Two Different Clinical Presentations and Stages of Loeffler Endocarditis Diagnosed by Multimodality Investigations

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INTRODUCTION

Loeffler endocarditis is a rare condition with various etiologies and clinical outcomes.[1,2] It is characterized by endomyocardial inflammation and infiltration of eosinophil leukocytes. The underlying causes of eosinophilia include hypersensitivity, rheumatological diseases, myeloproliferative disorders, cancer, and idiopathic hypereosinophilic syndrome.[3] Loeffler endocarditis can be divided into 3 clinical stages: (1) the acute necrotic stage, characterized by eosinophilic infiltration, degranulation, inflammation, and necrosis; (2) the thrombotic stage, characterized by mural thrombus formation; and (3) the fibrotic stage, characterized by fibrosis and restrictive physiology.[4] In the following, we present 2 cases of Loeffler endocarditis who presented with different clinical symptoms and were diagnosed at different stages through a comprehensive multimodal approach.

CASE PRESENTATIONS

Case 1

A 76-year-old woman presented to the emergency department with focal neurological symptoms suggestive of stroke. Magnetic resonance imaging of the brain showed multiple ischemic lesions suggestive of cardiac embolism. Transthoracic (TTE) and transesophageal echocardiography were performed to investigate the possibility of a cardiac source of embolism, but no structural abnormalities or signs of valve vegetations were detected. The patient's neurological workup revealed elevated levels of C-reactive protein and an eosinophil count of 3.0 * 109 cells/L (normal range <0.5) but no clear cause for the brain lesions was identified. Several days later, the patient experienced acute chest pain, which was accompanied by ST-segment depression on electrocardiogram (ECG; Figure 1A) and elevated serum troponin I levels. On physical examination the patient had stable vital signs and no jugular vein distension or peripheral edema. Coronary angiography showed no signs of stenosis or thrombotic occlusion. Repeat TTE did not reveal any regional wall motion abnormalities, but global longitudinal strain (GLS) analysis showed low values of −11.0% and signs of inverse apical sparing pattern (Figure 2A and B; Video 1). The mitral inflow had an E/A ratio of 0.8, E-deceleration time of 217 ms, and E/e′ ratio of 9.6. These findings indicated grade I diastolic dysfunction. Based on the previous observations and unexplained elevation of troponin levels, there was indication for cardiovascular magnetic resonance (CMR) imaging. The subsequent CMR scan revealed significant subendocardial late gadolinium enhancement (LGE) and signs of a small mural thrombus in the lateral region of the left ventricle (LV). These results led to suspicions of Loeffler endocarditis, subsequently establishing it as the primary diagnosis under consideration (Figure 2C and D). The suspicion was confirmed by endomyocardial biopsy (EMB). Comprehensive workup ruled out hypersensitivity, rheumatological diseases, myeloproliferative disorders, or cancer and led to the conclusion that the patient had idiopathic hypereosinophilic syndrome. Immunosuppressive therapy with corticosteroids and mycophenolate was initiated, resulting in normalization of C-reactive protein, troponin I, and eosinophil count after 4 weeks (Figure 1B). However, GLS values remained abnormal, while ECG changes were less pronounced, with no further episodes of chest pain.

Case 2

A 76-year-old woman was referred to our institution due to heart failure symptoms and suspicion of apical hypertrophic cardiomyopathy or noncompaction cardiomyopathy. The patient had previously been referred for a medical evaluation 10 months prior due to

VIDEO HIGHLIGHTS

Video 1: Two-dimensional TTE, apical 4-chamber view from case 1, demonstrates normal biventricular systolic function without apical thrombus.

Video 2: Two-dimensional TTE, apical 4-chamber view from case 2, demonstrates a large mass covering the apical two-thirds of the LV and with a demarcation zone between the mass and endocardium, small LV volume, dilated left atrium, and normal LV systolic function.

Video 3: Balanced steady-state free precession CMR cine-loop, apical 4-chamber view from case 2, demonstrates the large mass filling two-thirds of the distal LV cavity and subtle tissue demarcation between the mass and the endocardium, small LV, and dilated left atrium volumes.

