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Case Report

An overlap of Brugada syndrome and arrhythmogenic right ventricular cardiomyopathy/dysplasia

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ABSTRACT

Overlapping characteristics of Brugada syndrome (BrS) and arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) have been reported in recent studies, but little is known about the overlapping disease state of BrS and ARVC/D. A 36-year-old man, hospitalized at our institution for syncope, presented with this overlapping disease state. The electrocardiogram showed spontaneous coved-type ST-segment elevation, and ventricular fibrillation was induced by right ventricular outflow tract stimulation in an electrophysiological study. BrS was subsequently diagnosed; additionally, the presence of epsilon-like waves and right ventricular structural abnormalities met with the 2010 revised task force criteria for ARVC/D. After careful investigation for both BrS and ARVC/D, an implantable cardioverter defibrillator was inserted in the patient. This case revealed 2 important clinical findings: (1) BrS and ARVC/D clinical features can coexist in a single patient, and EPS might be useful for determining the phenotype of overlapping disease (e.g., BrS-like or ARVC/D-like). (2) An overlapping disease state of BrS and ARVC/D can change phenotypically during its clinical course. Therefore, careful examination and attentive follow-up are required for patients with BrS or ARVC/D.

1. Introduction

Brugada syndrome (BrS) is characterized by right precordial ST-segment elevation followed by a negative T wave and sudden cardiac death from ventricular fibrillation in patients with structurally normal hearts [1]. Recent studies have revealed structural or electrocardiographic abnormalities, such as right ventricular dilatation or epsilon-like waves, in some patients with BrS [2,3]. These abnormalities are commonly considered characteristics of arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D). It is generally known that there are clinical similarities between BrS and ARVC/D [4]; however, little is known about the clinical features of patients with an overlapping disease state of BrS and ARVC/D, and accordingly, treatment of such patients remains poorly understood. In order to understand this condition better, we report here, a case of overlapping disease state of BrS and ARVC/D.

2. Case report

A 36-year-old man presented to our institution with syncope, and was subsequently, hospitalized. He had no family history of sudden cardiac death. The electrocardiogram (ECG) showed spontaneous coved-type ST-segment elevation (Brugada type 1 ECG); we initially suspected BrS. In an electrophysiological study (EPS) conducted prior to pilsicainide infusion, neither ventricular tachycardia (VT) nor ventricular fibrillation (VF) was induced by a single or double stimulus to the right ventricular apex or right ventricular outflow tract. A single stimulus to the right ventricular outflow tract during pilsicainide infusion induced ventricular fibrillation, which was thereafter, inhibited during isoproterenol infusion. Therefore, the patient was diagnosed with BrS, although the clinical presentation differed from typical BrS to some extent. First, the chest radiograph and cardiovascular magnetic resonance imaging (CMR) showed mild right ventricular (RV) dilatation (Fig.1A, B). Second, RV angiography demonstrated RV dilatation and akinesis in the inferior wall (Fig.1C, D), although coronary angiography did not show critical stenosis, and the provocation test failed to induce coronary spasm. Finally, epsilon-like waves were seen in spontaneous type 1 ECG (Fig.2). As a result, the patient not only met the diagnostic criteria for BrS but also met the

