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CASE REPORT

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Four challenging cases of eosinophilic endocarditis or myocarditis with literature review

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Abstract

Background Eosinophilic endocarditis or myocarditis is a major complication of hypereosinophilic syndrome, characterized by eosinophilic infiltration leading to endocardial or myocardial necrosis, thrombosis formation, and fibrosis. For its rare morbility and various heterogenicity, eosinophilic endocarditis or myocarditis is prone to misdiagnosis and missed diagnosis. Neither large case series nor clinical trials on this specific endocarditis or myocarditis have been reported.

Case presentation Four middle-aged male patients had increased eosinophilia and elevated levels of troponin or lactate dehydrogenase. Cardiac ultrasound showed ventricular wall thickening with or without reduced cardiac systolic function, apical thrombosis or restrictive cardiomyopathy.one of these patients showed myocardial enhancement by CMR, and one of these patients showed endocardial enhancement by CMR. The coronary angiography results were negative. Three patients were diagnosed with eosinophilic endocarditis, and one was diagnosed with eosinophilic myocarditis. After the application of steroid treatment, eosinophil levels decreased rapidly, myocardial thickening was relieved, and cardiac function was gradually recovered.

Conclusion This case series embodies the high heterogeneity in the clinical manifestation of the eosinophilic myocarditis or endocarditis, and the important role of multi-module imaging. Early detection and early treatment is crucial for the prognosis of eosinophilic endocarditis or myocarditis.

Keywords Eosinophilic endocarditis or myocarditis, Eosinophilia, Hypereosinophilic syndrome, Echocardiography, CMR

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Introduction

Hypereosinophilic syndrome (HES) is a rare myeloproliferative disorder (MPD) characterized by persistent eosinophilia and damage to multiple organs [1, 2] caused by allergies, parasites, autoimmune diseases, infections, and cancer [3–7] with low morbidity and high mortality, which mainly affects men aged between 20 and 50 years old. The clinical manifestation is multi-system eosinophil infiltration, especially the skin, heart, and nervous system. Diagnosis requires an eosinophil (EO) count of at least 1.5×10^9/L twice (interval of more than 1 month) and/or bone marrow nucleated cell count with EO ratio ≥ 20%, and/or pathology confirmed extensive EO infiltration and/or significant deposition of eosinophilic granulocyte protein and evidence of organ damage except for other diseases that may be the primary cause of organ damage. HES can be classified into four subtypes based on etiology as follows: hereditary (familial) HE, secondary (reactive) HE, primary (clonal/neoplastic) HE, and idiopathic HE [8–10]. Heart involvement is the most serious complication and the main cause of death in HES, with complication rates of 40-50% [11–13]. Eosinophilic endocarditis or myocarditis, a serious heart complication of HES, results in damage to the endocardium or myocardium through eosinophil infiltration, leading to myocardial necrosis, thrombogenesis, and fibrosis. Eosinophilic endocarditis is also known as Löffler myocarditis (LE). Patients may lack specific symptoms but often experience dyspnea [14, 15] and a high risk of death [16, 17]. Acute cases can be severe, with systemic thrombo-embolic events, worsening cardiac failure, arrhythmia, and sudden cardiac death [18–21]. Patients with eosinophilic granulomatous vasculitis (EGPA) and allergies complicated with LE face significantly higher 120-day mortality of 23.3% and 46.3%, respectively, compared to those without LE [21, 22]. Early recognition and treatment of LE can improve prognosis [22]. In this article, four cases diagnosed with LE were screened based on patients who visited our hospital over the past five years, and retrospective analysis on their diagnosis and treatment will be given. Furthermore, a comprehensive literature review of the epidemiology, etiology, pathophysiology, diagnosis and differential diagnosis, treatment, and prognosis of eosinophilic endocarditis or myocarditis was conducted, aiming to establish a foundation for further research and to provide detailed insights for the clinical management of eosinophilic endocarditis.

Case presentation

Case 1

A 34-year-old male with a history of asthma for more than ten years presented to our hospital due to increasing level of eosinophil for over two months. Three months prior to visiting our hospital, he sought treatment at a local hospital for muscle soreness and numbness in the sole of his feet. Initial EO count was 1.74×10^9/L(normal range 0.02–0.50), which increased to 5.46×10^9/L on day 30 and 12.91×10^9/L on day 80. The level of cardiac troponin I (cTnI) was 2.37ug/L on day 35. Tests for the antibodies of liver flukes, lung flukes, hydatid, toxoplasmosis, sparganosis and cysticercosis were negative. Coronary angiography (CAG) showed no significant findings. The treatment was not clear. Later, due to fever, cough, and sputum, he visited another hospital where computed tomography (CT) of the chest showed bronchiectasis with infection and bronchial asthma. He was treated with which slightly relieved his symptoms of fever, cough, and expectoration. His EO count then was 9.21×10^9/L. To seek further diagnosis and treatment, he came to our hospital. Examination showed white blood cell count (WBC) of 16.9×10^9/L, EO of 8.76×10^9/L, ESR of 76 mm/hour, CRP of 16.4 mg/L (normal range < 3.1 mg/L) rheumatoid factor of 271.0IU/mL (normal range 0.0–20.0), ASO < 50.6IU/mL, and total IgE of 745KU/L, positive for Hepatitis E-IgG, negative for anti-myeloperoxidase antibodies (MPO-IgG) and anti-proteinase 3 antibodies (PR3-IgG). No malaria parasites were found in the blood, and stool tests for parasites were negative. All tests for autoimmune antibodies were negative. The Fip1-like1-platelet-derived growth factor receptor (alpha) fusion gene (FIP1L1-PDGRFα) FIP1L1/PDGFRα mutation at 4q12 was not present. ECG showed sinus tachycardia, poor R-wave progression in leads V2 and V3, and significant changes in the ST segment and T waves. Transthoracic echocardiography (TTE) showed significant thickening of the mid to apical segments of the left ventricular wall, the thickest part was around 18 mm at the apex (Fig. 1a), suggesting eosinophilic endocarditis. PET-CT showed slightly increased FDG uptake in the left ventricle, scattered inflammation in both lungs, and a small amount of pleural effusion on both sides. (Fig. 1c) Due to the complexity of the condition, multidisciplinary team (MDT) approach was adopted, and the patient was diagnosed with eosinophilia with involvement in heart, lungs, gastrointestinal tract, and hematological system. Treatment included methylprednisolone 50 mg QD for a week, along with medications to protect the stomach, calcium supplements, and nutritional support for the nerves. On the fourth day of treatment, a recheck showed WBC 13.2×10^9/L, CRP < 3.1 mg/L, RF 286.0IU/mL, ASO < 50.6 IU/mL, total IgE 554KU/L, CK-MB 35U/L, and BNP 4062ng/L. On the fifth day of treatment, a recheck showed WBC 11.7×10^9/L, EO 0.24×10^9/L, and BNP 2810ng/L. He was discharged and continued oral steroid treatment. During a two-year follow-up, the EO count gradually returned to normality within three months. TTE showed that the thickness of the myocardium at

