Syncope secondary to arrhythmogenic left ventricular cardiomyopathy: a case report

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Background: Arrhythmogenic cardiomyopathy (ACM) is an inherited cardiac disease characterized by fibrofatty replacement of ventricular myocardium. Ventricular arrhythmia and sudden cardiac death (SCD) are the main clinical manifestations. ACM was previously called arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D). However, recent studies have shown that this disease is not limited to the right ventricle; biventricular involvement occurs in 50% of ACM patients. The left-dominant subtype was subsequently identified, which supported the adoption of the broader term "ACM". The clinical literature includes more extensive reports on ARVC, but reports on arrhythmogenic left ventricular cardiomyopathy (ALVC), which is likely to be underrecognized, are limited.

Case Description: In this report, we describe a case of secondary syncope in a patient with ALVC who developed right bundle branch block with ventricular tachycardia (RBBB-VT), with VT originating in the left ventricle (LV). Cardiac magnetic resonance (CMR) revealed significant enlargement of the LV, with LV dysfunction. Late gadolinium enhancement (LGE) and fat sequencing revealed that most of the free wall of the LV was replaced by fibrofatty tissue.

Conclusions: This report could help improve the understanding of this rare disease, and its management. CMR plays a key role in the diagnosis of ACM.

Keywords: Arrhythmogenic left ventricular cardiomyopathy (ALVC); arrhythmia; syncope; heart failure; case report

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Introduction

Arrhythmogenic cardiomyopathy (ACM) is an inherited cardiac disease characterized by fibrofatty replacement of ventricular myocardium. Ventricular arrhythmia and sudden cardiac death (SCD) are the main clinical manifestations (1). ACM was previously called arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D). However, recent studies have shown that this disease is not limited

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to the right ventricle; biventricular involvement occurs in 50% of ACM patients (1-3). The left-dominant subtype was subsequently identified, which supported the adoption of the broader term "ACM" (4).

Mutations in several genes, including desmosomal and non-desmosomal proteins, that contribute to the pathogenesis of ACM have been identified through genetic studies (5-7), suggesting that mutation detection is essential for risk stratification and family screening because of the significant phenotypic variability among affected individuals (8).

The criteria for ACM diagnosis have evolved from the initial proposed in 1994 to revised criteria by the International Task Force (ITF) in 2010 (9), which had good accuracy for ARVC but they lacked sensitivity for identifying of the expanding phenotypic spectrum of ACM. The 2020 Padua criteria (10) have been developed by international experts with the aim of improving the diagnosis of ACM by incorporating new left ventricular (LV) phenotypic criteria. The novelty of the Padua criteria essentially consists in introducing tissue characterization by cardiac magnetic resonance late gadolinium enhancement (CMR LGE) for detecting fibro-fatty myocardial replacement of both ventricles. and the addition of new electrocardiography (ECG) criteria, including depolarization/repolarization abnormalities and ventricular arrhythmias, specific for the LV involvement.

Advanced imaging techniques, especially CMR, are crucial for assessing ACM, as CMR LGE provides detailed insights into myocardial structure and composition, enabling the differentiation of ACM from other cardiomyopathies.

This report could help improve the understanding of this rare disease, and the way of its management. CMR is an important screening tool for this disease. We present this article in accordance with the CARE reporting checklist (available at https://acr.amegroups.com/article/view/10.21037/acr-24-131/rc).

Highlight box

Key findings

- We report a rare case of arrhythmogenic left ventricular cardiomyopathy (ALVC).
- Cardiac magnetic resonance (CMR) is a critical screening tool for this disease.

What is known and what is new?

- Arrhythmogenic cardiomyopathy (ACM) was previously known as arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D); however, recent studies have shown that ACM also includes biventricular and left-dominant subtypes (ALVC).
- This manuscript adds improved criteria (Padua criteria) for the diagnosis of ACM and emphasizes the diagnostic value of CMR in ACM.

What is the implication, and what should change now?

