A 20-year-old soccer player died suddenly while watching a game with friends at home. At annual preparticipation screening, ECG was normal with consequent sport eligibility (Figure 1A). History for juvenile sudden death and hypertrophic cardiomyopathy was reported on the mother’s side of the family. Postmortem examination of the heart showed normal dimensions (weight, 347 g; wall thicknesses of left ventricle [LV] and septum 13 mm and right ventricle [RV], 3 mm), in the absence of aneurysms or chamber dilatation; a subepicardial scar-like grey rim was evident in the anterolateral and posterior LV free wall and in the septum (Figure 1B). Coronary arteries had a normal origin and course, with patent lumen. Histological examination revealed extensive subepicardial and intramural fibrous replacement with scarce fatty tissue infiltration, involving the entire LV circumference and the septum (Figure 1C). Right ventricular involvement was only focally detected, in the anterior wall. The features were in keeping with either chronic myocarditis or left-dominant arrhythmogenic cardiomyopathy (AC).

At postmortem, molecular pathology investigation by polymerase chain reaction ruled out the presence of viral genomes in the myocardium. Genetic testing of all AC-related genes was performed on DNA isolated from frozen tissue sample. A heterozygous nonsense mutation of desmoplakin (DSP) at position c.448C>T in exon 4, resulting in a premature stop codon and truncation (Arg150X) at the N-terminal domain of the protein, was detected in the proband (Figure 1D). Genetic testing of all AC-related genes according to the 2010 TFC.2 However, LV LE at CE-CMR (Figure 3B) allowed a final diagnosis of left-dominant AC as cause of sudden death. As such, it was the starting point for cascade genetic screening of the family members and cardiological workup, including CE-CMR in mutation carriers, despite the absence of morphofunctional abnormalities at 2-dimensional echocardiography.

Nonischemic Left Ventricular Scar
Sporadic or Familial? Screen the Genes, Scan the Mutation Carriers

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Images in Cardiovascular Medicine

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These data further highlight the limitations of 2010 TFC criteria for LV AC and the fundamental role of CE-CMR in achieving the correct diagnosis in gene mutation carriers.

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None.

References

Figure 1. A, Basal 12-lead ECG at annual preparticipation screening showing normal findings. B, Transverse section of the heart showing a subepicardial scar-like grey rim in the anterolateral and posterior LV free wall and in the septum, in the absence of wall thinning and aneurysm formation. C, Histological examination revealed focal RV involvement (on the left) and extensive circumferential, subepicardial, and intramural fibrous replacement of the LV free wall (on the right). LV indicates left ventricle; and RV, right ventricle.

Figure 2. Family pedigree. Squares indicate male sex, and circles indicate female sex. Black squares/circles indicate mutation carriers of DSP c.448C>T, Arg150X. The proband is indicated by an arrow. Linkage markers used to confirm paternity are indicated below subjects. DSP indicates desmoplakin.
Figure 3. The 54-year-old asymptomatic father, carrier of the DSP c.448C>T mutation. A, Basal 12-lead ECG showed low-voltage QRS and 1 PVC with LBBB morphology. B through E, Cardiac magnetic resonance. On the cine images, diastolic frame (B) and systolic frame (C), no LV cine abnormalities were found; on the contrary, a focal bulging on anterolateral apical region of RV was found (C, white arrow), not fulfilling the current task force criteria for AC, because it was not associated with RV dilatation or dysfunction (end-diastolic volume 62 mL/mq, ejection fraction 59%). On postcontrast sequences (D through E), late gadolinium enhancement with a midepicardial stria was found in the inferior LV wall. DSP indicates desmoplakin; LBBB, left bundle branch block; LV, left ventricle; RV, right ventricle; and PVC, premature ventricular complex.

Figure 4. The 19-year-old sister with a history of ventricular arrhythmias, carrier of the DSP c.448C>T mutation. A, Basal 12-lead ECG showed low-voltage QRS, inverted T wave V1, incomplete right bundle branch block, and nonpathological Q wave in inferior leads. B through E, Cardiac magnetic resonance. On the cine images, diastolic frame (B) and systolic frame (C), no LV cine abnormalities were found; on the contrary, focal bulging on RV anterolateral region was visible (C, white arrows), not fulfilling the current task force criteria for AC because it was not associated with chamber dilatation or dysfunction (end-diastolic volume, 72 mL/mq; ejection fraction, 65%). On postcontrast sequences (D and E) late gadolinium enhancement with a mid-stria was identified, almost circumferentially, in the inferior and anterior LV walls and septum. DSP indicates desmoplakin; LV, left ventricle; and RV, right ventricle.
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