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CLinical Case Report

Myocardial fragmentation associated with disruption of the Z-band in hypertrophic cardiomyopathy in Noonan syndrome

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ABSTRACT

A 13-year-old female with Noonan syndrome had been diagnosed with hypertrophic cardiomyopathy, and she died of heart failure at the age of 25 years. Light microscopic and electron microscopic examination of her biopsied myocardium and autopsy heart showed myocardial fragmentation associated with Z-band disruption as well as myocardial hypertrophy and disarray with interstitial fibrosis. Myocardial fragmentation associated with Z-band disruption may be related to the progression of cardiac dysfunction.

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1. Introduction

Noonan syndrome is a developmental disorder characterized by a combination of unique facial features, short stature, cardiac abnormalities, lymphatic vessel dysplasia, chest wall abnormalities, and developmental delay. Hypertrophic cardiomyopathy (HCM) is one of the most common cardiac abnormalities in Noonan syndrome. Although the pathological findings of the myocardium in HCM in Noonan syndrome have been reported [1], there have been no reports of the detailed myocardial changes in HCM in Noonan syndrome on electron microscopy. Sarcomere fragmentation and Z-band disruption, as well as myocardial disarray, in a patient with HCM associated with Noonan syndrome are described.

2. Case report

A 13-year-old Japanese female had been admitted to our hospital because of cardiomegaly detected on a medical check routinely performed at entrance into junior high school. She had had two operations: one for Bochdalek hernia at 8 months after birth and another one for cleft palate at 15 months after birth. She had ptosis, a webbed neck, prominence of the breast bone (pectus carinatum), cubitus valgus, micrognathia (undersized lower jaw), and bluntly ended fingers. She was diagnosed as having Noonan syndrome because of these dysmorphic features and a normal 46XX karyotype.

Electrocardiography (ECG) showed marked left ventricular (LV) hypertrophy, and chest X-ray showed cardiomegaly with a cardiothoracic ratio of 58%. Transthoracic echocardiography (TTE) showed diffuse hypertrophy of the left ventricle [interventricular septum (IVS), 17 mm; left ventricular posterior wall (LVPW), 19 mm], normal left ventricular end-diastolic dimension (LVDD) (42 mm), and a slight decrease of left ventricular systolic function with a left ventricular ejection fraction (LVEF) of 52% (Fig. 1a). At that time, her laboratory data were normal, including growth hormone levels. Cardiac catheterization was performed, and coronary angiography showed normal coronary arteries. An endomyocardial biopsy was performed from the left ventricle, and microscopic examination showed myocardial hypertrophy and disarray with mild interstitial fibrosis in the biopsied myocardium (Fig. 2a and b). Myocardial hypertrophy and disarray were also seen on electron microscopy (Fig. 3a). In some areas of the biopsied myocardium, disruption (Fig. 3b) and disappearance (Fig. 3c) of the Z-band were seen in the myocardium, and flexion and distortion of myofibrils were also seen at disappeared Z-band sites (Fig. 3d). Moreover, myofibrils were separated at disappeared Z-band sites (Fig. 3e). Those myofibrils were fragmented piece by piece (Fig. 3f). However, the structures of actin and myosin filaments were relatively preserved. These Z-band abnormalities were mostly seen around the nucleus with a tubuloreticular

