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Genetic insights into non-ischemic arrhythmogenic cardiomyopathy: a case report of desmoplakin mutation

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Abstract

We aim to describe a unique case of a desmoplakin gene mutation with refractory ventricular arrhythmia and cardiomyopathy. We describe a 29-year-old man hospitalized for chest pain and cardiomyopathy, who subsequently developed ventricular arrhythmia that was refractory to multiple antiarrhythmic agents, ablation, immunotherapy, and sympathectomy. Diagnostic studies included coronary catheterization, cardiac MRI, and endomyocardial biopsy. He underwent placement of an Impella 5.5 temporary mechanical support device for multi-organ failure; eventually requiring a Heartmate 3 left ventricular assist device. This report details how cardiac MRI, endomyocardial biopsy, and genetic testing are crucial diagnostic modalities when assessing patients with refractory arrhythmias or myocarditis. Pathogenic variants in the desmoplakin gene can be associated with significant morbidity in patients and require multidisciplinary care from cardiology, electrophysiology, advanced heart failure, and cardiac surgery. Arrhythmogenic cardiomyopathies should be considered for patients suffering repeated episodes of myocarditis or refractory ventricular arrhythmias. We utilized various criteria of functional, electrocardiographic, arrhythmic, tissue characterization, and genetic findings to establish the diagnosis of arrhythmogenic cardiomyopathy, which will be discussed later in this paper.

Keywords

Desmoplakin (DSP), desmoplakin cardiomyopathy, arrhythmia, case report

Introduction

Desmoplakin (DSP) is a critical desmosomal protein in maintaining myocardial structural integrity and intercellular adhesions. Variants in this gene have been recognized to contribute to a spectrum of cardiomyopathies, including arrhythmogenic cardiomyopathy. In this case report, we attempt to describe a unique case of a young patient with refractory arrhythmogenic cardiomyopathy, the workup to identify the cause, and detail the importance of genetics in cardiac disorders.

Case report

History of presentation

Patient is a 29-year-old man who presented with chest pain, dyspnea, and an EKG with sinus tachycardia without a pattern for ischemic injury. Initial laboratory studies were notable for a troponin I of 0.38 ng/mL, anion gap of 36.0 mmol/L, lactic acid of 10.85 mmol/L, and WBC count of 22.3 × 10^9/L. The ethanol level was 417 mg/dL and negative urine toxicology. Patient developed 30 s of self-terminating ventricular tachycardia. Initial echocardiogram revealed normal biventricular function without valvular or pericardial disease.

Past medical history

Past medical history includes poor dentition, active substance abuse (history of more than five years) with ethanol, kratom, and intermittent marijuana. Remote history of methamphetamine use. The use of these substances can lower the threshold for arrhythmia formation and end-organ damage.

Differential cardiac diagnosis

Acute myocarditis, left ventricular noncompaction, sarcoidosis, acute coronary syndrome, and pericarditis.

Investigations

Transthoracic echocardiogram (TTE) revealed a normal biventricular function with apical trabeculation and hyperdynamic left ventricular ejection fraction (LVEF). The following evening, he developed sustained pulseless ventricular tachycardia (Figure 1) treated with advanced cardiovascular life support (ACLS), including intubation and cardioversion to sinus tachycardia; however, he progressed to multi-organ system failure. A chest x-ray revealed bilateral pulmonary infiltrates (Figure 2). He was placed on amiodarone and lidocaine drips for rhythm control and laboratory findings revealed troponin > 440.00 ng/mL.

