

Patient with confirmed LEOPARD syndrome developing multiple melanoma

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ABSTRACT LEOPARD syndrome, also known as Gorlin syndrome II, cardiocutaneous syndrome, lentiginosis profusa syndrome, Moynahan syndrome, was more recently coined as Noonan syndrome with multiple lentigines (NSML), inside the RASopathies. Historically, the acronym LEOPARD refers to the presence of distinctive clinical features such as: lentigines (L), electrocardiographic/conduction abnormalities (E), ocular hypertelorism (O), pulmonary stenosis (P), genital abnormalities (A), retardation of growth (R), and sensorineural deafness (D). This condition is identified in 85% of patients with phenotype hallmarks caused by presence a germline point mutation in PTPN11 gene. Association of melanoma to NSML seems to be rare: to our knowledge, two patients so far were reported in the literature. We herein present a patient diagnosed with LEOPARD syndrome, in whom molecular investigation confirmed the presence of the c.1403C>T mutation in exon 12 of the PTPN11 gene, who developed four superficial spreading melanomas and three atypical lentiginous hyperplasias. Three of the melanomas were achromic or hypochromic, three were in situ, and one had a Breslow index under 0.5 mm. Dermoscopic examination showed some characteristic white structures in most of the lesions, which were a signature pattern and a key for the diagnosis.

Introduction

LEOPARD syndrome (LS) is also known as Gorlin syndrome II, cardiocutaneous syndrome, lentiginosis profusa syndrome, Moynahan syndrome, and more recently Noonan syndrome with multiple lentigines (NSML). It is a rare autosomal dominant fully penetrant multisystemic disorder with character-

istic features that include multiple lentigines and café au lait spots (L), electrocardiographic conduction defects (E), ocular hypertelorism (O), pulmonary stenosis (P), abnormalities of the genitalia (A), retardation of growth (R), and sensorineural deafness (D). Patients usually do not present with all of these classical clinical features.

A missense mutation in the protein tyrosine phosphatase non-receptor type 11 (PTPN11) gene is identified in about 85% of the LS patients. PTPN11 encodes for the SRC Homology 2 (SHP-2), a cytoplasmic protein tyrosine phosphatase which regulates intracellular signaling of RAS pathway downstream of receptors for growth factors, cytokines and hormones responsible for the development of NSLM [1,2]. Missense change in NSLM is responsible for conformational switch that leaves the protein in an active state but with unexpected decreased phosphatase activity.

We herein report a LS patient with multiple melanomas.

Case

A 62-year-old man was referred to our clinic for a lesion of the upper foot, which had already been biopsied. Pathologic examination showed mild atypical melanocytes.

On physical examination, he had a high number of flat, brown to dark brown, small macules symmetrically distributed over a large portion of the skin, including the face. These had irregular borders and ranged in size from 1 mm in diameter to café-au-lait spots of several centimeters in diameter. Some lentigines had been present at birth, but most of them occurred after the age of 3. The patient had a history of cryptorchidism surgery. Electrocardiographic conduction defect at the age of 49 led to the diagnosis of sick sinus syndrome. There was no cognitive disorder or intellectual disability so far.

The family history revealed similar findings: the patient's mother had lentigines and died of a melanoma and one of the patient's sisters had similar skin with associated cardiac abnormalities and partial deafness.

The upper foot lesion (Figure 1) was hypochromic and rough. Dermoscopic examination showed numerous white structures and dotted vessels. After removal of the whole lesion, pathologic examination concluded in a superficial spreading melanoma arising on a nevus, Clark's level II, Breslow index 0.42 mm, and regression in the papillary dermis.

After obtaining informed consent, direct sequencing of entire coding of PTPN11 gene was completed. The PTPN11 c.1403 C>T (p.T468M) mutation was identified, confirming LS. The same mutation was found in the patient's sister. No access to parents' DNA was available.

One year later, a new lesion appeared on the back. It was hypopigmented, well limited and slightly erythematous. Dermoscopy showed a lot of white lines with unusual thickening at their crossings (Figure 2A).

Pathologic examination of the clinically visible lesion revealed a lentigo maligna arising on a nevus with regression phenomenon. A large excision was performed, which was incomplete; however, a second excision with a 2 cm margin

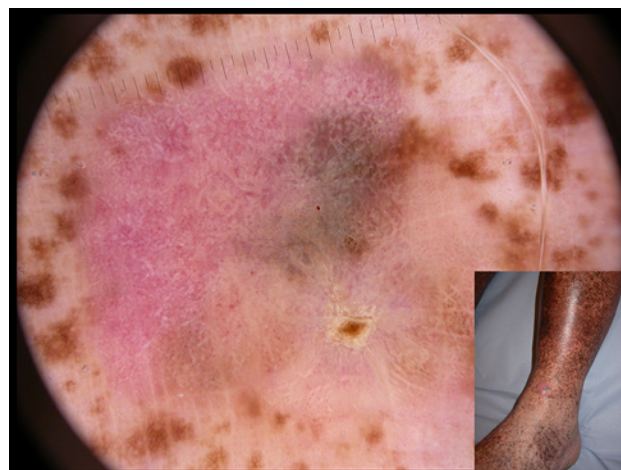


Figure 1. First melanoma of the foot: clinical aspect and dermoscopic aspect. Aspect of eczema. On dermoscopy, shiny white strands, dotted vessels and a structureless pink and brown-gray background (polarized dermoscopy, DermLite Foto, [3Gen, San Juan Capistrano, CA, USA]). Pathology: superficial spreading melanoma developed on nevus, Clark's level II, a Breslow index of 0.42 mm, and regression phenomenon in the papillary dermis. [Copyright: ©2018 Colmant et al.]

