Acute myocardial infarction in desmoplakin cardiomyopathy: beyond a 'hot phase'

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Abstract

Introduction: Desmoplakin (DSP) cardiomyopathy is a rare disease, a particular form of arrhythmogenic cardiomyopathy, with a high risk of life-threatening arrhythmia and heart failure.

Case presentation: A 53-year-old man presented to the emergency department with palpitations. He had no significant medical history, and his family history was unremarkable. The electrocardiogram revealed ventricular tachycardia with left bundle branch block morphology and inferior axis. Following cardioversion, sinus rhythm revealed first-degree AV block and T wave inversion in precordial leads. Echocardiography revealed biventricular dysfunction and right ventricular (RV) dilation, with impaired RV strain and regional kinesis abnormalities. Coronary angiography was normal. Cardiac magnetic resonance (CMR) showed late-gadolinium enhancement in a ring-like pattern, with septal sparring. Genetic testing was positive for the DSP variant, and the diagnosis of DSP cardiomyopathy was established. An implantable cardioverter-defibrillator was placed in secondary prevention, and subsequently, ventricular tachycardia ablation was performed due to repeated arrhythmia. Three years later, the patient presented with a myocardial infarction without ST elevation. Coronary angiography revealed critical stenosis of the circumflex artery, which was treated by implantation of a drug-eluting stent. Family screening revealed DSP cardiomyopathy in his daughter, who had subclinical findings on CMR.

Conclusion: While DSP cardiomyopathy is a complex disease and patients can sometimes present with myocarditis-like episodes, coronary angiography should always be performed in a patient presenting with acute coronary syndrome.

Keywords

desmoplakin, arrhythmogenic cardiomyopathy, ventricular tachycardia, genetics, familial screening

Introduction

Desmoplakin (DSP) cardiomyopathy is a form of arrhythmogenic cardiomyopathy (ACM), usually characterised by left ventricular (LV) involvement, extensive fibrosis and high arrhythmic risk, as well as episodes of acute myocardial injury. This is caused by a variant in the *DSP gene*, a desmosomal protein which plays a significant role in cell-to-cell adhesion and myocardial force transmission. It can be inherited in both autosomal-dominant and autosomal-recessive patterns; however, the penetrance of the variant is variable.

Case presentation

A 53-year-old patient presented to the emergency department with palpitations lasting a few hours prior. He reported recurrent brief episodes of palpitations over the preceding 3 months. He was haemodynamically stable, and his family history and past medical history were unremarkable, with no personal or family history of cardiac disease. Physical examination revealed tachycardia (heart rate >150 bpm), blood pressure of 110/60 mmHg and no evidence of systemic or pulmonary congestion. The electrocardiogram (ECG) showed ventricular tachycardia (VT) at 160 bpm with a left bundle branch block (LBBB) morphology and inferior axis deviation. Following pharmacological cardioversion, sinus rhythm was restored. The ECG after cardioversion showed a first-degree atrioventricular block, low-voltage QRS complexes and T-wave inversions in the precordial leads.

Laboratory studies revealed mildly elevated high-sensitivity troponin (103 ng/L) and NT-proBNP levels (357 pg/mL). Comprehensive two-dimensional (2D) and three-dimensional (3D) echocardiography demonstrated several significant findings: mildly reduced left ventricular ejection fraction (3D LVEF 42%) with diffuse hypokinesia and reduced global LV strain (Figure 1), dilated right ventricle (RV end-diastolic volume 85 mL/m^2) (Figures 2 and 3), thinning of the basal interventricular septum, mildly reduced RV ejection fraction (RVEF 40%) and an impaired RV longitudinal strain (Figure 4). The basal inferior and lateral segments of the RV were akinetic. The patient had moderate tricuspid regurgitation, but no other significant valvular disease or pericardial effusion.

Coronary angiography at presentation revealed no coronary artery disease. Cardiac magnetic resonance (CMR) imaging confirmed biventricular dysfunction with RV dilation and it revealed diffuse circumferential subepicardial LGE affecting the basal and mid-ventricular LV segments in a characteristic ring-like distribution, sparing the interventricular septum, without overt RV LGE.