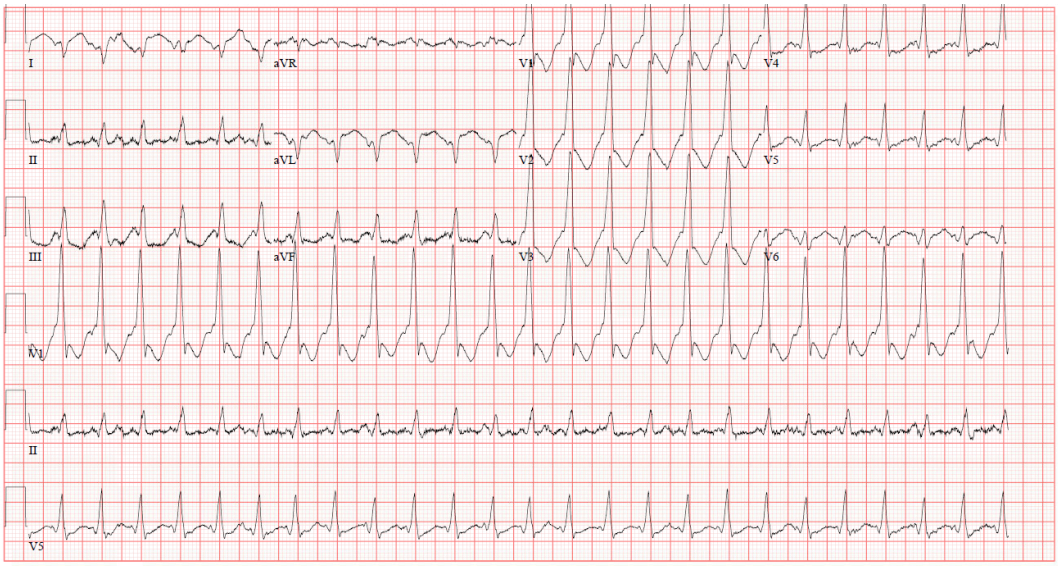

Figure 1. EKG upon presentation. EKG revealing pulseless ventricular tachycardia with a rate of 150 bpm prior to reversion to normal sinus rhythm

Management

A repeat TTE revealed an ejection fraction of 10–15% and an emergent right and left heart cardiac catheterization revealed normal epicardial coronary vessels and elevated left ventricular end diastolic pressure (LVEDP) at 40 mmHg. A right ventricle (RV) endomyocardial biopsy was performed, and he was empirically treated for presumed giant cell myocarditis with high dose corticosteroids. Endomyocardial biopsy results were negative for giant cell myocarditis, lymphocytic or eosinophilic myocarditis, and sarcoid associated cardiomyopathy, but did reveal scattered CD3 lymphocytes and changes consistent with

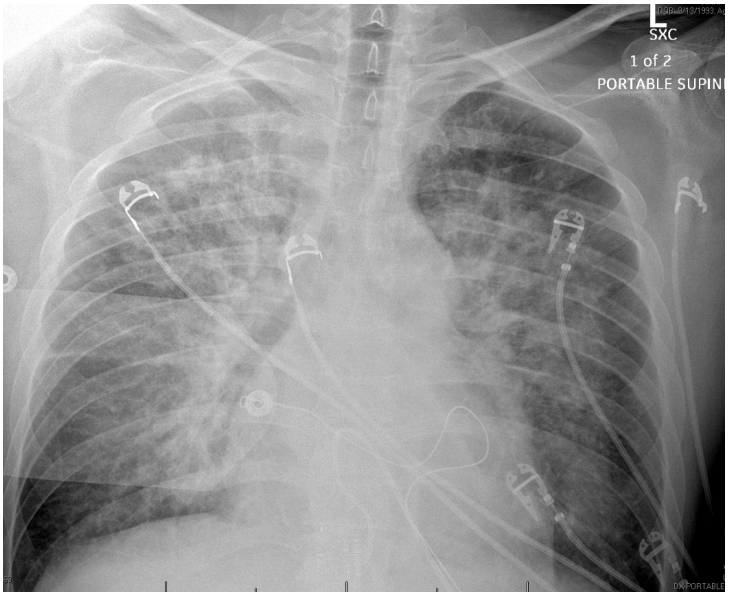

Figure 2. Chest x-ray obtained post-myocardial biopsy. Multifocal dense bilateral pulmonary opacities with small bilateral pleural effusions

early ischemia. The presence of ischemia is unique because in arrhythmogenic cardiomyopathy, often there is a nonischemic etiology that presents with ventricular arrhythmia. The propensity for electrical instability often precedes heart failure or ventricular dilation [1]. A subsequent cardiac magnetic resonance (CMR) was obtained, which revealed severely hypokinetic basal and mid segments, with a LVEF of 16%. T2-weighted imaging findings were consistent with a large area of myocardial edema. There was diffuse late gadolinium enhancement in all basal segments, findings suggestive of acute fulminant myocarditis associated cardiomyopathy (Figure 3). Rapid viral serologies were all negative and intravenous immunoglobulin was administered. He was eventually discharged on a steroid taper, colchicine, and a LifeVest.