allowed a complete excision, with melanoma in situ being still close to the lateral resection margins (< 2 mm).

Six months later, a new hyperpigmented and hypopigmented lesion appeared about 20 cm away from the last scar in the back (Figure 2B). The clinical and dermoscopic features suggested another melanoma. That lesion also displayed some white lines with thickening at their crossings, alongside some more classic negative pigment network. Due to the large dimensions of the lesion, several biopsies were performed. Histopathology and immunostaining (Pan-melanoma cocktail and HMB45) confirmed the diagnosis of lentigo maligna in situ with regression. Although recommended treatment for in situ melanoma is excision with a 0.5 cm margin, the previous diffuse melanoma history led us to use the "slow-Mohs," also called the "spaghetti technique" [3], suggested by some teams for the treatment of lentigo maligna melanoma. This allowed us to achieve complete surgical excision of the lesion. Six months later, we observed four new lesions suggestive of melanoma at dermoscopic examination (Figure 3). On two of them we found white lines again. One of the lesions was a lentigo maligna; the others were atypical lentiginous hyperplasias. Three of them were incompletely removed.

So many melanomas and atypical lentiginous hyperplasias with infra-clinic extension led us to think about other ways to prevent the relapses of the lesions. We suggested the application of imiquimod 5 days a week for 8 weeks on the concerned lesions [4]. This was successful in preventing relapses as after a follow-up period of three years, no more doubtful lesions could be found.

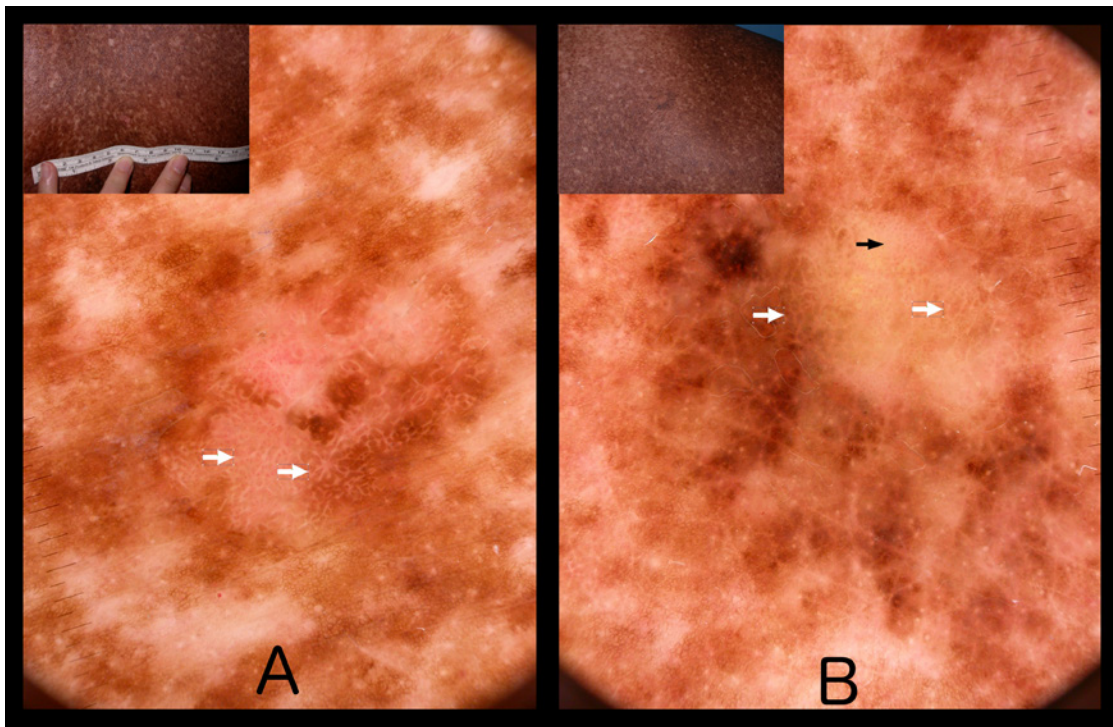


Figure 2. First and second melanoma of the back: clinical aspect and dermoscopic aspect. (A) First melanoma of the back: on dermoscopy white lines with thickening at their crossings (white arrows) (polarized dermoscopy, DermLite Foto). Pathology: lentigo maligna *in situ* arising on a nevus, with regression phenomenon. (B) Second melanoma of the back: on dermoscopy, classic negative pigment network (black arrow); negative pigment network with thickening at the crossings of some white lines (white arrows) (polarized dermoscopy, DermLite Foto). Pathology: lentigo maligna with regression. . [Copyright: ©2018 Colmant et al.]

