—Report on Experiments and Clinical Cases—

# Recurrent Myocarditis of Unknown Etiology

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**Abstract**

A 42-year-old man presented with dyspnea and common cold-like symptoms. His electrocardiogram showed complete atrioventricular block and chest radiography revealed cardiomegaly and pulmonary congestion. He had a history of three recurrences of active myocarditis proven by endomyocardial biopsy over a 14-year period. Viral studies showed no evidence of recent infection, and no medications had been taken prior to this episode. This myocarditis was suggested as an unknown etiology.
(J Nippon Med Sch 2004; 71: 292–296)

**Key words**: chronic myocarditis, recurrence, autoimmune myocarditis

## Case Report

A 42-year-old man was admitted with complaints of exertional dyspnea, orthpnea, and a low-grade fever on April 2, 2001. He had reported symptoms of a common cold one week previously. He had a history of prior episodes of myocarditis in 1988, 1991, and 1995. On the first admission in 1988, the myocarditis was characterized by symptoms of congestive heart failure, bradyarrhythmia, and increased serum cardiac enzyme activity. Echocardiography at that time revealed reduced wall motion. An endomyocardial biopsy, done 1 month after the onset, showed mild diffuse monocyte infiltration with mild fibrosis. He was asymptomatic for the next 3 years, but in March 1991 (second episode), he developed congestive heart failure and fever. Echocardiography revealed anteroapical wall hypokinesis. An endomyocardial biopsy obtained after 3 days showed massive inflammatory cell infiltration. However, 5 months later, there were only a small number of lymphocytes. The patient received medical treatment at another hospital during the first and second episodes of myocarditis, so the full details of those treatments were not available.

In 1995 (third episode), he was admitted to our hospital with chest pain and dyspnea. Chest radiography demonstrated cardiomegaly with pulmonary congestion, and the electrocardiogram showed complete atrioventricular block. The serum creatin kinase activity (455 IU/L) was increased and the IgE concentration (1,790 IU/mL) level was also increased, reflecting the role of some allergic mechanism. However, we could not determine the allergen. Radionuclide examination ($Tc^{99m}$ tetrofosmin) was performed and demonstrated irregular uptake in the myocardium (**Fig. 1**). Endomyocardial biopsy revealed inflammatory cell infiltration. Cardiac sarcoidosis was ruled out because of the normal level of serum angiotensin

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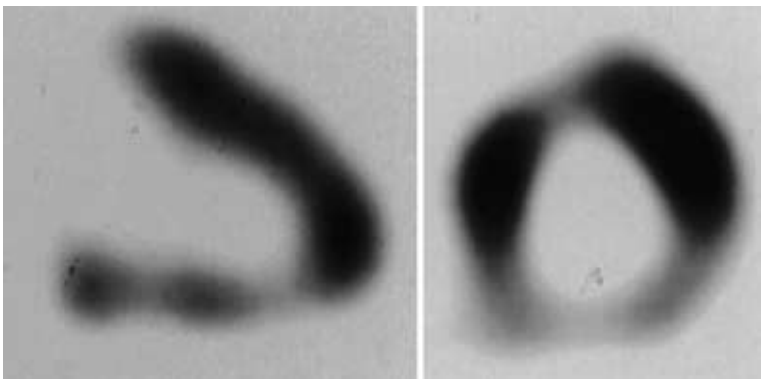

Fig. 1 Myocardial image (Tc$^{99m}$ tetrofosmin) performed in 1995 demonstrated irregular uptake in myocardium despite normal coronary angiogram.

converting enzyme (10.9 IU/L) and no mediastinal lymphnode swelling on chest radiography. Heart block improved 2 days after the admission.

