# An uncommon association between skin lesions and LEOPARD Syndrome affected an old patient.

## Case report

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**Un uncommon association between skin lesions and LEOPARD Syndrome affected an old patient. Case report**

*LEOPARD syndrome (LS) is a rare inherited autosomal dominant disease with high penetrance and markedly variable expression characterized by a spectrum of somatic abnormalities. In 1971, Gorlin proposed the well-known acronym LEOPARD (lentigines, electrocardiographic abnormalities, ocular hypertelorism, pulmonary stenosis, abnormalities of the genitalia, retardation of growth, deafness). The nature and clinical importance of cardiovascular phenotypes associated with LS remain uncertain, because few patients with the disease have undergone comprehensive cardiac evaluations. To date, 200 cases have been described and one review has been published. We emphasize that this case is exceptional insofar as life expectancy was longer than other LEOPARD syndrome cases described in previous reports; these have had an early mortality due to cardiopathies. The aim of our study is to report a rare case of a patient affected with LEOPARD syndrome, survived until 67 years with cutaneous associations never described in literature.*

KEY WORDS: Blue nevus, Keratoacanthoma, LEOPARD Syndrome, Nevocytic intradermal nevus.

### Introduction

LEOPARD syndrome (LS) is a rare inherited disease characterized by a spectrum of somatic abnormalities [1-3]. The acronym LEOPARD was coined by Gorlin et al. [1] in 1971 as a mnemonic of the major features of this disorder: multiple Lentigines, ECG conduction abnormalities, Ocular hypertelorism, Pulmonary stenosis, Abnormal genitalia, Retardation of growth, and sensorineural Deafness.
The diagnostic Criteria include Multiple Lentigines (ML) plus two other recognized features or a first-degree relative with ML plus three other features in the patient [2].
LS is a rare condition, but the exact birth prevalence is unknown. Not less than 200 patients have been reported and two reviews published [2,4]. This is an autosomal dominant multiple congenital anomaly syndrome, with high penetrance and markedly variable expression [4]. Molecular studies have shown that LS and NS are allelic disorders, caused by different missense mutations in PTPN11, a gene encoding the protein tyrosine phosphatase SHP-2 located at chromosome 12q22-qter [5,6].
The clinical diagnosis of LS is generally difficult in the first months of life because the distinctive lentigines are generally not present at birth and develop during childhood.
Multiple lentigines LEOPARD syndrome shares many features with Noonan syndrome (NS) [7-9], including facial anomalies, distinct congenital heart defects, pectus deformities, hearing loss, and growth retardation [10-12]. Skin pigmentary changes have been described in both disorders. NS often manifests with pigmented nevi and cafe´ au lait spots, whereas LEOPARD syndrome manifests with cafe´ au lait spots in early infancy and generalized LEOPARD Syndrome after 5-6 years of age [11].

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## Clinical Case

A 67-year-old man was referred to us with erythematous desquamative lesions in the crural region. He underwent direct microscopic and culture examinations testing positive for candida. The physical examination of the patient's skin revealed generalized lentiginosis (Fig. 1) that did not affect either the oral mucosa or the genitalia. It also revealed ocular hypertelorism, slight prognathism, pectus carenatum, short stature, deaf-mutism and hypospadia. The peculiarity of the clinical findings prompted the performance of a series of diagnostic and laboratory tests. The Otolaryngological consult documented severely retracted tympanic membranes with atelectasic areas in the right ear and Audiovestibular testing showed profound sensorineural hearing loss in the left ear and anacusis in the right ear.

The cardiovascular exams were slightly altered (Echocardiogram: "...Enlarged left atrium ... Mild mitral and tricuspid valve regurgitation ..."). Chest CT showed a solid, hypodense nodular formation of heterogeneous density, about 9 cm in diameter which may be associated with an angiomyolipoma. Cranial CT Angiography documented an extremely elongated left vertebral artery and basilar artery with a tortuous pattern at the level of the tip; moderate (especially left) ventricular dilatation.

Magnetic resonance imaging (MRI) of encephalon and MRI angiography showed cortical-subcortical, supratentorial, bi-hemispherical; rarefaction of the supratentorial white matter; elongated basilar artery with no evidence of endoluminal thrombotic vegetations nor aneurismal dilatations; neither areas of intraparenchymatous lesions nor consequences of a previous blood effusion are observed.

Mutation screening for the PTPN11 gene was performed in our patient: DNA was extracted from the peripheral blood lymphocytes and we screened the entire PTPN11 gene coding region for mutations. All fragments were amplified by polymerase chain reaction (PCR). Denaturing high-performance liquid chromatography (DHPLC) screening of PCR products was done using the WAVE DNA Fragment Analysis System (Transgenomic). Bidirectional direct sequencing of the purified PCR product of the conspicuous fragment with exon 7 was performed using the ABI Big Dye Terminator Sequencing kit and an ABI PRISM 377. The formula of the mutation, already known to be associated with the phenotype of LEOPARD syndrome, is as follows: 836A-G in codon 279 (Tyr279Cys). These findings confirm the diagnosis of LEOPARD syndrome.

