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Full Length Research Paper

Left ventricular non-compaction of myocardium in forensic autopsy

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Left ventricular non-compaction of the myocardium is a rare cardiac disorder characterized by prominent meshwork formation and deep intertrabecular recesses of the left ventricle. Echocardiography provides clinical diagnosis of the non-compaction region, but it is sometimes difficult to distinguish this disorder from cardiomyopathies of other types. This report describes two autopsy cases of sudden death with suspicion of this disease. One was a 38-year-old woman who was found to have died in a bathtub while taking a shower. The other, a 28-year-old man, was found early in the morning dead on his bed. Postmortem examination revealed characteristic features of left ventricular non-compaction, which included trabeculation and staghorn-like ventricular recess, accompanied by endocardial fibrosis in histology. Left ventricular non-compaction of the myocardium shows ventricular cavity expansion. Therefore, dilated cardiomyopathy endocardial fibroelastosis and differentiation are necessary.

Key words: Left ventricular non-compaction of the myocardium, autopsy, sudden death.

INTRODUCTION

Left ventricular non-compaction (LVNC), also known as isolated ventricular non-compaction (IVNC) or non-compaction of the ventricular myocardium, is a rare form of cardiomyopathy. This morphological abnormality originates from impaired cardiac development during fetal growth, which involves arrest of compaction of the loose interwoven meshwork of myocardial fibers (Jenni et al., 2002; Ritter et al., 1997). LVNC is classified into 'other cardiomyopathies' in the cardiomyopathy category of ICD10.

LVNC of the left ventricle has a spongy appearance, with prominent trabeculations deep recesses typical of the last half of the embryonic period (Valente, 2006). The ventricular wall exhibits thick and thin interlacing bands and trabeculations that extend from its midportion to its apex (Ritter et al., 1997; Valente and Bashore, 2006). Although LVNC was first reported in children and young adults (Chin et al., 1990), it has subsequently been found in adults (Jenni et al., 2006; Rigopoulos et al., 2002; Ritter et al., 1997). LVNC might often be misdiagnosed or unrecognized, because of the variety in its clinical observations (Rigopoulos et al., 2002). Moreover, LVNC is a genetic disorder for which several candidate genes have been identified, such as Dystrobrevin alpha (DTNA) (Ichida,

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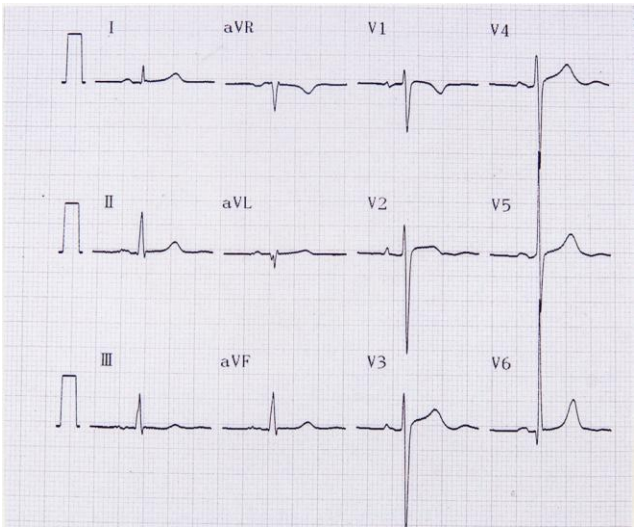

Figure 1. Electrocardiogram (case 1). The electrocardiogram demonstrated atypical ST elevation in leads V3–V6.

2009).

Jenni et al. (1986) presented gross observations and microscopic findings of clinically diagnosed LVNC subjects. In LVNC, the deep intertrabecular recesses communicate with the cavity of the left ventricle, but there are no specific microscopic findings, except for endocardial fibroelastosis.

At the bedside, LVNC is diagnosed definitively using echocardiography, but cases diagnosed by forensic autopsy are rare, indicating that it is not easy to note the typical findings, because of a lack of antemortem clinical information. In this study, two sudden death cases were experienced for which LVNC was strongly suspected. Their clinical courses and autopsy findings were introduced subsequently.

