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CASE SERIES
Cardiac imaging

A case series of desmoplakin cardiomyopathy: a mimic of viral myocarditis

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Background Clinical features and imaging presentation of myocarditis can overlap with other inflammatory or arrhythmogenic cardiomyopathies. Desmoplakin (DSP) is an important structural cardiac protein. Mutations in the DSP gene are associated with a variant of arrhythmogenic right ventricular cardiomyopathy (ARVC). Interestingly, this distinct genetic cardiomyopathy can also present with a myocardial inflammation and fibrosis pattern that may mimic other forms of myocarditis including viral myocarditis, which can raise a clinical challenge. We report two cases of DSP cardiomyopathy, which were initially thought to represent coronavirus disease of 2019 (COVID-19) myocarditis.

Case summary First patient is a 21-your-old woman with no past medical history but family history of presumed 'viral myocarditis' and ventricular tachycardia in her brother. She presented with acute chest pain and elevated cardiac enzymes. She tested positive for COVID-19 and given the suspicion for possible COVID-19 related acute myocarditis, cardiac magnetic resonance imaging obtained and revealed regional wall motion abnormalities, several areas of subepicardial and pericardial late gadolinium enhancement (LGE). Ambulatory cardiac monitoring showed runs of non-sustained ventricular tachycardia and considering her family history of arrhythmogenic myocarditis, genetic testing was performed that was positive for a likely pathogenic heterozygous mutation of DSP gene. She declined the recommended implantable cardioverter defibrillator (ICD).

Second patient is a 34-year-old physician with no significant past medical history who works at a COVID-19 unit and presented with syncope and was found to have ventricular tachycardia. Echocardiogram revealed severely dilated left ventricle and globally depressed systolic function with left ventricular ejection fraction of 20%. Coronary computed tomography angiography showed no evidence of coronary atherosclerosis. Cardiac magnetic resonance imaging revealed several areas of mid myocardial and pericardial LGE. Subcutaneous ICD was implanted and an endomyocardial biopsy had evidence of lymphocytic myocarditis and adipose tissue infiltration of the myocardium. Genetic testing revealed pathogenic heterozygous DSP mutation. He underwent epicardial ablation for the episodes of ventricular tachycardia despite medical therapy. He was able to return to work and has not had any further episodes of arrhythmia.

Conclusion Mutations in the DSP gene are associated with left dominant arrhythmogenic cardiomyopathy, which is a variant of ARVC. Beside left ventricular systolic dysfunction and ventricular tachyarrhythmias, carriers of these mutations may present with episodes of chest pain associated with elevated cardiac enzymes and cardiac imaging findings indistinguishable from other forms of acute myocarditis including viral myocarditis. Currently, there are no guidelines for diagnosis and treatment of this entity.

Keywords Arrhythmogenic right ventricular cardiomyopathy • Cardiac MRI • Case series • Desmoplakin • Genetic cardiomyopathy • Left dominant arrhythmogenic cardiomyopathy

ESC Curriculum 2.1 Imaging modalities • 2.3 Cardiac magnetic resonance • 5.6 Ventricular arrhythmia • 6.5 Cardiomyopathy

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Learning points

- Mutations in the desmoplakin (DSP) gene are associated with left dominant arrhythmogenic cardiomyopathy, which presents with left ventricular systolic dysfunction and ventricular tachyarrhythmias.
- Although genetic, DSP cardiomyopathy may have a myocarditis-like presentation that can mimic other forms of myocarditis including viral myocarditis. Therefore, DSP cardiomyopathy should be considered in the differential diagnosis of myocardites.

Introduction

Clinical features and imaging presentation of myocarditis can overlap with other inflammatory or arrhythmogenic cardiomyopathies. We report two cases of desmoplakin (DSP) cardiomyopathy, a variant of arrhythmogenic right ventricular cardiomyopathy (ARVC) with predominant involvement of the left ventricle (LV) [left dominant arrhythmogenic cardiomyopathy (LDAC)], which were initially thought to represent coronavirus disease of 2019 (COVID-19)-related acute myopericarditis.