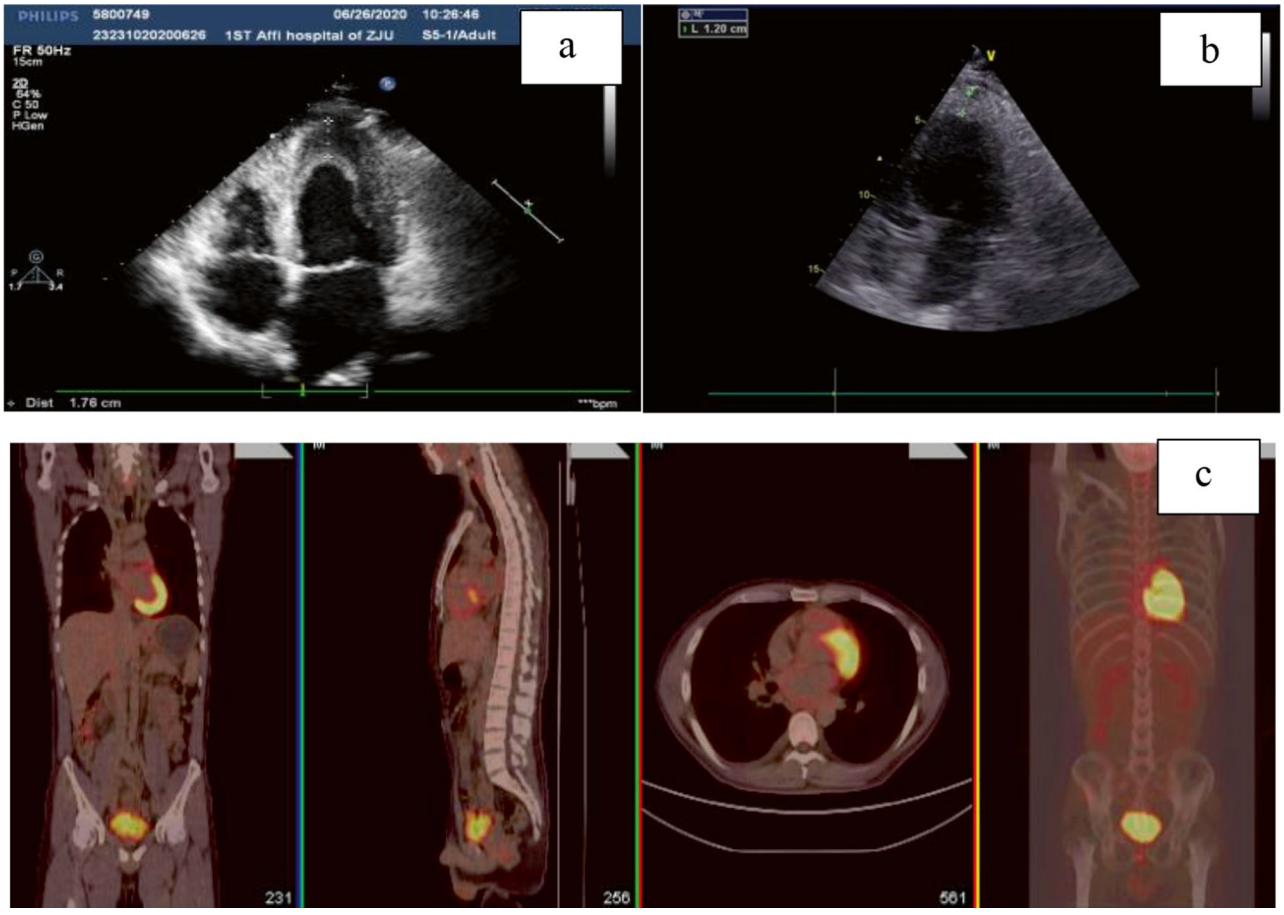

Fig. 1 **a** Two-dimensional (2D) TTE of apical four chamber view showed thickened left ventricular wall, with the thickest part at the apex, about 18 mm. **b** 2D TTE of parasternal short axis view showed the thickness of the left ventricular myocardial apex was about 9 mm. **c** PET-CT showed a mild increase in FDG metabolism in the left ventricular myocardium

the apex gradually returned to normality within a year. (Fig. 1b).

