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CASE REPORT

A Case of Left-Dominant Arrhythmogenic Cardiomyopathy Presenting with Cardiac Arrest

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Abstract

Arrhythmogenic cardiomyopathy (ACM) is a genetically inherited cardiomyopathy characterised by the fibro-fatty replacement of the myocardium. Patients can present with symptoms of arrhythmia or heart failure; it is a common cause of sudden cardiac arrest and death in young adults. Originally considered as right ventricular arrhythmogenic cardiomyopathy or dysplasia, this terminology has been updated to include left-dominant and biventricular phenotypes. We report a case of a 41-year-old man who presented with an out-of-hospital cardiac arrest due to ventricular arrhythmia as a first presentation. The patient underwent cardiac magnetic resonance imaging, which revealed severe left ventricular (LV) dysfunction with LV fibro-fatty infiltration and a ring-like subepicardial and mid-wall late gadolinium enhancement in the LV. Genetic sequencing identified a pathogenic desmoplakin gene variant. A diagnosis of left-dominant ACM (ALVC) was made based on his presentation, imaging, and genetic findings. Guideline-directed medical therapy with a beta-blocker and an angiotensin-converting enzyme inhibitor was initiated in the first instance. An implantable cardioverter-defibrillator was inserted for secondary prevention. This report highlights the presentation, current diagnostic criteria with a particular focus on ALVC, and the importance of the multimodality approach in the recognition and management of patients with ACM.

Key words: arrhythmogenic left ventricular cardiomyopathy; cardiomyopathies; magnetic resonance imaging; sudden cardiac death; genetic testing; case report

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Introduction

Arrhythmogenic cardiomyopathy (ACM) is a familial cardiomyopathy characterised by the replacement of ventricular cardiomyocytes with fibro-fatty tissue (Varrenti et al, 2024). This process predisposes individuals to ventricular arrhythmias, sudden cardiac death (SCD), and heart failure (HF) caused by ventricular dysfunction (El Hadi et al, 2023; Graziosi et al, 2022). Previously referred to as 'arrhythmogenic right ventricular cardiomyopathy' (ARVC), genotype-phenotype correlation, post-mortem and imaging studies with contrast-enhanced cardiac magnetic resonance (CMR) imaging have since shown biventricular involvement where left ventricular (LV) involvement can have severe phenotypic manifestation (Arbelo et al, 2023; Miles et al, 2019). Thus, ACM is now an umbrella term encompassing three phenotypes: arrhythmogenic cardiomyopathy with mainly right ventricular involvement, arrhythmogenic cardiomyopathy with mainly LV involvement,

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and arrhythmogenic cardiomyopathy with biventricular involvement (Corrado et al, 2020; Varrenti et al, 2024).

European study approximates ACM to be prevalent in 0.02–0.05% of the population (Pilichou et al, 2016). However, these figures are likely underestimated and do not reflect the incidence of ACM with left predominant or biventricular involvement (Maniar et al, 2023). Recent international epidemiological studies spanning from 2010 to 2020 show a rising incidence of ACM (Liu et al, 2024). The reported sex differences in prevalence are inconsistent, with a study noting a higher prevalence in men (Liu et al, 2024), whilst others reporting similar proportions (Choudhary et al, 2016). This condition can affect the young, with patients on average presenting in their 30s, but symptoms and signs can occur as early as 10 (Basharat et al, 2023; Groeneweg et al, 2015). Typically inherited in an autosomal dominant pattern, clinical presentation can be heterogeneous because of incomplete penetrance and variable expressivity (El Hadi et al, 2023). In most patients, alterations in the genes encoding desmosomal proteins which lead to cardiomyocyte detachment are considered responsible (Corrado et al, 2017). However, non-desmosomal genes also play a role in disease development (Bariani et al, 2022).

The pathogenesis of ACM involves cardiomyocyte death and subsequent progressive replacement of the ventricular myocardium with fibro-fatty tissue, starting from the epicardium to the endocardium (Basharat et al, 2023; Corrado et al, 2023). Mutations in genes responsible for cell-cell adhesion, ion channels, and cytoskeletal components affect the action potential of cardiac myocytes, predisposing patients to life-threatening arrhythmias and cardiac arrest (Basharat et al, 2023).

