An Autopsied Case of Acute Myocarditis With Myocardial Calcification

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A 47-year-old woman was admitted with fever, hypotension, an elevated serum creatinine kinase level, and electrocardiographic abnormalities, which led to the diagnosis of acute myocarditis. She was placed on percutaneous cardiopulmonary support because of hemodynamic collapse on the third hospital day. Serial echocardiography showed gradual recovery of profound hypokinesis and edematous thickening of the left ventricle, but she died of sepsis on the 17th day without overt renal insufficiency or electrolytic abnormalities. Autopsy revealed myocardial necrosis with lymphocytic infiltrates and extensive myocardial calcification. Calcification was dense in the area of severe myocardial necrosis, and the distribution of calcium deposits suggested that the calcification was a consequence of significant inflammation of the myocardium. Recovery of regional wall motion was prominent in the area of severe inflammatory change. Dissociation between the pathologic and echocardiographic findings suggested the possibility of functional reversibility of severely damaged myocardium and possible mechanisms of abnormal contractile function other than inflammatory change.

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Key Words: Acute myocarditis; Myocardial calcification; Percutaneous cardiopulmonary support

Acute myocarditis is an inflammatory disease of the myocardium with a variety of causes and clinical manifestations. It is most often a self-limiting process that results in minimal cellular damage and recovery, but occasionally it is more extensive and leads to significant cellular necrosis and marked hemodynamic compromise. Myocardial calcification has been observed in necrotic tissue following experimental viral myocarditis and acute myocarditis in human newborns and infants^{1–12}. Although the manifestations of acute myocarditis vary widely, myocardial calcification is unusual in adult patients without renal failure^{13,14}. We describe an adult patient with acute myocarditis associated with extensive myocardial calcification with preserved renal function. Dissociation between the asynergy of the regional ventricular wall and the extent of myocardial inflammation confirmed at autopsy was evident.

Case Report

A 47-year-old woman who had been experiencing fever, nausea, and general lassitude for 3 days was

admitted to our hospital. Her blood pressure was 62/40 mmHg, and her pulse was 76 beats/min and irregular. She had clear lungs, and had no cardiac murmurs. The moderately enlarged liver was gently palpated, and slight pretibial edema was present. A chest radiograph showed mild cardiomegaly. An electrocardiogram (ECG) revealed complete atrioventricular (AV) block with a ventricular rate of about 80 beats/min and ST segment elevation in leads V2–3. Laboratory data (Table 1) showed liver dysfunction and muscle injury. Two-dimensional echocardiography (2DE) disclosed proportionally reduced left ventricular (LV) wall motion with edematous thickening. Acute myocarditis was suggested, and cardiac catheterization was performed on the second hospital day. It revealed no coronary artery disease, elevated pulmonary capillary wedge pressure (22 mmHg), elevated LV end-diastolic pressure (25 mmHg), low cardiac index (2.15 L/min per m²), and reduced ejection fraction (41%) with diffuse hypokinesis. Temporary pacing of the right ventricle was performed because of a complete AV block. Infusion of a low dose of dopamine and furosemide was started. On the

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third hospital day, pacing failure was manifested. With manipulation of the pacing catheter under fluoroscopic guidance, ventricular capture could only be obtained in a small area of the right ventricular outflow tract. During manipulation, ventricular tachycardia (VT) of 160 beats/min occurred, and was successfully abolished with lidocaine. After termination of VT, severe hypotension was sustained and intra-aortic balloon pumping (IABP) assistance was initiated with only a partial effect. The patient was then placed on a percutaneous cardiopulmonary support (PCPS) system with flow rate of 3.5 L/min. Intensive therapy with IABP

and PCPS support and catecholamines was continued. VT requiring DC cardioversion recurred several times and, thereafter, the ECG showed a sine-wave-like configuration (Fig 1A). On 2DE examination, LV wall motion was negligible (Fig 2A), and opening of the aortic valve was not observed. Methylprednisolone at a dose of 1,000 mg/day was administered intravenously for 3 days from the fourth hospital day. On the seventh hospital day, edematous thickening of the LV wall decreased and the LV wall motion gradually improved as determined by 2DE examination. Recovery was prominent in the lateral wall and modest in the posterior, posteroseptal, and inferior walls, but akinesis persisted in the anteroseptal wall. Serum was assayed for virus-neutralizing antibodies upon admission and on the 17th hospital day. There was a significant increase in Coxsackie A2 ($\times 8 \rightarrow \times 64$). Thereafter, 2DE showed normalized LV wall thickness and increased ejection fraction up to 25% (Figs 2B and 3), and the ECG showed a low-voltage wide QRS complex (Fig 1B). The flow rate of PCPS was then reduced to 2.0 L/min, but the complications of bilateral pneumonia and hepatic failure led to a deterioration in hemodynamics refractory to catecholamines and an increase in PCPS flow. Sepsis was suggested, and the patient died on the 17th hospital day despite intensive antimicrobial treatment. An autopsy was performed.

