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Case Report

A case of desmoplakin mutation and delayed arrhythmogenic right ventricular cardiomyopathy/dysplasia after atrial septal defect closure

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ABSTRACT

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a slow-developing cardiomyopathy characterized by ventricular arrhythmias and fibrofatty replacement of the right ventricular (RV) myocardium. Its clinical diagnosis is challenging because of its variable clinical presentation and low genetic penetrance. We describe the case of a 67-year-old man who was diagnosed as having ARVC/D with a desmoplakin mutation that appeared after occlusion of an atrial septal defect (ASD). He underwent patch closure surgery for ASD at the age of 54 years. Four years later, he underwent catheter ablation for multifocal atrial tachycardias. Because of pre-syncope and inducible sustained monomorphic ventricular tachycardia, an implantable cardioverter defibrillator was implanted. When he was admitted for worsening heart failure at the age of 61 years, the desmoplakin mutation was detected with progressive left ventricular (LV) dysfunction. Subsequently, he was diagnosed as having ARVC/D with RV dysfunction. At cardiac autopsy, characteristics of ARVC/D, including dilatation, fibrofatty changes in the right ventricle, and diffuse fibrosis in the left ventricle were detected. Along with the effect of RV dysfunction caused by ASD, the progression of LV dysfunction after ASD closure was also possibly caused by the disease progression of ARVC/D. Physicians should carefully assess the various states of ARVC/D.
<**Learning objective:** Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a cardiomyopathy characterized by arrhythmias, fibrofatty replacement of the right ventricular (RV) myocardium, and slow progression to more diffuse ventricular dysfunction. This case involved an atrial septal defect (ASD) that promoted the RV failure and was complicated with delayed progression of ARVC/D after ASD closure. The present case suggests that physicians need to carefully assess the various states of ARVC/D.>

Introduction

The diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) can be challenging because its clinical presentation is highly variable and genetic penetrance is often low [1]. There may be a genetic predisposition in 30–50% of patients with ARVC/D [2], and it predominantly affects young individuals. Several genetic variations have been found in desmosomes that are responsible for cell-to-cell binding. Severe dilatation and reduction of right ventricular (RV) function with left ventricular (LV) involvement and/or histological evidence of fibrofatty replacement of the myocardium are two main criteria for the diagnosis of ARVC/D [3]. Clinical perspectives of ARVC/D primarily arise from experience with patients who present with arrhythmias of RV origin and/or sudden death. We describe a case of ARVC/D with a

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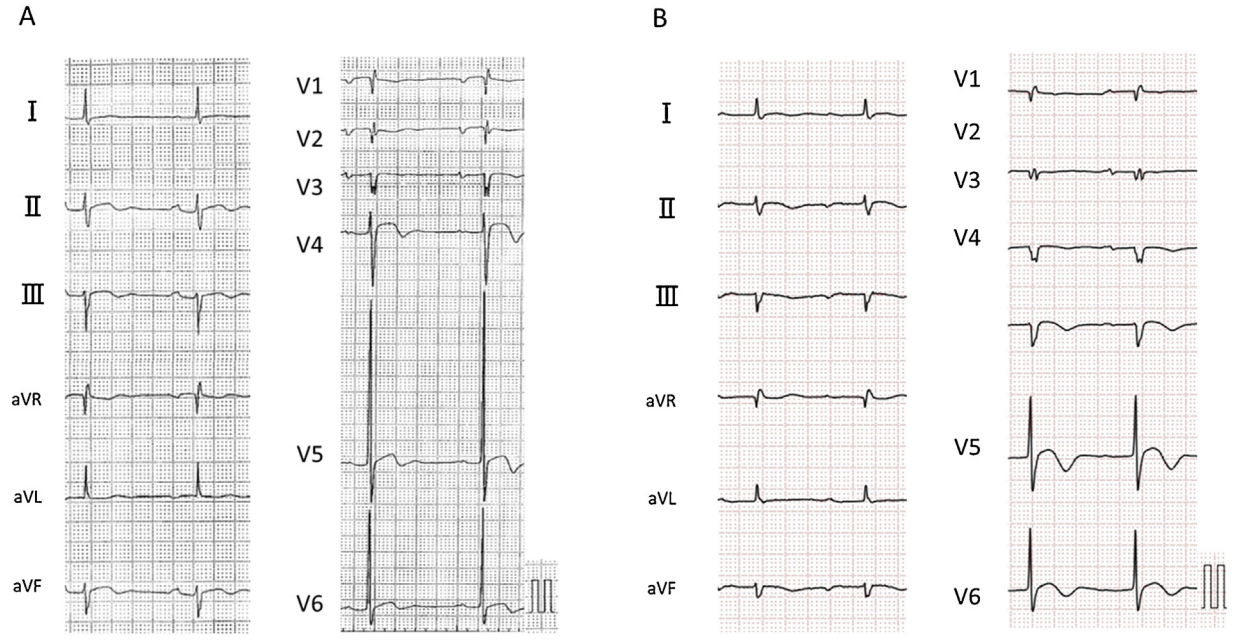