Case 2

A 37-year-old male without any prior medical history came to our hospital due to chest tightness for three days and chest pain for two days. Physical examination was within normal limits. EO count was 0.71×10^9/L (the 1st day of admission), 0.92×109/L (on the 2nd day), 1.17×10^9/L (the 4th day), 3.81×10^9/L (the 7th day), 7.15×109/L (the 10th day), and 11.39×10^9/L (the 12th day). The level of cardiac troponin T (cTnT) was 0.850ug/L, and the level of BNP was 786ng/L. ECG showed sinus tachycardia, abnormal Q waves on the high lateral wall, and rightward electrical axis deviation. The first TTE showed diffusely thickened left ventricular wall, approximately 15 mm, indicating hypertrophic non-obstructive cardiomyopathy, left ventricular dysfunction (LVEF 36% by Simpson's two-plane method), and mild to moderate pericardial effusion. (Fig. 2a). Myocardial speckle tracking imaging (STI) showed normal strain at the apex but reduced strain at the base of the left ventricle, suggesting cardiac amyloidosis (CA). (Fig. 2b). CMR indicated regional myocardial thickening, localized myocardial delayed enhancement in the left ventricular wall, and a small amount of pericardial effusion. (Fig. 2c). CT of lung suggested a history of tuberculosis in the upper right lung and calcification in the left pleura, without excluding previous tuberculous pleuritis. A bone marrow biopsy showed increased cell activity with an increase in eosinophils. P-ANCA, C-ANCA, M-bcr-abl/abl, and FIP1L1-PDGFRα, were negative. EO levels were persistently elevated from 0.71×10^9/L to 11.39×10^9/L within 12 days of admission, combined with the thickened myocardium, the patient was diagnosed with eosinophilic myocarditis and treated with dexamethasone 5 mg QD, medications to protect stomach, supplements for calcium and potassium, and isoniazid to prevent tuberculosis. The patient declined the recommended cardiac biopsy. Tests showed a continuous decrease in EO level until they normalized after one week's application of dexamethasone. On the 18th day of admision, EO count was 0.20×10^9/L, then dexamethasone was changed to 15 mg of prednisone QD. Three weeks after discharged,

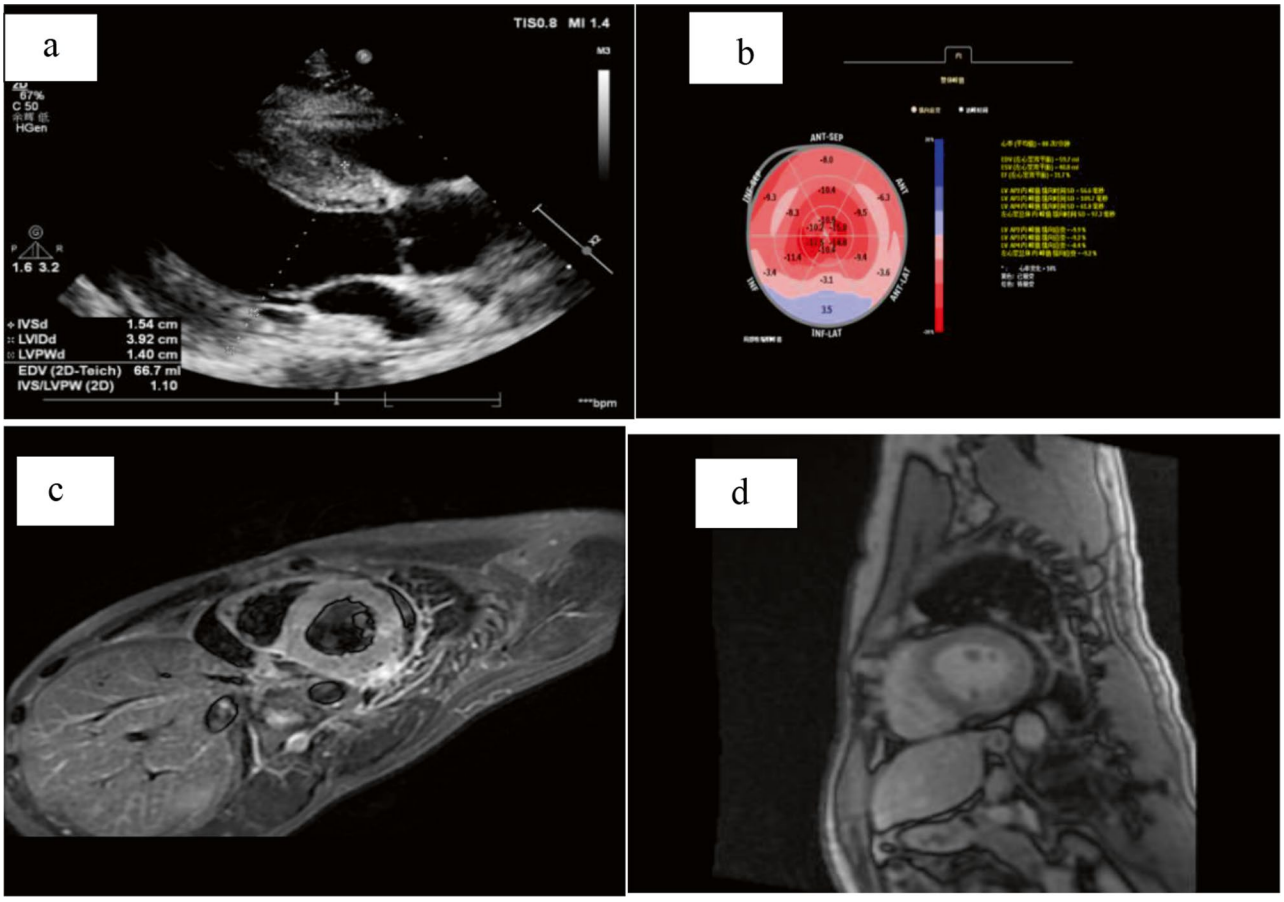

Fig. 2 **a** TTE performed during hospitalization shows thickened left ventricular wall, about 15 mm. **b** Spot tracking technology (STI) of heart showed normal strain in the left ventricular apex, reduced strain in the basal segment of the left ventricle, thickening of the left ventricular myocardium with echocardiographic changes, and left ventricular systolic dysfunction with an LVEF of 31.7%, thus suspected cardiac amyloidosis (CA). **c** CMR indicated regional myocardial thickening, thinned anterior and lateral walls of the left ventricular apex during diastole, and a small amount of pericardial effusion. **d** CMR follow-up indicates that there are no significant abnormalities in myocardial thickness and endocardium

prednisone was reduced to 5 mg QD. Two months later, prednisone was discontinued. Subsequent, repeated TTE and CMR (Fig. 2d) showed improvement in myocardium thickness and function back to normality. Repeated examination of cTn I back to normality.

