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ELECTROPHYSIOLOGY

CASE REPORT: CLINICAL CASE

Biventricular Arrhythmogenic Cardiomyopathy Mimicking Cardiac Sarcoidosis

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ABSTRACT

Noninvasive imaging is crucial for diagnosing and managing arrhythmogenic cardiomyopathy. Despite advanced multimodality imaging tools, challenges persist in differentiating it from other arrhythmogenic diseases (eg, cardiac sarcoidosis). We present a case of arrhythmogenic cardiomyopathy with an *FLNC* variant of uncertain significance exhibiting a phenocopy of cardiac sarcoidosis. (J Am Coll Cardiol Case Rep 2024;29:102198) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

An athletic 58-year-old man presented with a 1-month history of progressive dyspnea during intense physical activity. In the clinic, the patient's vital signs were within the normal range and the physical examination was unremarkable. The patient's body mass index was 26.6 kg/m^2. A 12-lead electrocardiogram (ECG) showed sinus rhythm, first-degree atrioventricular (AV) block, intraventricular conduction delay, T-wave inversions in leads V_1 to V_3, and a fragmented QRS in leads V_2 to V_3 (**Figure 1A**). A transthoracic echocardiogram showed severe dilation of the right ventricle (RV) and atrium, markedly reduced RV systolic function (**Figure 2**), and malcoaptation of the tricuspid valve leaflets with severe regurgitation. Computed tomography was negative for pulmonary embolism. An exercise nuclear myocardial perfusion imaging stress test revealed a small area of mild ischemia in the mid to basal inferoseptal wall of the left ventricle (LV). Subsequent coronary angiography did not show obstructive coronary artery disease. Right heart catheterization showed normal intracardiac filling pressures and normal pulmonary pressures.

LEARNING OBJECTIVES

- To recognize that an *FLNC* variant of uncertain significance can be associated with AC with biventricular involvement.
- To recognize that biventricular AC and cardiac sarcoidosis can be phenotypically similar on cardiovascular imaging.
- To understand the importance of a complete evaluation of a patient with suspected AC and differentiating AC from cardiac sarcoidosis.

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ABBREVIATIONS AND ACRONYMS

AC = arrhythmogenic cardiomyopathy

ARVC = arrhythmogenic right ventricular cardiomyopathy

AV = atrioventricular

CMR = cardiac magnetic resonance

ECG = electrocardiogram

FDG = ^{18}F-fluorodeoxyglucose

ICD = implantable cardioverter-defibrillator

LV = left ventricle/ventricular

RV = right ventricle/ventricular

PAST MEDICAL HISTORY

The patient had no known history of medical illness and no family history of cardiac disease or sudden cardiac death.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of right heart failure is broad and includes cardiac and pulmonary etiologies. Cardiac causes include right heart dysfunction due to left-sided valvular disease, pulmonary hypertension, restrictive cardiomyopathy, isolated RV dysfunction in the setting of RV cardiomyopathy (eg, arrhythmogenic right ventricular cardiomyopathy [ARVC] or RV myocardial infarction), intracardiac shunt, or other congenital heart disease. Pulmonary etiologies include pulmonary embolism and other chronic lung diseases.

INVESTIGATIONS

The patient's ECG upon presentation to the cardiology clinic showed atrial flutter with 4:1 AV conduction (**Figure 1B**) and fragmented QRS in leads V_2 to V_3, identified as epsilon waves. The T-wave inversions in leads V_1 to V_3 that were seen on the initial ECG fulfilled the 2020 International Criteria major criteria.[1,2] A 30-day event monitor showed 2 episodes of atrial fibrillation, 1 episode of atrial flutter, and isolated premature ventricular contractions. No nonsustained or sustained ventricular arrhythmias were identified.

