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【 CASE REPORT 】

Rapidly Progressive Heart Failure in a Female Carrier of Becker Muscular Dystrophy with No Skeletal Muscle Symptoms

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Abstract:
Becker muscular dystrophy (BMD) carriers are at risk to developing cardiac dysfunction. The prevalence of female BMD carriers remains underestimated, and the disease progression varies. We herein report the case of a young female BMD carrier who developed dilated cardiomyopathy (DCM) and heart failure without any skeletal muscle signs. Her cardiac dysfunction progressed over a mere two months, resulting in the need for left ventricular assist device implantation. Her case demonstrates that progressive cardiomyopathy can be the only clinical manifestation in some BMD carriers, suggesting the need for a more aggressive implementation of genetic testing in female DCM patients.

Key words: Becker muscular dystrophy, female carrier, heart failure, left ventricular assist device, cardiomyopathy

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Introduction

Becker muscular dystrophy (BMD) is an X-linked inherited disorder that causes an abnormal production of dystrophin, a large sarcolemmal protein that is present predominantly in the heart and skeletal muscle (1). Because of its hereditary pattern, it is well recognized that male BMD patients often develop dilated cardiomyopathy (DCM)-like cardiac dysfunction with varied skeletal muscle degeneration (2). Approximately 70% of BMD patients develop DCM in the third decade of life or later, and heart failure is a prognostic determinant in this disease population (3).

However, relatively little attention has been paid to cardiac involvement in female BMD carriers, in whom the disease progresses in a similar manner to that in men. This lack of attention is reflected by the lower rate of genetic screening in Japan than in other countries (4). In addition, the cardiac involvement in female BMD carriers is less symptomatic than male BMD patients (5), and the disease progression has not been well documented.

We herein report the case of a young female BMD carrier with no skeletal muscle signs who suffered from DCM-like cardiac dysfunction and overt heart failure. Her cardiac impairment progressed dramatically over a period of just two months, resulting in the need for implantation of a left ventricular assist device (LVAD). Her case demonstrates that, in some BMD carriers, progressive cardiomyopathy is the only clinical manifestation, suggesting the need for a more aggressive implementation of genetic testing in female DCM patients.

Case Report

A 29-year-old Japanese woman was referred to our hospital with a continuous inotropic infusion. She had experienced palpitations, dyspnea, and dizziness for the prior three weeks but had no remarkable medical history. In addition,

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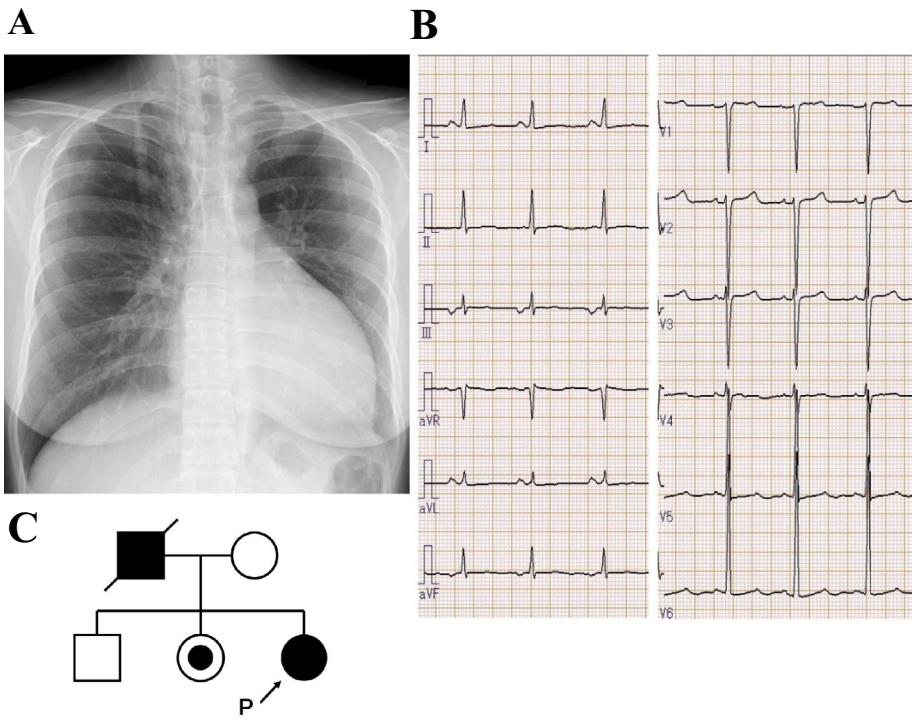

