CASE REPORTS/CLINICAL VIGNETTES

Large Apical Thrombus in a Patient with Persistent Heart Failure and Hypereosinophilia: Löffler Endocarditis

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Idiopathic hypereosinophilic syndrome is an uncommon leukoproliferative systemic disorder characterized by the overproduction of eosinophils and poor prognosis. A major source of morbidity and mortality of this syndrome is the associated cardiac involvement represented by endocardial thickening and mural thrombi. We report a 64-year-old woman with persistent symptoms of heart failure despite standard medical therapy. Echocardiography revealed reduced left ventricular filling due to a large apical mass; an abnormal diastolic filling pattern was also noticed. Complete blood count revealed remarkable hypereosinophilia. Cardiac magnetic resonance imaging demonstrated an apical thrombus and intense linear enhancement of the endocardium, which were compatible with Löffler endocarditis. Medical therapy, including corticosteroids and anticoagulation, was initiated promptly. The symptoms improved as the peripheral hypereosinophilia resolved in 15 days. The patient was asymptomatic at the 1-year follow-up visit with complete regression of the apical thrombus and no evidence of restrictive cardiomyopathy. We report this case to draw attention to this particularly rare condition with poor prognosis since quick and accurate diagnosis and prompt initiation of therapy may improve symptoms and survival.

KEY WORDS: cardiac thrombus; endocarditis; heart failure; Löffler endocarditis.
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INTRODUCTION

In 1936, Löffler[1] reported two patients who had marked peripheral eosinophilia and a peculiar type of fibrosing endomyocarditis, which is known as Löffler endocarditis. Other organs, such as the spleen, liver, eyes, skin, and lungs, may also be involved in this disorder, and since 1968, the term hypereosinophilic syndrome (HES) has been used in order to define such conditions of prolonged eosinophilia of unknown origin[2].

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Idiopathic HES is an uncommon systemic disease and is typically seen in men in their 4th decade who live in temperate climates, while there are few cases reported in children[3,4]. Since 1975, the diagnostic criteria for HES are presence of a persistent eosinophilia (1,500/mm3) for more than 6 months with signs or symptoms of organ involvement and lack of evidence for parasitic, allergic, or other known causes of eosinophilia[5].

Cardiac involvement in idiopathic HES is the rule, occurring in the majority of the patients[6]. Cardiovascular manifestations of the syndrome are the major cause of morbidity and mortality and include progressive subendocardial fibrosis with overlying mural thrombus formation leading to peripheral emboli, restrictive cardiomyopathy, valvular dysfunction, and heart failure[7–9]. Cardiac involvement is often biventricular, with intense endocardial fibrotic thickening of the inflow portions and apex of the ventricles that result in obstruction to inflow of blood into the respective ventricle, thus producing restrictive physiology[10]. Valvular regurgitation may occur because of involvement of the supporting apparatus of the mitral or tricuspid valves. The pathophysiology lies in the toxic effect of eosinophils on the heart. Echocardiography is helpful in the diagnosis of the disease and in assessing cardiac involvement. There is still no definite therapy for idiopathic HES, and the prognosis is poor with high mortality rates. Corticosteroids have proven benefit in the short term and have become a standard therapy.

We report the case of a 64-year-old woman who presented with persistent symptoms of heart failure and hypereosinophilia. After accurate diagnosis of Löffler endocarditis, medical therapy including corticosteroid and anticoagulation was initiated promptly. The patient improved dramatically, with no evidence of development of restrictive cardiomyopathy.

CASE

A 64-year-old woman was referred to our cardiology outpatient clinic with persistent symptoms of congestive heart failure despite standard medical therapy, including diuretics, angiotensin-converting enzyme inhibitor, beta blocker, and digitalis. She had atypical chest pain, exertional dyspnea, orthopnea, palpitations, productive cough, weight loss (8 kg in the last 3 months), and easy fatiguability for the past 4 months. She underwent coronary angiography 1 month ago, which revealed mild stenosis (<50%) in the right coronary artery with normal left anterior descending and circumflex arteries. She was a non-smoker, and her past medical history was unremarkable, except that she had had bronchial asthma for 20 years.

On physical examination, she had a fever of 38.9°C, blood pressure was 110/70 mmHg, and heart rate was 118/min. Cardiac auscultation revealed an apical holosystolic murmur with S3 gallop. Pulmonary sounds were decreased bibasally, and there were rales extending to apical zones on both sides. Her liver was enlarged, with a liver span of 15 cm. She also had splenomegaly, jugular venous distention (7 cm), and peripheral edema.

