DÜZCE TIP DERGİSİ
DUZCE MEDICAL JOURNAL

CASE REPORT / OLGU SUNUMU

[1] Ali KUTLUCAN

[2] Seyit Ali KÖSE

[2] Ahmet KARATAŞ

[3] Leyla Yılmaz AYDIN

[1] Hülya COŞKUN

[2] Müşerref ERKAN

[1] Seher KIR

[4] Hakan TURAN

[1] Duzce Unıversity Faculty of Medicine, Internal Medicine Department. Duzce

[2] Duzce Unıversity Faculty of Medicine, Obstretric and Gynecology Department. Duzce

[3] Duzce Unıversity Faculty of Medicine, Chest Disease Department. Duzce

[4] Duzce Unıversity Faculty of Medicine, Dermatology Department. Duzce

Submitted/Başvuru tarihi:
19. 12. 2011
Accepted/Kabul tarihi:
17. 09. 2012
Registration/Kayıt no:
11 12 175

Corresponding Address /Yazışma Adresi:

Dr. Ali Kutlucan, MD
Duzce University, Department of Internal Medicine Faculty of Medicine, Duzce, Turkey
E Mail:
dralikutlucan@gmail.com

e-ISSN 1307- 671X
www.tipdergi.duzce.edu.tr
duzcetipdergisi@duzce.edu.tr

Leopard Syndrome Presented With Hemolytic Anemia, Total Genital Prolapse And Ovarian Agenesis

Hemolitik Anemi, Total Genital Prolapsus Ve Ovaryen Agenezili Leopard Sendromu Olgusu

ABSTRACT
The LEOPARD syndrome is a rare autosomal dominant, multisystemic disease characterised by multiple lentigines, electrocardiographic conduction defects, ocular hypertelorism, pulmonary stenosis, abnormalities of genitalia, retardation of growth and sensorineural deafness. Most of the cases were reported during their childhood or young adulthood and they usually presented with cardiac anomalies and lentigines. In our case, portal hypertension depending on cardiac anomaly developed at the time of hospital admission because of the late diagnosis of leopard syndrome. Also diffuse ascites caused by portal hypertension and hemolytic anemia caused by massive splenomegaly developed at the time of diagnosis. There was not a genital operation history but ovarian agenesis and genital prolapse were detected. As the diagnosis was established at advanced age, this case was presented with the pulmonary stenosis complications and ovarian agenesis which were not reported before in literature.
Key Words: Leopard syndrome, Ovarian agenesis, Hemolytic anemia

ÖZET
Leopard sendromu, multipl lentigolar, elektrokardiyografik iletim kusurları, gözde hipertelorizm, pulmoner stenoz, genital anormallikler, büyüme geriliği ve sensorinöral sağırlıkla seyreden otozomal dominant geçiş gösteren nadir, multisistemik bir hastalıktır. Çoğu vaka çocukluk ve ergenlik döneminde bildirilmiş olup, genellikle kalp anormallikleri ve lentigolar şeklinde sunulmuştur. Bizim vakamız ise kardiyak anomaliye bağlı portal hipertansiyon gelişmesi sonucu ileri yaşta tanı almıştır. Ayrıca yatışı sırasında, portal hipertansiyonun neden olduğu diffüz asit, masif splenomegalinin neden olduğu hemolitik anemi saptanmıştır. Olguda genital operasyon öyküsü olmamasına rağmen, ovaryen agenezi ve genital prolapsus tesbit edilmiştir. İleri yaşta tanısı konulan, pulmoner stenoz komplikasyonları gelişmiş olup ovaryen agenezi olan böyle bir vaka, literatürde daha önceden bildirilmemiştir.
Anahtar Kelimeler: Leopard Sendromu, Ovaryen Agenezi, Hemolitik Anemi

INTRODUCTION

Multiple lentigines Leopard Syndrome (LS) is an autosomal dominant multiple congenital anomaly syndrome with high penetrance and markedly variable expression (1). The acronym LEOPARD was named to recall the syndrome: lentigines; electrocardiographic conduction abnormalities; ocular hypertelorism; pulmonary stenosis (PS); genital abnormalities; growth retardation and sensorineural deafness (2). Approximately 200 patients have been reported worldwide but the real incidence of LS has not been assessed (3). Patients do not usually present with all clinical features traditionally associated with this syndrome. Diagnosis of LS may be established exclusively on the basis of clinical criteria (4). Herein we present a case of Leopard Syndrome accompanied with anemia, pleural effusion, total genital prolapse and ovarian agenesis whom was diagnosed at advanced age.

CASE REPORT

A 55-year-old woman whom had been planned to be operated for total genital prolapse, was further evaluated for complaints of fatigue and shortness of breath. There were small, round dark brown lentigines, which were not elevated from the skin especially on the upper parts of her body (Figure 1, 2).

