LEOPARD SYNDROME

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ABSTRACT

The LEOPARD syndrome is a dysmorphogenetic and multisystem cardio-cutaneous syndrome.

A 32-year-old female is presented with multiple lentigines, hypertrophic obstructive cardiomyopathia (HOCM), right bundle branch block, mitral valve stenosis and insufficiency, scoliosis, ocular hypertelorism, gynocologic pathologies and iron deficiency anemia. Hyperthrophic cardiomyopathy was treated by septal ablation two years ago. Hyperthrophic cardiomyopathy was also diagnosed in her sister without lentigines and there was no family history of LEOPARD syndrome in the family. Patients with lentiginous lesions must be considered for systemic disease and should be investigated for cardiac disorders.

• ***Key Words:*** *LEOPARD syndrome, lentigine, hypertelorism, hypertrophic cardiomyopathy.* ***Nobel Med 2007; 3(3): 35-38***

ÖZET

LEOPARD SENDROMU

LEOPARD sendromu dismorfogenetik ve multisistemik kardiyokütanöz bir sendromdur. Aşağıda sunulan 32 yaşında kadın hasta multipl lentiginler, hipertrofik obstrüktif kardiyomiyopati (HOKM), sağ dal bloku, mitral kapak hastalığı, skolyoz, oküler hipertelorizm, jinekolojik patolojiler ve demir eksikliği anemisi tanıları ile izlenmiştir. İki yıl önce hipertrofik kardiyomiyopati için septal ablasyon tedavisi uygulanmıştır. Bir kız kardeşinde de HOKM tanısı konmuş ancak lentiginlere rastlanmamıştır. Ailede başka LEOPARD sendromu tanısı konan hasta yoktu.

Multipl lentiginleri bulunan hastalar, sistemik lezyonlar ve özellikle kalp hastalıkları açısından araştırılmalıdır.

• **Anahtar Kelimeler:** Leopard sendromu, lentigin, hipertelorizm, hipertrofik kardiyomiyopati. **Nobel Med 2007; 3(3): 35-38**

INTRODUCTION

LEOPARD syndrome (LS) was first defined by Moynahan in 1962. Gorlin proposed the acronym LEOPARD. It was called using the first letters of the findings (**L**entigines, **E**lectrocardiographic abnormalities, **O**cular hypertelorism, **P**ulmonary stenosis, **A**bnormal genitalia, **R**etardation of growth and **D**eafness) and later "café au lait macules" was added.[1,2] Synonym for this disorder include multiple lentigines syndrome, generalized lentiginosis, cardiocutaneous syndrome, lentiginosis profusa syndrome, Moynahan syndrome, spotting heart disease, lentiginocardiomyopathic syndrome and progressive cardiomyopathic lentiginosis syndrome.[1]

CASE REPORT

A 32-year-old woman referred to emergency department with dyspnea and palpitation. She had undergone coronary angiography and catheterization two years ago. Her coronary arteries were normal, but hypertrophic obstructive cardiomyopathia (HOCM) was detected and septal ablation was performed. She was very weak and pale with short stature. Her height was 140 cm and weight was 38 kg.

Dermatological examination revealed hundreds of dark brown, irregular shaped, 2-5 mm in size macules (lentigines) on whole body, especially on sun exposed area, in her face and neck. Melanocytic nevi, dermal nevi, spitz nevi, a nevus spillus on her lumber area; a few spots of café-au-lait on her legs and seborrheic keratoses were seen (Fig 1-2). She expressed that lentigines increased in size and number with age.

Examination of the cardio-respiratory system revealed fine crackles at bases of both lungs. A third grade murmur was heard on cardiac auscultation at the left sternal border and on other cardiac foci. Spleen was palpable 2 cm under the left costal margin. Electrocardiography showed sinus rhythm, q wave on D_1-aVL, negative T waves on V_{1-2} and right bundle branch block. Echocardiogram revealed HOCM (left ventricular outlet gradient was 100/55 mmHg) and moderate to severe mitral valve insufficiency. Mitral margins were fibrotic, and systolic anterior motion (SAM) of anterior leaflet was observed. Left atrium was enlarged and she also had pulmonary hypertension.