Transesophageal echocardiography with an agitated saline study showed no evidence of interatrial shunt. Cardiac magnetic resonance (CMR) demonstrated normal LV size, mildly reduced LV systolic function, and an LV ejection fraction of 44%. Also noted were severely increased RV size (RV end-diastolic volume index 146 mL/m^2), an RV ejection fraction of 26%, and focal RV mid-free wall dyskinesia. Additionally, CMR showed extensive epicardial and midmyocardial nearly circumferential delayed gadolinium enhancement involving the septum and anterior and inferior walls, sparing only the anterolateral LV segments. Gadolinium enhancement of the RV was nearly transmural (**Figures 3 and 4**). The 2020 International Criteria for diagnosis of arrhythmogenic cardiomyopathy (AC) were fulfilled by the major tissue characterization criteria of late gadolinium enhancement and major structural and functional criteria of RV dyskinesia and RV systolic dysfunction on CMR. The ECG finding of right precordial T-wave inversions fulfilled the major repolarization criteria, and the epsilon wave fulfilled the minor depolarization criteria.[1,2] Cardiac sarcoidosis and myocarditis were considered as possible mimickers because of the epicardial and midmyocardial involvement of the interventricular septum and LV.[3]

A whole-body ^{18}F-fluorodeoxyglucose (FDG) sarcoid positron emission tomography scan demonstrated significantly increased FDG uptake in the RV wall and LV, corresponding to the areas of delayed gadolinium enhancement on CMR. There was also focal extracardiac FDG uptake in a paratracheal lymph node.

Given a continued differential of cardiac sarcoidosis, the patient underwent endobronchial ultrasound-guided transbronchial biopsy of the paratracheal lymph node. This came back negative for granulomatous disease such as sarcoidosis. Genetic testing showed a variation involving the *FLNC* gene that was reported to be a variant of uncertain significance—p.(Arg1494Trp) (CGG>TGG): c.4480 C>T in exon 26. To our knowledge, this variant has not been previously reported in a case involving LV or RV cardiomyopathy.