In 2008, the patient presented two cutaneous lesions. The first one in corrispondence of the right auricolar padiglione (diameter of 0,5 cm ), it appears as solitary nodules with craterlike surfaces and a central keratin core, clinically corresponding to keratoacanthoma which underwent spontaneous resolution. The second lesion located in temporomandibular region on the left side, it was a nodule, 1.3x0.7x0.5 cm in size, that included two pigmented lesions respectively ranged in size from 0,5 to 0,8 cm and from 0.2 to 0.4 cm, histologically corresponding to nevocytic intradermal nevus and blue nevus.

## Discussion

A diagnosis of LEOPARD syndrome may be established exclusively on the basis of clinical criteria. In our case, the patient was diagnosed with the syndrome late in his life when he was already exhibiting all its distinctive clinical features. It should be pointed out that lentiginosis is the most frequently occurring feature, being observed in 100 percent of LEOPARD syndrome patients, followed by electrocardiographic abnormalities (80%), skeletal abnormalities (60%), hypertelorism (50%), short stature (42%), mental retardation (35%), abnormal male genitalia (29%), and deafness (27%). The most fre-

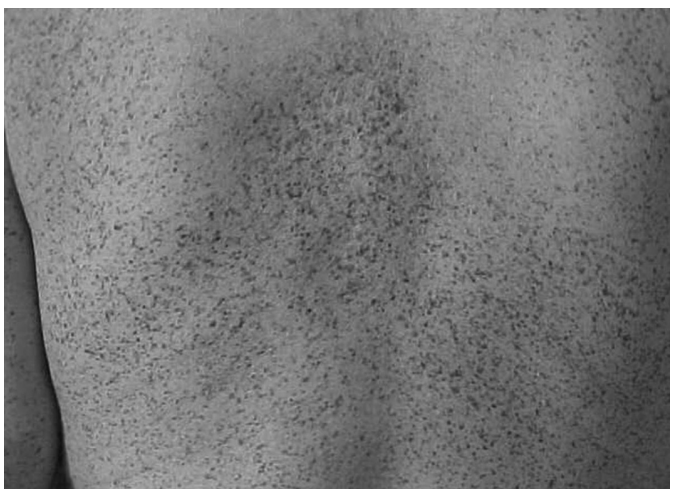

Fig. 1: Generalized lentiginosis.

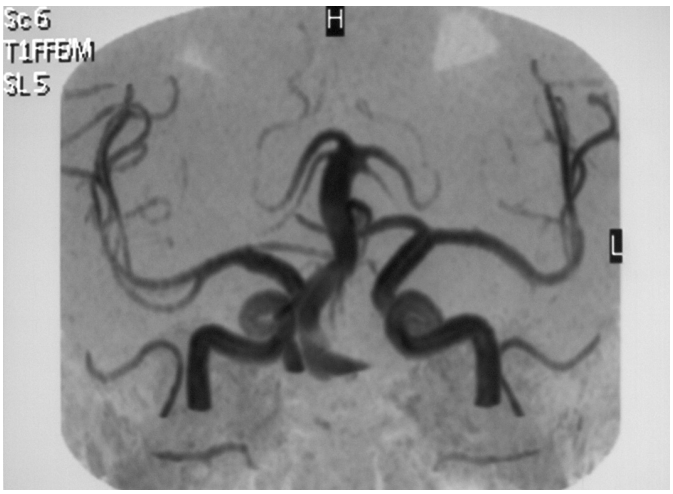


Fig. 2: Megadolichovertebrobasilar anomaly.

quently observed heart defect is pulmonary stenosis, described in 40 percent of the cases [11].

Clinically, lentigines are dark brown in color, irregularly shaped, and can range in size from that of a lentil, to 5 mm in diameter. They are usually found on sun-exposed areas and periorificial areas; they are less frequently observed on palms, soles and genitalia.

The oral mucosa is usually unaffected. Distinct facial features are usually exhibited by LEOPARD syndrome patients: triangular shaped face due to frontal swellings, hypertelorism and low-set ears. Most patients have lower-than-average weight and stature. Some skeletal abnormalities may be observed, including pectus excavatum (sunken chest) or carinatum (protruding breastbone), scoliosis, absence of ribs, abnormal elbow articulation.

Mild mental retardation is observed in some cases, although intellectual faculties may be normal in LEOPARD syndrome patients. Cardiac abnormalities include electrocardiographic conduction defects and anatomical malformations; electrocardiographic conduction abnormalities are especially frequent. Axial deviation, prolonged PR interval, left anterior hemiblock (LAH), bundle-branch block and complete heart block (CHB) are also described.