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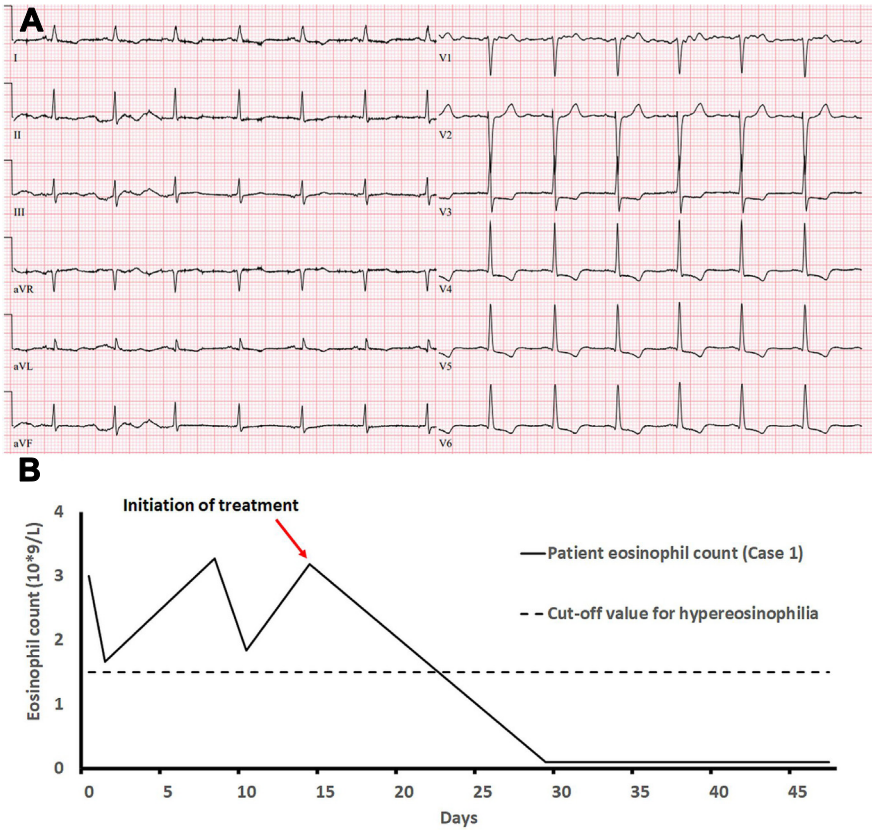

Figure 1 **(A)** The ECG acquired from case 1 exhibits sinus rhythm along with ST-segment depression in leads V3-V6. **(B)** The eosinophil count obtained from case 1 is displayed, with a *red arrow* denoting the initiation of treatment.

fatigue and mild functional dyspnea. Blood tests revealed mild leukocytosis of 10.8 * 109 cells/L but eosinophilia with a count of 2.4 * 109 cells/L, hemoglobin of 11.0 mmol/L, and thrombocytopenia with a count of 111 * 109 cells/L. In addition, there were normal findings in light chains, M component, and bone marrow examination. Computed tomography and positron emission tomography–computed tomography scans showed normal results. The patient did not receive any medical treatment and had not traveled abroad for years. Examinations were made by departments of infectious diseases, rheumatology, pulmonology, and gastroenterology, with normal results. The clinical condition remained stable in the following months, and 8 months after initial health care contact the eosinophil count was still elevated at 2.4 * 109 cells/L. The patient was hospitalized 2 months later due to clinical worsening with increased dyspnea and palpitations. Atrial fibrillation with a rapid ventricular response and pulmonary stasis on chest x-ray were noted, and diuretics, digoxin, low-dosage beta-blocker, and anticoagulation were initiated. A TTE was performed, which suggested the presence of an apical hypertrophic or noncompaction cardiomyopathy with preserved ejection fraction. Two weeks later the patient was transferred to our institution with dyspnea at a low physical activity. An ECG showed sinus rhythm at 100 beats per minute with ST-segment depression in V3-6 (Figure 3A), troponin I of 550 ng/L, N-terminal pro b-type natriuretic peptide 18.305 ng/L, creatinine 125 mmol/L, hemoglobin 9.1 mmol/L, leukocytes 31.0 * 109 cells/L with eosinophil count of 15.2 * 109 cells/L (normal range <0.5; Figure 3B) and C-reactive protein 50 mg/L, and a blood pressure 90/70 mm Hg. On physical examination, the patient had discrete jugular vein distension and no peripheral edema. A TTE revealed a large mass covering the apical two-thirds of the LV and with a demarcation zone between the mass and endocardium (Figure 4A, Videos 2 and 3). The LV ejection fraction was 58% with reduced LV volumes. The left atrium was enlarged, with a volume index of 56 mL/m^2. The mitral inflow was restrictive and consistent with grade III diastolic dysfunction with an E/A ratio of 3.6, short E-deceleration time of 61 ms, and E/e' ratio of 42. The stroke volume index was low 19.6 cm/m^2, and LV GLS analysis revealed very low values of −5.3% with inverse apical sparing pattern (Figure 4B). The inferior vena cava was significantly dilated (25 mm) with absence of respiratory changes. A CMR scan was warranted due to suspicion of an inflammatory condition. The CMR scan revealed large areas of subendocardial LGE and signs of a very large mural thrombus covering the apical two-thirds of the LV (Figure 4C and D). From this point Loeffler endocarditis was considered the leading diagnosis.