Histopathologic examination (Fig 4) disclosed widespread necrosis and degeneration of the myocardium with lymphocyte infiltration and a large number of calcium deposits. The calcium deposits were dense in

Table 1 Laboratory Findings on Admission

WBC	7,500/ μ l
RBC	390×10^4 / μ l
Hb	11.6 g/dl
Ht	33.6%
Plt	14×10^4 / μ l
CRP	2.11 mg/dl
GOT	392 IU/L
GPT	146 IU/L
LDH	1,870 IU/L
ALP	209 IU/L
CK	1,923 IU/L
BUN	50.1 mg/dl
Creatinine	1.2 mg/dl
Calcium	8.4 mg/dl
Phosphorus	4.2 mg/dl
Sodium	128 mmol/L
Potassium	4.5 mmol/L
Chloride	90 mmol/L

Fig 1. An electrocardiogram taken on the third hospital day (A) showed an irregular wide QRS complex and sine-wave-like configuration in the limb leads. On the 14th hospital day (B), regular rhythm was restored but the low-voltage wide QRS complex remained.

Fig 2. An echocardiogram taken on the fourth hospital day revealed edematous thickening and akinesis of the left ventricular wall (A). On the 14th hospital day, the edematous thickening had disappeared and partial recovery of posterior wall motion was observed (B).

Fig 3. Short-axis 2-dimensional echocardiogram in diastole (A) and systole (B) on the 14th hospital day. The LV wall thickness is normal. The lateral, posterior, and posteroseptal wall showed contraction, but the anteroseptal wall was still akinetic.

the area of severe inflammatory change. These findings were mainly observed in the posterior, posteroseptal, and lateral walls of the LV and were mild in the anteroseptal wall. Pneumonia and abscess in the bilateral lower lobe were also evident.

Discussion

Myocardial calcification following myocarditis has been reported in experimental studies¹⁻⁵ but it is unusual in clinical presentation. Although the mechanism remains unclear, aggregation of phagocytosed mitochondria that have undergone various degrees of

calcification has been proposed as a possible mechanism in an experimental study of viral myocarditis.⁵ Several reports have described myocarditis associated with calcification in newborn babies and infants⁶⁻¹¹ but only 2 cases, complicated with acute renal failure have been reported in adults.^{13,14}

In our case, renal function was preserved during the patient's entire clinical course. Serum calcium and phosphorus were within the normal range upon admission and serial examination was not performed. Parathyroid hormone concentration was not determined. The patient's clinical history and physical findings were negative for any previous disorders,

Fig 4. (A) A cross-section of the heart shows biventricular dilation and dark intramural hemorrhage. (B) Massive infiltration of inflammatory cells, mainly lymphocytes, with degeneration and necrosis of myocardial fibers is shown (hematoxylin and eosin). (C) Dark necrotic myocardium with mineralization is infiltrated and surrounded by mononuclear cells (hematoxylin and eosin). (D) Dense calcification in necrotic myocardial fibers is shown (von Kossa). (E) Antero-septal wall of the left ventricle. Mild infiltration of mononuclear cells is shown, but degeneration or necrosis is not evident (hematoxylin and eosin).

including cardiac, renal, metabolic, hormonal, or vascular disease, malignancies, or intoxications. Progressive inflammation of the myocardium could result in significant damage with subsequent calcification^{11,12}. The marked hemodynamic compromise and elevation of creatine kinase (CK), recurrent and serious tachyarrhythmia, and conduction disturbance present in our patient could be explained by the extensive myocardial damage, and the distribution of calcium deposits suggests that calcification might have occurred as a consequence of significant inflammation in the myocardium. In our case, there was an 8-fold increase in virus-neutralizing antibody to Coxsackie A2. However, an increase in neutralizing antibody does not by itself establish a definitive diagnosis of virus-induced

myocarditis¹⁵ and another diagnostic approach using molecular techniques would be required to establish the specific etiology¹⁶. The precise reasons for myocardial calcification are not known, but genetic factors may play an important role^{17,18}.

The clinical implication of myocardial calcification following myocarditis is not clear, but it is considered to be a predictor of poor outcome for myocarditis in newborn babies and infants¹⁰. Our patient died from sepsis despite gradual recovery of LV wall motion as observed on 2DE serial examinations. The degree of recovery was significant in the lateral wall but modest in the antero-septal wall. This finding was not in accordance with the distribution and severity of inflammatory change. Dissociation between profound

hypokinesis and mild inflammatory change may be caused by humoral or chemical factors such as nitric oxide or proinflammatory cytokines,^{19–25} but this explanation will require further histochemical examination. Also, a gradual improvement in regional wall motion as occurred in our patient suggests some potential for recovery despite severe inflammation^{26–29} accompanied by calcification?

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