A case for genetic testing: Arrhythmogenic cardiomyopathy presenting as myocarditis

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ABSTRACT

Arrhythmogenic cardiomyopathy (ACM) is an inherited cardiomyopathy associated with fibrofatty tissue replacement of the ventricular tissue. The disease can cause ventricular dysfunction and arrhythmias and can increase the risk of sudden cardiac death. This cardiomyopathy can have variable clinical presentations, especially in the pediatric and young adult populations. In this report, we describe the case of an 18-year-old female with myocarditis as the initial presentation of ACM. She presented following a resuscitated cardiac arrest due to ventricular arrhythmia. On arrival, myocardial edema and delayed gadolinium enhancement were present on cardiac magnetic resonance imaging, with no ventricular changes observed, making the diagnosis consistent with myocarditis. Genetic testing revealed a pathogenic mutation in the desmoplakin gene consistent with ACM. Given the unconventional initial presentation of this patient's disease, early consideration of genetic testing may be beneficial to aid in the early diagnosis and management of ACM in young patients.

Keywords: Arrhythmogenic cardiomyopathy, desmoplakin, genetic screening, late gadolinium enhancement, myocarditis

INTRODUCTION

Arrhythmogenic cardiomyopathy (ACM) is an autosomal dominant inherited disease due to mutations in genes encoding desmosome proteins. It results in fibrofatty tissue replacement of the ventricular myocardium and ventricular arrhythmias. Myocarditis manifests with variable clinical presentations and can be associated with the initial presentation of inherited cardiomyopathies such as ACM. Given the variable initial presentation of inherited cardiomyopathies, early use of genetic testing may be beneficial to facilitate early diagnosis and management of ACM in young patients.

CASE REPORT

A previously healthy 18-year-old female suffered a cardiac arrest at home, for which her family initiated cardiopulmonary resuscitation. On the first responder's arrival, she was defibrillated for ventricular fibrillation with subsequent return of spontaneous circulation. On admission to our intensive care unit, her vital signs were as follows: temperature 36.3°C, heart rate 101 beats/min, respiratory rate 25 breaths/min, blood pressure 89/59 mmHg, and oxygen saturation 100%. Her cardiopulmonary examination was initially unremarkable until she experienced several additional episodes of ventricular tachycardia, necessitating further defibrillations. She was admitted to the cardiac intensive care unit for further management.

Before the presentation, she had no known cardiac history or preceding cardiac symptoms. Her medical

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Website: https://journals.lww.com/aopc

DOI: 10.4103/apc.apc_122_23

How to cite this article: Srinivas RE, Wright LK, Nandi D, Hayes EA. A case for genetic testing: Arrhythmogenic cardiomyopathy presenting as myocarditis. Ann Pediatr Card 2024;17:55-8.

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Submitted: 21-Aug-2023 **Revised:** 02-Feb-2024 **Accepted:** 02-Feb-2024 **Published:** 24-May-2024

history was otherwise significant for depression and attention deficit hyperactive disorder, for which she was taking bupropion and amphetamine. Her family history was negative for cardiac disease, including sudden cardiac death, cardiomyopathy, and arrhythmias.

Laboratory evaluation revealed normal electrolytes, white blood cell count of 10.1 thousand/μL, hemoglobin of 12.0 g/dL, troponin I level of 2.85 ng/mL, negative urine toxicology screen, and negative SARS-CoV-2 polymerase chain reaction. Transthoracic echocardiogram showed an ejection fraction of 53%, normal biventricular size, and no other abnormalities. Initial 12-lead electrocardiogram (ECG) following cardiac arrest showed sinus bradycardia at a rate of 45 bpm with first-degree atrioventricular block and a markedly prolonged QT interval of >600 ms [Figure 1].

Cardiac magnetic resonance imaging (MRI) confirmed normal biventricular size and systolic function [Figure 2]. T1 and T2 imaging demonstrated myocardial edema, and delayed myocardial gadolinium enhancement was seen by myocardial tissue characterization in the basal anterolateral and inferolateral segments. There was no evidence of ventricular dilation or hypertrophy.

The patient was initially started on amiodarone and admitted to the cardiac intensive care unit for initiation of a cooling protocol, invasive ventilation, sedation, and intravenous (IV) vasopressors. She required multiple additional defibrillations for continued ventricular tachycardia and was noted to have a prolonged QTc interval on ECG. The prolonged QTc interval may have been associated with the use of amiodarone or the patient's prior use of bupropion and amphetamine. She was transitioned to lidocaine to decrease the risk of QTc prolongation due to amiodarone. Following completion of the cooling protocol, she was able to wean off IV vasopressors and sedation. She was then extubated with no significant deficits in her neurologic examination.

