Cardiology in the Young

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Emery-Dreifuss muscular dystrophy with dilated cardiomyopathy preceding skeletal muscle symptoms

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Brief Report

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Abstract

Emery-Dreifuss muscular dystrophy is a slowly progressive skeletal muscle and joint disorder associated with cardiac complications. Dilated cardiomyopathy was the initial manifestation of Emery-Dreifuss muscular dystrophy in an 8-year-old girl. Despite normal muscle and myocardial biopsies, genetic testing revealed *LMNA* mutations. As Emery-Dreifuss muscular dystrophy is associated with minimal skeletal muscle weakness, cardiac complications can facilitate its diagnosis.

Emery-Dreifuss muscular dystrophy is a rare cause of dilated cardiomyopathy in children (approximately 0.2% of cases).[1] It is a neuromuscular disease with three main features: musculoskeletal weakness and wasting, joint contractures, and cardiac disease. Muscle weakness can appear in early childhood (age <15 years); however, muscle wasting progresses slowly. Cardiac involvement usually becomes evident in the second or third decade of life and predominantly manifests as atrial cardiomyopathy (conduction disturbance, atrial standstill, and atrial arrhythmia); furthermore, it is occasionally accompanied by left ventricular systolic dysfunction.[2] We report the case of an 8-year-old girl with Emery-Dreifuss muscular dystrophy, who was diagnosed with acute heart failure without skeletal muscle symptoms.

Case

An 8-year-old girl with a normal family history, normal psychomotor development, and no significant past medical history was referred to our hospital because of nausea, cough, and generalised body swelling. At presentation, her characteristics were as follows: temperature, 36.4°C; pulse rate, 110 beats/min; respiratory rate, 30 cycles/min; and blood pressure, 90/70 mmHg. She had a gallop rhythm, a grade 3/6 parasystolic murmur at the cardiac apex, bibasal crepitation, and hepatomegaly. Chest radiography showed cardiac enlargement (cardiothoracic ratio, 60%). Echocardiography showed reduced left ventricular systolic function (left ventricular ejection, 25%) with marked ventricular dilation and severe mitral regurgitation. Her laboratory data showed that the troponin T and brain natriuretic peptide levels were 104.4 (upper limit: 26.2 pg/mL) and 2431 pg/mL (upper limit: 18.4 pg/mL), respectively. Cardiac catheterisation on hospitalisation day 9 showed no abnormalities in coronary artery blood flow, and myocardial biopsy showed no evidence of fibrosis other than a mild infiltration by inflammatory cells, which was diagnosed as acute myocarditis. She initiated catecholamine administration for heart failure, but her cardiac contractility and mitral regurgitation were not improved; thus, she was referred to our hospital.

On admission, the patient was stable. Her height was 123 cm (-0.8 SD) and her weight was 17.2 kg (-3.3 SD). A chest radiograph showed mild cardiac enlargement, and a 12-lead electrocardiogram showed reduced amplitude of the P wave and mildly prolonged PR interval, but not atrial or ventricular tachycardia (Fig 1). Holter electrocardiogram showed no arrhythmias. Laboratory data showed mildly increased creatinine kinase (338 U/L) and creatinine kinase-MB levels (26 U/L). Echocardiography showed diffusely decreased cardiac contractility (left ventricular ejection fraction, 40%) and severe mitral regurgitation. Despite heart failure management, cardiac function was not improved; therefore, she underwent mitral valvuloplasty for functional mitral regurgitation. The patient's condition initially improved and the brain natriuretic peptide levels decreased to 375 pg/mL, but later deteriorated, and she was repeatedly admitted and discharged. Because of the lack of improvement in the course of acute myocarditis, myocardial biopsy was repeated, but there was no fibrosis of the myocardium. Cardiac MRI findings showed delayed enhancement in the ventricular septum to the posterior inferior wall.

Neurological examination due to prolonged hyperCKemia revealed posterior neck joint contracture and proximal muscle weakness (deltoid manual muscle test; MMT 4-/4-, biceps MMT 4/4). We suspected that the patient may have had a form of skeletal muscle disease, but the dystrophin multiplex-ligation-dependent probe amplification test results and the

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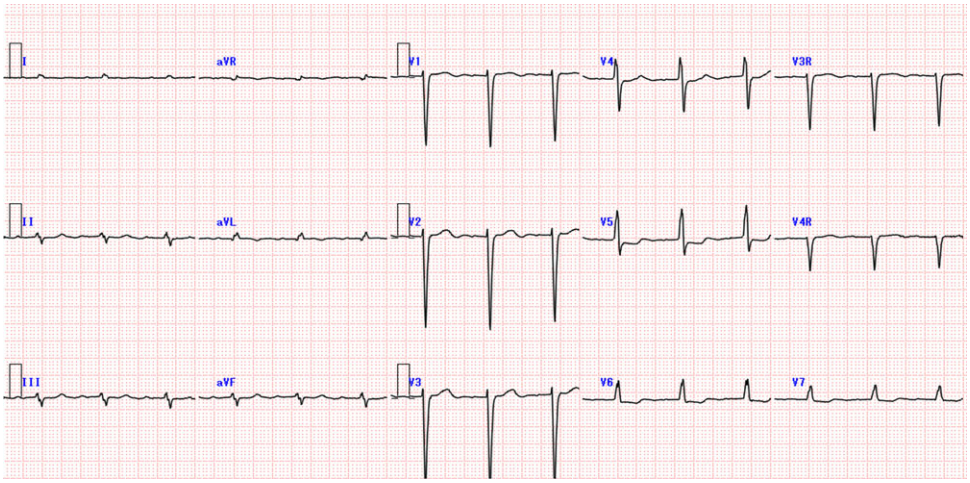

Figure 1. Twelve-lead electrocardiography shows reduced amplitude of the Pwave and a mildly prolonged PR interval.

