Diagnostic Utility of Cardiac Magnetic Resonance in Recurrent “Third Time” Myocarditis Without Electrocardiographic Changes
A Case Report and Literature Review

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Summary
A few studies have reported on recurrent myocarditis occurring more than twice in one patient. In this study, we present a recurrent “third time” acute myocarditis in a young female Japanese patient with a history of a definitive diagnosis of lymphocytic myocarditis by endomyocardial biopsy, cardiac magnetic resonance imaging (CMR), and catheter examination twice in the past. Although chest pain and an increase in the cardiac enzymes were observed the third time, no significant changes were noted in the 12-lead electrocardiogram (ECG), and a definitive diagnosis could be achieved by CMR. This case suggested that in patients with a history of myocarditis, if there is chest pain and elevated cardiac enzymes even without any changes in the 12-lead ECG, acute myocarditis should be considered, and CMR is useful for the differentiation.

Only four case reports including this present case were found through the previous literatures. More than two recurrent episodes of myocarditis have been extremely rare, but all cases have typical chest symptoms and a troponin level increase, leading to a relatively benign prognosis.

Key words: Acute myocarditis, Recurrence, More than two times, Diagnosis

Acute myocarditis can be caused by viruses, bacteria, fungi, drugs, radiation, or toxins. In acute myocarditis, an ST-T abnormality on the 12-lead electrocardiogram (ECG) is detected in almost all patients, typically with ST-segment elevation with a wide range of induction that is not consistent with coronary artery dominance. Atrioventricular block and ventricular arrhythmias may also be present in some cases. The European Society of Cardiology (ESC) guidelines for acute and chronic heart failure recommend cardiac magnetic resonance (CMR) imaging for the evaluation of myocarditis as a class I indication. Although the prognosis of acute myocarditis is generally good, there are cases of recurrence and dilated cardiomyopathy-like symptoms. There have been few reports on recurrent myocarditis that occurs more than two times in a single patient. In fact, in this study, we present a recurrent “third time” acute myocarditis, in which CMR was useful for the differentiation. Moreover, no obvious changes in the 12-lead electrocardiogram were observed; however, chest pain and an increase in the cardiac enzymes were observed during the third time.

Case Reports
A 24-year-old female with two histories of recurrent acute myocarditis 11 and 8 years prior complained of chest discomfort two weeks before admission. In her first admission, her medical record in another hospital confirmed acute myocarditis, and she had been hospitalized for 10 days, while the detailed laboratory and electrocardiogram (ECG) data were not available because over 5 years had passed since admission. The detailed medical information for the second acute myocarditis episode is shown in Table I.

She had no prodromal symptoms such as a cold. Her blood pressure during the initial examination was 104/68 mmHg, heart rate 64 bpm, respiratory rate 18/minute, and body temperature 36.8 degrees. A 12-lead ECG showed no significant ST-T changes even though she was complaining of chest pain (Figure 1). Transthoracic echocardiography (TTE) revealed a normal size and wall thickness of the left ventricle (LV) and a preserved LV function without asynergy, valvular disease, a D-shape, or pericardial effusion (Figure 2). The laboratory data during the initial examination revealed that the leukocyte count and fraction were within normal limits, but the cardiac enzymes, such as the creatinine kinase (CK) (169 U/L, CK-
Table I. Characteristics of the Second Myocarditis Episode

| Second myocarditis episode |  |  |
|----------------------------|---|---|
| Age                        | 16 years |  |
| Symptoms                   | Chest pain |  |
| Laboratory data on admission | Increase in the cardiac enzymes (CK 610 U/L, CK-MB 52 U/L, troponin I 11.6 ng/mL), Negative for viral markers and autoantibodies |  |
| ECG findings               | ST-segment elevation in the inferior leads |  |
| TTE findings               | WNL |  |
| CAG findings               | Intact coronary arteries and negative spasm provocation test |  |
| CMR                        | Edema in the T2-weighted imaging and positive LGE along the poster septal to the inferior wall on the left ventricular epicardial side |  |
| EMB                        | Lymphocytic myocarditis |  |
| Treatment                  | NSAIDs and high-dose intravenous methylprednisolone pulse therapy |  |
| Outcome                    | Discharged on the 17th hospitalization day |  |

CAG indicates coronary angiography; CK, creatine kinase; CMR, cardiac magnetic resonance; ECG, electrocardiogram; EMB, endomyocardial biopsy; MB, myoglobin; LGE, late gadolinium enhancement; NSAID, non-steroidal anti-inflammatory drug; TTE, transthoracic echocardiography; and WNL, within normal limits.