Electrocardiogram revealed sinus tachycardia with nonspecific ST segment changes and T wave abnormalities. Chest X-ray demonstrated moderate pulmonary congestion with bilateral pleural effusion. Pleural effusion was transudative and rich in eosinophils (total cell count: 910/mm^3, eosinophils: 270/mm^3; neutrophils: 410/mm^3, lymphocytes: 190/mm^3, monocytes: 40/mm^3). Her white blood cell count was 9,300/mm^3 (eosinophils: 3,440/mm^3; neutrophils: 3,730/mm^3, lymphocytes: 2,004/mm^3, basophils: 6/mm^3, monocytes: 120/mm^3). The rest of the complete blood count was normal (hemoglobin: 13.2 g/dl, hematocrit: 39.5%, and platelets: 326,000/mm^3). Peripheral smear revealed marked eosinophilia. Bone marrow examination showed normocellular marrow. There were moderate eosinophilia (39%), moderate myeloid hyperplasia (myeloid/erythroid ratio was 2.4:1), and adequate megakaryocytes. Erythropoiesis was normal. There was no abnormal myeloid maturation or blast. Molecular analysis of the bone marrow showed no clonality. There was no mutation in the Fip1-like platelet-derived growth factor receptor alpha chain (FIP1L1-PDGFRA). Biochemistry tests indicated a two-fold increase in liver enzymes [AST: 78 U/l (normal range: 10–37 U/l) and ALT: 82 U/l (normal range: 10–40 U/L)] with normal glucose, creatinine, and electrolytes. Due to presence of hypereosinophilia, stool examinations were performed in order to exclude parasite infestation. Three samples were collected on alternate days, and microscopic examination of stool revealed neither trophozoites nor cysts. Also the common serologic tests for Echinococcus, Toxocara, and Fasciola hepatica were negative. The abdominal ultrasound examination confirmed mild liver and spleen enlargement. Computed tomography of the chest, abdomen, and pelvis showed moderate pleural effusion, a large left ventricular mass, hepatosplenomegaly, and mild ascites; but there was no finding of neoplastic lesions.

Echocardiography showed moderate to severe mitral regurgitation with normal left ventricular dimensions and systolic function, while left ventricular filling was reduced because of endocardial thickening together with a large mass (3.4× 2.3 cm) in the left ventricular apex, which was suggestive of a thrombus (Fig. 1). The echocardiography also revealed biatrial dilation and moderate tricuspid regurgitation with a peak systolic pulmonary artery pressure of 70 mmHg. The inferior vena cava was dilated with no inspiratory collapse. Doppler studies detected restrictive-type diastolic filling with an E/A ratio greater than two and decreased deceleration time (125 ms). Cardiac magnetic resonance imaging (MRI) was performed for further evaluation of the apical mass. On T2-weighted serial images, there was an increased T2 signal at the endocardial rim, which was evident between apical hypointense thrombus formation and myocardium (Fig. 2 a and b). Gadolinium delayed enhanced viability images demonstrated apical large nonenhancing thrombus formation with intense linear enhancement of the endocardium (Fig. 3 a and b). The diagnosis was confirmed as Löffler endocarditis.

Oral anticoagulation with warfarin sodium and immunosuppression with 1 mg/kg methylprednisolone were initiated promptly. The treatment also included furosemide, spironolactone, angiotensin-converting enzyme, and beta-blocker as standard heart failure therapy. Steroid therapy was continued at a dose of 1 mg/kg/day for 2 weeks. At the end of the 2nd week, the clinical symptoms improved dramatically, and the eosinophil count decreased to normal ranges. The steroid dose was then tapered gradually. She stayed in the hospital for 2 months until a steady INR level was maintained, and the steroid dose was decreased effectively. The clinical course was uneventful, and she was discharged with 5 mg/day prednisolone, 5 mg/day warfarin, 40 mg/day furosemide, 25 mg/day spironolactone, 100 mg/day metoprolol, and 10 mg/day lisinopril. Control echocardiogram was performed every 2 weeks, and there was regression in the apical obliteration of

