

A 45-Year-Old Man With Progressive Dyspnea, Chest Pain, and Hypereosinophilia



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CASE PRESENTATION: A previously healthy 45-year-old man was admitted to our ED with a 3-week history of progressive dyspnea on exertion. He also presented with orthopnea, paroxysmal nocturnal dyspnea, and mild ankle swelling, but he showed no fever, wheezing, coughing, or sputum production. Outpatient laboratory studies, performed 1 week after symptom onset, revealed hypereosinophilia (4.100/ μ L). He was diagnosed with asthma and prescribed inhaled corticosteroids and low-dose prednisone, but he showed no symptomatic improvement. Over the last 48 h, he experienced rapid progression of dyspnea that made it difficult to speak with accompanying resting, substernal, nonradiating chest pain that became worse on inspiration. He had no allergies and reported no recent travels. Before symptom onset, he had not been taking any medication. He denied eating raw fish or meat and had not been exposed to mildew. His only exposure to animals was from his two indoor cats.

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Physical Examination Findings

On admission, heart rate was 150 beats/min, with a regular rhythm; BP was 95/64 mm Hg, respiratory rate was 33 breaths/min, and oxygen saturation was 85%. The patient appeared to be in acute respiratory distress, with cool extremities, prolonged capillary refill time, jugular vein distention, S3 gallop on cardiac auscultation, and crackles in both lower lung fields.

Diagnostic Studies

The patient's hemoglobin level was 15.4 g/dL, leukocyte count was 26.510/ μ L with an eosinophil count of 11.929/ μ L, and platelet count was 223 K/ μ L;

sodium level was 131 mmol/L, potassium level was 4.9 mmol/L, BUN level was 26 mg/dL, and creatinine level was 1.27 mg/dL. Arterial blood lactate level was 1.9 mmol/L, and high-sensitivity troponin T value was 58.850 ng/dL (reference $\leq$ 34.2 ng/dL). Erythrocyte sedimentation rate was 63 mm/h. ECG (Fig 1) was remarkable for ST segment elevation in inferior leads. Chest radiograph (Fig 2) revealed bilateral pulmonary congestion. Transthoracic echocardiogram (Fig 3, Video 1) showed a diffuse hypokinetic left ventricle, with left ventricular ejection fraction (LVEF) of 15%, normal valves, and severe pericardial effusion without signs of tamponade (Fig 3, Video 1).

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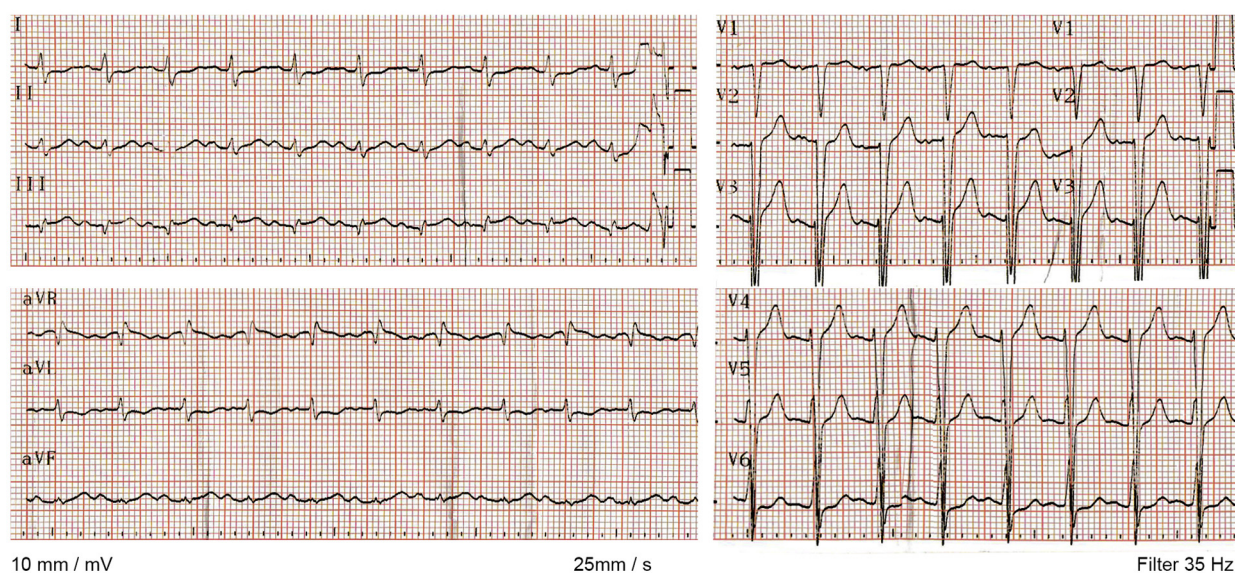


Figure 1 – ECG obtained at admission, showing Q wave and ST segment elevation in III, slight concave ST elevation in V2-4, and ST depression in I, aVL, and V6.

