Clinical Dermatology: Research and Therapy

Case Report

A Case of Lentiginosis Associated with LEOPARD Syndrome

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ABSTRACT

Noonan Syndrome with multiple lentigines (formerly called LEOPARD syndrome) is a rare hereditary disorder. It is mainly characterized by skin, facial and cardiac anomalies. LEOPARD is an acronym for the major features of this disorder, including multiple Lentigines, Electrocardiogram (ECG) conduction abnormalities, Ocular hypertension, Pulmonic stenosis, Abnormal genitalia, of growth Retardation and sensorineural Deafness. We report the case of 4-year-old boy with LEOPARD syndrome, diagnosed clinically and confirmed by molecular technology. Physical examination revealed short stature, multiple lentigines on the head and upper trunk, pectus carinatum and a systolic murmur in mitral area. Echocardiogram revealed Pulmonary Stenosis (PS), Atrial Septal Defect (ASD) and hypertrophic cardiomyopathy. Hearing test screening was normal. He has met the clinical criteria for LEOPARD syndrome. A pathogenic variant of the PTPN11 gene was detected using molecular analysis for confirming the diagnosis. He has been treated with propranolol. The prognosis of LEOPARD syndrome is determined mainly by the severity of cardiac defects, which is also the most common cause of mortality. Early diagnosis and intervention with a multidisciplinary team could decrease mortality, allowing patients to have a normal life. Genetic counseling is recommended for prenatal screening.

INTRODUCTION

LEOPARD Syndrome (LS) is an autosomal dominant disorder, also called Noonan syndrome (NS) with multiple lentigines, which condition related to Noonan syndrome and affects many areas of body. LEOPARD is an acronym, characterized by multiple lentigines or café au lait spots, Electrocardiographic (ECG) conduction abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, growth retardation and deafness. Though it is not involved in this acronym, hypertrophic cardiomyopathy is most common cardiac malformation in this disease, which represented a potentially life-threatening in patients. Not all of the findings are present in the affected patient. There are highly variable clinical presentations in individuals with this disorder, which makes the diagnosis difficult and under diagnosed cases. LS shares many features with NS, which is a characterized by an associated with congenital heart disease, short stature and craniofacial malformations but does not usually include multiple lentigines and deafness among its manifestations. Both disorders show considerable phenotypic variability, making them difficult to identify and diagnose correctly. Genetic studies can therefore provide a useful contribution to differential diagnosis.

LS can be sporadic or familial. Nevertheless, most of reported cases are familial. About 200 cases have been reported worldwide but the real incidence rate is not known. PTPN11, RAF1, BRAF and MAP2K1 are the genes to be detected in associations of this syndrome and are responsible for Ras/MARK signaling pathway, which are important for cell cycle regulation, differentiation, growth and aging [1-3]. PTPN11 gene mutations are the commonest appearance, approximately 85 percent of affect individuals. Another 10 percent have mutations in the RAF1 gene. In rare cases, mutations in the BRAF or MAP2K1 gene have been found to cause this condition. In addition, LEOPARD syndrome can also be associated with malignancy, e.g. leukemia or melanoma. Therefore, genetic counseling is necessary [1,3].

CASE PRESENTATION

A 4 years old Chinese boy was born at 37 Weeks's gestation (birth weight: 2360g). He presented with a systolic heart murmur since he was born. Echocardiography at birth revealed hypertrophic cardiomyopathy with normal ejection function and treated along with propranolol though he was asymptomatic. In addition, he was Found Failed to Thrive (FTT) since one year of age.

His parents are young and unrelated. Both have deafness. The father and uncle present multiple lentiginous lesions on the face and trunk since young. The paternal family members have the history of heart problem with unknown etiology. His uncle also died due to heart failure.

Physical examination revealed growth retardation, with growth chart (height-93cm; weight-12.2kg) all below the 5th centile, multiple dark lentiginous lesions on the face and trunk with diameter between 2mm and 10mm respectively. Two café-au-lait spots were presented. Mucous membrane was not involved, chest examination shown normal heart rate. The blood pressure was also on normal limits. We found pectus carinatum and systolic murnmur II/IV at left sternal border without radiation (Figures 1-3).

Complementary study revealed

- Echocardiography - Atrial Septal Defect (ASD) about 10mm in size, with left to right shunt, right Pulmonary Stenosis (PS), the gradient was 16mmHg with Hypertrophic Cardiomyopathy (HCM) in left ventricle and normal ejection junction (Figure 4).
- Hearting screen test was normal at birth
- Molecular genetic analysis revealed the heterozygous pathogenic variant was detected in PTPN11: Exon 7, nucleotide, c.836＞G, amino acid p.Tyr279Cys

Diagnosis

Based on the history and physical examination findings, the child was clinically suspected of LEOPARD syndrome and PTPN 11 gene was detected by molecular analysis, which confirmed the diagnosis.