Based on the 2020 International (Padua) Criteria [1], a diagnosis of biventricular ACM was established. The diagnostic criteria fulfilled in the present case are summarised in Table 1 and included major

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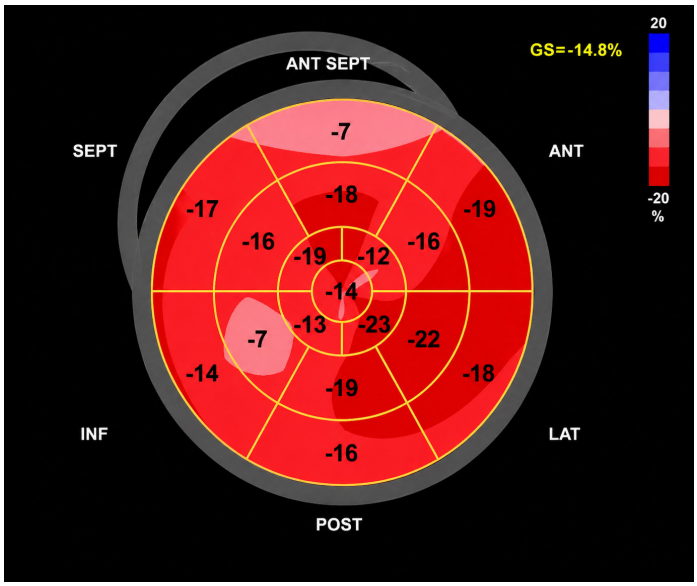

Figure 1 - Transthoracic 2D speckle tracking echocardiography showing global reduced LV strain. 2D, two-dimensional; LV, left ventricular.

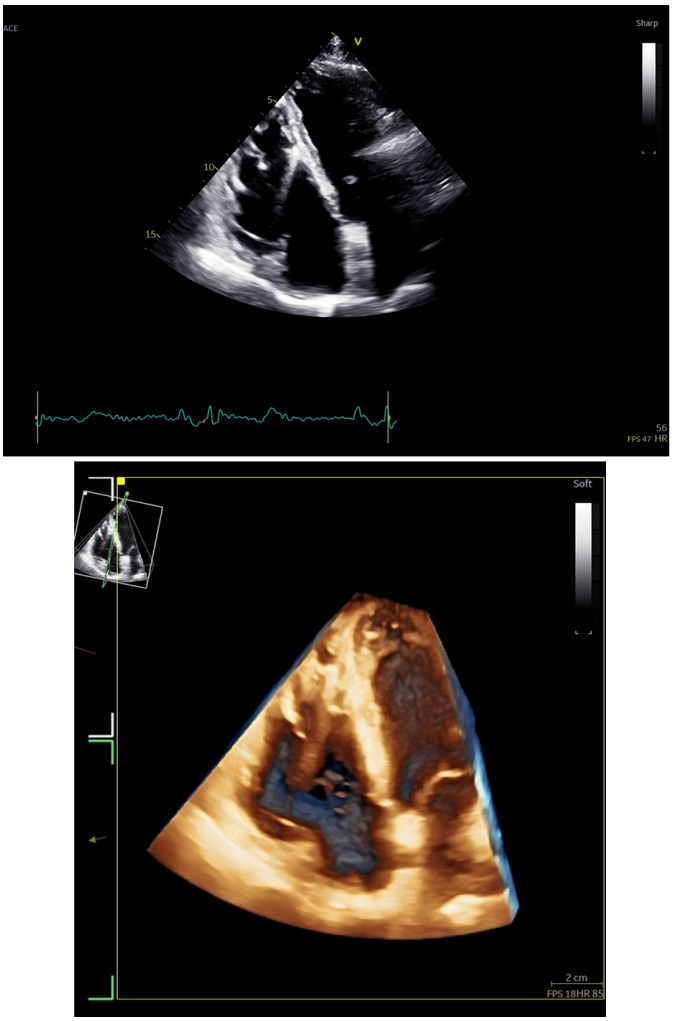

Figure 2 - Transthoracic 2D (A) and 3D (B) echocardiography, showing dilated RV.2D, two-dimensional; 3D, three-dimensional.

