

[CASE REPORT]

Arrhythmogenic Right Ventricular Cardiomyopathy Accompanied by Chronic Myocarditis

Makiko Nakamura, Teruhiko Imamura, Takuya Fukui, Naoya Kataoka and Koichiro Kinugawa

Abstract:

Patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) classically present with ventricular arrhythmias and less commonly heart failure. ARVC is an inherited cardiomyopathy and generally based on a variant of desmosomal genes. Recently, the association between myocardial inflammation and ARVC has been a matter of great concern. We encountered a patient with ARVC who had a desmoglein-2 mutation with advanced right ventricular failure accompanying a preserved left ventricular function. Concomitant right ventricular myocarditis was detected four years after the diagnosis of ARVC. ARVC and myocarditis might have a deep pathophysiological association, at least in some cases.

Key words: heart failure, cardiomyopathy, desmosome, hemodynamics, arrhythmia

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Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy that is mainly due to variant desmosomal genes, presenting with severely dilated right heart and a reduced right ventricular ejection fraction with fibrofatty replacement and leading to sudden death and heart failure (1-4).

Recently, myocardial inflammation has been considered to be involved in the pathogenesis of ARVC (5). Several case reports have described patients with ARVC initially presenting with clinical acute or recurrent myocarditis and predominantly showing left ventricular abnormalities (1, 5, 6). However, there have been a few reports of cases presenting with right ventricular abnormalities with chronic myocarditis in advanced-stage ARVC (7).

We herein report a patient with advanced right-sided heart failure with concomitant chronic myocarditis without a virus genome four years following the diagnosis of ARVC with a desmoglein-2 mutation.

Case Report

The diagnosis of ARVC (four years ago)

Four years ago, a 35-year-old woman was admitted to the previous hospital to investigate the etiology of frequent premature ventricular conduction. She had a family history of premature sudden death.

The echocardiography showed right ventricular (RV) enlargement and a reduced RV systolic function with an RV fractional area change of 25% and tricuspid systolic velocity of 6.0 cm/s. On cardiac magnetic resonance imaging, the RV end-diastolic volume index was 88.0 mL/m², and the RV ejection fraction was 12.1%, whereas the left ventricular (LV) ejection fraction was 57%. Delayed enhancement was observed at the outer side of the RV inferior wall. An endomyocardial biopsy of the RV showed fibrofatty tissue replacement with reduced residual myocytes (<60%). She was diagnosed with ARVC (Fig. 1A).

Sustained ventricular tachycardia (two years ago)

Two years ago, she suffered from sustained ventricular tachycardia and received catheter ablation as well as subcutaneous-implantable cardioverter defibrillator (ICD)