MB 7 U/L, and troponin-I 2.71 ng/mL), were elevated (Table II). The data revealed that the anti-nuclear antibodies and anti-ds-DNA antibodies were negative. In addition, there were no significant elevations in the thyroid hormone, angiotensin-converting enzyme (ACE), or soluble interleukin-2 receptor (sIL-2R) levels. The influenza antigen test and SARS-COV2 test at the time of admission were both negative. A coronary computed tomography scan revealed no significant stenosis in her coronary arteries (Supplemental Figure). She was then suspected of having acute recurrent myocarditis for the third time, because she had a history of having acute myocarditis twice in the past, at which time a catheter examination including a spasm provocation test denied any coronary vasospasms and endomyocardial biopsy confirmed lymphocytic myocarditis. The oral administration of non-steroidal anti-inflammatory drugs (NSAIDs) was then started, and on the second day, her chest symptoms improved as well as her troponin-I levels, as per her laboratory results. The viral serum markers were all negative both on admission and 2 weeks later (Table III). Furthermore, cardiac sarcoidosis was ruled out according to the diagnostic criteria.

CMR 10 days after admission revealed myocardial edema on the epicardial side of LV anterolateral wall (Figure 3A) in the T2-weighted imaging, and an epicardial late gadolinium enhancement (LGE) was observed on the LV anterolateral (Figure 3B) and inferior (Figure 3C) walls. Positron emission tomography-computed tomography (PET-CT) 8 days after discharge showed no abnormal accumulation in the heart (Figure 4) or in other organs.

From the above findings, she was diagnosed with an acute recurrent “third time” myocarditis; however, an endomyocardial biopsy was not performed because her hemodynamics were stable, and the myocarditis improved rapidly. The patient was in good general condition, the NSAIDs were completed four days after administration,
Figure 2. Transthoracic echocardiography on admission. The echocardiogram shows a normal left ventricular function with a normal size and wall thickness without a pericardial effusion. A: Long axis, and B: short axis.

Table II. Laboratory Data at the Time of Admission

| Item          | Item | Item       |
|---------------|------|------------|
| WBC 6,300/mm³ | T-Chol 209 mg/dL |
| Neut 52.9%    | HDL-Chol 76 mg/dL  |
| Eosi 3.3%     | LDL-Chol 104 mg/dL  |
| Baso 0.6%     | TG 62 mg/dL          |
| Mono 4.8%     | CK 169 U/L           |
| Lymph 38.4%   | CK-MB 7 U/L          |
| Hb 12.9 g/dL  | Troponin-I 2.71 ng/mL |
| P1t 19.6 x 10⁹/μL | NT-proBNP 111 pg/mL |
| BUN 11.5 mg/dL | TSH 1.56 μlU/mL   |
| Cre 0.71 mg/dL | Free T3 2.95 pg/mL  |
| eGFR 83.8     | Free T4 1.27 ng/mL  |
| CRP 0.1 mg/dL | PCT 0.02 ng/mL      |
| TP 6.8 g/dL   | KL-6 217 U/mL       |
| Alb 4.1 g/dL  | ACE 8.7 U/L         |
| T-Bil 0.66 mg/dL | sIL-2R 196 U/mL |
| AST 40 U/L    | Viral titer         |
| ALT 22 U/L    | Adeno 4             |
| LDH 189 U/L   | Echo-7 8 >         |
| ALP 147 mEq/L | Echo-11 8 >        |
| BS 94 mg/dL   | Coxsackie-A9 4 >    |
| HbA1c 5.2%    | Coxsackie-B1 4 >    |
| UA 5.8 mg/dL  | Coxsackie-B3 4 >    |
| Na 141 mEq/L  | HSV 4 >             |
| K 4.1 mEq/L   | PV-B19 IgM (-)      |
| Cl 107 mEq/L  | Anti-nuclear antibody (-) |
| Ca 9.2 mg/dL  | Anti-ds-DNA antibody 10 > |

