JACC: CASE REPORTS VOL. 2, NO. 6, 2020

MINI-FOCUS ISSUE: CARDIOMYOPATHIES

ADVANCED

CASE REPORT: CLINICAL CASE

Comprehensive Risk Management in Arrhythmogenic Cardiomyopathy Associated With Autosomal Dominant Carvajal Syndrome

Protecting Families

Maria Grazia De Gregorio, MD,[a] Francesca Girolami, BS,[b] Benedetta Tomberli, MD,[a] Guendalina Rossi, MD,[a] Alessia Tomberli, RN,[a] Katia Baldini, RN,[a] Iacopo Olivotto, MD[a]

ABSTRACT

In a 37-year-old cardiac arrest survivor with autosomal dominant Carvajal syndrome and arrhythmogenic cardiomyopathy, a desmoplakin mutation was identified. Cascade screening identified 2 affected family members and 2 healthy children carrying the mutation. Strategies for primary and secondary risk prevention emphasize the role of genetic testing in rare cardiomyopathies. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2020;2:925–9)

HISTORY OF PRESENTATION

A 37-year-old woman had a witnessed cardiac arrest while she was jogging, and she was resuscitated by DC shock following detection of ventricular fibrillation. She had been a competitive athlete until the age of 30 years and had never reported symptoms or events. On admission she was hemodynamically stable. The electrocardiogram (ECG) showed sinus bradycardia, low QRS voltages, and nonspecific repolarization abnormalities, especially in leads V_4 to V_6. This ECG was comparable to one performed 5 years earlier in the course of a sports medicine evaluation (which included a 12-lead ECG according to Italian laws) (**Figures 1A and 1B**). No major rhythm disturbances were recorded. The echocardiogram showed mild biventricular hypokinesia with reduced left ventricular (LV) systolic dysfunction (ejection fraction 46%) and limited areas of bulging of the free right ventricular (RV) wall, which was richly trabeculated (**Figure 1E**). Laboratory tests revealed a light increase in serum creatinine and troponin I levels.

From the [a]Cardiomyopathy Unit, Careggi University Hospital, Florence, Italy; and the [b]Cardiology Unit, Meyer University Hospital, Florence, Italy. Dr. Olivotto was supported by the European Union's Horizon 2020 Research and Innovation Programme under Grant Agreement 777204: "SILICOFCM - In Silico Trials for Drug Tracing the Effects of Sarcomeric Protein Mutations Leading to Familial Cardiomyopathy"; by the Italian Ministry of Health ("Left Ventricular Hypertrophy in Aortic Valve Disease and Hypertrophic Cardiomyopathy: Genetic Basis, Biophysical Correlates and Viral Therapy Models" (RF-2013-02356787) and NET-2011-02347173 ("Mechanisms and Treatment of Coronary Microvascular Dysfunction in Patients With Genetic or Secondary Left Ventricular Hypertrophy"); and by the Ente Cassa di Risparmio di Firenze (bando 2016) "Juvenile Sudden Cardiac Death: Just Know and Treat." All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Case Reports* author instructions page.

Manuscript received January 31, 2020; revised manuscript received March 23, 2020, accepted March 27, 2020.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2020.03.033

ABBREVIATIONS AND ACRONYMS

AC = arrhythmogenic cardiomyopathy

ECG = electrocardiogram

LV = left ventricular

RV = right ventricular

The only notable finding on clinical examination was marked palmar hyperkeratosis, attributed to her job as a gardener (Figure 1C).

PAST MEDICAL HISTORY

The patient was the mother of 2-year-old nonidentical male triplets. She had a positive family history of sudden cardiac death. Her brother, with a history of scalp dermatitis and woolly hair from infancy, died suddenly several years earlier at the age of 28 years. He was a competitive athlete with unexplained recurrent syncope, low-voltage complexes on the ECG, and polymorphic ventricular ectopies on 24-h Holter ECG. Cardiac investigations had been inconclusive at a time when arrhythmogenic cardiomyopathy (AC) was still little known. The patient's maternal grandmother's sister, reportedly affected by dilated cardiomyopathy, died suddenly at the age of 40 years. The proband's mother and maternal uncle showed mild RV abnormalities and scalp dermatitis.

