SHORT COMMUNICATION

ActaDV
Acta Dermato-Venereologica
ActaDV
Advances in dermatology and venereology

Melanoma and LEOPARD Syndrome: Understanding the Role of PTPN11 Mutations in Melanomagenesis

Rodolfo David PALACIOS-DIAZ[1], Mónica POZUELO-RUIZ[1], Blanca de UNAMUNO-BUSTOS[1,3], Margarita LLAVADOR-ROS[2] and Rafael BOTELLA-ESTRADA[1,3]
[1]Dermatology Department and [2]Pathology Department, Hospital Universitari i Politècnic La Fe, 106 Fernando Abril Martorell Avenue, ES-46026 Valencia and [3]Dermatology, Instituto de Investigación Sanitaria La Fe, Valencia, Spain. E-mail: blancaunamuno@yahoo.es
Submitted Jun 12, 2023. Accepted after revision Sep 25, 2023; Published Jan 8, 2024.
Acta Derm Venereol 2024; 104: adv14720. DOI: 10.2340/actadv.v104.14720

"RASopathies" is an umbrella term that includes multisystemic disorders with overlapping clinical features. They develop due to a genetic variation in components or modulators of RAS-MAPK signalling cascade (1). Skin involvement comprises a wide heterogeneous spectrum of cutaneous features including pigmentation anomalies (1, 2). Propensity to non-cutaneous malignancy and reports of cutaneous melanoma have drawn attention to the role of these germline mutations in melanomagenesis.

CASE REPORT

A 53-year-old woman presented to the Dermatology department of Hospital Universitari i Politècnic La Fe, Valencia, with a pigmented macule that had grown steadily to a maximum diameter of 40 mm on her right leg. Dermoscopic examination showed an atypical pigment network and dotted-whitish areas suggesting regression (**Fig. 1**A). Histopathological examination confirmed the diagnosis of melanoma in situ with a radial lentiginous growth pattern (Fig. 1B). Direct sequencing of melanoma tissue showed a *BRAF* and *NRAS* wild type. In addition, physical examination showed multiple lentigines predominantly in the head and neck, upper trunk, and proximal upper extremities (Fig. 1C). The patient had short stature, hypertelorism, low-set ears, exaggerated Cupid's bow and bilateral lymphedema. Pertinent personal history included Bricker's ureteroileostomy due to neurogenic bladder after spina bifida surgery, pulmonary valve stenosis and puberty delay. Exome sequencing (Custom NGS SureSelect panel, Illumina, San Diego, California) revealed a heterozygous variant c.1403C>T (p.Thr468Met) in exon 12 of *PTPN11*, compatible with Noonan syndrome with multiple lentigines (NSML). After 5 years of follow-up, the patient has not had any other atypical lesions.

DISCUSSION

NSML is a rare autosomal dominant inherited disorder, and it has been linked to mutations in *PTPN11* (90%) and, more rarely, to mutations in *RAF1* and *BRAF* (2). The most frequent *PTPN11* missense mutations cause p.Thr468Met and p.Thr279Cys variants in 82% of patients in a case series (3). Mutations in *PTPN11* in NSML affect the catalytic domain of SHP-2, resulting in decreased phosphatase activity (4).

Common clinical features are grouped in the formerly used "LEOPARD" acronym (multiple lentigines (ML), electrocardiogram (ECG) conduction abnormalities, ocular hypertelorism, pulmonary valve stenosis, genitourinary anomalies, growth retardation, and sensorineural deafness) (1, 2). ML are the most common

