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【 CASE REPORT 】

An Irreversible Worsening Cardiac Function after Withdrawing Medical Treatments in a Patient with Dilated Cardiomyopathy: A Pathological Analysis

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Abstract:
A 44-year-old man diagnosed with idiopathic dilated cardiomyopathy was admitted to our hospital with acute decompensated heart failure. Seven years before this admission, the first introduction of medication resulted in left ventricular (LV) recovery, which was sustained for several years. However, the patient stopped taking his medication, resulting in worsening of the LV function. Despite the second introduction of medication, the LV function did not improve. We performed cardiac magnetic resonance imaging and an endomyocardial biopsy, which revealed the significant development of cardiac fibrosis that had not been present at the time of the initial diagnosis.

Key words: cardiac fibrosis, beta-blocker, renin-angiotensin-aldosterone system inhibitors, magnetic resonance imaging

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Introduction

Dilated cardiomyopathy (DCM) is characterized by left ventricular (LV) dilatation and impaired LV contractility. Some patients with DCM demonstrate LV reverse remodeling after the introduction of medication, including beta-blockers and renin-angiotensin-aldosterone system (RAAS) inhibitors. LV reverse remodeling is characterized by a reduction in LV volume and an improvement in LV contractility (1). In addition, it has been also shown that the withdrawal of medical treatments is associated with re-worsening of LV contractility (2, 3).

We experienced a patient with DCM in whom the once-recovered cardiac function did not improve again after the withdrawal of medical treatment. We herein report the clinical course by cardiac magnetic resonance (CMR) imaging and an endomyocardial biopsy.

Case Report

A 44-year-old man was admitted to our hospital with acute decompensated heart failure (HF). Seven years before the patient's admission, he had first been admitted for the treatment of acute decompensated HF. The patient had a history of hypertension. His blood pressure was 140/80 mmHg when he was not taking any medication.

An echocardiogram showed LV systolic dysfunction and dilatation with no significant valvular disease. The degree of mitral regurgitation at the diagnosis was mild. The LV wall thickness was 8.0 mm. Blood urine examinations did not reveal secondary or infiltrative cardiomyopathy, with the following measurements: white blood cell count, 9,900/μL; C-reactive protein, 0.28 mg/dL; thyroid-stimulating hormone, 0.57 μIU/mL; free thyroxine, 1.71 ng/dL; anti-nuclear antibody negative; immunoglobulin G, 1,363 mg/dL; angiotensin-converting enzyme, 6.8 IU/L; and urinary Bence-Jones protein negative. The patient had no history of drug or alcohol consumption that could have caused LV

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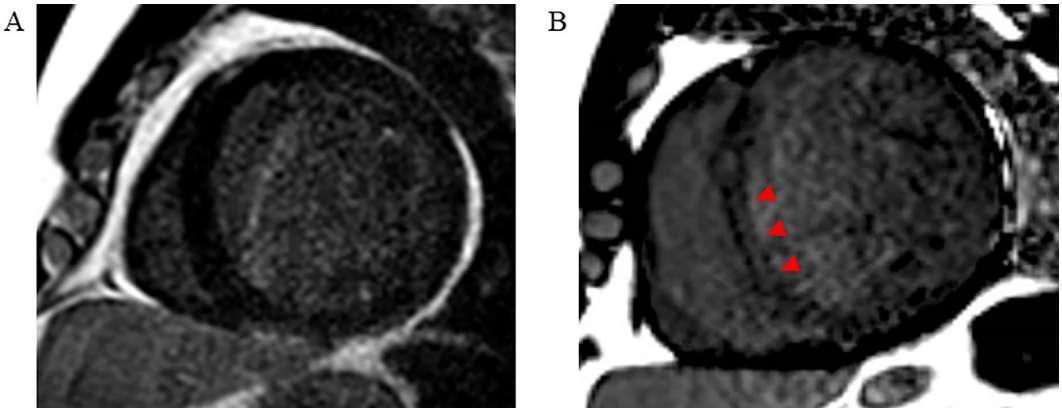

Figure 1. **(A) At the time of the diagnosis, cardiac magnetic resonance (CMR) imaging showed no delayed enhancement. (B) At re-admission, CMR imaging showed delayed linear enhancement of the ventricular septum (arrowheads).**

dysfunction.

