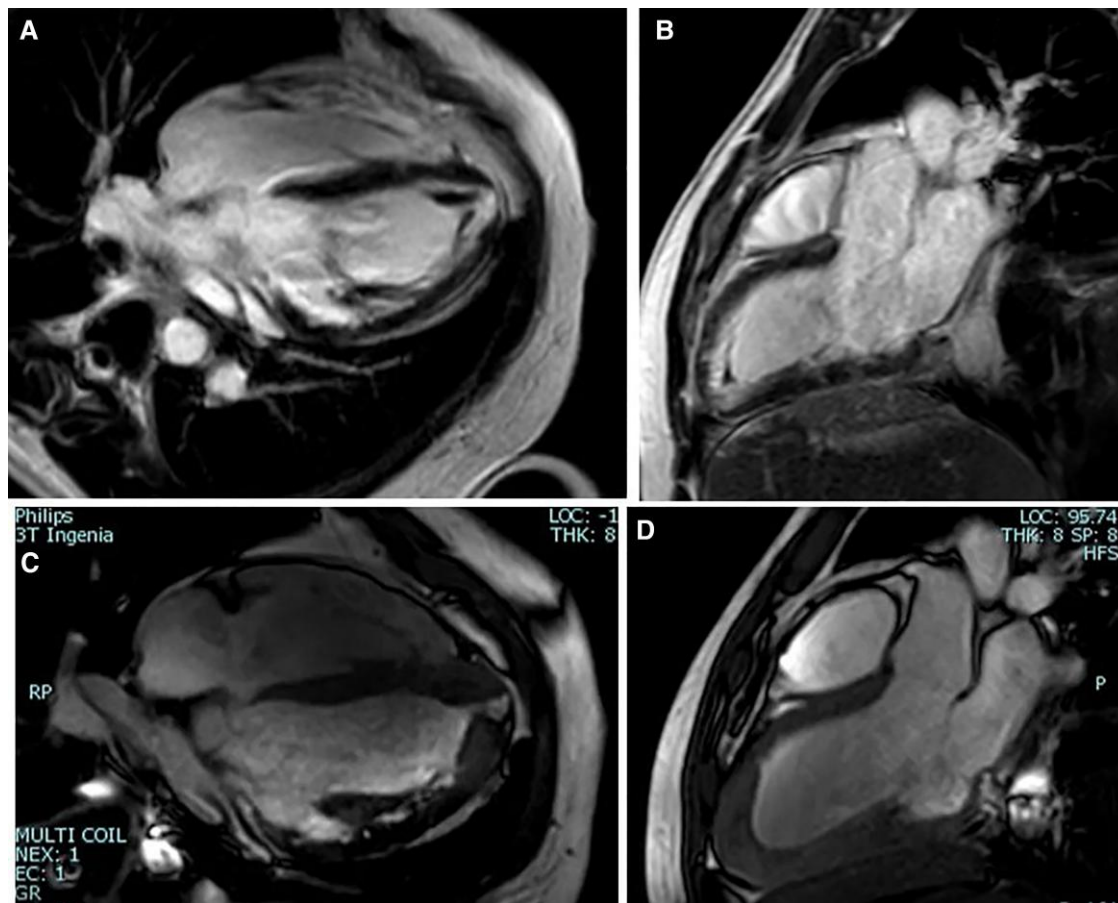
**Figure 2** Endomyocardial and bone marrow biopsy. (A) Bone marrow biopsy sections show markedly hypercellular trilineage bone marrow (haematoxylin and eosin; original magnification  $\times 40$ ), with abundant maturing and mature eosinophilic myeloid lineage cells (B); haematoxylin and eosin; original magnification  $\times 400$ ). (C) Endomyocardial biopsy showing eosinophilic (arrows) and mononuclear cell infiltration of the perivascular and interstitial space without myofiber necrosis (haematoxylin and eosin; original magnification  $\times 400$ ).