- An enhanced recognition and understanding of ALVC within the spectrum of ACM are crucial for accurate diagnosis and appropriate management.
- Clinicians should consider ALVC in patients presenting with syncope and ventricular arrhythmias, especially when CMR reveals left ventricle (LV) enlargement and fibrofatty replacement.
- The incorporation of CMR into routine diagnostic protocols for suspected ACM can improve diagnostic accuracy and guide therapeutic strategies, potentially reducing the risk of sudden cardiac death.

Case presentation

A 63-year-old woman was brought by ambulance to the emergency department after a syncopal event. When emergency responders arrived, the patient was responsive but groggy. She had been experiencing chest tightness, dizziness, and palpitations for 4 hours. Upon arrival at the emergency department, she experienced sustained monomorphic ventricular tachycardia (VT) with a heart rate of 200 beats/min (*Figure 1A*), followed by ventricular fibrillation associated with haemodynamic instability (blood pressure, 79/59 mmHg). Synchronized, biphasic, 200-J cardioversion followed by unsynchronized cardiac defibrillation converted the patient to atrial fibrillation with paroxysmal pleomorphic VT (*Figure 1B*). Intravenous amiodarone and noradrenaline infusions were administered. She was immediately sent to a tertiary hospital for further treatment.

Physical examination revealed a grade 2/6 systolic murmur in the auscultatory mitral area. No abnormalities were found by emergency coronary angiography. Her initial laboratory evaluation revealed moderately elevated serum troponin T (0.878 ng/mL) and N-terminal pro-brain natriuretic peptide (NT-proBNP) (3,970 pg/mL) levels. Dynamic ECG revealed frequent premature ventricular contractions (PVCs) with bigeminy (7,586 per 24 h).

A transthoracic echocardiogram (TTE) revealed increased left ventricular end-diastolic diameter (LVEDD, 73 mm) and left atrial diameter (LAD, 41 mm), along with regional thinning of the LV wall; hypokinesis of the inferior, posterior and lateral walls; and reduced left ventricular ejection fraction (LVEF, 33%) (*Figure 2*).

