A Case of Refractory Heart Failure in Becker Muscular Dystrophy Improved With Corticosteroid Therapy

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Summary
The patient was a 26 year-old man who was referred to our hospital in June 2011 because of severe heart failure. At age 24 years, he was found to have Becker muscular dystrophy. He received enalapril for cardiac dysfunction; however, he had worsening heart failure and was thus referred to our hospital. Echocardiography showed enlargement of the left ventricle, with a diastolic dimension of 77 mm and ejection fraction of 19%. His condition improved temporarily after an infusion of dobutamine and milrinone. He was then administered amiodarone for ventricular tachycardia; however, he subsequently developed hemoptysis. Amiodarone was discontinued and corticosteroid pulse therapy was administered followed by oral prednisolone (PSL). His creatinine phosphokinase (CPK) level and cardiomegaly improved after the corticosteroid therapy. The PSL dose was reduced gradually, bisoprolol was introduced, and the catecholamine infusion was tapered. A cardiac resynchronization device was implanted; however, the patient’s condition gradually worsened, which necessitated dobutamine infusion for heart failure. We readministered 30 mg PSL, which decreased the CPK level and improved the cardiomegaly. The dobutamine infusion was discontinued, and the patient was discharged. He was given 7.5 mg PSL as an outpatient, and he returned to normal life without exacerbation of the heart failure. There are similar reports showing that corticosteroids are effective for skeletal muscle improvement in Duchenne muscular dystrophy; however, their effectiveness for heart failure has been rarely reported. We experienced a case of Becker muscular dystrophy in which corticosteroid therapy was effective for refractory heart failure. (Int Heart J 2016; 57: 640-644)

Key words: Cardiomyopathy, Prednisolone (PSL), Creatinine phosphokinase (CPK)

Muscular dystrophy is a hereditary disease that causes degeneration and necrosis of the muscle fibers, and results in progressive muscle weakness. Myocardial disorder is known to be a complication. Muscular dystrophy is classified into several types according to etiology and clinical manifestation. The etiology of Duchenne muscular dystrophy (DMD) or Becker muscular dystrophy (BMD) is the abnormal production of dystrophin. BMD results from a partial defect of dystrophin, whereas DMD is caused by a complete loss of the protein. Heart failure may be one of the main clinical manifestations of DMD and BMD, and sometimes appears to be the only initial manifestation without skeletal muscle weakness in BMD.

The combination of an angiotensin-converting enzyme (ACE) inhibitor and a β-blocker is known to be effective for cardiac dysfunction in patients with DMD or BMD. However, ACE inhibitors and β-blockers would not influence the muscle degeneration caused by DMD or BMD of an inherited etiology.

Corticosteroid therapy for DMD has shown potential for improving the symptoms mainly by slowing the rate of muscle weakness progression, or stabilizing muscle strength and function. Recently, it was reported that prophylactic steroid therapy for DMD may be associated with a remarkable reduction in all-cause mortality and cardiovascular outcomes. However, little is known about the effect of corticosteroids in patients with BMD. We report here a case in which corticosteroid therapy was effective for improving refractory heart failure in a patient with BMD.

Case Report
The patient was a 26 year-old man who was referred to our hospital in June 2011 because of severe decompensated heart failure. He had no history of symptoms of heart failure in childhood; however, he was aware of having reduced exercise ability from the age of 12 years. He recognized having muscle weakness in his lower limbs from about age 16 years. When approximately 19 years old, he needed to assist his knee with a hand when ascending stairs. Later on, he needed to use his arms as support when standing up.

The patient experienced progressive muscle weakness in the proximal limbs at age 24 years, and visited a hospital for a
neurological examination. His laboratory test results showed a high creatinine phosphokinase (CPK) level (6678 IU/L), and partial loss of the immunohistochemical stain with anti-dystrophin antibody was observed in a muscle biopsy, which led to the diagnosis of BMD. At the time of the first medical evaluation, an echocardiogram revealed dilatation of the left ventricle (LV) and diffuse hypokinesis, with the following measurements: LV diastolic dimension (Dd) of 71 mm, systolic dimension (Ds) of 61 mm, and an ejection fraction (EF) of 28%. Enalapril 5 mg was started in May 2009.