Figure 1. **(A) Chest X-ray showing an increased cardiothoracic ratio (66%) without pulmonary congestion or pleural effusion. (B) An electrocardiogram indicating ectopic atrial rhythm and a high amplitude of the R wave with a flat T wave in I, II, III, aVL, and aVF leads. (C) Pedigree of the family. Squares represent men, and circles represent women. The arrow indicates the proband.**

no abnormalities had been noted on chest X-ray or an electrocardiogram at a periodic medical checkup in 2011. His father had been diagnosed with DCM and died due to worsening heart failure at 43 years of age. He was also suspected of having had muscular dystrophy in his childhood but had not been examined in detail; the diagnosis remained ambiguous. Her mother, an older brother, and an older sister had never been diagnosed with heart disease or muscular dystrophy (Fig. 1C), but her sister had a high possibility of being a heterozygous carrier of BMD.

On admission, our patient's blood pressure was 97/64 mmHg, and her heart rate was 90 beats per minute with a regular rhythm. A third cardiac sound was present on auscultation. The limbs' muscle strength was normal, and no atrophy or hypertrophy was detected in the thighs or calves. A neurologist concluded that the patient had normal deep tendon reflexes with no sensory disturbance or abnormal reflexes.

Chest X-ray indicated an increased cardiothoracic ratio (66%) without pulmonary congestion or pleural effusion (Fig. 1A). The electrocardiogram showed an ectopic atrial rhythm and a high voltage in precordial leads with a flat T wave in I, II, III, aVL, and aVF leads (Fig. 1B). The serum levels of muscular enzymes were within the normal range; creatinine kinase (CK) was 60 U/L, and the B-type natriuretic peptide (BNP) concentration was elevated to 229 pg/mL. As shown in Fig. 2, echocardiography revealed a markedly enlarged left ventricle (LV) (LV end-diastolic diameter, 73 mm) and severe diffuse LV hypokinesis with an ejection fraction (EF) of 15%. The LV wall thickness was within the normal range (6 mm). A right ventricular biopsy revealed a hypertrophied myocardium and interstitial fibrosis, but there was no evidence of myocardial inflammation, abnormal deposition, or granuloma formation (Fig. 3). Furthermore, coronary angiography showed no stenosis in the coronary arteries.

Since the patient's father had a possible history of muscular dystrophy, we evaluated the patient's skeletal muscle mass by whole-body magnetic resonance imaging (MRI) and computed tomography (CT), which revealed no evidence of muscle atrophy (Fig. 4). Given the patient's history, presentation and laboratory data, we diagnosed her with DCM. In a hemodynamic assessment with right heart catheterization (RHC), the patient's pulmonary capillary wedge pressure (PCWP) was 11 mmHg, the right atrium pressure (RA) was 2 mmHg, and the cardiac index (CI) was 2.65 L/min/m^2, indicating Forrester subset I. We therefore gradually tapered the patient's continuous dobutamine infusion and stopped it on the 21st day of hospitalization.

We then introduced carvedilol to the patient starting at 0.625 mg and titrated the dose to 1.25 mg. However, signs of low cardiac output syndrome, such as malaise and cold extremities, became evident, and the patient showed both a low CI (1.68 L/min/m^2) and high PCWP (29 mmHg) on a second RHC.