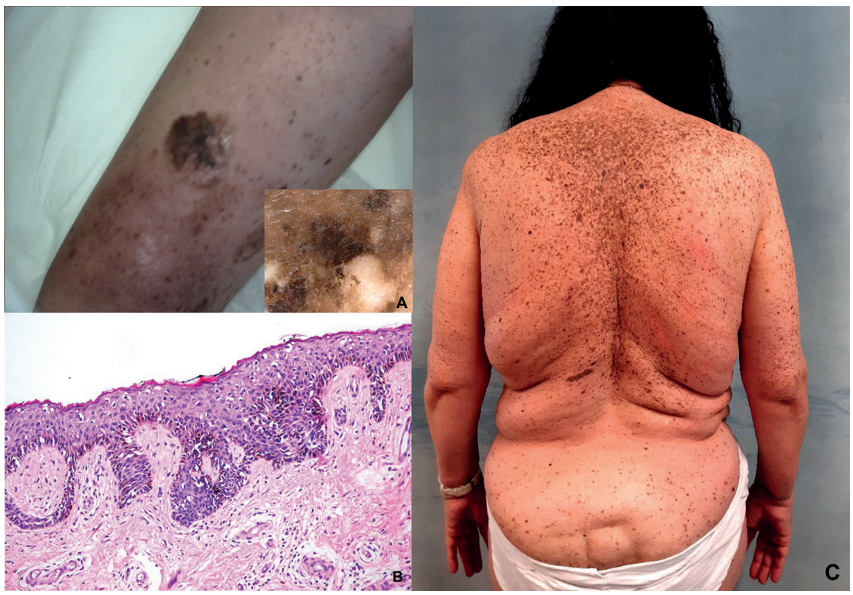

Fig. 1. (A) Pigmented macule with atypical pigment network and dotted-whitish areas in the patient's right leg (dermoscopic image in the lower right corner). (B) Melanoma in situ with a radial lentiginous growth pattern (haematoxylin and eosin (H&E); 40×). (C) The patient had also multiple lentigines predominantly on the upper trunk and proximal upper extremities.

Published by Medical Journals Sweden, on behalf of the Society for Publication of Acta Dermato-Venereologica. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (https://creativecommons.org/licenses/by-nc/4.0/)

pigmentary disorder in NSML, and they are present in 94% of NSML patients over the age of 1 year (3). ML have high specificity and increase in number in puberty and adulthood (2, 3). SHP-2 mutation causes an abnormal enhanced synthesis of melanosomes in melanocytes, which might be involved in the pathogenesis of ML (4). Furthermore, mutants of SHP-2 may also result in enhancement of migration and prevention of apoptosis of melanocytes (4).

Malignancy associated with NSML include leukaemia, cerebellar medulloblastoma, neuroblastoma and unilateral choristoma (5). Apart from the current case, only 4 other cases of melanoma in patients with NSML have been reported in the literature (6–9) (**Table I**). The patients had the most frequent germline *PTPN11* mutations: p.Thr468Met (40%; 2/5) and p.Tyr279Cys (40%; 2/5). All cases displayed an incomplete clinical "LEOPARD" acronym phenotype. Melanomas were on the back (40%; 2/5), lower extremities (60%; 3/5) and scalp (20%, 1/5). One patient (20%) had multiple primary melanomas without *CDKN2A* mutation (8). Except for a scalp melanoma of 5 mm, most of the melanomas were thin (<1 mm). One patient had an additional *BRAF* mutation (6). The authors hypothesized that a *BRAF* mutation on skin with a germline mutated *PTPN11* might severely affect MAPK signalling, resulting in the development of melanoma (6). The remaining melanomas did not have, or were not reported to have, *NRAS*, *HRAS* or *BRAF* mutations (7–9).

Beside its phosphatase activity, SPH-2 might function as a tumour suppressor protein (7). Mutations in SHP-2 induce activation of Akt/mTOR and STAT3 pathway, which plays an important role in melanoma tumorigenesis (4, 7). Moreover, development of two primary melanomas within a naevus spilus with a mosaic p.(Thr468Met) variant and heterozygous deletions involving *PTPN11* has been reported in 8 of 345 melanomas (10). These authors found a significant activation of the MAPK pathway, but not of the PI3K-protein kinase B-mTOR pathway, in generated cell lines with p.(Ala461Thr) and p.(Thr468Met) variants (10). Although more studies are needed to elucidate the role of NSML germline-*PTPN11* mutations in melanomagenesis, we believe that the risk of developing melanoma should encourage a close clinical and digital follow-up of patients with NSML.

ACKNOWLEDGEMENTS

The patient in this manuscript has given written informed consent to publication of their case details. The authors accept and agree with the United Nations's Declaration of Human Rights.

The authors have no conflicts of interest to declare.