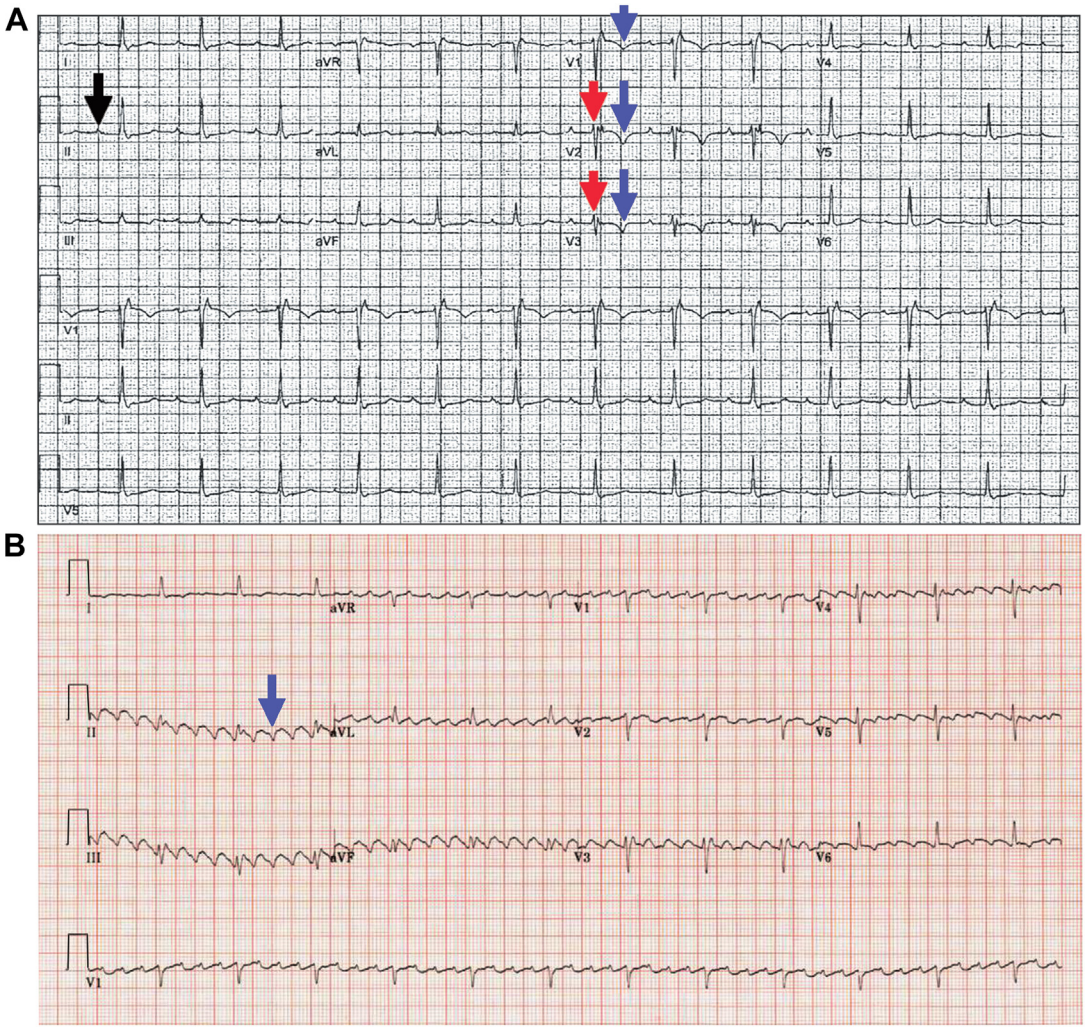
MANAGEMENT

The patient was referred to the electrophysiology service for atrial flutter ablation and placement of an implantable cardioverter-defibrillator (ICD) for primary prevention. The patient's guideline-directed medical therapy was optimized, including metoprolol, losartan, and empagliflozin. Given the most probable diagnosis of gene-negative ARVC with LV involvement, education and genetic counseling were provided during a follow-up visit.

DISCUSSION

AC is a rare genetic cardiomyopathy that can present with isolated RV dysfunction, biventricular involvement, ventricular arrhythmias, or sudden cardiac death.[2] Despite advancement in multimodality imaging, the diagnosis of AC can be challenging because other phenocopies such as cardiac sarcoidosis can overlap with AC.[2] The 2010 ARVC Task Force Criteria do not reliably differentiate between AC and cardiac sarcoidosis. Therefore, cardiac sarcoidosis is a frequent mimicker of AC.[4] The 2020 International Criteria were developed to optimize the accuracy of AC diagnosis by modifying the diagnostic morpho-functional abnormalities of the RV as well as by including the LV and adding structural myocardial

FIGURE 1 **Electrocardiography**

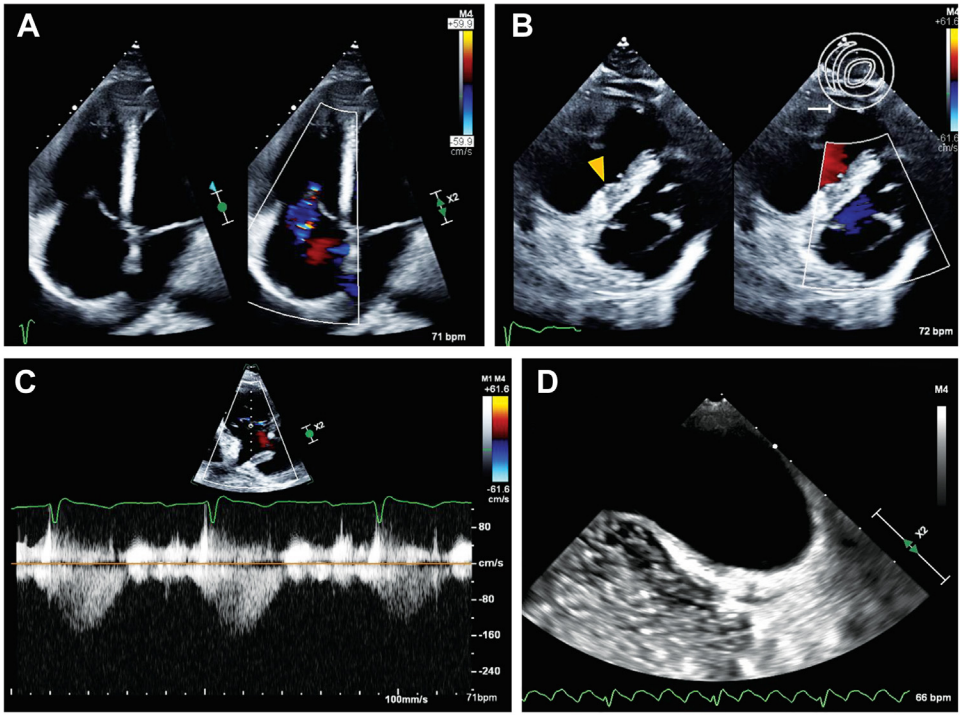


(A) The electrocardiogram at presentation demonstrates first-degree atrioventricular block (black arrow), T-wave inversions in leads V_1 to V_3 (blue arrows), and a fragmented QRS complex in V_2 and V_3 (red arrows). (B) The follow-up electrocardiogram performed in the cardiology clinic demonstrates atrial flutter with 4:1 atrioventricular conduction (blue arrow).

