Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.5018-20
Intern Med 60: 85-89, 2021
http://internmed.jp

【 CASE REPORT 】

Unusual Overlapping Cardiac Sarcoidosis and Long-QT Type 3 Induced Ventricular Fibrillation

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Abstract:

A 54-year-old woman had been resuscitated after ventricular fibrillation and her electrocardiogram showed a QT prolongation (QTc=510 ms), and genetic screening revealed a missense variant, R1644C, in the *SCN5A* gene. She was therefore diagnosed with congenital long-QT syndrome (LQTS) type 3. However, the patient had left ventricular dysfunction, and based on the findings of cardiac magnetic resonance imaging, positron emission tomography and pathological examinations, she was diagnosed with cardiac sarcoidosis. Although both are rare diseases, their overlapping presence in this case may have led to an increased cardiovascular risk compared with either alone. Thus, not only genetic but comprehensive clinical examinations are important for making a correct diagnosis.

Key words: long-QT syndrome, sarcoidosis, ventricular fibrillation, SCN5A

(Intern Med 60: 85-89, 2021)
(DOI: 10.2169/internalmedicine.5018-20)

Introduction

Congenital long-QT syndrome (LQTS) is a rare genetic arrhythmic syndrome, caused by mutation/variants in several ion channels genes and is observed in 0.1% of the general population in Japan (1). Among congenital LQTS, LQT type 3 (LQT3) caused by a mutation in the *SCN5A* gene (2), the alpha subunit of cardiac sodium channel Nav1.5, is usually diagnosed in only 10% of cases of genetically identified LQTS (3). A mutation in *SCN5A* has also been identified in cases of Brugada syndrome, progressive cardiac conduction defect, familial sick sinus syndrome, atrial fibrillation and dilated cardiomyopathy (4). However, some LQT3 patients are difficult to diagnose, being identified only after the occurrence of ventricular fibrillation (VF) or sudden cardiac death.

Sarcoidosis is a systemic granulomatous disease that affects various organs, such as the eyes, lung, heart, hilar lymph nodes, skin and kidneys (5). Among such cases, cardiac sarcoidosis (CS) is sometimes a critical issue for patients due to life-threatening ventricular tachyarrhythmia (VT/VF), complete atrioventricular block and severe heart failure. Because of the diversity of symptoms and clinical courses, CS is often only diagnosed after an episode of VT/VF or cardiac sudden death or due to the induction of congestive heart failure by a reduced systolic left ventricular (LV) function (6). Therefore, an early diagnosis and optimal treatment may improve the prognosis of patients with CS.

We herein report an extremely rare and complex case of a VF survivor who was ultimately diagnosed with CS overlapping with congenital LQTS type 3.

