

## A Case of Four Synchronous Cutaneous Melanomas: Melanocortin 1 Receptor Polymorphisms and Excessive Sun Exposure

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Accepted Nov 19, 2019; Epub ahead of print Nov 19, 2019

Synchronicity has been defined as melanomas occurring within 3 months of the first primary melanoma (1). According to the literature 0.5% of all patients with cutaneous melanoma (CM) have synchronous second primaries (2) and 26–40% of patients with multiple primary melanomas present with synchronous lesions (3). However, few cases have been reported with more than 2 synchronous CMs in the same patient (1, 4).

### CASE REPORT

A 79-year-old patient presented to the dermatology clinic for routine mole mapping. He reported no personal or familial history of melanoma and had recently had a basal cell carcinoma (BCC) excised. He reported prolonged sun exposure without sunscreen, and sailing and golf as hobbies. Clinical examination revealed that he had skin phototype II. He had fewer than 10 naevi and widespread photo-damage. Four suspicious pigmented lesions, presenting as light-brown macules with irregular borders and red-pink-white areas, were identified on the right leg, right thigh, left shoulder and left dorsal region, respectively (Fig. 1A–D). Dermoscopy of all lesions revealed suspicious features, such as amorphous homogenous brownish, milky red and whitish regression areas (Fig. 1E–H). Histology confirmed CMs for all 4 lesions (Fig. 1I–L). Three of the lesions (right leg, right thigh and left shoulder) were *in situ* superficial spreading melanomas (SSM), while the lesion on the left dorsal region was a SSM with 0.4 mm of Breslow thickness and Clark level II.

Genetic counselling was performed and the patient provided a blood sample from which genomic DNA was extracted for molecular analysis of the high penetrance CM susceptibility genes, cyclin-dependent kinase 2 A (*CDKN2A*) and cyclin-dependent kinase 4 (*CDK4*, exon 2) through Sanger sequencing. Medium-penetrance CM susceptibility genes, microphthalmia-associated transcription factor (MITF, exon 10) and melanocortin 1 receptor (MC1R), and protection of telomeres 1 (*POT1*) were analysed through a custom Next generation sequencing panel (5). The analyses revealed 2 variants of *MC1R*, R142H and R163Q, whereas no pathogenic variants were found in the other genes.

### DISCUSSION

Since this patient had extensive photodamage and developed multiple CMs in his 70s, at a first glance, excessive sun exposure would appear to be the risk factor for the occurrence of his multiple melanomas. However, chronic sun exposure is linked mainly to non-melanoma skin cancer (NMSC) and lentigo-maligna type CMs. Curiously, the patient developed a rather small number of NMSC

(only one BCC and few actinic keratoses of the face) and the CMs were histologically superficial spreading, non-lentigo maligna type. Thus, genetic factors should be investigated for the susceptibility to 4 synchronous CMs.

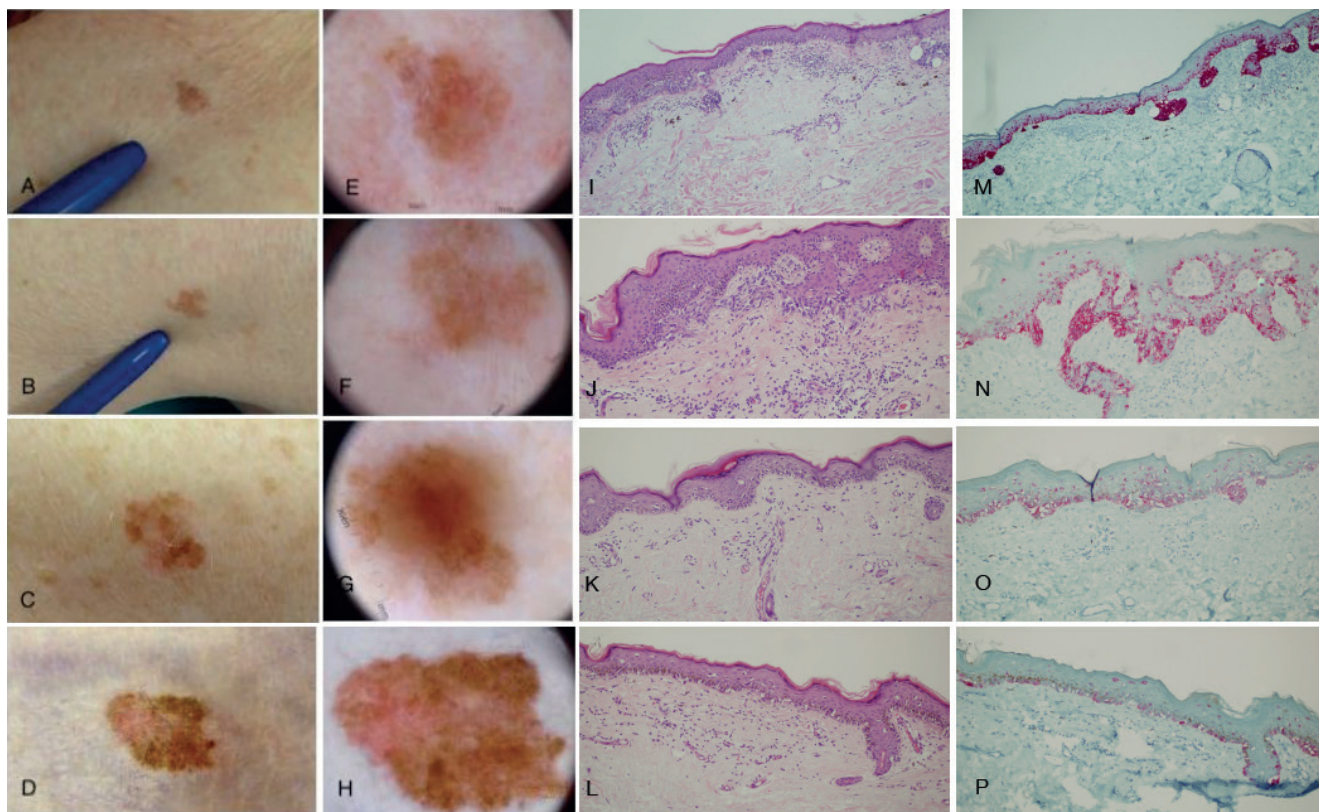
The unusual symptom in this case is the synchronous presence of 4 melanomas. This occurrence is quite rare, but it should be noted that 3 of them were melanoma *in situ*, which may have been present for a while and could have changed very slowly. It is therefore possible that these melanomas belong to the specific category of indolent slow-growing non-lentigo-maligna type melanomas (6).