The calculated stroke volume index from the CMR scan was 22 mL/m^2, which correlated well with invasive measurement. The patient was promptly transferred to the intensive care unit due to the imminent risk of cardiogenic shock, and treatment was initiated with intravenous diuretics, heparin, noradrenaline, 50 mg methylprednisolone, and oral hydrea 500 mg daily. Invasive hemodynamic monitoring revealed a decrease in cardiac index to 2.1 L/min/m^2 and a decrease in mixed venous oxygen saturation to 60%. However, the patient's condition continued to worsen within 4 to 5 days, with further decreases in cardiac index to 1.1 L/min/m^2 and SVO_2 to 40%. The LV mass remained unchanged.

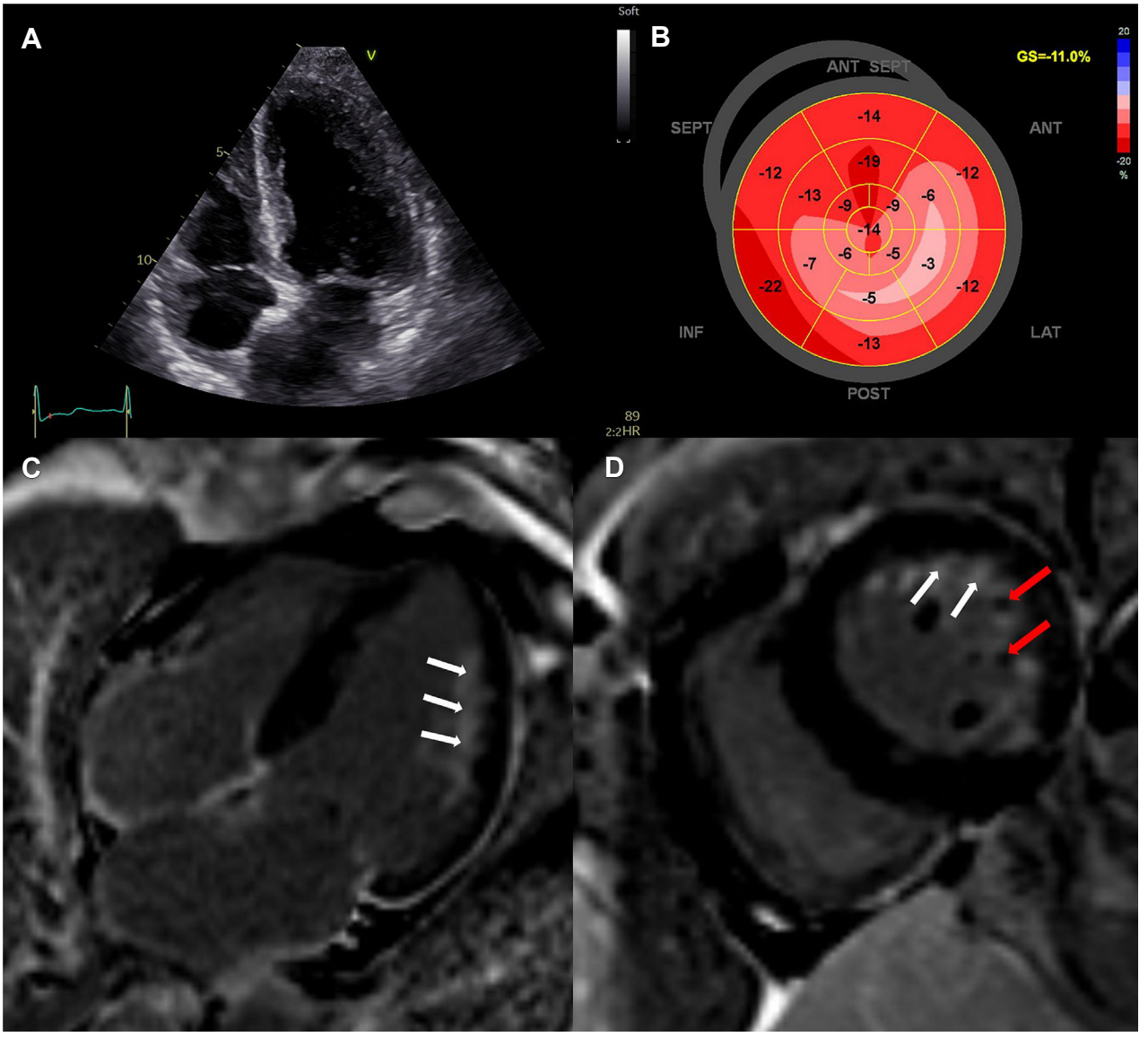

Figure 2 **(A)** TTE 4-chamber apical view from case 1 acquired in early systole. **(B)** Global longitudinal strain bull's-eye plot obtained from case 1 demonstrating decreased segmental values that are particularly noticeable in the lateral wall. **(C)** The CMR 4-chamber LGE sequence (phase-sensitive inversion recovery) from case 1 exhibits indications of subendocardial inflammation or necrosis indicated by *white arrows*. **(D)** The CMR short-axis LGE sequence (phase-sensitive inversion recovery) from case 1 exhibits indications of subendocardial inflammation or necrosis indicated by *white arrows*. *Red arrows* point to small areas of suspected mural thrombi.