Patients can present with symptoms of palpitations, syncope, or dyspnoea (He et al, 2020). However, presentation with malignant ventricular arrhythmias and cardiac arrest, which can lead to SCD, can also occur as a first presentation (Varrenti et al, 2024). Inflammatory changes have been thought to cause patients to present with acute chest pain and lead to the release of cardiac enzymes, which is described as the ‘hot phase’ of ACM (Protonotarios and Elliott, 2020). A three-phase disease progression has been described: an initial ‘concealed phase’ in which patients are asymptomatic but at risk of sudden cardiac death and arrhythmias; an ‘electrical phase’ in which symptomatic arrhythmias occur; and a diffuse progressive disease in which patients present with HF (Haugaa et al, 2016).

Left-dominant ACM (ALVC), as discussed in this case, has a distinct phenotype that allows us to differentiate it from the ARVC phenotype. Electrocardiogram (ECG) changes, such as low-amplitude QRS complexes, T wave inversion in the inferolateral leads, detection of ventricular arrhythmias with right bundle branch block, and changes on CMR suggestive of fibrofatty infiltration and LV fibrosis, are all indicative of the underlying disease process (Varrenti et al, 2024). Genetic testing plays an important role in ACM because there are high-risk genotypes associated with an increased risk of SCD, hence highlighting the importance of adapting a multiparametric approach that leads to an aetiology-specific diagnosis and personalised treatment plan for this disease (Arbelo et al, 2023).

Case Report

A 41-year-old man presented to the Emergency Department in 2019 following an out-of-hospital cardiac arrest. He had lost consciousness whilst swimming, with no preceding symptoms. Bystander cardiopulmonary resuscitation was immediately initiated, and defibrillation using an automated external defibrillator was successful in restoring spontaneous circulation. Apart from gout, he had no past medical history and denied the use of illicit drugs, cigarettes, or alcohol. Of relevance, there was a family history of sudden death in two first-degree relatives; the mother died at the age of 35 and the brother died at the age of 28.

On arrival, his vital signs and physical examination were normal. The initial high sensitivity troponin I was 208 ng/L, and peaked at 608 ng/L (normal range 0–34 ng/L), and N-terminal pro-brain natriuretic peptide (NT-proBNP) was 605 pg/mL (normal range <400 pg/mL). An electrocardiogram (ECG) (Fig. 1) showed sinus rhythm, with normal conduction intervals including a normal corrected QT interval. Low QRS voltages were observed in the limb leads. There was an isolated T wave inversion in lead augmented vector left (aVL). Self-terminating non-sustained ventricular tachycardia (NSVT) was observed on telemetry monitoring.