Lidocaine was transitioned to esmolol and ultimately metoprolol XL. Her cardiac MRI was consistent with myocarditis, and she therefore underwent placement of a subcutaneous implantable cardioverter-defibrillator (ICD) before discharge home.

Genetic testing ultimately revealed a pathogenic DSP variant, c.268C>T (p.Gln90), consistent with the diagnosis of ACM, as well as a variant of uncertain significance, c.304C>T (p.Arg102Cys). On follow-up, the patient's ECG and echocardiogram have remained normal and she has not received any shocks from her ICD. Her family underwent cascade screening, which confirmed the same pathogenic DSP mutation in her mother and brother. Both had similar findings on cardiac MRI and her mother underwent placement of an ICD.

DISCUSSION

ACM is a rare, inherited cardiomyopathy characterized by fibrofatty tissue replacement of the ventricles, resulting in ventricular arrhythmias and ventricular dysfunction with an increased risk of sudden cardiac death.[1] Clinical manifestations of ACM include global or regional dysfunction, ECG abnormalities, and arrhythmias, which typically develop between the second and fourth decades of life. Inherited in an autosomal dominant manner, ACM has age-related penetrance and variable expressivity ranging from premature ventricular contractions to arrhythmic sudden cardiac death or heart failure.[2,3] ACM patients historically have shown right ventricular involvement as evidenced by the criterion standard for clinical diagnosis of arrhythmogenic right ventricular cardiomyopathy in the revised 2010

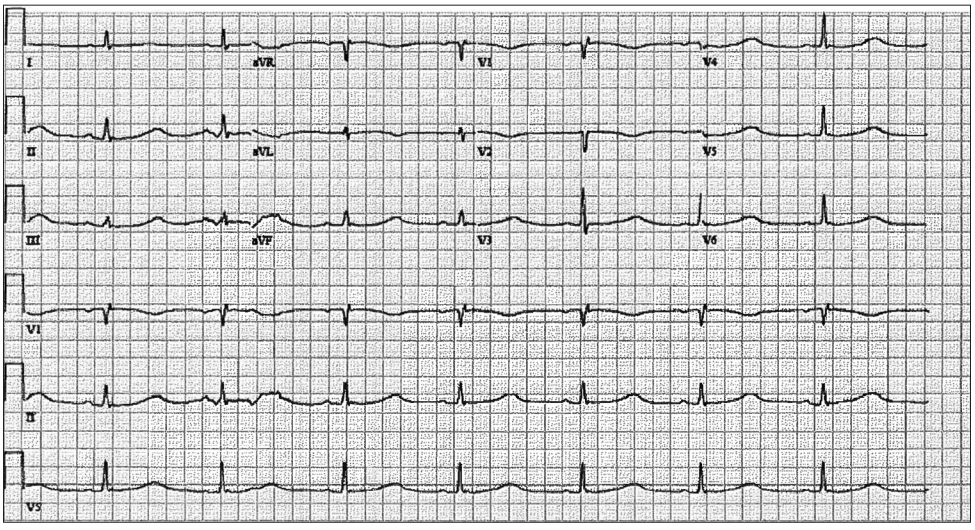

Figure 1: Initial electrocardiogram (ECG) at presentation: An ECG was recorded at the patient's presentation in the emergency department with findings of sinus bradycardia with first-degree atrioventricular block and prolonged QT interval (>600 ms)

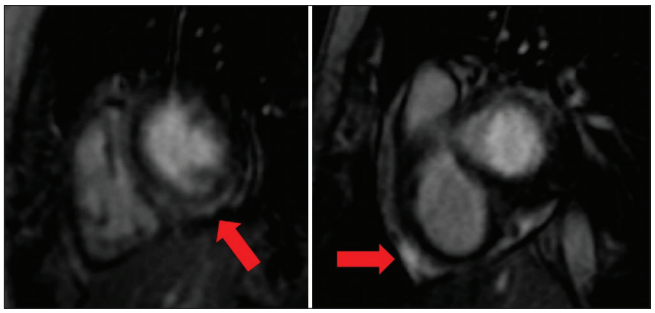

Figure 2: Cardiac magnetic resonance imaging: Normal biventricular size and systolic function with myocardial edema and delayed myocardial gadolinium enhancement in the basal anterolateral and inferolateral segments of the left ventricle (red arrows)

task force criteria (TFC).[4] However, biventricular and left-dominant subtypes have increasingly been recognized.[5,6] This led to the development of the 2020 Padua diagnostic criteria, which aimed to improve the diagnosis of ACM with the incorporation of new criteria focused on left-sided disease.[7]

