

Leopard Syndrome and Hypertrophic Cardiomyopathy: an Association Related to Sudden Death

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We describe an uncommon association between Leopard syndrome and hypertrophic cardiomyopathy in a 27-year-old woman, who was little symptomatic and came for sudden death risk stratification and prevention. She has a rare syndrome, whose symptoms are maculae over the body and abnormalities in eyes, genital organs, heart and in growth. Association of hypertrophic cardiomyopathy with sudden death risk factors determined the implantation of cardioverter-defibrillator (ICD) for primary prevention.

Introduction

Cardiomyopathy lentiginosis is known as Leopard syndrome, which is a mnemonic rule for multiple **L**entigines injuries, **E**lectrocardiographic conduction abnormalities, **O**cular hypertelorism, **P**ulmonary stenosis, genital and reproductive **A**bnormalities, **R**etarded growth and **D**eafness¹.

Patients have lentigines injuries over the body, which are a typical symptom of this disease. They may also present with other symptoms, such as ocular hypertelorism, low-set ears, retarded growth and delay of formation of secondary sexual characters².

There are cardiac abnormalities such as: prolongation of PR interval; bundle-branch blocks, complete atrioventricular block and asymmetrical hypertrophy of left ventricle. This last problem mainly affects the anterior wall and interventricular septum, which characterizes hypertrophic cardiomyopathy (HCM)³.

This is the first report of Leopard syndrome related to HCM in Brazil, in which we discuss the form of stratification and prevention of sudden cardiac death.

Case Report

A 27-year-old patient came for a sudden death risk consultation and assessment and reported a history of a cousin who had sudden death when he was 23 years old.

She complained about dyspnea during more-than-ordinary

Key Words

Leopard syndrome, hypertrophic cardiomyopathy, sudden death

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activities (New York Heart Association [NYHA] functional class II) and short-term tachycardia. She did not complain about syncope or chest pain.

She has Von Willebrand disease, which was diagnosed when she was 13 years old. When she was 23 years old, she was admitted to the hospital for an intravenous antibiotic treatment due to an infective endocarditis in the mitral valve. This infection occurred after a dental treatment.

On physical examination, she had multiple lentigines on the neck and torso (figure 1), ocular hypertelorism, exotropic strabismus and retardation of growth. Cardiac auscultation revealed a harsh murmur along the left sternal border (3+/6), which was intensified by Valsalva maneuver. It also revealed a mild murmur in the mitral area (2+/6), radiating to the axilla.

Electrocardiogram showed: left ventricular overload; prominent S waves in V2; R waves in V5; diffuse abnormalities of ventricles repolarization with ST-segment depression; strain type in precordial leads; and left atrial overload (fig. 2). HCM diagnosis was confirmed by echocardiogram, which shows septal wall thickness of 32 mm, obstruction of left ventricular outflow tract with dynamic gradient of 130 mmHg and left atrium enlargement of 43 mm. Ejection fraction was normal. Cardiac stress test showed normal blood pressure response and electrocardiographic abnormalities of ST-segment as left ventricular overload occurred.

24-hour holter showed ten episodes of non-sustained ventricular tachycardia (NSVT) and heart rate above 120 bpm. Magnetic resonance imaging (MRI) of the heart showed a diffuse myocardial fibrosis on inferior wall and septum of left ventricle. The patient was using atenolol 200 mg/day and losartan 100 mg/day. Although losartan had been proscribed in HCM treatment, especially in obstructive form, it was retained because the patient reported an improvement in dyspnea.

Discussion

A 27-year-old patient complains about dyspnea during more-than-ordinary activities and has HCM associated with Leopard syndrome.

HCM estimated prevalence is approximately 1:500 individuals (0.2%) aged 25 to 35 years. It is a genetic disease with dominant autosomal inheritance, which is caused by abnormalities in ten chromosomes and more than 400 mutations in genes encoding sarcomeric proteins⁴. Sudden cardiac death (SCD) is the most feared complication and occurs mainly in young and asymptomatic individuals. It can also reach an incidence of 30% when multiple risk factors are present⁵. Atrial fibrillation, ventricular dilatation and infective



Figure 1 - Multiple lentigines on the face and torso.