The patient complained of shortness of breath, abdominal distention, and coughing during work hours in May 2011 at age 26 years. He was hospitalized for heart failure, and referred to our hospital in June 2011 because his heart failure had not improved despite the administration of furosemide 10 mg and carvedilol 15 mg.

His medical history included both liver damage and arrhythmia diagnosed in infancy. He does not drink alcohol or smoke cigarettes. He had worked as a computer programmer since graduating from college at age 22 years. His family history indicated that his father died suddenly at age 46 years, and that his younger brother died of fulminant hepatitis at age 19.

Physical examination showed a height of 161 cm, body weight of 74 kg, blood pressure of 110/60 mmHg, heart rate of 96 beats/minute regularly, respiratory rate of 24 times/minute, body temperature of 37.0°C, and SpO2 of 97% under 2 L/minute oxygen. Jugular vein dilatation in the neck was present. A chest examination revealed audible wheezes and crackles in both lungs. Cardiac auscultation revealed that the third and fourth heart sounds had a gallop rhythm. His abdomen was distended. Generalized edema and ascites indicated anasarca. Fourth heart sounds had a gallop rhythm. His abdomen was markedly distended and diffuse hypokinesis, with the following measurements: LV diastolic dimension (Dd) of 71 mm, systolic dimension (Ds) of 61 mm, and an ejection fraction (EF) of 28%. Enalapril 5 mg was started in May 2009.

The laboratory tests showed the following results: white blood cell count, 6700/μL with normal segment (neutrophils 63.4%, lymphocytes 22.1%, monocytes 9.8%, eosinophils 2.1%, and basophils 0.6%); hemoglobin, 15.1 g/dL; and platelet count, 21.0 x 10^11/L. Biochemical examination showed a sodium concentration of 135 mEq/L, potassium of 4.2 mEq/L, chloride of 100 mEq/L, blood urea nitrogen of 21 mg/dL, and creatinine of 0.5 mg/dL. His total bilirubin level was increased to 2.7 mg/dL, and liver enzyme levels were elevated, as follows: aspartate aminotransferase, 110 IU/L; alanine aminotransferase, 222 IU/L; alkaline phosphatase, 173 IU/L; and lactate dehydrogenase, 460 IU/L. CPK level was markedly elevated to 2697 IU/L without isoenzyme level elevation of CPK-MB. His B-type natriuretic peptide (BNP) level was markedly elevated to 1393.5 pg/mL. An antinuclear antibody test was negative.

Electrocardiography showed a normal sinus rhythm of 90 beats/minute; QRS width of 105 ms; negative T wave in the III, aVF, V1-2, and V6 leads; ST depression in the II, III, and aVF leads; and QS pattern in the I and aVL leads.

Remarkable cardiac enlargement with pulmonary congestion and pleural effusion were observed on chest radiography. Echocardiography revealed an LVEF of 19% with marked dilatation and diffuse hypokinesis, moderate mitral regurgitation of grade 2 of 4, and LV dyssynchrony with septal flash and apical shuffle.

Clinical course: We provided continuous infusion of dobutamine, milrinone, and carperitide to the patient, and we administered oral carvedilol 5 mg and enalapril 2.5 mg. The pulmonary congestion gradually improved. Administration of amiodarone was started on the third day of hospitalization because of nonsustained ventricular tachycardia. Enalapril was changed to 2.5 mg midadipril because of liver enzyme elevation. The patient had fever, hemoptusum, and hypoxemia, and pulmonary infiltration was detected on a chest radiograph on the 20th day of hospitalization. Alveolar hemorrhage was detected on a chest computed tomography scan, which was probably an adverse effect of amiodarone. Therefore, amiodarone was discontinued and intravenous infusion of methylprednisolone was started, at 1 g/day for 3 days followed by oral prednisolone (PSL) at 1 mg/kg body weight. The fever and hemoptusum improved; the elevated CPK level decreased; the pulmonary congestion was also improved; and his body weight was reduced to 53 kg. The intravenous infusions of dobutamine and the other medications were stopped on the 30th day of illness. The β-blocker was changed from 5 mg carvedilol to 1.25 mg bisoprolol because of frequent ventricular tachycardia. The PSL dose could be gradually tapered without the recurrence of alveolar bleeding.

