Eosinophilic Myocarditis Associated With Toxicoderma Caused by Phenobarbital

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We report on a 37-year-old man with congestive heart failure caused by eosinophilic myocarditis associated with toxicoderma. He developed many annular skin eruptions and peripheral eosinophilia due to reactions against phenobarbital. Right ventricular endomyocardial biopsy revealed extensive infiltration of eosinophils in the myocardium. A drug lymphocyte-stimulating test (DLST) for phenobarbital was positive. His symptoms, cardiomegaly, and cardiac function were improved by discontinuing phenobarbital followed by oral administration of prednisolone. We conclude that this eosinophilic myocarditis must have been induced by an allergic reaction to phenobarbital and that long-term eosinophilia contributed to the myocardial injury. (*Jpn Circ J* 1998; 62: 132–135)

Key Words: Eosinophilic myocarditis; Phenobarbital; Toxicoderma; Hypersensitivity myocarditis; Eosinophilia

Eosinophilic myocardial disease is a single entity that consists of eosinophilic myocarditis, Loeffler's endomyocarditis, and endomyocardial fibrosis.¹ Although most patients with hypereosinophilia and endomyocardial disease have a disease of unknown cause, there are many well-described disorders that produce a similar clinical picture, including certain parasitic infections,¹ allergic diseases,¹ and, rarely, tumors, especially lymphomas² and carcinomas. Drug-induced hypersensitivity also causes hypereosinophilia, which results in myocarditis. A wide spectrum of drugs, antibiotics,³ anticonvulsants,⁴ antihypertensives,⁵ and diuretics⁶ have been reported as the causative agents. However, to our knowledge, this is the first report in English to present a patient in whom toxicoderma and eosinophilic myocarditis caused by hypereosinophilia occurred as a hypersensitivity reaction against phenobarbital.

Case Report

A 37-year-old man was admitted because of dyspnea on exertion on 16 October 1995. Four months previously, he had undergone surgical drainage of a chronic subdural hematoma; thereafter he was placed on 60 mg of phenobarbital and 100 mg of phenytoin twice daily. After about 1 month, many annular skin eruptions appeared over his trunk; these tended to coalesce and were associated with high fever and liver dysfunction. The patient was diagnosed as having drug-induced eruptions caused by phenobarbital or phenytoin, which were therefore discon-

tinued. Routine hematological study revealed a leukocyte count of 17600/mm³ with 10.0% eosinophils and a total eosinophil count of 1760/mm³. After 4 receiving mg of betamethasone daily for 4 weeks, the patient's symptoms improved and there was a rapid reduction in eosinophil count. Two weeks after steroid administration had been tapered off, the patient started to complain of dyspnea of New York Heart Association (NYHA) functional class III. His blood pressure was 100/60 mmHg with a regular pulse rate of 104/min. Summation gallop was detected by chest auscultation, but no cardiac murmur and rales or rhonchi were present. He had edema of the extremities, but no hepatomegaly or jugular vein dilation. The leukocyte count on admission was 10400/mm³ with 38.9% neutrophils, 23.6% lymphocytes, 6.0% monocytes, and 26.8% eosinophils and the total eosinophil count was 2780/mm³. Degranulation or vacuoles of eosinophils were not seen. The serum alanine aminotransferase concentration was 51 IU/L (normal 6–43), serum lactic dehydrogenase 933 IU/L (normal 180–460), serum creatine kinase (CK) 167 IU/L (normal 9–93) with 31% CK-MB (less than 5%) and C-reactive protein 0.9 mg/dl (less than 0.3 mg/dl). The erythrocyte sedimentation rate was 17 mm/h. A drug lymphocyte-stimulating test (DLST) was negative for phenytoin but positive for phenobarbital. Serum IgE concentrations were in the normal range (Fig 1). Stool examinations for ova and parasites were negative. Serologic tests for antibodies to viruses were negative. A bone marrow examination was normal except for a pronounced increase in the number of eosinophils. The chest radiograph showed cardiomegaly [cardiothoracic ratio (CTR) 51.5%] with slight congestion (Fig 2). Electrocardiography revealed normal sinus rhythm and low voltage with slight ST-segment depressions in leads I, II, aVL, aVF, and V_{4–6}, and ST-segment elevations in leads V₁ and V₂ (Fig 3a). Echocardiography showed a diffusely thickened left ventricular wall (interventricular septum 14 mm and posterior wall 13 mm) with a global reduction in systolic performance (ejection frac-

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Laboratory Date on Admission Oct. 16, 1995

WBC $10400/\mu\text{L}$ $\uparrow$ Eosinophils $2780/\mu\text{L}$ $\uparrow$			
(Eosinophils 26.8% Neutrophils 38.9% Lymphocytes 23.6% Monocytes 6.0%)			
RBC $473 \times 10^4/\mu\text{L}$ Hgb 14.0g/dL Ht 42.1% PLT $27.0 \times 10^4/\mu\text{L}$			
ESR	17/1hr $\uparrow$	CRP	0.9 mg/dL $\uparrow$
AST	36 IU/L	BUN	17 mg/dL
ALT	51 IU/L $\uparrow$	Crea	0.7 mg/dL
LDH	933 IU/L $\uparrow$	UA	7.8 mg/dL $\uparrow$
CPK	167 IU/L $\uparrow$	FBS	101 mg/dL
TP	5.6 g/dL $\downarrow$	TCHO	162 mg/dL
Alb	3.1 g/dL $\downarrow$		
DLST	(cpm)	S.I.%	
Phenobarbital	619	244	positive
Control	253		

Fig 1. Laboratory findings on admission. Total eosinophil count is $2780/\text{mm}^3$.

Fig 2. The chest radiograph shows cardiomegaly (CTR 51.5%) and slight congestion on admission.