CMR revealed that the LVEF was decreased, while

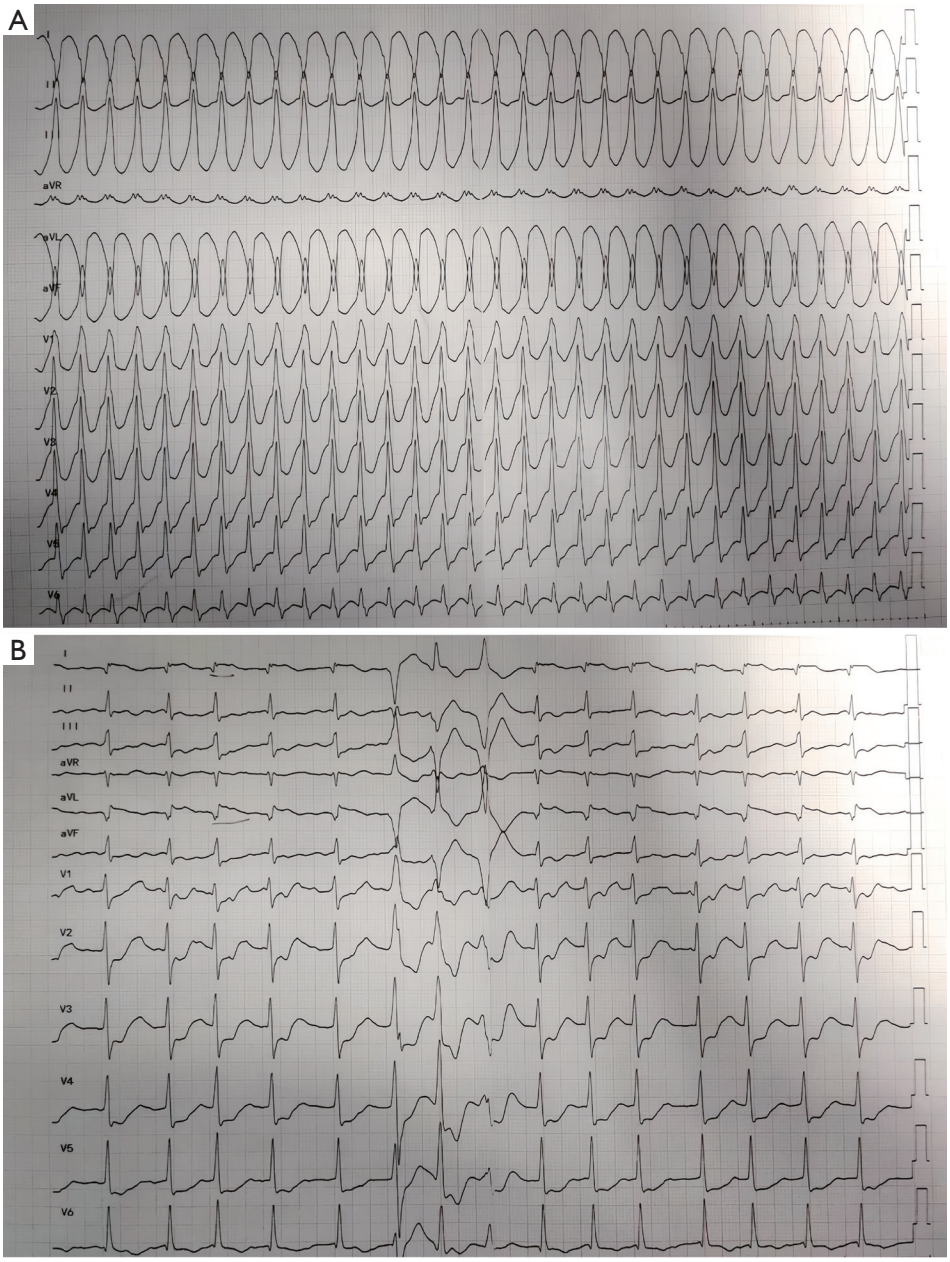

Figure 1 Twelve-lead ECG performed when the patient arrived at the emergency department. (A) The first recorded ECG; (B) the ECG recorded after electrical cardioversion and defibrillation. ECG, electrocardiogram.

most of the LV free wall, except the ventricular septum, was significantly thinned and dyskinetic. Late gadolinium enhancement (LGE) revealed LV fibrofatty replacement in an extensive area exclusively in the LV free wall [LVEDD, 77 mm; LA, 35 mm; left ventricular end-diastolic volume index (LVEDVi), 279.12 mL; and LVEF, 15.34%] (*Figure 3*).

The patient was in good physical condition and denied a history of diseases such as hypertension, diabetes and coronary heart disease, etc. She wasn't addicted to alcohol or tobacco, and reported no family history of SCD or unexplained premature death. We performed whole-exome sequencing (WES) including 21 genes (*CDH2*, *CTNNA3*, *DES*, *DMD*, *DSC2*, *DSG2*, *DSP*, *FLNC*, *JUP*, *LMNA*, *MYBPC3*, *OBSCN*, *PKP2*, *PLB*, *PLN*, *RYR2*, *SCN5A*,