suspected, and treatment with hydroxyurea was added. The patient was admitted shortly after with chest pain and an eosinophilic count of 33 000 cells/uL (normal reference range: 30–470 cells/uL). A repeat echocardiography demonstrated an apical left ventricular (LV) thickening, which primarily raised suspicion of a laminated thrombus in the setting of Löffler's endocarditis (see [Supplementary material online, Video S1A and S1B](#)). CMR was performed showing sub-endocardial late gadolinium enhancement (LGE) with LV apical thrombus creating a typical 'double V' sign by LGE ([Figure 3A and 3B](#)). Left heart catheterization showed normal coronary arteries. Despite the patient being on steroid therapy which was initiated few months prior, EMB demonstrated mild EM ([Figure 2C](#)). The dosage of steroid treatment and LMWH was increased and the patient was discharged with guideline-directed medical therapy (GDMT) for heart failure. Subsequently, the patient was treated with Imatinib 400 mg/day with complete resolution of eosinophilia and all related symptoms. A follow-up echocardiography with contrast performed few months later demonstrated a normal LV function without apical thrombus (see [Supplementary material online, Video S1C and S1D](#)).

## Case 2

A 71-year-old female with a history of persistent atrial fibrillation (AF) and hypothyroidism presented with worsening shortness of breath, orthopnea, and palpitations of one month duration.

Despite recommendations to take apixaban 5 mg twice daily (CHA2DS2-VASC score 6, HASBLED score 1), she did not take her medication on regular bases. Her ECG on admission showed AF with rapid ventricular response. Echocardiography demonstrated severely reduced LV systolic function with an ejection fraction (EF) of 25% (see [Supplementary material online, Video S2B](#)). After left atrial thrombus was excluded by transesophageal echocardiography (TEE), she was cardioverted and amiodarone was initiated as maintenance therapy along with apixaban 5 mg twice daily. Treatment with amiodarone was discontinued shortly after due to significant QT prolongation leading to a torsades de pointes event. Her laboratory tests revealed eosinophilia of 1700 cells/uL (normal reference range: 30–470 cells/uL), while troponin and thyroid-stimulating hormone (TSH) levels were normal. The patient was initiated on heart failure treatment, including bisoprolol 2.5 mg/day, ramipril 2.5 mg/day, and spironolactone 25 mg/day. In the differential diagnosis, tachycardia-induced cardiomyopathy, ischaemic heart disease, and EM were considered. Left and right heart catheterization revealed normal coronary arteries and elevated filling pressure, moderate pulmonary hypertension with reduced cardiac output, respectively. CMR showed increased T1 values and mid-myocardial LGE, whereas EMB findings were suggestive of myocardial inflammation involving the septum (see [Supplementary material online, Video S2A](#); see [Supplementary material online, Figure S1](#)). Moreover, EMB revealed significant eosinophilic infiltrates consistent with EM ([Figure 4](#)). Prednisone



**Figure 3** Cardiac magnetic resonance imaging (3T). A four- (A) and three-chamber view (B) showing a sub-endocardial late gadolinium enhancement consistent with apical fibrosis with a superimposed laminated clot creating the 'double V' sign. A four- (C) and three-chamber (D) steady-state free precession still image showing increased focal apical wall thickness.

and azathioprine therapy were initiated. The eosinophilia subsequently resolved and on a follow-up echocardiography done 7 months later showed a remarkable improvement of the LV systolic function, despite persistent AF (see [Supplementary material online, Video S2C](#)). Despite being put on rate control therapy with bisoprolol, the patient remained with symptoms of palpitation and eventually underwent pulmonary vein isolation using cryoablation. The aetiology of leucophilia remained unknown despite extensive investigation. At last follow-up in clinic, the patient remained in sinus rhythm with preserved LV systolic function, excellent functional capacity, and without heart failure symptoms.

