Vasospastic angina preceding diagnosis of arrhythmogenic cardiomyopathy in a young athlete

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Introduction

Arrhythmogenic cardiomyopathy (ACM) is an inherited heart disease in which penetrance and phenotypes are affected by lifestyles, particularly by exercise.[1] Though lethal arrhythmias are a main early phenotype of ACM, myocardial injuries, resembling heart attacks, have also been recognized as an initial manifestation of ACM in teenagers.[2,3] Since the prognosis can be affected by exercising, early identification of affected individuals is important in the treatment of ACM.[4–7] We experienced a female pediatric athlete who developed recurrent chest pain with elevated serum troponin I levels compatible with a vasospastic angina (VSA) more than 2 years prior to the definite ACM diagnosis. These symptoms and findings are consistent with the uncommon clinical presentation of ACM, named "hot phase" symptoms.[2,3] Our case is unique because her acetylcholine provocation test revealed epithelial cell dysfunctions, which is shown to be associated with the early pathophysiology of ACM.

KEY TEACHING POINTS

- Part of the mechanisms of "hot phase," an atypical presentation of arrhythmogenic cardiomyopathy, might be coronary vasospasm due to endothelial dysfunction.
- Chest pain control using calcium blocker was insufficient to suppress pathophysiology of arrhythmogenic cardiomyopathy.
- Since myocardial damages of arrhythmogenic cardiomyopathy with chest pains and leaky cardiac enzymes can be precipitated by exercise, examinations, including cardiac magnetic resonance imaging and genetic testing, are recommended if cardiomyopathies are suspected owing to family histories, arrhythmias, heart failure symptoms, atypical electrocardiogram for patients' age, or existence of ventricular aneurysm.

Case report

A 12-year-old female patient was referred to our hospital owing to chest pains, abnormal electrocardiogram (ECG), and elevated serum troponin I. She has never suffered from Kawasaki disease, and family history is negative for lipid metabolic disorders, cardiomyopathy, arrhythmia, and sudden cardiac death. Though she is involved in club activities such as long-distance relay and basketball, she has never had chest pain on exertions. She woke up at midnight owing to a chest pain that lasted for longer than 30 minutes, which then spontaneously resolved. She had several intermittent chest pain attacks on the first 2 nights. She visited a local hospital 4 days after the initial attack. Despite her symptom becoming milder, her ECG showed elevated ST-T segments in leads II-III and atypical T waves for her age in lead V_4 (Figure 1A).[4] Then, she was referred to our hospital for further treatments. The sensitive serum troponin I level was elevated at 30,324 pg/mL (reference value: $\leq$15.6 pg/mL). Her echocardiogram revealed normal coronary artery, a normal range of left ventricular ejection fraction with more than 60%, and no pericardial effusion. Holter electrocardiogram on the day of admission revealed premature ventricular contraction with only 0.14% of the total beat, and there was no atrioventricular block or sinoatrial block. No serum inflammatory markers, including C-reactive protein and procalcitonin, were elevated. No infectious signs, including fever, rhinorrhea, sore throat, or cough, were reported within 2 weeks. She was negative for COVID-19 screening or

