LEOPARD syndrome and hypertrophic obstructive cardiomyopathy: a case report

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The LEOPARD syndrome is a rare, autosomal dominant multisystemic disorder characterized by lentiginosis, ocular hypertelorism, abnormal genitalia, growth retardation, sensorineural deafness, and cardiac and electrocardiographic abnormalities. Although it is not cited, hypertrophic cardiomyopathy is often associated with the disease. In this study, we present a nine-year-old boy with LEOPARD syndrome and hypertrophic obstructive cardiomyopathy.

Key words: LEOPARD syndrome, lentiginosis, hypertrophic cardiomyopathy, familial horseshoe kidney.

LEOPARD syndrome is a rare, autosomal dominant condition with various abnormalities in multiple organ systems. The acronym LEOPARD was introduced in 1969 by Gorlin et al.[1], for the various features of the disease. L, lentigines (multiple); E, electrocardiographic conduction abnormalities; O, ocular hypertelorism; P, pulmonary stenosis; A, abnormalities of genitalia; R. retardation of growth and D, deafness (sensorineural). Not all of these findings may be present in any given patient. Synonyms of LEOPARD syndrome include multiple lentigines syndrome, progressive cardiomyopathic lentiginosis and cardiocutaneous syndrome[2].

In this report, we present a case of LEOPARD syndrome with severe hyeprtrophic cardiomyopathy.

Case Report

We present a new case of LEOPARD syndrome with hypertrophic cardiomyopathy from Turkey. A nine-year-old boy was admitted to our hospital for multiple skin lesions and short stature. He was the second child of nonconsanguineous parents. His 15-year-old brother had horseshoe kidney and hypertrophic cardiomyopathy and his father was deaf. We learned from the follow-up charts that the patient had been operated on for hypertrophic obstructive cardiomyopathy and cryptorchidic testes when he was four years of age at Hacettepe University, Thoracic and Cardiovascular Surgery Department. Histopathologic examination of the tissue specimens excised from the interventricular septum had revealed hypertrophied myocardium, although the macroscopic appearance had resembled tumor-like mass.

On physical examination, his height was 115 cm and his weight was 21 kg (HSDS= -2.83, BMI=15.8, BMI percentile=47.2%). He had numerous dark brown macules all over his face and body, including his hands, the scalp and buccal mucosa. Ocular hypertelorism, webbing of the neck with low-set cars and surgical scar for operated cryptorchid testes on the left side were the other physical findings (Fig. 1). On cardiac examination, blood pressure was 100/55 mmHg and pulse rate was 86/min. Diastolic and systolic ejection murmur was heard at the left sternal border. Electrocardiography showed prolonged PR interval, left axis deviation, and left bundle branch block (Fig. 2). On echocardiographic examination, mid portion of the interventricular septum was hypertrophic with a masslike protrusion towards the left ventricular cavity. Slightly

diminished systolic functions with ejection fraction and fractional shortening values of 56% and 27%, respectively, were recorded. Second-degree aortic valve insufficiency was detected by M-mode and continuous wave Doppler echocardiographic studies (Fig. 3). Complete blood count, serum zinc level and thyroid hormone levels were in normal ranges. Partial growth hormone deficiency and normal Leydig cell functions were found by stimulation tests. Audiologic tests and IQ test were normal. Renal ultrasonography demonstrated horseshoe kidney.

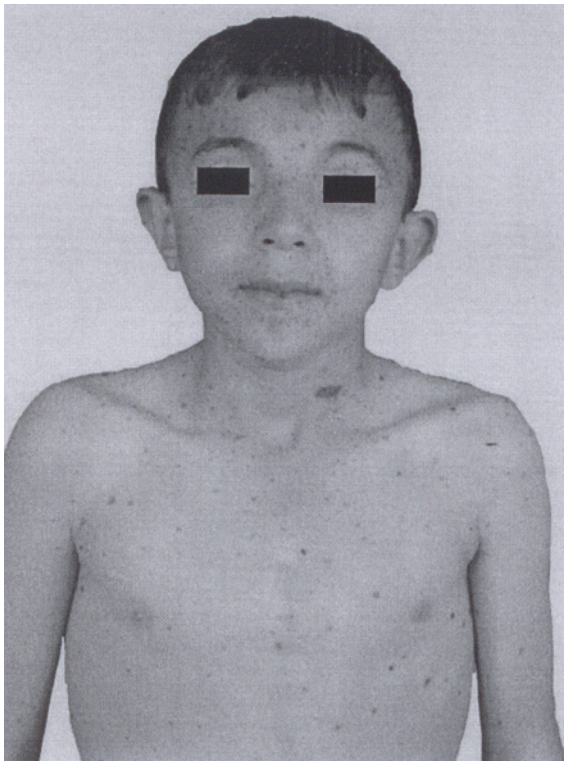

Fig. 1. Typical multiple lentigines of the patient.

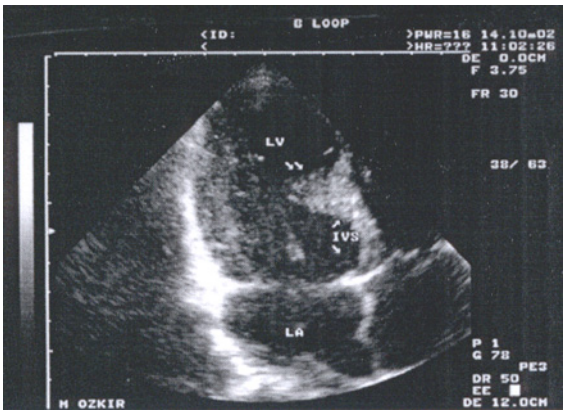

Fig. 3. Two dimensional echocardiogram in apical four chamber view: focal hypertrophy of the interventricular septum with a mass-like potrusion towards the left ventricular cavity (LA: Left atrium, LV: ventricle, IVS: Interventricular septum.