PTPN11Gene

PTPN11 gene is located on Chromosome 12q24.1. It encodes for the SRC homology 2 (SH2) domain-containing PTPase (SHP2) protein, characterized by two tandemly arranged SH2 (N-SH2 and C-SH2) domains and one Protein Tyrosine Phosphatese (PTP) domain. SHP2 functions as a cytoplasmic signaling transducer downstream of multiple receptors for growth factors, cytokines and hormones, with particular roles through the RAS-Mitogen Activated Protein Kinase (MAPK) pathway. Eleven different missense PTPN11 mutations in exon 7, 12, and 13(Tyr279Cys/Ser, Ala461Thr, Gly464Ala, Thr468Met/Pro, Arg498Trp/Leu, Gln506Pro, and Gln510Glu/Gly) have been reported so far, two of which (Tyr279Cys and Thr468Met) occur in about 65% of the cases. Among patients with PTPN11 mutations, an associated between exon 7 and 12 mutations and HCM, and between exon 8 mutations and PVS has been established. LS patients without PTPN11 mutations show a higher prevalence of ECG abnormalities and left ventricle hypertrophy. Analyses of the natural history of HCM in LS patients with different genotypes indicate that patients without PTPN11 mutations show a high frequency of family history of sudden death, increased left atrial dimensions, bradyarrhythmias and other adverse arrhythmic and non arrhythmic events. Mutations affecting exon 13 in the PTPN11 gene are often associated with an important cardiac phenotype, characterized by rapidly progressive severe biventricular obstructive HCM, often with prenatal onset and with serious cardiac complications during follow up (e.g. heart failure, septal myectomy and sudden death) [4]. Analysis of personal cohorts of LS patients indicate the mutation of the Thr468 residue is less frequently associated with short stature, compared to mutation of the Tyr279 residue, in which also deafness is more common [2].

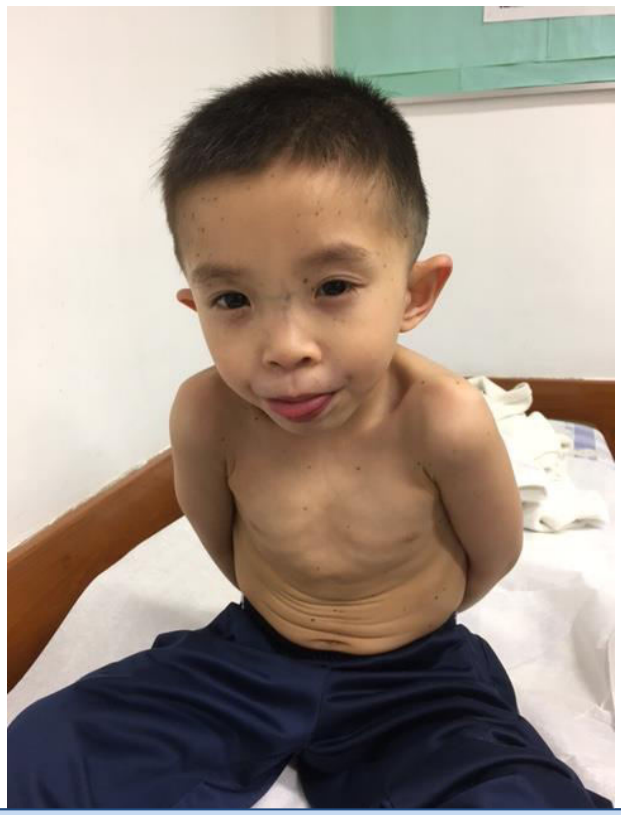

Figure 1: Epicanthic folds and lentiginous.

