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Photo vignette

LEOPARD Syndrome

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Abstract

LEOPARD syndrome (LS) is an autosomal dominantly inherited or sporadic disorder of variable penetrance and expressivity. The acronym LEOPARD stands for its cardinal clinical features including Lentigines, Electrocardiographic conduction abnormalities, Ocular hypertelorism, Pulmonary stenosis, Abnormalities of genitalia, Retardation of growth, and Deafness. We present herein a patient with LEOPARD syndrome and distinctive features. It was noteworthy that our patient presented with the concern of generalized lentiginosis and subsequent evaluation revealed that the patient had LEOPARD syndrome. In this report we would like to highlight the importance of detailed clinical examination and appropriate imaging in patients with multiple lentigines.

Case synopsis

A 22-year-old woman presented to us for the evaluation of numerous flat brown to black-colored macules (lentigines and café au lait macules) on the face, neck, torso, and limbs (Figure. 1 and 2). There were no systemic symptoms and her family history was non-contributory. Except a left parasternal impulse, a grade 3/6 systolic murmur at the pulmonary area, and soft pulmonary component of the second heart sound, physical examination was non-contributory. An ECG showed sinus rhythm, right ventricular hypertrophy, right axis deviation, and QTc prolongation (Figure 3). Transthoracic echocardiography showed right ventricular hypertrophy with mildly dilated right atrium and right ventricle and severe valvular pulmonary stenosis (Figure 4). The patient also had ocular hyperteleorism, broad nasal root, sensory neural deafness, and short stature. Ultrasonography of the abdomen detected polycystic ovaries. Based on the clinical features and imaging, a diagnosis of LEOPARD syndrome (LS) was made in the present case.

Her chromosomal study was normal. Skin biopsy specimen showed features suggestive of lentigo simplex (Figure 5). She underwent balloon pulmonary valvuloplasty successfully.

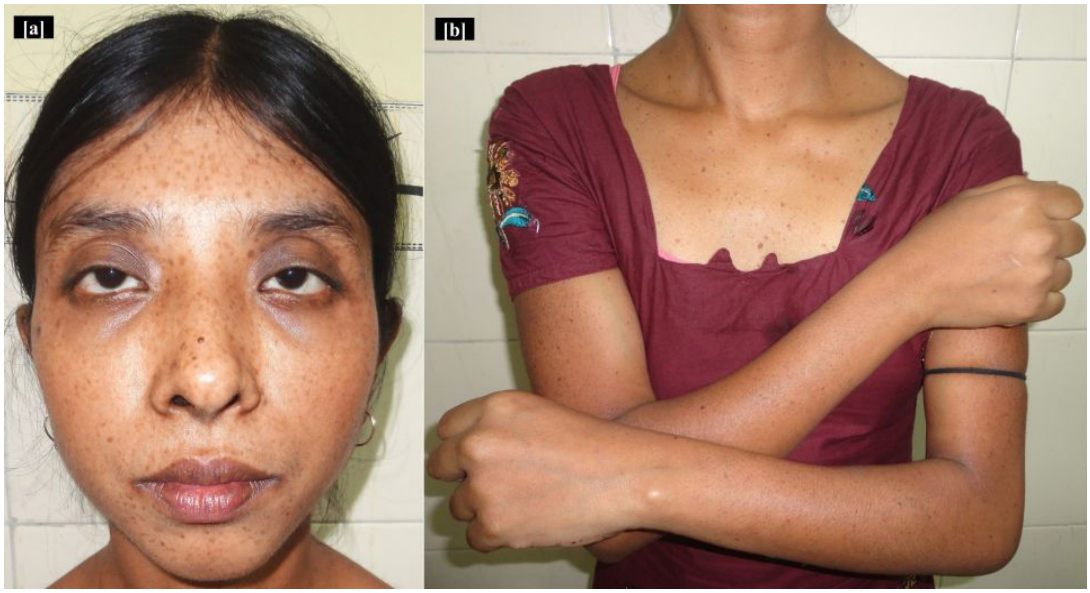


Figure 1. [a] Multiple lentigines on face along with hypertelorism and broad nasal root. [b] Multiple lentigines on upper chest, neck, and upper limbs.