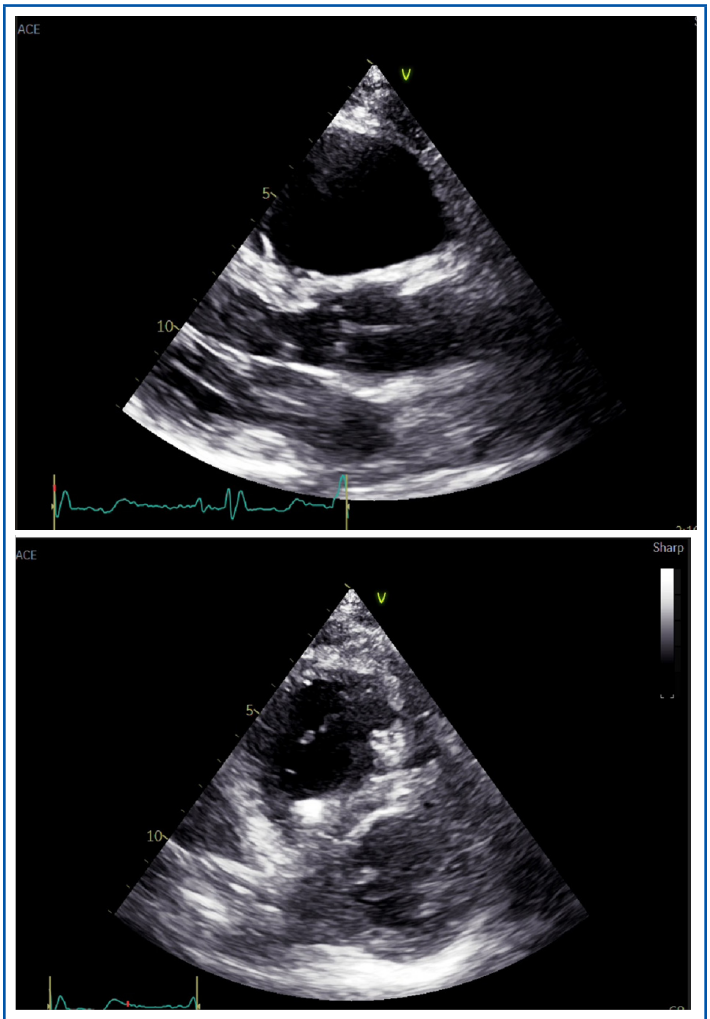

Figure 3 - Transthoracic 2D echocardiography, parasternal (long and short axis) view of the RV, showing dilated RV. 2D, two-dimensional; RV, right ventricular.

morpho-functional RV abnormalities, characteristic repolarisation abnormalities, sustained VT with LBBB morphology and extensive LV late-gadolinium enhancement on CMR, together with mild LV systolic dysfunction as a minor criterion. An implantable cardioverter-defibrillator (ICD) was placed for secondary prevention, according to current ESC guidelines for ventricular arrhythmia [2]. Genetic testing using a comprehensive ACM panel identified a DSP splice variant, establishing the final diagnosis of DSP cardiomyopathy.

Following ICD implantation, the patient returned to the emergency department three times due to appropriate device shocks for rapid VT that was unresponsive to antitachycardia pacing. Consequently, radiofrequency ablation of the VT was performed after high-density grid mapping revealed an extensive scar zone with late potentials at the level of the outflow tract. The clinical arrhythmia was successfully induced and ablated at this location, with post-procedural testing confirming non-inducibility.

Medical therapy included beta-blockers, sacubitril/valsartan, empagliflozin and canrenone, according to current guidelines for the management of heart failure [3].