REFERENCES

1. Zenker M. Clinical overview on RASopathies. Am J Med Genet Part C Semin Med Genet 2022; 190: 414–424.
2. Tajan M, Paccoud R, Branka S, Edouard T, Yart A. The RASopathy family: Consequences of germline activation of the RAS/MAPK pathway. Endocr Rev 2018; 39: 676–700.
3. Bessis D, Miquel J, Bourrat E, Chiaverini C, Morice-Picard F, Abadie C, et al. Dermatological manifestations in Noonan syndrome: a prospective multicentric study of 129 patients positive for mutation. Br J Dermatol 2019; 180: 1438–1448.
4. Motegi SI, Yokoyama Y, Ogino S, Yamada K, Uchiyama A, Perera B, et al. Pathogenesis of multiple lentigines in LEOPARD syndrome with PTPN11 Gene mutation. Acta Derm Venereol 2015; 95: 978–84.
5. Smpokou P, Zand DJ, Rosenbaum KN, Summar ML. Malignancy in Noonan syndrome and related disorders. Clin Genet 2015; 88: 516–522.
6. Seishima M, Mizutani Y, Shibuya Y, Arakawa C, Yoshida R, Ogata T. Malignant melanoma in a woman with LEOPARD syndrome: identification of a germline PTPN11 mutation and a somatic BRAF mutation. Br J Dermatol 2007; 157: 1297–1299.
7. Cheng YP, Chiu HY, Hsiao TL, Hsiao CH, Lin CC, Liao YH. Scalp melanoma in a woman with LEOPARD syndrome: possible implication of PTPN11 signaling in melanoma pathogenesis. J Am Acad Dermatol 2013; 69: e186–187.
8. Colmant C, Franck D, Marot L, Matthijs G, Sznajer Y, Blomme S, et al. Patient with confirmed LEOPARD syndrome developing multiple myeloma. Dermatol Pract Concept 2018; 8: 59–62.
9. García-Gil MF, Álvarez-Salafranca M, Valero-Torres A, Ara-Martín M. Melanoma in Noonan syndrome with multiple lentigines (LEOPARD syndrome): a new case. Actas Dermosifiliogr 2020; 111: 619–621.
10. Polubothu S, Bender N, Muthiah S, Zecchin D, Demetriou C, Martin SB, et al. PTPN11 mosaicism causes a spectrum of pigmentary and vascular neurocutaneous disorders and predisposes to melanoma. J Invest Dermatol 2023; 143: 1042–1051.e3.

Table I. Summary of the reports of melanoma in patients with Noonan syndrome with multiple lentigines

Number	Authors	Year	Sex	Age, years	Germline mutation	Clinical phenotype	Histopathological characteristics	Melanoma genes studied
1	Seishima M et al. (6)	2007	F	60	Thr468Pro (*PTPN11*)	L,cardiac abnormality, R	Heel: BI 0.9 mm	*BRAF* Val600Glu
2	Cheng Y et al. (7)	2013	F	24	Tyr279Cys (*PTPN11*)	L,E,O,R,D *	Scalp: SSM, BI 5 mm, no associated nevus	*BRAF, NRAS* & *HRAS* wt
3	Colmant C et al. (8)	2018	M	62	Thr468Met (*PTPN11*)	L,E,A	MPM: 1. Foot: SSM, BI 0.42 mm, associated nevus. 2,3 & 4. Back: LM	CDKN2A wt
4	García-Gil M et al. (9)	2020	M	44	Tyr279Cys (*PTPN11*)	L,E,P,D	Back: SSM, BI 0.15 mm	–
5	Palacios-Diaz RD et al.	2023	F	53	Thr468Met (PTPN11)	L,O,P,A,R	Leg: MIS	*BRAF* & *NRAS* wt

F: female; M: male; L: lentigines; E: electrocardiogram abnormalities; O: ocular hypertelorism; P: pulmonary valve stenosis; R: growth retardation; D: sensorineural deafness; BI: Breslow index; MIS: melanoma in situ; MPM: multiple primary melanomas; LM: lentigo maligna; SSM: superficial spreading melanoma; wt: wild type.
*The patient had regurgitation of the tricuspid valve, but it was not specified pulmonary stenosis.

ActaDV Acta Dermato-Venereologica ActaDV Advances in dermatology and venereology