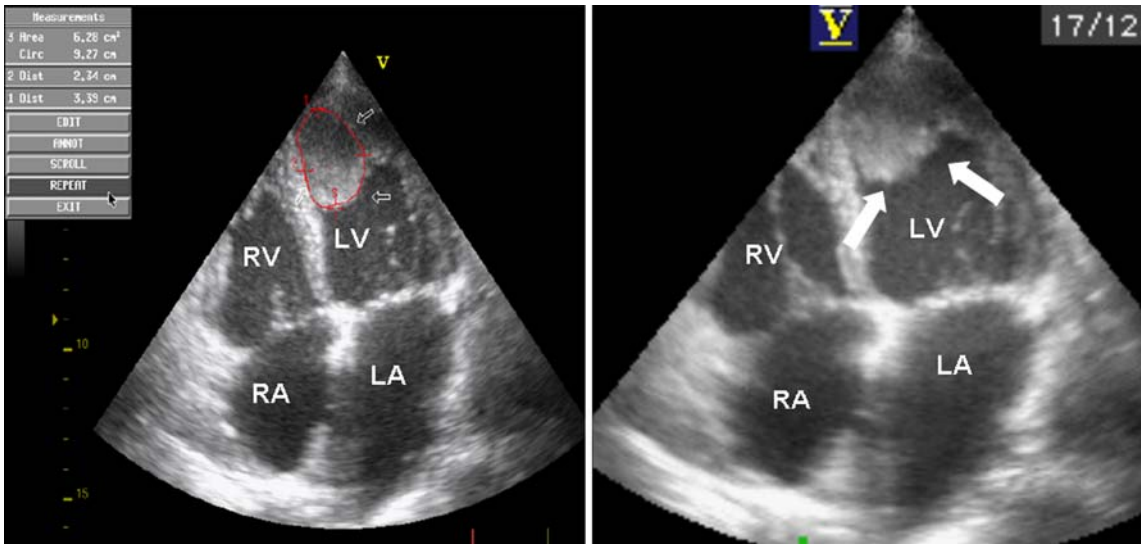

Figure 1. Echocardiographic four-chamber views presenting endocardial thickening together with a large mass (arrows) in the left ventricular apex, which was suggestive of a thrombus. (RV: right ventricle, LV: left ventricle, RA: right atrium, LA: left atrium).

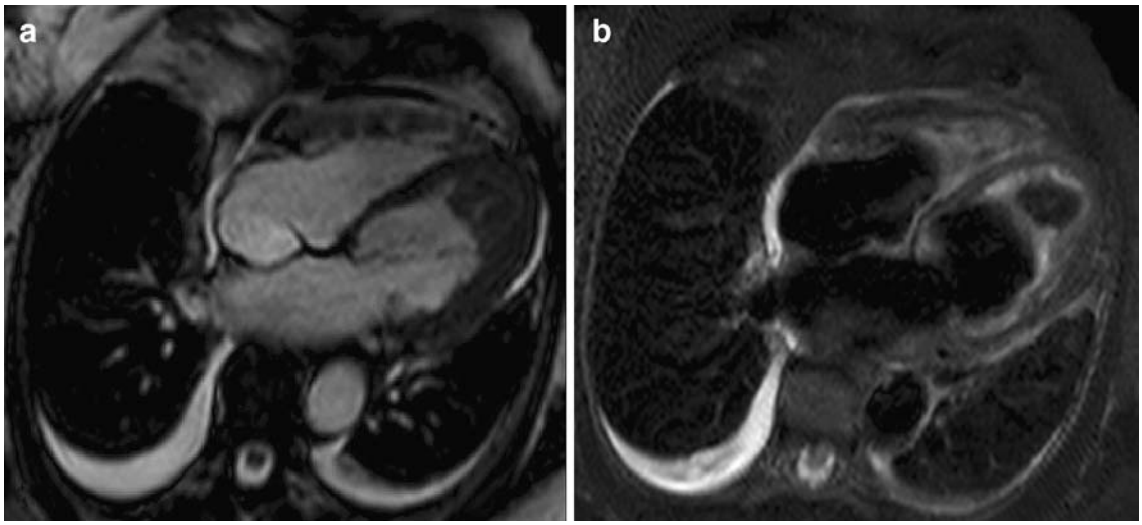

Figure 2. Transverse T2-weighted (a) and black-blood fat-saturated T2-weighted (b) images. Increased T2 signal at the endocardial rim is evident between apical hypointense thrombus formation and myocardium. Also bilateral pleural and minimal pericardial effusion can be seen.

the left ventricle starting from the 3rd month of therapy (Fig. 4 a). The apical mass had disappeared almost completely in the control echocardiography performed 12 months later (Fig. 4 b), and diastolic filling parameters had improved. The patient was still taking steroids and warfarin.