CASE REPORTS

Case 1

A 38-year-old female who had experienced prior syncopal episodes fell due to sudden loss of consciousness while riding a bicycle. After transportation to an emergency hospital, her consciousness was restored. Electroencephalography (EEG) and head magnetic resonance imaging (MRI) revealed epilepsy-like features of her syncopal attack. On EEG and head MRI, positive findings were absent. After this syncopal episode, she complained of earlier numbness in the tips of the fingers on her left hand and toes on her left foot. She was absent from work for three months after that hospital visit. Then, a colleague found her dead in an empty bathtub at home. Incidentally, the deceased had undergone a health examination the day before her death, in which an electrocardiogram showed atypical ST elevation with a heart rate of 59/min (Figure 1).

Case 2

A 28-year-old male with no noteworthy clinical history was witnessed sleeping while snoring at home. His family member later found him unconscious in the bedroom early in the morning. Despite an attempt at immediate resuciation, he was pronounced dead at hospital.

RESULTS

Case 1: Gross and microscopic examinations

Administrative autopsy was performed to examine her sudden death from unknown causes. She was 167 cm in height and 60 kg in weight. The heart, which weighed 355 g, and coronary arteries yielded no specific findings, such as advanced atherosclerosis or thrombosis. The ventricular walls were not hypertrophic: the left ventricular free wall was 12 mm thick, the ventricular septum was 10 mm, and the right ventricle wall was 3 mm. The left ventricular (LV) wall showed a deep recesses extending to the inner half of the ventricle (Figure 2A). The ratio of the non-compacted left ventricular myocardium to the compacted myocardium was 1.4.The heart was dissected by the short-axis method of cardiac dissection and the tissue was fixed in 10% buffered formalin. The excised tissue for microscopy was made into 10 blocks and embedded in paraffin following the standard procedure. The tissue blocks were cut into sections 4 μm thick, after which they were subjected to deparaffinization and dehydration through xylene and graded alcohol solutions. All sections were stained using hematoxylin-eosin and Masson-trichrome stains. Histology revealed mild hypertrophy of the left ventricular myocytes with subendocardial interstitial fibrosis. The spongy and non-compaction layer comprised polypoid endocardial trabeculated muscular bundles forming staghorn-like endocardial lined recesses (Figure 2B). Patchy contraction band necrosis was observed (Figure 2C). Examination of other organ tissues revealed no significant pathologic findings, except for congestion.

Case 2: Gross and microscopic findings

The deceased weighed 85 kg and was 175 cm in height. At autopsy, the heart, which weighed 536 g, showed dilation of the left ventricular cavity. The left ventricular free wall was 12 mm thick, the ventricular septum was 12 mm, and the right ventricular wall was 2 mm. The LV wall showed anastomosing coarse trabeculae resembling multiple papillary muscles. The left ventricular wall demonstrated deep recesses extending to the inner half of the anterior ventricle wall. The ratio of the non-compacted left ventricular myocardium to the compacted myocardium was 1.4 (Figure 3A). The left posterior ventricle wall was most prominent in the inner half of the apex (Figure 3B). The heart was dissected by the short-axis method of cardiac dissection, and microscopic sections were made, as in case 1. Histologic examination showed endocardial