Case Report

A 54-year-old woman who had been resuscitated after VF

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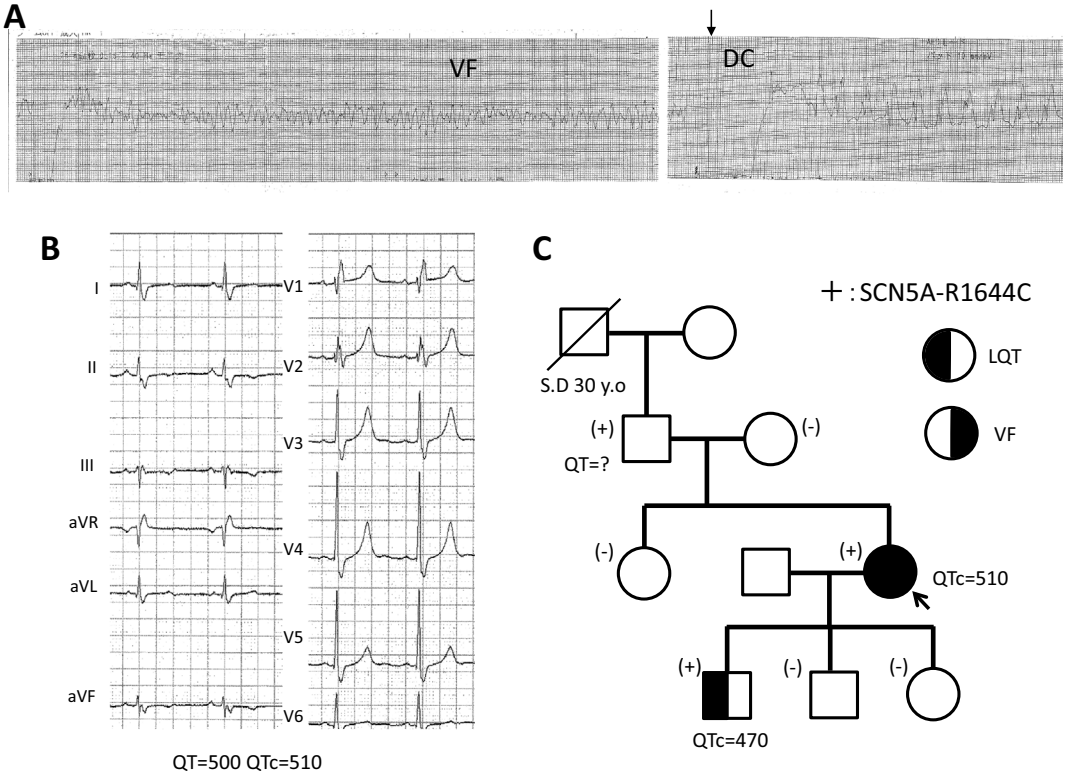

Figure 1. **A: Monitor Electrocardiogram recorded in AED. Ventricular fibrillation (VF) was able to be detected and terminated by direct current (DC) shock therapy. B: A 12-lead ECG on admission. C: Family pedigree of this patient. The proband (arrow), her elder son and her father had the same SCN5A variant (R1644C).**

(Fig. 1A) that occurred while playing piano was admitted to hospital. She had never had any cardiac diseases before. Coronary angiography showed no significant stenosis, but echocardiography showed a low left ventricular ejection fraction (LVEF=37%). There was no abnormality in the laboratory data except for hypokalemia [(K^+)o=2.8 mEq/L]. An electrocardiogram (ECG) showed QT prolongation (corrected QT interval: QTc=510 ms) (Fig. 1B), and her grandfather had suddenly died in his 30s, while her elder son had been found to have QT-interval prolongation on an ECG when he was young (Fig. 1C).

Genetic screening identified the missense variant R1644C (ex28 c.4930C>T) in the SCN5A gene, which had previously been reported as a susceptibility for LQT3 (7, 8) and Brugada syndrome (9), suggesting that the patient might have LQT3. In addition, her elder son (QTc=470 ms) and father (ECG not identified) had the same variant in SCN5A, although no other family members had it (Fig. 1C). LQTS patients usually have a normal cardiac function, and the present patient's LV dysfunction was considered to be a temporary change as a consequence of VF due to LQTS.

While the patient had been resuscitated after VF with a reduced LVEF, she refused device therapies, such as an implantable cardiovascular defibrillator (ICD) or cardiac resynchronized therapy with defibrillator (CRT-D), because of her panic disorder. Therefore, we introduced an oral sodium channel blocker mexiletine (300 mg/day) as a specific therapy, expecting a reduction in the QT interval in LQT3 (10), and the β-blocker bisoprolol (2.5 mg/day). After the introduction of these pharmacological therapies her QTc interval was abbreviated into 480 ms.

Two years later, she was admitted to our hospital due to acute decompensated heart failure. Cardiac magnetic resonance (CMR) imaging showed significant diffuse late gadolinium enhancement (LGE), mainly in the pericardial side of the LV base as well as the right ventricular (RV) septum (Fig. 2A). Positron emission tomography (PET) also showed a significant accumulation of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) with a maximum standardized uptake value (SUV_{max}) of 10.7 in the myocardium and swollen hilar lymph nodes (Fig. 2B). Pathological testing of an endomyocardial biopsy taken from the RV septum revealed typical fibrosis of the myocardium stroma with monocyte infiltration (Fig. 2C). The serum angiotensin-converting enzyme and lysozyme levels were within the normal ranges. Based on these medical findings and the results of CMR, PET and pathological examinations, she was diagnosed with CS overlapping with LQTS.

