CASE REPORT

Amelanotic melanoma: a unique case study and review of the literature

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SUMMARY

Amelanotic melanoma (AM) is a rare form of melanoma which lacks visible pigment. Due to the achromic manifestation of this atypical cutaneous malignancy, it has been difficult to establish clinical criteria for diagnosis. Thus, AM often progresses into an invasive disease due to delayed diagnosis. In this report, we describe the case of a 72-year-old Caucasian woman who had been diagnosed with AM after 3 years of failed treatments for what presented as a periorbital dermatitis. Her Clark's level 4, 1.30 mm thick melanoma required nine surgeries for successful resection and reconstruction. This case exemplifies the diagnostic pitfall of AM and the need for new criteria for early detection and management.

BACKGROUND

Amelanotic melanoma (AM) is a rare form of cutaneous melanoma frequently detected late due to the lack of clinical criteria and the of absence of pigmentation. While it has been reported that AM represents approximately 2%–8% of all melanoma cases, the true prevalence of this malignancy may be greater due to misdiagnosis.[1] This report describes the case of an AM which had been interpreted as an inflammatory dermatosis and progressed to an invasive melanoma.

CASE PRESENTATION

A 72-year-old Caucasian woman presented to her dermatologist 3 years prior with an erythematous patch on her left lower eyelid and eyebrow, as well as 'little red bumps' that seemed to come and go. The area of redness seemed to get larger each time it reappeared. She denied itching, pain, burning or bleeding.

The patient's medical history was significant for rosacea and centrofacial dermatitis. She had no personal or family history of melanoma. Review of systems was unremarkable. As such, her facial eruption was treated as an inflammatory process with various topical and oral medications, including topical tacrolimus, topical fluocinonide, oral fluconazole and oral doxycycline, as well as vascular laser therapy, resulting in only mild and temporary improvement. When the eruption became increasingly symptomatic with burning, itching and scaling, two punch biopsies were taken from the left lateral inferior eyelid and left zygoma (figure 1) that clarified the diagnosis as amelanotic malignant melanoma in situ, lentigo maligna type (MISLMA). At this point, the patient was referred for treatment.

On clinical exam, the lesion appeared as accuminate, pink and flesh-coloured papules with no pigment on dermatoscopy (figure 2). The pronounced telangiectasia in the malar region is consistent with the patient's history of erythematous rosacea, as this vascular prominence predated her use of topical corticosteroids. Only on Wood's lamp exam was there some evidence of melanin along the left lower eyelid. Below the left eyelid was a crescentic area of hypopigmented skin that extended from left lateral canthus medially towards the nose.

TREATMENT

To guide the surgical management, prior to excision (figure 3), four scouting punch biopsies were obtained to assess the perimeter. Three of the four displayed MISLMA and the fourth punch biopsy showed level 2 invasion to 0.40 mm at position A in figure 4. Wide local excision with microscopically controlled margins produced a 4.0 × 2.3 × 0.3 cm leaf-shaped excision specimen displaying two sites of invasive melanoma: level 4, 1.30 mm in thickness with a single dermal mitosis at position B in figure 4, corresponding to American Joint Committee on Cancer (AJCC) Stage 2a and a separate site of level 2 invasion to 0.22 mm at position C in figure 4. No residual invasive tumour was at prior punch biopsy site A. MISLMA extended to the entire epidermal rim of this initial attempt at complete excision.

An incidental small intradermal nevus at position E in figure 4, in addition to two small incidental intradermal nevi beneath MISLMA in both of the two initial punch biopsies (figure 1), accounted for the clinical 'flesh-coloured papules'. The lack of intervening scar between these three distant nevi, which happened to be in the malignant melanoma (MM) field, indicates that they were separate lesions and could not represent residual portions of one pre-existing intradermal nevus.