After consultation with the patient and family, it was decided to initiate cardiopulmonary support using venous-arterial extracorporal membrane oxygenation and subsequent thoracic surgery to attempt to remove the LV mass. During surgery, most of the mass was successfully removed, which was described as a solid fibrotic mass adherent to the LV endocardium. A mitral biological valve prosthesis was implanted due to infiltration of the subvalvular mitral apparatus by the mass. However, the patient remained hemodynamically unstable postoperatively and died the following day.

Histological examination of the removed LV mass revealed fibrotic and necrotic myocardium as well as thrombotic material with eosinophil infiltration, indicating that the patient had Loeffler endocarditis (Figure 5). The patient's clinical presentation, imaging, and pathological examinations all support this diagnosis.

DISCUSSION

Loeffler endocarditis is a very rare condition with various clinical manifestations. In the following, the clinical spectrum of the condition will be described based on the 2 cases.

Case 1 describes a patient with acute chest pain and neurological symptoms, where the diagnosis of Loeffler endocarditis was suspected after multiple imaging studies and signs of mural thrombus. The ST-segment depression on ECG and elevated serum troponin I levels were due to inflammation and necrosis typical for the early stages of Loeffler endocarditis. The diagnosis was confirmed by EMB, and the patient was treated with immunosuppressive therapy with corticosteroids and mycophenolate, leading to the normalization of the elevated C-reactive protein, troponin I, and eosinophil count. This