Timeline

Patient 1

Days 1–2	Presented with 2 days of chest pain, elevated troponin, positive COVID Ag polymerase chain reaction (PCR) test, left ventricular ejection fraction (LVEF) 55%, trivial pericardial effusion, family history of 'viral myocarditis' and ventricular tachycardia (VT) in brother, left against medical advice on the 2nd day
Days 4–5	Presented to our institution with persistent chest discomfort, anteroseptal T wave inversion, persistent troponin elevation, positive repeat COVID Ag PCR test, and cardiac magnetic resonance (CMR) showed mildly dilated LV, LVEF of 51%, mild hypokinesis of the mid-inferolateral wall, late gadolinium enhancement (LGE) pattern consistent with myopericarditis, and was discharged on beta blocker, angiotensin converting enzyme-inhibitor and colchicine
1 month after discharge	Troponin levels normalized, genetic test 'likely pathogenic' heterozygous DSP gene mutation, heterozygous mutation of uncertain significance of the Lamin protein gene
2–6 months after discharge	Repeat echocardiogram LVEF 55%, five runs of non-sustained VT on cardiac monitor, patient declined implantable cardioverter defibrillator (ICD) implantation. Brother declined genetic testing

Patient 2

Day 1	Presented with syncope and monomorphic VT, occupation exposure to COVID but tested negative for COVID Ag and Ab, troponin and C-reactive protein (CRP) within normal range, inferior and anterolateral T wave inversion, severely reduced EF of 20%, started on amiodarone for recurrent VT
Day 2	Coronary computed tomography angiography with normal coronaries, CMR showed severely reduced LVEF of 15% with and LGE pattern consistent with myopericarditis
Days 3–6	Started on second antiarrhythmic for VT suppression, ICD implanted
Days 7–10	Endomyocardial biopsy showed lymphocytic infiltration and adipose tissue infiltration. Started on high dose steroids due to VT recurrence. Positron emission tomography (PET) scan showed no active cardiac inflammation
1 month after discharge	Genetic test showed pathogenic heterozygous DSP mutation, appropriate shock by ICD for VT, underwent epicardial VT ablation

Case presentations

Patient 1

A 21-year-old woman with no significant personal medical history initially presented to another hospital with 2 days of intermittent, pressure-like, substernal chest pain with radiation to bilateral upper extremities. Of note, her family history was significant for a presumed 'viral myocarditis' and related VT in her brother at the age of 16. Patient's cardiovascular exam was unremarkable. The initial Troponin-I was significantly elevated (23.25 ng/mL; normal value <0.05 ng/mL). Transthoracic echocardiogram showed normal LV systolic function with a LVEF of 55% and a trivial pericardial effusion. Despite the lack of common COVID-19 related symptoms, she tested positive for COVID-19 Ag by PCR. She left that facility against medical advice and presented to our hospital the following day. On presentation, the high-sensitivity Troponin-T was significantly elevated (693 ng/L; normal