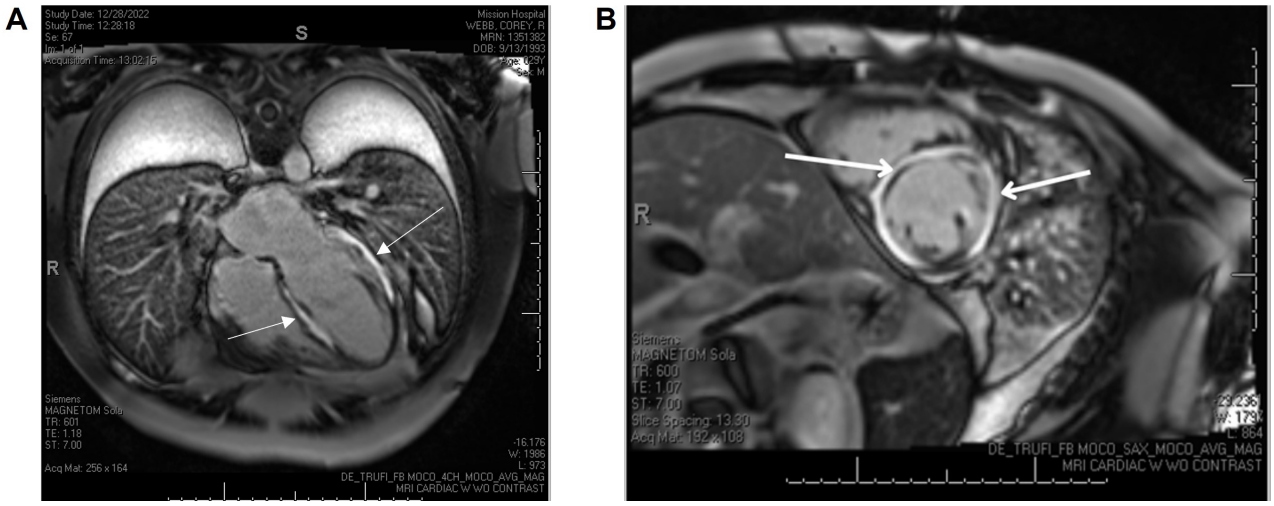

Figure 3. Cardiac MRI findings. A. Delayed gadolinium enhancement noted by the arrows. **B.** CMR showing mid myocardial diffuse late gadolinium enhancement in all basal segments, mid cavity segments, and upper distal cavity segments, suggestive of diffuse myocardial edema. CMR: cardiac magnetic resonance

Four days later, the patient re-presented after being found nonresponsive and treated with bystander cardiopulmonary resuscitation (CPR). The initial rhythm was rapid ventricular tachycardia and the Emergency Medical Service (EMS) defibrillated the patient to sinus rhythm with spontaneous return of circulation. Persistent depressed LVEF and cardiogenic shock required surgical implantation of an Impella 5.5, during which a left ventricular endomyocardial biopsy was performed due to concerns for sampling

error on the original RV septal endomyocardial biopsy. Left ventricular endomyocardial biopsy did not reveal features of myocarditis or infiltrative disease. After 7 days of support, the Impella device was removed, and a dual-chamber implantable cardioverter defibrillator (ICD) was placed. Despite multiple antiarrhythmic agents (amiodarone, lidocaine, procainamide, propranolol, and phenytoin), ventricular tachycardia episodes continued. He underwent thoracoscopic bilateral sympathectomy and one week later, an endocardial ventricular tachycardia ablation procedure. He was transferred to a high-volume heart transplantation center and was declined for urgent heart transplantation by a multidisciplinary team due to substance use, unstable psychosocial support, and malnutrition. Prolonged substance abuse can further exacerbate arrhythmogenic cardiomyopathy generation due to alterations in ion channel function. After returning to Mission Hospital (HCA North Carolina), the patient underwent high-risk implantation of a HeartMate 3 left ventricular assist device (LVAD), epicardial ablation of ventricular tachycardia, and left atrial appendage ligation. He was discharged from the hospital 16 days later. An Invitae cardiomyopathy panel returned with findings consistent with a heterozygous DSP mutation leading to a premature stop signal: c268C>T (p.Gln90).

Outcome and follow-up

After demonstrating abstinence from substance use, he has been listed for heart transplantation. His follow-up EKG also demonstrated resolution of his ventricular arrhythmia (Figure 4).

