Clinical Case Report

Medicine®

OPEN

Congenital heart disease combined with Arrhythmogenic Right Ventricular Cardiomyopathy

A CARE compliant case report and literature review

Chutong Ren, MD[a], Zhenfei Fang, MD[b], Yanshu Zhao, MD[b], Jun Luo, MD[b,*]

Abstract

Rationale: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a hereditary cardiomyopathy disease discovered in 1994. Though there are advances in diagnosis of arrhythmogenic right ventricular cardiomyopathy, early diagnosis is still difficult especially when it is combined with other diseases with similar pathophysiologic changes, such as left to right shunt congenital heart disease (CHD). In this paper, we reported a case of CHD combined with ARVC.

Patient concerns: The patient was referred to us for chest tightness and shortness of breath after physical activities. His cardiac MRI indicated the possibility of arrhythmogenic right ventricular cardiomyopathy. He was diagnosed with a large atrial septal defect (ASD) through ultrasound examination.

Diagnosis: CHD ASD combined with arrhythmogenic right ventricular cardiomyopathy.

Interventions: The patient underwent occlusion of the ASD and he was followed-up closely. His symptoms were relieved a lot and the activity tolerance was elevated.

Lessons: CHD may accompany with arrhythmogenic right ventricular cardiomyopathy. Careful history collection and comprehensive examinations should be emphasized. We firmly believe that our work will be helpful for the medical practice of similar complicated cardiovascular diseases.

Abbreviations: ARVC = arrhythmogenic right ventricular cardiomyopathy, ASD = atrial septal defect, CHD = congenital heart disease.

Keywords: arrhythmogenic right ventricular cardiomyopathy, atrial septal defect, congenital heart disease

Editor: Maya Saranathan.

The patient and his family members signed the consents about all clinical producers and agreed on this case report to be published.

This work was supported by the National Natural Science Foundation of China (Project 81870233 and 81600249) and the Hunan Provincial Natural Science Foundation of China (Project 2017JJ3455).

Supplemental Digital Content is available for this article.

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

[a] Department of Minimal Invasive Surgery, [b] Department of Cardiology, The Second Xiangya Hospital, Central South University, Changsha, Hunan Province, China.

[*] Correspondence: Jun Luo, Department of Cardiology, The Second Xiangya Hospital, Central South University, No. 139 Remin Middle Road, Changsha City, Hunan Province, 410000, P.R. China (e-mail: luojun2242004@csu.edu.cn)

How to cite this article: Ren C, Fang Z, Zhao Y, Luo J. Congenital heart disease combined with Arrhythmogenic Right Ventricular Cardiomyopathy: a CARE Compliant Case Report and Literature Review. Medicine 2020;99:25(e20279).

Received: 5 April 2019 / Received in final form: 3 April 2020 / Accepted: 14 April 2020

http://dx.doi.org/10.1097/MD.0000000000020279

Established Facts and Novel Insights

Established Facts:

1. Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a hereditary disease usually causing sudden cardiac death in youth, which indicates the importance of diagnosis in its early stage.
2. According to the pathological and physiological changes caused by ARVC, ARVC tends to be confusing when it combines with some diseases that may also lead to right ventricular enlargement, making the diagnosis more challenging.

Novel Insights:

1. ARVC can accompany with congenital heart disease; in such occasion, careful differential diagnoses are required.
2. Only 5 cases were reported as congenital heart disease combined with ARVC; so the summary of the clinical features of these cases may provide a great reference for further practice.

1. Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a family disease related to syncope and sudden cardiac death. It has an estimated prevalence of 1 in 5000 in the general population[1] and characterized by ventricular arrhythmia with left bundle branch block and progressive fibrofatty infiltrations of the right ventricle. The diagnosis of ARVC is rather challenging, especially in the early stage. Here, we present an interesting case of a 58-year-old male patient who was referred to us for chest tightness and shortness of breath after physical activities. After careful examination and evaluation, he was diagnosed with the atrial septal defect (ASD) while his clinical features also met the diagnosis criteria of ARVC. According to the literature review, only 5 cases (including the present case) were reported as congenital heart disease (CHD) combined with ARVC. Thus, we summarized these cases here, hoping to provide more data for further clinical practice regarding to these two diseases.