Cardiac catheterization was performed on the 47th day of illness, which showed right atrial pressure of 8 mmHg, pulmonary capillary wedge pressure of 29 mmHg, mean pulmonary artery pressure of 34 mmHg, and cardiac output and cardiac index of 5.9 L/minute, 3.7 L/minute·m², respectively. Left ventriculography showed a considerably reduced LVEF of 17% and elevated LV end-diastolic pressure of 33 mmHg. An endomyocardial biopsy was performed, which revealed slight interstitial fibrosis, enlarged nuclei, interstitial edema, and little lymphocyte infiltration between the myocardial fibers. Granuloma, giant cells, and eosinophils were not observed, and CD8-positive T lymphocytes were detected by immunohistochemistry staining. There were no findings of a specific myocardial disease.

The PSL dose was gradually tapered after improvement of the alveolar hemorrhage. Thereafter, ventricular tachycardia frequently occurred despite the increase of bisoprolol dose to 1.875 mg, and dyssynchrony was detected on echocardiography despite a narrow QRS width of 105 ms in the electrocardiogram. A cardiac resynchronization therapy defibrillator (CRT-D) was implanted on the 59th day of hospitalization. However, shortness of breath appeared again, and the cardiothoracic ratio (CTR) on the chest roentgenogram showed a narrow QRS width of 105 ms in the electrocardiogram. A cardiac resynchronization therapy defibrillator (CRT-D) was implanted on the 59th day of hospitalization. However, shortness of breath appeared again, and the cardiothoracic ratio (CTR) was found to be deteriorated on a chest radiograph (Figure 1). The patient seemed to be a nonresponder to cardiac resynchronization therapy (CRT). Dobutamine infusion was required for the worsening heart failure on the 113th day of illness (Figure 2).

During the corticosteroid therapy for alveolar hemorrhage, the patient’s heart failure improved with a reduction of the CTR on the chest roentgenogram and normalization of the serum CPK level. There was a possibility that the improvement in heart failure was due to the effect of the corticosteroid. Therefore, PSL administration was restarted from the 148th day of illness, at doses of 30 mg for 7 days, 15 mg for 7 days, and 7.5 mg for 7 days. Thereafter, the cardiomegaly improved and the CPK level decreased. The dobutamine infusion, which had been difficult to stop for 43 days, could be discontinued at 8 days after the PSL administration. The patient was discharged from the hospital on foot thereafter. He continued tak-
Figure 1. Clinical course of the patient, showing the results of chest radiography, cardiothoracic ratio (CTR), creatinine phosphokinase (CPK) level, and oral administration and infusion of medicine, from admission to after cardiac resynchronization therapy with an implantable cardioverter defibrillator. After prednisolone (PSL) administration, the CPK level and cardiomegaly improved temporarily.

Figure 2. Clinical course of the patient, showing the results of chest radiography, cardiothoracic ratio (CTR), and B-type natriuretic peptide (BNP) level after the administration of prednisolone (PSL). Medicines other than PSL were unchanged for this period. The CTR and BNP levels reduced simultaneously according to PSL administration.
ing PSL as an outpatient, and returned to normal daily life without the exacerbation of heart failure (Figure 2).

