Failure of ICD therapy in lethal arrhythmogenic right ventricular cardiomyopathy type 5 caused by the *TMEM43* p.Ser358Leu mutation

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Introduction

Arrhythmogenic right ventricular cardiomyopathy type 5 (ARVC-5) is a rare inherited autosomal-dominant cardiac disorder known to cause sudden cardiac death (SCD) in young people, mostly men and typically between second and fourth decade of life.[1–3] ARVC-5 is coupled to the p.Ser358Leu mutation in the transmembrane protein 43 gene (*TMEM43*) on chromosome 3p25 and is associated with myocardial fibrosis and progressive loss of predominantly right ventricular (RV) tissue with fibrofatty replacement, although left ventricular (LV) involvement is not uncommon.[1,2,4] *TMEM43* p.Ser358Leu is a fully penetrant mutation. Current diagnostic criteria of ARVC require a number of major and minor criteria, including structural and/or functional RV abnormalities, tissue characteristics, abnormalities of repolarization and conduction, and arrhythmias.[5] Previous studies on the *TMEM43* p.S358L mutation indicate an extremely severe phenotype where SCD commonly is the first symptom in high-risk patients.[1,2,6,7] As carriers of the gene mutation, patients are often offered prophylactic implantable cardioverter-defibrillator (ICD) for primary prevention therapy, despite lack of other cardiac symptoms.[8]

In this report we present 3 unrelated cases with ARVC-5 due to the *TMEM43* p.Ser358Leu mutation in which ICD therapy unfortunately could not prevent SCD.

Case report

Case 1

A 57-year-old man (III-6) with ARVC diagnosed at the age of 46 and a biventricular ICD (cardiac resynchronization therapy device; CRT-D) owing to heart failure collapsed in a conference room, and basic resuscitation was started immediately (Figure 1, Table 1). Paramedics arrived 6 minutes after cardiac arrest, observed no shockable rhythm, and therefore started treatment with intravenous adrenaline. In hospital, coronary angiography was normal, and echocardiography showed cardiac standstill and LV dilatation of 8 cm, RV with no significant dilatation, and no sign of pulmonary embolism. Admitted to the intensive care unit, the patient was declared dead less than 2 hours after cardiac arrest. The relatives refused autopsy. A few days before death, the index patient had been admitted to hospital with recurrent slow ventricular tachycardia (VT), terminated by antitachycardia pacing (ATP). The CRT-D was well functioning. We have indirect evidence of endomyocardial RV fibrosis from 2 previously performed 3-dimensional electroanatomic maps and catheter ablation procedures for monomorphic VT. Further, lack of R-wave progression in precordial leads was observed in the electrocardiogram at patient age of 42—4 years prior to diagnosis of ARVC (Figure 2A).

In regard to previously observed slow and fast ventricular arrhythmias, the CRT-D (Biotronik LUMAX 540 HF-T, Biotronik, Berlin, Germany) was programmed as follows: VT-1 zone 162 beats per minute (bpm) (therapy: ATP ×6, 40 J shock ×1), VT-2 zone 188 bpm (ATP ×2, 40 J shock ×1), and VF zone 250 bpm (40 J shock ×6). Postmortem device interrogation showed low-amplitude ventricular fibrillation (VF) detected in VT-1 and VT-2 zones with numerous unsuccessful ATP attempts (Figure 2B). Owing to intermittent under-sensing of VF, the CRT-D delivered only 2 direct current shocks, of which 1 converted the rhythm to short-lasting paced rhythm before reversal to VT (Figure 2C).

Molecular genetic testing for ARVC had revealed the p.Ser358Leu mutation in *TMEM43*, confirming ARVC type 5 in this patient. He had a family history of SCD. Seven out of 10 family members tested carried this mutation (Figure 1); of those, 5 had severe cardiac symptoms, 1 with heart transplantation (HTx) at age 44 years owing to progressive heart failure and multiple shocks from the ICD (III-5). All 5 met the diagnostic criteria for ARVC. Including the index case, 6 family members with a positive genetic test have an ICD.

KEYWORDS ARVC; Genetics; ICD; Sudden cardiac death; TMEM43
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KEY TEACHING POINTS

- Arrhythmogenic right ventricular cardiomyopathy type 5 (ARVC-5), caused by the *TMEM43* p. Ser358Leu mutation, has an extremely severe phenotype.
- Refractory low-amplitude ventricular tachycardia (VT) or ventricular fibrillation (VF) seems to be the main reason why the implantable cardioverter-defibrillator can be unable to defibrillate ARVC-5 patients.
- Heart transplant for patients with ARVC-5 with an impact on right ventricle and/or left ventricle function and numerous episodes of VT/VF could be the next line of treatment to consider.