2. Case presentation

2.1. Clinical history

A 58-year-old male was referred to the hospital for chest tightness and shortness of breath after physical activities for over 40 years. His symptoms were exacerbated for 1 month. Since the patient was a 10-year-old boy, he showed decreased exercise capacity compared to his peers. He could only tolerate 200 meters' run before symptoms such as chest tightness, shortness of breath and palpitation appeared. Amaurosis sometimes appeared after physical activities but these symptoms could relieve after rest. Since 8 years ago, the patient could not tolerate 4 to 5 floor climbing. And this year, he had chest tightness and shortness of breath after only 2-floor climbing, accompanied by precardium area pain radiating to the back and shoulders. He could not lie down at night and had edema, abdominal distension, weakness and loss of appetite. The patient had a history of chronic bronchitis which was well controlled. He had been smoking for over 30 years. The family history of the patient deserves to be mentioned. His mother died of a sudden heart attack at about 50 years old. And his daughter was diagnosed with ventricular septal defect (3 mm in diameter) during the antenatal examination. His physical examination results were listed as follow. The left boundary of his heart showed expansion. Cardiac auscultation showed arrhythmia and blowing systolic murmur at 2nd-3rd intercostal space at the left margin of the sternum. Pulse deficit was obvious. No other positive signs were found.

2.2. Accessory examination

A series of examinations were carried out after the patient was admitted to the ward. His 24-hour Holter showed that:

(1) atrial fibrillation with slightly slow mean heart rate,
(2) frequent multi-source premature ventricular contractions, part of which were bigeminal and part paired,
(3) occasional ventricular extrasystole,
(4) complete right bundle branch block,
(5) occasional change of T waves in partial lead connection.

The chest radiography showed an expanded heart boundary, which coincided with the physical examination. He also had an echocardiography examination (Fig. 1A–C), which shows:

(1) ASD (secondary orifice, left to right shunt), about 25.7 mm in diameter,
(2) Enlargement of right atrium, right ventricle and left atrium, slightly thin right ventricular wall and irregular shape of the right ventricle,
(3) uncoordinated ventricular wall movement,
(4) slightly wider ascending aorta,
(5) slight reflux in the mitral valve, tricuspid valve and pulmonary valve area,
(6) Arrhythmia,
(7) normal systolic function of left ventricular and small decrease in the function of right-side heart (EF was only for reference because of atrial fibrillation).

His cardiac MRI (Fig. 1D–F) showed the possibility of ARVC. The routine 12-leads electrocardiogram of this patient is showed in Fig. 2A. For the purpose of proving the MRI diagnosis, a fontaine lead electrocardiogram was performed in order to show right ventricular myocardial depolarization better. Consequently, a typical epsilon wave was detected (Fig. 2B). In addition, his blood pressure pro-BNP level was elevated evidently. The gene detection related to ARVC was advised to the patient's family. However, his family refused and chose to continue the follow-up.

2.3. Therapeutic regimen

After careful consideration, we advised the patients to undergo occlusion of ASD surgery. The patient underwent this surgery and his symptoms were relieved slightly after the surgery. The follow-up was of vital importance for the patient. In addition, gene detection should still be carried out if necessary during further consultation.

2.4. Follow-up

The patient went back to the clinic for his reexamination 6 months after the surgery. His symptoms were relieved a lot and his exercise tolerance increased evidently. The patient's blood pressure pro-BNP level decreased to be normal. The 12-lead electrocardiograph showed atrial fibrillation with a low ventricular rate, incomplete right bundle branch block and abnormal T wave (Fig. 3A). The echocardiography showed the decreased cardiac size and effective occlusion (Fig. 3B–D).

3. Discussion

ARVC is a type of inherited cardiomyopathy characterized by ventricular arrhythmia with left bundle branch block and progressive fibrofatty infiltrations of right ventricle.[2] Life-threatening ventricular arrhythmia is very common for ARVC patients and it usually leads to sudden cardiac death.[3] The diagnosis of ARVC is rather complicated. According to the 2010 Revised Task Force Criteria for the diagnosis of ARVC as listed in Table 1, it is based on structural alternations, histologic character, Electrocardiograph, arrhythmic, and familial features.[4] Although the new diagnosis material is more sensitive than the original one in 1994, the diagnosis of ARVC is still challenging, especially for the patients in the early stage of disease[5] and it cannot differentiate cardiac sarcoidosis from ARVC.[6]