The fourth procedure was a circumferential rim re-excision specimen displaying MISLMA extending to the epidermal rim in six separate zones about the periphery and an additional site of level 2 invasion to 0.35 mm depth at position D in figure 4. Three subsequent stages produced narrow peripheral strips creating the postoperative defect displayed in figure 3 and as outlined in green in the

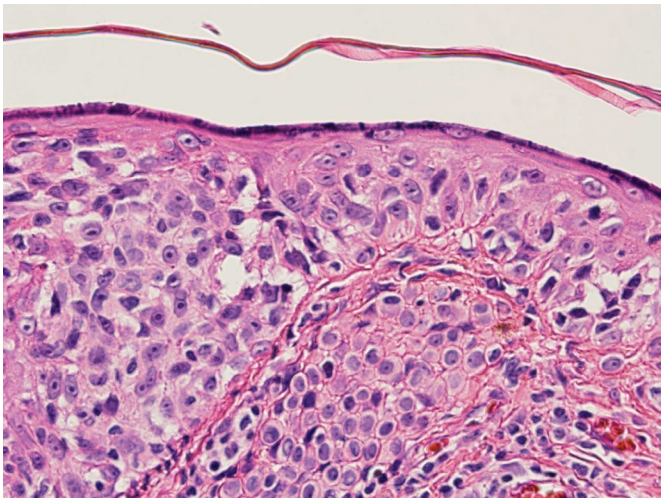

Figure 1 Initial biopsy. An atypical population of lower epidermal melanocytes with variable nuclear size and prominent nucleoli lack melanin pigment and show pagetoid rise above nevomelanocytes of an incidental underlying intradermal nevus lacking prominent nucleoli (×400).

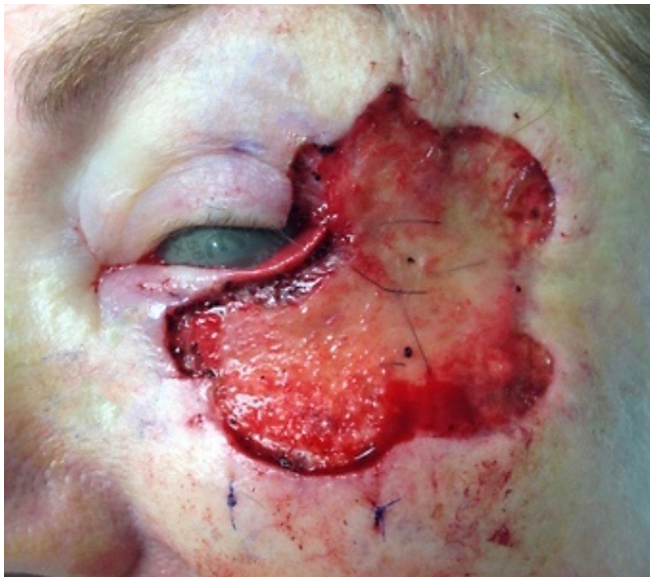

Figure 3 Postoperative defect following the fifth stage of a seven-staged excision, measuring.

schematic diagram presented as figure 4. Two additional stages produced the superomedial margin extension outlined in blue in figure 4, finally achieving a benign circumferential margin approximately 6 months from the initial punch biopsies that clarified the diagnosis.

The clinical appearance (figure 2) gave no warning as to the extent of this neoplasm. MISLMA extended far beyond the area that was originally biopsied and well into what appeared clinically as normal skin in this Caucasian woman with Fitzpatrick skin type I, spanning from left lateral canthus to malar cheek and involving 80% of the lower eyelid with margins extending to the lateral upper eyelid. All areas of the infraorbital region, including the pink and flesh-coloured papules, hypopigmented and achromic areas and normal-appearing skin, was involved by MISLMA, with four small invasive foci. The spot of deepest invasion 1.30 mm into the dermis, Clark's level 4 (AJCC stage 2a), at position C in figure 4 was located in an area of normal-appearing skin between the left lateral lower eyelid and superior zygoma.