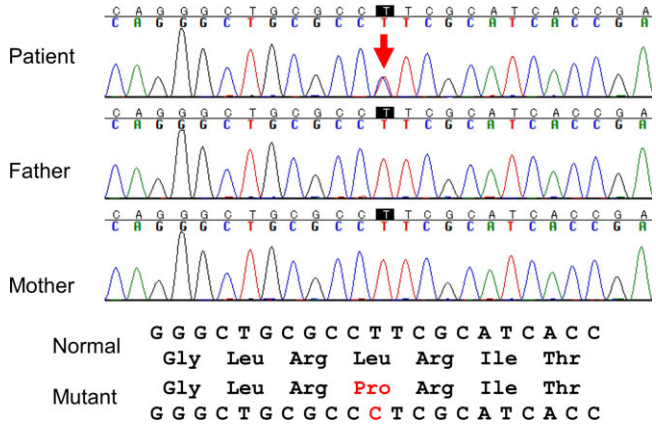

Figure 2. Sequence analysis of the *LMNA* gene. A mutation (c.182T>C:p. Leu6Pro) is observed in the proband.

skeletal muscle MRI findings were normal. Skeletal muscle biopsy showed no abnormal findings, and immunostaining was normal. Genetic testing using next-generation sequencing revealed a mutation in the *LMNA* gene (c.182T>C:p. Leu6Pro) (Fig 2). We confirmed that the mutation was a *de novo* mutation, which was not observed in either parent, and she was diagnosed with Emery-Dreifuss muscular dystrophy caused by an *LMNA* mutation, consistent with the clinical history. She was listed for heart transplantation, as it was difficult to manage her condition with medical treatment alone. Informed consent was obtained from the patient's parents for publication of this case report.

Discussion

We identified two important clinical issues in this study: cardiac complications in patients with Emery-Dreifuss muscular dystrophy can precede neurological symptoms, and muscle and myocardial biopsies can show normal findings even in cases diagnosed with Emery-Dreifuss muscular dystrophy.

First, cardiac complications in patients with Emery-Dreifuss muscular dystrophy can precede neurological symptoms. Cardiac complications usually appear after muscle weakness but can also be early symptoms.[3] However, in such cases, the symptoms are often related to bradycardia or arrhythmia,[4] and there have been no reports of heart failure being the trigger for diagnosis, as in this case. Generally, the first cardiac complication of Emery-Dreifuss muscular dystrophy is damage to the atrial myocardium and atrioventricular node, which causes atrial standstill and atrial arrhythmias (i.e., atrial fibrillation/flutter and atrioventricular block), and as the disease progresses, damage to the ventricle leads to ventricular arrhythmias and decreased cardiac function.[2] Although there were no subjective symptoms, the patient had joint contracture in the posterior neck, proximal muscle weakness, reduced P-wave amplitude, and mild prolongation of the PR interval on electrocardiography, which were suspected to be features of atrial dysfunction. Particularly, the presence of reduced P-wave amplitude despite atrial enlargement was different from the features of a typical dilated cardiomyopathy. She did not have a slow heart rate, atrial standstill, or advanced atrioventricular block; thus, a pacemaker was not placed.

Second, muscle biopsy and myocardial biopsies can show normal findings even in patients with Emery-Dreifuss muscular dystrophy, as these may not show specific pathological findings.[5] Myocardial biopsies from the right ventricle have rarely been reported,[6,7] However, pathological myocardial features of Emery-Dreifuss muscular dystrophy at autopsy have been reported, showing fibrosis and replacement of the atrial and ventricular myocardium with adipose tissue.[8] In our case, muscle biopsy and two myocardial biopsies were performed, but no specific pathological features, such as fibrosis, were observed in either specimen. The reason remains unknown but may be associated with the lack of muscle symptoms and absence of right ventricular dysfunction in the ventricular specimen that was biopsied. The observation of normal findings in the muscle or myocardium does not exclude a diagnosis of Emery-Dreifuss muscular dystrophy. When Emery-Dreifuss muscular dystrophy is suspected, genetic testing is useful for establishing a subtype-specific diagnosis.[5,9]

As this disease does not cause mental development disorders and the skeletal muscle symptom progression is slow, heart transplantation may be needed.[10] This case was also considered a good candidate for heart transplantation as the cardiac symptoms at rest were very mild.

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In conclusion, Emery-Dreifuss muscular dystrophy is a mild, slowly progressive, neuromuscular disorder with few subjective symptoms; therefore, cardiac complications, particularly cardiac dysfunction, can be the initial manifestation. Skeletal muscle biopsy and myocardial biopsy may not be diagnostic, and genetic testing should be performed if this disease is suspected.

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Conflicts of interest. None.

Ethical standards. Not applicable.

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