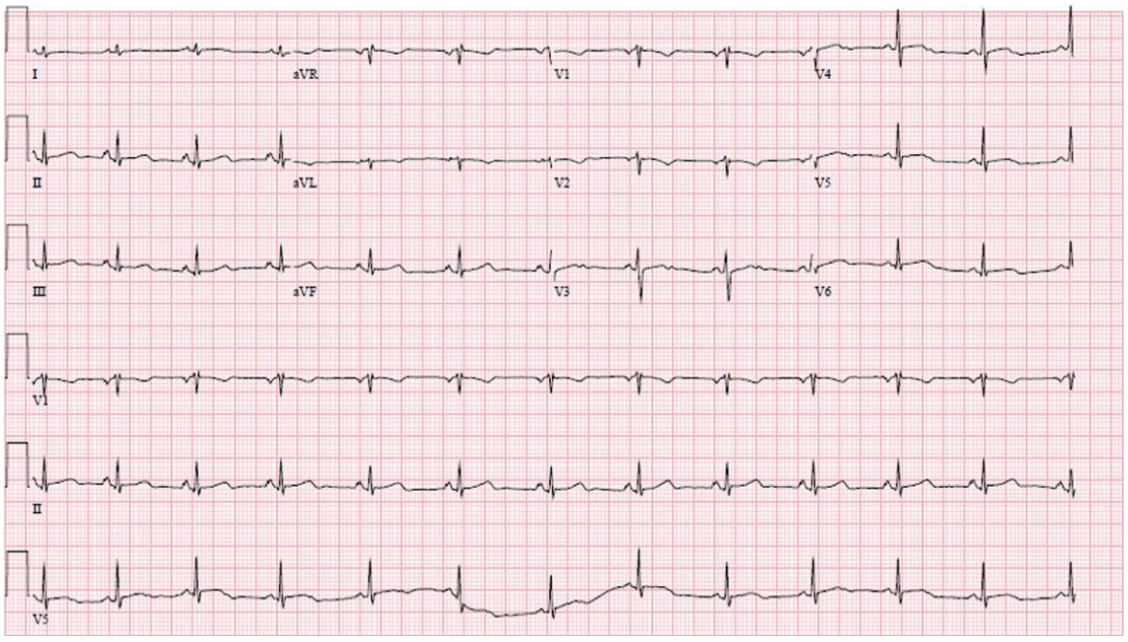


Figure 1 Electrocardiogram of Patient 1. T wave inversion in Leads V1–V2.

value <13 ng/L) and the electrocardiogram revealed nonspecific ST segment and T wave abnormalities including anteroseptal T wave inversion (*Figure 1*). Repeat COVID-19 Ag test was positive but both CRP and high-sensitivity CRP were within the normal range. Given the suspicion for possible COVID-19 related acute myopericarditis, she underwent CMR imaging (CMRI), which revealed mildly dilated LV [LV end-diastolic volume (LV EDV) index = 85 mL/m^2) with LVEF of 51% and mild hypokinesis of the mid-inferolateral wall. Right ventricle (RV) was normal in size and systolic function (Supplementary material online, *Video 1*). There was subepicardial LGE of the inferior, inferolateral, anterolateral, and anterior LV walls with mild overlying pericardial LGE suggestive of myopericarditis (*Figure 2*). Pre-contrast myocardial T1 relaxation time was prolonged (1177 ms, normal <1100 ms), whereas pre-contrast T2 time was within normal limits (52 ms, normal <60 ms).

She was treated with a beta blocker, angiotensin converting enzyme inhibitor and colchicine with normalization of the cardiac troponin levels on the follow-up visits. A 7-day ambulatory cardiac monitor showed five runs of non-sustained VT. Considering the family history of arrhythmogenic myocarditis in her brother, she was referred for genetic testing, which revealed a 'likely pathogenic' heterozygous mutation of the DSP gene (c.1267-2A > G variant) (based on the 2015 American College of Medical Genetics and Genomics guidelines 'likely pathogenic' means >90% certainty of a variant being disease-causing) and a heterozygous mutation of uncertain significance of the Lamin protein gene (c.1210T > A variant). Patient was referred to the cardiac electrophysiology service and she declined the recommended subcutaneous ICD implantation. One year later, the LVEF remaiend stable, and she continued on medical therapy. Her brother declined the recommended genetic testing.

Patient 2

A 34-year-old man with no significant past medical history who works as a COVID-19-unit hospitalist presented with sustained VT and syncope. Cardiovascular examination demonstrated a regular rate and rhythm with no murmurs, rubs, or gallops. Point of maximal impulse was laterally displaced. Jugular venous pressure was not elevated but he had trace lower extremity oedema. Electrocardiogram revealed nonspecific ST segment and T wave abnormalities including inferior and anterolateral T wave inversion (*Figure 3*). High-sensitivity Troponin-T was within the normal range (11 ng/L; normal <21 ng/L). He was started on amiodarone for controlling bouts of VT. He denied any recent COVID-19 related viral prodrome and tested negative for both COVID-19 antigen and antibody. The CRP level was also within the normal range. Transthoracic echocardiogram revealed severely dilated LV with a globally depressed systolic function (left ventricular internal diameter end-diastole 6.6 cm, LVEF of 20%). Coronary computed tomography angiography showed no evidence of coronary atherosclerosis. Cardiac magnetic resonance imaging redemonstrated a markedly dilated LV with a severely reduced global systolic function (LV EDV index = 143 mL/m^2, LVEF = 16%) and a normal size RV with a mildly reduced systolic function (RV EDV index = 66 mL/m^2, RVEF = 41%) (Supplementary material online, *Video 2*). There was mid myocardial LGE involving the inferoseptal and anteroseptal walls, subepicardial LGE along with mid apical anterolateral and inferolateral wall, and circumferential pericardial LGE favouring a pattern of myopericarditis (*Figure 4*). Pre-contrast myocardial T1 relaxation time was prolonged (1155 ms, normal <1100 ms), whereas pre-contrast T2 time was within normal limits (45 ms, normal <60 ms).

