Letter to the Editor

Underlying Amelanotic Lentigo Maligna Melanoma Uncovered After a Severe Blistering Sunburn

To the Editor:

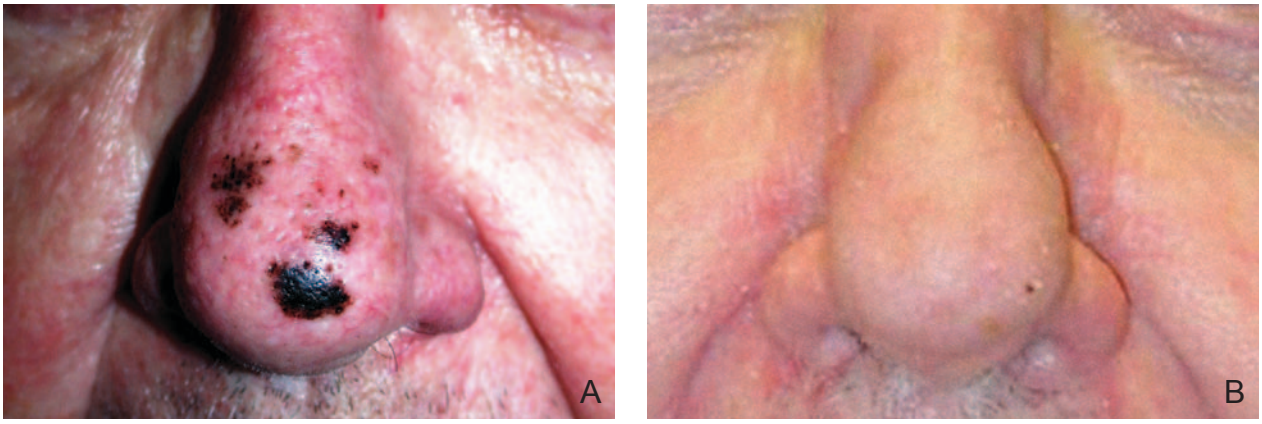
A 76-year-old Caucasian man presented with dark spots on his nose of 6 months' duration that developed immediately after a blistering sunburn (Figure, A). He insisted that there were no recognizable dark spots present on his nose prior to the sunburn and that the lesions developed as the sunburn healed. He provided us with photographs from 3 months prior to the sunburn, confirming that none of the lesions seen on examination were apparent at that time.

Physical examination demonstrated 4 brown to black macules in addition to hyperpigmented follicular ostia on the nasal tip. Full skin examination was otherwise unremarkable and no lymphadenopathy was noted.

Biopsies of the 3 distinct hyperpigmented areas were performed. Histopathologic evaluation revealed a nonulcerated lentigo maligna melanoma (LMM) with a greatest thickness of 0.85 mm. A subsequent scouting biopsy of the apparently healthy, interlesional skin revealed amelanotic melanoma in situ. A wide local excision was performed of the entire nasal tip and histologic examination of the final excision specimen was notable for a Breslow thickness of 1.48 mm, a vertical growth phase, lymphocytic infiltrate, and 13 mitoses in 10 high-power fields. Thus the patient had an LMM of the entire nasal tip with pigmented, amelanotic, and in situ components. The patient underwent an interpolated paramedian forehead flap repair (Figure, B). Recently, more than 3 years after the original presentation, the patient was diagnosed with metastatic melanoma in the abdominal cavity and is undergoing treatment.

Amelanotic melanoma is a rare subtype of melanoma with an incidence of approximately 2% to 8%.[1] While amelanotic melanoma exists as its own subtype, it may present as any of the more traditional clinical subtypes of melanoma. Of the melanoma subtypes, subungual and desmoplastic malignant melanomas appear to have the highest rates of amelanosis (15%–25% and >50%, respectively).[2,3] There have been scattered case reports of amelanotic lentigo maligna and amelanotic LMM, but overall this diagnosis appears to be a relatively rare event.[4] Our patient demonstrates an interesting case of a pigmented and amelanotic LMM that presented immediately following a blistering sunburn, providing a unique opportunity to examine the relationship between sunburn and melanoma development.

The close temporal relationship between the blistering sunburn and the subsequent discovery of melanoma in this patient raises 2 interesting questions and hypotheses: (1) Did this patient harbor an indolent amelanotic lentigo maligna that was only unveiled by severe UV radiation (UVR) exposure, which induced melanogenesis within the lesion? or (2) Did sudden severe UVR exposure and a burn lead to the development of a de novo LMM?



Patient before (A) and after excision with an interpolated paramedian forehead flap repair (B).