Case 3

A 46-year-old male with a diagnosis of liver cirrhosis for over three months and abdominal discomfort for over two months presented to our hospital. He had a long history of malaria from working in Cameroon treated with quinine for many years. His physical examination was within normal limits. After admission, laboratory tests showed that his WBC count was 8.38×10^9/L, EO count was 3.54×10^9/L, Cr level was 140umol/L, lactate dehydrogenase (LDH) level was 274U/L (normal range 120-250U/L), BNP level was 1528.60ng/L, total IgE level was above 5000.0KU/L, IgG level was 4268.0 (normal range 860.0-1740.0), IgG4 level was 11.700 g/L (normal range 0.030–2.010 g/L), PR3-IG level was 122.46RU (on the 2nd day of admission) and 149.20RU (on the 16th day of admission), T-SPORT and multiple antibodies of parasites were positive. His troponin level was normal, and the results of PDGFRa and (FGFR1, 8P11): FGFR1 was negtive. ECG indicated normal sinus rhythm, first-degree atrioventricular block and incomplete right bundle branch block and changes in the ST segment and T waves. TTE showed mural thrombi attached to the apices of the left and right ventricles (Fig. 3a and b), enlarged atria and right ventricle, restrictive filling of left ventricle (Fig. 3c), and the reduced systolic function of right ventricle (tricuspid annular plane systolic excursion (TAPSE)11 mm) (Fig. 3d), moderate regurgitation of tricuspid valve and mitral valve, and a small amount of pericardial effusion. PET-CT (18 F-FDG) revealed multiple lymph nodes of varying sizes with increased FDG metabolism on the deep surface of the right pectoral muscles, both axillae, retroperitoneal alongside the abdominal aorta, both iliac vessels, both pelvic walls, and both inguinal areas, enlarged cardiac silhouette and a small amount

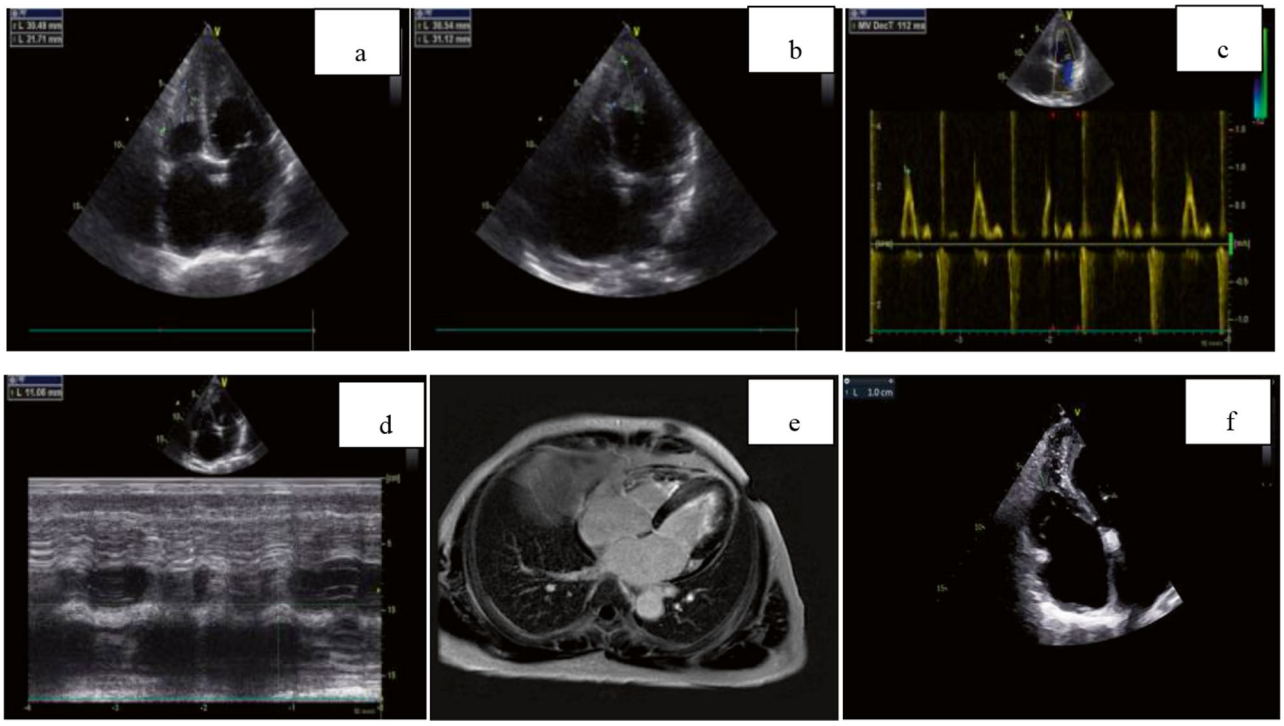

Fig. 3 **a** showing right ventricular apical mural thrombus measuring approximately 3.0 × 2.2 cm. **b** showing left ventricular apical thrombus measuring approximately 3.1 × 3.1 cm. **c** showing left ventricular lateral wall TDI E/A > 2, indicating left ventricular restrictive filling. **d** showing slightly reduced right ventricular systolic function (TAPSE: 11 mm). **e** CMR showing subendocardial late gadolinium enhancement (LGE) in both the left and right ventricles, thickened myocardium at the cardiac apex involving both ventricles and enlargement of the left atrium and right ventricle. **f** TEE show that the thrombus within the double chamber cavity disappeared and the wall thickness returned to normal after thrombolytic and steroid treatment