Given the history of sustained VT, a subcutaneous ICD was implanted and an endomyocardial biopsy was pursued which revealed lymphocytic myocarditis and adipose tissue infiltration of the myocardium concerning for AVRC (*Figure 5*). He was started on high dose steroids due to ongoing VT despite medical therapy. A cardiac 18F-fluorodeoxyglucose PET (FDG-PET) scan revealed no active inflammation. Genetic testing revealed 'pathogenic' heterozygous DSP mutation (c.2185dup variant). He continued to experience intermittent VT and was defibrillated by his ICD once. Therefore, he underwent epicardial VT ablation mapped to epicardial isthmus at apex. He has been receiving treatment with a beta blocker, angiotensin receptor blocker, mineralocorticoid receptor antagonist, sodium–glucose-cotransporter

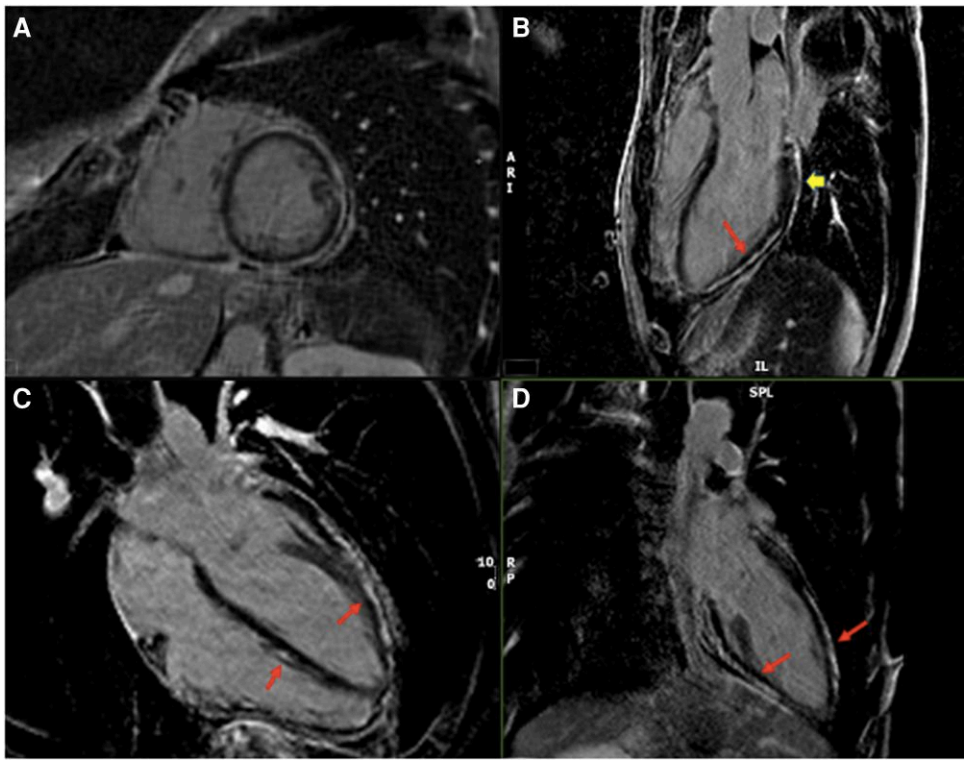


Figure 2 Late gadolinium enhancement pattern on cardiac magnetic resonance imaging of Patient 1. (*A*) Short axis, (*B*) three-chamber, (*C*) four-chamber, and (*D*) two-chamber views. Long arrows represent myocardial and short arrows indicate epicardial late gadolinium enhancement.