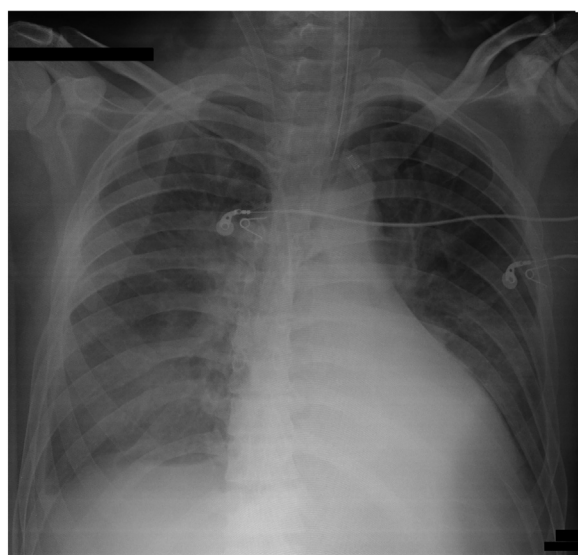


Figure 2 – Chest radiograph showing diffuse bilateral opacities and mild right-sided pleural effusion.

Clinical Course

The patient was emergently intubated, and inotropic support was initiated (milrinone 0.3 $\mu\text{g/kg/min}$ and noradrenaline 0.15 $\mu\text{g/kg/min}$). Coronary angiography revealed no stenotic lesions and elevated left ventricular end diastolic pressure (40 mm Hg). Because of progressive hemodynamic deterioration, at 4 h after admission, he was placed on an extracorporeal membrane oxygenator. High-dose IV corticosteroids were started. An endomyocardial biopsy (performed after 2 g methylprednisolone) showed diffuse interstitial inflammatory infiltration with lymphocytes, plasmacytes, and neutrophils and extensive myocardial necrosis.

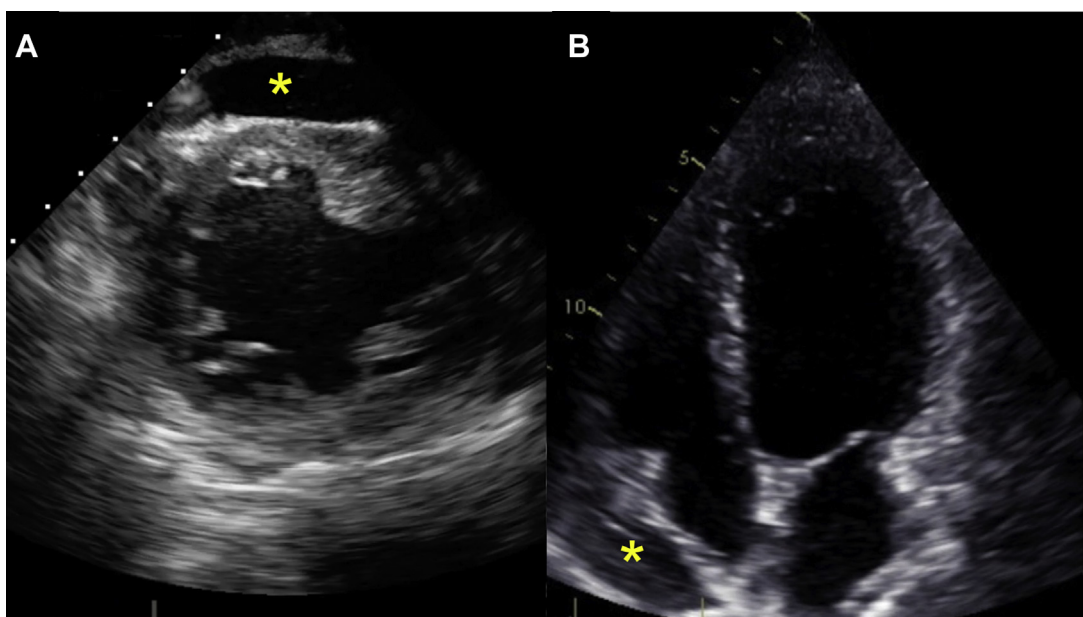


Figure 3 – A, B, Transthoracic echocardiographic views obtained at admission in (A) parasternal short-axis view and (B) apical four-chamber view, revealing severely thickened left ventricular wall (because of myocardial edema and tissue infiltration), reduced left ventricular cavity size, and severe pericardial effusion (asterisk) ([Video 1](#)).

