CASE REPORT

Atypical Presentation of Eosinophilic Endomyocardial Disease

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Idiopathic hypereosinophilic syndrome is classically defined as prolonged, unexplained peripheral eosinophilia in a patient presenting with evidence of end-organ damage. The heart is frequently involved, resulting in eosinophilic endomyocardial disease and eventually restrictive cardiomyopathy. The mortality rate is high because of progressive heart failure or ventricular arrhythmias. We describe a patient who presented with a left ventricular apical thrombus without notable peripheral eosinophilia. Findings from clinical evaluation and extensive diagnostic testing, including right ventricular biopsy, were inconclusive. Resection of the thrombus and subjacent endomyocardium revealed eosinophilic infiltration of the endomyocardium, which led to the diagnosis of eosinophilic endomyocardial disease. Clinicians should be aware of the variable presentation of patients with eosinophil-associated endomyocardial disease so that affected patients may benefit from early diagnosis and treatment.

Mayo Clin Proc. **2005;80(8):1078-1084**

CT = computed tomography; EED = eosinophilic endomyocardial disease; HES = hypereosinophilic syndrome; LV = left ventricular; MRI = magnetic resonance imaging; RV = right ventricular

Idiopathic hypereosinophilic syndrome (HES) with endomyocardial disease has been well described in the literature.[1-5] However, the diagnosis of this entity can be difficult because presentation of the patients and progression of the disease are variable. Historically, most patients have had peripheral eosinophilia for a long time. We describe a patient with no evidence of hypereosinophilia in whom cardiac biopsy revealed eosinophilic infiltration of the endomyocardium. This atypical presentation illustrates the challenge in diagnosing and treating this rare form of restrictive cardiomyopathy.

REPORT OF A CASE

A 74-year-old man with a history of coronary heart disease but no known myocardial infarction had been in apparently good health until 3 weeks previously, when increasing dyspnea and fatigue developed. He presented to his local physician. After transesophageal echocardiography showed a large left ventricular (LV) apical thrombus, the patient was admitted to a local hospital. Laboratory studies revealed an eosinophil count of 1.11×10^9/L, and bone marrow biopsy tissue was negative for hematologic disease. The patient was transferred to our institution for evaluation of the LV mass.

On admission, the patient denied chest pain, palpitations, syncope, ankle edema, nausea, and vomiting. He stated that a raspy voice and cough had developed in recent weeks and that he had had pruritus of the lower back and lower extremities during the previous 6 months. He had traveled to Mexico annually for the past several years.

The patient's medical history was notable for coronary artery disease, hypertension, hyperlipidemia, type 2 diabetes mellitus, chronic renal insufficiency, gout, and anemia. Current medications included aspirin, allopurinol, atenolol, fluvastatin, metformin, and triamterene-hydrochlorothiazide. His family history was remarkable for ischemic heart disease.

On physical examination, the patient appeared fatigued but not acutely ill. His temperature was 36.9°C, blood pressure was 110/48 mm Hg, pulse rate was 69/min, and respirations were 16/min. On cardiovascular examination, the heart rate and rhythm were regular, S_1 and S_2 were normal, and a 2/6 ejection murmur was heard, best at the right upper sternal border. Jugular venous pressure was 10 cm H_2O. Carotid artery pulses were brisk and equal bilaterally. No carotid, aortic, or femoral bruits were heard. Peripheral pulses were intact and symmetrical. No peripheral edema, clubbing, or cyanosis was present. Pulmonary and abdominal examination findings were essentially normal. The patient had multiple excoriations over the abdomen, back, and lower extremities.