Certain polymorphisms of the *MC1R* gene are reported to be associated both with melanoma risk and fair skin phenotype, while others are associated only with melanoma risk (7–9), suggesting that MC1R variants play a role in melanoma development via both pigmentary and non-pigmentary pathways (10). The current patient harboured one of the red hair colour (RHC) variants of MC1R, R142H, which is associated with both a UV-radiation sensitive phenotype and melanoma development (10–12).

The other variant harboured by our patient, R163Q, is associated with melanoma risk, but not with red hair or fair skin, therefore melanoma risk could be increased mainly via non-pigmentary pathways (10). R163Q was found to be related to lentigo maligna melanoma susceptibility in a Mediterranean population (13) as a possible consequence of the role of this variant in skin photodamage and photo-ageing.

Patients who are carriers of at least one *MC1R* RHC variant develop CMs that show lower total dermoscopy score values, reduced dermoscopic structures and lower prevalence of atypical pigment network compared with non-carriers (6, 9). The clinical and dermoscopic features of the 4 CMs in the current patient fit this description. Finally, the 4 CMs in the current patient shared similar clinical and dermoscopic findings, which is in keeping with a recent study showing that elderly patients with sun-damaged skin may present with multiple and synchronous, thin CMs characterized by atypical pigment-network and regression structures (13).

The genetic background in the current case contributed to onset of CMs both by determining his fair-skinned phototype II phenotype and his increased susceptibility



**Fig. 1. Clinical, dermoscopic, histopathological and immunohistochemical Melan-A staining of the 4 synchronous melanomas.** (A, E, I, M) Melanoma of the left dorsum; (B, F, J, N) melanoma of the left shoulder; (C, G, K, O) melanoma of the right leg; and (D, H, L, P) melanoma of the right thigh. (A–D) All lesions shared similar clinical findings, presenting as light-brown macules with irregular borders and red-pink-white. (E–H) Dermoscopy revealed common features in all 4 lesions. (E) Multicomponent pattern, milky red areas, a regression area, shiny white streaks. (F) Multicomponent pattern, brownish homogenous areas, regression areas, and polymorphic vessels. (G) Multicomponent pattern, central brownish homogenous area, regression area with peppering. (H) Multicomponent milky red area, shiny streaks and polymorphic vessels. (I–P) Histopathological and immunohistochemical images (haematoxylin-eosin stain, Melan-A stain; original magnification  $\times 10$ ). All 4 melanocytic lesions were large ( $>10$  mm of maximum diameter). They consisted of epidermal atypical melanocytic proliferation with a predominant lentiginous growth pattern and focally with pagetoid extension of atypical melanocytes up to the granular layer. For both the melanocytic atypia and the proliferation pattern, a diagnosis of melanoma was confirmed. Immunohistochemical assay for Melan-A helped in displaying the proliferation pattern.

to photo-damage, but the other MC1R variant may also increase melanoma risk via non-pigmentary pathways. The current patient also had large atypical naevi, which are unusual for a patient of his age, as junctional and atypical naevi involute with age, which suggests that lack of senescence may also have a role.

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