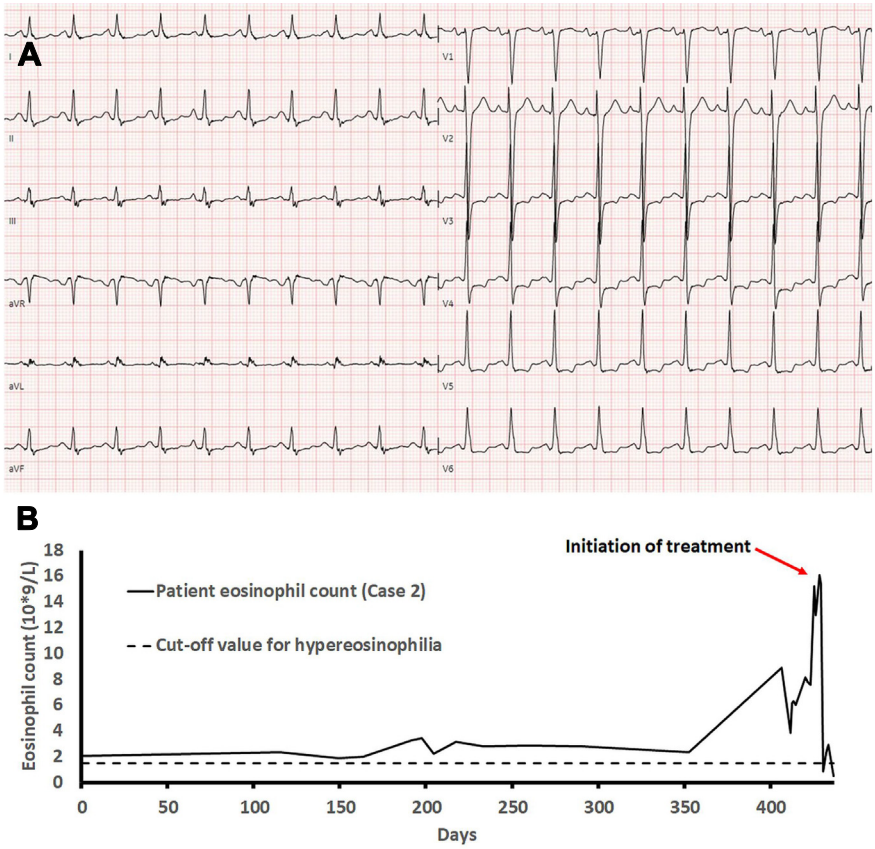

Figure 3 **(A)** The ECG acquired from case 2 exhibits sinus rhythm and tachycardia along with ST-segment depression in leads V3-V6. **(B)** The eosinophil count obtained from case 2 is displayed, with a *red arrow* denoting the initiation of treatment.

patient was in the early thrombotic stage and had a good outcome with appropriate treatment. Case 2 presents a patient with clinical heart failure and suspicion of apical hypertrophic cardiomyopathy, where the diagnosis was reclassified as Loeffler endocarditis after TTE and CMR showed a large mass covering the apical two-thirds of the LV. The patient was treated extensively with immunosuppression, heparin, cardiopulmonary support, and ultimately cardiac surgery to attempt to remove the LV mass. This patient was in the early fibrotic stage of the disease with histopathological findings of fibrotic scarring of the myocardium. Mural thrombus was still present but without endocardial fibrosis. The patient died despite relevant treatment.

As mentioned previously the patient had a mitral valve replacement during surgery. This was primarily due to entrapment of the subvalvular apparatus by the thrombus. This was anticipated from the presurgical imaging and also described elsewhere.[5] Direct involvement of the posterior mitral valve leaflet and subsequent regurgitation has also been described, but this particular mechanism was not observed in the current case.

The diagnosis of Loeffler endocarditis can be challenging due to its nonspecific clinical presentation, which can mimic other cardiac and noncardiac diseases. The use of multimodal imaging techniques, including CMR and TTE, as well as histological verification by EMB can aid in the diagnosis and staging of Loeffler endocarditis.[2,3,6,7] The presence of subendocardial LGE on CMR, which is indicative of myocardial fibrosis and inflammation, is a hallmark of Loeffler endocarditis.[8] In addition, TTE can show regional wall motion abnormalities, while strain analysis can further guide the diagnostic process. The bull's-eye pattern observed in case 2 using strain analysis showed a significant reduction in apical values, indicating inverse apical sparing. This pattern is commonly observed in patients with apical hypertrophic cardiomyopathy. However, in the present case, a notable decrease in global values (−5.3%) was observed, which is not typically seen in patients with apical hypertrophic cardiomyopathy. These patients also have reduced strain values in the apical segments but not globally reduced values. The strain values measured in the patient from case 1 also had segmentally reduced values in the lateral region of the myocardium corresponding to the most affected areas on the LGE sequences from the CMR. Consequently, myocardial strain analysis emerges as a highly sensitive tool that can be readily employed in the initial TTE evaluation of suspected Loeffler endocarditis patients.