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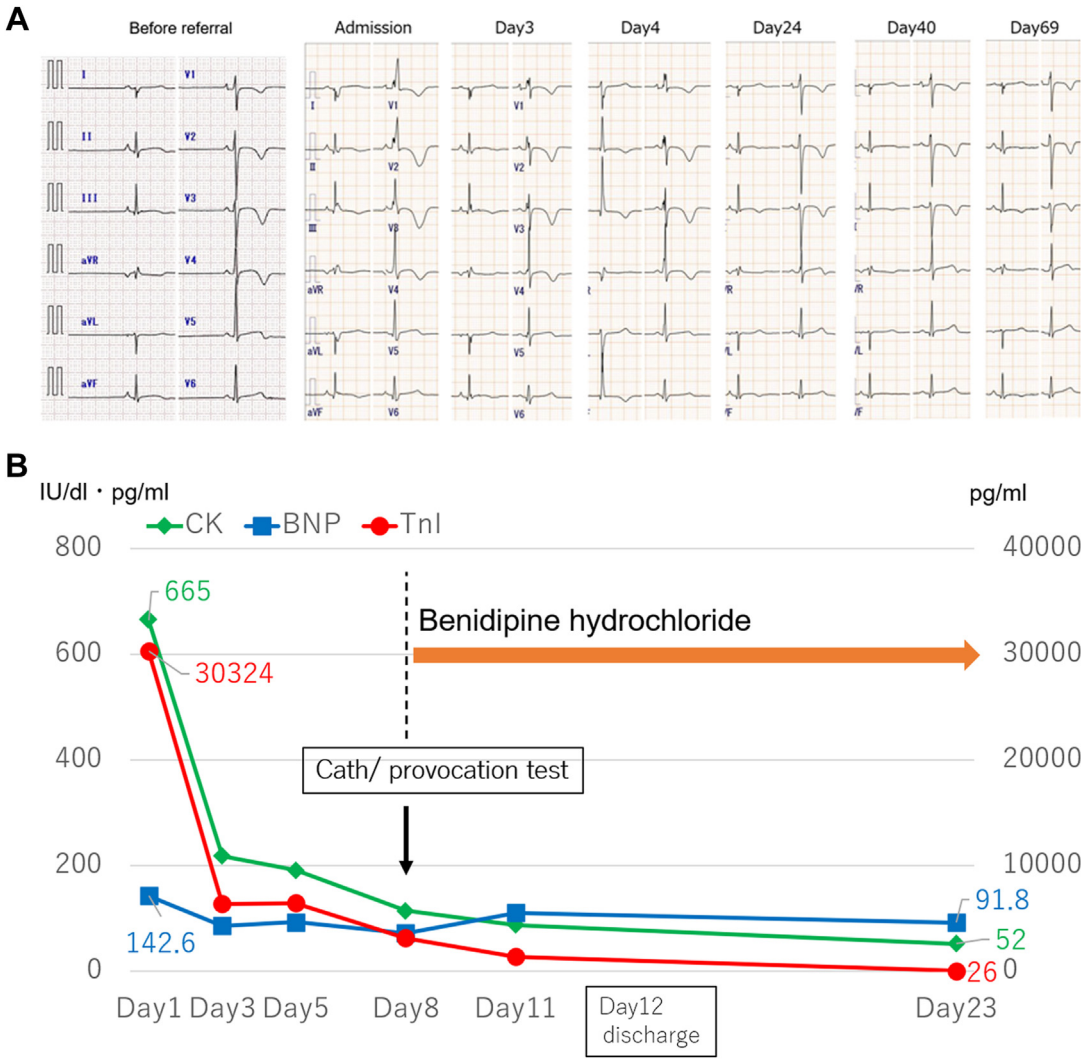

Figure 1 Chronological changes of the 12-lead electrocardiogram (ECG) and cardiac enzymes. **A:** Changes of the 12-lead ECG. Note that notched QRS waves were observed in the precordial leads on admission and on days 3 and 4 of admission, which normalized during further observations. Prolonged QT intervals were not observed throughout the clinical course. **B:** Changes of the cardiac enzymes. The green line depicts creatine kinase (CK); red line, Troponin I (TnI); and blue line, B-natriuretic peptide (BNP). Note that the BNP levels remain relatively low during acute phase.

vaccination. Therefore, we suspected vasospastic angina rather than myocarditis.

After her admission, she never complained of chest pains, and ECG changes and the high serum troponin level gradually improved (Figure 1A and 1B). On the eighth day of her admission, she had a coronary angiography and no significant stenoses were confirmed (data not shown). Her left ventriculogram showed an apical aneurysm and her right ventriculogram showed dilated chamber with preserved contractility (Figure 2A: right ventricular end-diastolic volume index of 172 mL/m^2, ejection fraction of 50%). Intracoronary injections of acetylcholine (20 μg) caused vasospasms in the septal branches of the left anterior descending artery. Higher doses of acetylcholine (50 μg) caused diffuse constriction in the left anterior descending artery and occlusion of segment #10. Isosorbide dinitrate injections reversed those changes (Figure 2B). The ECG change during the acetylcholine were consistent with the ECG changes while she had chest pains. Thus, our tentative diagnosis was VSA.