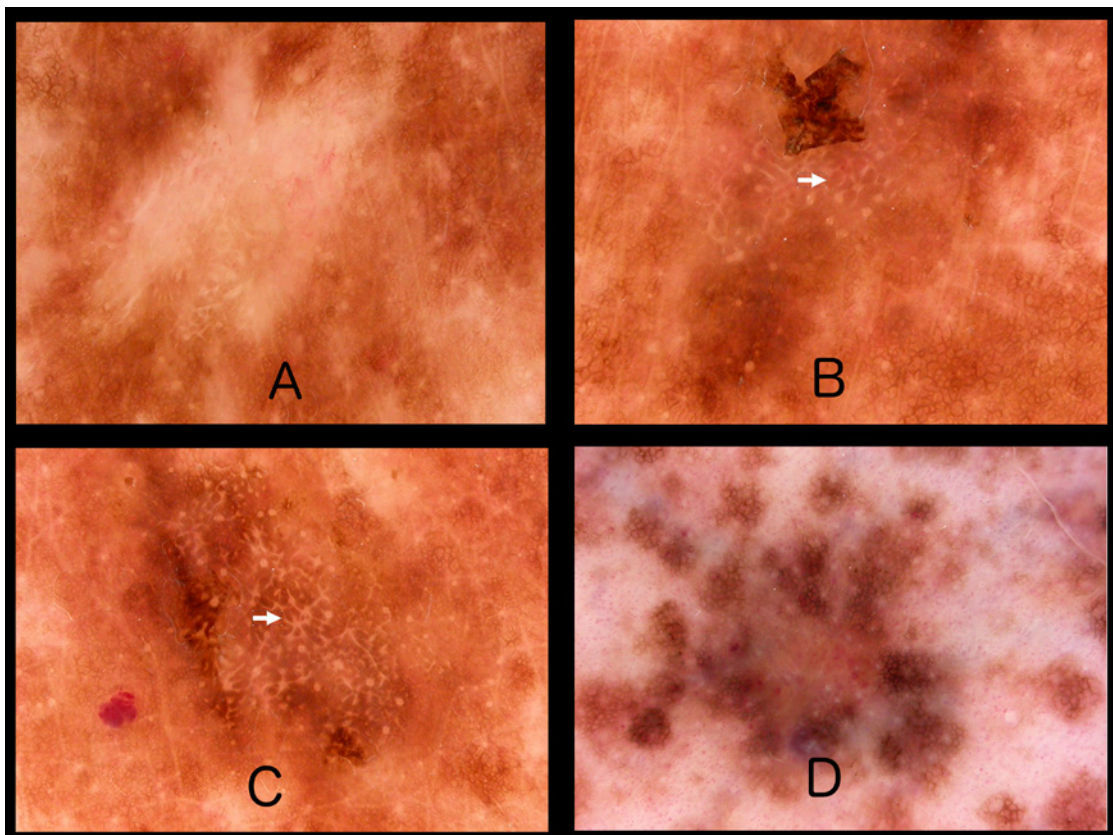


Figure 3. Dermoscopy of the four last lesions (A) Not well defined white lines, (B) and (C) Signature pattern: in the negative pigment network, the white lines show thickening at their crossings (white arrows). (D) Shiny white strands and dotted vessels (polarized dermoscopy DermLite Foto). Pathology: (A,) (B), (D) atypical lentiginous hyperplasia; (C) lentigo maligna. [Copyright: ©2018 Colmant et al.]

As a result of the multiple melanomas found in this patient and his positive family history, we looked for a mutation of the CDKN2a gene, which was not found.

Discussion

We report the first case of a LEOPARD patient with multiple melanomas. Two previous LEOPARD patients with melanoma have been described: a 62-year-old woman, who developed a melanoma with a somatic BRAF mutation on top of her germline PTPN11 gene mutation [5] and a 24-year-old patient who suffered from a scalp melanoma [6].

LS patients could present a higher risk for melanomas. Indeed, it has been suggested that, although SHP2, the protein encoded by PTPN11, acts usually as an oncogene, it could also, in specific cell types, act as a tumor suppressor [7]. This has been shown in hepatocellular carcinogenesis: deletion of SHP2 promotes malignant transformation through the Stat3 pathway [8]. Stat3 pathway is also important in melanoma genesis, and deletion of PTPN11/SHP2 could therefore promote survival of malignant cells, metastasis, angiogenesis and immune evasion [7].

On most of the melanomas we found a dermoscopic signature pattern: in the negative pigment network, the white lines showed thickening at their crossings. This pattern was very useful for diagnosing the clinically difficult melanomas

in this patient. We could see that pattern both in polarized and non-polarized dermoscopy.

This case report enhances the importance of careful skin examination in LS patients.

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