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Case Report

LEFT VENTRICULAR NONCOMPACTION WITH TRIPLE *TTN* VARIANTS MIMICKING ARRHYTHMIA-INDUCED CARDIOMYOPATHY

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ABSTRACT: Left ventricular noncompaction cardiomyopathy (LVNC) can lead to ventricular arrhythmias and may be misdiagnosed as arrhythmia-induced cardiomyopathy (AiCM). While LVNC is associated with genetic abnormalities, AiCM is triggered by arrhythmias and is typically reversible once the arrhythmia is eliminated. We report the case of a 59-year-old woman with LVNC carrying three *TTN* gene variants: c.100804A>T (p.Met33602Leu, exon 358), c.59200C>G (p.Pro19734Ala, exon 300), and c.52052T>C (p.Val17351Ala, exon 273). The patient was initially diagnosed with AiCM but showed no recovery of left ventricular function after successful catheter ablation of ventricular arrhythmias (left ventricular ejection fraction was 43.7% and 43.3%, respectively). Echocardiography and cardiac magnetic resonance imaging confirmed the LVNC phenotype. This case highlights the importance of distinguishing between these two entities in clinical practice.

Keywords: Cardiomyopathy, Noncompaction; TTN gene; Arrhythmia-Induced Cardiomyopathy

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1. INTRODUCTION

Left ventricular noncompaction (LVNC), also referred to as hypertrabeculation syndrome, is a structural cardiomyopathy characterized by prominent trabeculations in the left ventricle, particularly in the apical region[1]. Arrhythmias are commonly associated with heart failure and cardiomyopathies. However, arrhythmias are not only a consequence of heart failure and cardiomyopathy but can also serve as a cause of non-ischemic cardiomyopathy (NICM). Among these, atrial fibrillation (AF), tachycardia, and premature ventricular complexes (PVCs) are three common arrhythmias that can lead to a reversible form of cardiomyopathy collectively known as arrhythmia-induced cardiomyopathy (AiCM)[2]. We report a clinical case that was initially misdiagnosed as AiCM but was subsequently screened and accurately diagnosed as LVNC based on genetic testing, echocardiography, and cardiac magnetic resonance imaging. We hope that this case will enhance clinicians' ability to differentiate between these two conditions.

2. CASE REPORT

A 59-year-old female was admitted to the hospital due to progressively worsening dyspnea. The patient had been diagnosed with heart failure due to arrhythmia-induced cardiomyopathy, with an ejection fraction (EF) of 40% six months earlier, and a history of PVCs diagnosed six years ago, for which she received guideline-directed medical therapy including dapagliflozin, metoprolol succinate, sacubitril/valsartan, and spironolactone. She had no family history of hereditary cardiomyopathy. Upon admission, the ECG showed a regular sinus rhythm, normal axis, PVCs, and ST-segment depression in leads DII, DIII, and aVF (Figure 1A). The patient was subsequently monitored with a Holter ECG, which revealed a mean 9% burden of monomorphic PVCs, along with couplets and triplets — markedly reduced compared to a previous Holter recording that showed a 29% PVC burden and two episodes of short runs of ventricular tachycardia. Biochemical tests showed Troponin T – hs at 5.29 pg/mL (reference range <14 pg/mL) and NT-proBNP at 45.6 pg/mL (reference range <125 pg/mL). The echocardiogram at this time showed a left ventricular end-diastolic diameter of 60.5 mm and an EF of 43.7% (Figure 2A). Additionally, the parasternal long-axis and apical four-chamber views demonstrated left ventricular dilation with prominent trabeculations in the apical and lateral walls (Figures 2B-C). The medical status of patient was then consulted with electrophysiology specialists, who conducted an electrophysiological study and performed radiofrequency ablation of the PVCs located at the right ventricular outflow tract. Post-ablation, the ECG showed a sinus rhythm, normal axis, and inverted T-waves in leads DII, DIII, and aVF (Figure 1B), with no PVCs detected as seen in the pre-ablation ECG. At two-week follow-up after ablation, the post-ablation echocardiogram showed no significant changes compared to the previous findings, with the left ventricular end-diastolic diameter of 60.3 mm and an EF of 43.3% (Figures 2E-F). Trabeculations remained visible at the apical and lateral walls (Figures 2F-G). The global longitudinal strain through speckle-tracking echocardiography before and after ablation was recorded as -13.6% and -13.5%, respectively (Figures 2D-H). The patient also underwent cardiac magnetic resonance imaging, which showed prominent trabeculations at the apex (Figure 3A) and lateral walls (Figure 3B). Late gadolinium enhancement was detected in the mid-myocardium of the anteroseptal wall and in the basal-to-mid inferior wall (Figure 3C). Prolonged myocardial native T2 was noted (Figure 3D). Detailed parameters on cardiac magnetic resonance imaging are shown in Table 1. Three-dimensional reconstruction of the coronary system revealed no significant coronary artery stenosis (Figure 3E), but there was left ventricular dilation with prominent trabeculations in the apical and lateral walls (Figures 3F-H). Genetic testing revealed three variants in the TTN gene, including c.100804A>T (p.Met33602Leu), c.59200C>G (p.Pro19734Ala), and c.52052T>C (p.Val17351Ala). This genetic analysis was performed at MedGenome Labs Limited and is exclusively distributed in Vietnam by HEALTH PRECISION SERVICE Co., Ltd. After excluding autoimmune, metabolic, and infiltrative causes, the patient was diagnosed with left ventricular non-compaction. She was subsequently discharged and treated with heart failure management regimen for reduced ejection fraction.