In the case reported in this article, the patient had a large ASD. However, the patient's clinical presentation and accessory

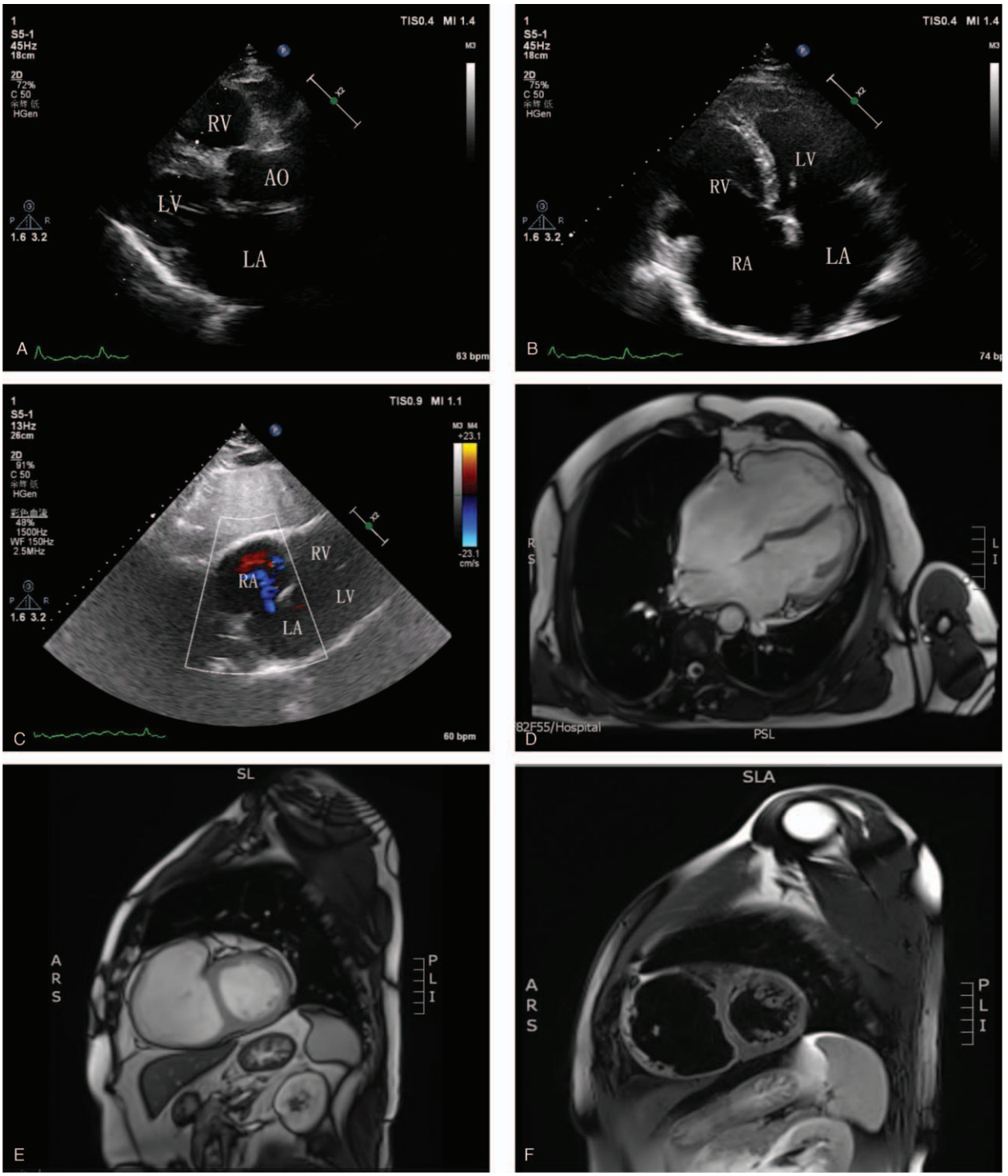

Figure 1. The echocardiography of the patient. (A) The parasternal long axis view; (B) The apical 4 chamber view; (C) The subxiphoid 4 chamber view. The cardiac magnetic resonance imaging of the patient which shows typical change of ARVC (D, E, F). ARVC = arrhythmogenic right ventricular cardiomyopathy.