Case 2

A 27-year-old man (III-1) massively predisposed to heart disease and SCD was found dead in his home (Figure 1). Eight months prior to death he had the diagnosis of ARVC and received an ICD (CPI 1715; Guidant, Indianapolis, IN) (Table 1). One month before death an ICD control revealed 2 episodes of VT (190 bpm), with appropriate shock therapy restoring sinus rhythm, and the ICD was found to be fully functioning. Unfortunately, no postmortem ICD interrogation could be obtained. Autopsy showed a well-placed ICD electrode and no major organic pathology responsible for death other than an enlarged and trabeculated RV. Histology of the RV myocardium showed marked lipid infiltration and fibrosis in the anterior and lateral wall.

The pedigree elucidates a severe family history of SCD, with a brother (III-5) who died suddenly and unexpected at age 29; mother (II-2) and grandmother (I-2), at ages 62 and 37, respectively; and an uncle (II-3), who experienced SCD at age 38 (Figure 1).

Also in this case, molecular genetic testing revealed the p. Ser358Leu mutation in the *TMEM43* gene, postmortem from a sample of paraffin cuts. Subsequently, cascade screening revealed the p.Ser358Leu *TMEM43* mutation in 3 out of 4 living family members tested (Figure 1). Two of these (III-2, III-3) exhibited significant cardiopulmonary symptoms with VF and several episodes of VT, and were treated with ICD. At age 49, patient III-3 survived cardiac arrest owing to external defibrillation of VF after failure of appropriate shocks from the ICD. Since then, amiodarone treatment kept this patient in sinus rhythm. HTx was considered, but with LV ejection fraction of 35% and stabilized heart rhythm HTx has not been performed so far. Patient IV-1 is still young (19 years) and undergoes annual clinical monitoring.

Case 3

A 33-year-old man with ARVC and ICD since the age of 24 years owing to numerous cases of nonsustained VT was hospitalized after cardiac arrest. The patient collapsed in his home with cardiac arrest and basic resuscitation was started immediately (Table 1). Repeated shocks from the ICD (Protecta XT DR; Medtronic, Minneapolis, MN) were observed clinically before the paramedics arrived, and an additional 12 external direct current shocks were delivered in hospital owing to VF. Despite continued attempts at resuscitation, the patient died shortly after arriving at the hospital.

Two days prior to cardiac arrest, the patient had 2 episodes with significant palpitations and was admitted to hospital. ICD interrogation showed successful ATP therapy of 2 episodes of fast monomorphic VT, all parameters (sensing, threshold, impedance) remained stable, and the patient was discharged the same day. Unfortunately, no postmortem ICD recordings could be retrieved. Medtronic found the ICD without any errors at postmortem investigation. Previously, 3 VT ablation procedures had been performed, the latest at age 28, with apparent success and freedom from VT for several years. Autopsy showed right-sided heart dilatation with a well-placed ICD electrode. Several white, pale, and yellow areas around the myocardium were observed, corresponding to late changes with fibrosis and fibrofatty replacement of the myocardium, as seen in most ARVC-5 patients. LV appeared unremarkable. Because the patient was an adopted child from Sri Lanka, family history was unknown.

Molecular genetic analysis

In these 3 families DNA was purified from peripheral leukocytes or paraffin cuts and used for Sanger sequencing of all exons including exon–intron boundaries of the *TMEM43* gene. The p.Ser358Leu mutation (c.1073C>T, NM_024334.2) was identified. Sanger sequencing was performed using BigDye v1.1 (Applied Biosystems) and Genetic Analyzer 3130XL (Applied Biosystems). None of the family members had mutations in the desmosome genes *PKP2*, *DSG2*, *DSC2*, *DSP*, and *JUP*, investigated with the same principle. For detection of large genomic deletions or insertions, multiplex ligation–dependent probe amplification was performed with the SALSA MLPA probemix P168-C1 ARVC-PKP2 (MRC Holland), which holds probes for exons 1–14 of *PKP2*; exons 1, 5, and 6 of *DSG2*; exons 1, 7, and 17 of *DSC2*; exons 1, 5, 7, 9, 21, and 24 of *DSP*; and exons 2, 9, and 17 of *JUP*. No large genomic rearrangements were detected.