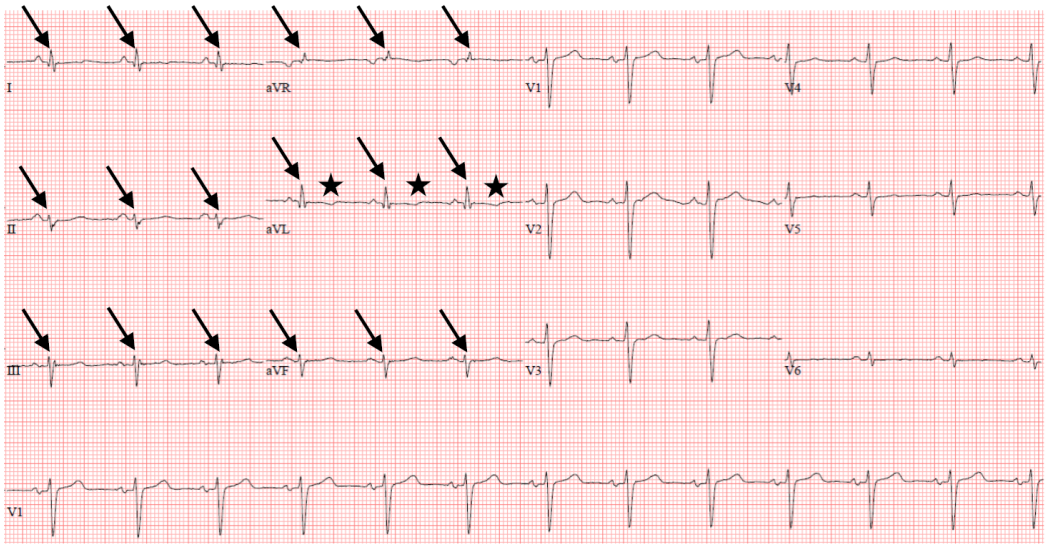

Fig. 1. The patient's electrocardiogram (ECG) during index admission in hospital. This shows a sinus rhythm with a ventricular rate of 76 beats per minute. The conduction intervals in this ECG are within normal limits: PR interval 152 milliseconds (ms), QRS duration 100 ms, QT/QTc 406 ms/456 ms. The T wave inversion in aVL is marked by the star symbols. The arrows highlight the low QRS voltages in the limb leads which is a typical feature of left-dominant arrhythmogenic cardiomyopathy. aVL, augmented vector left; aVR, augmented vector right; aVF, augmented vector foot.

Chest X-ray (**Supplementary Fig. 1A**) and computed tomography of the brain (**Supplementary Fig. 1B**) were normal. Transthoracic echocardiography (Vivid E95; GE Healthcare, Horten, Norway) showed a globular appearance of the left ventricle (LV) with mild dilation (LV end diastolic diameter 6.6 cm) (**Supplementary Fig. 1C**), and a Simpson's biplane LV ejection fraction (EF) of 33%, consistent

with severe LV systolic dysfunction (LVSD). The right ventricular (RV) size and function were within normal limits. No valvular abnormalities were detected. Invasive coronary angiography demonstrated unobstructed epicardial coronary arteries (**Supplementary Fig. 1D,E**).

The patient subsequently underwent CMR imaging (1.5 Tesla Avanto; Siemens Healthcare, Erlangen, Germany), showing a dilated LV (left ventricular end-diastolic volume index (LVEDVi) 128 mL/m^2), with severely impaired LV systolic function (left ventricular ejection fraction (LVEF) 33%). The images were suggestive of fatty infiltration of the LV myocardium with myocardial thinning and akinetic mid to apical anterolateral wall (Fig. 2A). There was borderline RV dilatation (right ventricular end-diastolic volume index (RVEDVi) 112 mL/m^2) with mildly impaired global RV systolic function (right ventricular ejection fraction (RVEF) 45%). The native T1 of the septal wall was low at 861 ms (normal range 908–988 ms by Modified Look-Locker inversion recovery) suggestive of possible fatty infiltration (Fig. 2B). There was extensive septal midwall and subepicardial late gadolinium enhancement (LGE) at the inferior, inferolateral, anterior and anterolateral walls in the LV, forming a ring-like LGE appearance (Fig. 2C,D). Considering his clinical presentation, the CMR appearance was highly suggestive of ALVC.

Subsequent genetic analysis using next generation sequencing was carried out to identify for gene variants in the 50 tested genes encoding arrhythmogenic disorders associated with SCD (**Supplementary Methods**). This identified a heterogeneous sequence change encoding a pathogenic desmoplakin (*DSP*) gene variant, *DSP c.928dupG; p.(Glu310Glyfs *1)*, confirming a diagnosis of ALVC.

The patient was initiated on appropriate therapy for LV dysfunction, including an angiotensin-converting enzyme inhibitor (Enalapril 2.5 mg twice daily) and a beta-blocker (Carvedilol 6.25 mg twice daily) in the first instance. Due to symptoms of postural dizziness, his treatment was slowly up-titrated to the maximal tolerated doses of Enalapril and Carvedilol. A secondary prevention dual chamber implantable cardiac defibrillator (ICD) was implanted.