ACE indicates angiotensin-converting enzyme; Alb, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Baso, basophil; BS, blood sugar; BUN, blood urea nitrogen; Ca, serum calcium; CCR, creatinine clearance; CK, creatine kinase; Cl, serum chloride; Cre, serum creatinine; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; Eosi, eosinophil; Free T3, free triiodothyronine; Free T4, free thyroxine; Hb, hemoglobin; HbA1c, hemoglobin A1c; HDL-Chol, high-density lipoprotein cholesterol; HSV, herpes simplex virus; IgM, immunoglobulin M; K, serum potassium; LDH, lactate dehydrogenase; LDL-Chol, low-density lipoprotein cholesterol; Lymph, lymphocyte; MB, myoglobin; Mono, monocyte; Na, serum sodium; Neut, neutrophil; NT-proBNP, N-terminal pro-brain natriuretic peptide; P1t, platelets; PCT, procalcitonin; PVB, human parvovirus; sIL-2R, soluble interleukin-2 receptor; T-Bil, total bilirubin; T-Chol, total cholesterol; TG, triglyceride; TP, total protein; TSH, thyroid-stimulating hormone; UA, serum uric acid; and WBC, white blood cells.
and she was discharged from the hospital on the sixteenth day. She has not experienced any episodes of arrhythmias or heart failure thereafter.

Discussion

As per the T2-weighted CMR images, myocardial edema appears as a regional or global signal hyperintensity. LGE reveals the presence of fibrosis and necrosis in myocarditis. These two imaging conditions are critical items in the Lake Louise Criteria, which are used for the diagnosis of myocarditis. The JCS Guidelines for “Diagnosis and Treatment of Myocarditis” generally recommended only observation without the use of NSAIDs in mild myocarditis, but we administered a NSAID in her second- and third time myocarditis episodes because a poor prognosis in cases with residual LGE on CMR has been reported. However, there are cases where these conditions do not point out any significant abnormality, and in that case, the pattern of the increased T1 or T2 mapping is considered to improve the diagnostic accuracy of the CMR. In this present case, cardiac sarcoidosis was suspected by CMR during the third episode of myocarditis, but it was accurately excluded because no elevation was observed in the biomarkers such as the ACE or sIL-2R in the laboratory data, no obvious abnormality in the ECG or echocardiography, no abnormal accumulation in the heart on the PET-CT, and no significant findings in the lungs, eyes, or skin. In addition, although coronary spasms could not be completely ruled out, they were considered negative based on the lack of ECG changes during the chest symptoms and a combination of the symptoms and CMR. In this case, we diagnosed it as not chronic myocarditis, but as recurrent “third time” acute myocarditis.

Table III. Viral Titer on Admission and 2 Weeks Later

|                  | At admission | 2 weeks later |
|------------------|--------------|---------------|
| Adeno           | 4            | 4 >           |
| Echo-7          | 8 >          | 8 >           |
| Echo-11         | 8 >          | 8 >           |
| Coxsackie-A9    | 4 >          | 4 >           |
| Coxsackie-B1    | 4 >          | 4 >           |
| Coxsackie-B3    | 4 >          | 4 >           |
| HSV             | 4 >          | 4 >           |

Figure 3. Cardiac magnetic resonance (CMR) on the tenth day. A: T2-weighted imaging shows myocardial edema on the epicardial side of the left ventricular (LV) anterolateral wall (arrows). B and C: Gadolinium enhancement imaging shows an epicardial late gadolinium enhancement on the LV anterolateral wall (B, arrow) and inferior wall (C, arrows).

