Arrhythmogenic right ventricular cardiomyopathy masquerading as peripartum cardiomyopathy

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Introduction

The diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC) can be challenging owing to variable clinical presentation and genetic expressivity. Here, we describe the case of a patient diagnosed with peripartum cardiomyopathy and a desmoplakin (*DSP*) gene mutation of unknown significance who underwent cardiac transplantation and was found to have ARVC on histopathological examination of the explanted heart.

Case report

A 49-year-old female patient with a long-standing diagnosis of peripartum cardiomyopathy following a pregnancy in 2005 presented for evaluation for heart transplantation. Prior to presentation, she had chronic fatigue and dyspnea with exertion. She had a medical history of peripartum cardiomyopathy diagnosed in 2005 after her first pregnancy and dual-chamber implantable cardioverter-defibrillator (ICD) implantation for primary prevention. She subsequently had appropriate ICD shocks owing to ventricular tachycardia. Her left ventricular ejection fraction (LVEF) and clinical status continued to decline despite being treated with optimal guideline-directed medical therapy, so she was referred for heart transplantation. There was no history of spontaneous abortion(s), hypertensive disorder of pregnancy, or family history of cardiomyopathy or sudden cardiac death. She had no subsequent pregnancies.

The differential diagnosis of heart failure around the time of pregnancy is broad and includes peripartum cardiomyopathy, dilated cardiomyopathy, stress cardiomyopathy, hypertrophic cardiomyopathy, and left ventricular (LV) noncompaction, among others.[1] Peripartum cardiomyopathy is usually a diagnosis of exclusion. Clinical, electrocardiographic, and echocardiographic data at the time of initial presentation postpartum were not available and hence it is unclear whether a diagnosis of ARVC could have been made at that time. However, as part of the evaluation for heart transplantation, the patient underwent an electrocardiogram, which showed atrial pacing, low-voltage QRS, and left anterior fascicular block (Figure 1). Transthoracic echocardiography showed an LVEF of 16%, severe LV hypokinesis, a left ventricular end-diastolic dimension of 58 mm, a left ventricular end-systolic dimension of 53 mm, moderate right ventricular (RV) dysfunction, moderate-to-severe RV enlargement, severe tricuspid regurgitation, and an estimated RV systolic pressure of 22 mm Hg (Figure 2). Cardiopulmonary exercise testing revealed a peak oxygen consumption of 11.1 mL/kg/min (40% predicted). Coronary angiography revealed normal coronary arteries. Blood chemistry panel was notable for an elevated creatinine level at 1.53 mg/dL.

The patient underwent genetic testing for 81 genes related to cardiomyopathy, which identified a variant of uncertain significance (VUS) in exon 9 of the *DSP* gene c.1045G>C (p.Ala349Pro). This was a suspicious VUS given that it is not present in population databases but has been observed in individuals with sudden cardiac death.[2] There was conflicting data for the in silico prediction of change in protein

KEY TEACHING POINTS

- This case describes a variant of unknown significance (VUS) in the desmoplakin (*DSP*) gene that was associated with pathologic manifestation of arrhythmogenic right ventricular cardiomyopathy. Therefore, a VUS should not be ignored and can be upgraded with relevant clinical data to be likely pathogenic.
- Peripartum cardiomyopathy is a diagnosis of exclusion and can only be made after genetic testing is performed.
- Genetic testing is important to establish an accurate diagnosis in patients with cardiomyopathies. It has significant disease-specific prognostic and therapeutic implications not only to the patient but also to their families.

KEYWORDS Arrhythmogenic right ventricular cardiomyopathy; Cardiomyopathy; Genetics; Heart failure; Peripartum cardiomyopathy

(Heart Rhythm Case Reports 2024;10:486–489)

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https://doi.org/10.1016/j.hrcr.2024.04.014