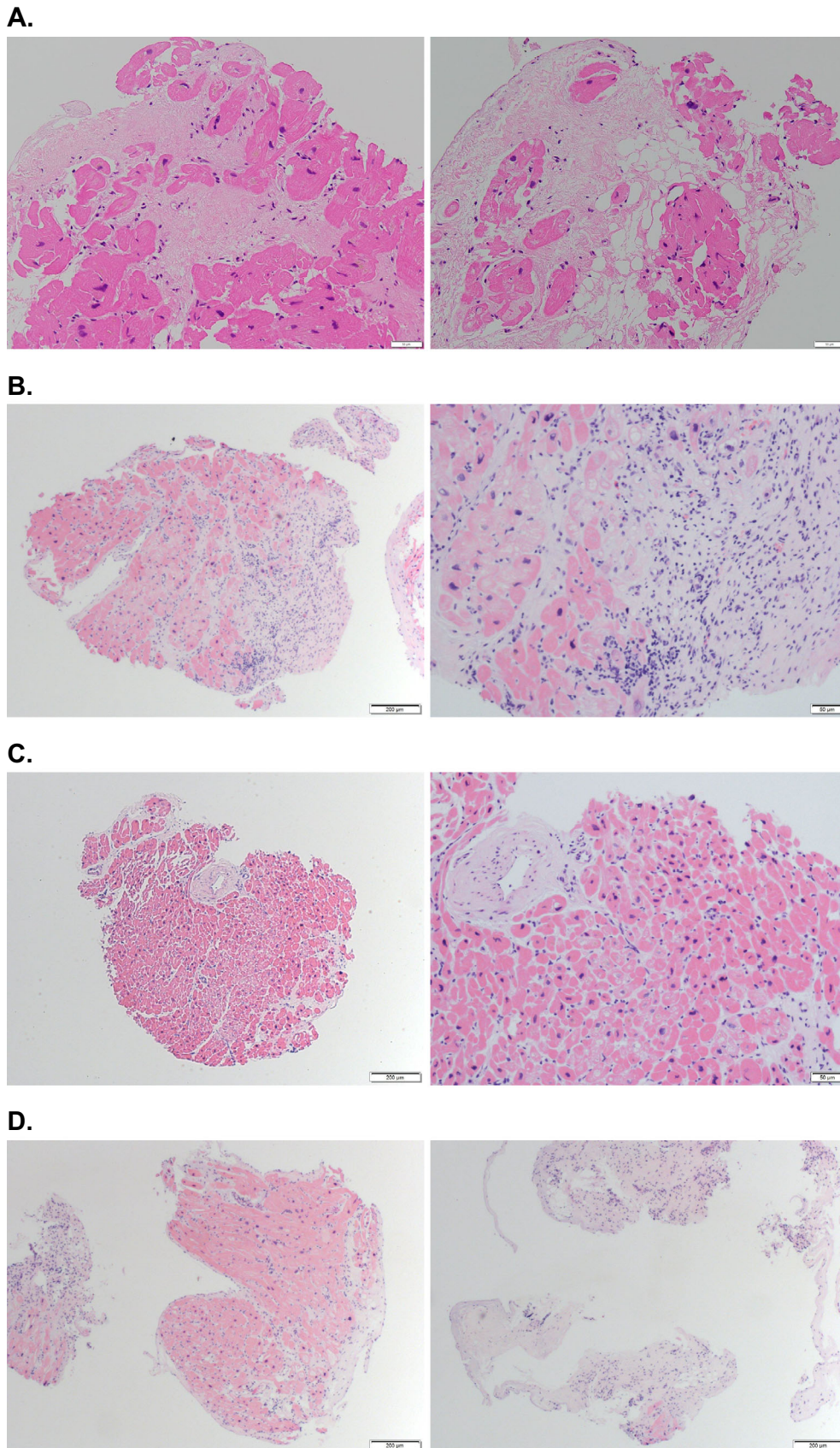


Figure 1. The pathology specimens of the endomyocardial biopsy. (A) Fibrofatty tissue replacement with residual myocytes reduction (<60%) in the right ventricle 4 years ago. (B) Numerous inflammatory cell infiltration mainly composed of mononuclear cell with cardiomyocyte shedding with fibrosis was shown in the right ventricle on admission. (C) A few lymphocytes were shown in the fibrotic replacement in the left ventricle. (D) One month after corticosteroid therapy, persistent inflammatory cell infiltration with fibrosis was shown in the right ventricle.