Benidipine hydrochloride was then started. She did not complain of any chest pains. Her ECG changes and troponin I levels gradually improved (Figure1A and 1B).

The aneurysm in the left ventricle had a contracted muscle layer and was thus considered to be a true ventricular aneurysm. Although congenital ventricular aneurysm is one of the differential diagnoses, the presence of characteristic T-wave features[4] implies that the aneurysm could have developed from a genetic cardiomyopathy background.[8] In addition, her cardiac magnetic resonance imaging (CMR) with gadolinium-DTPA showed delayed enhancement in the apex of the left ventricle and outlet portion of the right

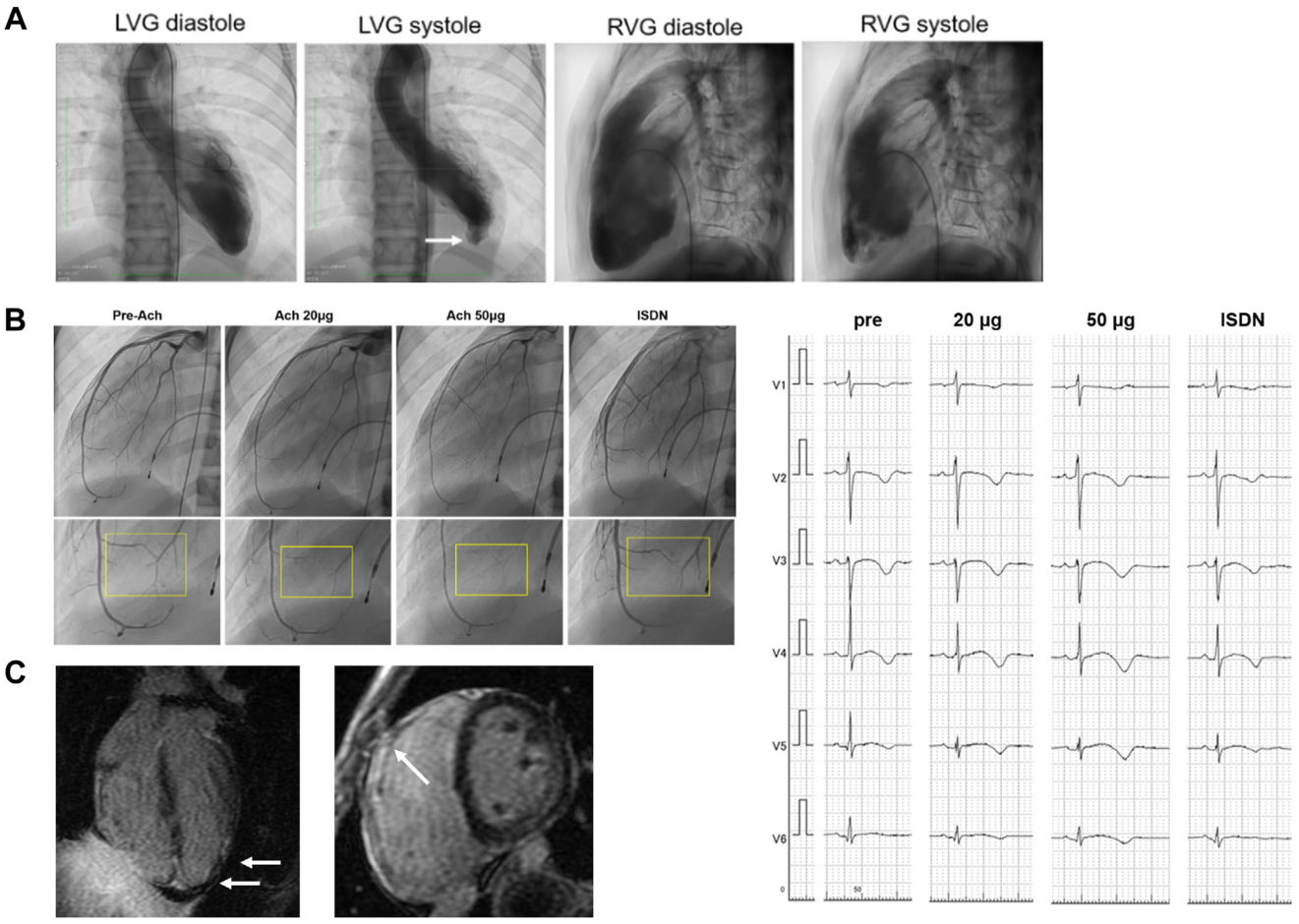

Figure 2 Cardiac catheterization and magnetic resonance imaging. **A:** Ventriculograms. An apical left ventricular aneurysm was seen by the left ventriculogram (LVG) (*white arrow*). The right ventriculogram (RVG) showed a dilated chamber, but the ejection fraction was preserved (end-diastolic volume index: 172 mL/m^2, ejection fraction 50%). The right ventricular outflow tract was not clearly dilated. **B:** Results of the acetylcholine provocation test. The left panels show left coronary arteriograms at baseline, after injection of 20 μg acetylcholine, after injection of 50 μg acetylcholine, and after injection of isosorbide dinitrate (ISDN). Note that diffuse vasoconstriction and focal semi-occlusion of #10 (*yellow square* in the high magnification panel) were observed. The right panels show the precordial leads of the electrocardiogram corresponding to each condition, indicating ST-T and T-wave morphological change in V_4-V_6. **C:** Cardiac magnetic resonance imaging with gadolinium-DTPA 2 months after onset showed delayed enhancement (*white arrow*) in the apex of the left ventricle (left) and free wall of the right ventricle (right).