On admission for the fourth episode (2001), the patient was awake and alert. Physical examination revealed a body temperature of 36.5℃, a regular heart rhythm at a rate of 42 beats/min, a respiratory rate of 26/min, and a blood pressure of 98/56 mmHg. Right-sided cervical lymphadenopathy was noted, but no other abnormalities were found. Chest radiography demonstrated mild cardiomegaly (cardiothoracic ratio: 60%) and pulmonary congestion. The electrocardiogram showed complete atrioventricular block with a ventricular escape rhythm at a rate of 42 beats/min (**Fig. 2**). Laboratory studies revealed leukocytosis (11,150/mm$^3$), elevated serum concentrations of C-reactive protein (21.35 mg/dL), Ig-E (470 mg/dL) and cardiac enzymes. The serum activity of creatine kinase was 507 IU/L, creatine kinase MB fraction was 39 IU/L, lactate dehydrogenase was 1,114 IU/L, and the troponin-T assay was positive. Echocardiography showed diffuse left ventricular hypokinesis, and the left ventricular ejection fraction was 19% (**Fig. 3**). Acute exacerbation of chronic myocarditis was suspected. Coronary angiography and endomyocardial biopsy were performed 4 days after admission. There were no stenose of the coronary arteries (**Fig. 4**), but left ventriculography demonstrated diffuse hypokinesis. Examination of the endomyocardial biopsy specimen showed interstitial edema, myocardial fibrosis, and

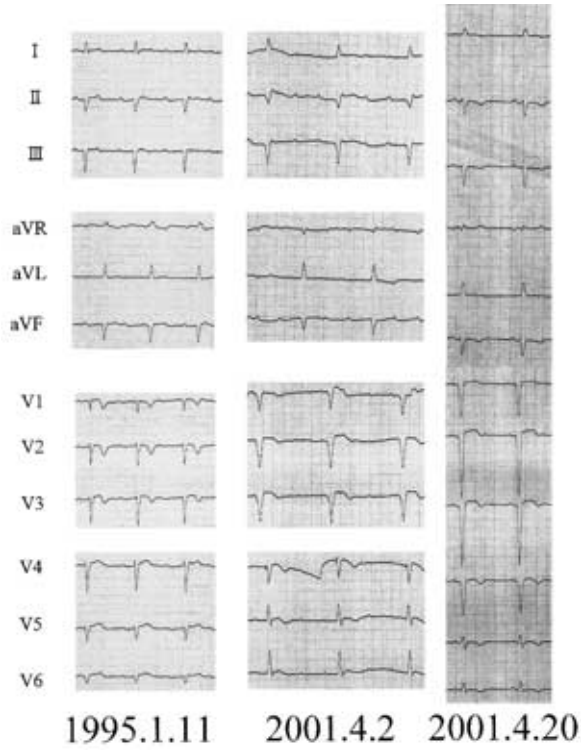


Fig. 2 Electrocardiogram recorded in third episode (left), on admission (center) and before discharge (right) of the fourth episode. Complete atrioventricular block and ST segment elevation in multi-leads were found.

inflammatory cell infiltration by lymphocytes, neutrophils, and eosinophils (**Fig. 5**). These findings were interpreted as reflecting both acute and chronic phases of myocarditis. Cephotiam (2 g/day) and gamma globulin (7.5 g/day) were administered for 7 and 3 days, respectively. The inflammation improved immediately and the concentration of C-reactive protein and the serum cardiac enzyme activity decreased to the normal range (**Fig. 6**).

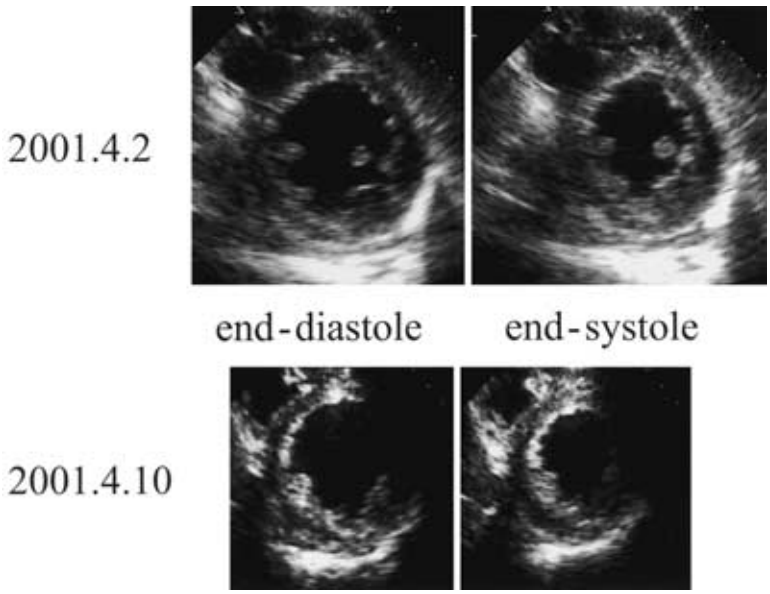


Fig. 3 Echocardiography on admission (top) and before discharge (bottom) of the fourth episode.
On admission (April 2, 2001), left ventricular wall motion was diffuse hypokinetic, but it recovered before discharge (April 20, 2001). Left ventricular ejection fraction improved from 19% to 41%.