After 1 year, echocardiography showed that the LVEF was slightly improved from 20% to 24%. Two years after hospital discharge, the patient regularly visited the outpatient department of our hospital without rehospitalization for heart failure exacerbation. He maintained a stable cardiac condition with a 7.5 mg maintenance dose of PSL, with a BNP level of about 130–200 pg/mL.

**DISCUSSION**

Becker muscular dystrophy (BMD) is an allelic variant of Duchenne muscular dystrophy (DMD) and occurs at one-tenth the frequency of DMD. Cardiac involvement is a frequent clinical finding in BMD, and may progress without symptoms and develop into dilated cardiomyopathy. Patients with BMD have a milder course than those with DMD, and develop difficulties in climbing stairs as well as cardiac abnormalities during the third decade of life. Our patient had a typical clinical course, and the diagnosis of BMD was confirmed with muscle biopsy showing a partial deficiency of dystrophin. At the time of the diagnosis at age 24 years, the patient’s cardiac involvement had already progressed and his cardiac function had been severely reduced. Although an ACE inhibitor was introduced for cardiac involvement, acute decompensated heart failure occurred 2 years later.

The onset and course of cardiac involvement may be largely variable even in monozygotic triplets. The manifestations of BMD may range from peripheral myopathy to severe congestive heart failure. It has been suggested that the clinical manifestations of cardiac involvement may be affected by acquired or environmental factors. The mechanical stress induced by intracardiac pressure or volume overload may be harmful for dystrophin-deficient myocardial cells. Myocardial damage may progress in patients with mild BMD with normal skeletal muscle strength, when the ability to perform vigorous physical exercise is still present. No specific medical therapy has been shown to reverse the cardiomyopathy related to muscular dystrophy. Although advanced studies have recently reported that a micro ribonucleic acid (microRNA), which was associated with cardiac hypertrophy and heart failure, has been targeting the dystrophin protein, and that DMD-specific cardiomyocytes were created from iPS cells of DMD patients, a specific cardiac treatment for muscular dystrophy has yet to be found. However, it was reported that the combination of an ACE inhibitor and a β-blocker is effective for LV enlargement and the symptoms and signs of heart failure in patients with DMD. In BMD, the effectiveness of the combination of an ACE inhibitor and a β-blocker was also reported in one case. The authors suggested that a trial with an ACE inhibitor and a β-blocker should be indicated in patients with BMD-related cardiomyopathy before they are considered for a heart transplant. Our patient received a combination of a β-blocker and an ACE inhibitor; however, his heart failure worsened. At the diagnosis of BMD at age 24 years, a marked LV dilatation had already appeared and LV remodeling had progressed. An ACE inhibitor had been started but a β-blocker, which is known to be effective for reverse LV remodeling, was not introduced initially.

This may be the reason for the lack of obvious efficacy of the β-blocker for heart failure at that time.

CRT could improve the symptoms of heart failure in patients with reduced EF and dyssynchrony in addition to optimal medical treatment. However, it was difficult to assess the symptoms in patients with muscular dystrophy with limited exercise capacity due to muscle weakness. Moreover, chest distortion makes the implantation procedure difficult, and it is important to take into account the septic risk in patients with a tracheostomy. Although the indication for CRT might be considered in selected BMD patients with heart failure, patients with neuromuscular disorders have a risk for respiratory insufficiency because of diaphragm involvement and chest deformities. Moreover, device implantation is problematic because of possible and serious mechanical and infective complications. Stöllberger and Finsterer reported the case of a 40-year-old BMD patient with severe heart failure (LVEF, 25%) who benefited from CRT. However, no improvement in the LVEF was found at 3 months after the CRT therapy. The patient died at 16 weeks after the implantation. In our patient, CRT was not only ineffective but his heart failure also worsened after the implantation of the defibrillator, although the preoperative echocardiography showed LV dyssynchrony despite a relatively narrow QRS width. CRT could correct the electrical disturbances of LV dyssynchrony; however, it could not improve myocardial disorders such as muscular dystrophy without cardiac conduction abnormalities.