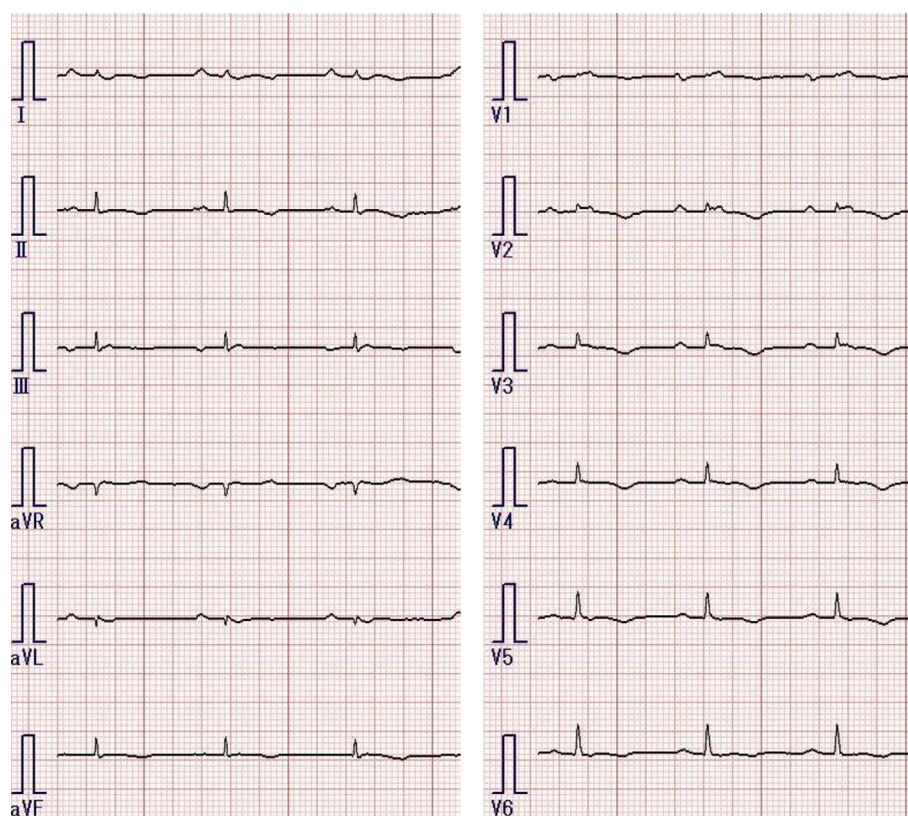


Figure 2. Electrocardiography findings on admission. A negative T wave in V2-5 and epsilon wave in V2-3, typical findings of ARVC, were shown.

implantation due to concerns about lead-related complications in the future and no sinus node dysfunction. Imidapril and bisoprolol were initiated. Transthoracic echocardiography showed the further progression of RV dysfunction and dilatation as well as progression of tricuspid valve regurgitation without inferior vena cava dilatation.

Refractory RV failure (index hospitalization)

She was admitted to our hospital complaining of leg edema and general fatigue with cold extremities. Her body height was 170 cm, and her body weight was 54.5 kg. The systolic blood pressure was 107 mmHg, and the heart rate was 75 bpm. The plasma level of B-type natriuretic peptide was 258.4 pg/mL on intravenous dobutamine at 1 μ g/kg/min. She had no rash, arthralgia, dry mouth, or Raynaud's symptoms, all of which indicate collagen disease. She also had no hilar lymphadenopathy, uveitis, or erythema nodosum.

Electrocardiography showed a negative T wave in V2-5, indicating enlarged RV impairment, and an epsilon wave in V2-3, which were typical findings of ARVC (Fig. 2).

Transthoracic echocardiography revealed a markedly enlarged RV dimension with a reduced systolic function accompanying severe tricuspid valve regurgitation (Fig. 3A, B). The LV end-diastolic diameter was 32 mm, and the LV ejection fraction was 54%.

On right heart catheterization, the mean right atrial pressure, right ventricular end-diastolic pressure, mean pulmo-

nary artery pressure, and pulmonary artery wedge pressure were 14, 16, 14, and 7 mmHg, respectively, and the cardiac index was 1.89 L/min/m². Her right ventricular stroke work index was 0.0 g/m.

To improve her low cardiac output by increasing the heart rate and adding anti-tachycardia pacing, the subcutaneous ICD was removed, and a transvenous dual chamber ICD was implanted, with an atrial pacing rate setting of 70 bpm.

RV myocarditis

The second RV endomyocardial biopsy showed myocardial shedding and massive fibrotic replacement with infiltration of CD3-positive T lymphocytes, which met the criteria of chronic myocarditis according to the Japanese Circulation Society (Fig. 1B) (8). We also performed an LV biopsy, but no features of myocarditis were noted (Fig. 1C). Neither epithelioid cell granuloma nor infiltration of eosinophils was seen in the RV or LV tissue.

The high-sensitivity cardiac troponin T level was increased to 0.031 ng/mL. The virus genome was negative. No abnormal accumulation was observed on systemic gallium scintigraphy. Intravenous methylprednisolone pulse therapy and subsequent oral prednisolone of 30 mg per day were initiated.

However, a third RV endomyocardial biopsy one month later showed persistent myocarditis (Fig. 1D). The existence of implanted ICD leads made it challenging to evaluate cardiac magnetic resonance imaging findings due to artifacts.