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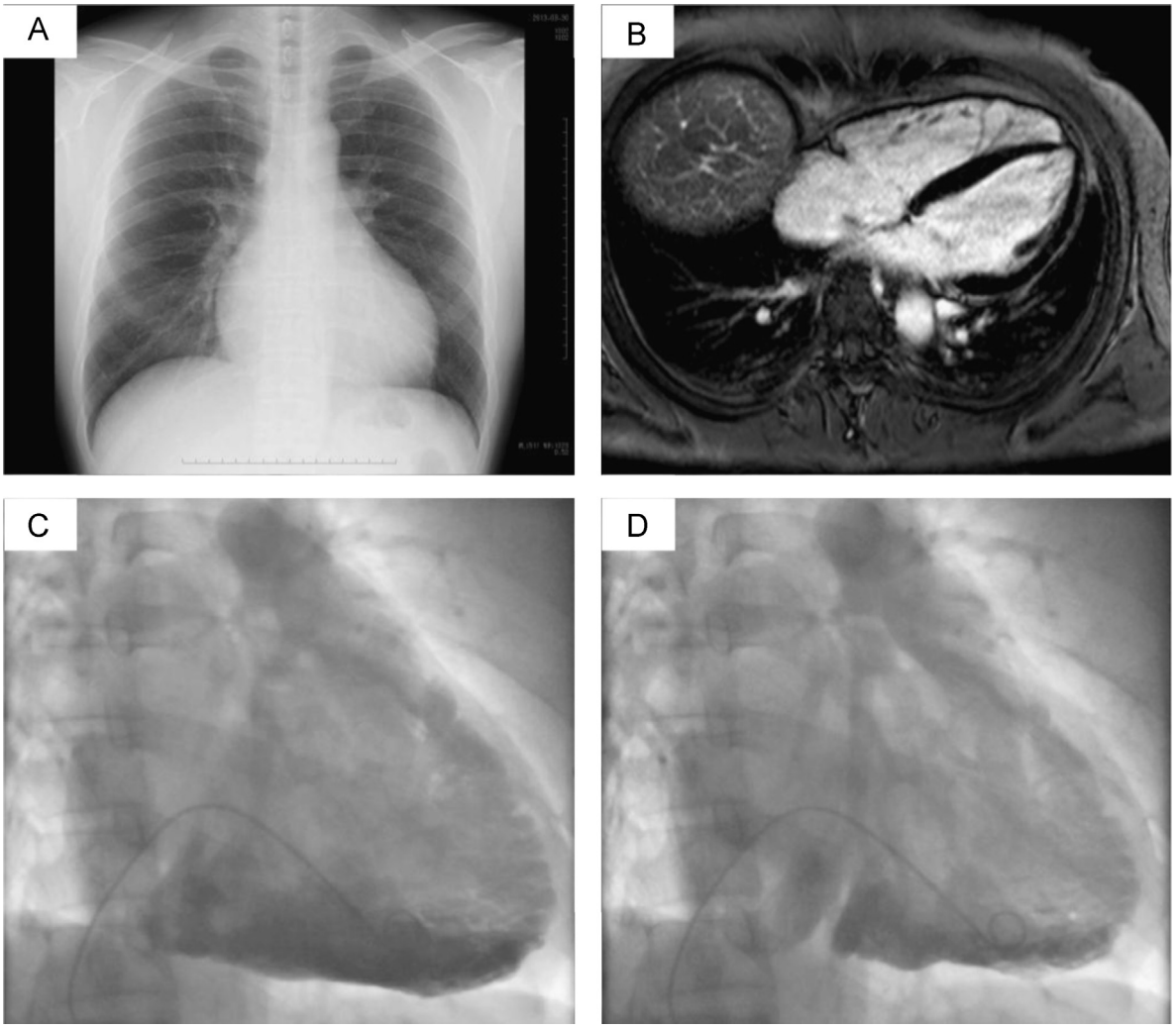

Fig. 1. (A)Chest radiograph reveals mild right ventricle dilatation. (B) Cardiovascular magnetic resonance imaging shows mild right ventricle dilatation and no late gadolinium enhancement. (C) Right ventricular angiography demonstrates right ventricular dilatation and akinesis in the inferior wall. (D) Computed tomography does not reveal fatty change in the right ventricular myocardium.

