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IMAGING CASES

Dermatology clinical case

Caso clínico dermatológico

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A 14-year-old male patient was referred to the Pediatric Endocrinology Clinic due to short stature and alopecia. He had apparently normal phenotype until the age of four years, with progressive onset of alopecia and multiple lentigines. The boy had a family history of hypoacusia and multiple lentigines in the mother, maternal grandmother, and aunts, none of whom performed genetic study. As relevant personal history, trachyonychia since the age of 11 years, attention deficit hyperactivity disorder, learning difficulties, and myopia were reported. The boy was followed in Pediatric Cardiology consultation for a patent foramen ovale (PFO) and electrocardiographic findings showing left axis deviation and supraventricular extrasystoles. On physical examination, he presented with short stature (140 cm, -3 SD score, for an adjusted mid-parental height of 169 cm, -1 SD score), alopecia areata with over 90% of the scalp with gray hair (**Figure 1**), trachyonychia of the nails of hands and toes (**Figure 2**), multiple lentigines mostly scattered over the trunk (**Figure 3**), four café au lait spots (CLS) with more than 1 cm of diameter, *pectus excavatum*, grade II/VI systolic heart murmur audible on all focuses, and Tanner stage G2P1A1.

What is your diagnosis?

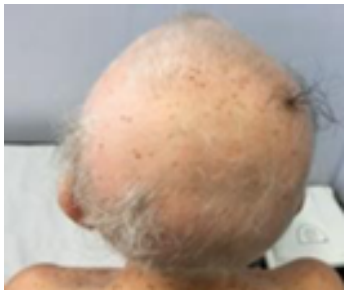

Figure 1

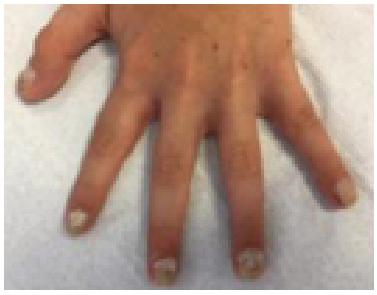

Figure 2

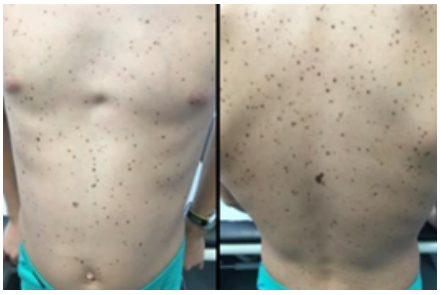

Figure 3

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DIAGNOSIS

LEOPARD syndrome

DISCUSSION

LEOPARD syndrome (LS) is a very rare autosomal dominant disease, with total penetrance and variable expression. Only about 200 patients have been globally reported.[1] LEOPARD is an acronym for: **L**entigines, **E**lectrocardiogram abnormalities, **O**cular hypertelorism, **P**ulmonic stenosis, **A**bnormalities of genitalia, **R**etardation of growth and **D**eafness. It is also called Noonan Syndrome with Multiple Lentigines or Cardiocutaneous Syndrome.[2] The most frequent ECG anomalies include Q waves, prolonged QTc interval and impaired repolarization, conduction disorders, and P-wave abnormalities. Although not included in the acronym, hypertrophic cardiomyopathy (HCM) is the most common cardiac anomaly found, representing a potentially fatal problem in these patients.[3] Other common features include CLS, thoracic abnormalities, cryptorchidism, late puberty, hypotonia, mild developmental delay, sensorineural deafness, and learning difficulties.[4] In the present case, the clinical diagnosis was based on the presence of multiple lentigines and CLS associated with changes in the electrocardiogram, short stature, *pectus excavatum*, pubertal delay, and learning difficulties.

Lentigo can be congenital, but usually manifests at the age of five years and increases during puberty. Lentigo histological examination shows acanthosis, large amount of melanin and melanocytes in the basal layer of the epidermis, and melanophages and small perivascular lymphocyte infiltrates in the upper part of the dermis.[5] The etiopathogenesis of the condition remains unknown. Some authors consider that patients with LS have high melanocytic activity and increased beta-adrenergic effector activity in the myocardium.[5]