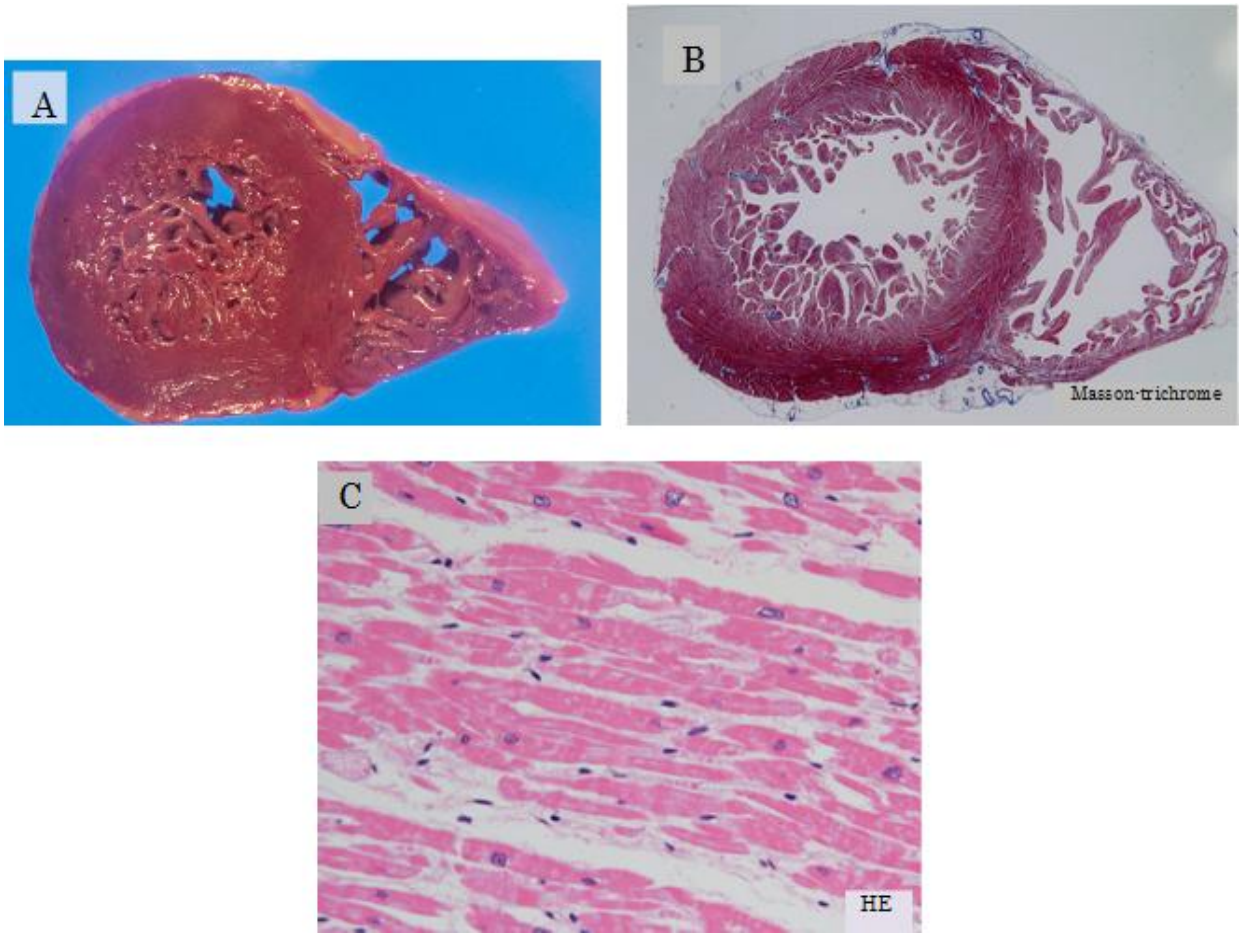

Figure 2. Left ventricular non-compaction (case 1). (A) Short-axis section of the heart with thicker non-compacted area composed of interlaced smaller muscle bundles and smooth endocardial surface (fresh specimen). (B) Deep recess in the left ventricle wall (Masson-trichrome, ×12.5). (C) Extensive contraction band necrosis in the cardiomyocytes of the left papillary muscle (hematoxylin and eosin, ×400).

fibroelastic proliferation on the left ventricle (Figure 3C). Mild left ventricular myocyte hypertrophy was apparent. No evidence was found of any abnormality in other organ systems.

In addition, the DNA of the subject was analyzed, because of the potential for a genetic contribution to the pathogenesis. However, the postmortem genetic testing using polymerase chain reaction (PCR) direct sequencing revealed no missense mutations in 10 LVNC-related genes: DTNA, LDB3, LVNC2, TNNT2, ACTC1, MYH7, MIB1, PRDM16, TPM1, and MYBPC3, apparently indicating the absence of a relevant genetic background. These DNA tests had been approved by the institutional ethical committee of Tokai University School of Medicine.