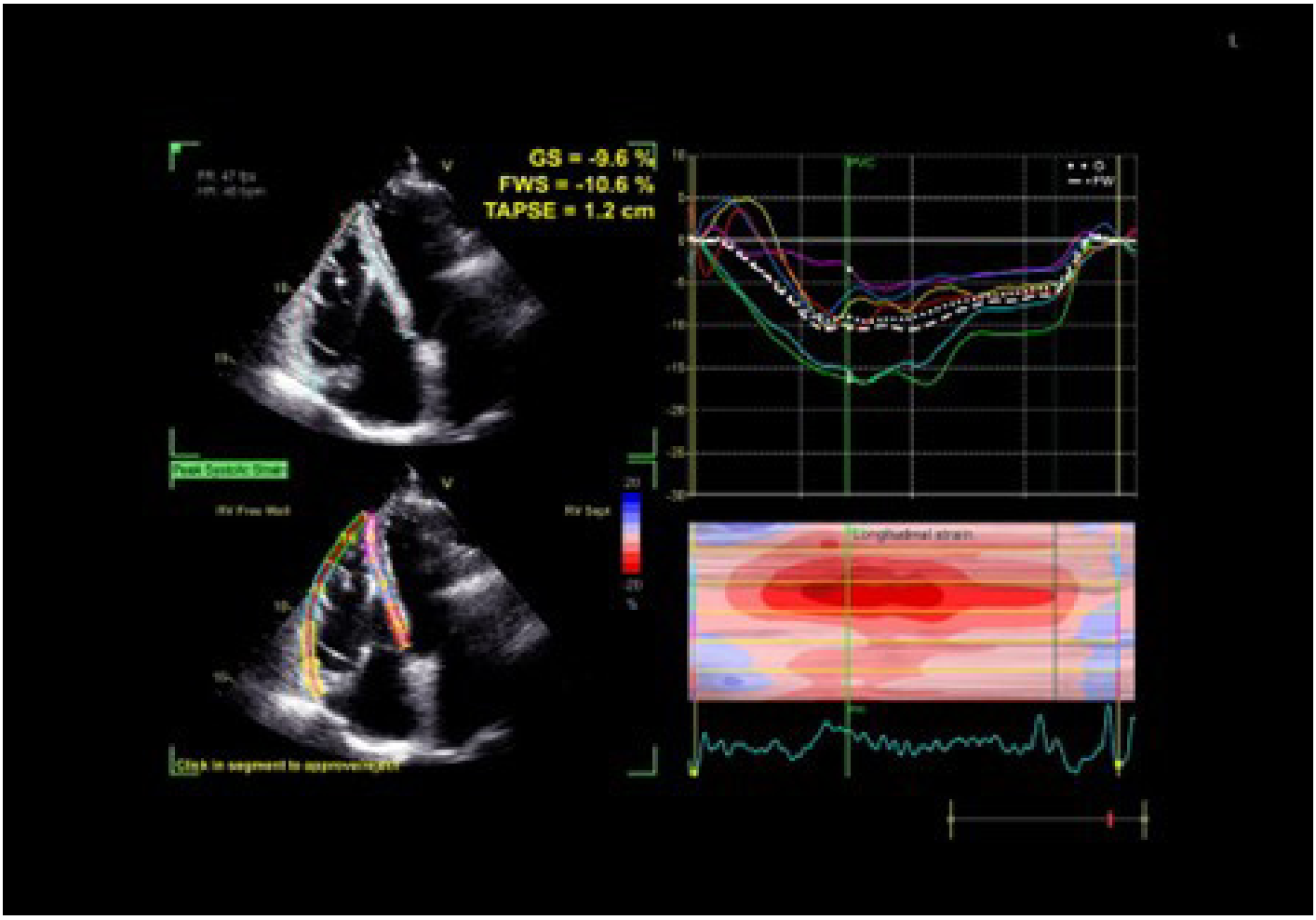

Figure 4 - Transthoracic 2D speckle tracking echocardiography showing severely reduced RV strain. 2D, two-dimensional; RV, right ventricular.

Table 1 - Diagnostic criteria fulfilled according to the 2020 International (Padua) Criteria for ACM in the present case

Category	Finding in the present case	Classification
Morpho-functional RV abnormalities	Regional RV akinesia and RV dilation on echocardiography	Major
Repolarisation abnormalities	T-wave inversion in precordial leads in the absence of RBBB	Major
Ventricular arrhythmias	Sustained VT with LBBB morphology and inferior axis	Major
Tissue characterisation by CMR	Extensive subepicardial LV LGE in a ring-like pattern	Major
LV systolic dysfunction	Mildly reduced LVEF (42%)	Minor

ACM, arrhythmogenic cardiomyopathy; CMR, cardiac magnetic resonance; LBBB, left bundle branch block; LV, left ventricular; LVEF, left ventricular ejection fraction; RV, right ventricular; VT, ventricular tachycardia.