Due to microscopic involvement of surgical margins, this tumour required seven stages for eradication, which tripled the size of the clinically erythematous area. The final surgical defect was 8.0 × 7.0 cm, extending into muscle and involving a significant portion of the eyelid margin and cheek. The wound was repaired predominantly with a large full-thickness skin graft

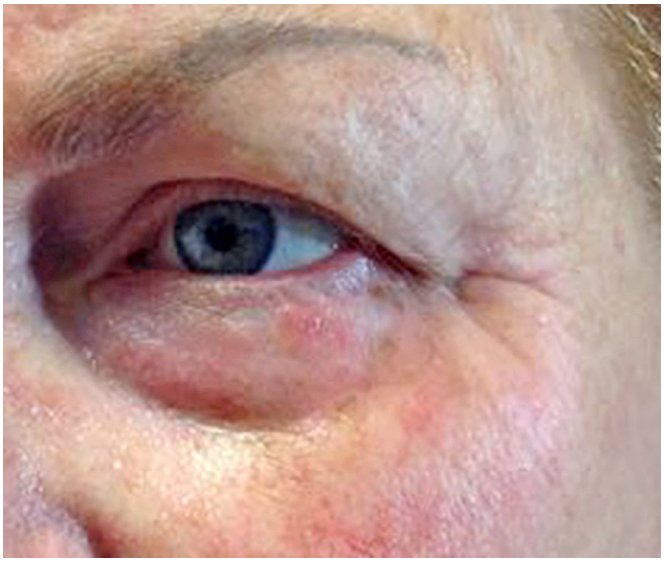

Figure 2 Amelanotic melanoma presenting in a 72-year-old patient. Following only the initial punch biopsies, the left eyelid and cheek area appeared as a red scaly erythematous patch without melanin pigmentation.

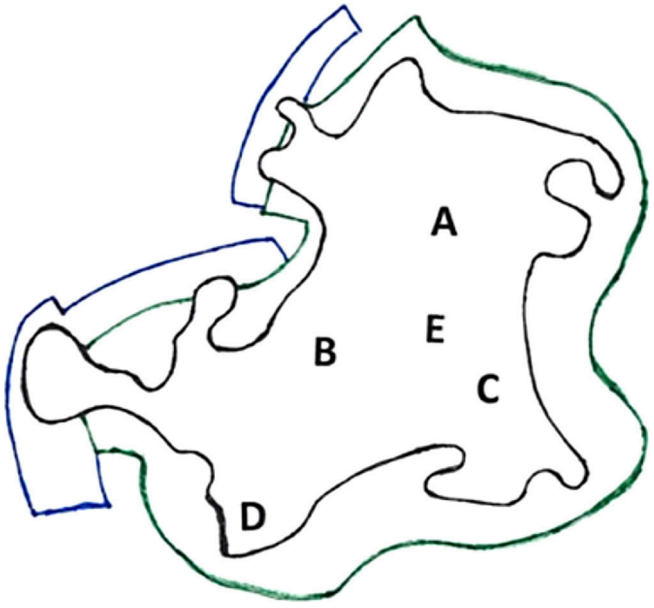

Figure 4 As reconstructed from the several specimens, the irregular outline of melanoma in situ is in black, set within the postoperative outlines of surgical stages 5 (green) and 6 (blue). The four focal sites of invasion are at letter positions: A = 0.42 mm, B = 1.30 mm, C = 0.22 mm and D = 0.35 mm. An incidental small papular intradermal nevus was at position E.

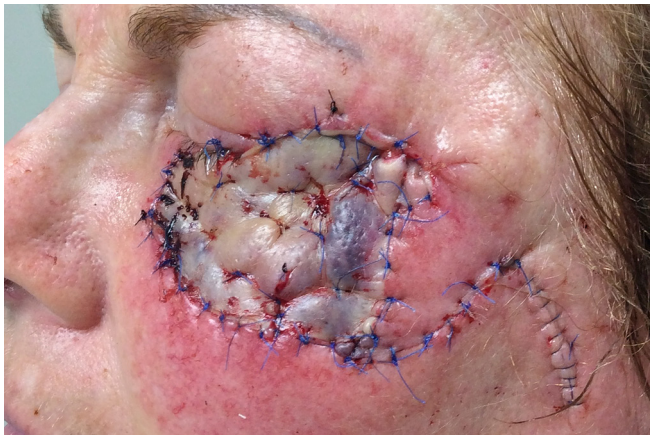

Figure 5 One week following repair with a full-thickness skin graft and laterally-based rhombic transposition flap.

taken from the submental region as well as a laterally-based rhombic transposition flap (figure 5).