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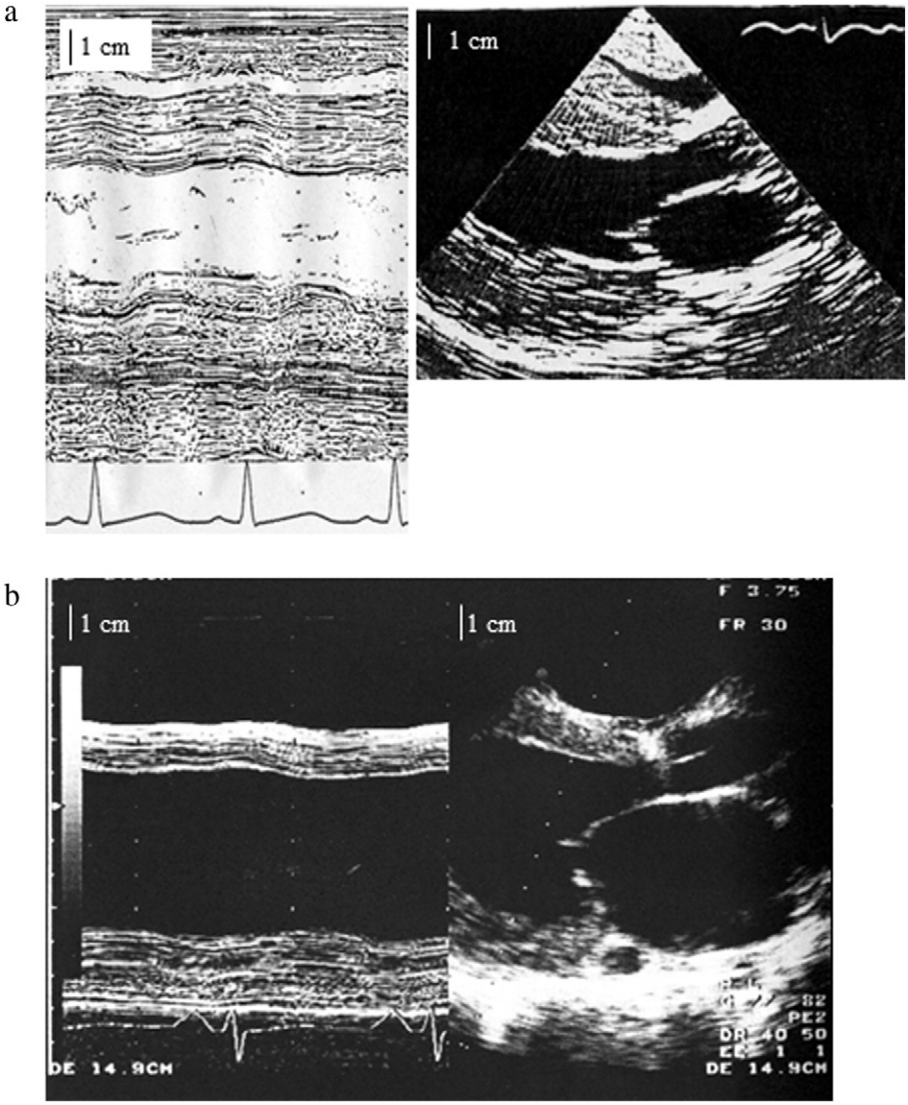

Fig. 1. TTE examinations at diagnosis of Noonan syndrome and at the late phase with heart failure. (a) TTE at the age of 13 years demonstrates severe LV hypertrophy and almost normal LV systolic function. (b) TTE at the age of 25 years demonstrates severely impaired LV systolic function.

structure within the nuclear cisterna, a so-called pseudoinclusion body, and its area was about 1% of the muscle bundles (Fig. 4).

The patient had had heart failure at the age of 22 years, and medication for heart failure was started. Her heart failure then gradually progressed, and she died of heart failure at the age of 25 years. At that time, ECG showed sinus tachycardia. Chest X-ray showed cardiomegaly with a cardiothoracic ratio of 67.3%. TTE showed IVS of 12 mm, LVPW of 14 mm, LVDD of 54 mm, and LVEF of 16% (Fig. 1b).

In order to evaluate the precise cause of death, a hospital autopsy was performed after obtaining the parents' consent. On autopsy examination of the heart, replacement fibrosis was seen, in addition to myocardial disarray and degeneration (Fig. 2c and d).

3. Discussion

HCM has been reported in Noonan syndrome [1], but other types of cardiomyopathy, i.e., dilated cardiomyopathy (DCM) [2,3] and restrictive cardiomyopathy [4,5], have also been reported. Those reports demonstrated the histological features of them as follows; myocardial disarray with hypertrophy similar to HCM in non-Noonan syndrome [1]; thinned, elongated, and loosely arranged myocardial fibers [2]; focal interstitial fibrosis and fiber hypertrophy of myocardium [3]; extensive patchy fibrosis with myocyte disarray and small foci of inflammatory cells (mainly monocytes and some eosinophils) [4]; and myocardial hypertrophy without disarray [5].

However, there have been no reports of electron microscopic examination of HCM in Noonan syndrome and no reports about the histopathology of HCM with progressive systolic dysfunction in Noonan syndrome. The present report demonstrated that (1) myocardial disarray with hypertrophy and mild interstitial fibrosis, disruption of Z-bands, and myocardial fragmentation were seen in biopsied myocardium when the patient was diagnosed as having HCM with Noonan syndrome without any symptoms and that (2) myocardial degeneration and marked replacement fibrosis were seen in her heart at autopsy after she died of heart failure with a reduced ejection fraction 12 years after the diagnosis.

These histological features in the present case indicate that Z-band damage is related to myofibril fragmentation that produces myocardial degeneration, and its progression seemed to cause fatal progressive cardiac systolic dysfunction. The mechanism of the morphological change of the present patient with HCM of Noonan syndrome was as follows: first, Z-bands were disrupted (Fig. 5b), and Z-bands disappeared (Fig. 5c). Then, flexion and distortion of myofibrils occurred at the sites of Z-band disappearance (Fig. 5d), and myofibrils were separated at disappeared Z-band sites (Fig. 5e). Finally, myofibrils were fragmented piece by piece with distorted sarcomere units (Fig. 5f). Moreover, nuclear abnormalities may be related to these mechanisms, although the precise mechanism is unknown.

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