As shown in Fig. 3, we started steroid therapy of prednisolone with an initial dose of 30 mg/day and then gradually reduced the dose by 5 mg every 2 weeks. One month after starting the steroid therapy, ^{18}F-FDG accumulation in the heart and hilar lymph nodes had almost disappeared (SUV_{max}: 2.8). Furthermore, her symptom of heart failure

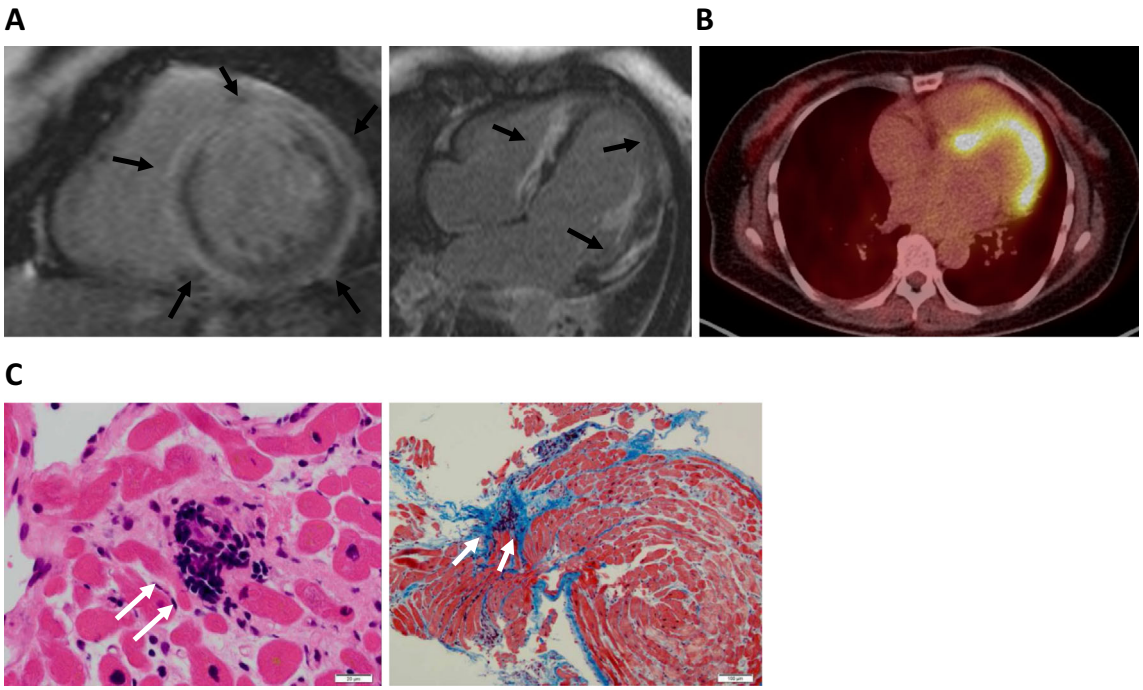

Figure 2. **A: Cardiac magnetic resonance imaging. Late gadolinium enhancement (LGE) is indicated by black arrows. B: Positron emission tomography (PET) imaging. Significant diffuse accumulation in the myocardium was observed. The patient had to fast for at least 18 h and avoid carbohydrates, fruits, sugar and alcohol at dinner before the examination. C: Pathological image of the RV septum obtained by an endocardial biopsy. Typical fibrosis of the myocardium stroma with monocyte infiltration is indicated by white arrows.**