The most recent transthoracic echocardiogram performed in 2023, four years after his index admission, has shown a decrease in the LV end diastolic diameter to 5.9 cm with improvement in the LVEF to 47% (**Supplementary Fig. 1F**), indicating mild LV systolic dysfunction. The RV size and function were within the normal limits. Recently, he experienced several episodes of palpitations due to ventricular arrhythmia, which was terminated by anti-tachycardia pacing from his ICD. Following these arrhythmic episodes, his Carvedilol was changed to Sotalol 80 mg twice daily in the first instance and further up-titrated to 120 mg twice daily, with no further arrhythmia noted thereafter. The possibility of catheter ablation was discussed with him if he continues to have frequent ventricular arrhythmias despite pharmacological therapy.

Discussion

ACM is a rare genetic cardiomyopathy, and diagnosis of this condition can be challenging due to its similar presentation to other conditions like dilated cardiomy-

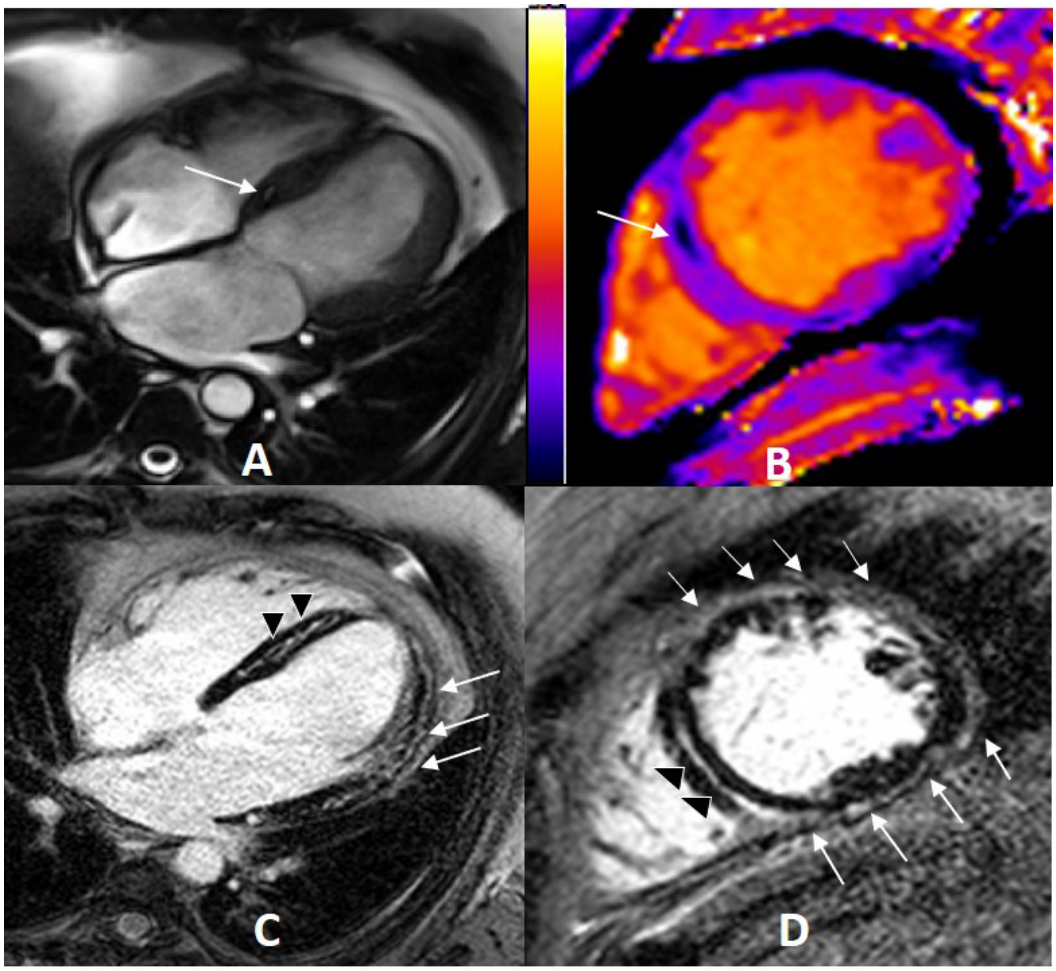

Fig. 2. The patient's Cardiovascular Magnetic Resonance imaging. (A) showed cine imaging of the 4-chamber suggestive of fat in the myocardium as shown by the arrow. (B) showed the T1 map (Modified Look-Locker inversion recovery) of the septal area had corresponding low native T1 as indicated by the dark blue area on the septum shown by the arrow. A region of interest drawn on this particular area confirmed low native T1 (861 milliseconds [ms], normal range 908–988 ms) which was suggestive of possible fatty infiltration in the myocardium. (C) showed extensive late gadolinium enhancement (LGE) observed throughout the mid-wall of the septum (as shown by the triangles) and subepicardial LGE shown at the anterolateral wall (as shown by the arrows). (D) showed LGE image of the short axis with mid-wall LGE at the septum (as shown by the triangles) and subepicardial LGE at the inferior, inferolateral, anterior, and anterolateral walls (as shown by the arrows) forming a typical ring-like LGE pattern, which can be seen in desmoplakin variants.

opathy, myocarditis, and sarcoidosis (Monda et al, 2023). Diagnostic work-up for ACM is currently guided by the updated international 'Padua criteria' (Corrado et al, 2020). It comprises three parts: characteristic functional and structural abnormalities detected by imaging; specific conduction abnormalities detected during rhythm monitoring; and detection of associated pathogenic gene variants related to ACM. It also separates the different phenotypic variants of the disease and highlights the different findings between them. Relevant to this case, ALVC is dependent on the presence of a major structural criterion and a related ACM gene variant, as imaging findings can be similar to conditions like myocarditis (Galizia et al, 2024).