Contrast-enhanced TTE is a sensitive technique for the detection of intracavitary thrombi in patients suspected of having Loeffler endocarditis. It eliminates the limitations of image quality associated with standard TTE and aids in the identification of thrombi, which appear as filling defects in the opacified ventricular lumen. This technique helps differentiate Loeffler endocarditis from apical forms of hypertrophic cardiomyopathy and LV noncompaction.[9]

The coexistence of Loeffler endocarditis with pericardial involvement and constrictive pericarditis has been documented. Typically, individuals with advanced Loeffler endocarditis exhibit cardiac physiology resembling restrictive cardiomyopathy. However, when the pericardium is simultaneously affected, a complex interplay between restrictive and constrictive physiology can arise.[9] Assessing

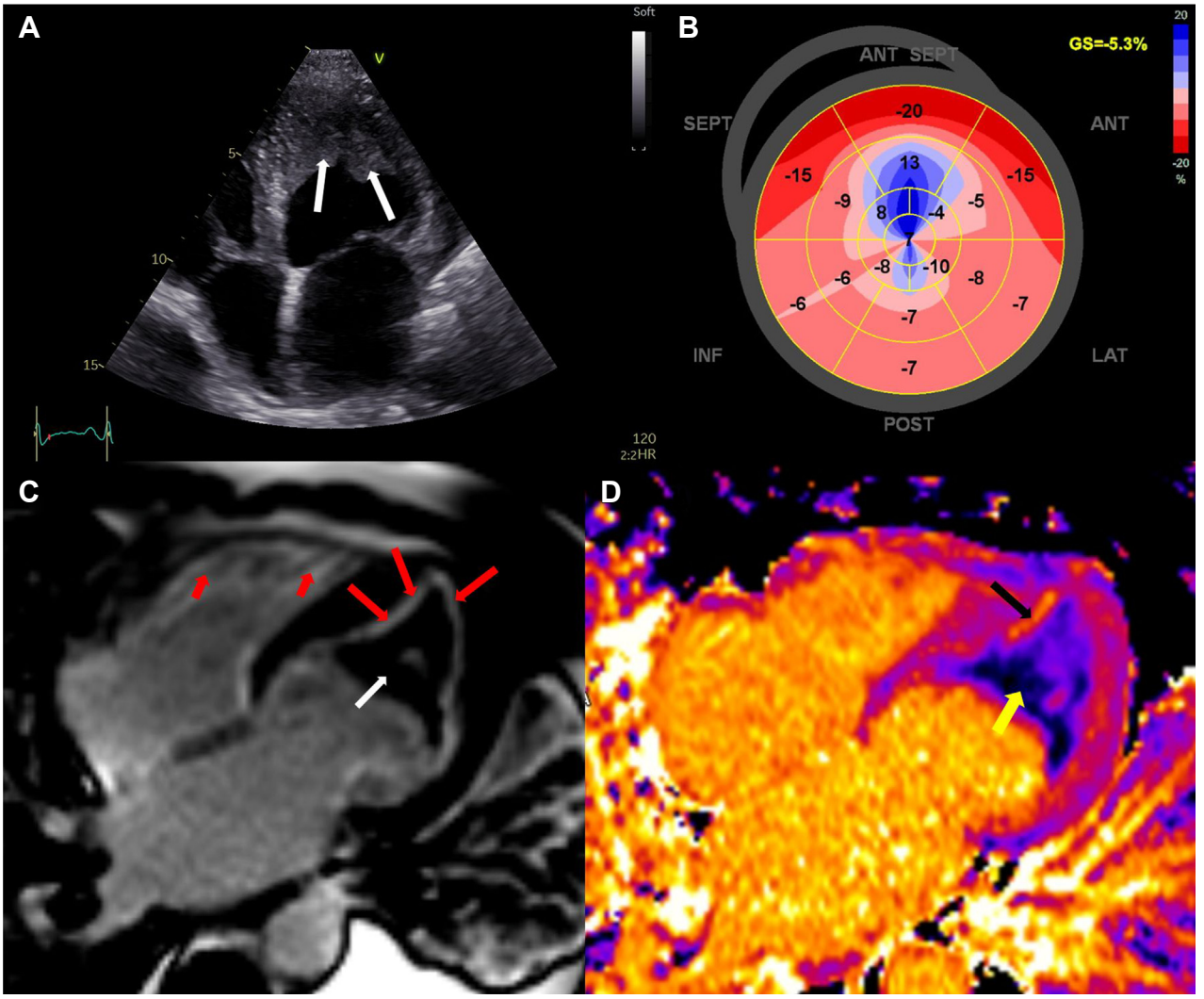

Figure 4 **(A)** Transthoracic echocardiography 4-chamber apical view from case 2 acquired in early systole. *Arrows* indicate extensive thrombus material in the LV. **(B)** Global longitudinal strain bull's-eye plot acquired from case 2 displays a significant reduction in segmental values, which are predominantly noticeable in the apical region (inverse apical sparing). **(C)** Cardiovascular magnetic resonance 4-chamber LGE sequence (phase-sensitive inversion recovery) from case 2. *White arrows* indicate extensive thrombus material, and *red arrows* indicate fibrosis. **(D)** Cardiovascular magnetic resonance T1-mapping sequence (modified Look-Locker inversion recovery) in the 4-chamber view from case 2. *White arrows* indicate extensive thrombus material, and *red arrows* indicate fibrosis.

parameters such as pulmonary vein flow, hepatic venous flow, mitral flow, tissue Doppler indices, CMR, and right heart catheterization aids in distinguishing the predominant physiology. These diagnostic tools play a crucial role in differentiating between the 2 entities.

