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AMELANOTIC MELANOMA IN OCULOCUTANEOUS ALBINISM: A GENETIC, DERMOSCPIC AND REFLECTANCE CONFOCAL MICROSCOPY STUDY

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Dear Editor

Herein we describe the usefulness of a successful combination of dermoscopy and in vivo RCM for the early diagnosis of 3 AM in 2 OCA patients.

OCA is a group of rare autosomal recessive disorders of pigmentation. It consists in the absence or reduction of melanin in the skin, hair, and eyes due to a partial or total deficit in the activity of tyrosinase (*TYR*)¹ or other related genes^{2,3}. Those patients are at higher risk of non melanoma skin cancer, while still debated is their increased risk of melanoma, in particular amelanotic⁴. They usually lack in clinical and dermoscopic pattern, what makes them challenging to be diagnosed, especially at early stage.

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Clinical picture of the three cases were quite similar presenting as pinkish macules. First one (case 1) showed an asymmetric reddish lesion of 1.8 cm in maximum diameter, with recent growth in upper side, in a pre-existing lesion on the abdomen of a lady in her middle 30's (patient 1) affected by OCA1, carrying the p.Cys46Tyr(c.137G>A) missense heterozygous mutation in exon 1 and the p.Val393Leufs*92(c.1177delG) frameshift heterozygous mutation in exon 3 of *TYR* gene (figure 1A).

The other two lesions (case 2 and 3) were located on the lower leg and came from a lady in her 40's (patient 2) also affected by OCA1, carrying the IVS2-7T>A(c.1037T>A) splicing heterozygous mutation in intron 2 and the p.tyr373Lys(c.1118 C>A) missense heterozygous mutation in exon 3 of *TYR* gene (figure 2A).

Both patients were carriers of V92M and T314T in heterozygosis in the Melanocortin 1 receptor gene (*MCLR*).

Dermoscopically, the 3 lesions showed an atypical vascular pattern mainly with dotted vessels (Figures 1B and 2B).

RCM findings of the 3 cases were alike, with some peculiar differences between case 1 and case 2/3. The images showed the epidermis with a well-preserved honeycombed pattern and hyper-refractile pagetoid small nests, quite regular and dense (figure 1C). In particular in case 1 (figure 1) some isolated bright pagetoid roundish cells were detected whereas they were not seen in the case 2 and 3. Cases 2 and 3 showed meanwhile absence of hyper-refractile cells and a different combination of hypo-refractile pagetoid cells (like dark holes) (figure 2 panel C).

At the dermo-epidermal junction (DEJ) some atypical single hyper-refractile cells were detected as well as dense bright nests, similar to the ones in the epidermis in case 1. No hyper-refractile cells had been detected in the lesions 2 and 3 at the DEJ. Meanwhile, hypo-refractile nests were detected at the DEJ surrounded by a dark cleft. Inside the nests, small dendritic and roundish cells were visible (figure 1 panel D). Other parameters usually detectable in melanoma (such as high number of large dendritic cells and atypical cells at the DEJ) were not clearly recognizable in present lesions.

The histopathological reports described melanoma in situ arising on a preexisting dermal naevus in case 1 (figure 1 panel E-F) while cases 2 and 3 were respectively a melanoma in situ and an invasive melanoma (Breslow 0.55mm, not ulcerated, mitosis <1 mm²).

Here, dermoscopy alone was not able to clearly orientate towards a malignant melanocytic lesion. On the contrary, RCM is a very useful tool in pink lesions when they lack specific features. Immunohistochemical and ultrastructural studies show that AM cells contain melanosomes and rare melanin granules even if they are not visible clinically⁵.

RCM revealed the presence of pagetoid nests within the epidermis and some bright nests in the papillary dermis. At the same hypo-refractile pagetoid cells previously described in AM were recognized in the epidermis of present cases⁶. No classical melanoma features (like large number of dendritic or roundish hyper-refractile cells)⁷ were visible in the epidermis.

Nests in melanoma and melanocytic benign lesions are almost always hyper-refractile at RCM, while hypo-refractile nests are usually features detected in basal cell carcinoma. In the present series the uncommon presence of both, associated with the presence of hyper-refractile single cells in an atypical fashion made us able to make the diagnosis of melanoma. Taking into account the genetic alterations of our patients, we could hypothesize that case 1 (from patient 1) and case 2/3 (from patient 2) showed a small melanine production with different phenotype of melanosomes suggesting a variable production of melanine even in the same OCA1 clinical condition.

OCA type 1 does not produce Tyrosinase or produces just a bit of it. Here, the presence of missense mutations or the splicing mutation can be the responsible for the small production of melanine, while if the patients carried the frameshift in homozygosis the production of melanine can be null. In fact the low production of tyrosinase allows the small production of either eumelanine depending from the *MC1R* genotype. Both patients carried a “not-red-hair” heterozygous polymorphisms, thus allowing the small production of eumelanine. This reflects variable clinical scenario from a total absence of pigment to a very low production. In albino OCA1 the production of both melanines is lower than not mutated subjects but still variable (according to the expression of the *MC1R* mutation) and this justify the presence of different refractivity structures between case 1 and case 2–3 at RCM.

In conclusion, the combination of dermoscopy and RCM should be used for pinkish atypical lesions in order to detect incipient amelanotic melanomas in oculocutaneous albinism.

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FIGURE 1. Melanoma in patient 1

A. Clinical view of the erythematous lesion of the right abdomen of patient 1.

B. Dermoscopy images: Over an erythematous background, a polymorphous vascular pattern characterizes the lesion, with the presence of dotted and comma-like vessels in two well differentiated areas.

C. High resolution confocal images (0.5×0.5mm) at the epidermis layer reveals a honeycombed pattern with atypical cells (green arrow) and hyper-refractile nests (red*), corresponding to the area with dotted vessels.

D. High-resolution confocal images (0.5×0.5mm) at the dermo-epidermal junction. Hyper-refractile (red*) and hypo-refractile (yellow*) nests plus nucleated hyper-refractile single cells (green arrows) are detected

E. Histopathology: Malignant melanoma in situ, arising on a preexisting dermal naevus. Some pagetoid cells are visible surrounded by clefting. Dermal papillary vertical vessels, corresponding to dotted vessels are present.

F. Immunohistochemistry (S100 stain): pagetoid single cells and pagetoid nests are visible in the epidermis. The latter have a perfect correlation with the nests detected by RCM. Nests at the papillary dermis (corresponding to the hypo-refractile nest with clefting at the RCM).

FIGURE 2. melanoma in patient 2

A. Clinical view of the two melanomas of the lower leg of patient 2.

B. Dermoscopy images: Erythematous background, with the presence of dotted vessels.

C. High resolution confocal images ($0.5 \times 0.5 \text{ mm}$) at the epidermis layer reveal a honeycombed pattern with atypical pagetoid hypo-refractile cells (green arrow)

D. High resolution confocal images ($0.5 \times 0.5 \text{ mm}$) at the epidermis layer reveal hyper-refractile nests (red*)