Discussion

Three cases of SCD despite ICD treatment, within unrelated families, suggest ARVC-5 to be even more serious than expected. These cases indicate that patients with ARVC-5 are at especially high risk of SCD. The p.Ser358Leu *TMEM43* mutation was identified as an underlying cause, with evidence of development of myocardial fibrosis, especially in the RV.

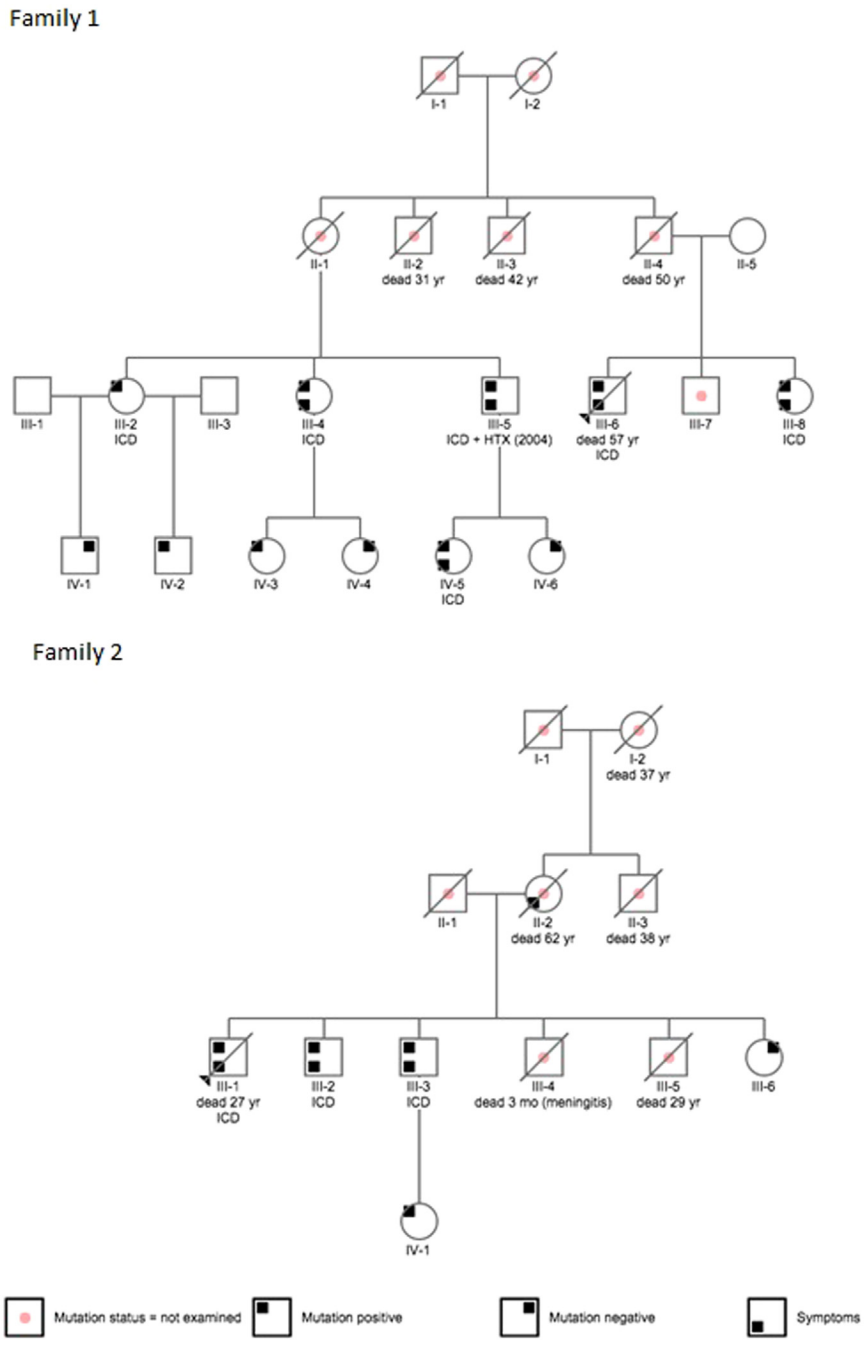

Figure 1 Pedigrees.