Laboratory test results were as follows: hemoglobin, 11.7 g/dL; hematocrit, 35.3%; leukocytes, 7.0×10^9/L; eosinophils, 0.50×10^9/L; and platelets, 174×10^9/L. Chemistry panel results were notable only for a creatinine level of 1.7 mg/dL. The erythrocyte sedimentation rate (55 mm/h), high-sensitivity C-reactive protein level (2.58 mg/L), and antinuclear antibody level (5.7) were elevated. The cytoplasmic antineutrophil cytoplasmic autoantibody titer was negative, but the perinuclear antineutrophil cytoplasmic autoantibody titer was positive. Concentrations of myeloperoxidase antibodies and C3, C4, and total complement were within the reference ranges. Results of special coagulation studies were negative. Urinalysis showed 1% to 5% eosinophils. Chest radiography revealed left pleural

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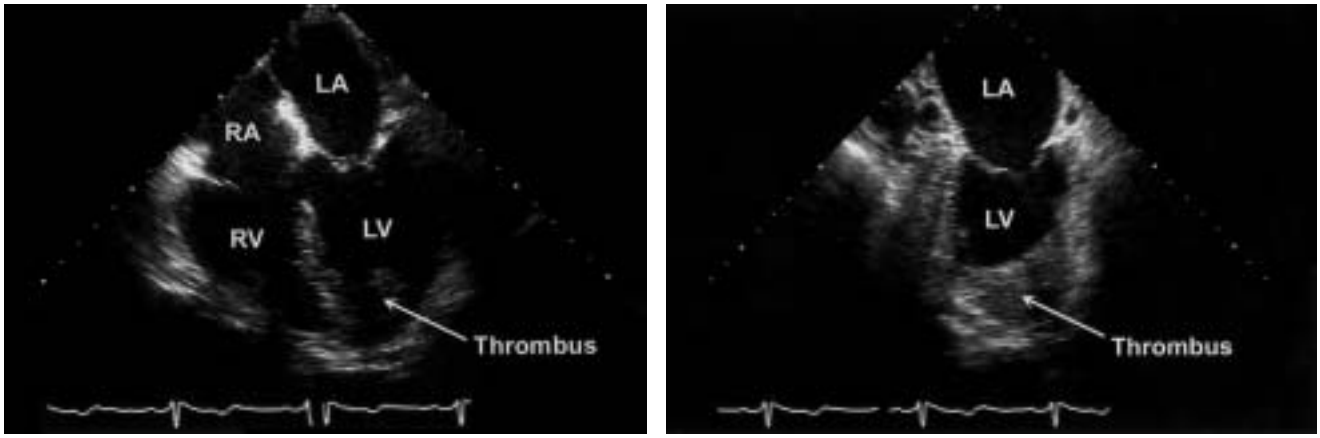

FIGURE 1. Transesophageal echocardiograms showing a 2.9-cm thrombus occupying the apex of the left ventricle (LV). Left, Four-chamber view. Right, Two-chamber view. LA = left atrium; RA = right atrium; RV = right ventricle.

effusion and mild cardiomegaly. Pleural fluid from thoracentesis was negative for malignancy.

Bone marrow biopsy tissue collected at the patient's local hospital was reviewed by our pathologists and interpreted as normocellular with normal trilineage hematopoiesis. Normochromic normocytic anemia was identified on the peripheral blood smear.

Electrocardiography showed a prolonged QT interval and sinus bradycardia with ST-segment and T-wave abnormalities suggestive of inferior and anterolateral ischemia. Transesophageal echocardiography revealed a gelatinous 2.9-cm mass with no mobile components occupying the entire LV apex. The LV ejection fraction was reduced to 45% because of apical akinesis. A restrictive filling pattern (grade 3/4) was evident, with markedly elevated LV filling pressures. The aortic and mitral valves were mildly regurgitant, and the left atrium and left ventricle were slightly enlarged. Right ventricular (RV) size and function were normal (Figure 1).

Magnetic resonance imaging (MRI) of the heart showed a suspected mass in the LV apex on black-blood sequences (Figure 2, left). The suspected mass appeared to be a thickening of akinetic apical myocardium on white-blood cine sequences (Figure 2, right).