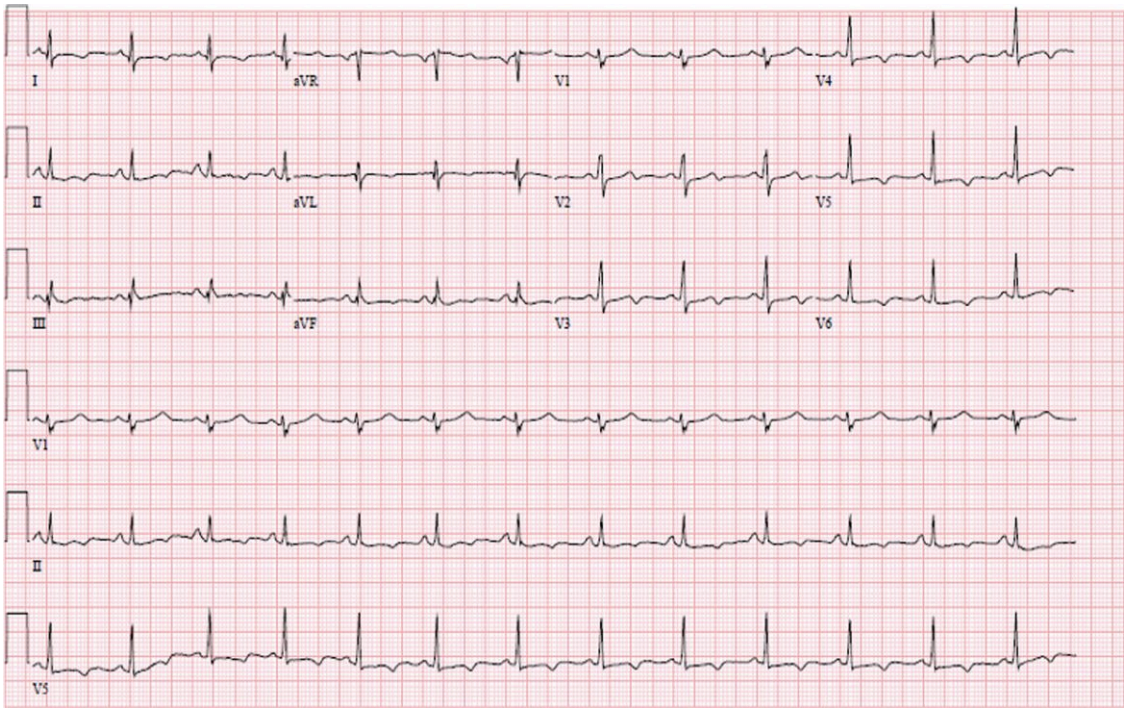


Figure 3 Electrocardiogram of Patient 2. T wave inversion in Leads I, aVL, II, aVF, and V3–V6.

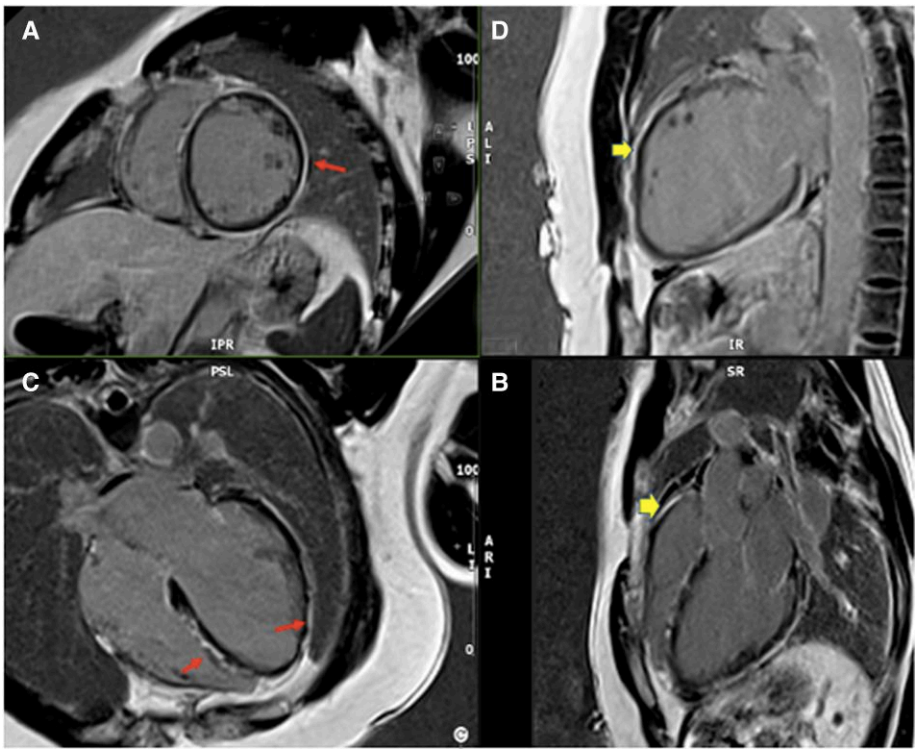


Figure 4 Late gadolinium enhancement pattern on cardiac magnetic resonance imaging of Patient 2. (*A*) Short axis, (*B*) two-chamber, (*C*) four-chamber, and (*D*) three-chamber views. Long arrows represent myocardial and short arrows indicate epicardial late gadolinium enhancement.