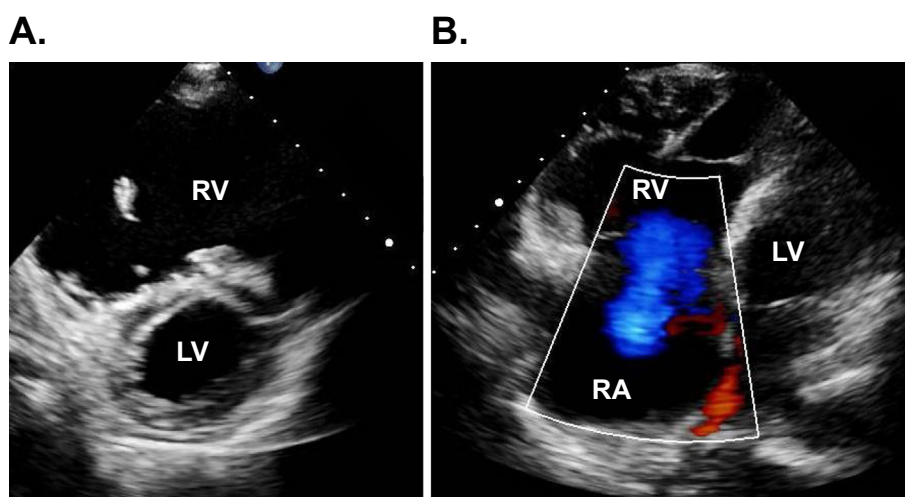


Figure 3. Echocardiography findings on admission. (A) The right ventricle was markedly enlarged. (B) Severe tricuspid regurgitation with a dilated right ventricle was seen on admission.

The cardiac troponin T level remained high. Given the limited efficacy of corticosteroid therapy, the maintenance dose of oral prednisolone was gradually reduced to 10 mg per day.

Riociguat administration

Riociguat was administered for further afterload reduction at the RV and preload increase at the LV. The mean right atrial pressure, right ventricular end-diastolic pressure, mean pulmonary artery pressure, and pulmonary artery wedge pressure 2 months later improved to 11, 12, 13, and 6 mmHg, respectively, and the cardiac index increased to 2.12 L/min/m². Her right ventricular stroke work index slightly improved to 0.81 g/m, but her plasma level of B-type natriuretic peptide remained unchanged at 254.0 pg/mL. The atrial pacing rate settled at 80 bpm, and she was discharged on foot on day 67.

Post-discharge course

There was no worsening heart failure following the index discharge. The maintenance dose of oral prednisolone was weaned by 1 mg per month. Her high-sensitivity cardiac troponin T level was 0.027 ng/mL at 3 months after discharge. Genetic testing showed pathogenic gene variants in desmoglein-2.

Discussion

Diagnostic criteria for ARVC

The diagnosis of ARVC is sometimes challenging given the variations in its clinical presentation. We referenced the diagnostic criteria of ARVC established by Task Force Criteria: 1) global or regional dysfunction and structural alterations; 2) tissue characterization of wall; 3) repolarization abnormalities; 4) depolarization/conduction abnormalities; 5) ventricular arrhythmias; and 6) a family history (3, 4). Our

patient met all of these criteria and was thus definitely diagnosed with ARVC.

ARVC and desmosomal gene mutations

ARVC is mainly caused by mutations in genes encoding the desmosomal protein family, including plakophilin-2, desmoglein-2, and desmoplakin (8). Desmosomes are membrane protein complexes that play an important role in intercellular adhesion and maintenance of the structural integrity of tissues subjected to mechanical stress, such as the heart and skin. These mutations usually have an autosomal dominant mode of inheritance with incomplete penetrance.

Our patient had a desmoglein-2 mutation, which is observed only in 4-15% of ARVC patients (9). Biventricular dysfunction is observed in 20% to 50% of patients with this mutation (9). To our knowledge, only two patients have been reported to have desmoglein-2 mutation, presenting with ARVC and concomitant biventricular myocarditis (5, 10). It seems that the clinical presentation, including LV involvement, cannot be explained simply by the type of gene mutation (10), although desmoplakin mutation carriers mostly develop LV involvement (2, 5, 6).

ARVC and myocarditis

The association between ARVC and myocarditis has been a matter of increasing concern. Several case reports recently described patients with ARVC that initially developed as acute myocarditis. Most of them were women with LV involvement and desmoplakin gene variants (5, 6).

The present patient did not fit these scenarios. Subclinical chronic myocarditis was identified four years following the diagnosis of ARVC without LV involvement. Given these findings, myocardial inflammation might play a key role in the progression of ARVC, although further studies are warranted to clarify the causality between myocarditis and ARVC. Some of the myocarditis emerges clinically at early phase, and others might persist without any symptoms for a

long time, as we presented. An autopsy study found that 67% of patients with ARVC had myocardial necrosis due to occult myocarditis (11). Future studies should explore why the presentation of myocarditis varies between acute onset and chronic progression, as in our patient, and between RV alone and LV involvement.

Riociguat for right heart failure

We sometimes use a pulmonary vasodilator for cases of severe RV failure during durable LV assist support, regardless of the existence of pulmonary hypertension, to further decrease the afterload on the RV (12). We administered riociguat in the present case to further decrease the afterload on the RV, maintaining systemic circulation and weaning from inotropes.

The authors state that they have no Conflict of Interest (COI).

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