Fig 3. (a) An electrocardiogram on admission shows ST depressions in leads I, II, aVL, aVF, and V₄₋₆, and ST elevations in leads V₁ and V₂. (b) An electrocardiogram shows atrial flutter with a ventricular rate of 40/min, after tapering off of steroid.

tion 50%) and a little pericardial effusion. Ten days after the treatment with oxygen, diuretics, and nitroglycerin, the patient became asymptomatic, but improvement in cardiomegaly and cardiac dysfunction was not satisfactory. Cardiac catheterization performed on 13 November

1995 showed normal coronary arteries and almost normal left ventricular contraction with an ejection fraction of 65% (Fig 4). Endomyocardial biopsy from the right ventricle showed slight necrosis and degeneration of the myocardial cells, which were predominant at the sub-

Fig 4. Coronary arteriography shows no obstructive lesions. Left ventriculography shows almost normal contraction.

Fig 5. Myocardial cell necrosis and an extensive infiltration of lymphocytes admixed with marked eosinophils are seen. Hematoxylin and eosin stain, $\times 400$.

endomyocardium. Extensive infiltration of lymphocytes admixed with marked eosinophils and slight interstitial fibrosis was also seen (Fig 5). We decided to give 30 mg of prednisolone daily because the peripheral blood eosinophil count was still $2150/\text{mm}^3$. After this treatment, eosinophilia, cardiac size, and cardiac function improved further (Fig 6). However, atrial flutter, which occurred on 8 December 1995 (Fig 3b), was persistent with a heart rate of 40/min. Pharmacologic attempts to convert to sinus rhythm using 300 mg of disopyramide or 150 mg of flecainide were ineffective. Although sinus rhythm was achieved by an electric cardioversion, it was transient. The patient was discharged on 16 February 1996 and placed on 15 mg of prednisolone daily.

Fig 6. Clinical course. The first steroid therapy was started with 30 mg of prednisolone. Echocardiography shows a diffusely thickened left ventricular wall, of which the interventricular septum measured 14 mm and posterior wall 13 mm, whereas the white blood cell count was $15,300/\text{mm}^3$ with $260/\text{mm}^3$ eosinophils 2 weeks after the start of steroid therapy. The cardiothoracic ratio and ejection fraction as determined by echocardiography improved from 51.2% to 43.7%, and from 0.65 to 0.79, respectively.

Discussion

Eosinophilic endomyocardial disease is a global entity that encompasses variable degrees of cardiac disorders induced by hypereosinophilia. It can be classified into 3 groups according to its pathologic stage: acute necrotic, later thrombotic, and late fibrotic. These 3 stages correspond clinically to eosinophilic myocarditis, Loeffler's endocarditis, and endomyocardial fibrosis, respectively. At times it is not easy to differentiate these diseases during life because they must be confirmed pathologically. Endomyocardial biopsy is helpful in making a correct diagnosis, but it is not always foolproof. From an etiologic viewpoint, collagen disease, parasitic infection, malignancies (eg, Hodgkin's disease, leukemia, or cancer), or bronchial asthma are thought to be the causative disorders that may induce hypereosinophilia, resulting in eosinophilic myocardial disease. However, such underlying pathogenesis cannot always be detected in patients with hypereosinophilia, and in some patients the disease has to

be described as "idiopathic".^{1,2} It is of interest that eosinophilic endomyocardial disease occurs predominantly in men.^{8,9} The reason for this is not known, but may be related in some way to hormonal or other sex-related factors involved in the regulation of eosinophil production.

Drug-induced hypersensitivity myocarditis has also been classified as hypereosinophilic myocardial disease, and antibiotics,³ anticonvulsants,⁴ antihypertensive agents,⁵ and diuretics⁶ have been reported as its causative agents. Clinical symptoms and signs are usually initiated by allergic reactive manifestations such as rash, high fever, sinus tachycardia, and eosinophilia. A physician must be aware of this clinical information because it provides the clues for making an early and correct diagnosis. To our knowledge, this is the first reported case (in English) of hypereosinophilic myocarditis caused by hypersensitivity against phenobarbital.

Eosinophilic myocarditis is characterized pathologically by an active infiltration of the myocardium by eosinophils, lymphocytes, and histiocytes. Recent immunopathologic techniques suggest that several toxic proteins derived from degranulation of eosinophils may play an important role in the pathogenesis of the cardiac disorder. Eosinophil major basic protein can be visualized by indirect immunofluorescence on trypsin-treated sections,¹⁰⁻¹³ and eosinophil cationic protein as well as eosinophil protein-X (identical to eosinophil-derived neurotoxin) have also been demonstrated in tissues.¹⁴ As we could not obtain purified antibody to eosinophil cationic protein, it could not be identified in the myocardial specimen obtained from the right ventricle (data not shown). The level of eosinophil cationic protein in peripheral blood was normal on 20 December 1995; this may be because the eosinophilic count had already been normalized after the steroid therapy.

Electrocardiographic abnormalities are also of interest in our patient. Although a wide range of electrocardiographic abnormalities have been seen in patients with eosinophilic endomyocardial disease, arrhythmias and conduction disturbances are thought to be restricted to patients with advanced disease.¹ Compared with ischemic myocardial disease, the cardiac conduction system is more susceptible to myocarditis.¹⁵ Longstanding and massive eosinophilic infiltration to the myocardium in our patient must have contributed to the persistent atrial flutter accompanied by slow ventricular responses.

As there is no microscopic finding specific for drug-

induced hypersensitivity myocarditis, discontinuing the suspect drug is necessary not only to make a correct diagnosis but to obtain a more reliable prognosis. Any drug can cause hypersensitivity myocarditis, therefore physicians should be aware of this rare entity, and the administration of a sufficient amount of steroids at an early stage should be considered.

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