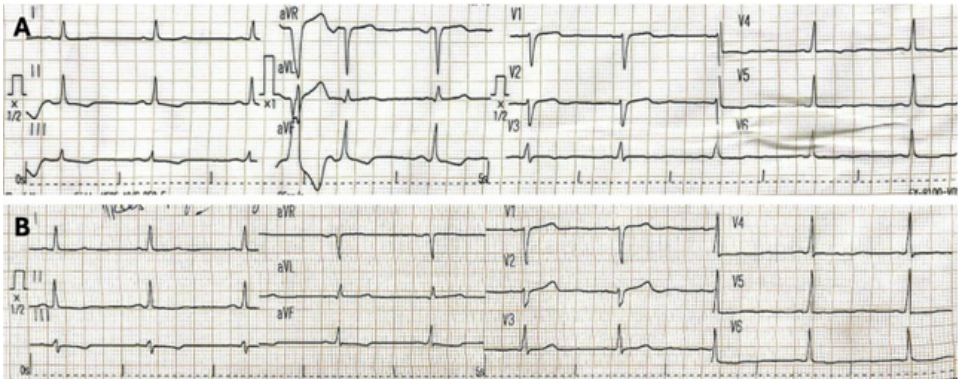

Figure 1. Electrocardiogram of the patient before (A) and after (B) radiofrequency ablation of premature ventricular contractions originating from the right ventricular outflow tract.

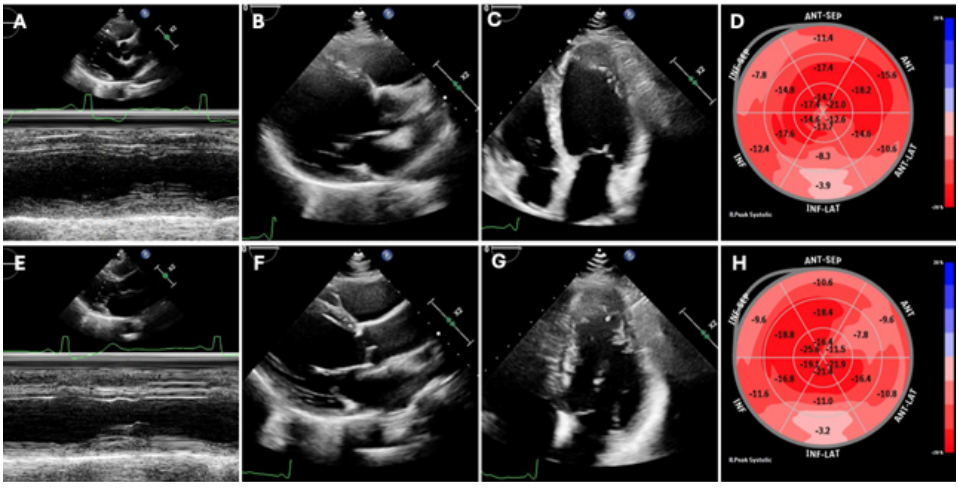

Figure 2. Echocardiography of the patient before (A–D) and after (E–H) radiofrequency ablation of premature ventricular contractions. The left ventricular end-diastolic diameter and ejection fraction were 60.5 mm and 43.7%, respectively (A), and showed no significant changes after ablation, with values of 60.3 mm and 43.4%, respectively (E). The parasternal long-axis view (B and F) and apical four-chamber view (C and G) demonstrated left ventricular dilation with prominent trabeculations in the apical and lateral walls. Speckle-tracking echocardiography before (D) and after (H) ablation revealed no significant change in global longitudinal strain, with values of –13.6% and –13.5%, respectively.