Gated computed tomography (CT) of the heart clearly identified a noncalcified mass filling much of the LV apex. Most of the mass showed no enhancement, although a rim of hyperenhancement was seen on delayed imaging (Figure 3, left). The mass abutted and adhered to the myocardium but did not appear to invade it. No LV aneurysm or diverticulum was noted (Figure 3, right). The RV apex appeared normal, with no evidence of thrombus. Lung lesions and hilar lymphadenopathy were not apparent.

Coronary angiography confirmed the presence of the LV mass and severe atherosclerotic coronary artery disease, with 50% obstruction in the left main coronary artery and 70% to 90% obstruction in the left anterior descending coronary artery and in the circumflex artery, its first 2 obtuse marginal branches, and its posterior descending branch. Right ventricular endomyocardial biopsy specimens showed mild focal perivascular inflammatory infiltrates (primarily lymphocytic with infrequent eosinophils and macrophages) and mild focal replacement fibrosis, which according to the Dallas criteria represents borderline myocarditis. The perivascular distribution suggested a drug-related phenomenon. No granuloma, mural thrombus, amyloid, or stainable iron was identified.

The patient underwent bypass grafting of 3 coronary arteries and resection of the LV thrombus (Figure 4). Microscopic evaluation of the resected LV tissue revealed a large, old, degenerating fibrin-rich mural thrombus with infrequent eosinophils. The base of the thrombus was organized, producing bandlike endocardial granulation tissue and dense fibrosis. Microfocal noncaseating granulomatous inflammation was multifocal, involving subjacent myocardium and perivascular and interstitial tissue. The microgranulomas were suggestive of hypersensitivity myocarditis or possibly sarcoidosis. However, approximately 75% of the resected thrombotic tissue was positive for eosinophilic granule major basic protein on immunofluorescence staining (Figure 5).

The patient's postoperative course was uneventful, and he was dismissed from the hospital 8 days postoperatively. Oral anticoagulation was initiated. When the patient was seen at follow-up 3 months later, he had completed his cardiac rehabilitation program and remained asymptomatic. Follow-up transthoracic echocardiography at that time showed an LV ejection fraction of 55% and persistent akinesis of the apex but no recurrence of thrombus in the apex.

FIGURE 2. Magnetic resonance images of the heart. Left, Spin-echo (black-blood) sequence reveals a slow flow–related signal artifact and a suspected mass (arrow) in the left ventricular apex. Right, On cine (white-blood) sequence, the suspected mass appears to be only a thickening of the akinetic apical myocardium.

DISCUSSION

The differential diagnosis in our patient included causes of ventricular mural thrombus and peripheral blood eosinophilia. In addition, biventricular tissue inflammation suggested drug-related myocarditis or a hypersensitivity reaction. Given the patient's history of ischemic heart disease and the echocardiographic features of the apical akinesis, stasis thrombosis was a likely possibility. Laboratory reports from his local medical institution indicated a slight peripheral blood eosinophilia, although serial eosinophil counts obtained at our institution were consistently at the upper limit of the reference range. When immunofluorescence staining of the resected LV tissue showed large concentrations of eosinophilic granule major basic protein, a definite diagnosis of eosinophilic endomyocardial disease (EED) was established. Inasmuch as possible causes of both clonal and nonclonal peripheral blood eosinophilia were ruled out, idiopathic HES with endomyocardial disease became the final diagnosis.

Although the association between peripheral eosinophilia and target-organ damage was first noted more than 100 years ago, it was not until 1968 that Hardy and Anderson[6] codified these entities into a spectrum of diseases that they termed *hypereosinophilic syndromes*. In 1975, Chusid et al[1] reviewed the findings in patients with eosinophilia referred to the National Institutes of Health and those in other HES patients and presented the 3 defin-