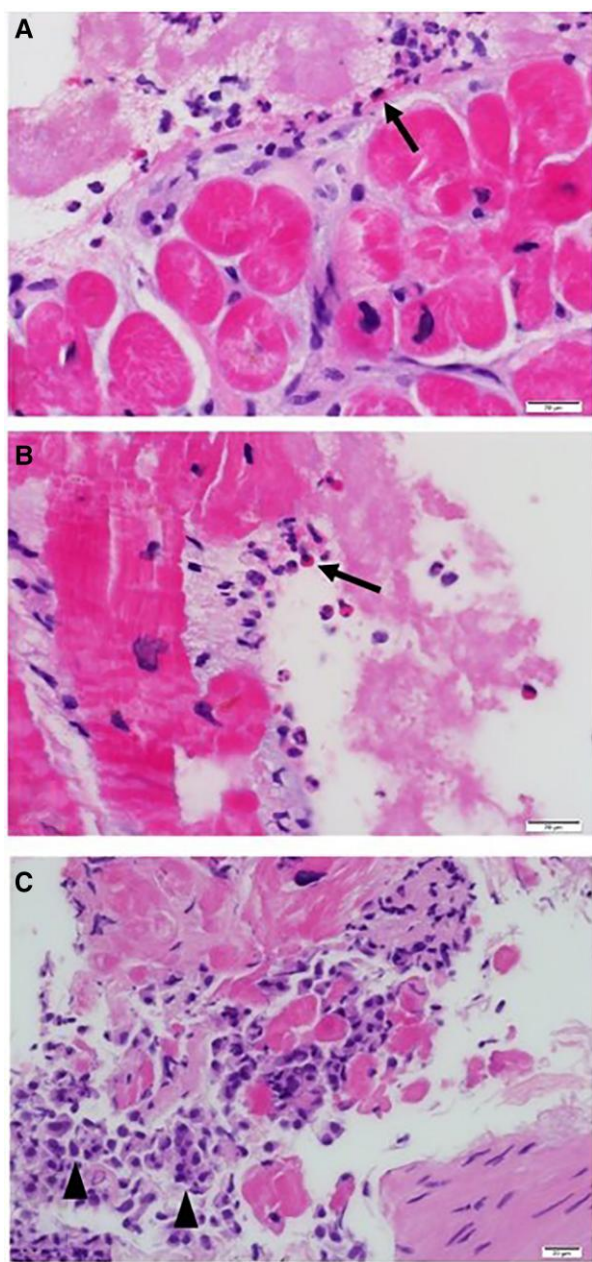
### Case 3

A 52-year-old male with a history of type 2 diabetes mellitus, prior tobacco use, and a family history of sudden cardiac death presented with exertional dyspnoea and chest pain of one-week duration. He also had a history of recurrent abdominal pain, diarrhoea, and diffuse rash. Blood tests showed eosinophilia which gradually increased to 20 000 cells/uL (normal reference range: 30–470 cells/uL), and a mildly elevated hsTnT. Echocardiography showed severely reduced LV and right ventricular (RV) systolic function with severe tricuspid regurgitation and moderate pulmonary hypertension. Coronary angiography showed normal coronary arteries. CMR demonstrated severely reduced LV function

with a non-specific LGE pattern seen on the septum and apical segments (see [Supplementary material online, Video S3; Figure 5](#)).

EMB mainly revealed focal interstitial, perivascular, and endocardial fibrosis without significant inflammation or granulomas (see [Supplementary material online, Figure S2C](#)). Congo red, Masson trichrome, and iron stains were negative. A CT scan showed cervical and mediastinal lymphadenopathy with minimal uptake on FDG PET scan. A mediastinal lymph node biopsy demonstrated benign lymphoid tissue without granulomas. Peripheral blood smear and bone marrow biopsy were not suggestive of haematologic disease. A technetium-99m 3,3-diphosphono-1,2-propanodicarboxylic acid ( $^{99m}\text{Tc}$ -DPD) scan and fat pad biopsy with Congo red staining were negative for amyloidosis. Evaluation for infections, including parasitic infections, was negative. Skin biopsy from a purpuric skin rash was compatible with eosinophilic vasculitis (see [Supplementary material online, Figure S2A and S2B](#)). An abdominal CT revealed a thickened sigmoid colon and biopsy taken on colonoscopy demonstrated oedema and proliferation of eosinophils in the lamina propria without dysplasia.