Although the drug treatment's efficacy was not fully

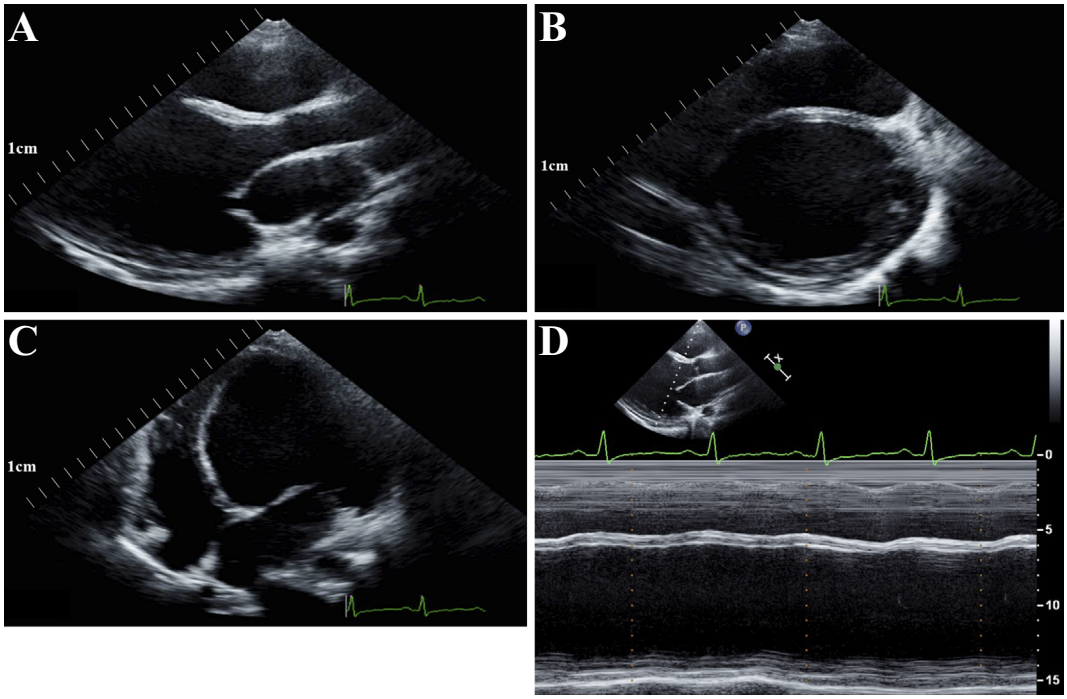

Figure 2. **Echocardiographic 2D images of the (A) parasternal long-axis view, (B) parasternal short-axis view, and (C) apical four-chamber view showing the marked enlargement of the patient's left ventricle (LV) with normal LV wall thickness. (D) An M-mode echocardiographic image revealing diffuse severe hypokinesis in LV wall motion.**