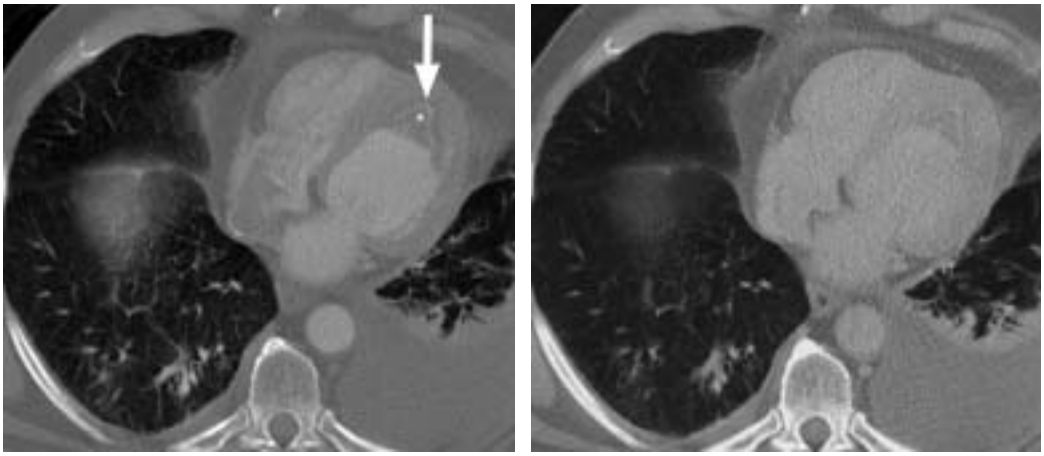

FIGURE 3. Cardiac computed tomographic images clearly identify a noncalcified mass filling much of the left ventricular apex. Left, Most of the mass (asterisk) shows no contrast enhancement, although a rim of hyperenhancement (arrow) is seen on delayed image. Right, The mass abuts and is adherent to the myocardium but does not appear to invade it. No left ventricular aneurysm or diverticulum is present.

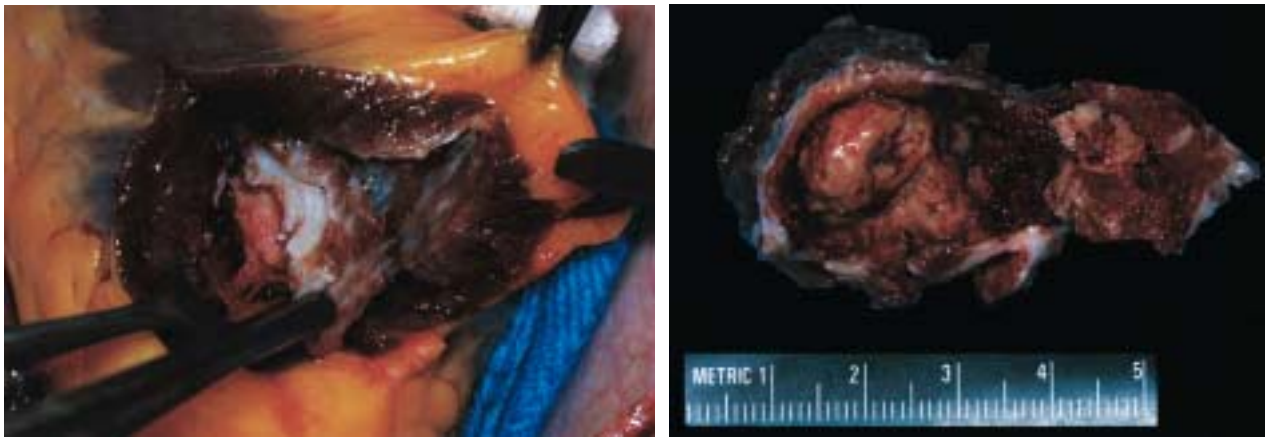

FIGURE 4. Surgical resection of left ventricular thrombus. Left, Opening the left ventricular myocardium. Right, Gross specimen of resected left ventricular thrombus.