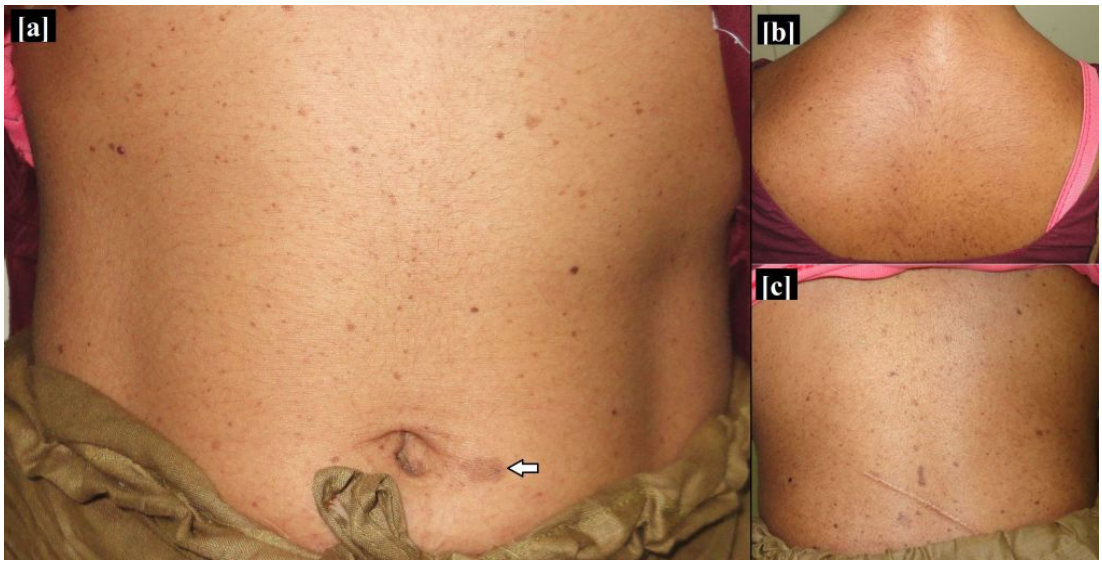


Figure 2. [a,b,c] Multiple lentigines and Café au lait macules (marked by arrow) on different parts of body

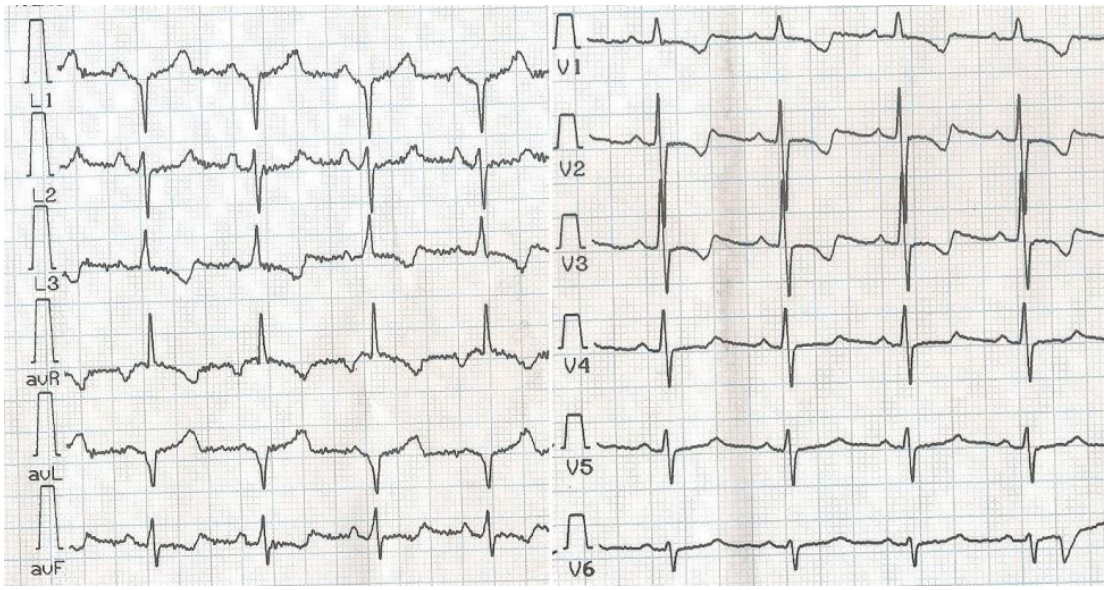
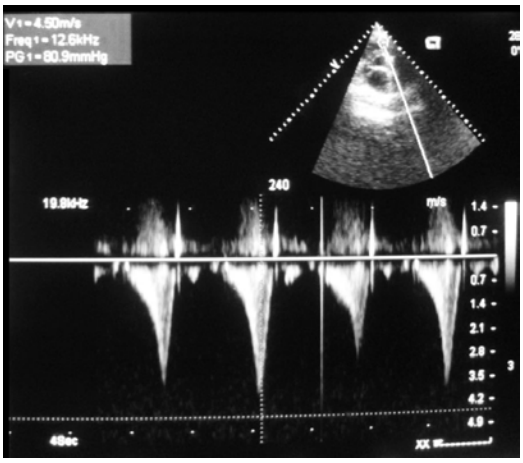


Figure 3. Electrocardiogram showing normal sinus rhythm with right ventricular hypertrophyand right axis deviation.