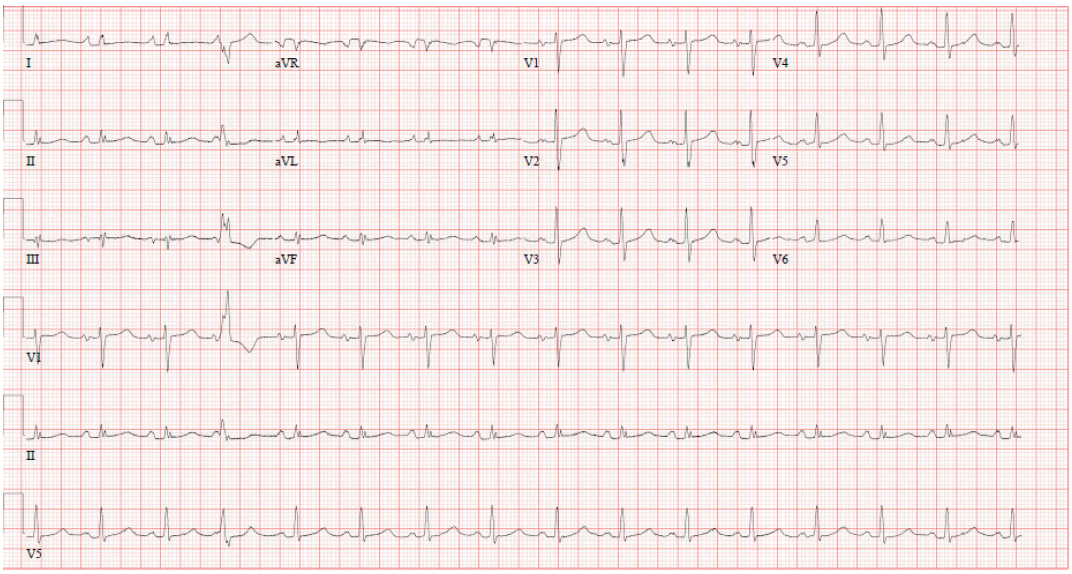

Figure 4. EKG upon stabilization of the ventricular tachycardia rhythm. Comparison EKG revealing normal sinus rhythm with no signs of depolarization or repolarization abnormalities (e.g., prolonged QRS interval, prolonged QT interval, T wave inversion)

Discussion

DSP is a 2,871 amino acid desmosomal protein encoded by the *DSP* gene on chromosome 6p24 that facilitates intercellular adhesion in various tissues, including the heart and epidermis [2]. Aberrations in this gene and its effect on cardiac function were first described in patients with Carvajal syndrome, but have since expanded to include patients with familial forms of arrhythmogenic and dilated cardiomyopathies [3]. Mutations in *DSP* can lead to detachment of cardiomyocytes, leading to cell death and inflammation [4]. DSP cardiomyopathy is a rare genetic condition that is typically diagnosed with a combination of CMR (showing late gadolinium enhancement), poor left ventricular function, ventricular ectopy, and genetic testing. Pancardiomyopathy genetic testing was vital for the diagnosis and the truncated variants (as in our case) of the *DSP* gene lead to more aggressive phenotypes compared to missense mutations [5]. In addition to the *DSP* gene variant the patient had, genetic testing also revealed a missense mutation variant in the *CACNAID* gene, which is associated with autosomal recessive sinoatrial

node dysfunction and the *KCNH2* gene, which is associated with autosomal dominant long QT syndrome type 2 and Brugada syndrome [6, 7]. Genetic variants in the *CACNAID* gene can modulate the presentation of arrhythmogenic cardiomyopathy by altering the gating properties of calcium channels, which may enhance cellular excitability and arrhythmogenic potential [8]. Similarly, variants in the *KCNH2* gene can disrupt the function of potassium channels, affecting cardiac repolarization and increasing the risk of ventricular arrhythmias [9]. However, the patient in our case likely had a benign variant of these mutations as he did not have Brugada syndrome, long QT syndrome, or sinoatrial node dysfunction. Typically, DSP cardiomyopathy presents as a predominantly left ventricular cardiomyopathy, whereas right ventricular involvement has only been seen in 14% of patients [10].

Inherited arrhythmogenic cardiomyopathies, such as those seen in heterozygous DSP mutations, can present with a "hot phase" that can mimic myocarditis. In this phase, inflammatory cells are in abundance in the affected myocardial tissue and patients can present with chest pain, elevated troponins, and EKG changes, despite having normal coronary arteries [11]. The cold phase of ventricular arrhythmias is associated with chronic systolic heart failure. Patients with heterozygous DSP mutations have variable phenotypic penetrance and often cycle between hot and cold phases, as detailed in our case report [12, 13].