examination results seemed to also meet the 2010 Revised Task Force Criteria for the diagnosis of arrhythmogenic right ventricular cardiomyopathy. Can CHD such as ASD appear accompanied by ARVC? We reviewed the case of CHD combined with arrhythmogenic right ventricular cardiomyopathy reported since the concept of arrhythmogenic right ventricular cardiomyopathy was put forward. Consequently, we found that such cases were too scarce that only 5 cases were reported. The clinical and pathologic features of these cases are listed in Table 2.[7–9] Through these cases, we can conclude that for the patients diagnosed with CHD, the clinical presentations of ARVC tend to be covered up. That is because ARVC and left-to-right shunting CHD at times share the common phenotype of right ventricle dysfunction despite different mechanisms of disease.[9] The

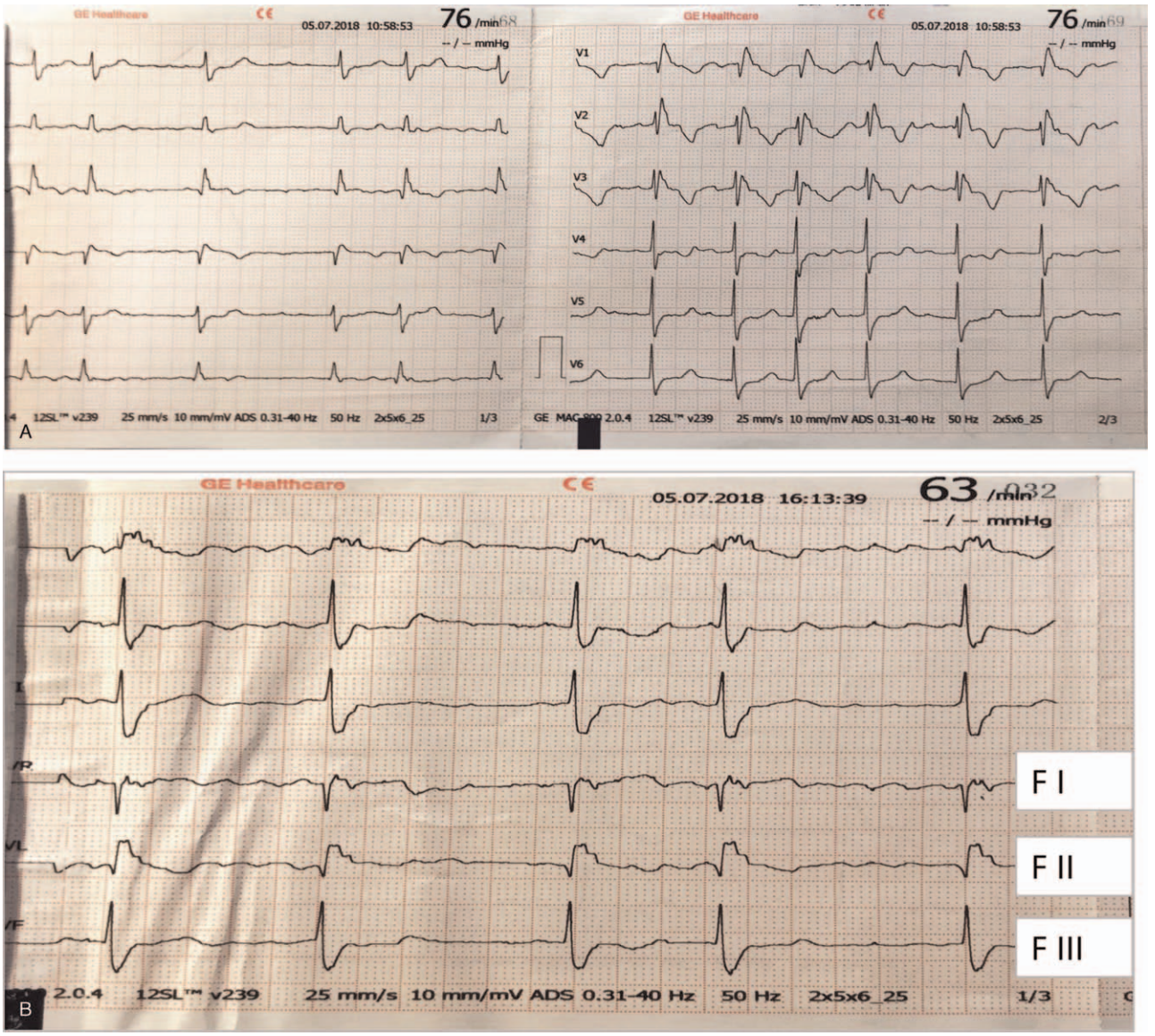

Figure 2. The ECG of the patient. (A) Routine 12-leads electrocardiogram; (B) Fontaine lead ECG which showed typical epsilon wave. ECG = electrocardiogram.