The patient underwent a complete staging workup to rule out metastasis. Blood work, positron emission tomography/CT scan and physical examination were unremarkable. A Decision Dx-Melanoma gene expression assay test classified the patient into molecular signature class 1 with a probability value of 0.48, which correlates with a low risk of metastatic disease within the next 5 years with 'reduced confidence'. Together, the Decision Dx-Melanoma test reveals that the patient has a 6% risk of metastatic disease within the next 5 years.

OUTCOME AND FOLLOW-UP

The patient healed without sequelae (figure 6) and is now tumour free at 2 years.

DISCUSSION

Cutaneous MM accounts for two-thirds of all deaths from skin cancer.[2] Poor prognosis for malignant melanoma of the eyelid is correlated to Breslow depth greater than 1.5 mm (Clark's level 4).[2] As with all melanomas, the key to cure is early detection and management. This is particularly problematic in a case like the present one where clinical characteristics for diagnosis of melanoma are absent.

Amelanotic melanoma is a rare form of melanoma characterised by lack of pigment on clinical examination. While certain clinical criteria have been useful in the diagnosis of cutaneous pigmented melanoma (ie, ABCDEs: asymmetry, irregular borders, colour variation, diameter over 6 mm and evolution), there is no explicit clinical appearance that is unique to the amelanotic variant of this disease. For this reason, Kelly *et al* have proposed the addition of the EFG criteria (elevated, firm, growing for more than 1 month) to the established ABCDE rule to aid in early detection.[3] In the present case, two out of the three EFG criteria were met: the patient noted elevated 'bumps' in the area, and the lesion had been enlarging for well over 1 month.

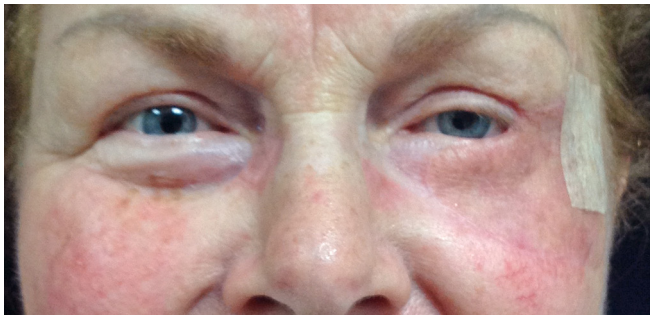

Figure 6 Final result at 6 months following reconstruction.

The clinical presentation of melanoma varies based on anatomic location and histopathology. Any of the four major histopathological subtypes of melanoma — nodular melanoma, superficial spreading melanoma, lentigo maligna melanoma and acral lentiginous melanoma — can be amelanotic. As such, distinguishing clinical features can be lost. Thus, the diverse clinical presentations of AM and associated lack of criteria established for detection pose a significant diagnostic challenge for the management of a potentially fatal disease.

In review of literature, a retrospective evaluation of 20 individuals diagnosed with non-nodular AM, Jaimes *et al* report that all lesions presented as erythematous macules or plaques.[4] Of those cases, 70% exhibited a scaly appearance, a clinical feature which has been reported in numerous other case reports of AM, including those performed by Tschen *et al* and Zalaudek *et al*.[5–7] Jaimes *et al* propose that this characteristic may be explained by a relationship between increased turnover of keratinocytes and the melanocytic regulation of keratinocyte differentiation and proliferation.[4] As such, neoplastic melanocytes may, in some way, increase keratinocyte proliferation.[4] Thus, suspicious lesions with prominent flaking or scaling with no other discernible cause, such as clinically observed in the present patient, warrant a biopsy for definitive diagnosis.

In the present case, no classic findings pointed to melanoma. Instead, she had a non-specific, poorly demarcated 'dermatitis' without notable pigmentation. That this nondescript process seemed to improve for weeks at a time and initially had no associated symptomatology besides occasional itching, reinforced misinterpretation as an inflammatory process.

