CASE REPORT

Dilated Phase of Hypertrophic Cardiomyopathy Caused by Two Different Sarcomere Mutations, Treated with Surgical Left Ventricular Reconstruction and Cardiac Resynchronization Therapy with a Defibrillator

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Abstract

We herein report the case of a 61-year-old woman with dilated phase of hypertrophic cardiomyopathy (D-HCM) who had been diagnosed with HCM 17 years previously. On admission, her left ventricle (LV) had marked dilation, dyssynchrony with diffuse severe hypokinesis, and ventricular tachycardia. She had two mutations in the cardiac myosin binding protein-C gene, which were suspected to be the causes of the D-HCM. We performed LV reconstruction surgery and cardiac resynchronization therapy with a defibrillator for her drug-resistant severe heart failure. After surgery, her New York Heart Association class dramatically improved, and she has not been re-hospitalized since these treatments.

Key words: dilated phase of hypertrophic cardiomyopathy (D-HCM), severe heart failure, sarcomere gene mutation, surgical ventricular reconstruction (SVR), cardiac resynchronization therapy with a defibrillator (CRT-D)

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Introduction

Hypertrophic cardiomyopathy (HCM) is one of the most common genetic heart diseases. Most HCM patients have normal systolic function. However, a minority of HCM patients develop an irreversible stage of disease characterized by systolic dysfunction and, left ventricular (LV) dilation resembling the morphological and functional features of dilated cardiomyopathy (DCM). This stage of HCM, called dilated phase of HCM (D-HCM), was reported to be associated with poor prognosis (1-3). Although the development and mechanism of progression from HCM to D-HCM remain unknown, it has been reported that mutations in sarcomere protein genes can cause either HCM or D-HCM (4). D-HCM is regarded as an indication for heart transplantation (5, 6). However, other possibly suitable treatment strategies in these patients remain incompletely defined.

We herein report a case of D-HCM who had two different mutations in the cardiac myosin binding protein-C (MYBPC3) gene. The patient had drug-resistant severe heart failure, and we performed surgical ventricular reconstruction (SVR) and cardiac resynchronization therapy with a defibrillator (CRT-D) to successfully treat the patient.

Case Report

A 43-year-old woman went to see a doctor because of an

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Gadolinium-enhanced magnetic resonance imaging (MRI) showed delayed enhancement in the same area of the aneurysmal changes from the mid-septal region to the apex, which corresponded with the echocardiographic findings. Coronary angiography revealed that her coronary arteries were intact, and left ventriculography showed systolic function (from 17.5% to 31.7% of LVEF) and LV synchro-
nization. Most of all, the patient’s subjective symptoms disappeared and her NYHA class improved from III to I. The pathological findings of the myocardial tissue obtained during the operation indicated myocardial fibrosis and a de-
creased vascular lumen due to the thickening of the intimal and medial layers of the intramural microvasculature, which are characteristics of D-HCM.

After SVR and CRT-D implantation, we were able to gradually taper the catecholamine and introduce cardioprotect ive drugs, including ACE-I and β-blockers. Furthermore, the QRS interval narrowed from 140 to 110 msec and the cardiothoracic ratio decreased from 68.4 to 53.3% (Fig. 4). Echocardiography showed a reduction of the LV volume (from 140 to 77.9 mL/m² of ESVI), improvement of systolic function (from 17.5% to 31.7% of LVEF) and LV synchron-
ization. Most of all, the patient’s subjective symptoms disappeared and her NYHA class improved from III to I. The pathological findings of the myocardial tissue obtained during the operation indicated myocardial fibrosis and a de-
creased vascular lumen due to the thickening of the intimal and medial layers of the intramural microvasculature, which are characteristics of D-HCM.

We suspected familial HCM because the patient had family members with a history of cardiac disease. Her parents’ marriage was consanguineous, and her mother had LV hypertrophy and had died a sudden death. After she provided informed consent for genetic testing, we performed a genetic

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**Figure 1.** ECG and chest X-ray findings on admission. (a) ECG showed sinus rhythm with abnormal Q waves and elevation of the ST segment of II III aVF V6, a prolonged QRS interval and left atrial overload. (b) Chest X-rays showed heart enlargement with slight lung congestion. ECG: electrocardiogram, CTR: cardiothoracic ratio.
The patient has not been re-hospitalized for heart failure since the surgical treatment and CRT-D implantation three years ago.