ing features of HES, which are still considered valid today (Table 1). In addition to these criteria, total leukocyte counts are usually elevated, with 30% to 70% eosinophils, and absolute neutrophilia may be present. Bone marrow eosinophilia ranges from 30% to 60%, often with a left shift in maturation.[7]

The prevalence of HES is unknown, although Spry[5] postulated a rate of 1 case per 200,000 people. The disease is more common in men and tends to occur between the ages of 20 and 50 years.[1] Various organs may be involved, but those most commonly affected are the heart, brain, skin, and lungs.[1,2,5,8] The primary cause of morbidity and death is cardiac involvement, which occurs in more than 75% of patients with idiopathic HES.[9,10]

The mechanism of tissue damage has not been delineated, although the cytotoxic effects of proteins produced by eosinophils are probably important.[11,12] In peripheral blood, eosinophils have a half-life of approximately 8 to 18 hours. However, after they are recruited in peripheral tissues by specific cytokines, eosinophils can survive for days or weeks as resident cells.[13] In patients with HES, circulating eosinophils generally have measurable structural and functional abnormalities, and many of them are degranulated.[10] Sequestration of eosinophils in the endocardium and in other organ tissues or systems occurs by unknown mechanisms.[14] Eosinophil-derived neurotoxin, eosinophil cationic protein, and major basic protein are enzymes released by eosinophils that cause endothelial damage and promote thrombosis.[11,12,15] Intact eosinophils and extracellular granules are present in affected tissues throughout most of the disease process; however, only granules remain during the final fibrotic stage of the disease.

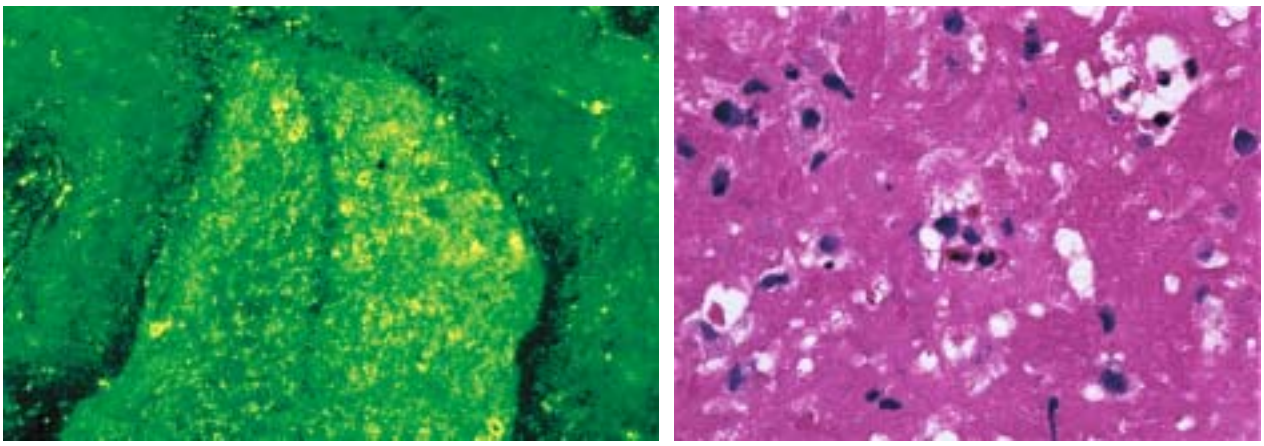

FIGURE 5. Immunofluorescence photomicrographs of left ventricular mural thrombus showing eosinophilic granule major basic protein. Left, Section stained with affinity-purified rabbit anti–human major basic protein shows extensive diffuse deposition of cytotoxic major basic protein from degranulated eosinophils (original magnification ×160). Right, Old degenerating thrombus with rare intact eosinophils (hematoxylin-eosin, original magnification ×150).