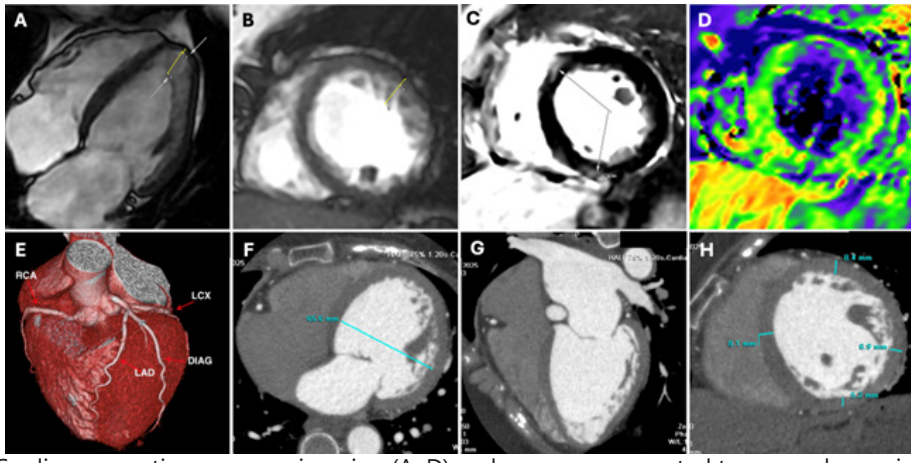

Figure 3. Cardiac magnetic resonance imaging (A–D) and coronary computed tomography angiography (E–H) of the patient. Prominent trabeculations were observed in the apical (A) and lateral (B) walls. The ratio of non-compacted to compacted myocardium was 3.2 in the lateral wall and 6.4 in the apex. Trabeculated LV mass/total LV mass was 25%. (C) Late gadolinium enhancement was detected in the mid-myocardium of the anteroseptal wall and in the basal-to-mid inferior wall. The scar mass was 2 g, accounting for 3% of the total left ventricular mass. (D) Prolonged myocardial native T2 was noted (native T2 = 59 ms). (E) Three-dimensional reconstruction of the coronary arteries showed no significant stenosis. (F–H) Left ventricular dilation with prominent trabeculations in the apical and lateral walls.

Table 1. Parameters on cardiac magnetic resonance imaging

NAME	VALUE
LVEDd	59 mm
LVEDV	160 ml
LVEF	40 %
LV mass	87 g
NC/C ratio in lateral wall	3.2
NC/C ratio in apex	6.4
Trabeculated LV mass	28.25 g
Trabeculated LV mass ratio	25%
Scar mass	2 g (3 %)
Native T1	977 ms
Native T2	59ms
ECV	34%

LVEDd: Left Ventricular End-Diastolic Diameter; LVEDV: Left Ventricular End-Diastolic Volume; LVEF: Left Ventricular Ejection Fraction; LV: Left Ventricular; NC/C ratio: Non-Compacted to Compacted Myocardial Thickness Ratio; ECV: Extracellular Volume Fraction

3. DISCUSSION

3.1. Approach to diagnosis of arrhythmia-induced cardiomyopathy

Arrhythmia-induced cardiomyopathy (AiCM) is a form of non-ischemic cardiomyopathy characterized by left ventricular (LV) systolic dysfunction secondary to sustained arrhythmias or a high arrhythmic burden, which can be partially or fully reversible following successful control or elimination of the arrhythmia[3]. AiCM includes tachycardia-induced cardiomyopathy (T-CM), atrial fibrillation–induced cardiomyopathy (AF-CM), and premature ventricular contraction–induced cardiomyopathy (PVC-CM)[3]. This terminology excludes cardiomyopathies related to conduction system abnormalities or mechanical dyssynchrony of the left ventricle, such as chronic right ventricular pacing, left bundle branch block (LBBB), or cardiac pre-excitation syndromes[4, 5].