Fig. 1. Electrocardiograms at 1 year (A) and 7 years (B) after occlusion of atrial septal defect. The R wave in the chest leads gradually becomes low voltage, and the left-axis deviation remains. The width of the QRS complex becomes wide (80 ms–120 ms), and the length of QT becomes long (460 ms–500 ms).

desmoplakin mutation that appeared after occlusion of atrial septal defect (ASD).

Case report

A 54-year-old man experienced dyspnea on effort, and secundum type ASD was detected by echocardiography. The defect measured 1.5 × 1.5 cm. In right heart catheterization, the rate of left-to-right shunt was 40% and Qp/Qs ratio was 1.61. His pulmonary pressure and LV contraction were normal. The right ventricle was dilated, and contraction was reduced (RV ejection fraction 26%). To reduce the load of the right ventricle, he underwent patch closure surgery for ASD at the age of 54 years. The characteristic abnormalities of fibrotic and fat tissues, such as "fibrofatty replacement," were not observed in the myocardial tissue collected at the time of ASD closure. Ventricular late potential was negative (fQRS 110 ms, RMS 59.5 μV, LAS 25 ms) on signal-averaged electrocardiography (SAECG). Losartan (25 mg) and furosemide (40 mg) were administered during hospitalization and after discharge.

At the age of 55 years, he underwent catheter ablation for atrial flutter. Although his RV function was still reduced, his LV ejection fraction (LVEF) was 60% (Figs. 1 and 2A). At the age of 58 years, he underwent catheter ablation for multifocal atrial tachycardias. Because he had frequent pre-syncope and inducible sustained monomorphic ventricular tachycardia (VT), an implantable cardioverter defibrillator was implanted. When he was admitted for worsening heart failure (HF) at the age of 61 years, digoxin (0.0625 mg/day) was prescribed, and reduced LVEF (49%) and a desmoplakin mutation were detected. Results of the RV