process of disease can be accelerated by conditions such as physical activities which disproportionately increase right ventricle stress.[10] The study of La Gerche A et al[11] showed that even for a healthy man, chronic right ventricle stress in an otherwise healthy heart could still result in a phenotype similar to ARVC in the absence of impaired desmosome. Thus, we can hypothesize that the chronic right ventricle volume overload secondary to left-to-right shunting CHD may cause structural and electrophysiologic findings to be consistent with those of ARVC. For one thing, the diagnosis of ARVC is challenging for young patients because absent phenotypic features and the overlapping of the findings with CHD are possible.[9] For another, the symptoms of CHD patients sometimes meet the diagnosis criteria of ARVC regarding the secondary pathophysiologic change. Therefore, the early detection of CHD should be emphasized. Moreover, the cardiac MRI[12] and gene detection may assist in the differential diagnosis.

When it comes to the therapy, structural CHD may be managed with percutaneous or surgical interventions,[13] and ARVC can be controlled by activity restriction, medical therapy, and antiarrhythmic therapies. Notably, an implantable cardioverter defibrillator should be placed when necessary.[14,15] With appropriate management, mortality rates of arrhythmogenic right ventricular cardiomyopathy and CHD are both low. Therefore, careful evaluation and differentiation are of vital importance. For this patient, the results of his follow-up proved the effect of therapy. This conclusion illustrates that the treatment for CHD is useful for the relief of symptoms when the CHD is combined with ARVC. Moreover, further reexamination is still of vital importance.

The patient in this case is relatively elder among patients diagnosed with CHD combined with ARVC. And through the literature review, we summarized the similarities and differences between the 2 diseases and emphasize careful evaluation and