of pericardial fluid. Due to the complexity of the condition, MDT approach was adopted, praziquantel 150 mg/kg for 5 days, was used against parasites, warfarin and nadroparin with dosage adjustments based on INR levels against the thrombi attached to the apices were applied. The biopsy from the right armpit lymph node showed active lymphoid hyperplasia with numerous plasma cells and EO infiltration. Despite praziquantel treatment, there was no significant decrease in EO and PR3-Ig levels. Considering the secondary increase in IgG4 and PR3-Ig levels, a rheumatology consultation was conducted to consider it was eosinophilic endocarditis secondary to ANCA-associated vasculitis, methylprednisolone 30 mg QD was applied. During methylprednisolone treatment, prophylactic treatment against tuberculosis with isoniazid was administered. Follow-up blood tests showed continuous decrease in EO until they returned to normal levels, and BNP levels gradually decreased. Nine days after discharge, IgG decreased to 3175.0 RU/ml and PR3-IgG decreased to100.98RU/ml. Three months after discharge, IgG and PR3-Ig were decreased to normal levels, and CMR showed thickened myocardium at the apices affecting both ventricles, accompanied by enlargement of the left atrium and right ventricle, subendocardial late gadolinium enhancement (LGE) in both ventricles, consistent with LE. (Fig. 3e) Monthly follow-up TTE showed a progressive decrease in myocardial thickness and the disappearance of thrombi. (Fig. 3f)

Case 4

A 52-year-old male without any prior medical history urgently admitted to our hospital due to chest tightness and anhelation for over a month, worsening over 3 days. The patient was with a GCS score of 3-3-5. Laboratory tests showed WBC 88.29×10^9/L, hemoglobin 81 g/L, EO 24.79×10^9/L, platelet 54×10^9/L, CRP 44.46 mg/L, lactate dehydrogenase 812U/L, BNP 2335.70pg/mL. ECG indicated multifocal atrial premature beats and paroxysmal supraventricular tachycardia. TTE showed significant thickening of the left ventricular apical wall (Fig. 4a) with a hypoechoic mass of uncertain nature (Fig. 4b), enlargement of both atria and the right ventricle, moderate to severe regurgitation of tricuspid valve (Fig. 4c), increased pulmonary arterial systolic pressure (PASP), and moderate pericardial effusion. Considering the rapid respiratory rate and poor oxygenation, the patient was intubated and mechanically ventilated. Treatments included norepinephrine to maintain blood pressure, piperacillin-tazobactam for infection, acid suppression, mucolytics, and aontinuous renal replacement therapy (CRRT) to stabilize the internal environment, dexamethasone 10 mg and hydroxyurea 1 g TID for symptomatic treatment. Bone

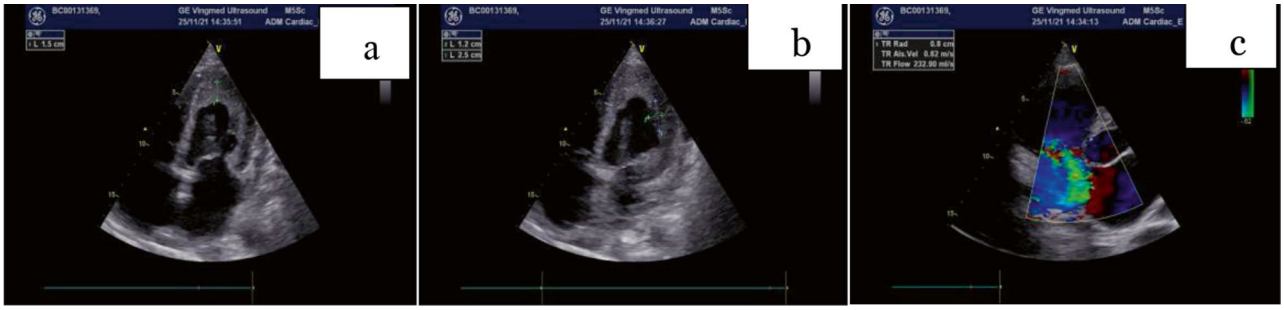

Fig. 4 Images from TTE of apical four chamber view of case 2 patient. **a** 2D showed thickened left ventricular wall, with the thickest part at the apex, about 15 mm. **b** 2D showed a hypoechoic mass of approximately 2.5 × 1.2 cm in size on the lateral wall of the left ventricle. **c** CW showed moderate to severe tricuspid regurgitation

marrow biopsy showed increased EO, with no abnormalities in leukemia immunotyping or genetic testing. Bone marrow pathology indicated eosinophil proliferation. Stool tests for schistosoma eggs were negative, and no schistosoma found in the blood. On the third day of admission, a recheck showed WBC count of 92.23×10^9/L and EO count of 31.16×10^9/L. The next day, imatinib 100 mg QD was administered. Left ventricular cardiomyopathy suggested localized abnormal thickening and high perfusion in the left ventricular myocardium with small patchy perfusion defects, considering LE with localized necrosis. On the fifth day after leukapheresis, a routine blood test showed WBC was 64.26×10^9/L. During this period, liver function tests showed albumin 34.4 g/L, ALT 188U/L, AST 60U/L, total bilirubin 95.6μmol/L, direct bilirubin 79.0μmol/L, and indirect bilirubin 16.6μmol/L, indicating progressive jaundice. Hepatobiliary ultrasound suggested bile stasis without obvious obstruction, possibly caused by eosinophil infiltration, treatment of liver protection and jaundice reduction continued. Additionally, during treatment, the patient's platelet count decreased, considered related to the side effects of hydroxyurea, and platelet transfusion was administered. On day 10, WBC count was 11.54×10^9/L, EO count was 8.17×10^9/L, hemoglobin was 78 g/L, and platelet count was 20×10^9/L. Considering the significant decrease in WBC, hydroxyurea was gradually discontinued, and dexamethasone was reduced to 5 mg QD, continuing imatinib treatment. On day 11, pain and sedative medications were stopped. The patient's oxygenation and circulation were stable, and the tracheal tube was removed and replaced with high-flow nasal oxygen, with an oxygenation index above 400. On day 14, the patient was found to have weak muscle strength in the right upper and lower limbs. MRI of head showed multiple acute infarcts in both frontal lobes, the centrum semiovale, near the posterior horn of the lateral ventricles, and the right temporal lobe. Neurology consultation was conducted to confirm the diagnosis of acute cerebral infarction, likely related to the increased EO. Treatment with clobazam was added. On day 18, a biochemical retest showed albumin decreased to 34.3 g/L, ALT to 42U/L, AST to 16U/L, total bilirubin to 39.8μmol/L, direct bilirubin to 27.4μmol/L, Cr to 48μmol/L, lactate dehydrogenase to 337U/L, and C-reactive protein (CRP) to 8.04 mg/L. Fungal D-glucan test showed β-1, 3-D glucan below 10.00pg/ml. Blood routine indicated WBC count was 5.29×10^9/L, EO count was 3.84×10^9/L on day 18, hemoglobin was 64 g/L, and platelet count was 15×10^9/L. CT of chest indicated increased infiltrates in bilateral, pulmonary moderate pleural effusion, and moderate pericardial effusion. The patient was currently being treated for the primary disease with 100 mg of imatinib and 5 mg of dexamethasone QD. The patient's EO count and ventricular wall thickness are gradually returning to normal.