Hypertrophic cardiomyopathy seems to be the most frequently reported anatomical anomaly [13]: the most frequently described valvular lesion is subaortic stenosis. About 50 percent of male patients exhibit hypospadias. Unilateral cryptorchidism may also be present. Female patients may have missing ovaries or unilateral ovarian hypoplasia. The presence of multiple lentigines should not be ignored; these may be evidence of other characteristic syndromes, including the Cronkhite-Canada syndrome, the Carney complex, and the Bandler syndrome, in which lentiginosis is circumscribed. The LEOPARD syndrome, like the Carney complex (LAMB and NAME syndromes, myxomas, lentigines, endocrine disorders, melanocytic schwannoma), another autosomal, dominant disorder, is characterized by generalized lentiginosis associated with other systemic anomalies. Clinically, the lentigines observed in the Carney complex are similar to those described in the LEOPARD syndrome and are present all over the patient's body: the only difference is that lentigines also appear on the oral mucosae unlike in the LEOPARD syndrome. On the contrary, facial dysmorphism, which is a characteristic feature of the LEOPARD syndrome, is absent in the Carney complex [14].

The clinical evaluation of the LEOPARD syndrome is based on an ECG, a chest X-ray and an echocardiogram. The prognosis is mainly determined by the nature and severity of the cardiopulmonary lesions. Patients should undergo periodic ECG, chest X-ray and echocardiographic examinations, depending on their clinical picture. When Gorlin et al. [1] first introduced the name "LEOPARD" some thirty years ago, the authors hoped that "careful family studies would clarify the minor manifestations of this syndrome," although they already suspected "it will not be possible to define the limits of the syndrome.

" Today, new "clinical abnormalities" (compared to those previously defined by Voron et al. [2]) are still being found in LEOPARD syndrome patients, confirming the highly variable expressivity and penetrance of the disease. This may be the result of a mutation in PTPN11, a gene encoding the protein tyrosine phosphatase SHP-2: this protein plays a key role in intracellular signal transduction pathways and interacts with the angiopoietin-1 receptor, essential for both angiogenesis and the signaling cascade of the endothelial growth factor [15]. Moreover, angiopoietin-1 has a mitogenic effect on endothelial smooth muscle cells induced by nitric oxide [16]. Such interactions may account for the vascular manifestations observed in our patient. We have reported the case of a LEOPARD syndrome patient exhibiting extremely elongated vertebral and basilar arteries previously undescribed in the literature. This finding may be explained by providing a better description of the functions of protein tyrosine phosphatase SHP-2, encoded by the PTPN11 gene (involved in the development of the disorder), so as to establish a better genotype-phenotype correlation. The PTPN11 mutation itself may account for the highly variable expressivity and penetrance of the syndrome.

The patient was diagnosed with the syndrome rather late in life by dermatologists, although he had been previously evaluated by other specialists who failed to associate all of the findings with the LEOPARD syndrome. The authors emphasize that this case is exceptional insofar as life expectancy was longer than other LEOPARD syndrome cases described in previous reports; these have had an early mortality due to cardiopathies [17].

## Conclusion

Our case underlines the rarity of LEOPARD Syndrome. In particular, our patient represents an exclusive case because of its survival until 67 years; in fact the other patients, described in literature, affected with its syndrome die in earlier age from cardiovascular disease. Further on, he presented a new clinical feature that is megadolichovertebrobasilar anomaly (Fig. 2). Other peculiar lesions which affected our patient were keratoacanthoma, nevocytic intradermal nevus and blue nevus. We don't know if these types of lesions can be occasional or associated with this syndrome.

## Riassunto

La sindrome di LEOPARD è una malattia autosomica dominante ad alta penetranza e ad espressività variabile caratterizzata da un ampio spettro di anomalie somati-

che. Nel 1971, Gorlin propose l'acronimo LEOPARD (Lentigines, Electrocardiographic abnormalities, Ocular hypertelorism, Pulmonary stenosis, Abnormalities of the genitalia, Retardation of growth, Deafness). La natura e l'importanza clinica delle manifestazioni cardiovascolari associate alla sindrome di LEOPARD rimangono incerte, poiché pochi pazienti affetti dalla sindrome suddetta sono stati sottoposti a valutazioni cardiache valide. Sino ad oggi sono stati descritti 200 casi ed una sola Review è stata pubblicata. Noi enfatiziamo l'eccezionalità del caso per l'aspettativa di vita del nostro paziente che risulta essere maggiore rispetto ai casi descritti in letteratura, i quali hanno presentato una mortalità precoce per cardiopatie. Lo scopo del nostro studio è riportare un caso raro di un paziente affetto dalla sindrome di LEOPARD, sopravvissuto sino a 67 anni con lesioni cutanee associate alla sindrome mai descritte in letteratura.

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