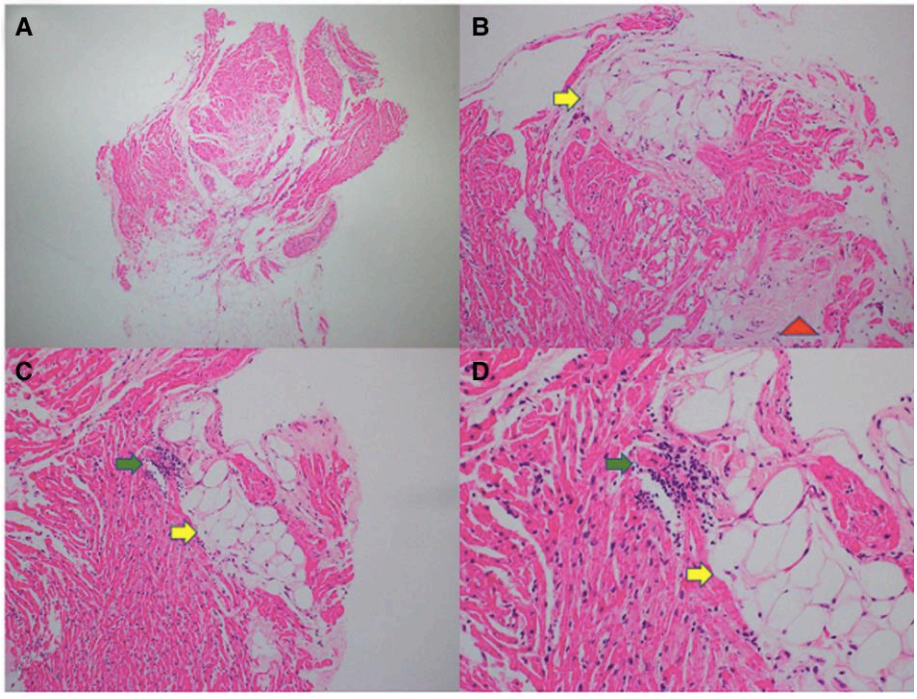


Figure 5 Endomyocardial biopsy of Patient 2. Low (*A*) and intermediate (*B–D*) power Haemotoxylin and Eosin-stained microscopic images of endomyocardial biopsy samples of Patient 2 showing mild myocardiocyte hypertrophy, fiber-type disarray, scattered lymphocytic infiltrate (green arrow) adjacent to adipose tissue depositions (yellow arrow), and patchy interstitial collagenous fibrosis (red arrowhead).

inhibitor, and continued on amiodarone for VT suppression. He has been able to return to work and has not had any further episodes of VT. The LVEF remained significantly reduced but stable on the follow-up echocardiography 1 year later. He was recommended to discuss screening genetic test with his first-degree relatives.

Discussion

Desmoplakin is a structural cardiac protein that is critical for normal force transmission in the myocardium.[1] Mutations in the DSP gene are associated with arrhythmogenic cardiomyopathies, which have been categorized as LDAC, a variant of ARVC with predominant involvement of the LV.[2–4] Subjects who carry these mutations usually present with clinical signs of LV systolic dysfunction and frequent premature ventricular complexes (PVCs) and VTs. Furthermore, it is suggested that an inflammatory component with a distinct fibrosis pattern may contribute to the development and progression of DSP cardiomyopathy.[5–7] This inflammatory component can mimic and be confused with other forms of myocarditis including viral myocarditis which can raise a challenge in diagnosis and management of these patients. Specifically, DSP cardiomyopathy needs to be considered in the differential diagnosis of myocarditis as the pattern of LGE on CMRI can be nearly indistinguishable between the two entities. Furthermore, this myocarditis-like presentation may have special clinical implications during the current COVID-19 pandemic where the COVID-19 related myocardial injury including acute myocarditis has been an ongoing concern.[8,9]

Mutations in the DSP gene were first identified in an autosomal recessive form[10] but these mutations have a high clinical penetrance for carriers and these subjects may have distinct phenotypic features. In a large multicentre cohort of 107 subjects with DSP mutation, including both probands and their genotype-positive family members, Smith *et al.*[11] reported that 69% of these subjects were female and 55% had characteristic curly hair and/or thick skin on the palms or soles (palmoplantar keratoderma).