Coronary angiography demonstrated no significant coronary disease. ^{18}F-fluorodeoxyglucose positron emission tomography and ^{67}Ga-scintigraphy showed no abnormal uptake in the LV. CMR showed no high-intensity regions on T2-weighted imaging or late gadolinium enhancement (LGE). An endomyocardial biopsy showed myocardial degeneration and mild interstitial fibrosis, but secondary cardiomyopathy was not observed. Therefore, the patient was diagnosed with idiopathic DCM.

Two and a half years after the first admission, the LV diastolic diameter decreased from 60 to 51 mm, and the LV ejection fraction (LVEF) increased from 10% to 67% after the administration of medication, including beta-blockers (carvedilol, 10 mg/day) and RAAS inhibitors (perindopril, 8 mg/day; spironolactone, 25 mg/day).

Three years after the first admission, the patient stopped taking medication of his own volition against medical advice. His LVEF decreased from 67% to 25%, and the LV diastolic diameter increased from 51 to 72 mm. After the patient discontinued medical treatment, his systolic blood pressure increased from 131 to 162 mmHg. A 12-lead electrocardiogram showed sinus rhythm with a ventricular rate of 99 bpm, which was not significantly different from the value before the discontinuation of therapy (97 bpm). We performed coronary angiography; however, no coronary stenosis was observed. In addition, secondary cardiomyopathy was investigated again by blood and urine examinations, but no significant observations were made. We also performed CMR imaging and an endomyocardial biopsy again. CMR at follow-up demonstrated an appearance of linear LGE in the ventricular septum, which was not observed at the baseline (Fig. 1). An endomyocardial biopsy also demonstrated a significant increase in interstitial fibrosis and the development of replacement fibrosis compared with the baseline evaluation (Fig. 2).

Although medications were re-introduced and the patient's compliance was good, the LV performance gradually worsened, and the B-type natriuretic peptide concentration increased over several years. Because of first-degree atrioventricular block and temporal complete atrioventricular block, beta-blockers could not be up-titrated to the target dose (final dose of carvedilol: 10 mg/day).

The patient was repeatedly admitted to the hospital because of HF (Fig. 3). Although adaptive servo-ventilation was introduced, the effect was poor. At this time point, the patient was considered to be indicated for cardiac resynchronization therapy (CRT) for the further up-titration of beta-blockers. However, a CRT device was not implanted since it was difficult to anticipate whether or not the patient might achieve reverse remodeling with the further up-titration of beta-blockers, causing biventricular pacing to potentially negatively affect his cardiac performance. A ventricular assist device and heart transplantation were repeatedly considered; however, the patient did not want to undergo therapy. The patient ultimately died four years later due to worsening HF.

Discussion

We demonstrated the significant development of cardiac fibrosis and a worsening LV systolic function after the withdrawal of medical treatment in a patient with DCM. The present case indicates the possible pathophysiological mechanism underlying the re-worsening of LV performance after the withdrawal of medical treatments in cases of HF with a reduced LVEF.

The administration of anti-neurohumoral agents, such as beta-blockers and RAAS inhibitors, has a strong impact on improving the prognosis in patients with HF and reduced LVEF by inhibiting LV remodeling (4, 5). Withdrawal of these medications is associated with increased mortality and admission for worsening HF (2, 3). Similar results were observed in a recent prospective randomized trial. It is important to note that improvements in the cardiac function following treatment reflect not a full and sustained recovery but rather remission (6). A previous case report showed increased sensitivity to the chronotropic effects of beta-