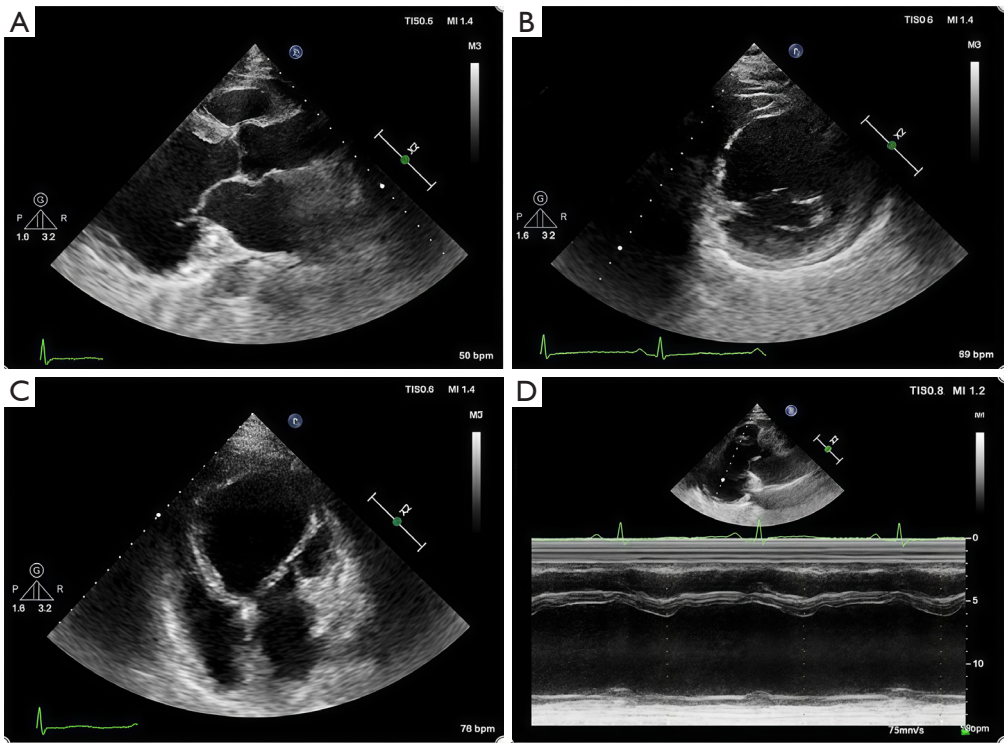

Figure 2 TTE findings. (A) Long-axis left ventricular outflow view; (B) short-axis left ventricular view; (C) four-chamber view; (D) long-axis M mode TTE. TTE, transthoracic echocardiogram.

TGFB3, *TMEM43*, *TP63*, and *TTN*) that had previously been reported to be associated with or are regarded as candidates for the development of ACM (5-7). Variants in 8 genes, *CACNA1C*, *DCHS1*, *DMD*, *DTNA*, *FBN1*, *HPS1*, *MEGF8*, and *MYH7*, were identified in genetic tests of the proband. After the gene variants were identified in the proband, genetic and clinical cascade screening was subsequently performed on first-generation family members. Sanger verification of the 8 mutated genes was performed, and mutations were found in some of the same sites (*Table 1*). However, no pathogenic genes highly related to ACM were identified.

Anti-heart failure and anti-arrhythmic drugs were administered during hospitalization. Implantation of an implantable cardioverter defibrillator (ICD) was suggested after the patient stabilized. However, the patient and her family members consented only to pharmacotherapy.

Over more than 2 years of follow-up, the patient avoided competitive sports, and didn't experience chest tightness, breathiness, palpitations or syncope. After discharge, the patient insisted on taking spironolactone, torsemide, metoprolol, amiodarone, and sacubitril-valsartan (target dose: 200 mg twice daily) for the next 6 months. Compared with that at the 6th month of follow-up, the dynamic ECG revealed an increased number of PVCs with transient VT at the 12th month of follow-up (5,245 per 24 h *vs.* 84 per 24 h). This difference was considered to be caused by the patient's voluntary discontinuation of metoprolol and amiodarone. After reverting to the original medication and adding dapagliflozin, the number of PVCs was significantly reduced (318 per 24 h), and the transient VT disappeared. Except for a slight decrease in NT-proBNP levels, TTE and CMR showed no significant improvement in various indicators of cardiac structure, accompanied by a progressive decline in LVEF (*Table 2*).