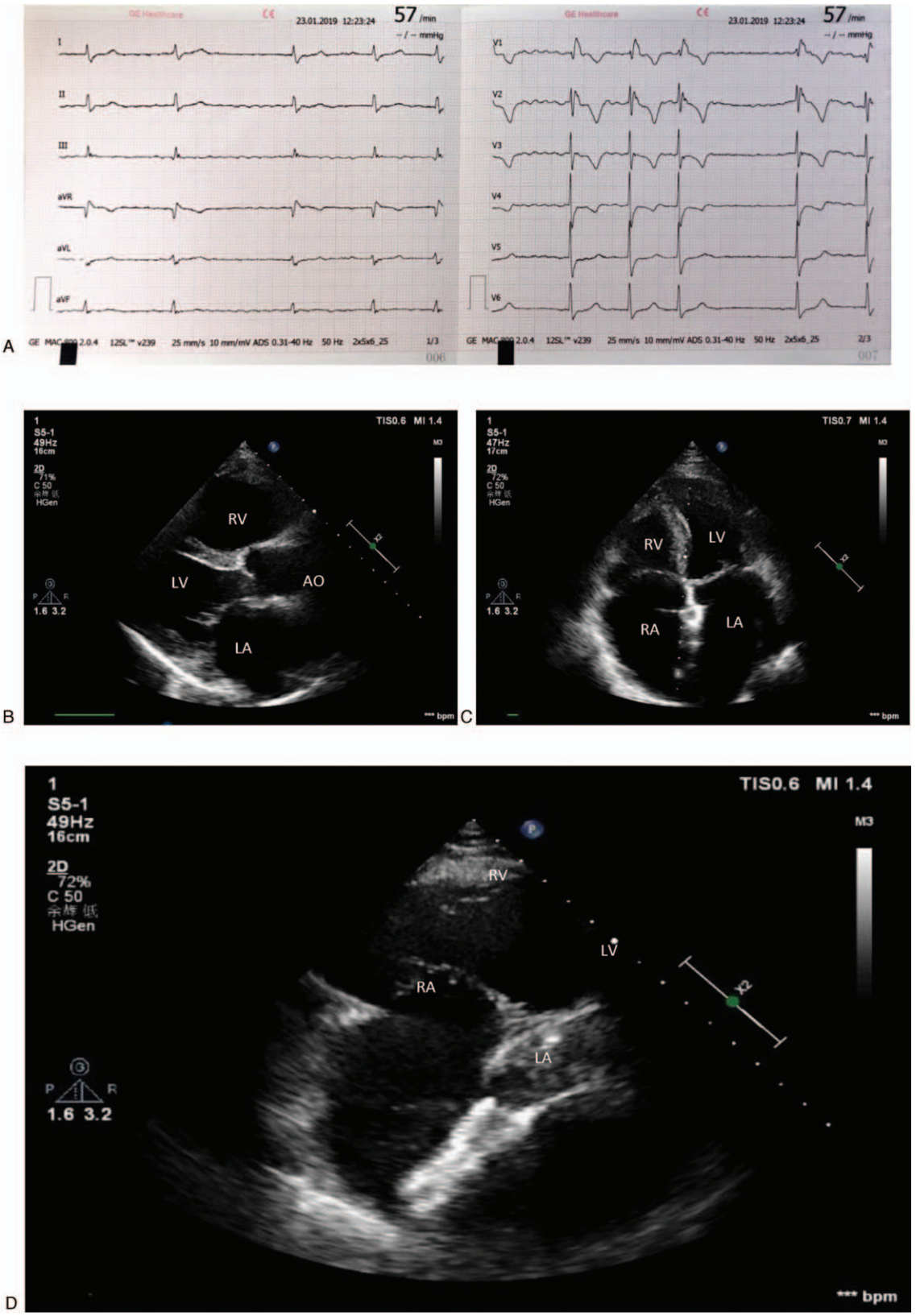

Figure 3. The follow-up examination of the patient 6 mo after surgery. (A) Routine 12-leads electrocardiogram; (B) The parasternal long axis view echocardiography; (C) The apical 4 chamber view echocardiography; (D) The subxiphoid 4 chamber view echocardiography.

Table 1

2010 Revised Task Force Criteria for the diagnosis of arrhythmogenic right ventricular cardiomyopathy.

	Major	Minor
Global or regional dysfunction and structural alterations	By 2D echo: Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end diastole): — PLAX RVOT ≥32 mm (corrected for body size [PLAX/BSA] ≥ 19 mm/m^2) — PSAX RVOT ≥36 mm (corrected for body size [PSAX/BSA]≥21 mm/m^2) — *or* fractional area change ≤33% By MRI: Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: —Ratio of RV end-diastolic volume to BSA ≥110 mL/m^2(male) or ≥100 mL/m^2 (female) — *or* RV ejection fraction ≤40% By RV angiography: Regional RV akinesia, dyskinesia, or aneurysm	By 2D echo: Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end diastole): — PLAX RVOT ≥32 mm (corrected for body size [PLAX/BSA] ≥ 19 mm/m^2) — PSAX RVOT ≥36 mm (corrected for body size [PSAX/BSA] ≥21 mm/m^2) — or fractional area change ≤33% By MRI: Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: — Ratio of RV end-diastolic volume to BSA ≥110 mL/m^2 (male) or ≥100 mL/m^2 (female) — or RV ejection fraction ≤40% By RV angiography: Regional RV akinesia, dyskinesia, or aneurysm
Tissue characterization of wall	Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy.	Residual myocytes 60%-75% by morphometric analysis (or 50%-65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
Repolarization abnormalities	Inverted T-waves in right precordial leads (V1, V2, and V3) or beyond in individuals >14 y of age (in the absence of complete RBBB QRS ≥120ms)	(1) Inverted T-waves in leads V1 and V2 in individuals >14 y of age (in the absence of complete RBBB) or in V4, V5, or V6 (2) Inverted T-waves in leads V1, V2, V3, and V4 in individuals >14 y of age in the presence of complete RBBB
Depolarization/conduction abnormalities	Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T-wave) in the right precordial leads (V1 to V3)	(1) Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRS duration of ≥110ms on the standard ECG (2) Filtered QRS duration (fQRS) ≥114ms (3) Duration of terminal QRS <40 μV (low-amplitude signal duration) ≥38ms (4) Root-mean-square voltage of terminal 40 ms ≤20 μV (5) Terminal activation duration of QRS ≥55ms measured from the nadir of the S-wave to the end of the QRS, including R', in V1, V2, or V3, in the absence of complete RBBB
Arrhythmias	Nonsustained or sustained ventricular tachycardia of LBBB morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)	(1) Nonsustained or sustained ventricular tachycardia of RV outflow configuration, LBBB morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis (2) >500 ventricular extrasystoles per 24 h (Holter)
Family history	(1) ARVC/D confirmed in a first-degree relative who meets current Task Force (2) Criteria ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative (3) Identification of a pathogenic mutationa categorized as associated or probably associated with ARVC/D in the patient under evaluation	(1) History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force Criteria (2) Premature sudden death (<35 y of age) due to suspected ARVC/D in a first-degree relative (3) ARVC/D confirmed pathologically or by current Task Force Criteria in second-degree relative