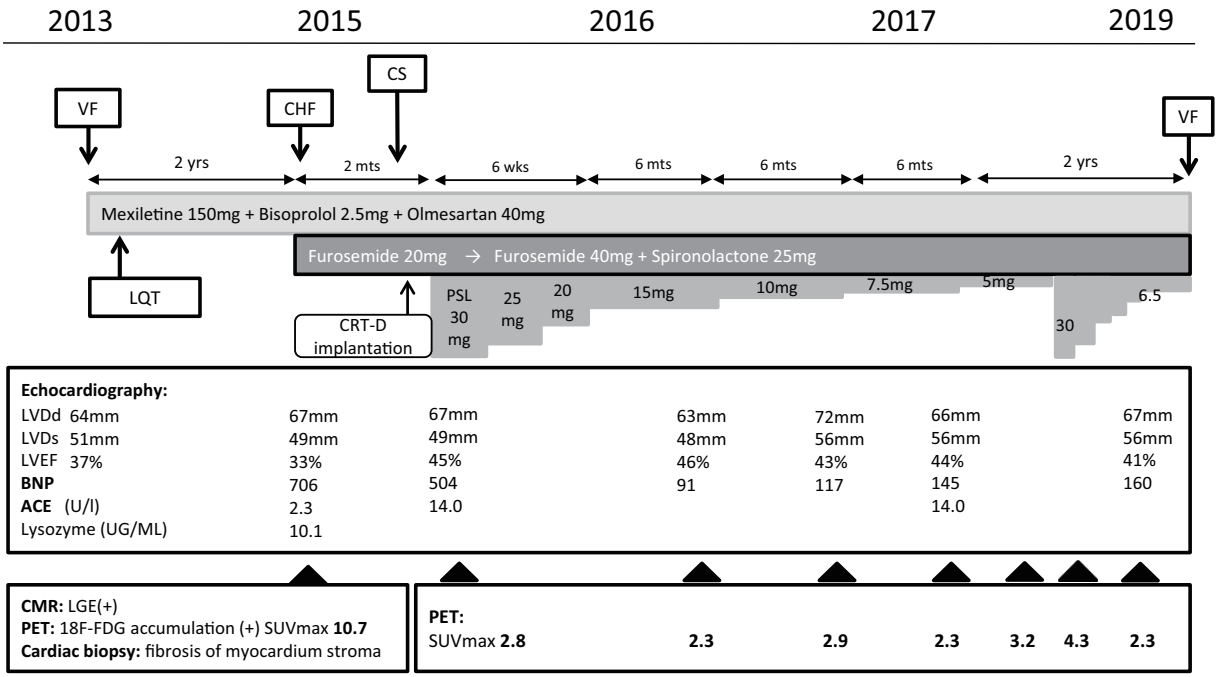

Figure 3. **Clinical course and therapeutic strategy in a case after resuscitation of VF. VF: ventricular fibrillation, LQT: long QT syndrome, CHF: chronic heart failure, CS: cardiac sarcoidosis, CRT-D: cardiac resynchronization therapy-defibrillator, PSL: prednisolone, CMR: cardiac magnetic resonance, LGE: late gadolinium enhancement, PET: positron emission tomography, SUV: standardized uptake value, FDG: fluorodeoxyglucose, LVDd: left ventricular diastolic diameter, LVDs: left ventricular systolic diameter, LVEF: left ventricular ejection fraction, ACE: angiotensin-converting enzyme**

had improved from a New York Heart Association (NYHA) classification level of III to II. Finally, the patient underwent CRT-D for the prevention of sudden cardiac death and treatment of heart failure because of her reduced LVEF (33%), although her ECG did not show any left bundle branch block pattern or atrial-ventricular block, but only showed a wide QRS (164 ms) duration.

Subsequently, the patient was followed up approximately every six months with PET and echocardiography. Oral prednisolone was gradually decreased to 5 mg/day, and her LVEF improved to 44%. However, the PET data suggested re-exacerbation of CS because of an increased SUV_{max}, and one episode of VF occurred without any change in the QT interval.

Discussion

This is an unusual case of overlap between congenital LQTS (LQT3) and CS, which has never been reported. The present patient had a relatively good prognosis after the introduction of prednisolone treatment. However, the extent to which LQTS and CS contribute to the occurrence of VF remains unclear.