DISCUSSION

Hypereosinophilia can be observed either as a reactive phenomenon of a wide range of diseases and conditions (secondary eosinophilia) or as a primary hematological disorder (primary eosinophilia). Primary eosinophilia is considered either "clonal" or "idiopathic" based on the presence or absence, respectively, of either a cytogenetic abnormality or bone marrow histological evidence for a myeloid disorder, such as acute or chronic myeloid leukemia, myelodysplastic syndrome, chronic myelomonocytic leukemia, or systemic mast cell disease. Clonal eosinophilia might accompany Fip1-like-1-platelet-derived growth factor receptor alpha [FIP1L1-PDGFRA(+)] systemic mastocytosis, platelet-derived growth factor receptor beta (PDGFRB)-rearranged atypical myeloproliferative disorder, chronic myeloid leukemia, and the 8p11 syndrome, which is associated with fibroblast growth factor receptor 1 (FGFR1) rearrangement[11]. A small subset of cases in which both reactive and clonal causes of eosinophilia are excluded may be classified as idiopathic HES[12]. Idiopathic HES is a multisystem disease with persistent peripheral eosinophilia with >1,500 eosinophils/mm3 for at least 6 months, multiple organ system involvement, and no evidence for other known causes of eosinophilia[13]. It affects mostly men between 20 and 50 years of age, with a peak in the 4th decade of life. While a variety of organs are usually involved, including the lungs, bone marrow, and brain[14], cardiac involvement in HES is the rule.

Cardiac lesions may occur on the left or right side or both (more prominent at the apex), and are characterized by dense fibrosis in the ventricular endocardium, which reduces the ventricular cavity, diastolic filling, and the pump function of

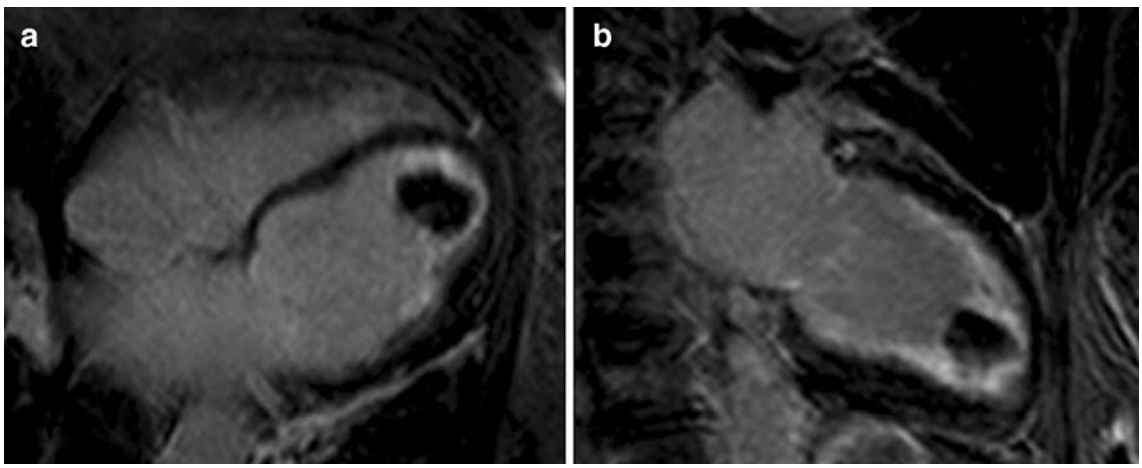

Figure 3. Gadolinium delayed enhanced viability magnetic resonance images. Apical large nonenhancing thrombus formation and the intense linear enhancement of the endocardium can be identified. Four-chamber (a) and two-chamber (b) images.

