

Tumoral melanosis associated with combined *BRAF/MEK* inhibition (dabrafenib/trametinib) in metastatic melanoma



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Key words: *BRAF*; dabrafenib; *MEK*; melanoma; metastatic; regression; trametinib; tumoral melanosis.

INTRODUCTION

Tumoral melanosis describes a pigmented lesion clinically suspicious for melanoma but characterized histopathologically by aggregates of melanin-laden macrophages without malignant cells.^{1,2} Limited cases of tumoral melanosis exist in the literature; often it is identified on the skin as a macule or papule or may present in the lymph nodes of a patient with a history of melanoma or a longstanding atypical lesion, and further investigation can yield undiagnosed local or metastatic disease.^{2,3} Recently, there are examples of tumoral melanosis arising during treatment for melanoma, mostly with anti-PD-1 or anti-CTLA-4 therapy.^{1,2} Garrido et al⁴ reported on a patient who developed plaques near in-transit metastases after starting dabrafenib-trametinib, with biopsy showing granulomatous inflammation admixed with melanophages. They are the first, to our knowledge, to describe tumoral melanosis with this treatment.⁴ The following is a unique case of nodular tumoral melanosis identified in a patient on dabrafenib-trametinib for metastatic melanoma.

CASE REPORT

A 29-year-old man with no prior history of skin cancer presented to a general practitioner with a pigmented lesion overlying his right scapula that had been increasing in size over the previous months. Biopsy found an ulcerated, level-IV malignant melanoma with a 2.3-mm Breslow thickness. Immunohistochemical testing showed *BRAF* V600E mutation. The patient underwent an excision and sentinel lymph node biopsy followed by a right axillary dissection with 2 of 30 nodes involved. His stage at this time was IIIB (T3b, N2a, M0).

The patient was enrolled in a stage III resected disease trial of pembrolizumab versus placebo for 4 cycles until he had locoregional recurrence requiring excision of subcutaneous in-transit metastases on the right back and axilla. He was unblinded on placebo and crossed over to the pembrolizumab treatment arm. Positron emission tomography-computed tomography (PET-CT) performed 6 weeks later showed further disease with subcutaneous metastases and a new T2 fracture. The patient was changed to therapy with dabrafenib 150 mg twice daily plus

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Funding sources: This research was conducted with the support of the Centre of Research Excellence for the Study of Naevi funded by the National Health and Medical Research Council (NHMRC; grant ID: APP1099021).

Conflicts of interest: Dr Victoria Atkinson served on the Advisory Board for BMS for which she received financial compensation in the form of speaker's fees, travel support, and honorarium; served on the Advisory Board for MSD for which she received speaker's fees and honorarium; served on the Advisory Board for Novartis for which she received speaker's fees and honorarium; served on the Advisory Board for Pierre Fabre; served on the Advisory Board for Merck Serono; and received an NHMRC grant. Professor H. Peter Soyer consults for Canfield

Scientific Inc. The other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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JAAD Case Reports 2018;4:921-3.

2352-5126

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<https://doi.org/10.1016/j.jidcr.2018.06.024>



Fig 1. Surveillance image of participant using Vectra WB360 3D Whole Body Imaging System and associated dermoscopic image of left popliteal fossa mimicking a nodular melanoma (lesion 38). Dermoscopic features of interest include a central 10- x 9-mm purple-black, nonulcerated nodule (*star*) with an adjacent brown-black macule with peripheral brown clods (*arrows*).

trametinib 2 mg once daily, and had an urgent resection of the T2 lesion. After 4 cycles of dabrafenib-trametinib, scans showed no evidence of disease progression.

At this time, the patient presented to our center for 3D total body photography (Vectra WB360, Canfield Scientific Inc, Parsippany, NJ). He had a large nodule in the left popliteal fossa (Fig 1). The patient reported the lesion had been present for 10 years but had become rounder and smoother since starting dabrafenib-trametinib. Dermoscopic examination found a central 10- x 9-mm purple-black, nonulcerated nodule with an adjacent brown-black macule with peripheral brown clods, which was clinically and dermoscopically mimicking a primary melanoma (Fig 1).