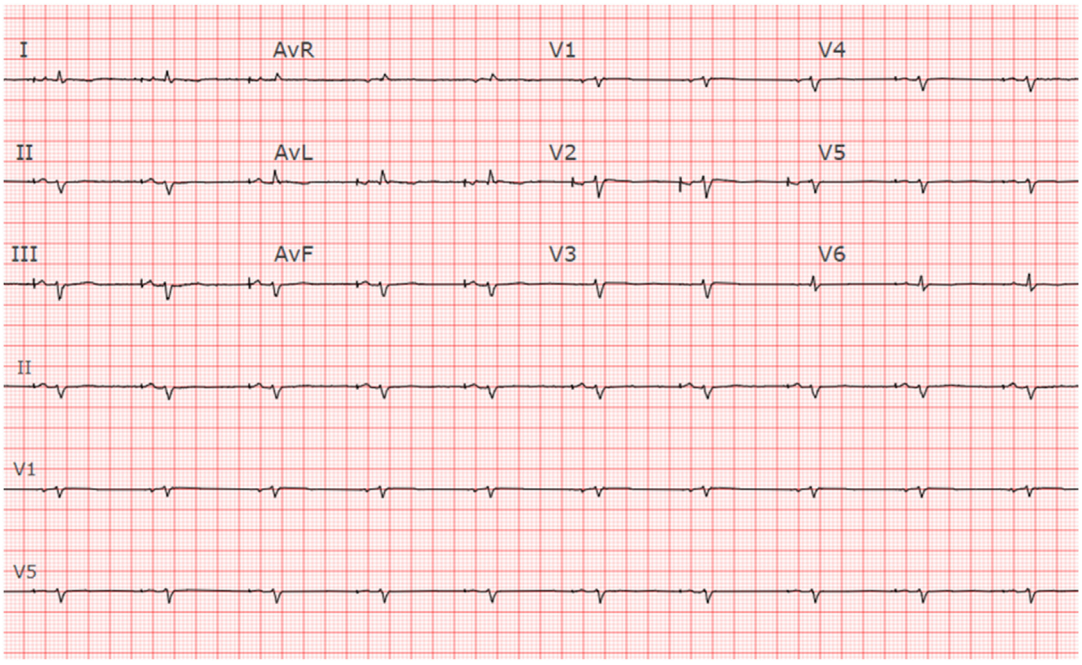

Figure 1 Resting electrocardiogram showing atrial pacing, low-voltage QRS, and left anterior fascicular block.

structure and function with this variant. Therefore, at the time of testing, there was not enough information to determine its pathogenicity. Although the patient had biventricular cardiomyopathy based on electrocardiography and echocardiography, she did not meet any of the 2010 Task Force diagnostic criteria of ARVC.[3] She had runs of ventricular tachycardia (VT) detected on device interrogation which were responsive to antitachycardia pacing. However, the VT exit location could not be identified solely based on the ICD electrograms.

Six months after the evaluation, the patient underwent cardiac transplantation. Pathology features of the explanted heart were consistent with ARVC, including LV fibrofatty replacement in a midmural and subepicardial distribution with mild dilatation and RV near-total replacement by fibroadipose tissue with marked dilatation (Figure 3). Following cardiac transplantation, the patient has had resolution of heart failure symptoms, and transthoracic echocardiography post-transplant demonstrated an LVEF of 58%.

Discussion

ARVC is a disease characterized by fibrous or adipose tissue replacement of myocardium that typically starts from the epicardium and progresses towards the endocardium. The abnormal tissue provides a substrate for reentrant arrhythmias,[4,5] which was not a noteworthy component of the patient's initial presentation. While commonly thought of as a

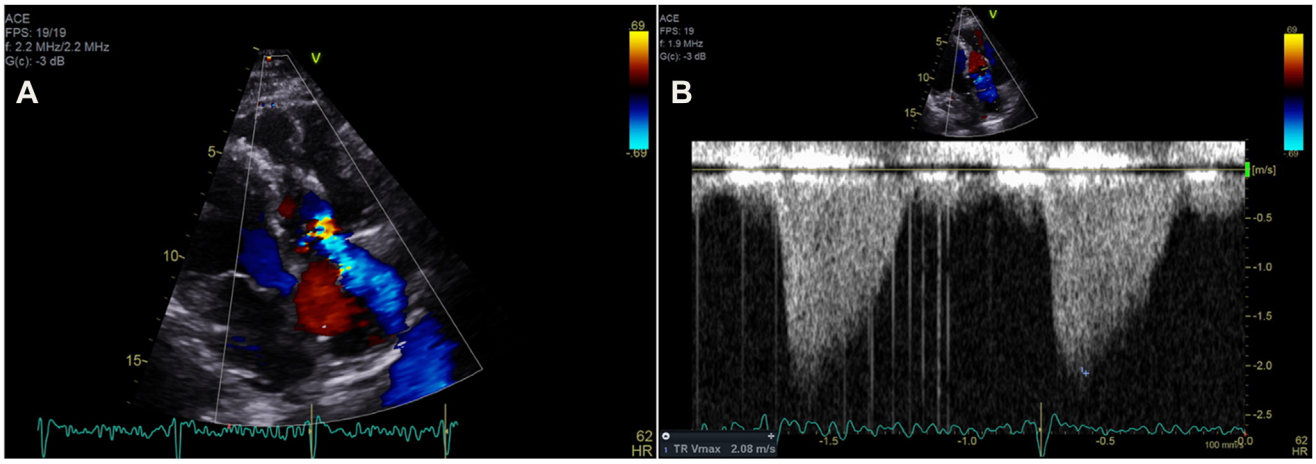

Figure 2 Two-dimensional echocardiography showing severe right ventricular enlargement and moderate-to-severe tricuspid regurgitation. **A:** Four-chamber view with color Doppler. **B:** Continuous wave Doppler assessment of the tricuspid regurgitation velocity.