No specific aetiology for hypereosinophilia was identified in this case, making idiopathic hypereosinophilic syndrome (HES) the most likely diagnosis with skin, gastrointestinal, and cardiac involvement. The patient was started on prednisone therapy followed by mepolizumab and azathioprine with improvement in his gastrointestinal and skin symptoms. However, despite GDMT for heart failure, including



**Figure 4** Endomyocardial biopsy. (A, B). Endomyocardial tissue with interstitial oedema, scattered eosinophils (arrows) (haematoxylin and eosin; original magnification  $\times 600$ ), and macrophage infiltration (C, arrowheads) of the perivascular and interstitial space without necrosis of myofibers (haematoxylin and eosin; original magnification  $\times 600$ ).

bisoprolol 2.5 mg twice daily, losartan 50 mg once daily, spironolactone 25 mg once daily, and furosemide 60 mg once daily and later on sacubitril/valsartan 49/51 mg twice daily instead of losartan, his cardiac function and functional capacity continued to deteriorate, eventually requiring LV assist device (LVAD) implantation as a bridge to heart transplantation. Postoperatively, the patient's functional capacity significantly improved, and currently the patient is active on the waiting list for heart transplantation.

## Discussion

EM is a rare form of myocarditis with varying clinical presentations. Initial clues include elevated cardiac biomarkers and peripheral eosinophilia although peripheral eosinophilia may not be significantly elevated initially or may even be absent in 25% of patients.<sup>1,2</sup> Furthermore, in hypersensitivity EM, peripheral eosinophilia may be absent in 35–40% of cases, thereby emphasizing the crucial role EMB in establishing the diagnosis of EM in many cases.<sup>1</sup>

Several aetiologies for EM have been previously described. In one study involving 179 histologically-proven EM, hypersensitivity was the most common aetiology (34%) followed by eosinophilic granulomatosis with polyangiitis (12.8%) and HES (8.4%).<sup>1</sup> HES is defined as sustained eosinophilia ( $\geq 1500$  cells/uL for at least 6 months) combined with target organ damage, with cardiac involvement observed in 40–50% of patients.<sup>3</sup>

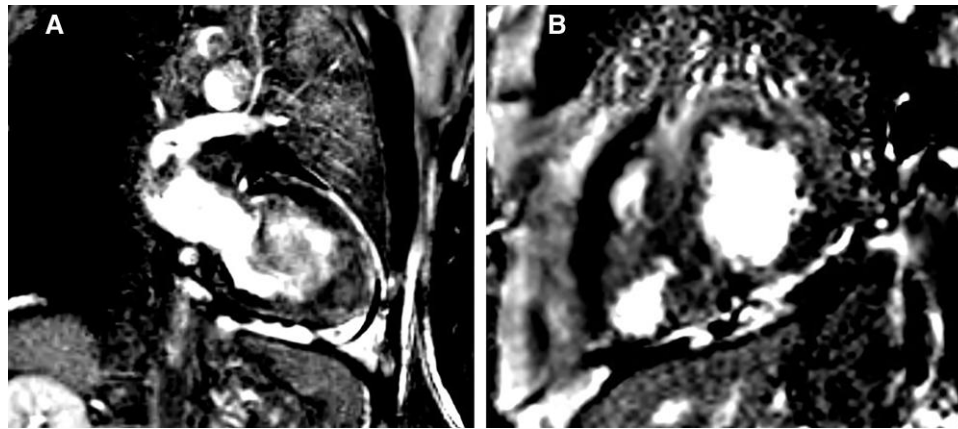
EM has an overall poor prognosis with a mortality rate reaching up to 22%. EM presenting as fulminant myocarditis is often fatal and associated with high in-hospital mortality. Brambatti *et al.*<sup>1</sup> have reported that EM related to hypersensitivity has the highest rate of in-hospital mortality and the poorest mid-term outcome, including increased mortality, need for total artificial heart, and ventricular assist device at 4 months post hospitalization as compared to other aetiologies of EM.