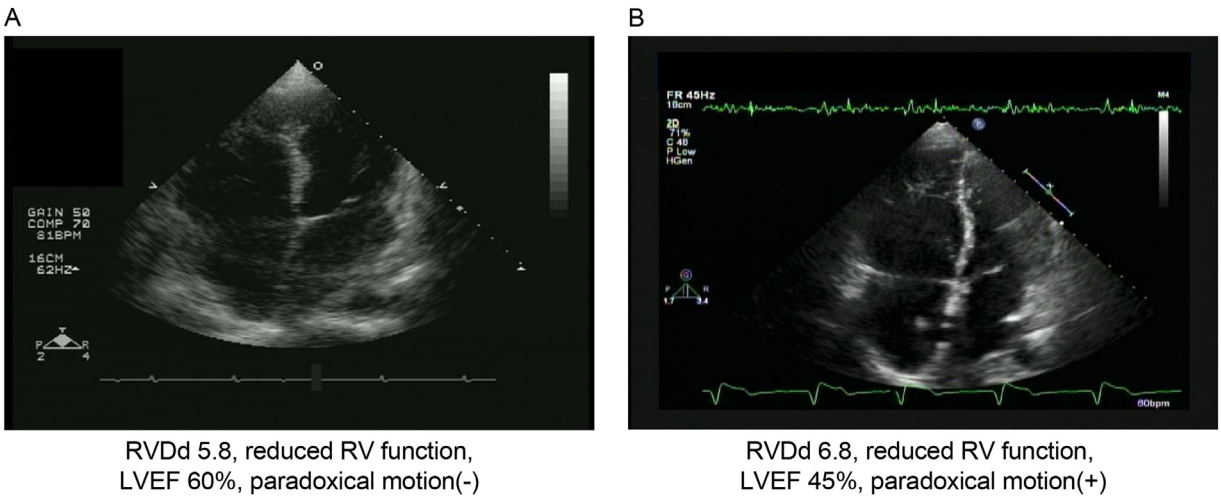

Fig. 2. Echocardiograms at 1 year (A) and 7 years (B) after occlusion of atrial septal defect (ASD). The right ventricle is gradually expanding, and it has become possible to detect paradoxical motion of the ventricular septum. ASD was suspected as a cause of the decreased right ventricular function. However, gradual deterioration of the left ventricular function is recognized. RVDd, right ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; RV, right ventricular.