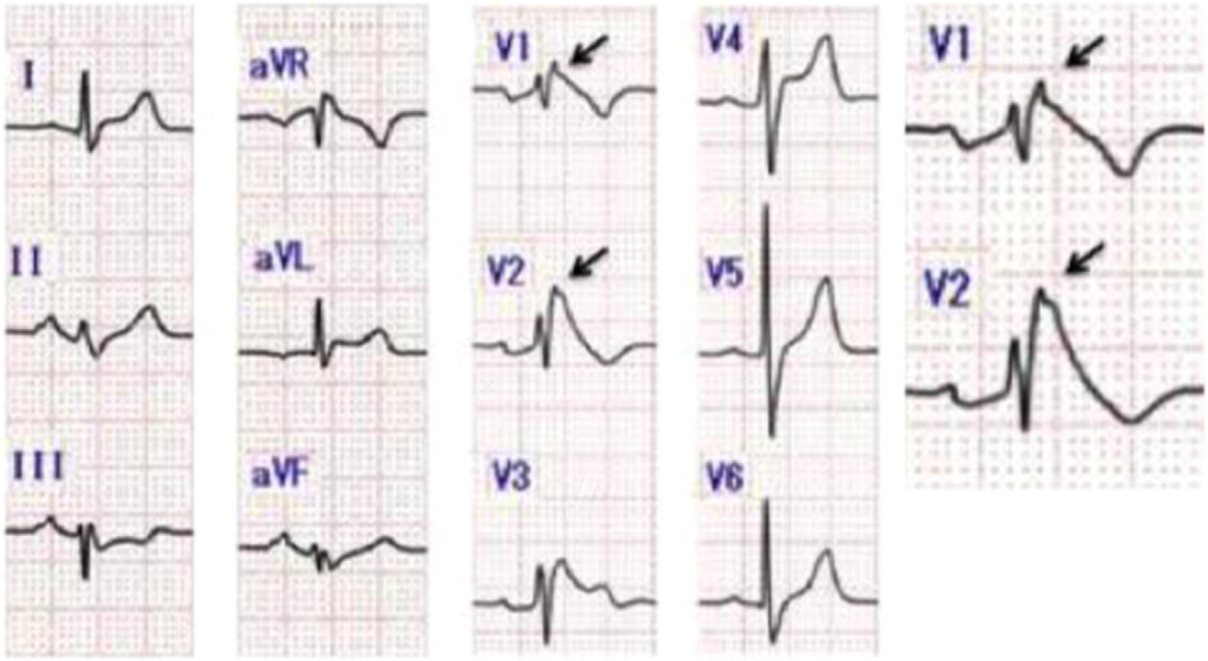

Fig. 2. The patient's electrocardiogram shows spontaneous coved-type ST-segment elevation and epsilon-like waves in type 1 ECG.

Table 1
Clinical characteristics of the present case.

Age at presentation		36 years old
Sex		Male
QTc		416 ms
Head-up tilt test		Negative
Atrial arrhythmias		None
AV conduction		Normal
CAG		No significant stenosis
LVEF		47%
RVEF		43%
LVEDV(I) / ESV(I)		136(76) / 68(39) ml (ml/m^2)
RVEDV(I) / ESV(I)		233(134) / 134(77) ml (ml/m^2)
Spasm provocation test		Negative
CMR		No Late gadolinium enhancement
Characteristics of ARVC / D	Symptoms	Syncope
	Family history of ARVC/D	None
	RV angiography	Regional RV akinesis
	ECG depolarization	Epsilon wave
	Late potentials	f-QRS = 174 ms, LAS40 = 79 ms, RMS40 = 7.7 μV
	ECG changes	Fixed
	Imaging	RV dilatation
	Gene mutation of ARVC/D	None
Characteristics of BrS	Symptoms	Syncope
	Family history of SCD	None
	Family history of BrS	None
	ECG repolarization	Spontaneous coved-type ST segment elevation
	Ventricular arrhythmias	VF/Polymorphic VT (induced in the EPS)
	Beta-stimulation	Inhibited (in the EPS)
	Pathology	Not specific
	Gene mutation of BrS	None

ARVC/D = Arrhythmogenic right ventricular cardiomyopathy/dysplasia , AV conduction = atrioventricular conduction, BrS = Brugada syndrome, CAG = coronary angiography, CMR = cardiovascular magnetic resonance, EPS = electrophysiological study, f-QRS = filtered QRS, LAS40 = duration of terminal QRS < 40 μV, LVEF = left ventricular ejection fraction, LVEDV (I) = left ventricular end-diastolic volume (index), LVESV(I) = left ventricular end-systolic volume(index), QTc = corrected QT interval, RMS40 = root-mean-square voltage of terminal 40 ms, RV = right ventricle, RVEF = right ventricular ejection fraction, RVEDV(I) = right ventricular end-diastolic volume(index), RVESV(I) = right ventricular end-systolic volume(index), SCD = sudden cardiac death, VF = ventricular fibrillation, VT = ventricular tachycardia

2 major parameters of 2010 revised task force criteria for ARVC/D (regional RV akinesis by RV angiography and the presence of an epsilon wave in the right precordial leads). The patient was discharged from the hospital after insertion of an implantable cardioverter defibrillator (ICD).

3. Discussion

In this case study, we determined 2 important clinical issues. First, the phenotype of an overlapping disease state for BrS and ARVC/D may vary between individuals, and therefore, EPS may be useful for determining the phenotype of an overlapping disease (e.g., BrS-like or ARVC/D-like). Second, careful examination is needed to confirm diagnosis in the cases suspected of overlapping BrS and ARVC/D, and to determine better treatment course for these patients.