Immediate bystander resuscitation and defibrillation were key to aborting cardiac arrest in this case and preventing worse outcomes. Males with ACM have a higher incidence of cardiac arrest as the initial manifestation, without any prior symptoms, and have a higher mortality rate (Miles et al, 2019). A study of 74 patients with CMR features of ALVC with a median follow-up of 3.7 years reported major adverse cardiovascular events in 32% of the cohort, including SCD in 8.1% (Feliu et al, 2020). The multi-national DSP-ERADOS (Desmoplakin SPecific Effort for a RAre Disease Outcome Study) Network patient registry including 471 patients with *DSP* identified female sex, NSVT, premature ventricular contraction (PVC) burden, and LV and RV dysfunction as independent predictors of ventricular arrhythmia (Carrick et al, 2024).

Subtle, electrophysiological changes in ACM can be present before structural or functional changes (Boonstra et al, 2023). Depolarisation abnormalities due to ALVC manifest with low-voltage QRS in limb leads (<0.5 mV peak to peak), in the absence of obesity, emphysema, or pericardial effusion (Corrado et al, 2020; Spadotto et al, 2022). In ALVC, the presence of T wave inversion in the left precordial leads V4–V6, in the absence of bundle branch block is a minor criterion (Corrado et al, 2020).

From an imaging perspective, the detection of global LV systolic dysfunction with or without dilatation and regional wall motion abnormalities of the LV free wall, septum, or both are minor criteria for ALVC (Corrado et al, 2020). CMR allows a more accurate evaluation of cardiac function and structure while also allowing for non-invasive tissue characterisation (Arbelo et al, 2023). T1-weighted imaging and T1 mapping can be used to identify areas of fibrofatty infiltration (Dowd et al, 2021; Monda et al, 2023). LGE allows for the identification of areas of myocardial fibrosis or oedema, and distinct patterns of LGE can be detected in different disease processes (Arbelo et al, 2023). Using CMR, the presence of transmural RV LGE in one or more regions of the RV, or presence of LV LGE in at least one segment of the LV septum or free wall were defined as the major criteria for the diagnosis of ARVC and ALVC, respectively (Corrado et al, 2020). ACM typically presents with LGE in the subepicardial space, usually at the inferior and lateral ventricular walls, with a ring-like subepicardial pattern seen in certain variants (Arbelo et al, 2023; Galizia et al, 2024).