What is the likely diagnosis? How would you confirm it?

Answer: An evaluation of hypereosinophilia (Table 1) that included an IgG enzyme-linked immunosorbent assay and IgG western blot confirmed the diagnosis of fulminant eosinophilic myocarditis because of toxocariasis (visceral larva migrans).

Discussion

Eosinophilic myocarditis (EM) is a form of myocardial inflammation characterized by parenchymal infiltration with eosinophils, usually accompanied by peripheral eosinophilia. It comprises 0.5% of patients biopsied for suspected myocarditis, but it is often discovered in autopsy. EM is considered a syndrome with multiple etiologies, such as hypersensitivity reactions (34.1%), eosinophilic granulomatosis with polyangiitis (12.8%), and hypereosinophilic syndrome (8.4%). Infections, such as toxocariasis, are thought to represent a minority (5%) of cases. A significant proportion of cases remains idiopathic (35.7%). Regardless of the original insult, the pathogenesis is initiated by overproduction of cytotoxic eosinophils that infiltrate the myocardium and

degranulate, therefore releasing their major basic and cationic proteins, which mediate tissue damage.

Clinical presentation of EM ranges from mildly symptomatic disease to cardiogenic shock, which occurs in one-third of patients. The most common complaint is dyspnea (59.4%), followed by chest pain (43.4%), fever (35%), and malaise. Extracardiac manifestations, such as skin rash, altered liver enzymes, and acute renal failure, are relatively common, especially if EM occurs as a consequence of hypersensitivity reaction to medications. Peripheral eosinophilia is present in 75% of cases, but levels do not correlate with the severity of disease. Cardiac biomarkers (CK-MB and Troponin T) are elevated in > 90% of affected patients. ECG changes include ST segment elevation (38.6%), unspecific ST-T abnormalities, bundle branch block, or ventricular arrhythmias. Chest radiograph can show cardiomegaly or signs of pulmonary congestion. Echocardiography often reveals severely thickened ventricular walls with depressed contractility, pericardial effusion, and in some cases, intraventricular thrombus. Prognosis of EM is poor, particularly when it presents as a fulminant disease, with mortality rates > 20%. Transition to a

TABLE 1] Hypereosinophilia Workup

Test	Result
Strongyloidiasis, ELISA IgG, western blot IgG	Negative
Schistosomiasis, ELISA IgG, western blot IgG	Negative
Distomatosis, ELISA IgG, western blot IgG	Negative
Chagas disease, ELISA IgG	Negative
Trichinosis, ELISA IgG, western blot IgG	Negative
Toxoplasmosis, ELISA IgG and IgM	Negative
Toxocariasis ELISA IgG, western blot IgG	Positive
HIV 1 and 2, ELISA IgG	Negative
HTLV 1 and 2, ELISA IgG and P24 antigen	Negative
Hepatitis B surface antigen	Negative
Hepatitis C total antibody	Negative
Stool testing for ova and parasites	Negative
Serum complement (C3, C4)	Normal
Immunoglobulin count	Normal
Antinuclear antibody	Negative
Extractable nuclear antibody panel	Negative
Anti-neutrophil cytoplasmatic antibody	Negative
Myeloperoxidase and peroxidase 3 antibody	Negative
Bone marrow biopsy and flow cytometry	No abnormal populations
Genetic testing for 9:22 translocation and JAK-2	Negative

ELISA = enzyme-linked immunosorbent assay.