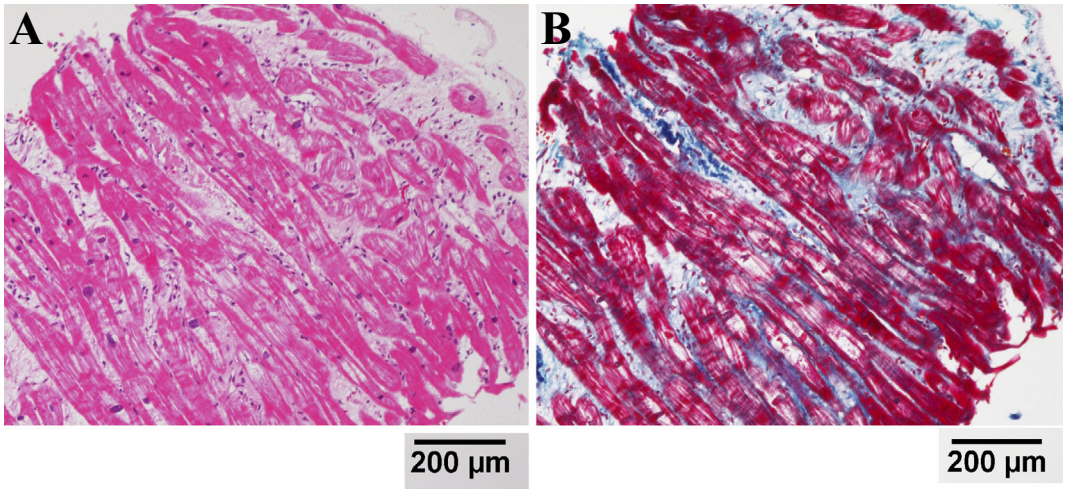

Figure 3. **Histologic findings of an endomyocardial biopsy specimen taken from the right ventricle. (A) Hematoxylin and Eosin staining indicating cardiomyocyte hypertrophy. (B) Marked myocardial interstitial fibrosis assessed by Masson's trichrome staining.**

evaluated due to the patient's early disease progression, her cardiac dysfunction was likely irreversible based on her family history of DCM, so we decided to implant an LVAD. Two weeks after the LVAD implantation, genetic testing by multiplex ligation-dependent probe amplification (MLPA) detected a deletion of exons 45-48 in the patient's dystrophin gene. Immunostaining of dystrophin protein in myocardial tissues obtained during the surgery revealed patchy and discontinuous patterns with a low staining intensity, which was compatible with BMD (Fig. 5). At three months after the surgery, the patient is hemodynamically stable and waiting for a heart transplant under LVAD support.

Discussion

We encountered a young female BMD carrier with no skeletal muscle abnormalities (such as muscle atrophy assessed by MRI or CK leakage) who developed DCM-like cardiomyopathy. This case of BMD-related cardiac dysfunction was refractory to standard heart failure drugs and was soon dependent on inotropic agents, leading to the requirement of LVAD support in just two months.

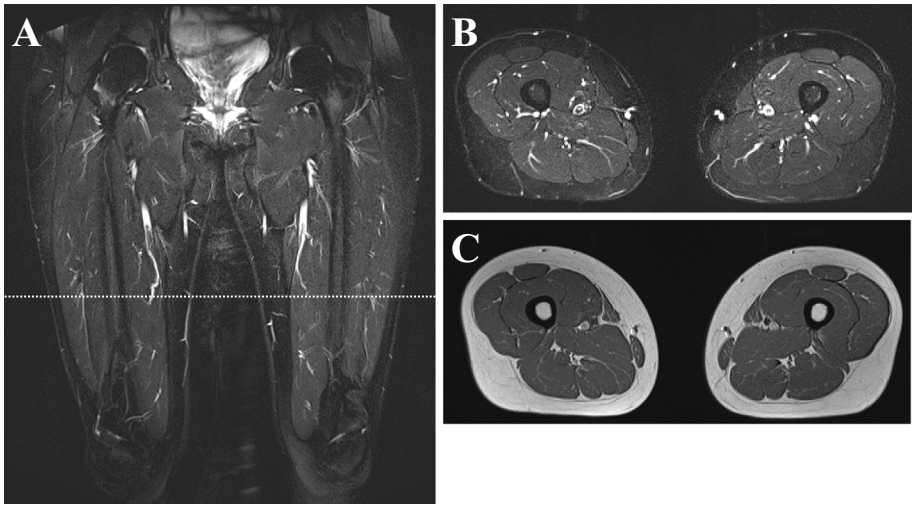

Figure 4. **Pelvic and thigh muscles on MRI. (A) Coronal short tau inversion recovery (STIR) images, (B) axial STIR, and (C) axial T1-weighted imaging (T1WI) showing no evidence of atrophy, fatty infiltration, or edema in the skeletal muscle.**