Cascade genetic screening identified the same DSP variant in his 33-year-old daughter. The ECG and echocardiographic evaluation showed no significant abnormalities, with normal LV and RV dimensions, systolic function and strain parameters (Figures 5 and 6). However, CMR demonstrated extensive non-ischaemic LGE, predominantly subepicardial in the medio-basal inferior and inferolateral LV walls, with additional intramyocardial enhancement of the basal septum. According to the 2020 International (Padua) Criteria, these findings fulfilled diagnostic criteria for arrhythmogenic LV cardiomyopathy. She was advised to avoid high or moderate-intensity physical exercise and remains under periodic follow-up, including ECG, Holter monitoring, echocardiography and serial CMR assessment.

Three years after the initial diagnosis, the patient presented to the emergency department with a non-ST-elevation myocardial infarction, experiencing typical anginal symptoms. The hscTnI was highly elevated (1753 ng/L), and the ECG showed new ST-segment depression in lateral leads. Coronary angiography revealed critical stenosis of the circumflex artery, which was successfully treated with drug-eluting stent placement without periprocedural complications.

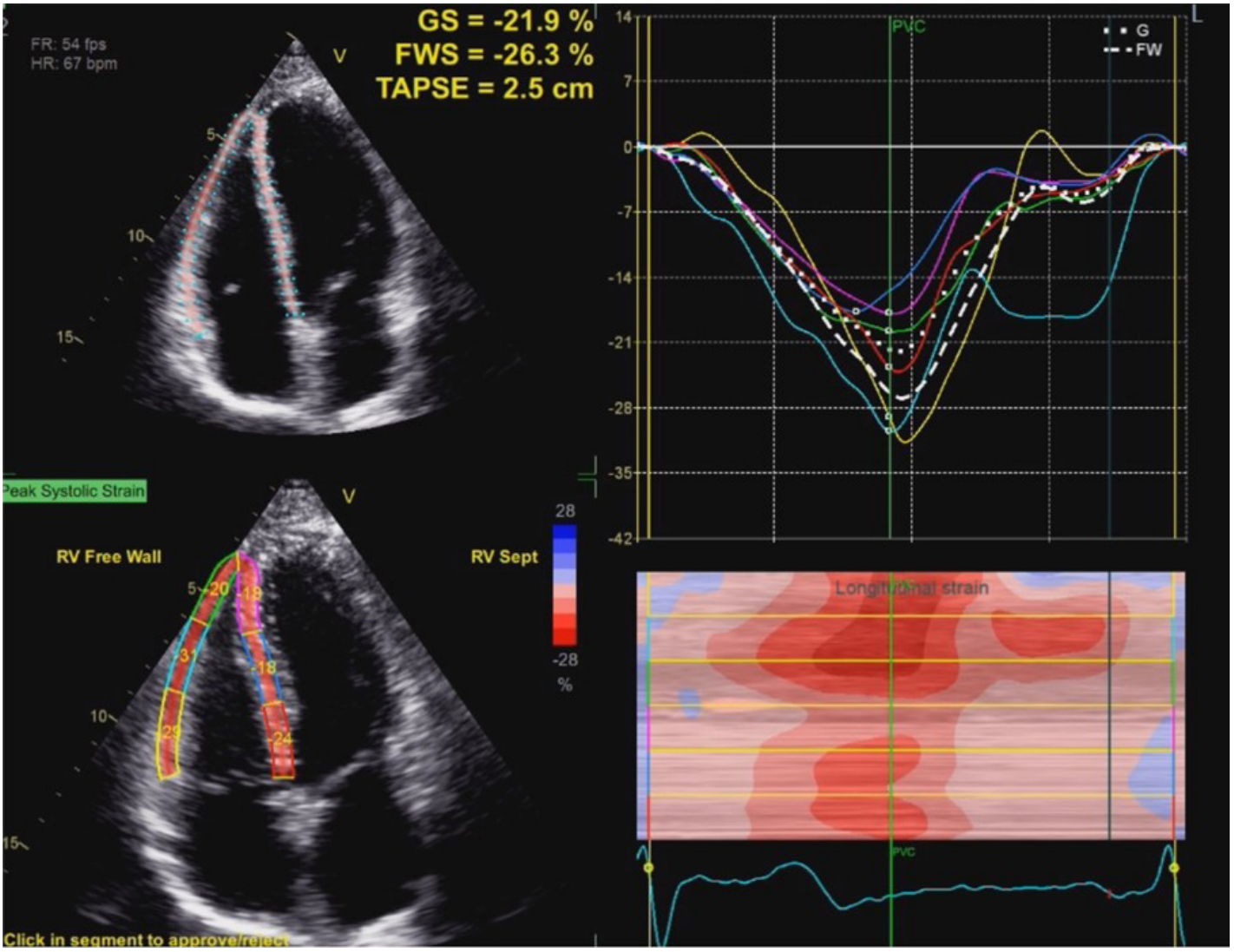

Figure 5 - Transthoracic 2D speckle tracking echocardiography showing normal RV strain in patient's daughter with DSP variant. 2D, two-dimensional; DSP, desmoplakin; RV, right ventricular.

However, echocardiography showed further deterioration in LV function (LVEF 38%) with new akinesia of the basal and mid-inferior and inferolateral walls.