Endomyocardial biopsy remains the gold standard for the diagnosis of Loeffler endocarditis, allowing for the assessment of eosinophilic infiltration and necrosis.[6] Initial clinical suspicion should arise in situations with elevated eosinophil count and cardiovascular symptoms.[10] However, Loeffler endocarditis may manifest independently of hypereosinophilia.[11] As a result, clinicians are advised to conduct comprehensive assessments of patients utilizing multimodality imaging techniques. In certain instances where Loeffler endocarditis is suspected, EMB should be considered, even in the absence of elevated eosinophil levels.

The treatment of Loeffler endocarditis is based on the underlying etiology, disease stage, and severity of symptoms. In cases of idiopathic hypereosinophilic syndrome, immunosuppressive therapy with corticosteroids and/or other immunosuppressive agents, such as mycophenolate or cyclophosphamide, is recommended to reduce eosinophil counts and inflammation.[3] Anticoagulation is recommended in patients with thrombotic Loeffler endocarditis, while heart failure treatment is indicated in patients with fibrotic Loeffler endocarditis. The response to treatment varies depending on the stage of the disease, with acute necrotic Loeffler endocarditis having a better prognosis than thrombotic and fibrotic Loeffler endocarditis.[3] Therefore, timely diagnosis of Loeffler endocarditis through multimodal imaging is essential.

CONCLUSION

In conclusion, Loeffler endocarditis is a rare condition with various etiologies and clinical presentations, which can be challenging to diagnose and treat. Multimodal imaging techniques, including CMR and TTE, as well as histological verification by EMB, is essential in the