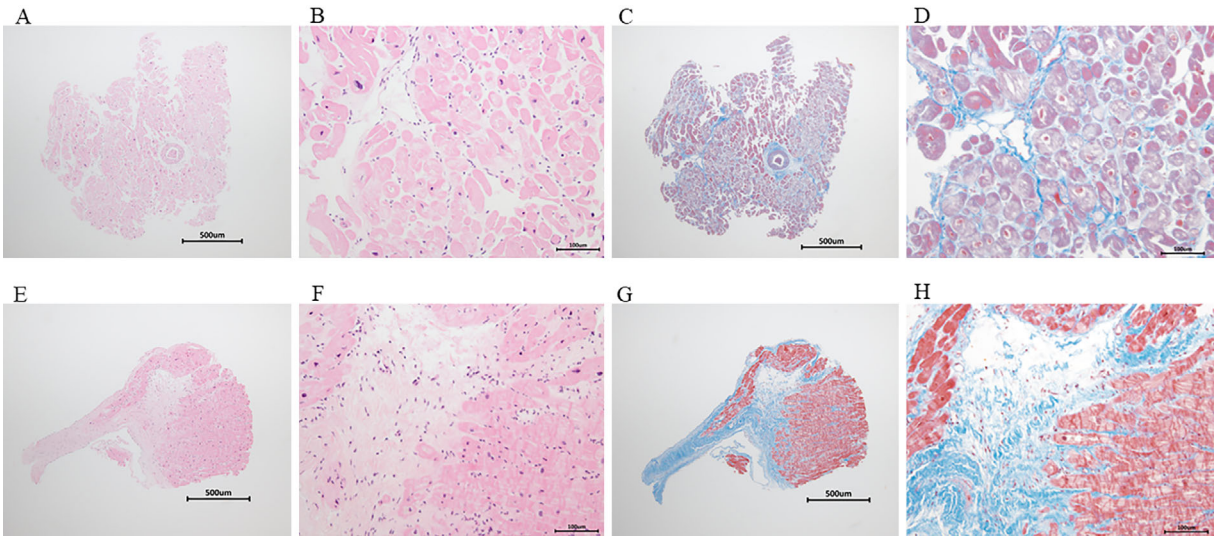

Figure 2. **(A, B) Moderate myocardial hypertrophy and cellular degeneration were observed. No inflammatory cell infiltration was observed [Hematoxylin and Eosin (H&E) staining, magnification: ×40, ×200]. (C, D) Only mild interstitial fibrosis was observed in the left ventricular myocardium at the diagnosis (Masson's trichrome staining, magnification: ×40, ×200). (E, F) A high degree of myocardial hypertrophy and cellular degeneration were observed (H&E staining, magnification: ×40, ×200). (G, H) Increased interstitial fibrosis and replacement fibrosis were observed in the right ventricular myocardium at re-admission (Masson's trichrome staining, magnification: ×40, ×200). The collagenous volume fraction increased from 10% to 20%.**