abnormalities of fibrofatty replacement. Our proband fulfilled the 2020 International Criteria based on 2 major CMR findings and 1 major and 1 minor ECG finding.[1]

Distinguishing between AC and cardiac sarcoidosis is clinically important because treatment and prognosis vary significantly. A large, observational database has been used to evaluate patients with ARVC and showed that older age on presentation, PR prolongation, high-grade AV block, significant LV dysfunction, myocardial delayed enhancement involving the septum, and mediastinal lymphadenopathy favored a diagnosis of cardiac sarcoidosis.[4,5] Of these, our patient demonstrated conduction abnormalities, LV dysfunction, septal involvement, and biventricular FDG uptake with involvement of the paratracheal lymph nodes, making cardiac sarcoidosis high on the differential. AC can also present with a myocarditis-like phenotype and should be considered in the differential diagnosis. These conditions could be reasons why isolated FDG positron emission tomography activity or CMR findings may be misleading, underscoring the importance of an extracardiac biopsy and genetic testing in assisting with the diagnosis. In our proband, a diagnosis of gene-negative AC was favored because of the

FIGURE 2 Transthoracic and Transesophageal Echocardiography



(A) The 4-chamber apical view shows severe right ventricular enlargement and dysfunction. (B) Flattening of the septum (arrowhead) due to pressure and volume overload and (C) continuous Doppler color flow through the tricuspid valve are suggestive of severe tricuspid regurgitation. (D) The bicaval view on transesophageal echocardiography shows a negative agitated saline study.

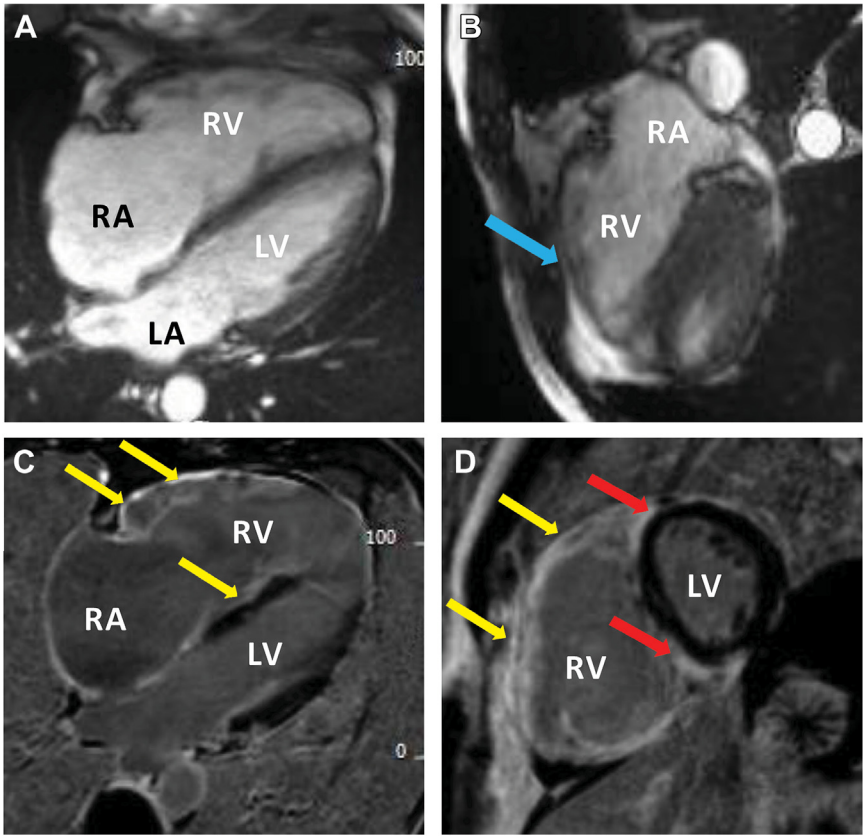
negative extracardiac biopsy and fulfillment of the 2020 International Criteria.

