Cardiology in the Young

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Cardiac features in a patient with erythrokeratodermia cardiomyopathy syndrome

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Brief Report

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Abstract

Patients with erythrokeratodermia cardiomyopathy syndrome exhibit congenital, generalised erythrokeratoderma and dilated cardiomyopathy during early childhood. We report a case of erythrokeratodermia cardiomyopathy syndrome in a 15-year-old male patient and focus this report on cardiac features that were present.

Both the heart and skin are exposed to mechanical stress and maintain tissue integrity by distributing the strain through desmosomes, which connect intermediate filaments to cell-to-cell junctions.[1] Desmoplakin is highly expressed as desmosomal protein and is distributed in the skin and heart.[1] Mutations in *DSP* encoding desmoplakin result in skin and heart diseases with overlapping clinical features including Carvajal syndrome, erythrokeratodermia cardiomyopathy syndrome, dilated cardiomyopathy with woolly hair, keratoderma, and tooth agenesis , severe dermatitis, multiple allergies, and metabolic wasting syndrome.[2] Erythrokeratodermia cardiomyopathy syndrome is known to be induced by mutations in the spectrin repeat 6 domain of the desmoplakin.[1]

Erythrokeratodermia cardiomyopathy syndrome is a rare disease that manifests as generalised erythrokeratoderma and dilated cardiomyopathy in their early childhood.[3] We describe clinical findings that relate to the heart of a patient with erythrokeratodermia cardiomyopathy syndrome.

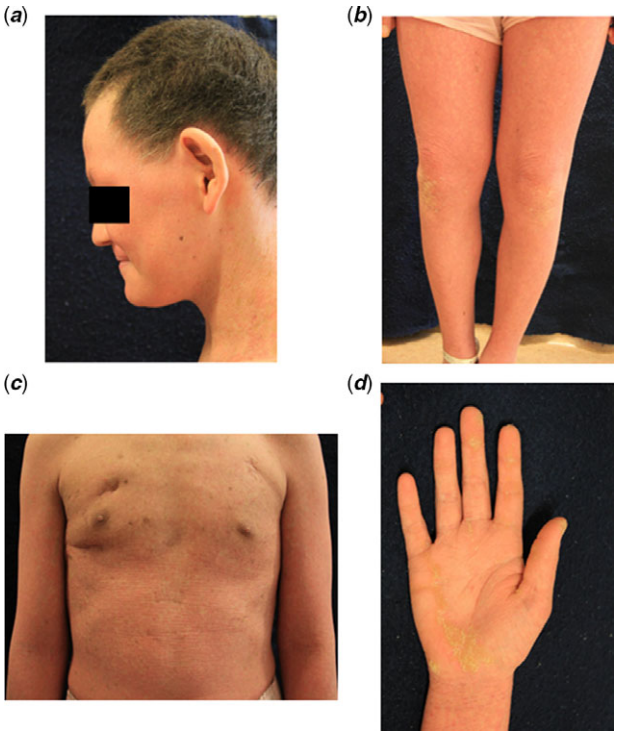

Figure 1. Clinical features of the reported case. (***a***– ***c***) Ichthyosiform erythroderma, (***a***) woolly hair, and (***d***) palmoplantar keratoderma.

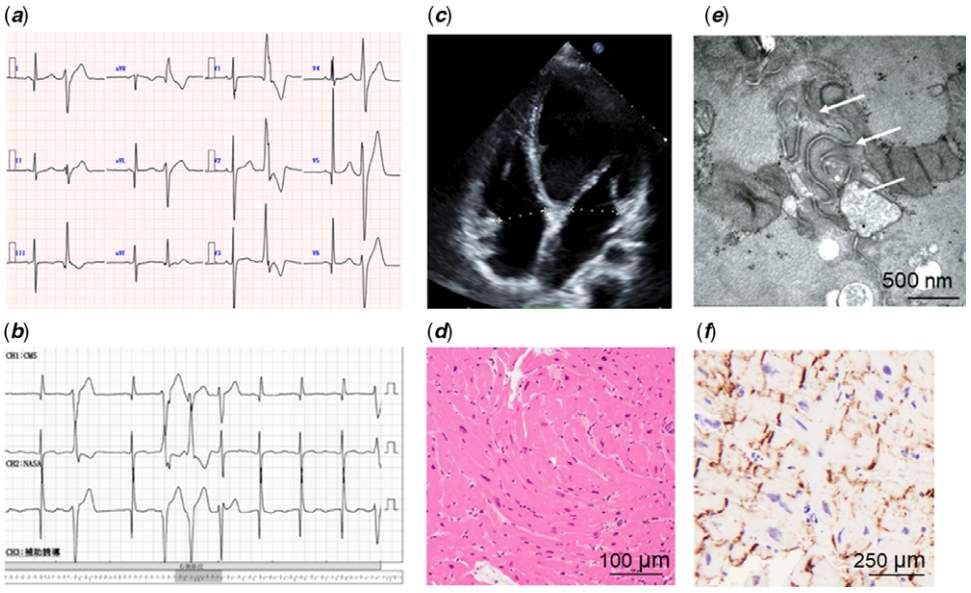

Figure 2. (***a***) ECG, (***b***) 24-hour monitoring ECG, (***c***) echocardiogram, (***d***) histological image of haematoxylin and eosin staining, (***e***) an ultrastructural image, and (***f***) connexin 43 immunohistochemistry in the myocardial tissue of the reported case. Arrows indicate a distorted intercalated disc.