While clinical criteria are non-specific, dermatoscopic findings have been helpful in guiding the diagnosis of AM. Due to the absence of pigment, the significance of dermatoscopic analysis of non-pigmented skin lesions is based on examination of vascular morphologies and distribution. Dermatoscopic analysis has revealed distinct vascular morphologies specific to AM: serpentine (or polymorphous) vessels, irregular linear vessels, pinpoint (dotted) vessels and hairpin vessels.[8 9] In particular, Menzies *et al* reported the combined presence of dotted and irregular linear vessels to be a positive indicator of AM.[10] In contrast, 'comma-like' vessel morphology was found to be a significant negative indicator for AM.[10] Research has also shown that vascular morphology is dependent on tumour progression.[10] Dotted vessels, homogenous in shape and arrangement, are associated with early (or 'flat') AM, while linear vessels appear in increasing number as the tumour advances; longer vessels that are more coarse and variable in shape are associated with the most advanced disease.[10] Additionally, the specific distribution of the vasculature can support the diagnosis of AM, as atypical distribution of vasculature along the peripheral edges of the skin lesion has been reported to be a positive indicator of AM.[8 11] Because distinct morphology and distribution of vasculature is essential to AM diagnosis, one must be extremely cautious of applying too much pressure with the dermatoscope during clinical examination to avoid compression, and subsequent distortion, of vascular patterns.[8]

Dermatoscopic vascular clues and increased pigmentation were lacking in the present case. The clinical appearance and dermatoscopic indications were further obscured by pulsed-dye laser therapy the patient received, as these vascular

laser treatments may have contributed to the lesion's achromic progression. Blay highlights the potential danger of vascular laser treatment of unidentified skin lesions, particularly those in sun-exposed areas, such as the face, to prevent accurate clinical and histological examination.[12] Pulsed-dye laser therapy can alter vascular morphology, preventing the identification of vascular patterns indicative of AM. Vascular laser therapy can directly impact melanogenesis, resulting in decreased melanin production/pigmentation.[12] Thus, the treatment of ambiguous skin lesions with pulsed-dye laser therapy, especially recurring lesions with a history of unsuccessful treatment, may hinder the appreciation of malignancy.

Amelanotic melanoma presents a diagnostic challenge due to the lack of clinical criteria established for detection and because AM often resembles inflammatory skin disorders including eczema, psoriasis, rosacea and contact dermatitis.[4 13] AM can also clinically resemble benign neoplasms (nevi, haemangiomas, seborrheic keratosis) as well as malignant tumours such as Bowen's disease and basal cell carcinoma.[3 4 13 14] AM often presents as a solitary, scaly patch or plaque that does not respond to various topical treatments.[4 14] AM should be considered in the differential diagnosis, and a biopsy should be obtained, for any lesion that fails to respond to treatment after 1 month. While this patient's valid history of rosacea and centrofacial dermatitis seemed to support the diagnosis of an inflammatory process, that the lesion failed to respond to a variety of treatment methods over the course of 3 years was an important signal to biopsy.

Learning points

- Early detection is the mainstay of therapy for melanoma.
- Amelanotic melanoma should be included in the differential diagnosis of non-pigmented skin lesions.
- Providers should maintain a low threshold for biopsy when normal-appearing skin or achromic skin lesions have failed to respond to treatment and demonstrate at least one of the following three criteria which serve as potential indicators of the disease: (1) vessel morphology, (2) ABCDEFG (asymmetry, irregular borders, colour variation, diameter over 6 mm, evolution, elevated, firm, growing for more than 1 month) criteria and (3) persistence (despite treatment) for more than 1 month.

Contributors RJH has been responsible for ongoing management of the patient as her medical dermatologist. BDR was the dermatopathologist on this case. RDS was the patient's dermatologic surgeon. KKS was the medical assistant for RDS on this case as well as the project administrator, responsible for literature review, drafting of manuscript, and final editing. RJH, BDR, RDS: supervision, critical revision for content, final approval of article.

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