In conclusion, excluding potentially treatable forms of noncoronary acute cardiomyopathies with CMR and endomyocardial biopsy and evaluating genotypic variants while supporting patients with acute and chronic mechanical circulatory dysfunction allowed for a diagnosis of DSP associated cardiomyopathy in our case (Figure 5). DSP cardiomyopathy is a rare arrhythmogenic condition associated with recurrent episodes of ventricular arrhythmias and myocarditis. Managing episodes of ventricular arrhythmia is challenging and the lack of data regarding long-term treatment of this condition makes specific guideline recommendations difficult.

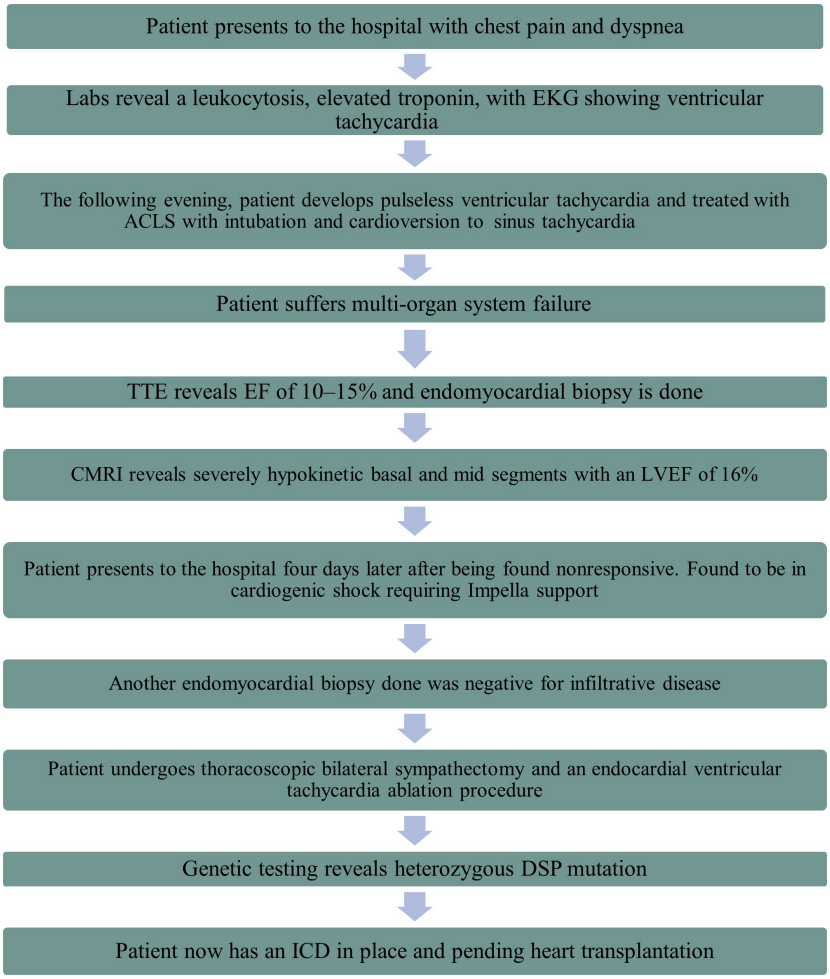

Figure 5. Timeline of events. ACLS: advanced cardiovascular life support; TTE: transthoracic echocardiogram; CMRI: cardiac magnetic resonance imaging; LVEF: left ventricular ejection fraction; DSP: desmoplakin; ICD: implantable cardioverter defibrillator

Abbreviations

ACLS: advanced cardiovascular life support

CMR: cardiac magnetic resonance

CMRI: cardiac magnetic resonance imaging

CPR: cardiopulmonary resuscitation

DSP: desmoplakin

EMS: Emergency Medical Service

ICD: implantable cardioverter defibrillator

LVAD: left ventricular assist device

LVEDP: left ventricular end diastolic pressure

LVEF: left ventricular ejection fraction

RV: right ventricle

TTE: transthoracic echocardiogram

Declarations

Disclaimer

The views expressed in this publication represent those of the author(s) and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.

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Author contributions

JV: Conceptualization, Investigation, Writing—original draft. DN: Investigation, Conceptualization, Writing—original draft. VT: Investigation, Writing—review & editing, Validation, Supervision. All authors read and approved the submitted version.

Conflicts of interest

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Ethical approval

The study complies with the Declaration of Helsinki (2024 version). Ethical approval for the case report was not required according to the requirements of Mountain Area Health Education Center Ethics and Research Department.

Consent to participate

Informed consent to participate for the study was obtained from the participant.

Consent to publication

Informed consent to publication was obtained from the participant.

Availability of data and materials

The data for this study could be available from the corresponding authors upon reasonable request.

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