Discussion

The vast majority of eosinophilic endocarditis or myocarditis cases occur in middle-aged men around 40 years of age, and less than 10% of eosinophilic endocarditis or myocarditis cases occur in individuals younger than 16 years of age [22]. Factors that increase the risk of cardiac injury in HES patients include HLA-Bw44 positivity, thrombocytopenia, elevated $VitB_{12}$ levels, splenomegaly, and the presence of FIP1L1-PDGFRA fusion tyrosine kinase [23, 24]. People living in areas with high parasite infection rates may be at higher risk for cardiac damage due to activation of secondary eosinophilia. Autopsy cases have revealed that 0.5% involve eosinophilic endocarditis or myocarditis, and among drug-induced heart transplant recipients, this figure reaches as high as 20% [25]. Eosinophilic endocarditis or myocarditis has an insidious onset and exhibits high clinical heterogeneity. The initial manifestations of eosinophilic endocarditis or myocarditis are nonspecific cardiogenic symptoms, such as progressive heart failure, breathlessness, pulmonary edema, leg edema, pericarditis, pericardial effusion, chest pain, and splenomegaly, embolism associated with high levels of eosinophils in peripheral blood [26–28]. The

disease manifests variably at different stages, characterized by diverse clinical and imaging findings, high rates of misdiagnosis and missed diagnoses, and significantly varied prognoses.

Eosinophilic endocarditis or myocarditis progresses through three stages [29]. The initial stage, occurring in the first 1–2 months of the disease, involves acute inflammatory necrosis of myocardial cells, where eosinophils infiltrate the heart tissue, degranulate, and release toxic cationic proteins such as eosinophil cationic protein (ECP) and major basic protein (MBP), which mediate myocardial damage [30, 31]. Early histopathological features include acute myocarditis with eosinophil and lymphocyte infiltration. During this phase, eosinophils infiltrate myocardial interstitium, degranulate, and release toxic cationic proteins, inducing apoptosis and necrosis. However, patients typically exhibit no cardiac-specific symptoms or signs at this stage [32]. The second phase is the thrombus formation period (about 10 months later), during which endothelial damage and thrombus formation occur, potentially leading to valvular dysfunction. Thrombo-embolism can lead to acute cerebral infarction [33]and acute abdominal aortic occlusion [34]. These conditions may initially manifest without specific cardiac symptoms or signs.The occurrence of systemic thromboembolic events secondary to intravenular thrombosis is a major risk factor for morbidity and mortality in patients with eosinophilic endocarditis or myocarditis [35]. The third stage is the fibrotic scarring formation stage (after 1 to 2 years), characterized by endocardial fibrosis and restrictive filling impairments, also known as constrictive endocarditis, whose pathological features were attributed to endocardial fibrosis resulting from the fibrous inflammatory process and granulation tissue remodeling, and not to amyloidosis, hemochromatosis, or non-caseating granulomas [36–38]. Thrombi are replaced by fibrosis, which can involve the endocardium, valves, and chordae tendineae. The cardiac endothelial cells and valves become fibrotic and thickened, and mitral valve regurgitation may also occur, possibly due to fibrotic scars or direct involvement of the mitral valve. The fibrotic stage can also affect the cardiac conduction system, leading to severe arrhythmias.

The key points for the diagnosis of eosinophilic endocarditis or myocarditis are as follows. Laboratory tests show persistent elevation of EO, and myocardial injury markers such as LDH and troponin may be elevated. GAG shows no significant abnormalities. Genetic testing for FIP1L1-PDGRFA has been added to the diagnostic algorithm of HES [39]. The FP fusion gene can activate tyrosine kinase activity, stimulate proliferation, and mediate survival of eosinophils [40–42]. ECG may reveal sinus tachycardia, nonspecific ST segment abnormalities, or conduction blocks, but these findings are typically not significant. ECG can provide diagnostic clues for eosinophilic endocarditis or myocarditis. Additionally, ultrasound contrast can enhance the clarity of cardiac chamber anatomical features, greatly aiding in the identification of intracavitary mural thrombi. In detecting ventricular thrombi, CMR and cardiac acoustic contrast are generally more sensitive and specific than traditional TTE alone [43]. A myocardial biopsy remains the gold standard for definitive diagnosis, by which deposits of major basic proteins (MBP), eosinophil cationic proteins (ECP), and eosinophil peroxidase can be found in the endocardium of patients with LE.