Although it is unknown whether patients with BMD can safely undergo cardiac transplantation, the survival of muscular dystrophy patients was similar to that of controls after cardiac transplantation. This suggests that the clinical outcomes after cardiac transplantation in selected patients with muscular dystrophy are similar to those seen in age-matched patients with nonischemic cardiomyopathy. Finsterer, et al reported the case of a 33-year-old man with BMD who needed a heart transplantation, 6 years before apparent skeletal muscle involvement. When the present patient experiences worsening heart failure even with optimal medical therapy, it would be advisable to consider registration for cardiac transplantation.

Chronic steroid therapy has become the standard of care for DMD. Prolonged ambulation, reduced scoliosis, and improved pulmonary function have been attributed to steroid use. However, there are limited published studies documenting the impact of steroid treatment on cardiac dysfunction. Steroid therapy is known to delay the progression of skeletal muscle disorder in DMD, and may reduce the progression of dilated cardiomyopathy. Silversides, et al also reported that steroid therapy was associated with the preservation of cardiac function in patients with DMD, although they considered that it is directly related to the improvement of pulmonary and skeletal muscle strength.

Although it is universally agreed that steroids prolong ambulation in DMD patients, the current study failed to identify a cardioprotective effect of steroids by using magnetic resonance imaging. However, in their retrospective investigation, Markham, et al demonstrated that no obvious ventricular dysfunction estimated by echocardiography was observed in 92% of the DMD patients treated with steroids for approximately 50 months versus in 53% of the untreated cases. The same authors demonstrated that steroid treatment might delay or prevent the development of ventricular dysfunction. Recently, it
was reported that prophylactic steroid therapy for DMD may be associated with a remarkable reduction in all-cause mortality and cardiovascular outcomes. The mechanisms by which corticosteroids may slow the cardiomyopathic process are not yet fully understood. Myocardial changes, as a result of the lack of dystrophy, consist of cell membrane degradation, interstitial inflammation, edema, fatty replacement, and fibrosis. Moxley, et al reviewed the mechanisms of action of the corticosteroid hormone in the mouse model of DMD. They showed that corticosteroids reduce muscle fiber necrosis, apoptosis, and cellular infiltration. Arakata, et al reported that infiltration of macrophages and cytotoxic T cells appeared in the necrotized cardiac muscle of patients with DMD. Their results indicated that humoral and cell-mediated immune reactions may participate in the pathological process of DMD. Moriiuchi, et al reported that the autopsy findings of 30 muscular dystrophy patients showed focal degeneration of fibrotic cardiomyocytes with CD68-positive cells in capillary hyperplasia and granulation tissue of CD45-positive cells. In 2 reported cases of DMD, cardiac pathological findings revealed degenerated cardiac muscle cells, infiltration of inflammatory cells, and swelling and increased chromatin in the nucleus of cardiomyocytes in the epicardium.

Jones, et al reported the case of a 22-year-old man in whom myocarditis was diagnosed on the basis of myocardial biopsy at age 17 years; this patient thereafter underwent heart transplantation for postmyocarditis cardiomyopathy. However, an increase in serum CPK (1298 U/L) occurred in the 18th month after cardiac transplantation. Skeletal muscle biopsy and genetic testing led to a diagnosis of BMD. Myocardial inflammation and fibrosis similar to myocarditis initially appeared even in inherited diseases, such as BMD. An inflammatory process may contribute to muscle degeneration and the progression of disease.

Our patient seemed to achieve a functional improvement of heart failure by using corticosteroids, although anatomical and structural changes were not obviously seen on the echocardiogram or roentgenogram. Corticosteroid therapy may not only prevent the degeneration of cardiomyocytes, but may also improve the functional cardiac status in a patient with refractory heart failure due to BMD.

Conclusion: We experienced a case of heart failure due to secondary cardiomyopathy of BMD for which a steroid hormone seems to be effective. A corticosteroid hormone may be useful for patients with BMD, in combination with an ACE inhibitor and a β-blocker.

References