Although it has often been categorized as ARVC, LV involvement is more common in DSP cardiomyopathy and, therefore, the term LDAC was introduced by Sen-Chowdhry *et al.*[12] in 2008. Smith *et al.*[11] reported that of all 107 subjects of their cohort, 51% had LV predominant, 14% had RV predominant, and 4% had isolated RV cardiomyopathy, however, 36% had normal LV and RV function. Larger portion of probands had LV dysfunction when compared with genotype-positive family members.

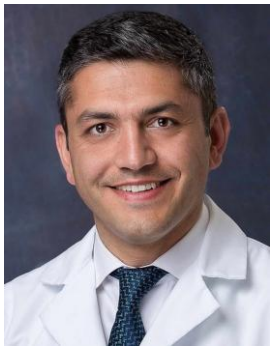
Cardiac magnetic resonance imaging can play a crucial role in the diagnosis of DSP cardiomyopathy. Like our presented cases, in their cohort, Smith *et al.* showed that 40% of all subjects who had CMRI, and 74% of subjects with LV predominant cardiomyopathy, exhibited LV LGE. The pattern of LGE was mostly subepicardial in the inferior segment with extension to the mid-myocardium in the septum in some cases. Circumferential subepicardial LGE distribution and intramyocardial fat in or adjacent to regions of subepicardial fibrosis were also seen in some cases.[11] This distribution of intramyocardial fat has also been reported by histopathologic analyses performed on the autopsy samples from sudden death cases associated with LDAC.[7]

Despite being a genetic cardiomyopathy, patients with DSP cardiomyopathy may uniquely present with clinical features of acute myocardial injury and inflammation including chest pain and elevated troponin as was seen in case 1. Smith *et al.*[11] reported that 15% of subjects with DSP mutation had evidence of acute myocardial injury and most of them (9/10) demonstrated LV LGE on CMRI. Acute episodes of myocardial injury occurred even in the presence of normal systolic function, and they suggested that myocardial injury and fibrosis may herald ventricular systolic dysfunction. The proportion of DSP nonprobands who presented with chest pain, troponin elevation, and LV LGE was similar to probands (13% vs. 18%, respectively). In contrast to our Case 2, in their cohort, four of the patients with troponin elevation underwent cardiac FDG-PET scanning, which revealed active myocardial inflammation. These features are distinct from ARVC and the revised 2010 ARVC Task Force criteria were proven to be insensitive for clinical diagnosis of patients with DSP mutations even in the minority of RV predominant patients.[11] The inflammatory process as a precursor of myocardial fibrosis and cardiac dysfunction makes inflammatory signalling pathways as appealing novel therapeutic targets for the DSP cardiomyopathy patients.

As shown in our cases, DSP cardiomyopathy is associated with increased risk of ventricular arrhythmias and sudden cardiac death with LVEF <55% and frequent PVCs accounting as strong predictors for these events.[11] Unlike other forms of dilated cardiomyopathy, an LVEF threshold of <35% rendered to be an insensitive marker for future arrhythmic events in DSP cardiomyopathy.

Desmoplakin gene mutations have high clinical penetrance and, therefore, the family members of patients with DSP cardiomyopathy carry a substantial risk of adverse events, which highlight family screening with genetic tests, CMRI (for assessment of LV LGE regardless of LV function by echocardiogram), and rhythm monitoring for PVC burden assessment.[11]

Lead author biography



Kaveh Rezaei Bookani completed medical school at Tabriz University of Medical Sciences in his home country, Iran. During his general cardiology fellowship at the University of Chicago-Northshore programme, he became interested in multimodality imaging and is currently an advanced cardiac imaging fellow at Cedars Sinai Medical Center in Los Angeles. He hopes to become a physician-scientist in this field.

Supplementary material

Supplementary material is available at *European Heart Journal—Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case series including images and associated text has been obtained from the patients in line with COPE guidelines.

Conflict of interest: None declared.

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