Although presentation of the overlapping disease state may vary among patients, past investigations have demonstrated some common features of the overlap. First, sodium channel blockers can induce BrS ECG in a subgroup of patients with ARVC/D [5], and epsilon-like waves are seen in some patients with type 1 ECG. Epsilon-like waves are more common in drug-induced type 1 ECGs than in spontaneous type 1 ECGs [3]. Rather than using the term "epsilon wave," we use the term "epsilon-like wave" because distinguishing the epsilon wave from the fragmented QRS wave was difficult. The epsilon wave is located between the end of the QRS complex and beginning of the T-wave. In contrast, a fragmented QRS (f-QRS) is defined as the presence of additional spikes within the QRS complex. In patients with BrS, defining the end of QRS complex is difficult, and it is still controversial where the J wave represents depolarization component or repolarization component. Therefore, occurrence of additional spikes at the end of QRS complex or immediately after the QRS complex in BrS is not certain. The term "epsilon-like wave" has been used to avoid such discrepancies in ECG interpretation. [3] Some previous studies revealed that epsilon potentials and QRS fragmentation have similarly high diagnostic values, and epsilon-like potentials in different leads at the beginning, top, or end of the QRS complex are typical ECG findings in patients with ARVC/D. [6,7]. Second, imaging studies have revealed RV wall motion abnormalities or RV dilatation, which are characteristic of ARVC/D, in some patients with BrS [2,8]. Third, the fibro-fatty replacements required to diagnose ARVC/D have been detected during endocardial biopsies of patients with type 1 ECG [9]. Finally, specific gene mutations involving ARVC/D have been identified in some patients with BrS [10]. These overlapping features are considered a result either of genetic interactions or of the combined influence of BrS' electrophysiological abnormalities and ARVC/D's structural abnormalities. Accordingly, ARVC/D patients can satisfy the diagnostic criteria of BrS, and BrS patients can satisfy the diagnostic criteria of ARVC/D.

A disease state combining both conditions has a different clinical course than uncomplicated BrS. A subgroup of BrS patients may demonstrate the features of ARVC/D long after the initial BrS diagnosis. Structural heart diseases and histological findings consistent with ARVC/D have been revealed after autopsy of patients who were diagnosed with BrS and who died suddenly [11]. Thus, careful observation of the changing clinical course is vital and may indicate the transformation from BrS to ARVC/D.

Detailed evaluation in the cases of suspected overlap of BrS and ARVC/D is also needed to determine a better treatment course for these patients. In this case, we used a range of methods, from physical examination to genetic testing (BrS- and ARVC/D-specific), to confirm dual diagnosis and to determine a better course

Table 2
Analyzed gene mutations.

Gene	Phenotype
RYR2	CPVT1/ARVC2
SCN5A	LQTS/BrS1
CACNA1C	LQT8/BrS3
CACNB2	BrS4
CACNA2D1	BrS9
SCN1B	BrS5
SCN3B	BrS7
GPD1L	BrS2
KCND3	BrS10
KCNJ8	ERS1/BrS8
KCNE3	BrS6
KCNE4	
KCNE5	BrS/IVF
SCN10A	BrS
MOG1 (RANGRF)	BrS11
DSP	ARVC8
PKP2	ARVC9
DSG2	ARVC10
DSC2	ARVC11
JUP	ARVC12

of treatment (Tables 1, 2). Since this patient experienced an episode of syncope, demonstrated epsilon-like waves in spontaneous type 1 ECG, and showed RV dilatation and RV wall motion abnormalities, a diagnosis of overlap disease of BrS and ARVC/D for the patient can be asserted with certainty.

Although treating patients with BrS features in the case of structural heart disease remains challenging, this patient received an ICD because of spontaneous type 1 ECG and an episode of syncope. Nevertheless, the phenotype of this case may change in future, demonstrating clinical features of ARVC/D, such as symptoms of heart failure and RV arrhythmias.

Characteristic clinical features of an overlap disease of BrS and ARVC/D remain unclear, and consensus on a better treatment course for this type of overlap disease remains. After studying the present case, we recommend EPS evaluation to determine the phenotype of overlapping disease (e.g., BrS-like or ARVC/D-like) because clinical features of BrS and those of ARVC/D can coexist in a single patient. The phenotype observed in this case resembled BrS rather than ARVC/D. This case had neither late gadolinium enhancement on CMR nor inducibility of VT/VF during EPS before pilsicainide infusion. Therefore, the existence of scar areas or substrates, which are characteristics of ARVC/D, was unlikely. VF was easily inducible after pilsicainide infusion and was obviously inhibited after ISP infusion. These findings exactly match the characteristics of BrS. Identification of the phenotype of overlapping disease is important because responses to exercises or drugs, such as beta stimulants or sodium channel blockers, differ considerably between BrS and ARVC/D. In addition, upon confirmation of the overlap state, the clinician should recall that the phenotype may change during the clinical course. Therefore, more attentive follow-up is required. As more cases are discovered and reported, this disease state will be expected to be clarified further.

Conflict of interest

No authors in this study report a conflict of interest or need for financial disclosure.

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