Patterns of myocardial fibrosis may also be linked with pathogenic gene variants with a higher arrhythmic propensity and risk of SCD (Arbelo et al, 2023). Augusto et al (2020) reported a 'ring-like' subepicardial LGE pattern in patients with *DSP* and filamin C (*FLNC*) genotypes, as also seen in this patient. This 'ring-like' LGE pattern can also be seen in association with phospholamban (*PLN*) and desmin (*DES*) pathogenic gene variants (Arbelo et al, 2023). CMR has been shown to provide prognostic value when assessing ACM. Patients with a negative CMR (absence of CMR signs of ACM) have lower PVC counts than those with ALVC and biventricular ACM who have higher rates of aborted cardiac arrest, SCD, and appropriate ICD intervention (Aquaro et al, 2020).

ACM can be challenging to differentiate from other cardiac conditions with similar LGE patterns, such as myocarditis and cardiac sarcoidosis. Thus, a detailed family history and genetic sequencing are recommended to guide diagnosis (Monda et al, 2023). Confirmation of ACM in first-degree relatives or detection of associated gene variants is a major criterion for diagnosis. Both desmosomal and non-desmosomal genes are linked to ACM (Bariani et al, 2022). The involved desmosomal genes include *DSP*, plakophillin (*PKP*), desmoglein-2 (*DSG2*), and desmocollin-2 (*DSC2*) (Li et al, 2023). Non-desmosomal gene variants involved in ion channel control (*PLN*, sodium channel protein type 5A [*SCN5A*]), coding of structural proteins (lamin a/c or *LMNA*, *DES*) (Basharat et al, 2023; Li et al, 2023) are also responsible. Specific genotype-phenotype correlations have been reported: *PKP2* and *DSC2* variants typically present with an ARVC phenotype; *DSP* variants with ALVC and biventricular ACM; and *DES* and *FLNC* with ALVC (Bariani et al, 2022; Galizia et al, 2024; Wilde et al, 2022). *DSP* variants particularly cause a unique form of cardiomyopathy with an increased prevalence of myocardial inflammatory episodes, LV fibrosis, and systolic dysfunction (Smith et al, 2020).

Identifying and understanding different gene variants may help us understand individual prognosis and clinical outcomes. In an 11-year follow-up study of patients with ARVC, Christensen et al (2022) reported a higher incidence of arrhythmia in those with the *PKP2* genotype than in those with the *DSC2*, *DSG2* and *DSP* genotypes. Another group reported that *DSP* gene variants have higher rates of LV dysfunction and HF compared with *PKP2* carriers (Bhonsale et al, 2015). Pathogenic *DSP* variants are also associated with a high risk of cardiac arrest, sustained ventricular arrhythmias (Wang et al, 2022), and high rates of SCD in the young (Bhonsale et al, 2015).

However, genetic testing and a subsequent diagnosis of inherited cardiomyopathy may lead to anxiety, guilt, and uncertainty for the individual and their family (Moharem-Elgamal et al, 2020). Genetic counselling to discuss inheritance patterns, phenotypic implications, and provide psychological support is crucial in the patient journey and strongly emphasised in clinical practice guidelines (Arbelo et al, 2023). Once a proband in a family is confirmed to have ACM, first-degree relatives are recommended to undergo cardiac testing (12 lead ECG, ambulatory ECG, and imaging), alongside cascade genetic testing to identify the presence of pathogenic gene variants (Towbin et al, 2019).

Following diagnosis, treatment strategies are based on the clinical presentation and symptoms, with the goal of preventing future complications. Antiarrhythmic medications, such as beta-blockers and amiodarone, can be used to control arrhythmic burden; however persistent symptoms may require catheter ablation therapy (Tadros et al, 2023). Avoidance of intense physical exertion is recommended because of its association with exercise-related arrhythmias and progression of pathological structural changes (Arbelo et al, 2023; Corrado et al, 2023; Zathar et al, 2024).

HF with reduced ejection fraction should be managed as per the guidelines with beta-blockers, angiotensin receptor-neprilysin inhibitors or angiotensin-converting enzyme inhibitors, mineralocorticoid receptor antagonists, and sodium-glucose co-

transporter-2 inhibitors (Haydock and Flett, 2022). Heart transplantation may be required for patients who fail to respond to treatment, have end-stage HF, or present with refractory ventricular arrhythmias (Petruescu et al, 2023).