**Discussion**

HCM is a cardiac disorder characterized by LV hypertrophy with predominant involvement of the interventricular septum in the absence of other causes of hypertrophy (9). Although LV systolic function is usually normal or supernormal in patients with HCM, a progression of LV enlargement and systolic dysfunction occurs in about 3.5-4.9% of patients (1, 3). These particular progressive changes in HCM are often designated as dilated phase or end stage of HCM (10-12). The diagnosis of D-HCM is clearly based on the presence of cavity size enlargement and LV systolic dysfunction (13, 14).

Many D-HCM patients have been reported to have ventricular wall scarring, myocardial fibrosis and microvascular dysfunction (15-17). Although the mechanisms underlying
the development and progression of D-HCM are not understood, the patients with D-HCM were reportedly younger at the time of their first evaluation and more often had a family history of HCM or sudden death than the other HCM patients (1). In the present case, the patient’s mother was diagnosed with LV hypertrophy and had died a sudden death. We believe that the patient’s mother had HCM, because the patient has double mutations in the \textit{MYBPC3} gene, which are known as a common genetic cause of familial HCM. Patients with compound heterozygous or double mutations (i.e., patients with two distinct mutations in the same or different sarcomere genes) have been described in 3% to 6% of consecutively screened cohorts, and such mutations have been shown to be associated with an earlier onset and more severe clinical profile compared with single mutation cases (18-21). In our case, the compound heterozygous mutations in the \textit{MYBPC3} gene likely caused the D-HCM. The patient’s two mutations, Arg835Leu and IVS11 +1 g> t,
were discussed more fully by Otsuka et al. in a previous report (8).

The prognosis of patients with D-HCM is very poor because the condition of their heart failure is generally severe (1-3). The overall annual mortality rate of 11% per year is in sharp contrast to the 1% per year for the overall HCM population (22, 23). Harris et al. reported that, in a multicenter cohort of >1,200 HCM patients, about two-thirds of the D-HCM patients died of progressive heart failure, had sudden death events or underwent heart transplantation within three years after the diagnosis of D-HCM (5).

Therefore, they concluded that definitive management strategies may be required, because once D-HCM is in place, it usually follows an aggressive course. However, it is difficult to stop the progression of cardiac dysfunction in the severe state of D-HCM by medical therapy. We were also unable to control our patient’s severe heart failure by medical therapy.

It has been reported that the only definitive surgical treatment option for drug-resistant D-HCM is heart transplantation (5, 6, 24). However, it is difficult to perform this treatment in Japan because of the scarcity of heart donors. In addition, the heart transplantation committee of the Japanese Circulation Society suggests that recipients should be less than 60 years old. In this case, the patient was over sixty, and also did not agree to undergo heart transplantation. Kawaguchi et al. reported that in the current Japanese environment, where heart transplantation is not readily available, SVR has improved the cardiac function in D-HCM patients even when they were over 60 years old (25). In addition, SVR not only improves the ventricular function, but also improves the long-term outcome (26). The overlapping left ventriculoplasty, which is a modified SVR procedure, reduces the LV volume and reshapes the left ventricle in association with improvement of the cardiac efficiency in DCM patients with severe heart failure and ischemic heart disease (27). We therefore decided to perform SVR with an overlapping technique and mitral valve plasty. It was previously demonstrated in a report of SVR that included more than 5,000 patients that, an approximately 40% ESVI decrease was needed for clinical improvement (28). We obtained a 44.4% reduction of ESVI in the present patient, which was considered to be one of the main factors underlying the success of our surgical procedures.

In previous studies, CRT improved exercise tolerance, functional class and quality of life, and decreased hospitalizations due to heart failure in large trials (29). It was reported that CRT might be useful in a subset of D-HCM patients with wide QRS prolongation and LV dyssynchrony (30-32). Sustained or non-sustained ventricular tachycardia is frequently seen in D-HCM patients, and sudden death often occurs in the presence of severe heart failure (33). Several reports have noted that the observation of late gadolinium enhancement on MRI, presumed to represent fibrosis and replacement scarring, was probably largely responsible for the malignant ventricular tachyarrhythmias observed in these patients (34-36). In this case, the patient not only had a broad QRS and LV dyssynchrony but also had late gadolinium enhancement on MRI and non-sustained ventricular tachycardia, even after SVR. Therefore, we performed CRT-D implantation.

To the best of our knowledge, this is the first report of using SVR and CRT-D to treat D-HCM in a patient who had drug-resistant severe heart failure. She has not been rehospitalized for heart failure since the treatment was performed three years ago. This combination of SVR and CRT-D has the potential to become an effective standard treatment for D-HCM patients with drug-resistant severe heart failure.

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

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References