Dual antiplatelet therapy (aspirin and clopidogrel) was added to his regimen, along with high-dose statin and ezetimibe combination therapy. Since this intervention, he has experienced no further cardiac events and remains symptom-free except for dyspnoea on moderate exertion. ICD interrogation revealed no ventricular arrhythmias following the ablation procedure. Both right and LV function and volumes have remained stable.

Discussion

ACM is an inherited myocardial disorder which is characterised by fibrofatty infiltration of the myocardium, predisposing to ventricular arrhythmias and sudden cardiac death. Although initially described as RV cardiomyopathy, biventricular or predominantly LV involvement is often observed. It is typically caused by genetic abnormalities of cardiac desmosomes [4]. A variant in the *DSP gene* – a desmosomal gene that plays an important role in cell-to-cell adhesion - is the second most frequent variant in patients with ACM, after PKP2. Because of its characteristics – frequent involvement of the left ventricle and high arrhythmic risk, DSP cardiomyopathy has been recently described as a distinct entity [5].

In this case, we report a biventricular form of DSP-related cardiomyopathy in a previously healthy 53-year-old man who presented with sustained VT, fulfilling multiple major Padua criteria for ACM and with positive genetic testing [1].

The clinical presentation with sustained VT and echocardiographic findings of biventricular dysfunction and akinesia in specific RV segments is characteristic of advanced disease. The CMR findings of a ring-like pattern of LGE with septal sparing further support the diagnosis, as this LGE pattern is seen in 84% of DSP carriers and has been recently described as a hallmark imaging feature of DSP-related cardiomyopathy.