ventricle (Figure 2C), suggesting she could have suffered from acute phase of ACM.[2] To further clarify the diagnosis, a genetic analysis was performed, and a homozygous missense variant in desmoglein 2 (*DSG2* c.874C>T:p.Arg292Cys) was identified. This variant has been reported in individuals with arrhythmogenic right ventricular cardiomyopathy.[5,9,10]

She remained asymptomatic with the calcium channel blocker and was quite eager to return to exercising. We monitored her B-type natriuretic peptide (BNP) as a risk indicator to developing heart failure and arrhythmias.[11] However, her BNP repeatedly increased even with light exercise, which was instructed as "physical activities do not increase respiratory rate." Thus, we restricted her vigorous exercise (Figure 3A). During the next 2 years, her right ventricular ejection fraction decreased with outflow dilatation, and myocardial delayed enhancement in the right ventricular outflow tract became obvious in the CMR (Figure 3B). She also manifested polymorphic ventricular extrasystoles, positivity of late potentials, progression of inverted T wave in lead V_4, and newly developed epsilon wave in lead V_3 by the age of 15 (Figure 3C). Her left ventricular aneurysm remained unchanged (Figure 3D).

Discussion

In this case report, we, for the first time, observed VSA taking place as a probable hot-phase event of ACM[2,3] in a 12-year-old female athlete who harbors homozygous *DSG2* c.874C>T:p.Arg292Cys variant.[5,9,10] Similar cases have been increasingly reported. Singh and colleagues[7] reported that 2 young siblings with ACM harboring a *DSP* p.Thr564Ile variant showed temporal acute myocardial injuries with ST elevations. However, the underlying mechanisms remain unelucidated in their cases.[7]