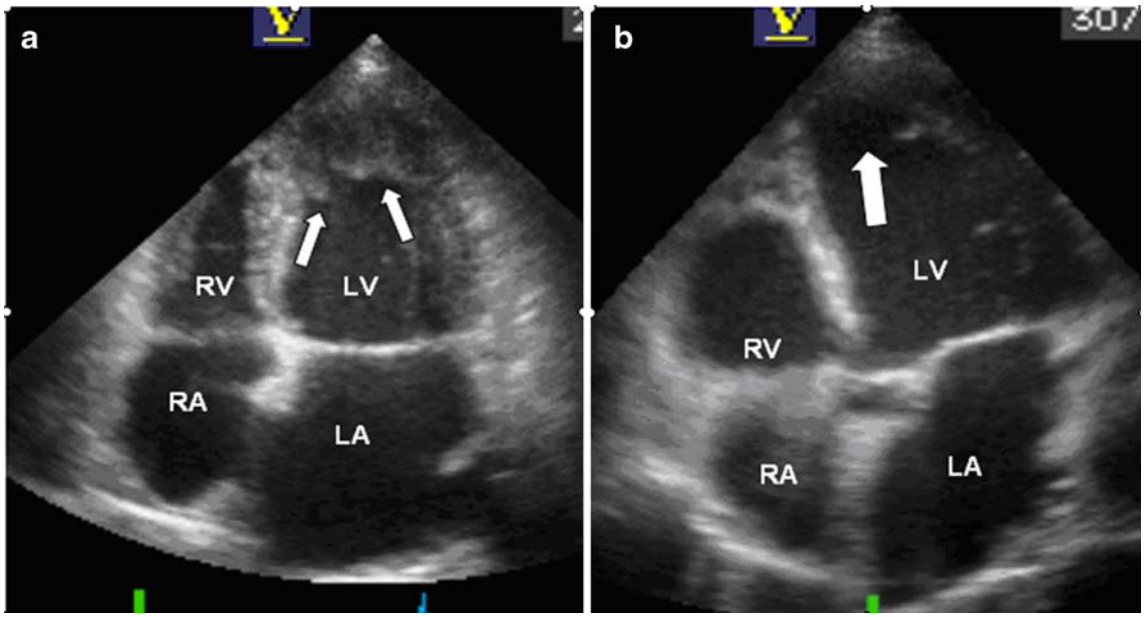

Figure 4. Control echocardiographic examination reveals regression in the apical obliteration of the left ventricle 3 months after treatment (a). The mass disappeared 12 months after treatment (b). (RV: right ventricle, LV: left ventricle, RA: right atrium, LA: left atrium).

the heart. Overt cardiac dysfunction occurs in more than half of the patients[14]. The exact mechanism of eosinophil-induced tissue damage is not known, but eosinophils are directly cytotoxic and can affect a local release of toxic substances like enzymes, reactive oxygen species, pro-inflammatory cytokines, and arachidonic acid-derived factors[15]. However, there are a few reports of Löffler endocarditis without peripheral hypereosinophilia[16]. The cardiac damage is a multistep process. At first, hypereosinophilia results in damage to the myocardium by infiltration of myocardium and toxic degranulation, which produces the necrotic first stage. During the early necrotic phase, cardiac involvement is generally unrecognized, and echocardiographic examination can be normal. Necrotic stage is then followed by thrombotic stage with mural thrombi development and high risk of embolization. Finally, there is a fibrotic stage in which thrombus organization leads to a fibrotic endocardium[17–19] and to a life-threatening disease. The prognosis is poor, and death is usually due to congestive heart failure, often with associated renal, hepatic, or respiratory dysfunction.

Echocardiography is a mandatory evaluation in HES patients and enables sufficient detection of thickened endocardium and intraventricular thrombus. Nevertheless, acute necrotic stage can come along with absolute normal echocardiographic findings[19]. The combination of inflammatory material and superimposed thrombus produces the appearance of an obliterative left ventricular apical homogenous mass, which is typical for HES. Systolic function often is well preserved in keeping with the restrictive picture seen in this condition. Mitral and tricuspid valves can be involved, leading to marked valvular regurgitation, which is the consequence of the fibrosis and thrombus formation. Outflow tracts near the aortic and pulmonic valves are usually protected, although rarely these valves may be comprised[20]. Congestive heart failure may result from the valvular abnormalities or the resulting endomyocardial fibrosis (or both)[21].

In our case, echocardiographic examination revealed biatrial dilation, significant mitral and tricuspid regurgitation, and endocardial thickening together with a large mass in the left ventricular apex, which was suggestive of a thrombus. The left ventricle systolic function was preserved, while diastolic function was impaired, showing a restrictive pattern. Apical thrombus in the presence of normal apical contractions, endocardial thickening, and preserved left ventricular systolic function with restrictive-type diastolic filling, together with the presence of hypereosinophilia, reminded us of Löffler endocarditis. The patient also showed most of the principal clinical features of Löffler endocarditis, such as weight loss, fever, cough, and congestive heart failure. Since the World Health Organization classification recommends the exclusion of any cause of secondary eosinophilia like malignant or autoimmune diseases, parasitic disease, allergy, or drug reactions in the clinical workup of patients with Löffler endocarditis eosinophilia[13,22], we explored any other cause that might explain the hypereosinophilia. Stool examinations were negative, and there was no sign of a malignancy, allergy, or drug reaction.