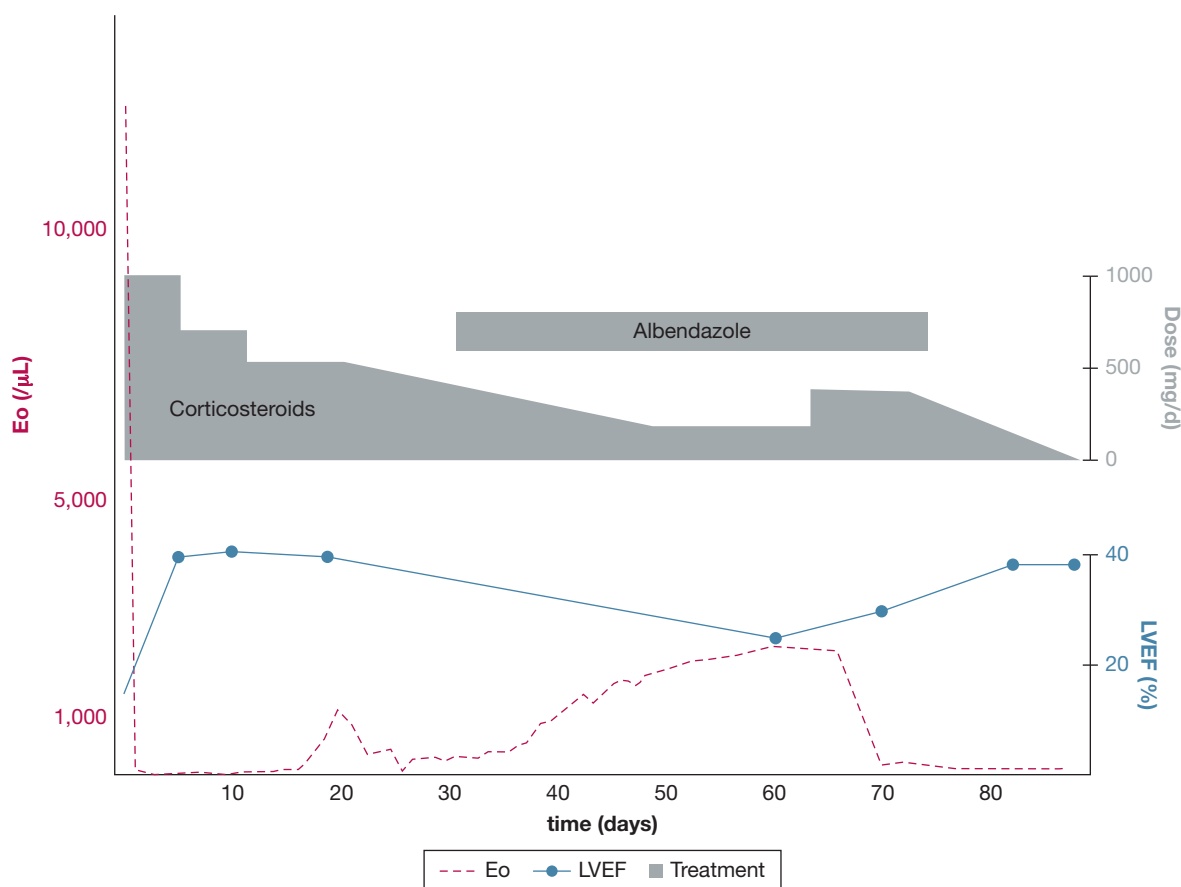


Figure 4 – Treatment-induced changes in LVEF and peripheral eosinophil count. After initiation of corticosteroids, LVEF improved and peripheral eosinophil count decreased to zero. With corticosteroid tapering, LVEF worsened and eosinophilia reappeared, with rapid improvement after the corticosteroid dose was increased again. Corticosteroids were safely tapered when treatment with albendazole was completed. Corticosteroid dose is expressed as methylprednisolone equivalent. Eo = peripheral eosinophil count; LVEF= left ventricular ejection fraction.

restrictive cardiomyopathy—known as Löffler endocarditis—is common among survivors.

The diagnostic criteria proposed for EM include the clinical, ECG, and echocardiographic changes previously discussed; elevated cardiac enzymes; and eosinophilia. Definite diagnosis of EM is confirmed by endomyocardial biopsy, which reveals findings of myocarditis together with eosinophilic infiltration. However, endomyocardial biopsy sensitivity—compared with autopsy—is low, which may be because of the patchy distribution of myocardial compromise and previous exposure to corticosteroids. Moreover, because prompt diagnosis is critical in fulminant presentations, to provide immediate treatment with corticosteroids, diagnosis often relies solely on clinical, laboratory, and imaging criteria.