She had pale conjunctivas and icteric scleras. Breath sounds were found to be decreased in the middle and lower zones of the right lung. Cardiac sounds were arrhythmic and there was 3/6 systolic murmur in apex. Spleen was palpated 8 cm under the costa. IQ test of the patient who had mental retardation was reported as 50. Laboratory results of the patient are presented in Table 1. There was atrial fibrillation in the electrocardiography and she had submassive pleural effusion in the right lung on chest radiography. In her peripheral blood smear examination, there was hemolytic findings and her reticulocyte count was found to be 3,5 %. Direct-indirect coombs tests of the patient, whose haptoglobin level was low, were founded to be negative. The osmotic fragility test and hemoglobin electrophoresis were also normal. In her abdominal ultrasonography (USG), there was splenomegaly and dilatation in intrahepatic veins. Portal vein doppler USG; portal vein diameter was found to be increased. In hre echocardiography, moderate mitral insufficiency and advanced tricuspid insufficiency were detected. Ejection fraction was found to be 55% and pulmonary artery pressure was 105 mmHg. In thoracic computed tomography, 4.5 cm sized pleural effusion and adjacent atelectasis were found in the right lung. Pleural effusion was transudative. Erythrocyte transfusion and therapeutic thoracentesis were performed in order to relieve the symptoms of the patient. In audiogram, hearing loss was detected in the left ear. In her trans-vaginal USG who had total genital prolapse and had not genital operation history, bilateral ovaries weren't observed in their normal localization. Since the presence of clinical findings such as lentigos on the whole body, electrocardiographic anomaly, pulmonary stenosis, genital anomaly, deafness, mental and motor retardation all-together, the patient was diagnosed as the Leopard Syndrome.

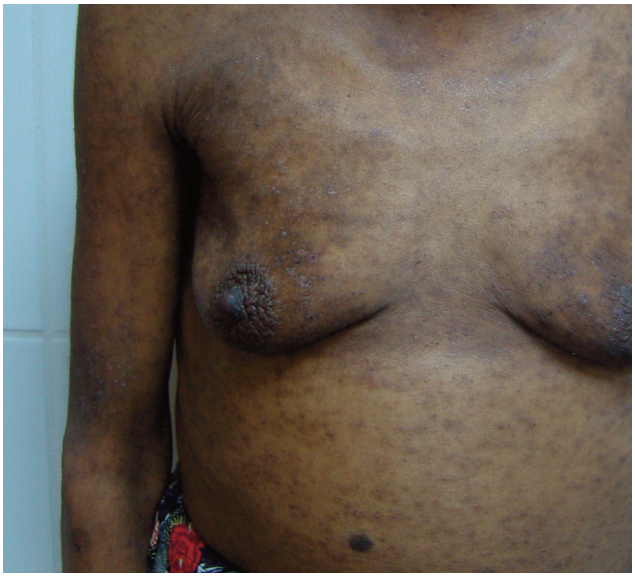

Figure 1: Multiple lentigines (front)

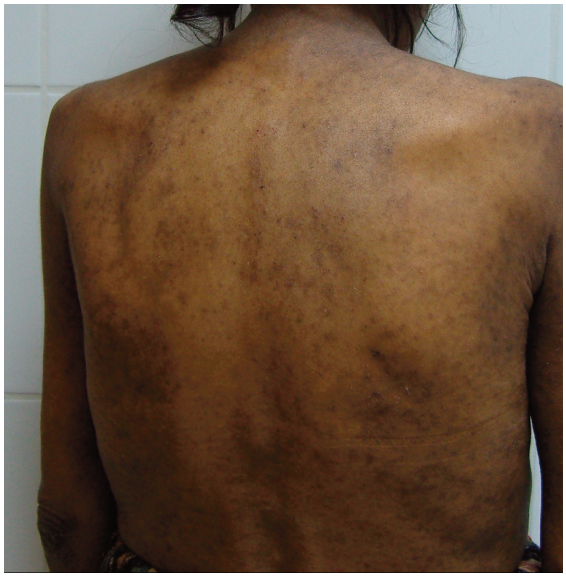

Figure 2: Multiple lentigines (back)

DISCUSSION

Multiple lentigines syndrome was named as Leopard syndrome by Gorlin, Anderson and Blaw in 1969. It is a rare disease and affects males and females, equally. It's pathogenesis is still unknown (5). The most plausible explanation for the pathogenesis of the syndrome is an abnormality of the neural crest cell. The cells derived from the neural crest form spinal and autonomic ganglion cells. Neural crest cells also give rise to melanocytes, thereby explaining the associated lentigines (6). The underlying genetic defect associated with the development of the syndrome has been located on chromosome 12 (gene map locus 12q24.1), and the responsible gene is PTPN11 (protein tyrosine phosphatize non-receptor type 11), which codes for non-receptor protein tyrosine phosphatize, SHP2 (7).