Due to the variable presentation, the diagnosis of ACM can be challenging, particularly in pediatric and young adult patients. The lack of clear diagnostic criteria in younger patients places an emphasis on genetic testing to make an accurate diagnosis. Causative mutations for ACM have been identified in up to 60% of cases, primarily affecting the genes encoding for desmosomal proteins, including plakoglobin, plakophilin-2, desmoglein-2, and DSP.[8] Current evidence suggests that genotype may influence the risk of arrhythmias and heart failure, though genotype-phenotype studies are limited due to the rarity of the disease. In contrast to other forms of cardiomyopathy, genetic testing is an integral part of the diagnosis in ACM and counts as a major criterion in both the TFC and Padua diagnostic criteria.[4]

This case highlights several important points in diagnosing and treating ACM in pediatric and young adult patients. The diagnostic TFC was developed from an adult cohort and focused on right-sided disease, which limits its utility in younger patients, particularly those with predominantly left-sided involvement.[9] A revised TFC that includes left or biventricular involvement, as proposed in the Padua criteria, is needed. Furthermore, acute myocarditis may be an initial manifestation of ACM in younger patients, particularly when associated with malignant arrhythmias. Scheel *et al.* found that a group of patients with ACM who initially presented with myocarditis shared distinct characteristics, including younger age at initial presentation, female gender, left ventricular involvement, and DSP genetic variants. In these patients with atypical features, genetic testing was essential for diagnosis as many of them did not meet TFC without it.[10] In our patient who presented with arrhythmic myocarditis, genetic testing ultimately revealed a pathogenic DSP variant. This finding led to the diagnosis of ACM based on the Padua criteria. Timely diagnosis of these patients has significant implications for patient management, including exercise restriction, risk stratification and prevention, and cascade screening in family members.

ACM may have variable early clinical presentations, including findings consistent with myocarditis, and is often a challenging diagnosis to make in younger patients, especially among those with predominantly left-sided disease. Given the occurrence of myocarditis as an initial presentation of ACM, the use of genetic testing in young patients presenting with atypical and primarily arrhythmic myocarditis should be considered to enhance early diagnosis and facilitate genotype-specific management.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Thiene G, Nava A, Corrado D, Rossi L, Pennelli N. Right ventricular cardiomyopathy and sudden death in young people. N Engl J Med 1988;318:129-33.
2. Bauce B, Frigo G, Marcus FI, Basso C, Rampazzo A, Maddalena F, *et al.* Comparison of clinical features of arrhythmogenic right ventricular cardiomyopathy in men versus women. Am J Cardiol 2008;102:1252-7.
3. Nava A, Thiene G, Canciani B, Scognamiglio R, Daliento L, Buja G, *et al.* Familial occurrence of right ventricular dysplasia: A study involving nine families. J Am Coll Cardiol 1988;12:1222-8.
4. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, *et al.* Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: Proposed modification of the task force criteria. Eur Heart J 2010;31:806-14.
5. Casella M, Gasperetti A, Sicuso R, Conte E, Catto V, Sommariva E, *et al.* Characteristics of patients with arrhythmogenic left ventricular cardiomyopathy: Combining genetic and histopathologic findings. Circ Arrhythm Electrophysiol 2020;13:e009005.
6. Stadiotti I, Piacentini L, Vavassori C, Chiesa M, Scopece A, Guarino A, *et al.* Human cardiac mesenchymal stromal cells from right and left ventricles display differences in number, function, and transcriptomic profile. Front Physiol 2020;11:604.
7. Corrado D, Perazzolo Marra M, Zorzi A, Beffagna G, Cipriani A, Lazzari M, *et al.* Diagnosis of arrhythmogenic cardiomyopathy: The padua criteria. Int J Cardiol 2020;319:106-14.
8. Pinamonti B, Brun F, Mestroni L, Sinagra G. Arrhythmogenic right ventricular cardiomyopathy:

From genetics to diagnostic and therapeutic challenges. World J Cardiol 2014;6:1234-44.

9. Te Riele AS, James CA, Calkins H, Tsatsopoulou A. Arrhythmogenic right ventricular cardiomyopathy in pediatric patients: An important but underrecognized clinical entity. Front Pediatr 2021;9:750916.
10. Scheel PJ 3rd, Murray B, Tichnell C, James CA, Tandri H, Calkins H, *et al*. Arrhythmogenic right ventricular cardiomyopathy presenting as clinical myocarditis in women. Am J Cardiol 2021;145:128-34.