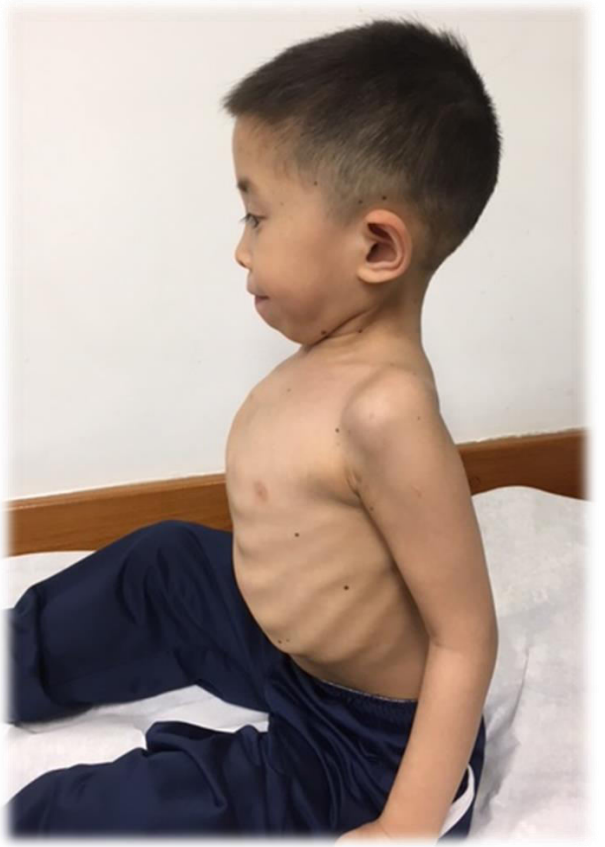

Figure 2: Lentiginous over the face and trunk and pectus carinatum.

Figure 3: Multiple dark brown spots and café-au-lait spot on the back.

MANAGEMENT AND OUTCOME

The patient kept to take propranolol and follow up in outpatient department. He managed by multidisciplinary team: cardiologist for heart monitor, physiotherapist for rehabilitation and geneticist for prenatal counseling.

The prognosis is mainly determined by cardiac complications (e.g. severity of cardiomyopathy, arrhythmias). In general, long-term prognosis of LS patients is favourable.

DISCUSSION

The patient was clinically and genetic diagnosis of LEOPARD Syndrome .There are about 85% of the patients with a definite diagnosis of LS, a missense mutation is found in the PTPN11 gene [5]. Eleven different missense PTPN11 mutations have been reported so far in LS, 2 of which (Tyr279Cys and Thr468Met) occur in about 65% of the cases [2]. PTPN11 mutations could occur in several types of hematologic malignancies, most notably juvenile myelomonocytic leukemia. Most cases have deafness diagnosed at birth or childhood, but some are report to have developed it in adult life [2].

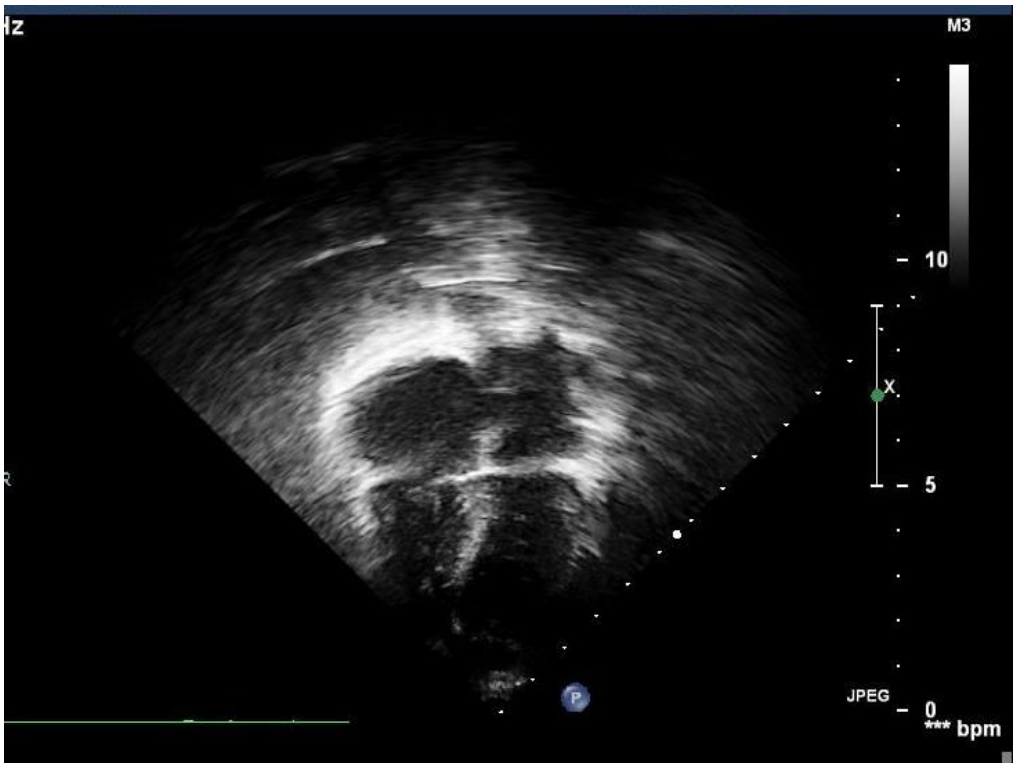

Figure 4: Image of echocardiography shown Atrial Septal Defect (ASD).

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