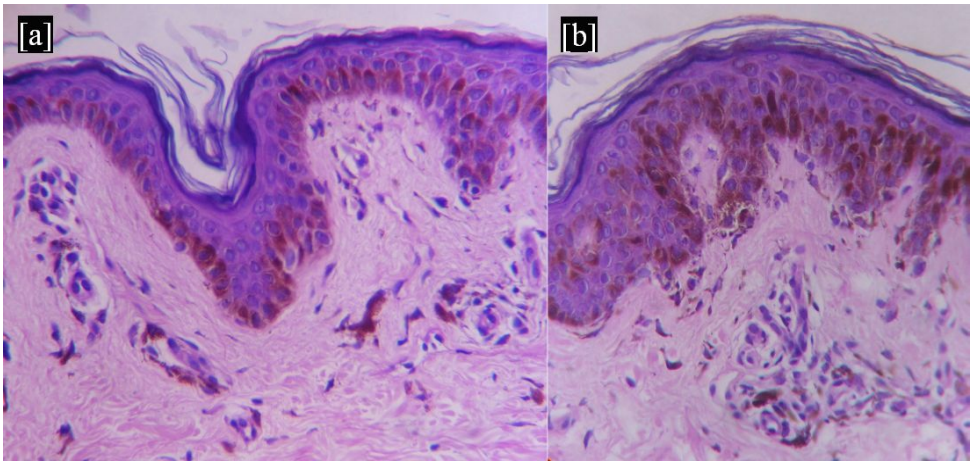


Figure 4. Continuous wave doppler showing peak systolic gradient of 80.9 mm Hg across pulmonary valve, suggestive of severe pulmonary stenosis. **Figure 5.** [a and b] Histopathological features of lentigo simplex (H and E, x 100)

Discussion

LEOPARD syndrome, synonymously known as multiple lentigines syndrome, is an autosomal dominantly inherited or sporadic disorder of variable penetrance and expressivity [1, 2,3]. The acronym LEOPARD stands for its cardinal clinical features including Lentigines, Electrocardiographic conduction abnormalities, Ocular hypertelorism, Pulmonary stenosis, Abnormalities of genitalia, Retardation of growth, and Deafness [1, 2, 3].

Café au lait macules are observed in approximately 50% of the affected individuals with LS [1]. Approximately 70%-85% of affected individuals have heart defects including hypertrophic cardiomyopathy (up to 70% of individuals with heart defects), pulmonary valve stenosis (approximately 25% of affected individuals), and rarely abnormalities of the aortic and mitral valves [1, 2]. ECG abnormalities, in addition to those typically associated with hypertrophic cardiomyopathy, include prolonged QTc (23%) and repolarisation abnormalities (42%), conduction defects (23%), and p wave abnormalities (19%) [1,2].

The features of facial dysmorphism comprise inverted triangular-shaped face, downslanting palpebral fissures, low-set posteriorly rotated ears with thickened over-folded helices, and hyperteleorism [1, 2]. Sensorineural hearing deficits are present in approximately 15-25% of persons with LS [1, 2].

Postnatal growth retardation resulting in short stature, intellectual disability, cryptorchidism, hypospadias, urinary tract defects, and ovarian abnormalities are also observed rarely [1, 2]. The diagnosis of LEOPARD syndrome is essentially clinical [3]. Voron et al proposed the diagnostic criteria, which consists of the presence of multiple lentigines plus two of the other cardinal features. Alternatively, in the absence of lentigines, three of the other cardinal features plus a first-degree relative with this syndrome is accepted [4]. PTPN11, RAF1, and BRAF are the genes known to be associated with LS [2]. The treatment of this condition depends on the type and extent of organ involvement. It is worth mentioning that our patient presented with generalized lentiginosis and subsequent evaluation revealed the presence of several features of LEOPARDsyndrome. Generalized lentigines are also the commonest presenting feature of Carney complex [5], which is characterized by skin pigmentary abnormalities, myxomas, endocrine tumors or overactivity, and schwannomas. Hence, in this report we would like to emphasize the importance of detailed clinical evaluation and appropriate imaging in patients with multiple lentigines. In patients with LEOPARD syndrome, one needs to work them up properly for all the concerning features including pulmonary valve abnormalities even when the patients appear asymptomatic.

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