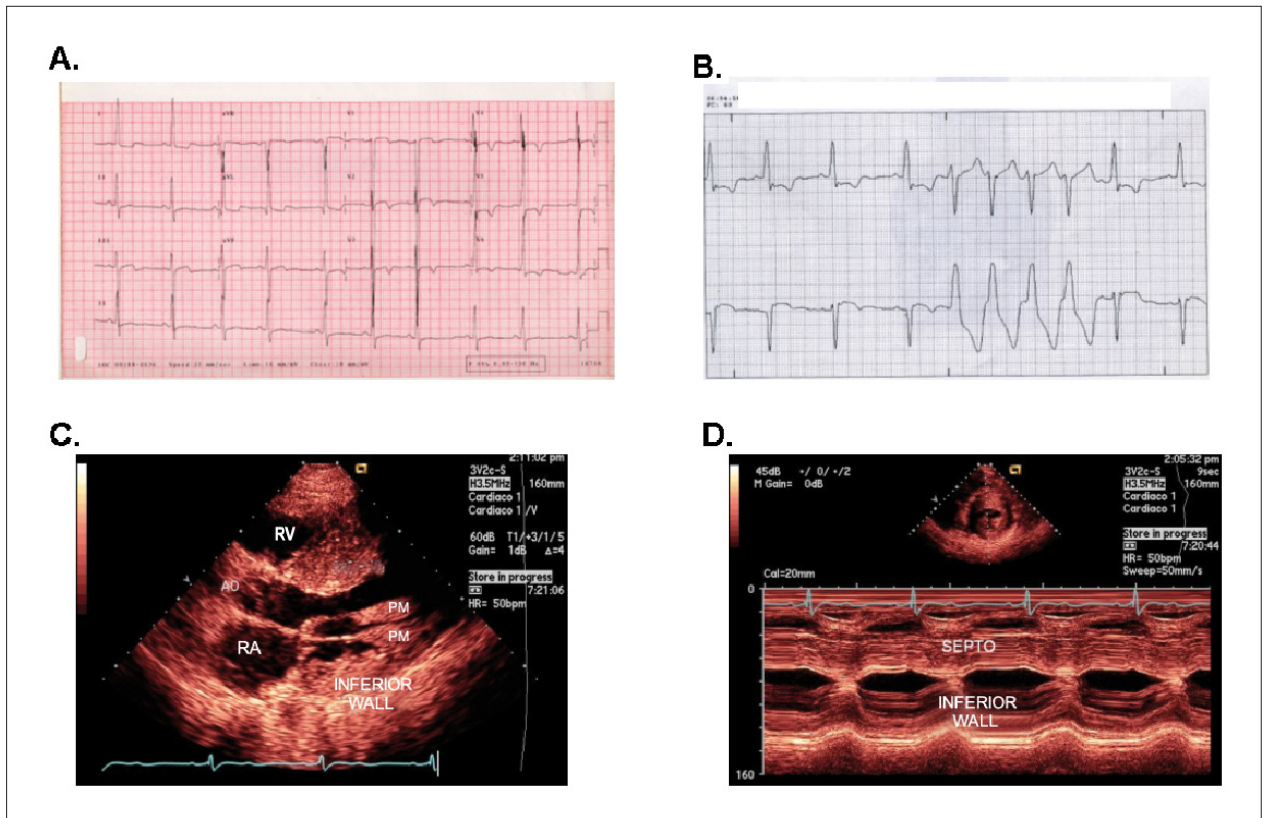


Figure 2 - A - Electrocardiogram shows left ventricular overload; B - 24-hour holter shows non-sustained ventricular tachycardia; C - Two-dimensional echocardiogram, longitudinal section shows hypertrophy of ventricular septum; D - M-mode echocardiogram of the LV in the short-axis view; RV – right ventricle; RA - right atrium; AO – aorta; PM – papillary muscle.

endocarditis (in the obstructive form when prophylaxis is mandatory) are common complications as disease develops.

HCM may also be related to different congenital malformations and rarely to Leopard syndrome⁶.

Multiple lentigines syndrome was named as Leopard syndrome by Gorlin, Anderson and Blaw in 1969. It is a

dominant autosomal genetic disease and has high penetrance and variable expression¹. It is a rare disease (100 cases approximately were reported as of 2006) and affects equally males and females. Its pathogenesis is still unknown¹.

A possible explanation of pathogenesis of this syndrome is an abnormality in neural crest cells – from which autonomic

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ganglia cells and Schwann cells of peripheral nerves originate – and an abnormality in nerve endings of the parasympathetic nervous system in heart ventricles. These cells can also increase melanocytes and could explain the association with lentiginosis. A genetic defect related to the syndrome development has been located on chromosome 12 (12q24.1). Mutations on this gene may cause other genetic diseases with heart malformations, such as Noonan syndrome, lentiginosis cardiomyopathy and Leopard syndrome⁷.

Regarding our patient, who was little symptomatic and has important hypertrophic cardiomyopathy, the key-point is to stratify sudden death risk and determine the best treatment option.

The ACC/AHA/ESC 2006 guidelines for SCD determine five major risk factors⁸:

- 1) family history of sudden death (under 45 years old);
- 2) unexplained syncope;
- 3) septal thickness \geq 30 mm;
- 4) NSVT on holter (HR > 120 bpm);
- 5) abnormal blood pressure response during activity (non-elevation or drop in systolic pressure > 20 mmHg during activity)⁸. There is a 5% risk for SCD per annum if patients have two or more risk factors, and there is only 1% when none of these factors is found⁵.

Other factors should also be considered in patient assessment: age when disease was diagnosed; left ventricular outflow tract gradient > 30 mmHg; mainly genetic malignant mutations (troponin T gene and beta-myosin heavy chain)⁸. If MRI of heart shows late enhancement and fibrosis areas, it has prognostic value. Diffuse fibrosis distribution was related

to worse SCD prognosis and left ventricle hypertrophy⁹.

Previous studies failed to show the benefit of antiarrhythmic drugs, which were used for sudden death prevention. Amiodarone can eliminate complex ventricular arrhythmias, but it does not protect against SCD. It would be used only in patients in whom ICD implantation is not feasible and in patients with SCD risk factors or even history of non-sustained ventricular tachycardia (VT) or ventricular fibrillation (VF)^{8,10}.

Regarding high-risk patients who have two or more risk factors, ICD implantation is recommended for primary SCD prevention, with a 5% annual incidence of appropriate shocks⁷.

Our patient has a rare syndrome related to HMC and has a high sudden death risk due to: family history of sudden death; myocardial hypertrophy > 30 mm; NSVT on holter; and myocardial fibrosis which was observed in MRI. In this case, ICD implantation was recommended for primary prevention.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any post-graduation program.

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