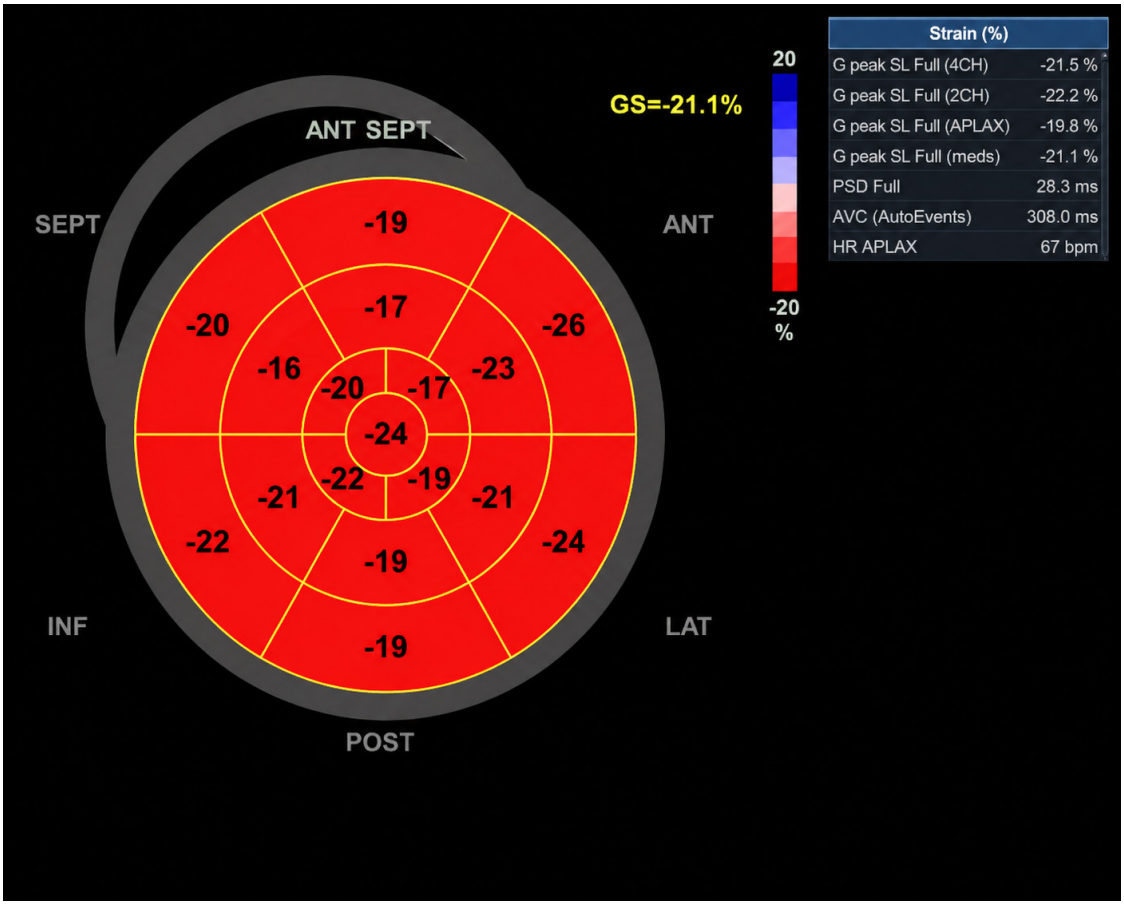

Figure 6 - Transthoracic 2D speckle tracking echocardiography showing normal LV strain in patient's daughter with DSP variant. 2D, two-dimensional; DSP, desmoplakin; LV, left ventricular.

Importantly, DSP cardiomyopathy is known for its episodic nature of myocardial injury and progressive fibrotic replacement, often mimicking myocarditis or acute coronary syndrome—episodes described in the literature as 'hot phases'[5]. Recent studies and reviews reported a relatively high prevalence of these myocarditis-like episodes among DSP variant carriers, reaching up to 22% in some cohorts [6,7]. In most reported cases, patients present with chest pain, troponin elevation and ECG abnormalities despite the absence of obstructive coronary artery disease.

However, our case draws attention to an important clinical consideration: patients with DSP cardiomyopathy may also develop concomitant atherosclerotic coronary artery disease and true myocardial infarction. Reports describing the coexistence of DSP cardiomyopathy and obstructive coronary artery disease remain rather limited in the current literature, making the differential diagnosis particularly challenging. Therefore, coronary angiography should always be performed in ACM patients presenting with acute coronary syndrome, as a DSP-related 'hot phase' should remain an exclusion diagnosis rather than a presumptive explanation for myocardial injury. At present, there is no evidence supporting a direct association between DSP cardiomyopathy and accelerated atherosclerosis.

The arrhythmic burden in DSP cardiomyopathy is typically higher than in other forms of ACM [8]. Risk stratification remains challenging, as severe ventricular arrhythmias may occur even in patients with only mildly reduced ventricular function. Recent studies have proposed genotype-specific risk models for DSP variant carriers, incorporating factors such as non-sustained VT, PVC burden, RV dysfunction and LVEF <50% to better predict ventricular arrhythmic risk. In addition, extensive myocardial fibrosis and characteristic ring-like LGE patterns have emerged as important markers of adverse arrhythmic outcomes [9].

Our patient exhibited several features associated with increased arrhythmic risk, including sustained VT, extensive ring-like LGE, biventricular involvement and mildly reduced ventricular function. This further illustrates that severe ventricular arrhythmias in DSP cardiomyopathy may occur even before the development of advanced systolic dysfunction. Despite only mildly reduced LV and RV ejection fractions, the patient experienced multiple VT episodes requiring appropriate ICD therapies shortly after discharge. The subsequent successful radiofrequency ablation highlights the utility of invasive electrophysiologic mapping in targeting substrate-driven VT in these patients, particularly when pharmacologic and device therapy alone are insufficient.