DISCUSSION

LVNC has been regarded as a rare disorder, with an incidence of 0.014% reported in early studies. For treatment, patients have been regularly referred to tertiary care echocardiography centers (Chin et al., 1990). Botto (2004) estimated the incidence of LVNC in children of 0 to 10 years of age as 0.12/100,000 population. Men appear to be affected more often than women, accounting for 56 to 82% of cases (Burke et al., 2005).

Isolated LVNC was reported by Engberding and Bender (1984) for the first time. This is particularly rare, because LVNC is almost invariably associated with other congenital cardiac malformations, such as ventricular septal defect, coronary artery anomaly, pulmonary stenosis, coarctation of the aorta, histiocytoid cardiomyopathy, and partial anomalous pulmonary venous return (Jenni et al., 2002; Ritter et al., 1997).

Cases of LVNC have been primarily misinterpreted as hypertrophic cardiomyopathy (Corrado et al., 2000), did not visualize the recesses between the trabeculae, by a lack of commonly accepted diagnosis criteria, by a lack of awareness of LVNC among echocardiographers, and by the aforementioned cardiac disorder (Ichida et al., 2001).

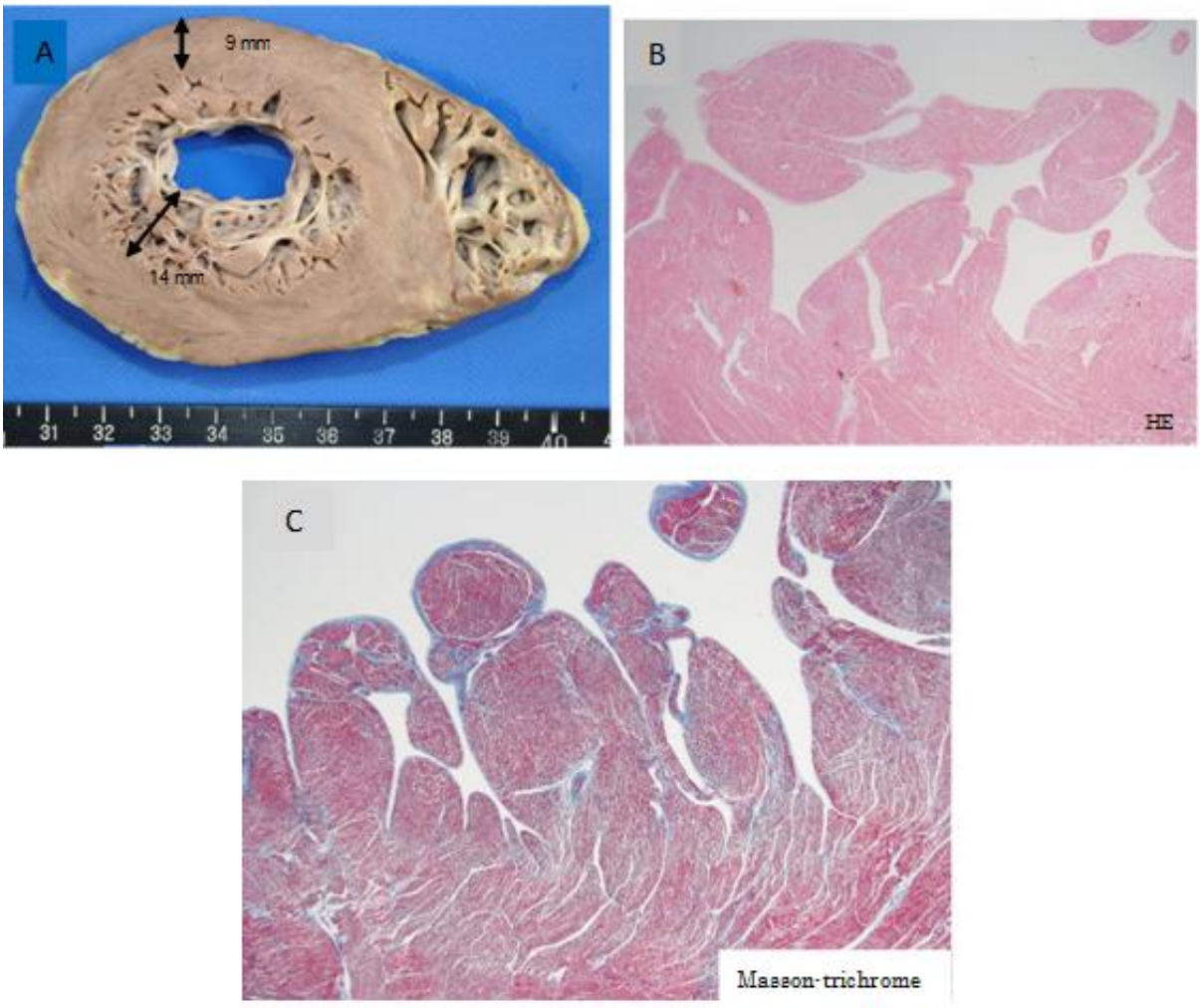

Figure 3. Left ventricular noncompaction (case 2). (A) Short-axis section of the heart with thicker noncompaction area, together with coarse trabeculae resembling multiple papillary muscles on the left anterior wall. (B) Deep papillary trabeculae and recesses in the left posterior wall (hematoxylin and eosin, magn. ×12.5). (C) Broad trabeculae with thick fibrous endocardium in the left ventricle (Masson-trichrome, magn. ×12.5).

Echocardiography has been the routine initial non-invasive diagnostic test used to detect LVNC. When transthoracic echocardiography is insufficient, contrast echocardiography and real-time three-dimensional echocardiography are also useful in diagnosing LVNC. With the advancement of echocardiographic technology, better image quality has considerably improved the resolution of the finer details of the trabeculations, with results that seem to resemble what has been reported from pathological studies. The widely accepted criteria for diagnosis are as follows: (1) a ratio of the compacted layer to the total thickness of the LV of less than 0.5, measured at the end distal from the parasternal short-axis