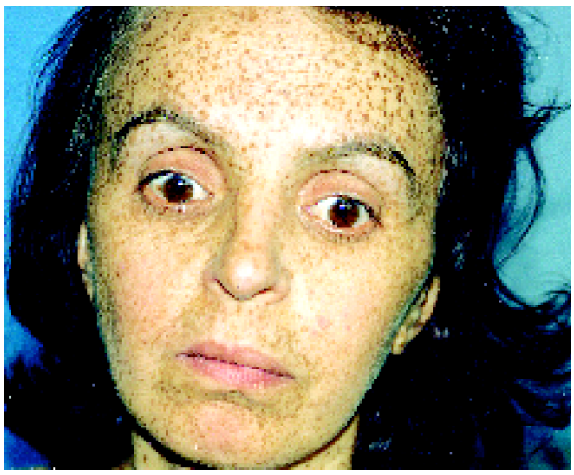

Figure 1: Multiple lentigines on the face and hypertelorism.

Hypertelorism and nevic pigmentation on sclera were pertinent findings in eye. There was a remarkable asymmetry on her face. She had also scoliosis accompanied by a right scapular protuberance that resembled a bird's wing. Auditory system, neurological examination and cranial CT were normal. Gynecological examination revealed an enlarged uterus and bilateral ovarian cysts.

When her family members were screened, hyperthyroidism was found in one sister and HOCM in another. There was no family history of lentigines.

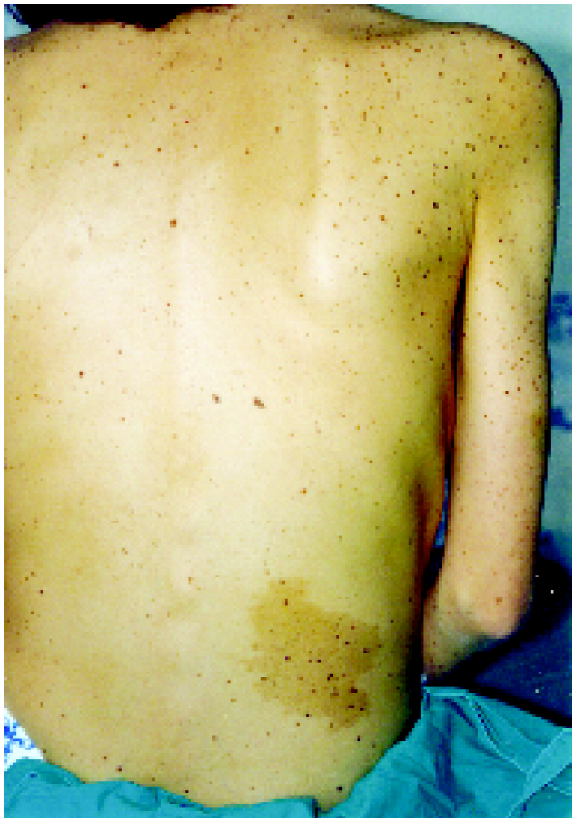

Figure 2: Multiple lentigines and café-au-lait macule on the back.

Hypochromia and microcytosis were detected on blood film. The laboratory tests were as follows: Hemoglobin: 4.5 gr/dl, hematocrit: 16.6%, MCV: 62.6 fL, serum iron: 20 µg/dl, total iron binding capacity: 370 µg/dl, ferritin: 110 ng/dl. Serum T3, T4 and TSH levels were 2.77ng/ml, 15.8 ng/ml and 0.13 µIU/ml respectively.

Our case exhibited multiple lentigines, nevi, HOC, ECG abnormalities, hyperthyroidism, short stature, skeletal abnormalities, uterine and ovarian pathologies, cephalofascial anomalies including ocular hypertelorism. Anemia was explained by hypermenorrhea. Iron replacement therapy was planned. Propylthiouracil, beta receptor blocker and diuretic treatment were prescribed. When Hb and Hct level increased to 9.5 g and 29.2%, dyspnea and palpitation improved.