All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

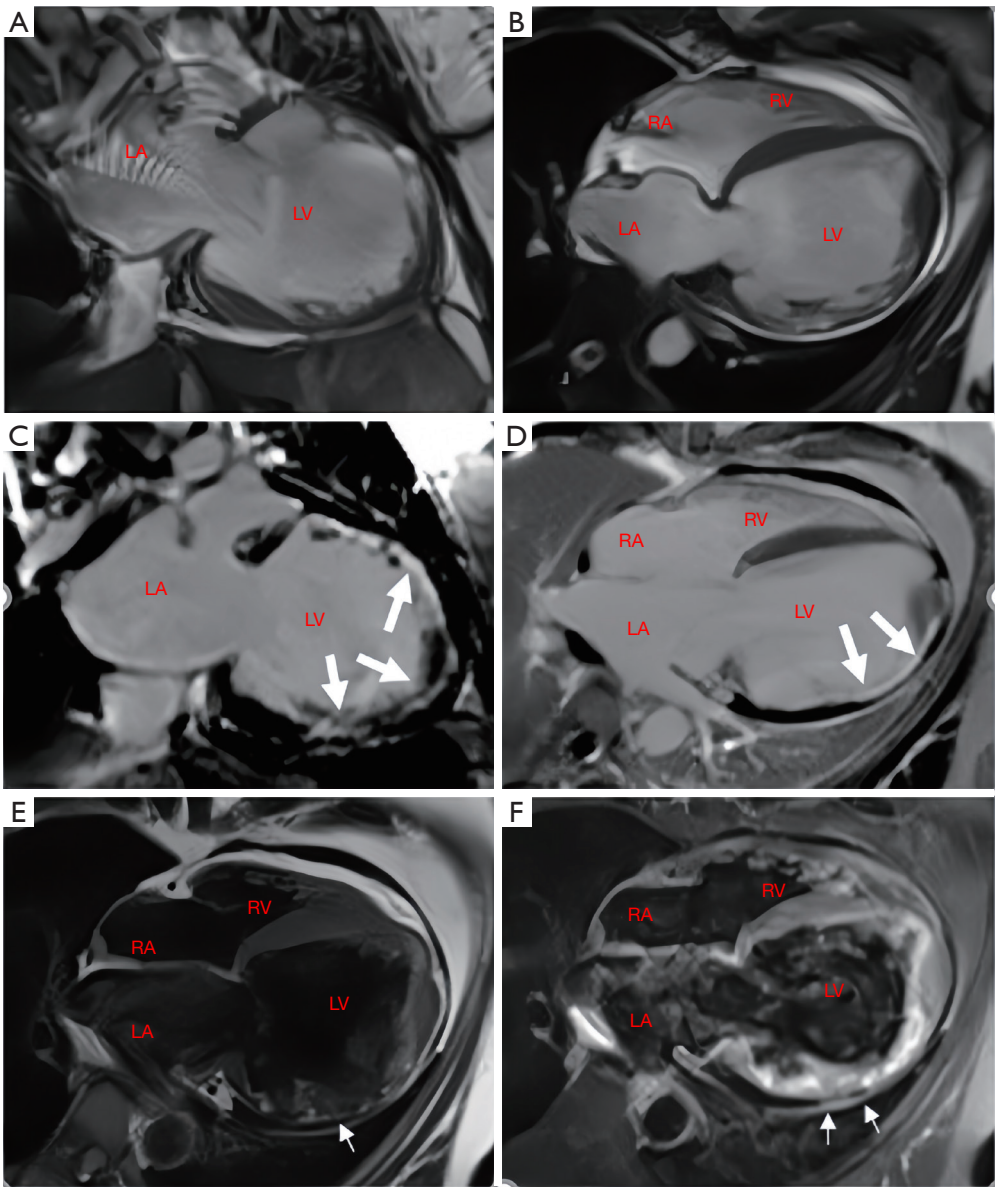

Figure 3 CMR findings. (A,B) The LV was dilated with severely reduced systolic function (LVEF, 15.34%), and the anterior, inferior and lateral walls of the LV thinned and exhibited hypokinesis. (C,D) CMR LGE images showing extensive enhancement of the anterior, inferior and lateral walls of the LV (arrows). (E,F) Images of T2-weighted sequences with and without fat suppression showing fatty infiltration in the lateral wall of the LV (arrows). CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; LVEF, left ventricular ejection fraction.