DIFFERENTIAL DIAGNOSIS

Coronary angiography excluded epicardial stenoses. Cardiac magnetic resonance revealed patchy areas of edema within the LV lateral wall in T_2-weighted images and mild RV dilation with sparse areas of noncompaction and saccular dilatations; the left ventricle showed hypokinesia of the distal interventricular septum with an LV ejection fraction of 52%, apical noncompaction, and diffuse subepicardial late gadolinium enhancement (Figures 1D and 1F). The combination of clinical and instrumental findings raised the suspicion of AC on the basis of her family history.

INVESTIGATIONS

Genetic testing was performed by whole exome sequencing, allowing the identification of 2 rare variants of heterozygosity co-segregating with the cardiocutaneous phenotype in the mother and uncle (Figure 2): 1) c.878A>T, p.(Glu293Val) in the desmosomal protein gene desmoplakin (*DSP*); and 2) c.626A>C, p.(Tyr209Ser) in *SCO2,* a cytochrome c oxidase (COX) assembly gene. Of these, the *DSP* variant appeared fully compatible with the initial clinical suspicion and the phenotypic features of the proband and her family. Because the cardiomyopathy related to *SCO2* gene variants is usually recessive and associated with encephalopathy and it is fatal in children, we excluded the causative role of this gene in our family. On the basis of these results, a diagnosis of autosomal dominant Carvajal syndrome was made.

LEARNING OBJECTIVES

- To diagnose rare forms of arrhythmogenic cardiomyopathies associated with extracardiac manifestations and increased risk of SCD.
- To understand the complexities of genetic testing interpretation in the era of next-generation sequencing.
- To perform cascade genetic screening in family members, to identify early manifestation and implement tailored preventive strategies for sudden cardiac death possibly ranging from device implantation to lifestyle interventions, depending on the patient.