TABLE 1. **Diagnostic Criteria for Idiopathic Hypereosinophilic Syndrome**

Eosinophil count >1.5 × 10^9/L for ≥6 mo (upper limit of reference range, 0.50 × 10^9/L)
No evidence of parasitic, allergic, or other known causes of eosinophilia
Signs or symptoms of organ involvement that appear related to eosinophilia (heart, nervous system, skin, lungs, liver, gastrointestinal tract)

Data from Chusid et al.[1]

The correlation between the extent of tissue involvement and the degree or duration of peripheral blood eosinophilia has been debated.[1,13,15-17] Kobayashi et al[17] and Leiferman and Gleich[14] suggested that the threshold eosinophil count for the diagnosis and treatment of hypereosinophilic disease is 2×10^9/L or greater for a prolonged period because that level of eosinophilia seems to be associated with the greatest risk of organ involvement. However, Fauci et al[4] reported that peripheral eosinophil counts may remain normal for weeks or months during the course of the disease, and Schooley et al[3] suggested that factors other than the absolute number of circulating eosinophils may contribute to the severity of the disease (eg, maturity, granule content, and migration patterns). Our patient had no documented history of sustained peripheral blood eosinophilia over a long period before his evaluation at our institution, although he had not been followed up regularly by a physician and thus had minimal prior laboratory study results available in his medical record. His eosinophil count was slightly elevated on presentation at our institution but subsequently normalized without treatment. This presented a diagnostic dilemma because our patient did not meet the classic criteria for a diagnosis of idiopathic HES with cardiac involvement.

Chusid et al[1] were the first to describe 3 stages of EED. With chronic eosinophilia, eosinophilic myocarditis develops because eosinophilic infiltration of the endocardium and myocardium leads to microabscesses. This first stage is the necrotic stage. The second, or thrombotic, stage is characterized by the formation of thrombi along the damaged endocardium of either or both ventricles and occasionally the atria. Typically, the ventricular outflow tracts and semilunar valves are spared. Thrombi may also form on the atrioventricular valve leaflets. The third stage is fibrotic. Morphologic findings at this stage include mural thrombus and fibrotic thickening of the endocardium, which affects the apex and inflow tract of one or both ventricles and frequently involves one or both atrioventricular valves.[4] Entrapment of leaflets and chordae tendineae cordis may cause mitral or tricuspid regurgitation or both.

Common clinical manifestations of EED include cardiomegaly, congestive heart failure (right-sided, left-sided, or both), atrioventricular valve regurgitation, arrhythmias, and restrictive cardiomyopathy.[1,2,5,18]

Typically, diagnostic tests yield a constellation of findings that suggest EED. Chest radiographs frequently show cardiomegaly and pulmonary congestion or less often pulmonary infiltrates. The most common electrocardiographic abnormalities are nonspecific ST-segment and T-wave changes (which our patient had), ventricular premature beats, and LV hypertrophy.[2] Other reported disturbances include marked ST-segment depression,[19] low-voltage QRS complex,[20] arrhythmias (especially atrial fibrillation),[21] and conduction disturbances, particularly right bundle branch block when the RV apex is fibrotic.[1]

Echocardiographic assessment is key to the diagnosis of EED. The most common findings are ventricular apical obliteration and posterior mitral leaflet thickening with absent or markedly limited motion.[2,22] Additional findings may include atrial enlargement and evidence of atrioventricular valve regurgitation. Systolic function is often well preserved, but Doppler flow imaging reveals a physiologically restrictive pattern, which is most likely due to endomyocardial fibrosis. However, findings of a recent strain and strain-rate study suggested that the restrictive pattern may result solely from a decrease in end-systolic cavity size due to the presence of the mural thrombus.[23] Our patient had echocardiographic evidence consistent with these findings, including the presence of an apical LV mass and aortic and mitral valve regurgitation. Normally, cardiac catheterization shows elevated RV and LV end-diastolic pressures, and cardiac angiography shows apical ventricular obliteration and valvular incompetence.[9,19]