Diagnosis of AiCM typically relies on ambulatory ECG (Holter) monitoring and cardiac magnetic resonance imaging (CMR). Improvement in LV function following arrhythmia control is often essential for confirming the diagnosis[3].

Among the AiCM subtypes, T-CM is defined by reversible LV dysfunction resulting from persistent or paroxysmal tachycardia, regardless of the arrhythmia's origin[3]. Supraventricular arrhythmias, particularly atrial fibrillation and atrial flutter with rapid ventricular response, are the most common underlying causes[6]. Clinical studies have shown that T-CM may develop within 3 to 120 days after the onset of tachycardia, with an average reduction in left ventricular ejection fraction to approximately 32%[7]. Imaging typically reveals a dilated cardiomyopathy phenotype, with increased LV end-diastolic diameter and moderate-to-severe biventricular dysfunction, while wall thickness (e.g., interventricular septum and posterior wall) remains preserved. Functional mitral regurgitation may result from annular dilation and LV remodeling[8]. A definitive diagnosis of T-CM is made when systolic function improves or normalizes within 6 months of arrhythmia control[6].

AF-CM refers to LV systolic dysfunction in patients with paroxysmal or persistent AF, even when rate control is considered adequate[6]. Ventricular rate control is a key factor in differentiating AF-CM from T-CM[3]. However, unlike T-CM, AF-CM may occur in the absence of a high ventricular rate, suggesting that other mechanisms such as irregular ventricular rhythm, post-extrasystolic potentiation and mechanical dyssynchrony also contribute[3]. AF-CM remains a diagnosis of exclusion and should be considered particularly in patients with non-ischemic cardiomyopathy and persistent AF, where no significant improvement in cardiac function is observed despite optimal medical therapy and adequate rate control[6]. Diagnosis is confirmed when LV systolic function improves or normalizes after successful rhythm control[3].

PVC-CM is defined as LV dysfunction attributable solely to frequent premature ventricular contractions. Additionally, a "PVC-CM overlap" may be described in patients with preexisting cardiomyopathy

who exhibit ≥ 10% absolute reduction in LVEF associated with frequent PVCs[4]. PVC-CM should be suspected in patients with a PVC burden >10 000 per 24 hours (i.e., >10%), especially in the setting of nonischemic cardiomyopathy[3].

AiCM presents a wide clinical spectrum, from asymptomatic individuals to those with overt heart failure. Therefore, clinicians should maintain a high level of clinical vigilance for AiCM, even when another plausible cause of cardiomyopathy is evident.

3.2. Approach to diagnosis of left ventricular noncompaction cardiomyopathy

In Viet Nam, LVNC has mainly been reported through case reports, with no official epidemiological data available. Existing reports have provided detailed descriptions of imaging findings from echocardiography and CMR, as well as clinical course, but genetic testing has not been systematically performed[9]. Consequently, the evidence remains largely descriptive rather than elucidating pathogenesis. The most commonly reported manifestations include heart failure with reduced ejection fraction, ventricular arrhythmias, and intracardiac thrombus, sometimes in association with coronary artery disease or congenital heart defects. However, the lack of genetic data (MYH7, ACTC, TNNT2, TAZ, LMNA, DES, etc.) makes it difficult to distinguish isolated LVNC from overlapping phenotypes of dilated or hypertrophic cardiomyopathy, while also missing the opportunity for family screening [9].

Given the nonspecific clinical presentation of LVNC, the diagnosis should be considered in both symptomatic and asymptomatic patients who exhibit prominent trabeculations on cardiac imaging. Diagnosis is primarily based on morphological criteria, which should be applied with caution, particularly in individuals without accompanying clinical manifestations. Clinical features are nonspecific and therefore not diagnostic on their own. Careful assessment is essential to avoid misclassification of healthy individuals and to minimize the risk of overdiagnosis.

Transthoracic echocardiography remains the initial and most widely used modality for diagnosis. Among the proposed echocardiographic criteria, the Jenni criteria are the most commonly applied and include: bilayered myocardium composed of noncompacted and compacted layers, ratio of the noncompacted layer to the compacted layer >2 at endsystole, absence of other congenital cardiac abnormalities and inter trabecular recesses perfused from the ventricular side[1]. In this patient, echocardiography demonstrated a non-compacted to compacted myocardial ratio exceeding 2, with no additional findings suggestive of congenital heart disease.