DISCUSSION

Voron proposed the diagnostic criteria for LS. Apart from lentigines, they grouped the features of the syndrome into nine categories: other cutaneous abnormalities, cardiac, electrocardiographic, genitourinary, endocrine abnormalities, neurologic deficits, cephalofacial dysmorphism, short stature and skeletal abnormalities. Multiple lentigines and at least two other categories must be present for definite diagnosis of LS. If lentigines are absent, at least three other categories and first degree member of family with lentigines are needed for the diagnosis.[3]

Features of LS may be seen either at birth or can develop later during childhood. The diagnosis of LS in the first months of age can be clinically suspected in patients presenting with three main features, that is, characteristic facial features (100%), hypertrophic cardiomyopathy (HCM) (87%), and café-au-lait spots (75%). Characteristic facial features can be mild or severe, and consist of hypertelorism, downslanting palpebral fissures, ptosis, and dysmorphic ears. Digilio claims that LS should be suspected when the baby has at least three of the following clinical criteria: congenital heart defect (CHD), café-au-lait spots, sensorineural deafness, hypotonia or delayed motor development, distinct facial anomalies or one parent affected by LS. Café-au-lait spots can be helpful in diagnosing LS in the first year of life. HOCM and café-au-lait spots are found with a higher prevalence in young patients with LS.[4]

In our case multiple lentigines, ephelids, seborrheic keratoses, café-au-lait macules, nevus spilus, dermal and melanocytic nevus, pigmented lesion on sclera, ocular hypertelorism, fascial asymmetry, short stature, scoliosis, bird wing scapula, cardiac abnormalities (HOCM, mitral insufficiency, pulmonary hypertension, ECG abnormalities), genital abnormalities (enlarged uterus, ovarian cysts, small breasts), and hyperthyroidism as an endocrinological abnormality were observed.

She did not have all of the features of the syndrome but most patients with LS have only three to five of the diagnostic findings.LS should differentiate from LAMB syndrome (**L**entigines, **A**trial myxoma, **M**ucocutaneous myxoma and **B**lue nevus) and NAME syndrome (**N**evus, **A**trial myxoma, **M**yxoid neurofibroma, and **E**phelid), Noonan Syndrome (NS), centrofascial lentiginosis, Albright syndrome, Carney syndrome.[1,5] The skin may distinguish LS from NS in classic cases when multiple lentigines are present.[6] However, lentigines are rare at birth and, classically, develop during childhood, increasing in number until puberty and hyperpigmentation increases with age.[3,6,7] Café-au-lait spots precede appearance of the lentigines. They are present in the first months of age in about 75% of the patients.[6]

LS is an autosomal dominant disorder with high penetrance and variable expressivity. Molecular studies have shown that LS are caused by mutations in PTPN11 gene which encodes for the protein tyrosine phosphatase SHP-2.[5] It is observed in about 90% of patients. Seven different mutations have been identified in exons 7 and 12, which are present in 86% of the cases, and exon 13. The clinical spectrum associated with PTPN11

mutations was markedly variable, with no pathognomonic feature. Common clinical features include multiple lentigines (86%), facial dysmorphisms (90%), congenital heart defects (71%; which 80% of these were HOCM), and sensorineural deafness (25%). No obvious clinical difference was seen between patients with different mutations, except for bilateral deafness.[5]

Our case did not have a family history of LS but her sister had HOCM without lentigines and other phenotypic anomalies of LS. Similar cases were also reported by Sarkozy and Digilio.[4-6]

Electrocardiographic abnormalities, especially left axis deviation, prolonged PR interval and RBBB may be found frequently in these patients, reflecting the underlying cardiac anomalies. HOCM (47-87%) and congenital heart disease (70-100%), the most prevalent heart defect in patients with mutations, should be searched for in otherwise asymptomatic individuals.[4,5,8] HOCM, which is reported about 80%[6,7] is the most serious cardiac finding in patients with LS.[9,10] Our case had also underwent septal ablation for septal hypertrophy.

Multiple lentigines and pigmented macules may represent an undiagnosed lentiginous syndrome or in existence of HOCM, all patients should be examined for multiple lentigines, which may reflect a possible cardio-cutaneous syndrome.

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