In ARVC, late pathologic processes such as replacement of the myocardium by fatty and fibrous tissue and myocardial atrophy, predominantly in the RV, are progressing, and risk of low-amplitude VF increases.[9] From ICD interrogations, under-sensed low-amplitude VF seems to be the reason why long-term ARVC patients experience SCD without any ICD therapy.[9,10] This phenomenon may also play a role in our 3 index patients, although there was only 1 case in which we had available ICD recordings that documented intermittent under-sensed low-amplitude VF. Our patient histories also support that failure of ICD therapy may be due to treatment-refractory VF, likely because of severe progression in myocardial fibrosis. Another common electrocardiogram abnormality is poor R-wave progression in the right precordial leads, predominantly observed in patients with biventricular ARVC disease.[11] To what extent the poor R-wave progression is different in *TMEM43* p.Ser358Leu mutation–carrying ARVC-5 patients compared with other ARVC patients remains unclear. In addition, the large difference in age at death between index cases may still

Table 1 Key clinical findings

	Case 1	Case 2	Case 3
Clinical	Diagnosed at age 46 Dead at age 57 Episodes of VT Heart failure with dilated LV and LVEF 30% Endomyocardial RV fibrosis in 3-D maps	Diagnosed at age 27 Dead at age 27 Episodes of VT No LV involvement, LVEF 65%	Diagnosed at age 24 Dead at age 33 Episodes of VT, LVEF 50%
Medication	ACE-I, metoprolol	Sotalol	Sotalol
Autopsy	Not performed (family refusal)	Enlarged trabeculated RV with lipid infiltration and fibrosis in anterior and lateral wall	Right heart dilatation with fibrosis and fibrofatty replacement of myocardium in RV Normal LV
2010 revised ARVC criteria			
Structural/functional abnormalities in echo/MRI	++	-No MRI	++
Tissue characteristics	NA	++	–
Repolarization abnormalities in ECG	–	++	++
Depolarization/ conduction abnormalities in ECG	–	–	++
Ventricular arrhythmias	++	++	++
Family history	++	++	++
Fulfill criteria of ARVC	Yes	Yes	Yes

+ = minor criterion; ++ = major criterion.

ARVC = arrhythmogenic right ventricular cardiomyopathy; ECG = electrocardiogram; Echo = echocardiogram; LV = left ventricle; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; NA = not available; RV = right ventricle; VT = ventricular tachycardia.

reflect a variable phenotypic clinical expression of ARVC, even with this specific mutation.

Patients in 2 of our index cases underwent several catheter ablations for monomorphic VT in order to obtain rhythm control. A previous study suggests that catheter ablation may be an effective tool in suppressing VT occurrence in the short term but not effectively preventing VT recurrence over the long term.[12] The arrhythmia control by catheter ablation led to an improvement in quality of life, but neither catheter ablation nor ICD treatment improved the overall survival.[12] However, results reported by Hodgkinson et al[8] suggest a beneficial impact on survival, primarily in male ARVC-5 patients, with the use of ICD.

For most ARVC patients ICD prophylaxis is sufficient treatment. Nevertheless, ICD is not effective in preventing SCD in all cases, and was not effective for the 3 ARVC-5 patients described. Despite significant RV dysfunction, the majority of ARVC patients are not considered for HTx owing to relatively mild symptoms of heart failure. When cardiac arrest occurs, the ICD can be unable to defibrillate these patients owing to treatment-refractory low-amplitude VT or VF. The heart-transplanted patient in family 1, who received a new heart owing to progressive heart failure and multiple ICD shocks, is doing well 10 years later. The optimal timing of HTx, however, has not been discussed. Gilljam et al[13] suggest consideration of HTx in patients with repeated admissions to hospital with VF or VT, and especially in RV-dysfunctional ARVC patients with increased filling pressures, which corresponds to Fontan-type physiology, which may be impossible to effectively defibrillate.

Conclusion

Despite a fully functional ICD, patients with ARVC-5 caused by the *TMEM43* p.Ser358Leu mutation may die of SCD, which indicates an extremely severe phenotype. In the future, prophylactic ICD as primary prevention of SCD probably still will be the treatment of choice. However, considering HTx for patients with ARVC-5 with impact on RV and/or LV function and numerous episodes of VT/VF could be next in line. This type of treatment already has been demonstrated to have positive results, but further research is needed for this to be incorporated in the treatment of severe myocardial involvement in ARVC-5.