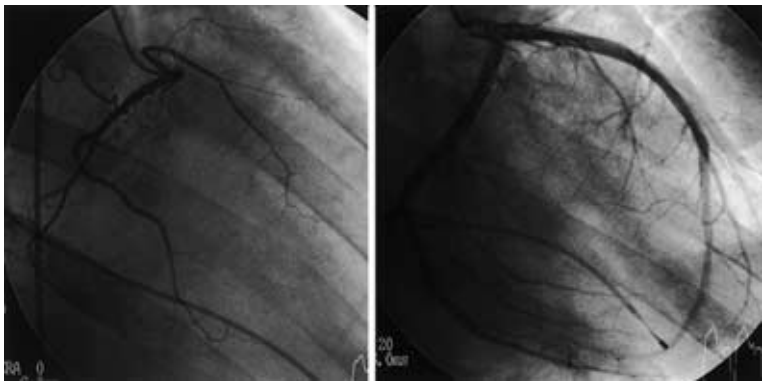

Fig. 4 Coronary angiography in the fourth episode. There were no organic lesions in either the right coronary artery (left) or the left coronary artery (right).

Heart block also improved 2 days after admission.

The differential diagnosis included viral infection, allergic reaction, and autoimmune reaction. Virology studies showed no evidence of recent infection (**Table 1**), and the patient had not taken any medications prior to the onset of this episode, although we suspected that his previous episode (1995) had been induced by analgesic administration, which responded to corticosteroid therapy. The final diagnosis was established as recurrent myocarditis of unknown etiology.

## Discussion

A number of factors, including viral infection, collagen vascular disease, sarcoidosis, allergic reaction, and exposure to toxic agents, can induce myocarditis. Of these, viral infection is the most common etiology. Inflammation in the setting of myocarditis tends to be panmyocardial, involving not only the myocardium, but also the endocardium and epicardium as well[1]. Myocarditis is classified as acute or chronic according to the onset of the disease.

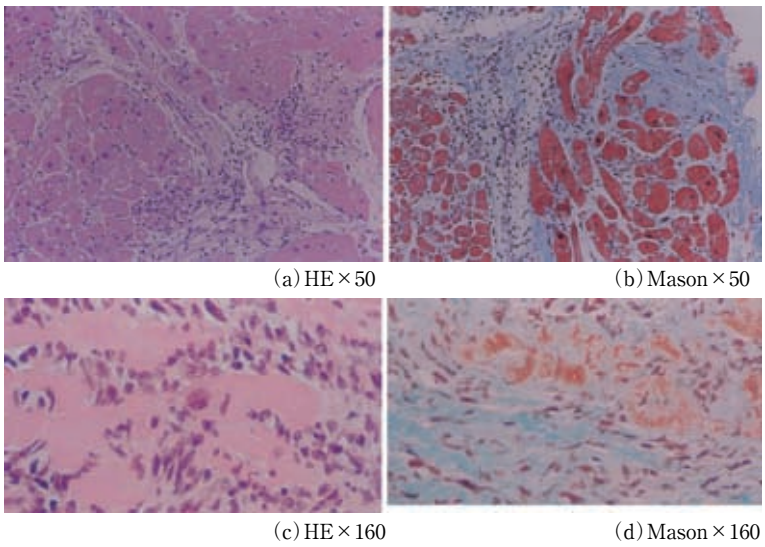


Fig. 5 Pathological findings of endomyocardial biopsy specimen obtained on April 5, 2001. Necrosis and degeneration of myocardial cells with extensive infiltration of lymphocytes into the interstitial space were revealed (a and c). Mason stain showed massive myocardial fibrosis and elastic tissue (b and d). These findings were characterized by mixture of acute and chronic phase of myocarditis.