Diagnostic terminology for revised criteria: definite diagnosis: 2 major or 1 major and 2 minor criteria or 4 minor from different categories;
borderline: 1 major and 1 minor or 3 minor criteria from different categories;
possible: 1 major or 2 minor criteria from different categories.

ARVC = arrhythmogenic right ventricular cardiomyopathy; aVF = augmented voltage unipolar left foot lead; aVL = augmented voltage unipolar left arm lead; BSA = body surface area; ECG = electrocardiogram, LBBB = left bundle branch block; PLAX = parasternal long-axis view; PSAX = parasternal short-axis view; RBBB = right bundle branch block; RVOT = right ventricle outflow tract.

[*] A pathogenic mutation is a DNA alteration associated with ARVC/D that alters or is expected to alter the encoded protein, is unobserved or rare in a large non-ARVC/D control population, and either alters or is predicted to alter the structure or function of the protein or has a demonstrated linkage to the disease phenotype in a conclusive pedigree.

Table 2

Clinical and pathologic features of 5 patients with ARVC versus CHD.

	Case 1	Case 2	Case 3	Case 4	Case 5
Reference No.	9	9	8	7	Case in this report
Age	11-yr-old	6-yr-old	19-yr-old	71-yr-old	58-yr-old
Gender	Male	Female	–	Male	Male
Clinical manifestation	Palpitations	Palpitations	–	Atrial fibrillation	Chest tightness and shortness of breath after physical activities
Family history	Consanguinity	SCD in maternal grandfather	–	–	SCD in his mother
ECG	Borderline RBBB	IRBBB, AVNRT	–	Atrial fibrillation	Atrial fibrillation, rare PVCs and CRBBB
Holter monitoring	>2000 PVCs	Rare PVCs	–	–	
Exercise tesing	Normal	PVCs of RVOT origin	–	Persistent atrial fibrillation	
Echocardiogram	Normal	ASD, mild MR, RV and RA dilation	–	RA and RV dilation, severe TR and 2 small ASDs	ASD, enlarged RA RV and LA, mild TR MR and PR
Gnen detection	Negative	Pending	A novel mutation in the gene p.S194L DSG2 homozygous	–	–
CMR	RV dilation	RV dilation, WMA, myocardial thinning, delayed enhancement	–	–	enlarged RA RV and LA, WMA, serrated change in RV free wall
Biopsy	Mitochondrial changes	–	–	–	–
Intervention	–	ASD repair, slow pathway modification	ASD repair and ICD implantation	ASD repair and ICD implantation	ASD repair and close follow-up
ARVC diagnosis	Definite	Borderline	Definite	Definite	Definite
Final diagnosis	PAPVC combined with ARVC	ASD combined with ARVC	ASD combined with ARVC	latrogenic atrial septal defect and ASD	ASD combined with ARVC

ARVC = arrhythmogenic right ventricular cardiomyopathy, ASD = atrial septal defect; AVNRT = atrioventricular nodal reentrant tachycardia, CHD = congenital heart disease, CMR = cardiac magnetic resonance, CRBBB = complete right bundle branch block, ECG = electrocardiogram, ICD = implantable cardioverter defibrillator, IRBBB = incomplete right bundle branch block, MI = myocardial infarction, MR = mitral regurgitation, PAPVC = partial anomalous pulmonary venous connection, PR = Pulmonary regurgitation, PVC = premature ventricular contraction, RA = right atrium, SCD = sudden cardiac death, TR = Tricuspid regurgitation, WMA = wall motion abnormality.

differentiation. Close follow-up will be necessary for the patients. We hope that more accurate criteria and better therapy for similar cases could be put forward in the near future.