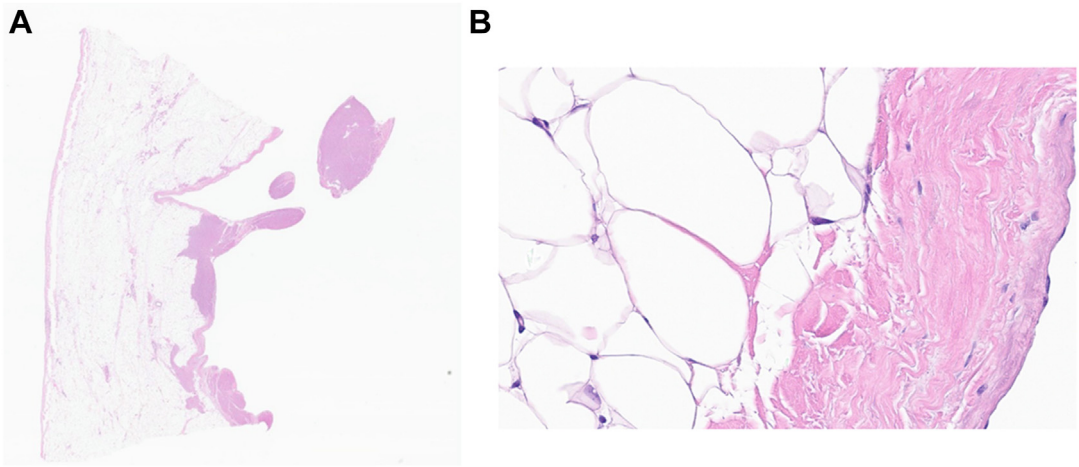

Figure 3 **A:** Histopathological examination of the right ventricular anterior wall showing near-total replacement of the myocardium by fibroadipose tissue (hematoxylin–eosin stain). **B:** Original magnification: ×40.

heritable disease, identifiable genetic abnormalities are present in fewer than 50% of ARVC cases.[6,7] Our patient had a VUS in the *DSP* gene, which has been associated with arrhythmogenic cardiomyopathy.[6] It is noteworthy that even though *DSP* gene mutations have not been linked with peripartum cardiomyopathy, mutations in other genes, such as the titin (*TTN*) gene, have been reported in peripartum cardiomyopathy, likely reflecting a more diverse Mendelian genetic substrate for this condition.[8]

Making a diagnosis of ARVC or a genetic cardiomyopathy in patients presenting around the time of pregnancy is imperative given the differences in prognosis and long-term management when compared with peripartum cardiomyopathy. Prognostically, many patients with peripartum cardiomyopathy demonstrate improvement in ventricular function, whereas most patients with ARVC have progressive decline.[9–11] It is worth noting that even though peripartum cardiomyopathy has been associated with a higher rate of recovery as compared to other forms of cardiomyopathy, reported recovery rates have varied depending on the patient population and the definition of recovery.[11] Current recommendations for management of ARVC, earlier implementation of which could attenuate disease progression, include restriction from high-intensity exercise, pharmacologic therapy, catheter ablation, and placement of implantable defibrillators, depending on the patient's clinical presentation and risk stratification.[12,13] Exercise increases myocardial strain, which exacerbates the mechanical uncoupling of cardiomyocytes and increases the risk of disease progression in patients with ARVC. Therefore, patients with ARVC should be restricted from competitive high-intensity exercise.[12] Pharmacologic therapy often includes early use of antiarrhythmics. Catheter ablation, especially combined endocardial-epicardial approaches, have been shown to result in better long-term suppression of VT as compared to endocardial-only approaches.[14–16] In contrast, management of peripartum cardiomyopathy could include prolactin inhibitors.[10,17]

Conclusion

The present case helps establish the pathogenicity of a *DSP* VUS by demonstrating the phenotype during histopathologic examination of the explanted heart. The clinical overlap between many cardiomyopathies is extensive, and genetic testing could assist in the differential diagnosis of peripartum cardiomyopathy, which is crucial for therapeutic and prognostic purposes.

Funding Sources: None.

Disclosures: The authors have no conflict of interest to disclose.

Data Availability: The clinical patient information underlying this article will be made available in compliance with HIPAA regulations on request to the corresponding author.

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