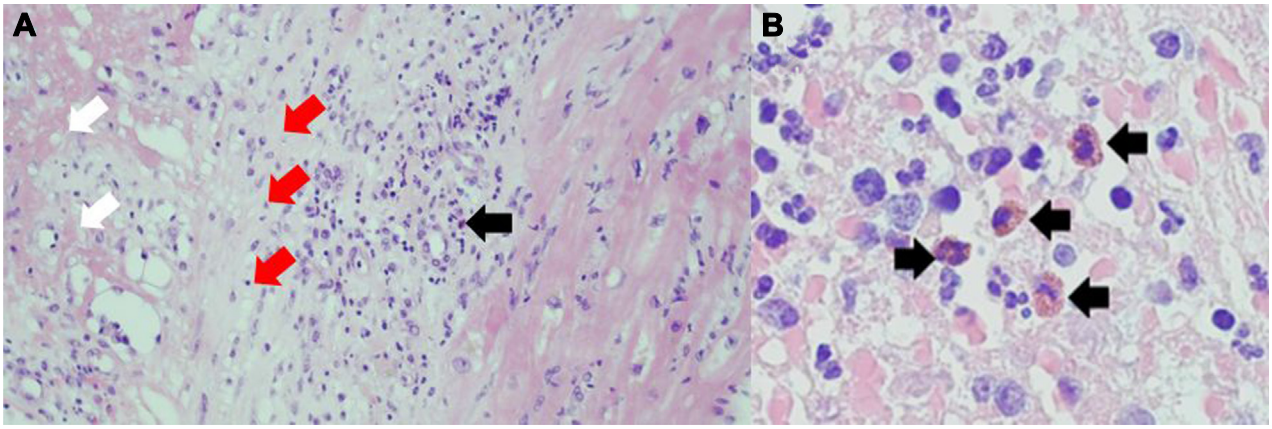

Figure 5 **(A)** The surgically removed endomyocardial mass obtained from case 2 displays regions of interstitial fibrosis, highlighted by the *red arrow*. Additionally, a *black arrow* denotes an eosinophil leukocyte, while *white arrows* indicate the presence of mural thrombus. **(B)** A section of the mural thrombus is presented (case 2), wherein several entrapped eosinophil leukocytes are highlighted using *black arrows*.

establishment of the diagnosis and stage of Loeffler endocarditis, while treatment is based on the underlying etiology, disease stage, and severity of symptoms.

ETHICS STATEMENT

The authors declare that the work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

CONSENT STATEMENT

The authors declare that since this was a noninterventional, retrospective, observational study utilizing deidentified data, informed consent was not required from the patient under an IRB exemption status.

FUNDING STATEMENT

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DISCLOSURE STATEMENT

The authors report no conflict of interest.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.case.2023.09.003.

REFERENCES

1. Fozing T, Zouri N, Tost A, Breit R, Seeck G, Koch C, et al. Management of a patient with eosinophilic myocarditis and normal peripheral eosinophil count: case report and literature review. Circ Heart Fail 2014;7:692-4.
2. Ammirati E, Frigerio M, Adler ED, Basso C, Birnie DH, Brambatti M, et al. Management of acute myocarditis and chronic inflammatory cardiomyopathy: an expert consensus document. Circ Heart Fail 2020;13:e007405.
3. Brambatti M, Matassini MV, Adler ED, Klingel K, Camici PG, Ammirati E. Eosinophilic myocarditis: characteristics, treatment, and outcomes. J Am Coll Cardiol 2017;70:2363-75.
4. Bondue A, Carpentier C, Roufosse F. Hypereosinophilic syndrome: considerations for the cardiologist. Heart 2022;108:164-71.
5. Gottdiener JS, Maron BJ, Schooley RT, Harley JB, Roberts WC, Fauci AS. Two-dimensional echocardiographic assessment of the idiopathic hypereosinophilic syndrome. Anatomic basis of mitral regurgitation and peripheral embolization. Circulation 1983;67:572-8.
6. Ginsberg F, Parrillo JE. Eosinophilic myocarditis. Heart Fail Clin 2005;1:419-29.
7. Silva C, Moon JC, Elkington AG, John AS, Mohiaddin RH, Pennell DJ. Myocardial late gadolinium enhancement in specific cardiomyopathies by cardiovascular magnetic resonance: a preliminary experience. J Cardiovasc Med (Hagerstown) 2007;8:1076-9.
8. Kleinfeldt T, Nienaber CA, Kische S, Akin I, Turan RG, Körber T, et al. Cardiac manifestation of the hypereosinophilic syndrome: new insights. Clin Res Cardiol 2010;99:419-27.
9. Polito MV, Hagendorff A, Citro R, Prota C, Silverio A, De Angelis E, et al. Loeffler's endocarditis: an integrated multimodality approach. J Am Soc Echocardiogr 2020;33:1427-41.
10. Morimoto S, Kubo N, Hiramitsu S, Uemura A, Ohtsuki M, Kato S, et al. Changes in the peripheral eosinophil count in patients with acute eosinophilic myocarditis. Heart Vessels 2003;18:193-6.
11. Mankad R, Bonnichsen C, Mankad S. Hypereosinophilic syndrome: cardiac diagnosis and management. Heart 2016;102:100-6.