view or the apical view (Jenni et al., 2001); (2) in the two-layer structure of the LV, a ratio of non-compacted layer (NC) to compacted layer (C) of more than 2 in the parasternal short-axis view, at end systole, with the absence of other coexisting cardiac structural abnormalities plus numerous excessively prominent trabeculations and deep intertrabecular spaces, as well as recesses perfused by interventricular blood as seen on color Doppler imaging (Ritter et al., 1997); and (3) more than three trabeculations protruding from the left ventricular free wall apically to the papillary muscles seen on one imaging plane, with intratrabecular spaces perfused from the left ventricular cavity shown by color Doppler imaging (Stollberger and Finsterer, 2004).

The clinical manifestations are highly variable, ranging from no symptoms to severe heart failure, ventricular arrhythmia, bundle branch block, syncope, and cardio-embolic events (Bott, 2004; Chin et al., 1990; Rigopoulos et al., 2002). The prognosis of symptomatic patients is not good, with a mortality rate of 47% being reported in adults during a six-year follow-up period after the onset of

the onset of symptoms (Chin et al., 1990). The common causes of death are intractable heart failure and ventricular arrhythmias leading to sudden cardiac death (Burke et al., 2005; Ichida, 2009). Ventricular arrhythmias and sudden death are common in adult patients with LVNC with co-occurrence rates of 53 and 17%, respectively (Burke et al., 2005).

However, because of the lack of antemortem data of Doppler imaging, how can forensic pathologists approach suspected subjects? Burke et al. (2005) reported pathological findings of 14 heart tissues affected by LVNC. As gross observations, the LV wall developed deep recesses extending to the inner half of the ventricle, most prominently in the midventricle and toward the apex. The appearance on short-axis sections varied from anastomosing trabeculae to a smooth endocardial surface, with narrow openings of the recesses to the ventricular cavity. The patterns of recesses were divided by gross findings into three types: anastomosing broad trabecular type, coarse trabecular type resembling multiple papillary muscles, and interlacing type of smaller muscle bundles and smooth endocardial surface with compressed invaginations identified primarily microscopically.