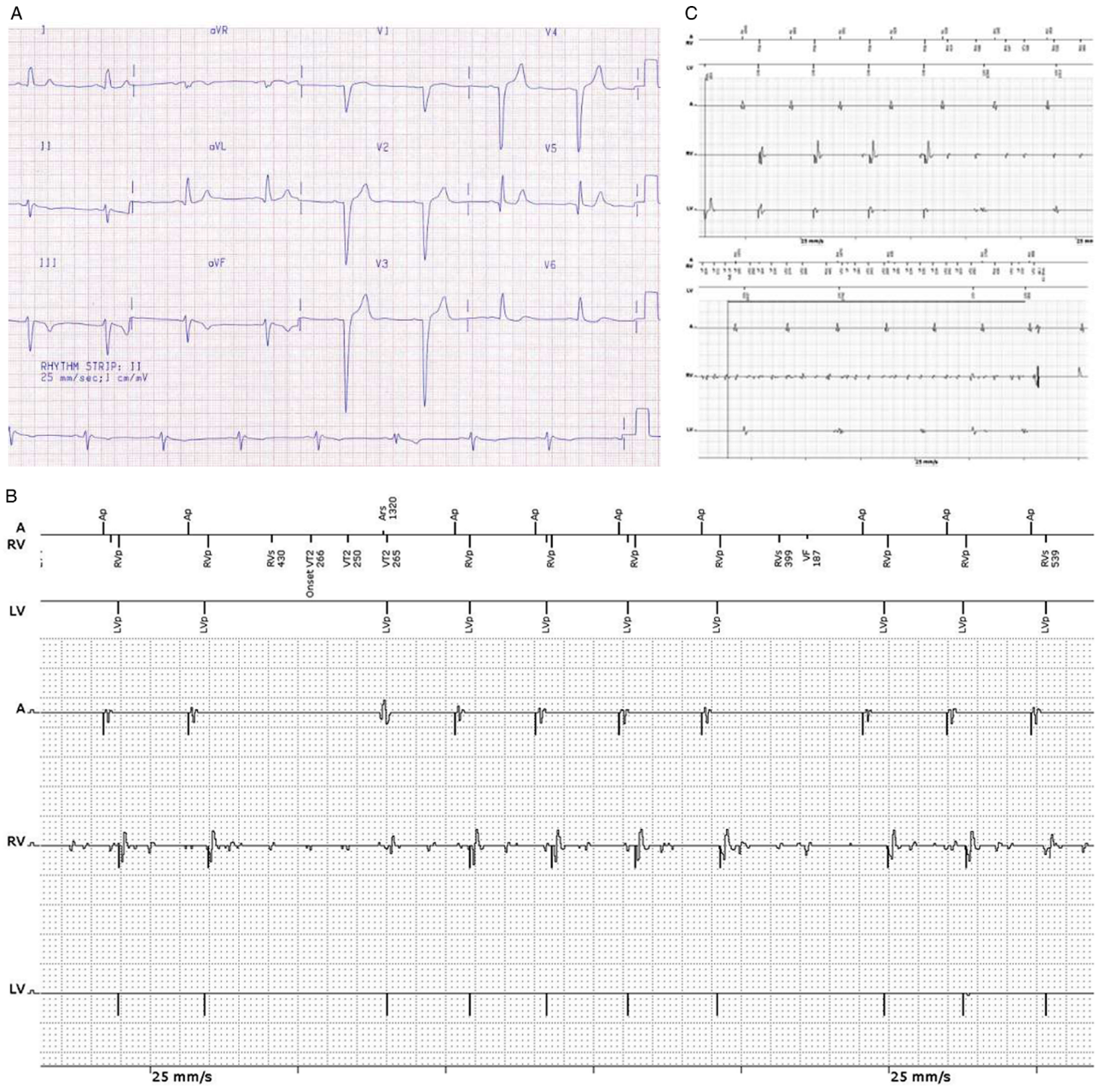

Figure 2 Electrocardiogram (ECG) and implantable cardioverter-defibrillator (ICD) recordings. **A:** 12-lead ECG from index patient at age 42 in family 1. **B:** Intermittent under-sensing of low-amplitude ventricular fibrillation (VF). **C:** Appropriate ICD shock with conversion of VF to short-lasting sinus rhythm and recurrent slow ventricular tachycardia.

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