Discussion

Progressive generalized lentiginosis was first described by Zeisler and Becker[3] in 1936. The association of lentigines with cardiac abnormalities and short stature was reported by Moynahan[4]. Although there are sporadic cases of LEOPARD syndrome, the inheritance of this rare disorder is believed to be autosomal

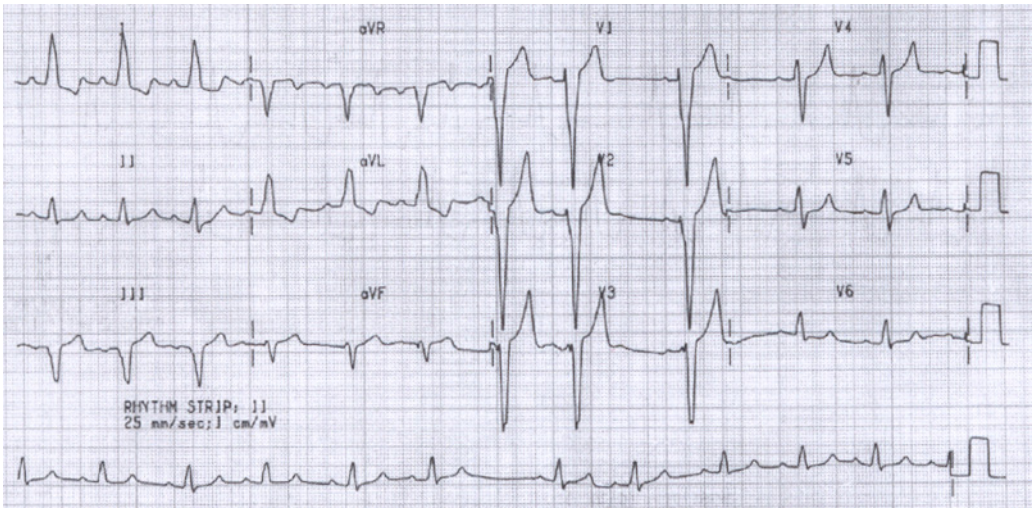

Fig. 2. Electrocardiogram of the patient (prolonged PR interval, left axis deviation, and left bundle branch block).

dominant. Penetrance is high but may be incomplete. Expressivity is highly variable. Many of the families reported are discordant, particularly for the cardiac manifestations. Renal abnormality and cardiomyopathy in our patient's brother, and hearing loss in his father suggested the autosomal pattern of inheritance in this family. Hypoplastic ovaries and delay of menstrual cycles in girls have been reported, but occurrence of horseshoe kidney as in our patient's brother has not been mentioned before. There are a number of hypotheses regarding the pathogenesis of this syndrome. A mutation in the stem cells of the neural crest in embryonic life is a favorite one[5,6]. Another is the maldevelopment of embryonic neural crest to explain the presence of cutaneous and neurological defects. The neural crest origin hypothesis was expanded by Somerville and Bonham-Carter[7] to include a possible metabolic or enzyme defect resulting in excessive pigmentation and cardiac muscle hypertrophy. The association of hypertrophic obstructive cardiomyopathy and other neurocutaneous syndromes, such as neurofibromatosis, tuberous sclerosis, or phenochromocytoma, has also been reported and seems consistent with a neuroectodermal defect[8]. No association was found in our patient. He had multiple lentigines, ocular hypertelorism, cryptorchism and growth retardation (HSDS= -2.83, BMI=15.8, BMI percentile=47.2%). Mental retardation and sensorineural hearing loss are frequent neurological abnormalities seen in about 30% of patients. Our patient was mentally normal, and he had no hearing loss. The endocrine evaluation of the patient was concordant with the previous reports[8]. Hypospadias can be seen in 50% of the patients, whereas unilateral or bilateral cryptorchidism is more frequently seen in these patients. Our patient was also operated because of cryptorchidic testes. There was no association with iron deficiency anemia as reported by Dündar et al.[9]. Patients with LEOPARD syndrome may have various kinds of cardiac abnormalities[7,10,11]. The most common cardiac abnormality is pulmonary stenosis. Other kinds of structural cardiac defects and several cases of atrial myxoma have also been found in this syndrome[12,13]. Electrocardiographic abnormalities, especially left axis deviation, may be found frequently in these patients, reflecting the underlying cardiac anomalies[14,15]. Post-operatively our patient had left axis deviation and left bundle branch block on electrocardiogram, concordant with the previous reports. We are not sure if the patient had the same electro-cardiographic findings pre-operatively. Hypertrophic obstructive cardiomyopathy is the most serious cardiac finding in patients with LEOPARD syndrome[16-18]. The previous follow-up chart of our patient revealed that surgical excision and myectomy had been performed because of the left ventricular outflow obstruction with a tumor-like severe septal hypertrophy[19]. On the follow-up, electrocardiographic studies showed that the septal hypertrophy recurred without obstruction, and the patient is still clinically asymptomatic at the third year of his operation.

Lentigines and deafness in LEOPARD syndrome are the only distinguishing features between this and Noonan's syndrome. The cardiovascular, growth, and dysmorphic findings are identical. The presence of lentigines and family history led us to exclude Noonan's syndrome. Also, the difference in skin lesions and lack of neurofibromas and Lisch nodules were not compatible with neurofibromatosis type I.

In conclusion, hypertrophic obstructive cardiomyopathy is a progressive condition and may play a major role in the clinical features of LEOPARD syndrome. Cardiac evaluation is an important part of follow-up, and may help to detect new onset of cardiac abnormalities and the progression of existing cardiac disease in patients with LEOPARD syndrome.

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