Histologically, two patterns of myocardial structure are apparent in the superficial non-compacted layer. In most affected hearts, the following patterns are present in an admixed state. One is anastomosing muscle bundle formation, with irregularly branching endocardial recesses with a staghorn appearance. The other is more reminiscent of multiple small papillary muscles, forming an irregular appearance at the surface. This pattern, which is free of staghorn invaginations, corresponds roughly to the coarsely trabecular gross subtype.

A notable feature in case 1 was that the subject suffered two syncopal attacks. Such attacks might have resulted from arrhythmia. Supraventricular arrhythmias are a common type of arrhythmia in patients with LVNC, with a reported incidence of between 7% (Murphy et al., 2005) and 26% (Oechslin et al., 2000). This patient was thought to have died of lethal arrhythmia due to LVNC. Gross observation of the LV wall showed interlacing smaller muscle bundles and smooth endocardial surface. Microscopic findings showed multiple small papillary muscles, forming an irregular appearance on the surface. Regarding case 2, the subject had no noteworthy clinical history, and died suddenly in his sleep while snoring, yielding no particular findings in an autopsy other than in the heart. It was suspected that he died of lethal arrhythmia that resulted suddenly from LVNC. Gross findings of the LV wall showed coarse trabeculae resembling multiple papillary muscles. Microscopic findings of anastomosing broad trabeculae, namely, coarse trabeculae resembling multiple papillary muscles, were found.

For the forensic autopsy case, the pathologists selected the short-axis method of cardiac dissection as the method of choice. This is the method of choice not only for the evaluation of ischemic heart disease, but for virtually all other cardiac conditions, because the slices expose the largest surface of myocardium (William, 2002). However, in LVNC cases, the inflow-outflow method can show numerous trabeculations and is apparently diagnostic.

Regarding autopsy cases for which the cause of death is unknown, it is common to choose the short-axis method. Therefore, the cardiac muscle of the apex was dissected by the short-axis method and the method that involved cutting of the basal portion by the inflow-outflow method was chosen. According to a report on LVNC in forensic pathology, the heart is cut by the short-axis method (Li et al., 2010).

The number of etiological studies on LVNC has been increasing recently. LVNC is regarded as a generally heterogeneous disorder. Both familial and sporadic forms have been described (Chung et al., 2004; Ichida et al., 2001; Monserrat et al., 2007; Sasse-Klaassen et al., 2003). In familial cases, which account for approximately 18 to 50% of cases in published case series, the inheritance pattern varies, with most familial cases following an autosomal dominant pattern, but some families showing X-linked or mitochondrial transmission (Burke et al., 2005; Chung et al., 2004; Digilio et al., 1999; Monserrat et al., 2007; Ritter et al., 1997; Sasse-Klaassen et al., 2003). Some reports have described G4.5 and α-dystrobrevin genes located on the X-chromosome in pediatric patients, and a relevant gene locus has been mapped to human chromosome 11p15 with autosomal dominant inheritance in adult patients (Ichida et al., 2001; Sasse-Klaassen et al., 2003, 2004). It is particularly interesting that familial recurrence is apparently more common in adults with LVNC than in pediatric populations (Ichida et al., 2001; Jenni et al., 2001). In these cases, there is no family history of sudden death or LVNC, and the hereditary presence is unknown. The diagnosis of LVNC depends on the morphologic features of the LV (Chin et al., 1990; Oechslin et al., 2000; Ramaraj et al., 2008; Stollberger and Finsterer, 2004). Additionally, the DNA sequence in the subjects as postmortem genetic testing was analyzed, because of the potential genetic contribution to the pathogenesis. However, PCR direct sequencing revealed no missense mutations in DTNA, LDB3, LVNC2, TNNT2, ACTC1, MYH7, MIB1, PRDM16, TPM1, or MYBPC3. This appeared to indicate no relevant genetic background.

In conclusion, LVNC is a heart disorder found from the neonatal period to adulthood. LVNC rarely passes without symptoms until sudden death. Forensic pathologists must recognize the potential involvement of LVNC in cases of sudden death. The diagnosis can be made via gross and microscopic examinations based on its morphological features, which include trabeculation, staghorn-like ventricular recess, and endocardial fibrosis.

Conflict of Interests

The author(s) have not declared any conflict of interests.

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