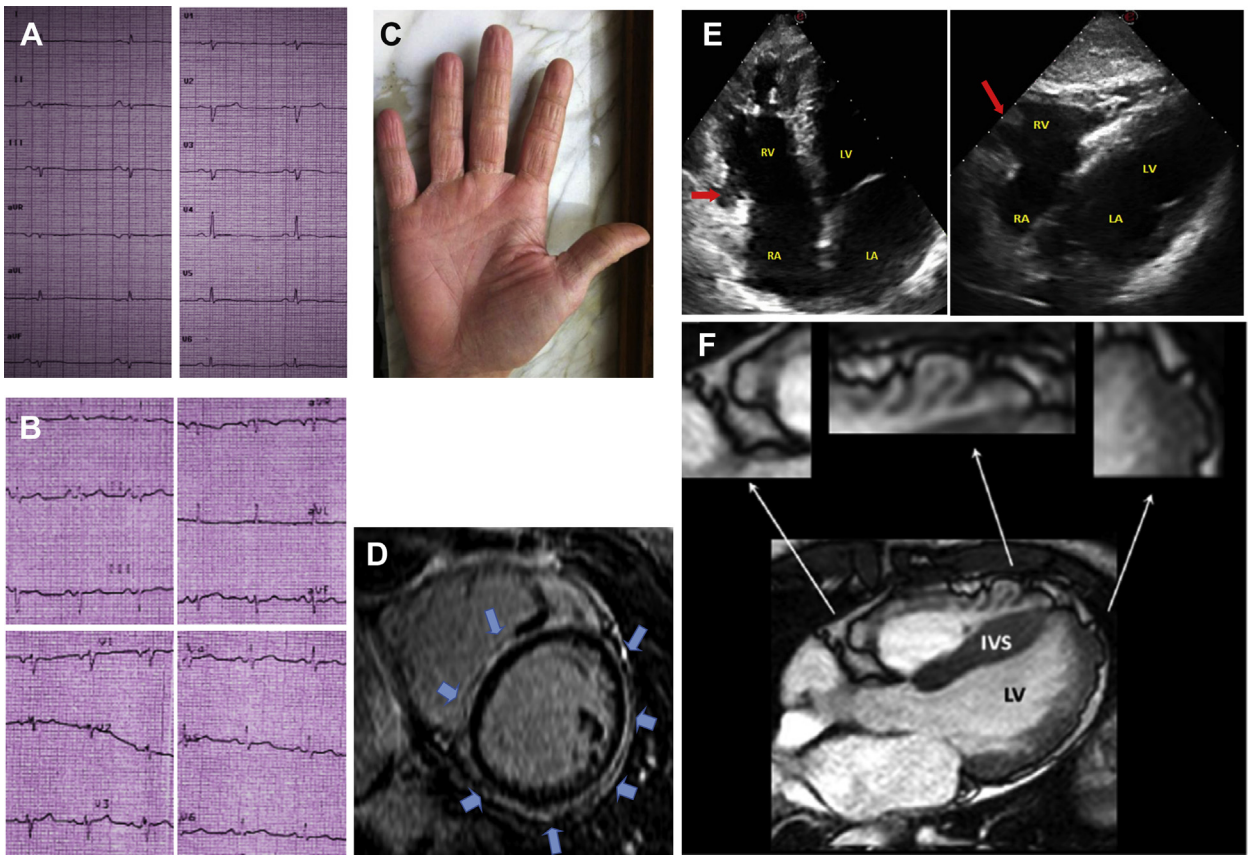
MANAGEMENT

The patient was discharged following implantation of a single-lead cardioverter-defibrillator. Two months after discharge, she was hospitalized twice for recurrent episodes of incessant monomorphic ventricular tachycardia unresponsive to medical therapy. Electrophysiological LV mapping was compatible with a large area of scar in the midbasal anterolateral wall that was successfully treated by epicardial transcatheter ablation.

Following multidisciplinary consultation, including the cardiomyopathy team, a psychiatrist, and a clinical geneticist, the proband's sons underwent cascade genetic screening at the age of 10 years. Two of 3 were found to carry the *DSP* variant, in the absence of cardiac abnormalities or arrhythmias. After proper counseling with the help of an experienced psychiatrist, both were gradually diverted from competitive sports and encouraged to pursue alternative activities. This strategy was chosen despite the lack of clinical manifestations because of the impact of sports in their family, and it was based on recent published reports on AC that showed an association of earlier and more severe phenotypes with vigorous physical activity in mutation carriers.

The proband's mother and uncle had a definite but mild AC phenotype; both carried the *DSP* variant. Following thorough noninvasive investigation, no arrhythmic propensity could be demonstrated except for a limited number of ventricular ectopies on 24-h Holter monitoring. Both were in their late 60s and judged to be at low arrhythmic risk. They were started on nadolol and entered routine clinical follow-up.

FIGURE 1 Clinical, ECG, and Instrumental Features



(A) The 12-lead electrocardiogram on admission was comparable to **(B)** one performed 5 years earlier. **(C)** Palmar keratoderma. **(D and F)** Cardiac magnetic resonance and **(E)** echocardiographic images of right ventricular wall aneurysms **(red and white arrows)** and hypertrabeculation; diffuse subepicardial late gadolinium enhancement is evident **(blue arrows)**. IVS = interventricular septum; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