Even though ARVC is a genetic condition, a pathogenic desmosome gene variant is found in only half of patients.[6] Nondesmosome disease genes involving filamin C variants have been identified as causes of ARVC but are even more rare. In a study by Brun et al,[6] *FLNC* gene truncations were identified as the cause of dilated cardiomyopathy with ventricular arrhythmia and sudden cardiac death, a phenotype that partially overlaps with the ARVC and AC spectrum. LV involvement has been more commonly seen among those with *FLNC* variations of uncertain significance.[7]

Patients with AC who have an *FLNC* variation tend to experience disease onset at a later age, usually after 40 years of age, and about 50% have a positive family history; RV involvement is rare.[7] Our patient did not present with a family history of sudden cardiac death or malignant arrhythmia and demonstrated extensive gadolinium enhancement in the LV and RV on CMR. The novel variant observed in our patient broadens the clinical spectrum of AC. Although the significance of this gene variant is unknown, reporting such variants can assist in future genetic testing and the diagnosis of AC and its mimickers.

Managing ARVC with LV involvement includes using standard heart failure therapies. However, patients with ARVC typically have a poorer prognosis than those with sarcoidosis. Steroids are the primary treatment for cardiac sarcoidosis, which generally has a better outlook because of its greater treatability.[8] Patients with ARVC may also be candidates for an ICD implant based on certain criteria, which is important in left-dominant phenotypes without arrhythmias. In our patient, who met the major criterion of having an LV ejection fraction <50% as well as 3 minor criteria—being male, being a proband, and having RV dysfunction—ICD implantation was a Class IIb recommendation according to the 2010 Task Force Criteria.[9] It is currently uncertain whether exercising worsens the prognosis in individuals with this specific genotype variant. Further studies are necessary

FIGURE 3 Cardiac Magnetic Resonance



(A) The 4-chamber cine view shows an enlarged right ventricle (RV) and right atrium (RA). (B) The RV axial cine view shows RV dyskinesia (blue arrow). (C) Four-chamber delayed enhancement shows nearly transmural enhancement of the RV (yellow arrows). (D) The short-axis mid ventricle delayed enhancement view shows epicardial enhancement of the left ventricle (LV) (red arrows) and RV enhancement (yellow arrows). LA = left atrium.

to determine the potential benefits of restricting exercise in athletic individuals with an *FLNC* variant.

FOLLOW-UP

After successful ICD implantation and optimization of guideline-directed medical therapy, the patient experienced significant improvement in symptoms and quality of life.

CONCLUSIONS

AC with biventricular involvement with an *FLNC* variant of uncertain significance mimics a phenocopy of cardiac sarcoidosis, making diagnosis challenging.[3,5] The presence of interventricular septal involvement, conduction abnormalities, and increased biventricular FDG uptake may suggest cardiac sarcoidosis; however, these are not sufficient to confirm the diagnosis.[3] Both extracardiac or cardiac biopsy and genetic testing can aid in the differentiation of these 2 entities as well as other mimickers.[3] Differentiation between these 2 entities is important because treatment and prognosis vary significantly.

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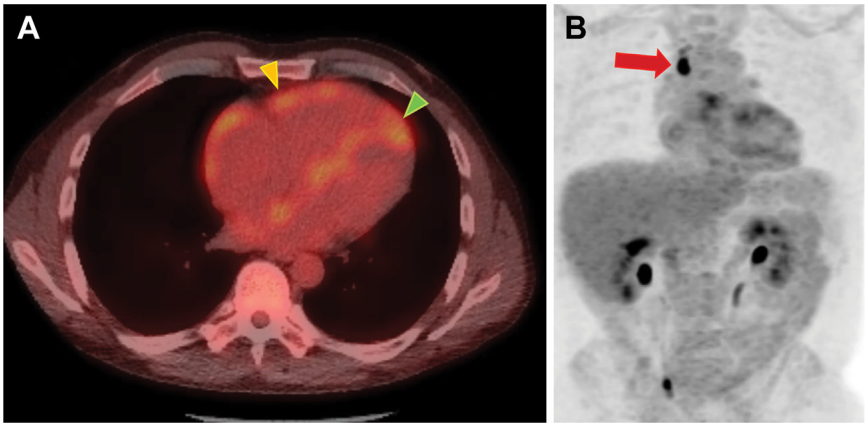
FIGURE 4 FDG Sarcoid PET Computed Tomography



(A) An ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) image in the axial plane demonstrates right ventricular FDG uptake (yellow arrowhead) extending to the left ventricle (green arrowhead). (B) A whole-body PET scan shows FDG uptake in a paratracheal lymph node (red arrow).

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KEY WORDS arrhythmogenic cardiomyopathy, atrial flutter, cardiac sarcoidosis, epsilon wave, *FLNC* gene