In the present case, LS diagnosis was confirmed after a missense mutation (c.836A> G) in the protein tyrosine phosphatase non-receptor type 11 gene (PTPN11) in exon 7 (Tyr279Cys) was identified in genetic testing. PTPN11 mutation is the most common cause of LS, accounting for approximately 90% of cases. This gene, located on chromosome 12q24.1, encodes a cytoplasmic tyrosine phosphatase protein (SHP-2) that regulates intracellular signaling and controls several distinct developmental processes. Loss-of-function mutations in SHP-2 protein lead to the pleiotropic LS manifestations previously described. Germline mutations in PTPN11 cause Noonan and LEOPARD syndromes, which have overlapping clinical features.[6] Except for its most striking feature – multiple lentigines –, LS largely overlaps with NS.[4,7] While patients with NS have more typical facial features in infancy and childhood, single ventricular physiology is the most commonly reported cardiac defect in the condition, and skin abnormalities and deafness are less frequent. On the other hand, LS diagnostic clues include skin manifestations, such as CLS and multiple lentigo, HCM, and deafness.[4,7] The phenotypic overlap between NS and LS can complicate the differential diagnosis in young individuals not presenting with lentigo.[8-9] LS also displays an important phenotypic overlap with neurofibromatosis-Noonan syndrome, a clinical entity that manifests through the association of facial and cardiac features of NS with clinical features of neurofibromatosis 1, including CLS, neurofibroma, and central nervous system and skeletal anomalies.[10] Although alopecia areata is not a feature often associated with LS, at least two cases have been reported in the literature.[11-12] In the present case, alopecia was the worrying feature that made the mother seek for medical help.

The clinical management should assess growth, motor development, and congenital anomalies, especially cardiac defects, which should be monitored annually. HCM requires careful risk assessment and prophylaxis against sudden death in at-risk patients. It is usually asymptomatic, progressive, and often involves obstruction of the left ventricular intraventricular outflow tract (≈40% of cases). In the present case, the patient underwent 24-hour Holter monitoring, which turned out to be normal, maintaining vigilance in Pediatric Cardiology consultation due to risk of cardiomyopathy. Deafness is mostly diagnosed at birth or during childhood, but some patients develop it in adulthood.[4] Hearing should be annually evaluated until adulthood. With the only exception of ventricular hypertrophy, adults with LS do not require special medical care, and the long-term prognosis is favorable.[7-8]

With this case, the authors intend to draw attention to a very rare diagnosis, only reported in 200 patients worldwide. Although rare, LS should always be considered in patients with multiple lentiginous and cardiac abnormalities. Many cases are underdiagnosed or misdiagnosed, as several of its typical features are mild, and the correct diagnosis may be missed when lentiginosis is not present. The management of LS requires a multidisciplinary approach involving Dermatology, Cardiology, Endocrinology, and other appropriate specialties. Early diagnosis is useful for prospective management of associated medical conditions and genetic counseling.

ABSTRACT

Multiple lentigines (LEOPARD) syndrome is an inherited autosomal dominant disorder. LEOPARD is an acronym for the most important features of the disease: multiple lentiginous lesions, abnormal electrocardiogram, ocular hypertelorism, pulmonary stenosis, genital and reproductive abnormalities, growth retardation, and sensorineural deafness. Herein is reported the case of a 14-year-old male who presented with short stature and alopecia. The mother, maternal grandmother, and aunts had multiple lentigines all over the body and hypoacusia. Systemic examination revealed short stature, alopecia reaching over 90% of the scalp, trachyonychia, multiple lentigines mostly scattered over the trunk, four café-au-lait spots, *pectus excavatum*, grade II/VI systolic heart murmur, and Tanner

stage G2P1A1. The genetic study confirmed LEOPARD syndrome diagnosis. Early diagnosis is useful for prospective management of associated medical conditions and genetic counseling.

Keywords: café-au-lait spot; delayed puberty; LEOPARD syndrome; multiple lentigines; Noonan syndrome; short stature

RESUMO

A síndrome de múltiplos lentigos (LEOPARD) é uma doença genética autossómica dominante. LEOPARD é um acrónimo para as características mais importantes da doença: lentigos múltiplos, anomalias de condução no eletrocardiograma, hipertelorismo ocular, estenose pulmonar, anomalias genitais, atraso de crescimento e surdez neurossensorial. Os autores descrevem o caso de um adolescente de 14 anos referenciado por baixa estatura e alopécia, com história familiar de múltiplos lentigos distribuídos pelo corpo e hipoacusia na mãe, avó materna e tias. O exame físico evidenciou baixa estatura, alopécia atingindo mais de 90% do couro cabeludo, traquioníquia, múltiplos lentigos espalhados pelo tronco, quatro manchas café-com-leite, *pectus excavatum*, sopro cardíaco sistólico de grau II/VI e estadio de Tanner G2P1A1. O estudo genético confirmou o diagnóstico de síndrome de LEOPARD. Um diagnóstico precoce da doença é fundamental para a gestão prospetiva de problemas médicos associados e aconselhamento genético.

Palavras-chave: baixa estatura; lentigos múltiplos; mancha café-com-leite; puberdade tardia; síndrome de LEOPARD; síndrome de Noonan

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