Magnetic resonance imaging of the heart is being used increasingly to assist in diagnosing EED because of its ability to demonstrate the presence and extent of infiltration and to localize the site for endomyocardial biopsy. Magnetic resonance imaging findings suggestive of EED include a marked signal increase in the apical portion of the interventricular septum and apex, predominantly in the subendocardium, which suggests the presence of infiltration.[13] Cine MRI typically shows akinesia of the apical LV wall and thrombus in the LV apex, RV apex, or both.[24] The MRI that was obtained in our case was inadequate to establish a definitive diagnosis. The addition of a perfusion sequence and postcontrast sequences to detect myocardial or any mass enhancement likely would have provided the necessary information, and CT would not have been performed.[25-27] In view of the MRI results, contrast CT was performed to define more clearly the character of the mass.

Endomyocardial biopsy is the gold standard for diagnosing EED, although the biopsy findings are not always positive. Because the disease is often focal, RV biopsy

sampling may miss left-sided disease, as in our patient. A left-sided biopsy specimen is not recommended because sampling may dislodge the mural thrombus, with resultant systemic embolization.

Traditionally, 3 criteria are used to diagnose EED: (1) the criteria for HES must be met, (2) there must be pathologic evidence of eosinophil infiltration with degranulation, and (3) classic cardiac features must be evident.

Our patient did not have peripheral eosinophilia while at our institution, so he did not meet the classic criteria for HES. However, other cases of possible HES with EED but no peripheral blood eosinophilia at the time of diagnosis have been reported.[28,29] The reasons for this discrepancy are unclear, but possible mechanisms include dysregulation in eosinophil dynamics or a defect in eosinophil migration.[28] Possibly, cases with an atypical presentation may be underreported in the literature.

Treatment of EED focuses on long-term maintenance to control eosinophilia and prevent further damage to the cardiovascular or other organ systems. Supportive treatment for congestive heart failure, including digitalis, diuretics, and afterload reduction, is often necessary. The use of anticoagulation in HES patients is debatable—some investigators do not recommend its use because it seems ineffective in preventing further thrombosis,[5] but others do advocate its use in HES patients presenting with a thrombotic process.[15] Serial eosinophil counts are recommended. Regularly scheduled cardiac function testing is mandatory because, with the possibility of embolization, a new endocardial lesion warrants immediate medical, and occasionally surgical, attention.

The National Institutes of Health produced a scoring system to predict which patients with HES need intensive medical therapy.[3] Various treatment algorithms have been proposed,[15,16] with glucocorticoids generally accepted as being first-line therapy. Adjunctive or alternative therapies include hydroxyurea, vincristine, alkylating agents, and etoposide. Interferon alfa[30,31] and imatinib mesylate[32,33] have shown promising results in selected patient populations. Currently, anti–interleukin 5 is under investigation as a possible corticosteroid-sparing agent.[34] If the disease is extremely aggressive, allogeneic bone marrow transplantation may be performed.[35]

After the fibrotic stage of EED has occurred, surgical resection may offer clinically meaningful palliation of symptoms. Typically, decortication (endocardiectomy), with or without valve replacement, is performed. Surgery is not without risk, however: the mortality rate is 16% to 20% for univentricular disease and 40% for biventricular disease.[36-38] Late postoperative death, primarily related to prosthetic valve disorders, occurs in 12% of patients.[38] After resection, endocardial fibrosis usually does not recur.

CONCLUSIONS

The manifestations of HES with endomyocardial disease are not uniform, and our case illustrates some of the difficulties that may be encountered in diagnosing this entity. Our patient clearly had EED but lacked evidence of notable sustained peripheral eosinophilia at the onset of symptoms. Causes of EED were ruled out systematically, leading to the diagnosis of HES. Similar cases may be underdiagnosed and underreported in the literature. Endomyocardial biopsy is essential, and it should be considered for all patients who have unexplained heart failure or ventricular arrhythmias. Because patients with advanced disease have a poor prognosis, early diagnosis is crucial to initiate appropriate therapy that may slow the progression of the disease.

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