Genetic testing was essential in confirming the diagnosis. The identification of a pathogenic DSP splice variant confirmed the inherited basis of the disease and prompted family screening, which

revealed early phenotypic expression in the patient's daughter, detectable on CMR despite entirely normal echocardiographic findings. She had <1% PVCs on 24-hr ECG monitoring. This highlights the importance of cascade screening in families of index cases, allowing early identification and risk stratification of affected relatives.

However, at present, there are no clear indications for primary prevention ICD implantation in patients with DSP variants, preserved LVEF and minimal arrhythmic burden. Previous studies suggest that patients with normal LVEF and a low PVC burden on ambulatory ECG monitoring derive limited benefit from prophylactic ICD implantation[7]. On the other hand, the daughter also fulfils the definition of non-dilated LV cardiomyopathy and presents extensive LGE on CMR, considered a high-risk feature according to current ESC cardiomyopathy guidelines; therefore, ICD implantation may be considered (Class IIb recommendation) in this setting.

Taking all available data into consideration, a strategy of close clinical surveillance was adopted, including 24-hr ECG Holter monitoring and echocardiographic evaluation every 6 months, together with annual CMR reassessment for longitudinal arrhythmic risk stratification. Regarding medical therapy, although beta-blockers may be considered in DSP cardiomyopathy due to arrhythmogenic substrate, evidence supporting prophylactic treatment in asymptomatic patients with preserved ventricular function remains limited. She was advised to avoid moderate- and high-intensity exercise activity.

Therapeutic management of DSP cardiomyopathy follows heart failure and arrhythmia management guidelines. The patient was managed with guideline-directed medical therapy, including beta-blockers, angiotensin receptor-neprilysin inhibitors, mineralocorticoid receptor antagonists and SGLT2 inhibitors. The addition of antiplatelet and lipid-lowering therapies was necessary following the NSTEMI event. An ICD was implanted as recommended in current guidelines for patients with ACM and ventricular tachycardia [3]. Ablation also proved to be an effective therapy, as he did not develop other ventricular arrhythmia afterwards.

To our knowledge, the coexistence of DSP cardiomyopathy and obstructive coronary artery disease is not unique. However, this case illustrates the potential diagnostic challenge of differentiating true ischaemic events from myocarditis-like 'hot phases' in DSP cardiomyopathy.

Long-term prognosis in DSP cardiomyopathy remains guarded due to progressive myocardial fibrosis, but arrhythmia control and heart failure management can significantly improve quality of life and outcomes.

Conclusions

This case highlights the complex nature of DSP cardiomyopathy, a genetic myocardial disease that can blur the line between arrhythmogenic and dilated cardiomyopathy phenotypes. In a patient with mildly reduced biventricular ejection fraction, the arrhythmic burden was high and necessitated going a step further to the catheter ablation after the placement of an ICD.

Moreover, the episode of acute myocardial infarction without ST elevations points out the potential coexisting coronary artery disease in patients with genetic cardiomyopathies, reinforcing the need for complete investigation of any acute coronary syndrome. Although myocarditis-like episodes can be common in these patients, they should remain an exclusion diagnosis. In addition, the importance of family screening is emphasised by the identification of a pathogenic DSP variant in the patient's daughter, who had a normal echocardiography and ECG, but presented late-gadolinium enhancement on CMR.

Overall, this case underscores the value of an integrated diagnostic approach combining clinical, imaging, genetic and electrophysiological data to guide individualised treatment in DSP cardiomyopathy. Early recognition and risk stratification are essential to improve outcomes and prevent life-threatening arrhythmias in this patient population.

Conflicts of Interest

The authors have each completed the International Committee of Medical Journal Editors Form for uniform Disclosure of Potential Conflicts of Interest. No authors have any potential conflict of interest to disclose.

Funding

The authors have no other relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilised in the production of this manuscript.

Ethics Approval

The study was approved by an institutional medical research ethics committee and conducted in accordance with the Declaration of Helsinki.

Consent to Participate

All participants were provided an informed written consent to participate in the study in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki) for experiments on humans.

Acknowledgments

This clinical case was documented during a Training Fellowship awarded by the Romanian Society of Cardiology.

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