The differential diagnosis should include cardiac diseases with myocardial thickening or ventricular thrombosis, such as hypertrophic cardiomyopathy (HCM) and cardiac amyloidosis (CA). All of them can show the characteristics of RCM when developing into the terminal stages. However, they differ in etiology, pathogenesis, laboratory tests, ECG, echocardiography, and CMR. For eosinophilic endocarditis or myocarditis or infiltrative cardiomyopathy such as CA, characterized by reduced QRS complex voltage due to interstitial space expansion, whereas storage cardiomyopathies show normal or elevated QRS complex voltage. The difference in ventricular wall thickness and surface ECG QRS voltage may help differentiate between CA and HCM. For patients with intracavitary thrombosis, speckle tracking imaging reveals a reduction in global longitudinal strain (GLS) in the affected areas, which is typically considered normal if GLS ≤ -20% [44]. LVEF in the early period of of eosinophilic endocarditis or myocarditis patients is often normal, decreasing as the disease progresses [45]. If the endocardial boundaries of left ventricle by TTE are unclear, it is recommended to use acoustic enhancing agents for a more accurate assessment of left ventricular volume and LVEF in RCM patients. HCM is primarily caused by pathogenic mutations in genes encoding sarcomere-related proteins or is idiopathic, characterized by myocardial thickening, commonly involving the left ventricular wall. Other cardiovascular or systemic, or metabolic diseases causing ventricular wall thickening should be excluded [46]. CA, an infiltrative cardiomyopathy, is characterized by the deposition of insoluble amyloid proteins in the interstitial spaces of tissue cells. TTE of CA may also show left ventricular wall myocardial thickening, with myocardium appearing as ground-glass granular echoes (a pattern resembling frosted glass). Early-stage CA patients with normal LVEF may exhibit reduced longitudinal systolic function [47]. This is characterized by decreased two-dimensional longitudinal strain in the basal and mid segments of the left ventricle, while the apical longitudinal strain is preserved—a phenomenon referred to as apical sparing [48]. This characteristic can serve as a basis for differentiating CA from

Table 1 Clinical summery of four patients with eosinophilic endocarditis or myocarditis

Patient	Gender	Age	Chief complaint	Medical history	Myocardial injury	TTE	CMR	Other positive	Possible	Dignosis	Treatment	Prognosis
Case 1	male	34	muscle soreness and numbness in the sole of his feet	asthma for more than ten years	cTnI 2.37ug/L, BNP4062ng/L	diffusely thickened left ventricular wall,about 15mm,mild to moderate pericardial effusion	-	-	asthma	reactive HE with LE	methylprednisolone	good
case 2	male	37	chest tightness for three days and chest pain for two days	Lung CT suggested a history of tuberculosis in the upper right lung	cTnT 0.850ug/L,BNP 786ng/L	thickened left ventricular wall, about 15mm	LGE in left ventricular myocardium	total IgE of 745KU/L	tuberculosis	reactive HE with myocarditis	methylprednisolone	good
case3	male	46	abdominal discomfort for over two months.	a long history of malaria from working in Cameroon treated with quinine for many years,liver cirrhosis for over three months	LDH 274U/L, BNP 1528.60ng/L	mural thrombi attached to the apices of the left and right ventricles, enlarged atria and right ventricle, restrictive filling of left ventricle,TAPSE 11mm, moderate regurgitation of tricuspid valve, moderate regurgitation of mitral valve, a small amount of pericardial effusion.	subendocardial LGE in both ventricles	total IgE > 5000.0KU/L IgG4 was 11.700g/L	EGPA	EGPA, reactive HE with LE	methylprednisolone and prednisone, prophylactic treatment against tuberculosis with isoniazid	good
case4	male	52	chest tightness and anhelation for over a month, worsening over 3 days	no	BNP 2335.70pg/mL	significant thickening of the left ventricular apical wall, enlargement of both atria and the right ventricle, moderate to severe regurgitation of tricuspid valve, increased PASP, and moderate pericardial effusion.	-	Bone marrow biopsy suggesting eosinophil proliferation	-	undefined HE with I imatinib and dexametha slightly worse		

other RCM, although it is not the definitive diagnostic gold standard [49]. Case 1 involves a patient with a history of asthma for over ten years, who exhibits significantly elevated total IgE and troponin levels, and negative CAG results, suggesting possible asthma-induced secondary eosinophilia associated with eosinophilic myocarditis. The patient of case 2 without significant medical history was repeatedly misdiagnosed by TTE. For the thickened left ventricular wall, it was misdiagnosed as HCM, for the myocardial strain results showed that the apical segment strain was lower than the middle segment and the basal segment strain, it was misdiagnosed as CA. Subsequent increases in EO count and cardiac biomarkers post-admission led to a diagnosis of LE (stage I). The patient of case 3 with a history of tuberculosis and malaria, his troponin and other myocardial injury markers was within normal ranges, but IgG4 was significantly elevated. Despite treatment with quinine, eosinophil levels remained high, suggesting potential ANCA-associated vasculitis with LE (stage III). The patient of case 4 in poor condition at admission, showed elevated EO counts and thickened left ventricular wall by TTE, along with acute cerebral infarction, considered to be undefined HE complicated by eosinophilic endocarditis.