In literature, we mostly encounter cardiac involvement and lentigos in leopard syndrome cases. A French multicenter study pooled 30 cases, among which 28 had lentiginosis which Sarkozy et al. (1) reported. Our case also had lentigos especially on the upper parts of the body. Electrocardiographic conduction abnormalities and PS were the two major criteria proposed by Gorlin et al. (8) Sarkozy et al. (1) reported 30 cases in which there were two cases with arrhythmia, three with PS, and 14 with hypertrophic cardiomyopathy. Atrial fibrillation, ventricular dilatation and infective endocarditis (in the

Table 1: Laboratory values of the patient

		Patient's values	Normal values
White Blood Call (WBC)	(/mm3)	8160	5200-12400
Hemoglobin	(gr/dl)	9.6	12-16
Platelet	(/UL)	272.000	150.000-450.000
Creatinine	(mg/dl)	0.58	0.7-1.3
Alanine Transaminase (ALT)	(IU/L)	6	0-55
Aspartate Transaminase (AST)	(IU/L)	22	5-34
Gamma-glutamyl transferase (GGT)	(IU/L)	19	9-36
Alkaline phosphatase	(IU/L)	62	40-150
Albumin	(g/dl)	3.7	3.5-5
Total bilirubin/Indirect bilirubin	(mg/dl)	4.2 / 3.5	0.2 -1.2
Iron	(µg/dl)	43	25-156
Ferritin	(ng/ml)	149	15-150
Vitamin B12	(pg/ml)	332	193-982
Folate	(ng/ml)	7.32	3-17
Hbs Ag		Negative	
Anti-HBs		Negative	
Anti-HCV		Negative	
Anti-nuclear antibody		Negative	
Anti-mitochondrial antibody		Negative	
Liver-kidney microsomal antibody		Negative	

obstructive form when prophylaxis is mandatory) are common complications as disease develops (9). There were also atrial fibrillation and PS in our case. Sensorineural hearing loss has been documented in about 25% of patients with LS (2). Colomb and Morel et al. (10) reported mental retardation in 35% of cases. Sarkozy et al. (1) reviewed 30 cases and eight had mental retardation. Genital abnormalities include hypospadias and cryptorchidism (10). In 1984, Colomb et al. (11) reviewed 38 cases and found that 29% had abnormal genitalia (males). There was ovarian agenesis in our case but it has not been reported in literature before.

Leopard Syndrome is a rare disease that there had been a total 200 cases reported in literature before (3). Majority of the reported cases include the patients in childhood or young adulthood and they are generally presented with cardiac anomalies. Since our case was diagnosed at an advanced age, portal hypertension was detected depending on cardiac anomaly. She had also diffuse ascites and hemolytic anemia at the time of diagnosis. While genital anomalies are mostly seen in males in the form of hypospadias and cryptorchism, in our case ovarian agenesis and genital prolapse were detected without a history of genital operation. Since the diagnosis was established at advanced age, this case was presented with the PS complications and ovarian agenesis which were not reported before in literature.

REFERENCES

1. Sarkozy A, Conti E, Digillio MC, et al. Clinical and molecular analysis of 30 patients with multiple lentigines LEOPARD syndrome. J Med Genet. 2004;41:68.
2. Voron DA, Hatfield HH, Kalkhoff RK. Multiple lentigines syndrome. Case report and review of the literature. Am J Med. 1976;60:447–56.
3. Sarkozy A, Digiolio MC, Dallapiccola B. Leopard Syndrome: Orphanet J Rare Dis. 2008;3:13.
4. Porciello R, Divona L, Strano S, Carbone A, Calvieri C, Giustini S. Leopard Syndrome. Dermatol Online J. 2008;14:7.
5. Cerqueira RS, Romiti AR, Belda Jr W, Oliveira ZNP, Machado MCR, Romiti R. Você conhece esta síndrome? An Bras Dermatol. 2006;81:599-601.
6. Adriaenssens T, Ibrahim T, Seyfarth M. The LEOPARD syndrome: a rare condition associated with hypertrophic cardiomyopathy. Eur Heart J. 2007;28:3066.
7. Keren B, Hadchouel A, Saba S, et al. PTPN11 mutations in patients with LEOPARD syndrome: a French multicentric experience. J Med Genet. 2004;41:117.
8. Gorlin RJ, Cohen MM, Hennekam RCM. Syndromes of the Head and Neck. 4th ed. New York: Oxford University Press; 2001.
9. Antunes Mde O, Arteaga E, Matsumoto AY, Ianni BM. Leopard Syndrome and Hypertrophic Cardiomyopathy: an Association Related to Sudden Death. Arq Bras Cardiol. 2009;92:e44-6,e71-73.
10. Chong WS, Klanwarin W, Giam YC. Generalized lentiginosis in two children lacking systemic associations: case report and review of the literature. Pediatr Dermatol. 2004;21:139–45.
11. Colomb D, Morel JP. Multiple lentigines syndrome. Apropos of 2 cases. Critical study of the leopard syndrome. Ann Dermatol Venereol. 1984;111:371–81.