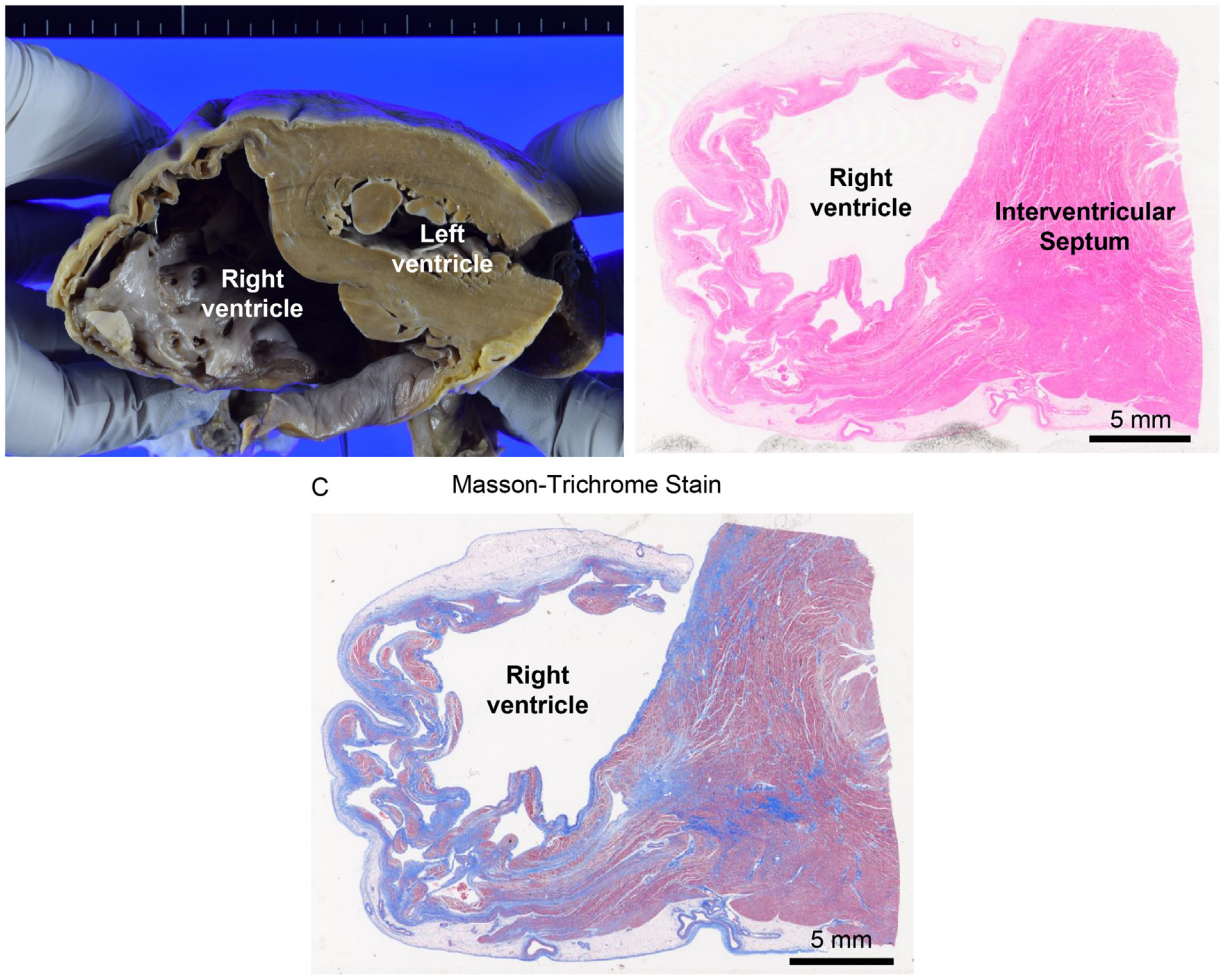

Fig. 3. Autopsy findings. (A) Photograph of the macroscopic view of the heart. The right ventricle is markedly dilated with diffuse thinning of the wall. Additionally, there is mild concentric hypertrophy of the left ventricle with multifocal interstitial fibrosis. (B, C) Histological stains of the right ventricle. There is prominent fibrofatty change in the right ventricle.

endomyocardial biopsy showed fibrofatty tissue replacement and estimated residual myocytes of <60%. Non-sustained VT (NSVT) of the left bundle-branch morphology with superior axis was detected with RV dysfunction [RV fractional area change (RV FAC) 0.21]. By using SAECG, we detected positive late potential (fQRS 105.5 ms, RMS 15.27 μV, LAS 34.5 ms) with a narrow QRS complex on the 12-lead electrocardiogram and more than 1000 ventricular extrasystoles on the Holter electrocardiogram. Then he was diagnosed as having ARVC/D. On the electrocardiogram, the R wave in the chest leads gradually became low voltage, and the left axis deviation remained. The width of the QRS complex became wider (Fig. 1B). Over time, the echocardiogram showed gradual dilation of the right ventricle and gradual reduction of the LVEF (Fig. 2B).

Although he was treated with pimobendan and tolvaptan, he had repeated hospitalizations for HF with decreasing LVEF (46%) and RV FAC (0.06). Because LV dyssynchrony was negative by speckle tracking strain imaging, the improvement in cardiac function by the upgrading to CRT could not be expected. When he was 67 years of age, he developed worsening HF caused by volume overload resistant to diuretic medication so he was introduced to dialysis therapy. After 4 months of dialysis, he was admitted for shortness of breath and a decreased blood pressure. We attempted to adjust his volume by dialysis control, but his pleural effusion worsened. His blood pressure gradually decreased. Finally, he died at 32 days after the admission.

On autopsy, the right ventricle was markedly dilated with diffuse thinning of the wall (Fig. 3A). Additionally, there was mild concentric hypertrophy of the left ventricle with multifocal interstitial fibrosis (Fig. 3A). By histological stain of the ventricle (Fig. 3B,C), there was prominent fibro-fatty change in the right ventricle. In this case, along with the influence of the RV dysfunction caused by ASD, it was suggested the LV dysfunction due to ARVC/D with desmoplakin mutation.

Discussion

In this case, ARVC/D was diagnosed based on the 2010 Task Force Criteria [3]. Among the main criteria, four items (RV FAC, residual myocytes <60% with fibrous replacement detected by RV biopsy, NSVT of the left bundle-branch morphology with superior axis, and identification of a desmoplakin mutation) were met. Among the minor criteria, two items (late potentials detected by SAECG in ≥1 with a narrow QRS complex on the 12-lead electrocardiogram and >500 ventricular extrasystoles on the Holter electrocardiogram) were met. ASD is reported to lead to RV dysfunction and elevated right chamber pressures, causing the appearance of arrhythmogenic RV cardiomyopathy [4]. In the

reported case with progressive RV dysfunction and diagnosis of ARVC/D, the diagnosis of atrial shunt was difficult [5]. This case had RV dysfunction and dilatation, which are also characteristics of ASD. At the time of 1 year after ASD closure, T wave inversion was detected that is consistent with one of the ARVC/D characteristics. A few years after ASD closure, due to the development of atrial and ventricular tachyarrhythmias, ARVC/D was assumed, and he underwent myocardial biopsy and genetic diagnosis. Based on the findings of electrocardiographic, pathological, and genetic studies, he was finally diagnosed with ARVC/D.