4. Statements

The video of the patient's echocardiography are provided in the supplemental videos.

Echocardiography1: The parasternal long axis view, http://links.lww.com/MD/E381.

Echocardiography2: The apical four chamber view, http://links.lww.com/MD/E382.

Echocardiography3: The subxiphoid four chamber view, http://links.lww.com/MD/E383.

Acknowledgment

We would like to acknowledge the librarians at the Libraries of Central South University for their efforts in obtaining primary resources for this case report and literature review. Additionally, we would like to acknowledge professors, colleagues, friends, and family members who assisted in the writing procedure of this case report.

Author contributions

DR Chutong Ren and DR Jun Luo provided main efforts in the writing and analyzing procedure. Meanwhile, DR Yanshu Zhao and DR Zhenfei Fang as specialists in department of cardiology found the value of this case and provided great help in the diagnosing process.

Funding acquisition: Zhenfei Fang, Yanshu Zhao.
Investigation: Chutong Ren.
Supervision: Zhenfei Fang, Yanshu Zhao, Jun Luo.
Writing – original draft: Chutong Ren.
Writing – review & editing: Zhenfei Fang, Yanshu Zhao, Jun Luo.

References

[1] Peters S, Trummel M, Meyners W. Prevalence of right ventricular dysplasia-cardiomyopathy in a non-referral hospital. Int J Cardiol 2004;97:499–501.
[2] Basso C, Corrado D, Marcus FI, et al. Arrhythmogenic right ventricular cardiomyopathy. Lancet 2009;373:1289–300.
[3] Blusztein DI, Zentner D, Thompson T, et al. Arrhythmogenic right ventricular cardiomyopathy: a review of living and deceased probands. Heart Lung Circ 2018;28:1034–41.

[4] Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria. Eur Heart J 2010;31:806–14.
[5] Corrado D, Link MS, Calkins H. Arrhythmogenic right ventricular cardiomyopathy. N Engl J Med 2017;376:61–72.
[6] Philips B, Madhavan S, James CA, et al. Arrhythmogenic right ventricular dysplasia/cardiomyopathy and cardiac sarcoidosis: distinguishing features when the diagnosis is unclear. Circ Arrhythm Electrophysiol 2014;7:230–6.
[7] Lee A, Mahadevan VS, Gerstenfeld EP. Iatrogenic atrial septal defect with right-to-left shunt following atrial fibrillation ablation in a patient with arrhythmogenic right ventricular cardiomyopathy. HeartRhythm Case Rep 2018;4:159–62.
[8] A. Shapieva N, A. Shestak G, E. Zaklyazminskaya V, et al. Arrhythmogenic cardiomyopathy of the right ventricle comorbid with hemodynamically significant secondary interatrial septal defect. Russian Journal of Cardiology 2015;109:61–5.
[9] Kiamanesh O, Farhan M, Sanatani S, et al. Congenital heart disease confounding the diagnosis of arrhythmogenic right ventricular cardiomyopathy. HeartRhythm Case Rep 2016;2:290–5.
[10] James CA, Bhonsale A, Tichnell C, et al. Exercise increases age-related penetrance and arrhythmic risk in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers. J Am Coll Cardiol 2013;62:1290–7.
[11] La Gerche A, Claessen G, Dymarkowski S, et al. Exercise-induced right ventricular dysfunction is associated with ventricular arrhythmias in endurance athletes. Eur Heart J 2015;36:1998–2010.
[12] Etoom Y, Govindapillai S, Hamilton R, et al. Importance of CMR within the Task Force Criteria for the diagnosis of ARVC in children and adolescents. J Am Coll Cardiol 2015;65: 987–95.
[13] Pillutla P, Shetty KD, Foster E. Mortality associated with adult congenital heart disease: trends in the US population from 1979 to 2005. Am Heart J 2009;158:874–9.
[14] Schinkel AF. Implantable cardioverter defibrillators in arrhythmogenic right ventricular dysplasia/cardiomyopathy: patient outcomes, incidence of appropriate and inappropriate interventions, and complications. Circ Arrhythm Electrophysiol 2013;6:562–8.
[15] Bhonsale A, James CA, Tichnell C, et al. Incidence and predictors of implantable cardioverter-defibrillator therapy in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy undergoing implantable cardioverter-defibrillator implantation for primary prevention. J Am Coll Cardiol 2011;58:1485–96.