Case

The patient is a 15-year-old male, born full term as the first child. Erythrokeratodermia was pointed out during the patient's 1-month check-up. The patient, when 3 months old, was referred to our institution to monitor the progression of erythrokeratodermia.

The patient was referred to us on suspicion of dilated cardiac myopathy when he was 10 years old. An echocardiogram found a dilated left ventricle dimension, decreased ejection fraction, and thinning of the left ventricular wall. The patient was prescribed diuretics and lisinopril with careful cardiac follow-up.

At the age of 15, the patient was admitted to the hospital because of general fatigue. On admission, the patient was 158 cm in height and had a body weight of 52 kg. The patient had erythrokeratodermia, palmoplantar keratoderma, and woolly hair (Fig 1a–d). He had no permanent teeth. An electrocardiogram found an abnormal Q wave and a prolonged QT interval of 480 ms that was associated with polymorphic premature ventricular contraction (Fig 2a). A 24-hour electrocardiogram revealed episodes of ventricular tachycardia (Fig 2b). An echocardiogram showed decreased cardiac function (left ventricle dimension diastole of 70.2 mm, ejection fraction of 16.9%, and a fractional area change in right ventricle of 22.6%) (Fig 2c). An echocardiogram also exhibited neither aneurysm nor abnormal movement in the right ventricle. Dobutamine, olprinone, and carvedilol were administrated. A follow-up echocardiogram showed improved cardiac function. A myocardial biopsy was performed before discharge. Plasma BNP level was decreased from 463 pg/mL to 286 pg/mL during the admission. The patient was discharged from our hospital 24 days after admission.

Based upon the patient's clinical findings, erythrokeratodermia cardiomyopathy syndrome was suspected. Genetic testing revealed a heterozygous missense variant NM_004415.3: c.1828T > C (p. Ser610Pro) in *DSP* within the spectrin repeat 6 region. Genetic testing of the patient's parents found no mutations were present.

A review of the histological slides found moderately disarranged, variously sized, and occasionally hypertrophic myocardial cells. Fibrosis and inflammatory change were not apparent. On ultrastructural examination, distortion of the intercalated discs was observed. Immunohistochemistry showed that cardiac gap junction protein connexin 43 was appropriately localised to the longitudinal ends of cardiac myocytes (Fig 2d–f).

Discussion

This is the first report to present cardiac pathology and physiology for a patient with erythrokeratodermia cardiomyopathy syndrome. In a previous report, clinical findings for arrhythmia in patients with erythrokeratodermia cardiomyopathy syndrome were not determined.[1] We successfully showed the characteristics of erythrokeratodermia cardiomyopathy syndrome on an electrocardiogram. We do not know the exact cause of arrhythmia underlying erythrokeratodermia cardiomyopathy syndrome, though the reason why arrhythmia happens could be due to heart failure. In a previous report, individuals that carried a mutation in *DSP* exhibited polymorphic premature ventricular contraction and non-sustained ventricular tachycardia.[4] Mutations in *DSP* in patients with erythrokeratodermia cardiomyopathy syndrome affect localisation of connexin 43.[3] Connexin 43 is associated with gap junctions that form electrical and mechanical connections in the heart; reduced connexin 43 expression induces arrhythmia.[5] Chen et al. showed that the expression of connexin 43 was significantly reduced in myocardium of arrhythmogenic right ventricle cardiomyopathy.[6] Although we cannot know whether connexin 43 expression in the patient's heart tissue is decreased or not without normal control sample, altered connexin 43 expression of patients with erythrokeratodermia cardiomyopathy syndrome might be associated with cases of arrhythmia. These issues need to be further investigated in future studies.

Mutations in the desmoplakin gene are known as the cause of arrhythmogenic right ventricle cardiomyopathy. Our case exhibited not only left ventricular dysfunction but also right ventricular dysfunction. Though there was no strong evidence that his diagnosis was arrhythmogenic right ventricle cardiomyopathy from the echocardiogram and electrocardiogram, careful follow-up for biventricular cardiac function will be necessary.

Desmoplakin is also a major component of gap junctions, which are an anatomical structure present in myocardial intercalated discs.[1] In our case, ultrastructural changes in the intercalated discs were found. Distortion of the intercalated discs might be associated with erythrokeratodermia cardiomyopathy syndrome. In a

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previous report, histological changes of myocardial tissue from patients with Carvajal syndrome, which also results from a mutation in *DSP*, were described.[7] Similar to our case, ultrastructural abnormalities in the intercalated discs of myocytes were observed.[6]

Erythrokeratodermia cardiomyopathy syndrome can be sometimes life-threatening. Physicians should carefully monitor patients with erythrokeratodermia for signs of cardiomyopathy.

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Conflicts of interest. None.

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