Clinical, dermoscopic and confocal features of nevi and melanomas in a multiple primary melanoma patient with the *MITF* p.E318K homozygous mutation

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INTRODUCTION

The *MITF* gene is an oncogenic melanocyte lineage-specific transcription factor involved in cell survival, differentiation and proliferation¹. The *MITF* p.E318K variant has been associated with an increased melanoma risk, development of multiple melanoma (MPM) and high nevus count^{2,3,4,5,6}. We report the first case of the *MITF* p.E318K mutation occurring in homozygous in melanoma.

MATERIALS AND METHODS

A man was referred to our Clinic for a routine follow-up visit because of a personal history of three primary melanomas, all located on the back, and a high number of melanocytic nevi (total nevi count >250). Dermoscopic (DerLite Photo[®], 3Gen, San Juan Capistrano, California) and confocal (Vivascope[®] 1500, MAVIG, Germany) images were available for two out of three melanomas and for several patient's melanocytic nevi. We describe the phenotypic characteristics of the patient and the dermoscopic and confocal features of his melanomas and melanocytic nevi.

Germline DNA was extracted from whole blood by standard procedures using QIAamp DNA Blood kit (Qiagen, Hilden, Germany). Germline mutations of exons 1α, 1β, 2 e 3 including the exon-intron boundaries of *CDKN2A*, exon 2 of *CDK4*, the entire open reading frame of *MC1R* and exon 10 of *MITF* susceptibility genes were screened by direct Sanger sequencing of PCR amplicons on Genetic Analyzer 3500 (ThermoFisher Scientific, CA). The p.S270N *POT1* mutation was analyzed by TaqMan Real Time-PCR genotyping probes (ThermoFisher Scientific).

RESULTS

The patient had skin type II with light brown hair and green eyes and a personal history of three primary melanomas. Melanoma n.1 was a 1 cm large, clinically flat to palpable lesion, asymmetrically pigmented; dermoscopically, it was characterized by a peripheral atypical network, areas of negative pigment network and different degrees of pinkish and grey pigmentation (figure 1b). A regular hypopigmented component related to a pre-existing dermal nevus was present. At the confocal examination, a severe cytoarchitectural atypia was observed, with polymorphous cells and atypical melanocytic nests at the junctional layer and within the upper dermis (figure 1c). Melanoma n.3 was a 6 mm flat lesion, dermoscopically characterized by an irregular brown network associated with a widespread negative pigment network (figure 1d). Confocal examination showed intraepidermal and junctional atypical melanocytic proliferation and architectural disarray (figure 1e). Two main dermoscopic nevus patterns were observed in our patient: a hypopigmented type with a predominant dermal-congenital pattern (figure 2a and 2b) and a pigmented type with a predominant reticular/homogenous pattern (figure 2c and 2d). Sequencing data revealed the presence of the *500C>G polymorphism in *CDKN2A*, a homozygous p.E318K mutation in *MITF* (figure 3) and the p.R160W R allelic variant in *MC1R*, while no melanoma predisposing mutations were found in *CDK4* and *POT1* genes.

Figure 1. (a) Clinical image of the back of a 48 year-old male patient. Arrows indicate two of the three melanomas; (b) Dermoscopic image of Melanoma n.1. Strongly asymmetrical structure and dermoscopic islands are the main dermoscopic features; (c) Confocal image at the lower junctional layer of the dermoscopic island of the lesion in 1b showing thickened atypical meshwork with numerous atypical nests at the junction and upper dermal layer (yellow arrows); (d) Asymmetrical distribution of dermoscopic features of melanoma n.3. Areas of stypical network associated with a negative pigment network area (white star); (e) Confocal image at the junctional layer of the lesion in 1d showing an atypical meshwork with numerous atypical nucleated cells (white arrows).

Figure 2. a-b) Hypopigmented nevus with a predominant dermal-congenital pattern: globular/homogenous with a pink to light-brown pigmentation and numerous comma vessels. c-d) Pigmented nevus, with a predominant reticular/homogenous pattern: a brown pigmented network, associated with areas of homogeneous brown pigmentation or follicular hypopigmentation with regularly distributed globules, as observed in acquired nevi of the patient.

Figure 3. Chromatograms corresponding to a *MITF* wild-type sample (upper panel) and to the *MITF* p.E318K homozygous variant (lower panel) of our patient.

CONCLUSIONS

- This is the first case of the *MITF* p.E318K mutation occurring in homozygosis in melanoma
- A similar finding was only reported in 2 of 555 patients with pheochromocytoma and was associated with high aggressiveness of the disease suggesting a more pronounced effect of the risk allele supported by the additive genetic model⁷
- A high number of patients is needed to define the impact of the *MITF* p.E318K homozygous genotype on melanoma aggressiveness.

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