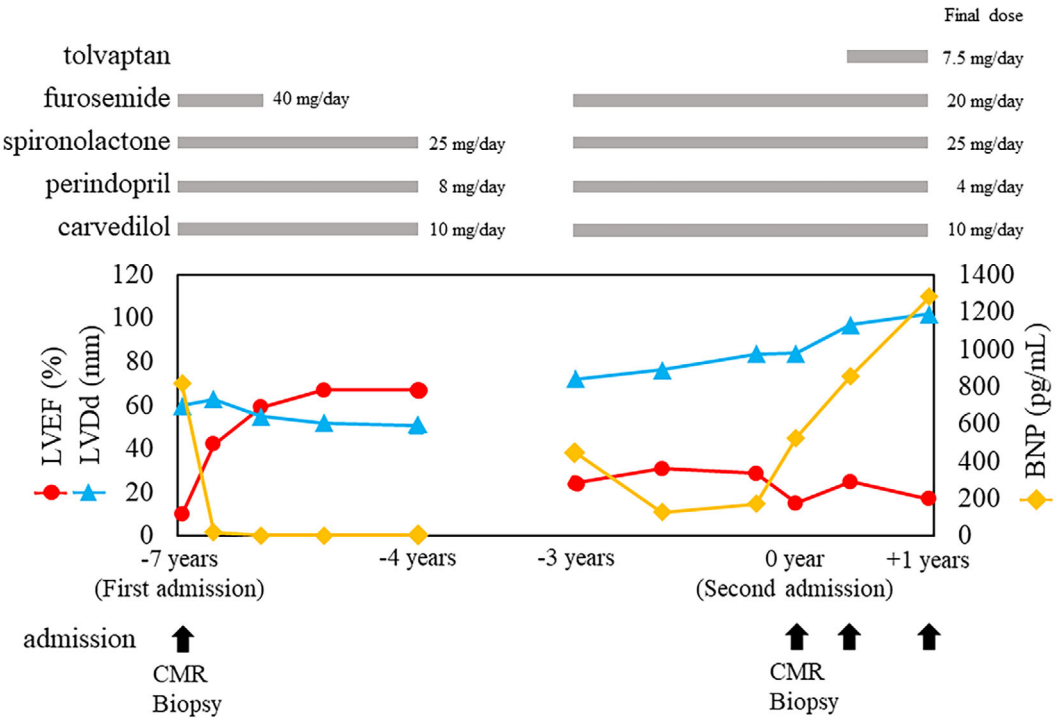

Figure 3. **At the time of the diagnosis, LVEF was 10%, and the LV diastolic dimension was 60 mm. The LVEF recovered after administration of medication, including carvedilol and perindopril. After withdrawal of medication, the LV performance worsened. Despite the re-introduction of medication, the LV performance did not improve. The patient was repeatedly hospitalized due to worsening heart failure (arrows). LVEF: left ventricular ejection fraction, LVDd: left ventricular diastolic dimension, BNP: B-type natriuretic peptide, CMR: cardiac magnetic resonance**

agonists after the withdrawal of propranolol (7). Beta-blockers are reported to decrease myocardial oxygen consumption and improve the efficiency of myocardial metabolisms (8). Therefore, mid-term withdrawal of beta-blockers might be related to irreversible changes in myocardial metabolism. Withdrawal of RAAS inhibitors is also reported to cause LV remodeling, increased blood pressure, and endothelial dysfunction. Increments in neurohumoral activation, including plasma catecholamine concentrations and RAAS activity, play a key role in worsening of the LV performance in patients who have withdrawn from medical treatment (9). In contrast, there have been no reports demonstrating the irreversibility of cardiac performance after the re-introduction of anti-neurohumoral agents. The present case showed no improvement in the LV systolic function despite the re-introduction of medication. The dose of carvedilol could not be increased above 10 mg/day due to the patient's atrioventricular block. Because carvedilol produced dose-related improvements in the LVEF (10), it is recommended to reach the target dose. Not only withdrawing medical treatments but also underdosing of beta-blockers might have been related to the lack of improvement in the LV function in this patient.

Replacement or scarring fibrosis corresponds to the replacement of myocytes by plexiform fibrosis after cell damage or necrosis. Replacement fibrosis is observed as advanced myocardial damage in the later stages of cardiomyopathies. LGE by CMR, which has been reported as representative of replacement fibrosis, is associated with an increased mortality rate and lack of LV recovery after treatment in patients with DCM (11, 12). In the present case, CMR imaging showed a new LGE lesion after withdrawal of medical treatment, which indicated the progression of myocardial damage. Thus, the myocardial damage was considered to have been an inhibiting factor of LV reverse remodeling. As a pathophysiological mechanism, high plasma catecholamine concentrations have been reported to induce myocardial necrosis, leading to progressive myocardial degeneration (4). Withdrawal of medical treatment may have induced advanced myocardial damage through persistently high neurohumoral activation in this patient.

Conclusion

We herein report a case of DCM with irreversible LV dysfunction and the development of cardiac fibrosis after withdrawing medical treatment. The present findings suggest that the response to treatment differs with the progression of myocardial damage, even in the same patient. We emphasize the importance of continued anti-neurohumoral therapy, even after LV reverse remodeling, to prevent progression of myocardial damage.

The authors state that they have no Conflict of Interest (COI).

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