FOLLOW-UP

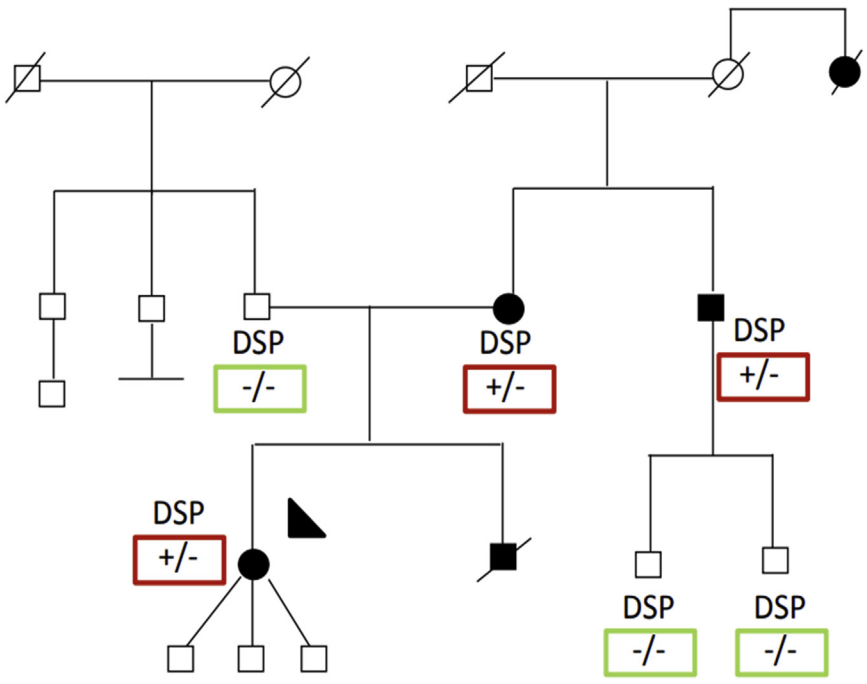
The proband remained asymptomatic and free of arrhythmic recurrences in the ensuing 8 years while taking nadolol, 80 mg once daily, and avoiding sports and strenuous exercise in general. No further arrhythmic events were recorded by the implantable cardioverter-defibrillator.

DISCUSSION

Desmosomes are highly specialized cell adhesion junctions, comprising several different proteins such as desmoplakin and plakoglobin, that confer resistance to mechanical stress and preserve cellular integrity in cardiac tissue and epidermis. Carvajal disease is a rare autosomal recessive cardiocutaneous syndrome, characterized by biventricular or LV dilated cardiomyopathy, palmoplantar keratoderma, and woolly hair, that is associated with *DSP* gene mutations (1-4). Desmoplakin plays a critical role in the desmosomal junction by anchoring the cytoskeleton to the plasma membrane. Altered protein-protein interactions at the intercalated disk level are responsible for contractile and electrical dysfunction in Carvajal syndrome (2). Very few cases of dominant inheritance have been described (5,6), and little is known regarding desmosomal gene-related cardiocutaneous syndromes.

Even though the diagnosis of arrhythmogenic cardiomyopathy is multiparametric and mostly clinical, genetic testing plays a leading role in management, both for differential diagnosis with cardiocutaneous or Costello syndromes and for proper screening in pre-symptomatic relatives. Next-generation sequencing has revolutionized the field of

FIGURE 2 Genetic Findings



A dominant pattern of inheritance was evident in the family pedigree after genetic cascade screening. DSP = desmoplakin gene.

inherited cardiomyopathies and has led to the discovery of novel disease-causing genes (7,8). In the present case, a whole exome sequencing approach allowed the identification of the *DSP* variant. A positive genetic test result has important implications for risk management in AC-affected families. Here, we were able to identify 2 affected family members with a mild AC phenotype. In both these family members, a diagnosis would likely have been overlooked on the basis of clinical criteria alone. This finding allowed tailored arrhythmic risk assessment and implementation of surveillance strategies. Importantly, in 2 of the proband's triplets, gene testing allowed early implementation of lifestyle preventive measures, by restricting participation in the competitive sports in which both sons were engaged. Although the ultimate efficacy of such a strategy will be observed only in the very long term, the rationale is sound and is based on the established association between sports and arrhythmic risk in desmosomial diseases (9,10). Of note, similar measures possibly could have prevented major arrhythmic events in the proband and in her brother, both with long records of competitive sports participation.

CONCLUSIONS

We report an autosomal dominant form of AC in the context of Carvajal syndrome caused by a novel *DSP* gene variant. This case exemplifies the different levels of prophylactic interventions required in the management of genetic arrhythmic diseases, including lifestyle modifications in healthy mutation carriers.

ADDRESS FOR CORESPONDENCE: Dr. Maria Grazia De Gregorio, Cardiomyopathy Unit, AOU Careggi, Largo Brambilla 3, I-50134 Florence, Italy. E-mail: mariag.degregorio@gmail.com.

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KEY WORDS **arrhythmic risk, Carvajal syndrome, cascade screening, desmoplakin, genetic testing, sudden cardiac death**