ARVC/D is a cardiomyopathy that progresses to RV and LV dysfunction and is divided into three phases by a condition. In the early phase, structural change is absent or minor, but patients may be at risk for sudden cardiac death by VT or ventricular fibrillation (VF). In the overt phase, patients have symptomatic ventricular arrhythmia with manifested structural abnormality. In the later phase, patients experience progressive HF [6]. In the retrospective study by Kikuchi et al. [7] of 90 Japanese patients with ARVC/D, 30% of the patients experienced worsened HF, and about 50% experienced sustained VT or VF. In our case of a 67-year-old man with ARVC/D who developed a desmoplakin mutation, RV and LV dysfunction and frequent ventricular arrhythmias appeared after occlusion of ASD, and refractory HF developed a few years later. If we could diagnose ARVC/D in an earlier phase, prediction and treatment might have been provided earlier. In fact, there was the case in which it was diagnosed as ASD and rapid evolution of RV cardiomyopathy after ASD closure [8]. Although the accurate early diagnosis is important, it is difficult to diagnose ARVC in some cases with complicated conditions. It is necessary to evaluate patients by following the disease progression carefully, particularly in the case of ASD with RV dysfunction after diagnosis and treatment of ASD.

ARVC/D-related mutations in desmosomal genes and, less commonly, non-desmosomal genes are identified in more than 60% of cases. Desmosome is one of the structures involved in cell adhesion, and its disruption leads to various diseases. Among desmosomal genes, mutations in plakophilin-2 are most frequently identified in patients with ARVC/D. The desmoplakin mutation seen in this case is rare, and it reportedly accounts for only 4% of gene mutations [9]. Further improvement of genetic evaluation is needed for the detection and evaluation of AVC/D patients.

At cardiac autopsy, characteristics of ARVC/D, including dilatation, fibrofatty changes in the right ventricle, and diffuse fibrosis in the left ventricle were detected in our patient. In addition to the RV dysfunction caused by ASD, the LV dysfunction may have been due to ARVC/D with a desmoplakin mutation. In subjects with ARVC/D, ventricular fatty infiltration is common and associated with an advanced stage of ARVC/D. In Sepehrkhouy et al.'s report [10], desmosomal-associated and phospholamban-associated cardiomyopathies have a fibrosis pattern distinct from the patterns in other hereditary cardiomyopathies. The posterolateral LV wall appeared to be the most discriminative region between those mutation groups. The relationships between gene mutation and cardiac imaging interpretation may help detect underlying disease mechanisms.

Conclusions

This was a complicated case of delayed onset ARVC/D confirmed after ASD closure. Physicians should detect and carefully assess the various states of ARVC/D, especially in the case of ASD complicated with RV dysfunction.

Conflicts of interest

The authors declare that there is no conflict of interest.

Acknowledgments

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References

[1] Gemayel C, Pelliccia A, Thompson PD. Arrhythmogenic right ventricular cardiomyopathy. J Am Coll Cardiol 2001;38:1773–81.
[2] Franz WM, Müller OJ, Katus HA. Cardiomyopathies: from genetics to the prospect of treatment. Lancet 2001;358:1627–37.
[3] Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. Circulation 2010; 121:1533–41.
[4] Quarta G, Husain SI, Flett AS, Sado DM, Chao CY, Tomé Esteban MT, et al. Arrhythmogenic right ventricular cardiomyopathy mimics: role of cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2013;15:16.
[5] Cubero JM, Gallego P, Pavon M. Arrhythmogenic right ventricular cardiomyopathy and atrial right-to-left shunt. Acta Cardiol 2002;57:443–5.
[6] Basso C, Corrado D, Marcus FI, Nava A, Thiene G. Arrhythmogenic right ventricular cardiomyopathy. Lancet 2009;373:1289–300.
[7] Kikuchi N, Yumino D, Shiga T, Suzuki A, Hagiwara N. Long-term prognostic role of the diagnostic criteria for arrhythmogenic right ventricular cardiomyopathy/dysplasia. JACC Clin Electrophysiol 2016;2:107–15.
[8] Sivasubramonian S, Alphonso N, Qureshi SA, Anderson D. Rapid evolution of right ventricular cardiomyopathy after surgical closure of a secundum atrial septal defect. Pediatr Cardiol 2004;25:541–4.
[9] Ohno S. The genetic background of arrhythmogenic right ventricular cardiomyopathy. J Arrhythm 2016;32:398–403.
[10] Sepehrkhouy S, Gho JMIH, van Es R, Harakalova M, de Jonge N, Dooijes D, et al. Distinct fibrosis pattern in desmosomal and phospholamban mutation carriers in hereditary cardiomyopathies. Heart Rhythm 2017;14:1024–32.