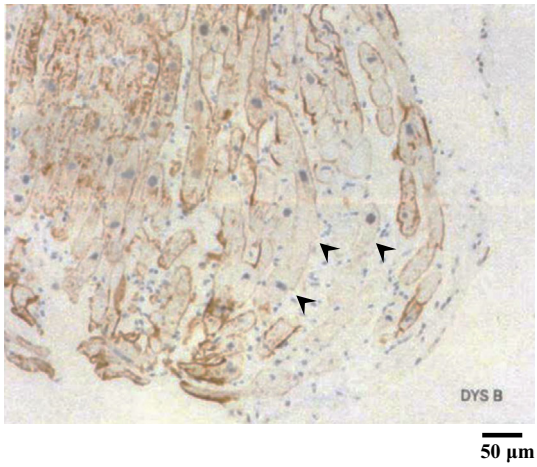

Figure 5. **The immunostaining of dystrophin protein in myocardial tissues collected during the left ventricular assist device (LVAD) implantation, revealing a patchy or discontinuous staining pattern with low staining intensity (black arrowheads).**

A recent report from Japan's national registry for hereditary muscular disorders identified 130 female dystrophinopathy patients with some sort of genetic mutation (4). However, the genetic screening rate was estimated to be 6-11%, which was far lower than the 67-95% rate in European countries. This low genetic testing rate suggests that the risk of cardiac dysfunction in female carriers has not been fully recognized in Japan. The prevalence of DCM-like cardiac dysfunction in BMD carriers ranges from 7% to 75%, and it varies depending on the definition of DCM (6). Florian et al. recently reported that 25% of BMD carriers had a significant LV dysfunction or the presence of myocardial fibrosis on cardiac MRI by a mean age of 44 years (5). Although subclinical myocardial injury seems to progress slowly in BMD patients over the years due to relatively preserved dystrophin protein (7), there are a few reports of male BMD patients showing the early onset of severe DCM requiring mechanical support (8). To our knowledge, such a clinical course in a female BMD carrier has yet to be reported. We speculate that one potential inducing factor for cardiac dysfunction may be an excessive exercise load, as our patient continued to exercise regularly without limitation for three months before she was hospitalized due to worsening heart failure.

Of note, this cardiac involvement is not always concomitant with skeletal muscle impairment, as some BMD carriers with DCM are reported to have no evidence of muscle weakness (9). Indeed, the case of our present patient with BMD-related DCM had no findings of muscle weakness and/or atrophy in terms of symptoms, muscle volume on MRI, or CPK leakage. In female carriers of BMD, it is often difficult to rule out BMD based solely on the phenotype. In our patient's case, genetic testing was likely to be the only approach to able identify the cardiomyopathy caused by BMD, and the major motivation for the genetic testing was her father's medical history of suspected neuromuscular disorder. Therefore, it is still essential to obtain a detailed family history in order to decide whether or not to perform genetic testing.

The causative link between dystrophin gene mutations and skeletal muscle or the cardiac phenotype in BMD remains inconclusive (9-11). The present case showed the in-frame deletion of exons 45-48, which corresponds to the distal rod domain of dystrophin protein. Kasper et al. reported that the mutation of the region of exons 45-49 is associated with a risk of an earlier onset of DCM than that of a longer region including exons 50-51 that encodes a hinge III region (9). In contrast, the mutation of exons 50-51, which disrupts a hinge III region, has been implicated in the pathogenesis of skeletal muscle impairment (11). As such, the current case showing preservation of the hinge may be attributed to the lack of skeletal muscle symptoms.

Although genotype-phenotype correlations for specific mutations in dystrophin have been proposed in male BMD patients, these are less apparent in female carriers due to the mosaic mutant cells based on Lyonization, wherein one of the X chromosomes in some or all cells is randomly inactivated (12). Despite the present limited ability to predict the phenotype, more frequent genetic screening should be carried out in female DCM patients in Japan in order to rule out cardiac lesions associated with dystrophinopathy carriers.

Conclusion

In women manifesting an early onset of severe progressive DCM, the possibility of their being dystrophinopathy carriers should be considered even when there is a lack of skeletal muscle symptoms. The identification of BMD carriers by genetic testing and subsequent cardiac surveillance would enable the earlier introduction of cardioprotective medications and improve the prognosis.

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

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