For patients presenting with cardiac arrest, like the patient in this case, or those with sustained ventricular tachycardia with haemodynamic compromise (>30 seconds), an ICD is recommended for secondary prevention (Arbelo et al, 2023; Towbin et al, 2019). Risk stratification is challenging for patients in primary prevention settings (Spadotto et al, 2022). Recently, a gene-specific risk score was developed to help estimate the risk of ventricular arrhythmia in people with *DSP*-related cardiomyopathy (Carrick et al, 2024). There is limited data on risk prediction for primary prevention of SCD in ACM. However, genotype is likely to play a role with variants such as *PLN*, Transmembrane protein 43 (*TMEM43*), *DES*, *DSP*, *LMNA*, *FLNC* (truncating variants), and RNA binding motif 20 (*RBM20*) having a significantly higher rate of major arrhythmic event regardless of their LVEF (Arbelo et al, 2023). Other factors that can be considered include a family history of SCD, NSVT, or the presence of significant LGE (Arbelo et al, 2023). A better understanding of genotype-phenotype correlation can help build risk stratification models to assess individuals at greater risk of arrhythmias or HF progression (Murray and James, 2022). Currently, it is unclear whether specific genotypes respond better to certain therapies, and further work is required to elucidate this (Gaine and Calkins, 2023).

Few cases of cardiac arrest as the initial presentation of ACM have been reported and to our knowledge, we describe a novel case of a patient with a *DSP* gene variant who presents with a cardiac arrest as the first manifestation of ACM. We discuss the visualisation of fibrofatty infiltration with T1 mapping using CMR and demonstrate a typical LGE pattern associated with the *DSP* gene. A limitation of this study would be the lack of histological confirmation to support the findings of fibrofatty infiltration from T1 mapping although there are extensive references of the use of this sequence in detecting fat (Cipriani et al, 2023; Dowd et al, 2021).

Conclusion

Inherited cardiomyopathy, such as ACM, is a key differential diagnosis in younger patients presenting with cardiac arrest or ventricular arrhythmias, in the absence of any obvious cause and relevant family history. We present a case of a 41-year-old man who suffered an out-of-hospital cardiac arrest while swimming. Further investigations, including echocardiography, CMR, and genetic sequencing led to a diagnosis of ALVC. The Padua guidelines create a systematic approach for identifying clinical features to support making a diagnosis of ACM. Early diagnosis of this disease, aided by genetic testing and multimodality cardiac imaging, is important to try and mitigate the risk of future arrhythmias and HF. Further work on understanding the genotype-phenotype correlation may aid in risk stratification and allow for personalised treatment.

Learning Points

- The pathogenesis of ACM involves fibrofatty infiltration in the ventricular myocardium, predisposing patients to life-threatening ventricular arrhythmias and the development of heart failure.
- ECG abnormalities may be subtle, particularly in left dominant ACM.
- Tissue characterisation and accurate structural and functional assessment with CMR is central to the detection of characteristic morphological and functional changes seen in ACM.
- Identification of pathogenic gene alterations associated with the development of ACM is key to enable phenotype-genotype correlation enabling personalised treatment for the patients, and appropriate genetic counselling and clinical screening for their families.

Availability of Data and Materials

The data sets created for the study are available from the corresponding author upon request.

Author Contributions

SP contributed to the data gathering, design, drafting, editing and revision of the manuscript. SN contributed to the conception, data gathering, interpretation, design, editing and revision of the manuscript. AJ contributed to the acquisition, analysis, interpretation, editing and revision of the manuscript. CJC contributed to the acquisition, analysis, interpretation, editing and revision of the manuscript. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this case report.

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Conflict of Interest

CJC has received advisory fees from Cytokinetics and Roche Diagnostics, speaker fees from Pfizer and Alnylam and grant support from Roche Diagnostics, outside the submitted work. AJ has received speaker fees from Pfizer, outside the submitted work. Other authors declared no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://www.magonlinelibrary.com/doi/suppl/10.12968/hmed.2024.0674.

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