Long-QT syndrome

LQTS patients often experience syncope due to torsade de pointes, and some of them may degenerate into VF. Particularly, in LQT3, the first cardiac event may be fatal, such as VF or sudden cardiac death (3). Previous studies have suggested that female LQT3 patients with QTc>500 ms have an intermediate (35-50%) risk of cardiac events (syncope, cardiac arrest or sudden death) under 40 years old (11). The present patient was 54 years old, and her QTc interval was 510 ms, so she may have had a moderate risk for ventricular arrhythmia.

The *SCN5A* variant R1644C causes different types of clinical phenotypes, such as Brugada syndrome and LQTS. Frustaci et al. reported 18 patients with Brugada syndrome, including 1 with the *SCN5A*-R1644C variant and cardiomyopathic changes on a histological examination of right and left ventricular biopsy specimens (9). In contrast, two papers have reported *SCN5A*-R1644C as a cause of LQTS (7, 8). Therefore, although its clinical significance is still not indicated in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/RCV000058725/), it is 'Likely Pathogenic' according to the ACMG classification using Varsome (https://varsome.com/).

Although the patient's father and son have the same variant, they had no arrhythmia or heart failure symptoms, except for the mild QT prolongation in her son. There has been only 1 previous report of a similar topic, involving a 61-year-old Japanese woman with LV aneurysm, RV dilatation and electrical storm of VF who was ultimately diagnosed with CS associated with an *SCN5A* variant (L1951L) (12), which is a variant of unknown significance (VUS) and phenotype unlike the LQTS. Taken together, the present findings suggest that the *SCN5A* R1644C variant in the present case may not have directly but somehow increased the susceptibility for VF due to the coexistence of CS.

Cardiac sarcoidosis

Sarcoidosis is generally treated by a steroid therapy; however, the protocol concerning the specific dose and duration is not completely established. In the present case, we introduced 30 mg (0.5 mg/kg) of prednisolone as an initial dose. A previous study suggested that steroid therapy improved the LV volume and function in patients with CS, particularly for those with mild to moderate LV dysfunction (LVEF <54%). However, in patients with severe LV dysfunction (LVEF <30%), it was not always able to improve the LV volume or function (13). In the present case, since the initial LVEF was 33%, which is classified as the middle stage, oral prednisolone improved the PET findings as well as the cardiac function. (LVEF: 33% to 44%). Consequently, due to the preservation of the intrinsic atrioventricular conduction with an RBBB pattern on an ECG, bi-ventricular pacing by CRT-D was not necessary for this patient. Taken together, these findings suggest that the improvement of the cardiac function was due solely to the steroid therapy.

In CS patients, sustained VT was not associated with the intensity of the gallium (Ga) uptake in Ga-67 citrate scintigraphy (14). Furthermore, steroid therapy does not always reduce the risk of VT/VT in CS. The progression of CS can be unpredictable, and there is no established way of predicting sudden death in CS. These findings suggest that VT/VF was not always directly associated with the inflammatory activity in CS. Sustained VT or VF in CS was mostly due to scar-related reentry. Thus, the LVEF was significantly lower in patients with VT/VF than in those without VT/VF (13). Furthermore, cardiac MRI with LGE in RV was significantly related to VT/VF or death in CS (15). In the present case, the patient had a moderately reduced LVEF as well as a large LGE in both the left and right ventricles on CMR imaging. The present patient may therefore have had a high risk of sudden cardiac death.

LQTS or CS, which mainly caused VF?

Even if VF had only been induced by LQT3, the cardiac events were probably suppressed by treatment with mexiletine and beta blockers as well as the pacing therapy, all of these can be effective for LQT. However, VF occurred even after the administration of these full pharmacological and non-pharmacological therapies. We therefore cannot conclude the cause of VF as either LQT or CS, although myocardial structural substrates induced by the inflammation caused by sarcoidosis might be a more consequential cause of VF compared with any effects of LQTS.

Conclusion

We experienced a case of a VF survivor who was diagnosed with CS overlapping with LQT type 3. Although both

are rare diseases, their overlapping presence in this case may have led to an increased cardiovascular risk compared with either alone. Thus, not only genetic but comprehensive clinical examinations are important for making a correct diagnosis.

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

Acknowledgement

We are grateful to Hiroaki Masuda and Rieko Osawa for expert technical assistance in genetic study.

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