In contrast with other forms of fulminant myocarditis, EM is a corticosteroid-responsive entity, and doses must be titrated according to disease severity. Usually, IV methylprednisolone pulses of 1 g/d are administered for

fulminant cases and oral prednisone of 1 mg/kg/d are administered for nonfulminant presentations; a maintenance dose of prednisone of 5 to 10 mg/d is used to prevent relapses. In addition, many EM etiologies need specific treatments, which may be necessary to achieve a complete response. This is the case for cyclophosphamide in EM related to eosinophilic granulomatosis with polyangiitis or tyrosine kinase inhibitors in EM related to hypereosinophilic syndrome. This is also applicable for toxocariasis-related EM because toxocariasis can be successfully treated with albendazole (as subsequently described).

Toxocariasis is a zoonosis caused by *Toxocara* species (*Toxocara canis* and *Toxocara cati*). The prevalence of antibodies against *Toxocara* species in the general population is high, reaching 24% in the United States. Among infected hosts, up to 15% develop histologically documented myocarditis. However, just 3.4% of EM cases have been attributed to toxocariasis; this condition may be underdiagnosed because serologic evaluation of

toxocariasis is not always performed, and many cases of EM remain diagnosed as idiopathic. Furthermore, this is the first adult patient with toxocariasis-induced fulminant EM reported outside Japan or Korea, which may represent a lack of clinical suspicion in the western world, even in developing countries.

The natural reservoirs of *Toxocara* species are dog and cat intestines. Infective eggs reach the human intestine, mainly from ingestion of contaminated water or undercooked meat from other paratenic hosts. The eggs hatch and larvae penetrate, and they invade nearly every organ through systemic circulation. In the heart, EM is its most frequent manifestation, and this form shares similar features with non-toxocariasis-associated EM. Extracardiac manifestations of visceral larva migrans syndrome, such as fever, weight loss, chronic diarrhea, and rash, often precede cardiac symptoms. However, these may be absent in fulminant cases.

The diagnosis of toxocariasis relies mainly on the clinical picture, epidemiologic exposure, and serologic testing. Among serologic tests, an IgG enzyme-linked immunosorbent assay (ELISA) kit for detecting *Toxocara* species antigens is commercially available. However, given the high seroprevalence of toxocariasis, a single positive titer cannot confirm an active infection. This can be achieved by documenting an increase in titers over time, by western blot or biopsy. Histologic findings, including granuloma and larvae remnants, may be missing because toxocariasis-induced cardiac damage is mainly a consequence of eosinophilic infiltration, rather than that of direct parasitic invasion. For patients with moderate to severe symptoms, first-line treatment is albendazole, usually maintained for 3 to 8 weeks. In contrast with other forms of EM, most patients achieve complete resolution of myocarditis after treatment.

Clinical Course

The diagnosis of EM was suspected because of the presence of cardiogenic shock with normal coronary arteries and hypereosinophilia. The patient fulfilled the five diagnostic criteria previously exposed, and endomyocardial biopsy confirmed myocarditis. Toxocariasis was suspected early, given the patient's exposure to cats. IgG ELISA results that were positive for *Toxocara* species were obtained; however, diagnosis of active infection was delayed while the results of confirmatory tests (western blot and increasing ELISA titers) were awaited.

After initiation of high-dose corticosteroids, LVEF improved up to 40% on the sixth day, and the patient

was decannulated. However, LVEF worsened after corticosteroid tapering, with rapid improvement after the corticosteroid dose was increased again (Fig 4). Only after toxocariasis was confirmed and treatment with albendazole was completed for 3 weeks was tapering of corticosteroids tolerated. LVEF remained at 40%, and the patient is currently asymptomatic.

Clinical Pearls

1. Fulminant EM represents an important etiology of cardiogenic shock and requires urgent evaluation, especially in patients with unexplained systolic dysfunction, normal coronary arteries, and peripheral eosinophilia.
2. High-dose corticosteroids represent effective therapy for fulminant EM. Initiation of corticosteroids should begin when a patient meets diagnostic criteria and should not await confirmation of EM by myocardial biopsy.
3. Because some patients with EM have treatable underlying conditions, an urgent eosinophilia workup should be done for every patient. Toxocariasis represents an underdiagnosed cause of EM that requires serologic evaluation to permit prompt initiation of albendazole.

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Additional information: The Video can be found in the Supplementary Materials section of the online article.

Suggested Readings

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