Cardiac MRI provides superior spatial resolution compared to echocardiography and is particularly useful when image quality is limited or findings are inconclusive. It enables better delineation of noncompacted and compacted layers and allows assessment of late gadolinium enhancement, which may indicate myocardial fibrosis. The most cited MRI criteria, proposed by Petersen et al. in 2005, define LVNC as a bilayered myocardium is present and if the ratio of noncompacted to compacted myocardium is >2.3 at end-diastole[1].

A bilayered myocardium can also appear in healthy individuals, athletes, pregnant women or patients with aortic stenosis. Therefore, diagnostic criteria should be interpreted carefully in the clinical context to prevent overdiagnosis or mislabeling of physiological variants. Cardiac magnetic resonance imaging in this patient demonstrated non-compacted to compacted myocardial ratios of 3.2 in the lateral wall and 6.4 in the apex, without any additional findings indicative of congenital heart disease.

When an adult patient is identified with isolated LVNC, the first step is to evaluate whether any associated features are present, such as reduced left ventricular ejection fraction (LVEF), cardiomyopathy, arrhythmias, congenital heart defects (e.g., bicuspid aortic valve – BAV), or systemic manifestations such as musculoskeletal abnormalities or developmental delay. If such features are present, genetic testing should be considered. In the absence of associated features, a detailed family history should be obtained. If a significant family history is identified, genetic testing should still be considered. Conversely,

if there is neither family history nor associated features, the diagnostic yield of genetic testing is likely to be low, and clinical follow-up alone is sufficient[10].

In patients with LVNC who are identified as having left ventricular thrombus on imaging modalities or who have a history of atrial fibrillation, anticoagulation therapy should be initiated. For patients without these absolute indications, the decision to use anticoagulants should be based on the thromboembolic risk as assessed by the $CHADS_2$-VA score[11].

Applying the current guidelines for ICD implantation for both primary and secondary prevention of sudden cardiac death (SCD) is appropriate in patients with LVNC. In patients diagnosed with LVNC but with preserved ejection fraction, the benefit of ICD is greater in those who also have one additional risk factor (including a family history of SCD, nonsustained ventricular tachycardia (NSVT) on Holter monitoring, or a history of syncope)[11].

3.3. Association between the TTN gene variants and the patient's cardiomyopathy phenotype

Heterozygous mutations in TTN are frequently linked to cardiomyopathies and TTN is considered the most commonly implicated gene in these conditions. These mutations are generally divided into two main categories: truncating mutations and missense mutations. Truncating mutations cause premature termination of titin protein synthesis, which may produce an abnormal protein or lead to the loss of functional domains. In contrast, missense mutations involve the substitution of amino acids, potentially disrupting the normal function of the titin protein[12]. Next-generation sequencing revealed that the patient carries three heterozygous missense variants in the TTN gene: one in exon 273 (chr2:g.178609258A>G, p.Val17351Ala), one in exon 300 (chr2:g.178592919G>C, p.Pro19734Ala), and one in exon 358 (chr2:g.178535811T>A, p.Met33602Leu). The variant in exon 273 is located within the "Immunoglobulin I-set domain" of the TTN protein and has a minor allele frequency (MAF) of 0.01997%. The exon 300 variant lies within the "Fibronectin type III domain" and has a MAF of 0.00066%. The exon 358 variant is located in the "3′5′-cyclic nucleotide phosphodiesterase" domain of the TTN protein, also with a MAF of 0.00066%. Although all three variants were predicted to be benign by the in-silico tool MutationTaster2, the patient's phenotype suggests a possible association of these variants with a non-compaction cardiomyopathy phenotype. Among the three variants, only c.52052T>C has been reported in genetic databases, whereas c.59200C>G and c.100804A>T appear to be novel variants that have not been documented previously[13]. Further functional studies and investigations in additional patients are needed to clarify the role of gene–gene interactions and the potential contribution of these variants to cardiomyopathy.

4. CONCLUSION

Our clinical case demonstrates that cardiac arrhythmias may occur in patients with cardiomyopathy associated with genetic disorders. Differentiating between LVNC and AiCM is crucial for establishing an appropriate treatment strategy for the patient. Particular attention should be paid to the burden of ventricular premature beats, the recovery of left ventricular function following ablation, and the degree of non-compaction observed on echocardiography and cardiac magnetic resonance imaging.

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