According to pathologic findings, myocardial involvement can be classified into three clinical stages: acute necrotic stage, characterized by acute EM; subacute early stage, characterized by deposition of mural endocardial thrombi (Loffler endocarditis); and a late fibrotic stage with progressive endomyocardial fibrosis and chronic restrictive cardiomyopathy.<sup>4</sup>

The treatment of EM usually includes immunosuppressive therapy after excluding parasitic infection. Glucocorticoids therapy, with or without azathioprine, are commonly the initial choice of therapy, and steroids are known to effectively reduce symptoms and prevent disease progression. In patients with reduced cardiac function, conventional heart failure medications are recommended, while fulminant cases of EM may require mechanical circulatory support. Intravenous (IV) Immunoglobulins have been used in some cases while methotrexate and cyclophosphamide has been used as steroid-sparing agents. Identifying the underlying cause of eosinophilia is vital, although not always possible, to initiate appropriate management beyond steroids and to gain insights into prognosis. Mepolizumab, an anti-interleukin-5 monoclonal antibody, has been shown to improve clinical outcomes and achieve remission in cases of eosinophilic granulomatosis with polyangiitis (EPGA)-associated myocarditis refractory to steroid therapy. Sufficient data and clinical trials are lacking regarding treatments with hydroxyurea, interferon- $\alpha$ , and Imatinib mesylate in the setting of EM.<sup>5</sup>

Case 3 represents an advanced EM of late fibrotic stage with significant myocardial fibrosis and heart failure. As in this case, once extensive fibrosis developed in the myocardium, the response to immunosuppressive therapy is generally limited, emphasizing that prompt diagnosis and treatment are of paramount importance. In patients with predominant endomyocardial fibrosis, treatment options are also limited and may require surgical intervention, such as endocardial stripping, or heart transplantation in more advanced cases.<sup>6</sup>

Active EM is characterized by endomyocardial inflammation and intramural thrombus formation as observed in Case 1. Despite prophylactic anticoagulation therapy, this patient developed a mural thrombus as a manifestation of worsening cardiac involvement. This finding raises the question of whether or not initiating full-dose anticoagulation therapy in patients diagnosed at early stage of EM is necessary. However, clinical trials or clear recommendations to support routine prophylactic anticoagulation in EM are lacking and warrant further investigation.



**Figure 5** Cardiac magnetic resonance imaging (1.5T). A two-chamber view (A) show patchy late gadolinium enhancement mainly on the apical region. A short axis view (B) shows a sub-epicardial late gadolinium enhancement on the antero-septal and anterior segment.

## Conclusions

EM is an underdiagnosed and potentially life-threatening disease. Therefore, a high clinical suspicion for cardiac involvement should arise when patients with hypereosinophilia develop symptoms and signs pertaining to the cardiovascular system or vice versa. CMR provides non-invasive myocardial tissue characterization and identification of endocardial thrombi. EMB plays a crucial role in establishing the diagnosis, especially in the absence of eosinophilia.

## Lead author biography



Bethlehem Mengesha, MD, is a general cardiologist, whose main area of interest is Multimodality cardiac imaging and cardiomyopathies. Graduated from Jimma University, Ethiopia, and completed Internal medicine and cardiology fellowship in Shamir medical center, Israel. Currently works in Hadassah University Medical Center, Jerusalem, Israel, and enrolled to begin advanced cardiac imaging fellowship this year.

## Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

**Slide sets:** A fully edited slide set detailing these cases and suitable for local presentation is available online as Supplementary data.

**Consent:** A written informed consent was obtained from all patients for the submission and publication of these case series in accordance with Committee on Publication Ethics (COPE) guidelines.

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**Conflict of interest:** None declared.

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