The first hypothesis highlights the biologic relationship between UVR and the induction of melanogenesis, while the second underscores the relationship between UVR and melanocytic carcinogenesis. Several pieces of evidence lend support to both hypotheses.

Lentigo maligna develops on chronically sun-damaged skin. There is a relative paucity of information regarding the long-term risk for invasion of lentigo maligna. Population-based analyses of patients with lentigo maligna estimate the lifetime risk for the subsequent development of invasion to be between 2.2% and 4.7%, depending on the age of presentation with lentigo maligna,[5] which emphasizes the chronic nature of lentigo maligna and the increased likelihood that our patient harbored at least a clinically indolent amelanotic lentigo maligna because the lesion would have had to be present for a long period of time for it to become an LMM.

Melanogenesis is the method by which melanocytes provide photoprotection; it is dependent on the rate-limiting enzyme tyrosinase. In most melanomas, however, tyrosinase is produced at equal or slightly reduced levels compared to healthy human melanocytes. In a minority of melanomas, tyrosinase is absent. It has been suggested that in tyrosinase-negative amelanotic melanoma cells, tyrosinase is down-regulated by dominantly acting oncogenes.[6]

In accordance with these data and in support of our hypothesis, the amelanotic tumor cells in our patient may have had decreased tyrosinase levels. The subsequent intense exposure to UVR may have overridden the inhibition of tyrosinase while stimulating melanogenesis. UV radiation–induced hyperpigmentation of the human epidermis first involves melanocytic hyperplasia, followed by the synthesis and activation of tyrosinase that increases melanogenesis, and lastly the transfer of melanosomes to keratinocytes.[7] The skin's melanogenic potential in response to UVR also is partially mediated by the expression of various melanocortin 1 receptor, *MC1R*, isoforms. Different isoforms of *MC1R* respond differently to UVR. Some isoforms increase tyrosinase content in response to UVR, while others inhibit melanin synthesis from UVR exposure.[8]

In our patient, it is reasonable to assume the existence of a clinically unapparent amelanotic lentigo maligna before his blistering sunburn. The overwhelming UVR exposure and blistering sunburn may have stimulated melanocytic hyperplasia and induced the production of tyrosinase by altering the balance between several *MC1R* isoforms, ultimately causing the efflorescence of a pigmented LMM in the background of his preexisting amelanotic lentigo maligna or LMM.

The precise relationship between UVR exposure, sunburns, and melanoma is not completely understood, but it is clear that UVR is a major risk factor for melanoma.[9] Several reported risk factors lend support to this relationship, such as the increased incidence of melanoma in individuals with lighter skin colors and lighter hair and eye colors as well as in individuals that reside in lower latitudes.[10] Additionally, patients with xeroderma pigmentosum who lack DNA repair mechanisms have an increased risk for developing melanoma.[11]

A meta-analysis by Gandini et al[12] corroborated earlier findings that intermittent, irregular, intense sun exposure considerably increased the risk for melanoma in contrast to more regular consistent exposures, mirroring our patient's exposure pattern. Murine studies have even suggested that melanocyte proliferation in normal skin is most efficiently induced by a single UVB overexposure.[13] Similarly, in humans, single broad-band erythematogenic doses of UVR were found to cause melanocytic activation in nevi,[14,15] which is consistent with findings suggesting that sunburn is a more statistically significant risk factor for melanocytic nevus–associated melanomas than for de novo melanomas in humans ($P=.011$).[16]

There is, however, some suggestion that UVR exposure can induce a de novo melanoma. One study demonstrated that a single dose of UVR, corresponding to a sunburning dose at midlatitudes in midsummer, was enough to stimulate the development of melanoma in neonatal albino mice transgenic for hepatocyte growth factor/scatter factor.[17] There is no corresponding evidence in humans. Thus, although hypothetically possible, it would appear to be unlikely that our patient developed a de novo melanoma on normal skin following a single intense sunburn.

We conclude that the evidence strongly supports the hypothesis that our patient developed a newly pigmented LMM in a subclinical amelanotic LMM following a single blistering sunburn. Our case highlights the relationship between UVR and melanogenesis and tumorigenesis. Most relevant and possibly fortunate for our patient was that his amelanotic LMM was induced to produce pigment by an acute UVR exposure, alerting the patient to seek medical attention. In this case, a sunburn may have saved his life.

Sincerely,
Daniel I. Wasserman, MD
Amy Chang, MD
Dennis Lee, MD
Arnold Lee, MD
Daniel Finn, MD
Boston, Massachussets

The authors report no conflict of interest.

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