Discussion

ACM is a genetic cardiac disease characterized by replacement of the ventricular myocardium with fibrous adipose tissue and SCD (1). Recent studies have shown that biventricular involvement occurs in 50% of ACM patients, and LV involvement is predominant in some patients (1-3). In 2019, a study published by Fuwai Hospital in China classified ACM according to the clinical features, genetics, and pathological features of myocardial tissue (11); this study was the first international establishment of an accurate classification of ACM and was named the "Fuwai classification" (12). In this study, ACM was divided into

Table 1 Genetic testing of the proband and Sanger verification results

Gene	Gene verification site	Patient's first child	Patient's second child
CACNA1C	12:2778134:C>T	Heterozygous mutation	Heterozygous mutation
DCHS1	11:6644107:T>C	Heterozygous mutation	No mutation
DMD	X:32662337:C>A	No mutation	Hemizygous mutation
DTNA	18:32468684:T>G	No mutation	No mutation
FBN1	15:48736796:A>G	No mutation	No mutation
HPS1	10:100177359:G>A	No mutation	No mutation
MEGF8	10:100177359:G>A	No mutation	Heterozygous mutation
MYH7	14:23884292:T>C	No mutation	Heterozygous mutation

Table 2 Changes in CMR, TTE and NT-ProBNP during hospitalization and follow-up

Parameters	11th December 2019	16th July 2020	9th December 2020	24th April 2022
CMR				
LVEDD (mm)	77	78	78	76
LAD (mm)	35	42	34	31
LVEDVi (mL)	279.12	338.08	246.17	233.73
LVESVi (mL)	236.29	275.94	197.9	196.89
LVEF (%)	15.34	18.38	19.61	15.76
TTE				
LVEDD (mm)	73	76	73	82
LVESD (mm)	61	63	60	71
LAD (mm)	41	39	41	42
LVEF (%)	33	34	36	27
NT-ProBNP (pg/mL)	3,970	1,293	1,251	1,288

CMR, cardiac magnetic resonance; TTE, transthoracic echocardiogram; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LAD, left atrial diameter; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; NT-ProBNP, N-terminal pro-brain natriuretic peptide.

four categories, of which type 4 was typical LV-dominant ACM, with little or no right ventricular involvement, and no known gene mutation. Moreover, this study analyzed the degree of ventricular involvement through CMR LGE, and based on the results, ACM was divided into three subtypes: single right ventricular type, biventricular type, and left ventricular dominant type. This classification is based primarily on CMR, regardless of the underlying genotype and histopathological characteristics (11). The recent International Expert Consensus document proposes the Padua criteria, an upgrade of the criteria for diagnosis of the entire spectrum of phenotypic variants of ACM, particularly left-dominant forms, highlighting the use of CMR (10). The approach used in the 1994 and 2010 ITF scoring systems, classifying morphofunctional, structural, histological, ECG, arrhythmic, and genetic features of ARVC as "major" and "minor" criteria on the basis of their disease-specificity is maintained in the Padua criteria. In the newly proposed diagnostic criteria for LV involvement, they are classified as "major" when they are deemed specific and necessary for diagnosis and "minor" when they are not required, but contribute to refining the characterization

of the LV phenotype. A diagnosis of arrhythmogenic left ventricular cardiomyopathy (ALVC) is met in patients fulfilling the LV criteria for "definite", i.e., 2 major, 1 major and 2 minor, or 4 minor criteria from different categories [major: LV LGE was detected by CMR; minor: global LV systolic dysfunction was detected by echocardiography and CMR; minor: PVCs (500 per 24 h), non-sustained or sustained VT with a right bundle branch block (RBBB) morphology].

