Emery-Dreifuss muscular dystrophy (EDMD) is one of the three most common types of muscular dystrophy. It is characterized by the presence of slow, progressive muscle wasting and weakness, early contractures, and cardiac-conductive disturbances (1-4). Pacemaker implantation is encouraged to prevent sudden death from atrioventricular block or from sick sinus syndrome (1, 2, 5). In this case report, we present an autopsy of an X-linked EDMD patient who died from ventricular arrhythmia despite undergoing a previous pacemaker implantation.

Key words: Emery-Dreifuss muscular dystrophy, arrhythmia, autopsy, emerin, dilated cardiomyopathy

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Introduction

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Case Report

A 31-year-old Japanese man was referred to our hospital due to complete right hemi paralysis and semiconsciousness after playing a game of softball. He was diagnosed with concurrent acute heart failure and cerebral infarction. Electrocardiography showed a complete atrioventricular block, and severe congestion was found in both lung fields by thoracic radiography (Fig. 1). Transthoracic echocardiography revealed decreased ejection fraction, thickened walls and left atrium dilatation (ejection fraction 37%, wall thickness 13 mm, left ventricular diastolic diameter 61 mm, left ventricular systolic diameter 50 mm, left atrium diameter 50 mm). An emergent temporal pacemaker was inserted, followed by a permanent pacemaker implantation during admission. Meanwhile, cerebral infarction was diagnosed due to a cardiac embolism from paroxysmal atrial fibrillation, and anti-coagulation therapy with warfarin was initiated.

Upon inquiry, it was revealed that the patient’s brother had a history of X-linked EDMD. Although his brother had muscle weakness and contractures, the patient experienced only mild fatigue while exercising and no noticeable symptoms of EDMD. Polymerase chain reaction of potential gene sequences (6) confirmed his development of the disease, and he was carefully monitored in the outpatient clinic. During the follow-up, the patient remained stable with normal blood pressure and unchanged cardiac performance. However, 1 year after discharge, he was found dead in bed. The pacemaker record at that time indicated that ventricular tachycardia followed by ventricular fibrillation was the cause of death.

A complete postmortem examination was performed 1 day after death. The heart weighed 690 g and showed significant hypertrophy, which was most severe in the left ventricle (Fig. 2). A diagnosis of dilated cardiomyopathy associated with EDMD was established. The coronary arteries

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Figure 1. (Left) Electrocardiography shows a complete atrioventricular block with an escape rhythm of 40 bpm and a regular P wave at 113 bpm. (Right) Thoracic radiography revealed severe congestion in both fields with an increased cardiothoracic ratio (65.9%).

Figure 2. Cross-section of the heart at autopsy. Significant hypertrophy and a cloudy film on the left ventricle can be observed as well as dilatation of cardiac chambers.

were intact and there was no thrombosis in the cardiac chamber. Skeletal muscles were well preserved and old infarctions were found in the cerebrum and left kidney. Histological examination of the heart revealed diffuse myocardial degeneration over both atria and ventricles. This was characterized by fibroadipose tissue replacement, specifically in the atrium. In addition to that, depletion of cardiomyocytes and interstitial fibrosis were found predominantly throughout the septal and posterior wall of the left ventricle (Fig. 3). However, only mild fibrosis was observed in the skeletal muscles (Fig. 3). Although the degree of fibrosis was significantly different between cardiac and skeletal muscles, immunological staining showed a deficiency of nuclear emerin in both cardiac and skeletal muscles.

Discussion

Patients with EDMD exhibit one of two major mutations found in the genes that encode the proteins of the nuclear envelope (2-4, 7). Mutations in the LMNA gene, which encodes lamins A and C, cause autosomal dominant (AD) EDMD, which is often more severe, and includes early onset, even in very early childhood (7). X-linked EDMD is distinguished by mutations in the EMD (STA) gene which encodes the protein, emerin. As seen in the present case, such patients exhibit a deficient emerin level in the nuclear envelope. Cardiac involvement is the most critical manifestation of the two diseases, and it usually becomes evident as contractures and muscle weakness progress. Conduction abnormalities are often observed as ranging from sinus bradycardia, to prolongation of PR interval, to complete atrioventricular block, and thus pacemaker implantation has been encouraged to prevent sudden death (1, 2, 5).

In the present case, two characteristic forms of disease manifestation were found. First, almost no symptoms of contractures and muscle weakness were present despite advanced cardiac malfunction, which may have caused extreme difficulty in diagnosing the disease without collecting the medical history of his family first. Generally, contractures and muscle symptoms start occurring during early childhood (in most cases before 10 years of age), followed by the development of cardiac abnormalities during early to mid adulthood (1, 4, 5). Although varying degrees of disease progression have been well documented (5, 8, 9), EDMD patients with cardiac abnormalities rarely have the ability to participate in sports. Considering that his brother exhibited muscular symptoms with the same genetic abnormality, the lack of muscular symptoms in this patient may be due to the wide variety of phenotypic patterns in this disease.

The second characteristic feature that we found was diffuse myocardial fibrosis in the ventricles. Although significant hypertrophy may have attributed to bradycardia, the cause of cardiac dysfunction was probably due to the pathological condition of EDMD, considering the inhomogeneous
distribution of fibrosis. As in this case, previous studies have also reported fibrosis of the ventricle walls, however, significant atrial dilation and loss of atrial myocardium with fibroadipose tissue replacement have been the focus, and thus conduction block was considered the major cause of sudden death (10, 11). Recently, several cases have reported sudden death despite a pacemaker implantation (9, 12-14), but the numbers are still small and all reports were of patients with AD-EDMD. There is no report that investigated the frequency of ventricular arrhythmias in X-linked EDMD. However, Merlini et al. reviewed 73 cases of X-linked EDMD patients from six families, and found that 30 of 73 cases (41%) died suddenly between ages 25-59 (8). It is natural to think, considering the involvement of the myocardial fibrosis in this disease, that some of these sudden deaths were attributed to ventricular arrhythmias.

Dilated cardiomyopathy associated with EDMD is not generally recognized. However, when we look into the previous studies, cardiac function in EDMD patients varies from normal to severe depression of ejection fraction at less than 20% (2, 14, 15). Whether the fatal arrhythmia in this case was caused by the arrhythmogenesis of degenerated cardiomyocytes or secondly through impaired cardiac function is still unknown, however, there is no doubt that myocardial fibrosis played a critical role in the development of the arrhythmia. Therefore, physicians treating patients with X-linked EDMD and severe ventricle fibrosis should consider the use of an implantable cardioverter defibrillator in place of a pacemaker.

Due to the nature of its recessive inheritance, a family tree shows a sporadic appearance of patients with symptoms of X-linked EDMD. In addition, isolated cases with de-novo mutation in the emerin gene have been reported (4). Without symptomatic muscle weakness, it might be difficult to properly diagnose these patients, and the possibility of death from arrhythmias still remains. However, patients who develop atrioventricular block in their twenties or thirties are somewhat rare (16), while at the same time, emerin deficiency can be detected in 95% of X-linked EDMD patients (3, 4). Therefore, biopsy with immunological staining could be helpful to diagnose this disease in young male with atrioventricular block.

In conclusion, young males with complete atrioventricular block, regardless of contractures or muscle symptoms, require careful review of family history and should always be evaluated for the possibility of EDMD. At the same time, the risk of ventricular arrhythmias should be taken into consideration for those with severe ventricle damage.

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

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