A rare cause of dyspnoea: the LEOPARD syndrome
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Abstract
The LEOPARD syndrome is a rare hereditary disorder in Asian countries. This syndrome involves complex malformations and other features. Though the LEOPARD syndrome is rare, diagnosis is important since it can be related with serious cardiac ailments. Patients must be followed up regularly in order to reduce the risk of sudden death which is the most severe complication. The study presents the case of a 23-year-old woman who had dyspnoea on daily exercises. She had multiple lentigines, cardiac anomalies (apical hypertrophic cardiomyopathy, left ventricular hypertrophy and pulmonary stenosis), ocular hypertelorism and abnormal electrocardiographic findings. Based on the findings, the patient was diagnosed with the LEOPARD syndrome.

Keywords: LEOPARD syndrome, Multiple lentigines, Cardiac anomalies.

Introduction
LEOPARD syndrome (LS), also known as the cardiocutaneous syndrome, is a rare multi-systemic autosomal disease. LEOPARD is a mnemonic rule for multiple ‘Lentigines,’ ‘Electrocardiographic’ conduction abnormalities, ‘Ocular’ hypertelorism, ‘Pulmonary’ stenosis (PS), genital and reproductive ‘Abnormalities,’ ‘Retarded’ growth and ‘Deafness.’

Hypertrophic cardiomyopathy, though not included in mnemonic, is often associated with the signs and symptoms generally experienced by people with the syndrome. Some patients may have a partial form of the syndrome and may suffer mild symptoms, while others with the full-blown syndrome are more severely affected. If this syndrome is diagnosed, sudden death and mortal tachycardia risks can be reduced through regular follow-ups.

Case Report
A 23-year-old female patient presented to the emergency room (ER), with dyspnoea. The condition (New York Heart Association Class II) became apparent during the daily activities, but no chest pain or syncope was accompanying it.

The patient was conscious, well-oriented and cooperative. Her arterial blood pressure was 90/60mmHg, heart rate 50/min and the respiratory rate was 17/min. Numerous dark brown lentigines with irregular borders and measuring 2-5mm in size were visible on the patient’s face and body, focussing primarily on the areas exposed to sunlight (Figure-1). She had no growth retardation and her weight and height were average (165cm, 62kg) for her age. During her cardiac examination, a systolic murmur radiating along the left side of the sternum was detected. Pulmonary auscultation revealed rales in the basal parts bilaterally. Traube’s space was clear and the abdominal examination was normal, and she had ocular hypertelorism. Her electrocardiography (ECG) revealed widespread T-negativity (Figure-2) and her dyspnoea ameliorated after the administration of parenteral

Figure-1: Lentigies.
diuretics. During her ECG examination, a distinct hypertrophy in the apical area (apical thickness 18mm) and a mild pulmonary stenosis were observed. The ejection fraction (EF) was adequate (Figure-3). No peculiarities were found in the other systemic examinations and laboratory tests were within normal limits. The triphasic computed tomography scan of the abdomen and pelvis did not reveal any pathology. No abnormalities were found in the patient’s genitourinary examination or hearing tests. She was placed under observation and oxygen therapy was given to her in the ER and 40mg intravenous furosemide was applied. Since her dyspnoea had disappeared, she was discharged from hospital and taken under follow-up. Based on the findings at hand, the patient was diagnosed with the LEOPARD syndrome. When the family history was evaluated, no findings were observed in her parents or sisters pointing to the syndrome.

Discussion

LS is a rare hereditary disorder characterised by the anomalies of the skin, inner ear, head and face (craniofacial) area, cardiac structures and function and/or the genitalia. The frequency and severity of the symptoms as well as the physical features may vary in patients. The acronym ‘LEOPARD’ signifies the characteristic anomalies related to the disorder: Lentigines, black or brown ‘freckle-like’ spots on the skin (liver spots); Electrocardiographic conduction defects pointing out electrical anomalies of the heart; Ocular hypertelorism describing wide-set eyes; Pulmonary stenosis indicating an obstruction of blood flow from the right ventricle; Anomalies of the genitalia; Retarded growth leading to short stature; and hearing loss or Deafness due to the malfunction of the inner ear. Some individuals may show mild mental retardation, speech disorders and/or additional physical anomalies. The disorder is believed to show an autosomal dominant hereditary character. Not all diagnostic traits may be observed in all the patients, therefore, studies have reorganised the diagnostic criteria. According to the new classification, the anomalies are organised in 9 categories: the lentigines, cardiac anomalies, abnormal ECG findings, genitourinary anomalies, endocrine pathologies, neurological deficits, cephalofacial dysmorphism, short stature and skeletal anomalies. In addition to the multiple lentigines, the presence of 2 out of the above-listed anomalies is sufficient for diagnosis. If no lentigo is present, findings from at least 3 categories must be present and a first-degree relative of the patient must have lentigines. In our patient, abnormal ECG findings, cardiac anomalies and ocular hypertelorism were observed in addition to multiple lentigines.

It has been suggested in previous studies that the appearance of multiple lentigines coincides with the left ventricular hypertrophy (LVH). Lentigines are flat, black-brown macules, dispersed mostly on the face, neck, and upper part of the trunk. In general, lentigines appear at 4–5 years and increase into thousands until puberty, independent from sun exposure. Lentigines are characterised by pigment accumulation in the dermis and deeper epidermal layers, with increased number of melanocytes per unit skin area. Our patient had the same history about her lentigines.

ECG anomalies are observed in approximately 75% of the patients with LS and 46% of the patients have either left ventricular or biventricular hypertrophy. The most frequent ECG anomalies include prolonged QTc interval, re-polarisation anomalies and q-wave anomalies. In our patient, widespread T-negativity was detected. Cardiac involvement in patients with LS is usually characterised by LVH, PS, and ECG anomalies. Cardiac anomalies observed are similar to the Noonan syndrome, but an accurate diagnosis can be reached with careful investigation. Research on LS has revealed that the most commonly observed cardiac anomaly is LVH. Asymmetrical LVH is observed much more commonly.
than apical hypertrophy. In 30% of the patients, right ventricular hypertrophy (RVH) may accompany LVH and PS.\(^8\) In our patient (with asymmetrical hypertrophy), apical hypertrophy was present. This hypertrophy observed in patients with LS is a primary myocardial disease and can be classified as cardiomyopathy. This important condition is associated with significant mortality and these patients are under the risk of arrhythmia, and sudden death is observed in hypertrophic cardiomyopathies. Hypertrophic cardiomyopathy may be related to rare disorders like the LS or to various other congenital malformations.\(^9\) PS is observed less frequently than LVH and has been reported in approximately 40% of the patients.\(^10\) We also observed it in our patient.

Patients must be followed up regularly in order to reduce the risk of ‘sudden death’ which is the most severe complication. In some patients in whom ventricular tachycardia has developed, tachyarrhythmias have been reported to be taken under control through international classification of disease (ICD) and medical treatment.\(^10\) In our case, the patient was diagnosed for hypertrophic cardiomyopathy and she was using a 50mg daily course of metoprolol and no tachyarrhythmias were observed in her follow-up.

**Conclusion**

As soon as a lentigo is detected, the physician should think of LS and make proper cardiac assessment. Cardiac disease can be progressive, and is associated with bad prognosis. Thus, patients should be evaluated regularly. This case illustrates many of the classical findings in this syndrome and highlights the need to be alert to the possibility of cardiac abnormalities.

**References**