To confirm the diagnosis, we performed cardiac MRI. Cardiac MRI proves a rapid noninvasive modality for diagnosing myocardial fibrosis with the use of an inversion-recovery prepared T1-weighted gradient-echo sequence after intravenous administration of gadolinium chelate[23] and allows the monitoring of the myocardial process and its response to therapy. MRI demonstrates the nonviable tissue as hyperenhancement or bright. The mechanism of hyperenhancement in myocardial fibrosis is related to a combination of delayed wash-in and wash-out kinetics of fibrotic tissue and different volume of distribution of gadolinium in viable and fibrotic regions[24]. Because fibrotic tissue increases the interstitial volume per unit volume and gadolinium diffuses more rapidly into the interstitial than the intercellular space, the fibrotic myocardium has increased concentrations of gadolinium per unit volume of tissue, thus resulting in hyperenhancement

relative to viable myocardium. The endomyocardial fibrosis detected by cardiac MRI may provide a diagnostic clue to the presence of hypereosinophilic syndrome, and thus performing a myocardial biopsy is not always necessary[25]. On T2-weighted serial images, we detected endocardial changes characterized by hyperintensity and linear contrast enhancement, which confirmed the diagnosis of Löffler endocarditis. Since percutaneous endomyocardial biopsy is not invariably positive[14], we did not perform cardiac biopsy.

The prognosis of Löffler endocarditis is poor. Treatment is unsatisfactory, and the deposit regression is seldom described[26]. Therapy of idiopathic HES is directed to reduce peripheral and tissue levels of eosinophils, prevention of end-organ damage, and thromboembolic events[27]. Medical therapy during the course of early Löffler endocarditis and surgical therapy during the latter phases of fibrosis may have a positive effect on symptoms and survival[6]. Recent reports suggest that aggressive medical therapy may prevent progressive restrictive cardiomyopathy. Bone marrow examination, karyotype analysis, and additional molecular studies are mandatory in order to provide accurate prognostic information and to select appropriate therapy. In idiopathic HES, prednisone and hydroxyurea constitute the first-line therapy. Corticosteroids appear to have a beneficial effect on acute myocarditis, and together with cytotoxic drugs (hydroxyurea in particular) may improve end-organ damage and result in a 5-year survival of about 80%[28–30]. A limited number of patients not responding to standard therapy have responded to treatment with interferon alpha[10,27]. There are also reports about the use of cromolyn, intravenous gamma globulin, vincristine, cyclosporin A, tyrosine kinase inhibitor imatinib mesylate, and anti-interleukin-5 agent mepolizumab[5,31–33]. In the presence of either PDGFRA or PDGFRB mutations, the use of imatinib has been shown effective[11,34]. Routine cardiac therapy with digitalis, diuretics, afterload reduction, and anticoagulation are adjuncts in the management of these patients and should be initiated early[6]. However, the majority of deaths in patients with HES are as a result of thromboembolic events, which may lead to neurological and renal dysfunction, and cardiac complications[13]. Surgical therapy appears to offer significant palliation of symptoms when the fibrotic stage has been reached[35–37].

Fortunately, our patient responded well to steroid and anticoagulation therapy. Although heart failure symptoms persisted for 4 months, with accurate diagnosis of Löffler endocarditis and prompt initiation of steroid and warfarin together with standard heart failure therapy, the symptoms of the patient improved dramatically. No thromboembolic events or major cardiac complications including arrhythmias occurred in the follow-up. Even the apical thrombus showed complete regression, and diastolic filling improved echocardiographically with no evidence of development of restrictive cardiomyopathy during 12-month follow-up.

CONCLUSION

Idiopathic HES is an uncommon leukoproliferative systemic disorder characterized by the overproduction of eosinophils and poor prognosis. Cardiovascular manifestations of the syndrome are the major cause of morbidity and mortality. Although it is a rarely seen condition, it should be kept in mind in a patient with persistent symptoms of congestive heart failure, especially in the presence of endocardial thickening, mural thrombi, and hypereosinophilia. Quick and accurate diagnosis with prompt initiation of medical treatment may improve symptoms and survival.

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