With the development of imaging technology, CMR can be used to better assess the histology, function, and morphology of the heart, improving diagnostic sensitivity (13,14). In this case, CMR revealed that the left ventricle (LV) was dilated with severely reduced systolic function (LVEDD, 77 mm; LVEDVi, 279.12 mL; LVEF, 15.34%). Thinning of the walls with hypokinesia of the anterior, inferior, and lateral walls of the LV was detected on CMR. The LV anterior, inferior, and lateral walls showed LGE on CMR. The presenting arrhythmia contained frequent PVCs (7,586 per 24 h) and non-sustained VT with an RBBB morphology, which met the Padua criteria for the diagnosis of ALVC (1 major and 2 minor criteria) (10). According to the "Fuwai classification" (12), ALVC is LV-dominant subtype of type 4.

Patients with ACM often suffer from tachyarrhythmia dominated by VT and ventricular fibrillation, and are prone to SCD. The ACM expert consensus published by the Heart Rhythm Society (HRS) in 2019 and the Cardiac Society of Australia and New Zealand (CSANZ) statement on ACM both stated that an ICD is the preferred solution for the prevention of SCD. The 2023 ESC task-force expert consensus on the management of cardiomyopathies recommended ICD implantation for the primary prevention of SCD in patients with ALVC depending on genotype specificity (15).

Catheter ablation is an effective preventive measure for controlling persistent simplex VT, but the recurrence rate is very high. This technique is effective in improving symptoms but cannot completely prevent the occurrence of SCD, so ablation cannot replace ICD as a treatment for VT.

Antiarrhythmic drugs are another effective intervention in ACM in addition to catheter ablation and ICD implantation. These drugs can reduce the recurrence rate of VT but cannot effectively prevent the occurrence of SCD. Beta-blockers or amiodarone alone or in combination are by far the most effective drugs and have a low incidence of associated arrhythmias. In addition, standardized anti-heart failure drugs such as angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs)/angiotensin-neprilysin inhibitors (sacubitril/valsartan), beta blockers, and aldosterone antagonists are recommended for patients with ACM associated with heart failure.

The progressive decline in LV systolic function in the patient was believed to be due to the severe degree of LV fibrosis over the 2 years of follow-up. Although adequate doses of sacubitril-valsartan were administered, LV remodelling was not reversed. However, the effects of antiarrhythmic drugs were significant in terms of changes in PVCs and tachycardia after treatment.

Ye *et al.* (5) categorized genes according to the confidence that the genes are indeed associated with ACM, and identified three genes (*OBSCN*, *MYBPC3*, and *DMD*) as "low confidence" genes. In this case, although a DMD mutation was identified by genetic testing, it was classified as highly unlikely to be a monogenic variant that causes ALVC. The progeny verification of the 8 mutated genes revealed that some relatives had mutations at the same site, which can be confirmed to be hereditary but not disease-causing genes.

ALVC is a complex disease, and genetic mutations alone are not sufficient for a diagnosis. Owing to the phenotypic diversity of ACM and incomplete dominance, disease-causing genes are not found in 30% of patients (11,16,17). In the age of expanding access to genetic testing, the specifics of clinical genotype-phenotype correlations are growing rapidly (18). We acknowledge that there are some limitations in our case report, such as the lack of identified genetic mutations and limited follow-up data. Therefore, further research is needed, including a better understanding of the genetic background, more in-depth genetic testing, and extended follow-up.

Conclusions

This report could help improve the understanding of ALVC. This multidisciplinary perspective is crucial for early recognition and intervention, given the risk of SCD associated with ALVC. Continued research into the clinical and genetic characteristics of ALVC, along with advancements in imaging modalities, are vital for improving patient management and exploring targeted treatment strategies for this rare cardiomyopathy.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://acr.amegroups.com/article/view/10.21037/acr-24-131/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://acr.amegroups.com/article/view/10.21037/acr-24-131/coif). All authors report that this work was supported by the National Natural Science Foundations of China (No. 82160100). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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