Left-Dominant Arrhythmogenic Cardiomyopathy

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A 50-year-old recreational futsal player was referred to our sports cardiology outpatient clinic for palpitations and detection of frequent (>5000) ventricular premature beats with bigeminy and runs of nonsustained ventricular tachycardia at 24-hour Holter monitoring. Rest ECG showed normal QRS morphology with negative T waves in precordial lateral (V4 to V6) and inferior leads (Figure 1A). Less-prominent negative T waves in lateral but not inferior leads also were present in previous ECGs obtained during routine sports preparticipation evaluation at age 26 years (Figure 1B) but in the absence of symptoms and arrhythmias at Holter monitoring; no other diagnostic test was performed at that time.

A stress ECG failed to reveal ST-segment changes diagnostic for myocardial ischemia, whereas frequent polymorphic ventricular premature beats with right bundle branch block morphology and a short run of nonsustained ventricular tachycardia were observed during the recovery phase. Two-dimensional echocardiography showed a mild reduction of ejection fraction with a diffuse apical a-dyskinesia of the left ventricle (LV), whereas the right ventricle (RV) presented normal dimensions and global function but hypokinesia of the apex and the basal portion of the free wall. Cardiac MRI showed the presence of an extensive akinetic area at the apex of the LV characterized by wall thinning and associated with midwall and subepicardial delayed enhancement of lateral and apical walls (Figure 2A through 2C). Apical and posterobasal segments of the RV also were characterized by wall thinning associated with wall motion abnormalities. In addition, areas of fatty replacement were observed in the epicardial portion of LV lateral and inferior walls (Figure 2D).

The patient was then submitted to an invasive study, including cardiac catheterization with coronary angiography, electroanatomic mapping-guided endomyocardial biopsy, and programmed electric stimulation, to identify the substrate of electrical and structural cardiac abnormalities observed. Coronary angiography showed normal coronary arteries, whereas LV angiography confirmed the presence of an apical dyskinesia with a mildly reduced global systolic function. RV angiography showed a mild enlargement of the ventricle with moderate ectasia of the free wall (online-only Data Supplement Movies 1 and 2). Biventricular electroanatomic mapping revealed the presence of low-voltage areas at the apex of the LV and the basal portion of the RV free wall (Figure 3A and 3B). Multiple endomyocardial biopsies were drawn from low-voltage areas of both the LV and the RV as previously described, and programmed electric stimulation failed to induce sustained ventricular arrhythmias.

Histological analysis of LV specimens showed extensive areas of replacement fibrosis with multiple areas of fatty replacement, whereas the RV specimens were characterized by areas of fibrofatty replacement with residual myocardial tissue inferior to 60% of the total area (Figure 4A and 4B). Mutation screening of 5 desmosomal genes (plakoglobin, desmoplakin, plakophilin-2, desmoglein-2, and desmocollin-2) by direct sequencing failed to detect any gene mutation associated with arrhythmogenic cardiomyopathy.

On the basis of clinical, ECG, and histological features, left-dominant arrhythmogenic cardiomyopathy (LDAC) was diagnosed. The patient was adequately informed about the risk of life-threatening ventricular arrhythmias and about the efficacy on preventing sudden death and the possible complications of both implantable cardioverter-defibrillator and radiofrequency catheter ablation, but he refused any invasive therapeutic intervention and was discharged to treatment with amiodarone.

LDAC is a rare form of arrhythmogenic RV cardiomyopathy frequently associated with PKP2 gene mutations and characterized by fibrous or fibrofatty replacement of the LV, with possible less-prominent focal arrhythmogenic abnormalities of the RV. Like in its right-dominant counterpart, ventricular arrhythmias (in this case of LV origin) are the clinical hallmark of LDAC, and this disease represents a possible, although rare cause of sudden death.
Figure 1. Rest ECGs. A, Rest ECG obtained in 1984 showing negative T waves in lateral precordial leads (V4 to V6). B, Rest ECG obtained in 2010 showing more-prominent negative T waves in lateral precordial leads.
in young persons, including athletes. Repolarization abnormalities (negative T waves) in the lateral precordial leads are a frequent finding, and the loss of myocytes may lead to a progressive reduction of QRS voltage in severe forms.

In the present case, the presence of negative T waves in lateral precordial and inferior leads together with the absence of right precordial QRS prolongation suggested a prevalent LV disease and an absent or marginal involvement of the RV. Regional wall motion abnormalities or, less frequently, global LV dysfunction, generally out of proportion with respect to arrhythmic burden, can be detected by echocardiography and cardiac MRI. Moreover, late contrast enhancement in the subepicardial and midmyocardial layers of the LV walls may further suggest the diagnosis. Nevertheless, standardized diagnostic criteria are still lacking, and other cardiac disorders, such as LV chronic myocarditis or dilated cardiomyopathy, may mimic clinical and instrumental findings of LDAC. Differentiation between LDAC and chronic myocarditis or dilated cardiomyopathy is clinically relevant for risk stratification and familial evaluation but can be difficult on the basis of clinical evaluation and noninvasive findings. Similarly, genetic evaluation may be helpful in the setting of a familial disease, although its role for diagnosing index cases with possible LDAC still appears limited by the complex genetic background of the disease, which accounts for the low penetrance and variable expression of the phenotype. In this regard, the present case suggests that 3D electroanatomic mapping-guided endomyocardial biopsy, providing a definite tissue characterization, may be crucial for differential diagnosis.

Figure 2. Cardiac MRI findings. A, Cine image showing thinning of the apex (arrow). Long-axis (B) and short-axis (C) images showing midwall and subepicardial late gadolinium enhancement of lateral and apicodistal walls. D, Fat infiltration (hyperintense signal) (arrow) of the distal segment of the lateral and inferolateral walls. Balance fast field echo sequence (A); turbo gradient echo T1-weighted sequence prepared with an inversion recovery pulse (inversion time, 250 ms) (B and C); black blood T1-weighted fast spin echo sequence (echo time, 9 ms; repetition time, 780 ms) (D).

Figure 3. Electroanatomic mapping. A, Right ventricular electroanatomic map showing low-voltage (red-yellow-green) areas in the outflow tract and diaphragmatic wall. B, Electroanatomic map of the left ventricle showing a low-voltage (yellow-green) area in the apex.
Disclosures

None.

References


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