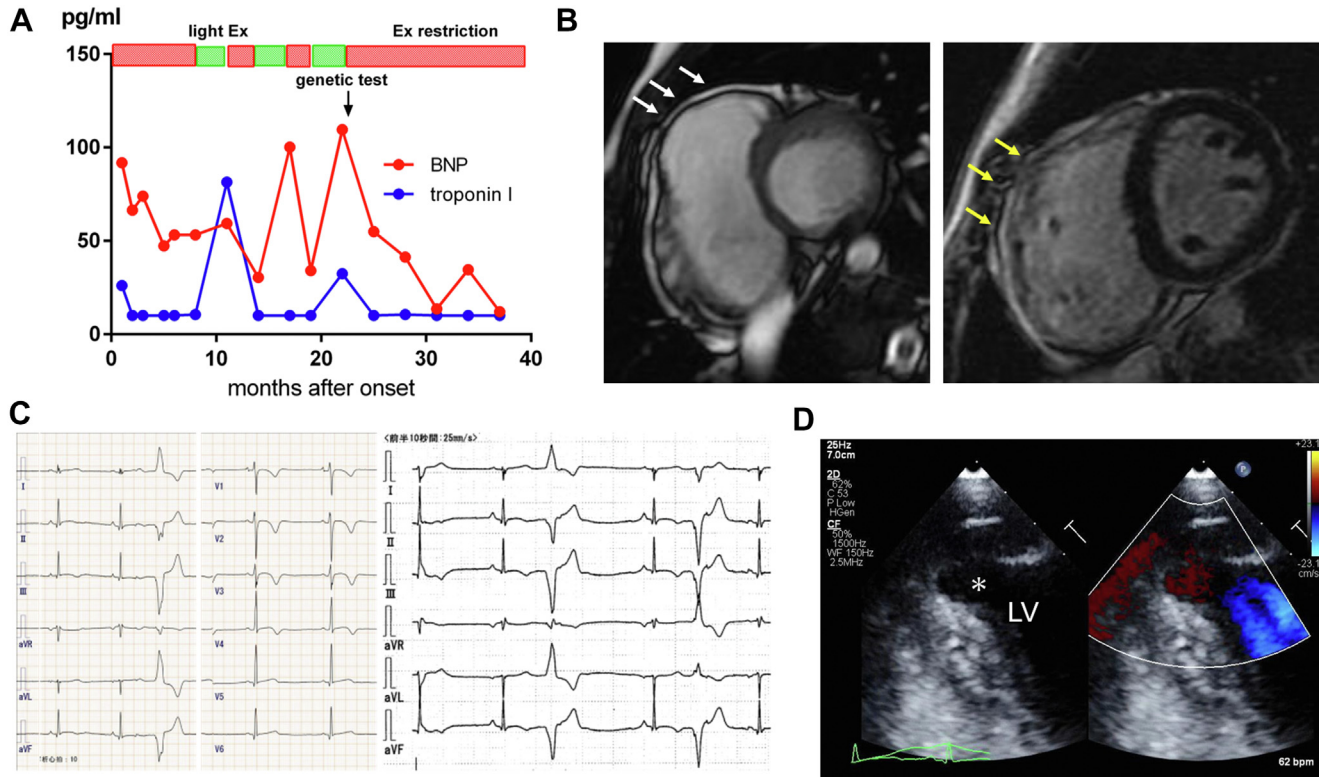

Figure 3 Two-year clinical courses after the first chest pain attack. **A:** The chronological changes of BNP and troponin I levels after discharge. Red bars depict exercise restriction; green bar, light exercise. Note that the plasma BNP levels repeatedly increased with light exercising. **B:** The cardiac magnetic resonance image 2 years after onset shows marked dilatation of right ventricular outflow tract, which was not apparent at the onset (*white arrows*). Delayed enhancement with gadolinium contrast was observed (*yellow arrows*). **C:** A 12-lead electrocardiogram 2 years after onset (left panel). Premature ventricular contractions with superior axis were observed (right panel). **D:** An echocardiogram 2 years after onset shows the left ventricular aneurysm observed at the onset (*).