The treatment of eosinophilic endocarditis or myocarditis depends on a comprehensive assessment of the condition and an accurate etiological diagnosis. For cases with identified or suspected causes, initial treatment should target these specific causes. In cases of parasitic infections, antiparasitic agents are administered. Allergen avoidance is recommended for allergy-related LE. In cases of eosinophilic granulomatosis with polyangiitis (EGPA)-related LE, treatment may include steroids or the immunosuppressant cyclophosphamide. Imatinib may be used for the treatment of LE associated with myeloproliferative neoplasms [50]. Imatinib can achieve complete hematologic and molecular remission within weeks to months, but cannot eliminate the FLP1L1-PDGFRA clone in most patients [51, 52]. Corticosteroids, which inhibit eosinophil degranulation, are proposed as a first-line treatment for LE [53]. Consequently, early initiation of treatment in LE may potentially reverse the disease progression. For patients who do not respond well to steroids, treatment options may involve cytotoxic drugs (such as hydroxyurea, azathioprine) or immunomodulator tyrosine kinase inhibitor of eosinophils (such as imatinib), or anti-tumor target (such as merizumab). In these patients, interferon and hydroxyurea are second-line therapeutic agents [26, 54–56]. For patients unresponsive to both first-line and second-line treatments, high-dose imatinib is the treatment of choice [55]. These treatment guidelines ensure a tailored approach based on individual patient response and specific disease etiology. For patients with ventricular thrombi, it is imperative to administer prompt thrombolysis to prevent thromboembolic events. For patients with LE myocardial fibrosis, some of them respond well to corticosteroid therapy. If medical treatment is ineffective, surgical endocardial decortication may be considered, which generally improves symptoms in most patients postoperatively. When valvular regurgitation is severe, valve replacement surgery may be indicated. Due to the risk of thrombotic complications from mechanical valve replacements, bioprosthetic valves are recommended as the preferred option [56]. If all the above treatments are still ineffective, heart transplantation may be considered. Initial treatment should involve a medical regimen to reduce eosinophil counts, with surgical interventions as a secondary consideration. After corticosteroid therapy, the four patients of this article showed continuous decrease in EO levels. Subsequently, myocardial wall thickness and cardiac function gradually normalized.The diagnosis and treatment procedures of the 4 patients are shown in Table 1.

Generally, patients who are responsive to steroids exhibit a favorable prognosis, while those unresponsive to steroids generally face a poor prognosis. However, a good prognosis is also observed in patients with LE caused by genetic mutations after treatment with tyrosine kinase inhibitors. Studies show that patients with HES have a 10-year survival rate of less than 50%, while during the fibrotic stage of LE, the 1-year survival rate is

70–80% [53], the 2-year survival rate is 30–50% [57], and the 10-year survival rate is 30% [53].

Conclusion

Eosinophilic endocarditis or myocarditis is easily misdiagnosed as acute coronary syndrome or other heart disease with hypertrophy of endocardium or myocardium. When there is severe myocardial necrosis or thrombus dislodgement blocking the coronary arteries, symptoms and signs similar to acute myocardial infarction will appear. The clinical presentation ranges from mild to severe symptoms, with most patients primarily experiencing shortness of breath. The mitral valve is most commonly affected, with mitral regurgitation being the most common issue. Early detection, diagnosis, and treatment of eosinophilic endocarditis or myocarditis is crucial, as early treatment can reverse cardiac damage. Many patients with persistent eosinophilia may experience sudden unexplained death, potentially associated with underlying myocarditis, leading to malignant arrhythmia and sudden cardiac arrest. Echocardiography plays a key role in the preliminary screening of eosinophilic endocarditis or myocarditis. For all patients with persistent eosinophilia, close monitoring with serial echocardiography is necessary, even if they are asymptomatic, to prevent missed diagnoses of endocarditis and delays in treatment. As echocardiographers, attention should be paid to dynamic changes in myocardial thickness and cardiac function. CMR is the secondary gold standard in addition to endocardial or myocardial biopsy and is essential for further diagnosis of eosinophilic myocarditis or endocarditis, with characteristic myocardial or subendocardial delayed enhancement. PET-CT plays an irreplaceable role in the localization and characterization of myocarditis or endocarditis.For unknown causes of eosinophilic endocarditis or myocarditis, the first-line treatment option is a combination of corticosteroids and anticoagulants, aimed at rapidly reducing eosinophil counts and preventing thrombus formation and embolic events, followed by etiological treatment. For severe complications, consider surgical interventions such as valve replacement, endocardial decortication, and heart transplantation. The prognosis of eosinophilic endocarditis or myocarditis patients is related not only to the severity of the disease but also to its cause. Published case reports indicated that patients with earlier intervention or non-fibrotic progression had better outcomes, whereas progression to fibrosis is associated with a poorer prognosis.

Abbreviations

LE	Löffler Endocarditis
HES	hypereosinophilic syndrome
HE	hypereosinophilia
EO	eosinophil cell
HE^R	reactive HE
WBC	white blood cell
ESR	erythrocyte sedimentation rate
CT	computed tomography
ASO-A	anti-streptolysin A
BNP	B-type natriuretic peptide
cTnI	cardiac troponin I
ECG	electrocardiogram
CAG	coronary angiography
TTE	transthoracic echocardiography
LVEF	left ventricular ejection fraction
2D	2-dimension
CDFI	color Doppler flow imaging
PW	Pulse Doppler
MDT	multidisciplinary team
CRRT	aontinuous renal replacement therapy
PASP	pulmonary arterial systolic pressure
Cr	creatinine
ALT	alanine aminotransferase
AST	aspertate aminotransferase
TAPSE	tricuspid annular plane systolic excursion
LDH	lactate dehydrogenase
CMR	cardiac magnetic resonance imaging
LGE	late gadolinium enhancement
EGPA	eosinophilic granulomatous vasculitis
HCM	hypertrophic cardiomyopathy
RCM	restrictive cardiomyopathy
CA	cardiac amyloidosis
STI	speckle tracking imaging
ECP	eosinophil cationic protein
MBP	major basic protein
CLS	global longitudinal strain
FIP1L1-PDGRFA	Fip1-like1-platelet-derived growth factor receptor (alpha) fusion gene
MPO-IgG	anti-myeloperoxidase antibodies
PR3-IgG	anti-proteinase 3 antibodies

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Author contributions

Yun Mou proposed the study and was the guarantor. Ping Chen performed the research, wrote and revised the manuscript. Huiling Cheng revised the manuscript. All authors contributed to the design and interpretation of the study.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval

Patients signed an informed consent process that were reviewed by the Ethics Committee of Zhejiang University, who certified that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki.

Patient consent

The patients of the four cases authorized the study, both of them signed a written authorization consent.

Competing interests

The authors declare no competing interests.

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