Figure 4. Positron emission tomography-computed tomography (PET-CT) on the eighth day after discharge. PET-CT showed no abnormal accumulation in the heart. A: Coronal plane, B: sagittal plane.
of myocarditis, the ECG can display a variety of non-
abnormalities, but it may have been that the mild inflam-
mation did not cause any potential changes. In patients
with myocarditis, the ECG can display a variety of non-
specific abnormalities. The sensitivity of the ECG for di-
agnosing myocarditis is estimated at 47%, but the speci-
ficity remains unknown. However, a wide QRS complex,
prolonged QT interval, high-degree atrioventricular block,
etc., have been associated with a poorer prognosis. On the
contrary, ST elevation with a typical early repolarization
pattern is associated with a better prognosis. During the
second episode of myocarditis, the ECG showed ST-
segment elevation in the inferior leads, and the laboratory
data showed a great increase in the cardiac enzymes (CK
610 U/L, CK-MB 52 U/L, troponin-I 11.6 ng/mL). In the
third episode of myocarditis, the degree of increase in the
cardiac enzymes was lower, and the symptoms were rela-
tively mild, so we thought that no obvious ECG changes
had occurred. Peters et al. suggested that CMR is useful
in the diagnosis of recurrent acute myocarditis mimicking
an ST-segment elevation myocardial infarction, and the
present case reported the diagnostic effectiveness of CMR
in recurrent acute myocarditis without any significant ST-
T changes.

**Conclusion**

Acute recurrent myocarditis that occurred more than
twice is considered rare, and only 4 case reports including
this present case were found through the previous litera-
ture. All cases including the present case had typical chest
symptoms and a troponin level elevation leading to a rela-
tively benign prognosis; however, the accumulation of fur-
ther cases is necessary for interpretation. We concluded
that if patients with a history of recurrent myocarditis
complain of chest symptoms and dyspnea, we should con-
sider the possibility of recurrent myocarditis, evaluate the

| Case authors | This case | Kanazawa, et al. | Matsue, et al. | Peters, et al. |
|--------------|-----------|-----------------|--------------|------------|
| **Age/Sex** | 24 years/female | 42 years/male | 64 years/male | 29 years/male |
| **Number of episodes of myocarditis** | Three times | Four times | Three times | Three times |
| **Age at the onset of myocarditis** | First time: 13 years | First time: 29 years | First time: 57 years | All time: 29 years |
| **Second time: 16 years** | Second time: 32 years | Second time: 36 years | Second time: 61 years | |
| **Etiology of myocarditis** | Unknown | Unknown | Unknown | Unknown |
| **Fulminant type** | No | No | Yes (1st and 2nd) | No |
| **History of a fulminant type** | No | No | General fatigue | Chest pain |
| **Presenting symptoms** | Chest discomfort | Dyspnea | Fever | GI symptoms |
| **Prodomal symptoms** | None | No | None | None |
| **Serum troponin level (on admission/peak value)** | Troponin I (ng/mL): 2.7/2.7 | Troponin-T assay was positive on admission | Troponin I (ng/mL): 9.1/ND | Troponin I (ng/mL): 8.5/39.5 |
| **12-lead ECG** | No significant ST-T changes | Complete atrioventricular block, and ST-segment elevation in multi-leads | Convex ST-segment elevation in the precordial leads | ST-segment elevation in multi-leads |
| **TTE during admission** | WNL | Diffuse left ventricular hypokinesis (EF 19%) | Diffuse left ventricular hypokinesis (EF 20%) | ND |
| **CMR** | Edema in T2-weighted imaging, and LGE positive in left ventricular epicardial side | ND | ND | Multi-focal LGE positive in inferior wall |
| **Outcomes** | Survival discharge | Survival discharge | Survival discharge | Survival discharge |

ECG indicates electrocardiogram; CMR, cardiac magnetic resonance; GI, gastrointestinal; LGE, late gadolinium enhancement; ND, no data; TTE, transthoracic echocardiography; and WNL, within normal limits.
serum troponin, and perform CMR, even if there are no characteristic findings on the ECG or TTE for myocarditis.

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Disclosure

Conflicts of interest: None.

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Supplemental Files

Supplemental Figure
Please see supplemental files; https://doi.org/10.1536/ihj.21-169