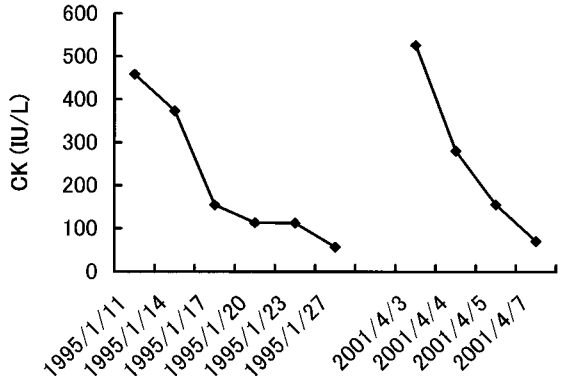


Fig. 6 Serum creatine kinese (CK) level in the clinical course of the third and fourth episodes.

Table 1 Viral Titer

| | 2001. 4. 3 | 2001. 6. 23 |
|---|---|---|
| Adeno | < 4 | < 4 |
| Echo-4 | 8 | 8 |
| Echo-6 | 64 | 128 |
| Echo-9 | 8 | 16 |
| Echo-11 | < 4 | < 4 |
| Coxsackie-A16 | 16 | 16 |
| Coxsackie-B3 | 128 | 128 |
| Coxsackie-B5 | 16 | 8 |
| Cytomegalovirus Ig-M | < 10 | < 10 |
| Cytomegalovirus Ig-G | 40 | 20 |

Chronic myocarditis is subdivided into 3 types: a persistent type, a recurrent type, and a latent type[2]. The current case is considered recurrent, which is very rare, although several cases of recurrent myocarditis have been reported[3–13]. But, those reports described only a single episode of recurrence, while our patient has had recurrence of myocarditis 3 times.

On the fourth occasion, the myocarditis followed an episode of common cold-like symptoms, and was associated with complete atrioventricular block and congestive heart failure. In attempting to determine the specific cause of this myocarditis, viral infection, recent or previous exposure to the same or other viruses, and some allergic or autoimmune reaction were considered. We suggest that the initial cause of the myocarditis in this case was viral infection, most probably Coxsackie or Influenza virus. However, viral infection could not be implicated in the episode of myocarditis in 2001. Furthermore, the patient had not taken any medicine, so the likelihood of a drug-induced allergic reaction was low. The cause of the increased serum Ig-E concentration remained unclear.

Generally, human beings are not usually reinfected

by the same virus because the immune system produces sufficient numbers of antibodies to protect the host during reexposure to the vector[14]. But it is possible to reactivate the myocarditis by the exposure to the same vector. Kodama et al[15]. suggested that an autoimmune reaction is the trigger for recurrent myocarditis in the rat. In these studies, myocarditis was induced in Lewis rats by injecting cardiac myosin subcutaneously and when the rats were reexposed to the same dosage of cardiac myosin, they developed myocarditis 4 months after the initial exposure. This experiment shows that it is possible to induce myocarditis without recent exposure to the original virus, and the autoimmune pathogenesis involving both cellular and humoral pathways may play a grater role in altering myocardial function than the viral infection itself in some cases. We suspect that a similar reexposure to endogenous factors might have occurred in our patient.

A significant feature of chronic myocarditis is congestive heart failure and various kinds of arrhythmias. The common remedy for this disease is symptomatic treatment. To control the myocardial inflammation , gamma globulin , virucide , corticosteroids and immunosuppressant agents have been used. However, there is still no standardized therapy. Dennis reported that high dose (2 g/Kg) immune globulin therapy improves the left ventricular ejection fraction (LVEF) in patients with suspected autoimmune myocarditis[16], and also high dose immune globulin therapy markedly improves the survival rate[17]. When later used in the post-viremic phase, immune globulin-treated mice had less myocardial necrosis than control animals[18]. That is the reason we used gamma globulin to treat our patient. We were not permitted to use high-dose immune globulin therapy, so we administered a low dose (150 mg/Kg). Even with low-dose intravenous immune globulin therapy, we were able to manage the recurrent myocarditis.

Our patient has had four episodes of active myocarditis proven by endomyocardial biopsy during the past 14 years. This is the first report describing three recurrences of myocarditis.

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(Received, November 4, 2003)
(Accepted, March 16, 2004)