Hot-phase symptoms may be caused by inflammatory responses associated with structural changes originating from genetic variants in a relatively young cohort of ACM.[2] In contrast, it has been reported that VSA is caused by microvascular inflammation related to lifestyle or hormonal imbalance and usually occurs in adults.[12] As inflammation can impair endothelial function and induce coronary vasospasm, it is plausible that inflammation during the hot phase could induce vasospasm with a genetic background in patients with ACM.[12] Though it is usually difficult to reproduce chest pains during acetylcholine provocation tests in children owing to the requirement of general anesthesia, endothelial VSA was diagnosed in our case by the provocation test (Figure 2B).[13,14] In a cohort with history of acquired coronary inflammation and control patients with congenital heart diseases (mean age of 13 years), Yamakawa and colleagues[14] demonstrated that patients with endothelial dysfunction had coronary arteries contract with low-dose acetylcholine, whereas they were dilated in controls. Since our patient demonstrated diffuse coronary artery contraction even with low-dose acetylcholine, endothelial dysfunction exists, at least in the coronary arteries in this patient.

Assuming endothelial dysfunction is also involved in the mechanism of the hot-phase symptoms, medications to prevent vasoconstriction can be a beneficial treatment of ACM. Martins and colleagues[6] reported that the hot-phase symptoms are often repetitive in pediatric cohorts, suggesting progressive myocardial injuries. Since our patient did not complain of chest pain, calcium channel blocker might have been effective in suppressing hot-phase symptoms. However, her myocardial injuries progressed despite her chest symptoms improving with benidipine hydrochloride, which indicates chest pain controls are insufficient to suppress pathophysiology of ACM.

Myocarditis-like episodes in teenagers are increasingly being recognized as the initial manifestation of ACM.[2] Examinations, including CMR and genetic testing, are recommended if cardiomyopathies are suspected owing to family histories, arrhythmias, heart failure symptoms, atypical ECG for patients' age,[4] or existence of ventricular aneurysm.[8] Though the patient in our case was diagnosed with ACM, it was difficult to restrict her from exercising owing to her strong desire to be an athlete. However, repetitive increases of BNP levels caused by light exercise led us to do so.[11] Accumulating evidence suggests that increased BNP and N-terminal pro-BNP levels are associated with sudden cardiac death in patients not only with heart failure but also with inherited arrhythmogenic disorders.[15] Indeed, our patient did not complain of any symptoms with the initiation

of light exercise; thus, exercise restriction based on the plasma BNP level might have contributed to the prevention of cardiovascular events. Further evidence is warranted to establish BNP-guided exercise management.

Among desmosomal genes in Japanese ACM cases, *DSG2* variants are most frequently identified, and mostly, they are homozygous or compound heterozygous missense variants.[5,9,10] Regarding a *DSG2* Arg292Cys, an ACM autopsy case was previously reported to carry the same homozygous variant.[9] To our interest, similarly in this family and other *DSG2*-related ACM,[10] all the family members carrying a heterozygous Arg292Cys variant did not show any sign of ACM. The variant is a rare single nucleotide polymorphism in East Asia, especially in Japan (rs770921270, TogoVar: https://grch38.togovar.org/: 277/108602 (0.0026), ToMMo 54KJPN, accessed on January 30, 2024), and has been classified as a conflicting pathogenicity (VUS; CliniVar ID: 466351). The DSG2 proteins regulate the Ca^{2+}-dependent functions of the desmosomal cadherins that are essential components of cardiac structures and functions. Thus, in the presence of more severe genetic burden, or in other words homozygous or compound heterozygous DSG2 variants, Ca^{2+} overloading, such as exercising, may predispose vulnerable individuals to rapid progression of ACM. It is warranted to accumulate more cases and establish experimental evidence using a model animal.

Conclusion

Our case highlights the importance of aggressive examinations for suspected ACM in pediatric patients with hot-phase symptoms. In such cases, the acetylcholine provocation test may additively contribute in identifying the attribution of vasospasm to the symptom, implying the indication of calcium channel blockers. Since myocardial damage of ACM with chest pains and leaky cardiac enzymes can be precipitated by exercise, precise examinations, including CMR and genetic testing, should be performed.

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