Histopathology of the lesion showed a nodular collection of heavily pigmented melanophages within the dermis (Fig 2, A). No viable melanoma cells were identified morphologically in serial sections. Immunohistochemical stains were positive for CD68 and negative for S100 (Fig 2, B and C). These features were in keeping with tumoral melanosis and suggestive of a fully regressed melanoma or other nodular melanocytic neoplasm. Follow-up examination found no further suspicious lesions and no regression of the nevi on serial imaging.

Unfortunately, scans after 8 months of dabrafenib-trametinib found new brain metastases. The patient's treatment was changed to ipilimumab and nivolumab; however, he died of his disease two months later.

DISCUSSION

Tumoral melanosis lesions appear clinically and dermoscopically suspicious; however, histopathology

shows abundant melanophages with no malignant cells present. Immunohistochemical staining is positive for CD68 and negative for S100.² Tumoral melanosis is not restricted to melanocytic lesions and can arise secondary to regressed pigmented epithelial lesions, such as basal cell carcinoma.⁵

Recently, there are cases of tumoral melanosis emerging in patients treated with immune checkpoint inhibitors pembrolizumab, ipilimumab, and nivolumab.^{1,2,6,7} We identified only 1 report of tumoral melanosis arising with targeted therapy.⁴ Garrido et al⁴ presented a patient with a history of melanoma who developed cutaneous in-transit metastases on his trunk and neck. After 10 months of dabrafenib-trametinib, he presented with erythematous plaques on his trunk near the in-transit lesions, and biopsy found granulomatous inflammation admixed with melanophages representing tumoral melanosis. With pembrolizumab, our patient experienced disease progression, and there was no change in the left popliteal fossa lesion until treatment with dabrafenib-trametinib, suggesting anti-PD-1 therapy was not effective.

Our case is distinct from prior reports of tumoral melanosis in several respects. First, most cases of tumoral melanosis occurring with therapy for advanced melanoma develop adjacent to a previously excised melanoma or in-transit metastases, and complete regression of primary melanoma with treatment is not well documented. The primary melanoma in our patient was overlying the right scapula, and the tumoral melanosis was identified in the left popliteal fossa. The patient reported the lesion had been present for 10 years and had changed with dabrafenib-trametinib. Although it is impossible to know the exact nature of the preceding

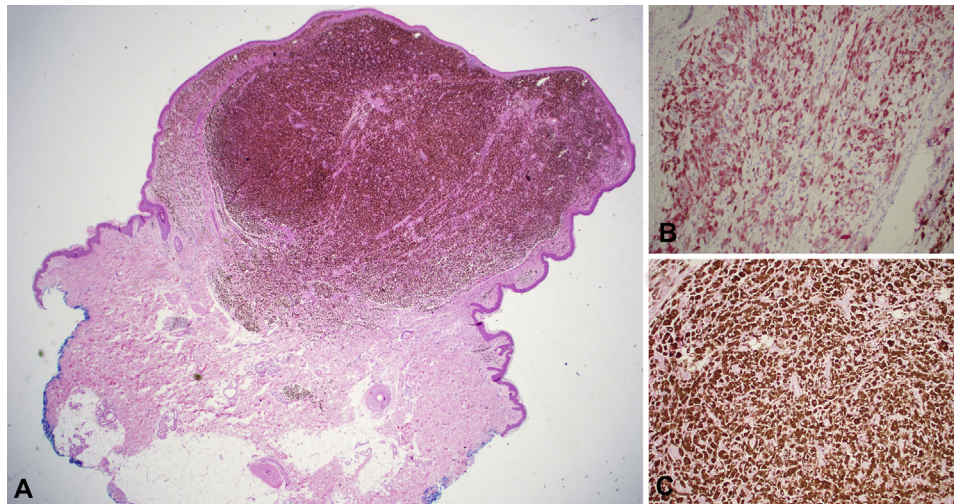


Fig 2. **A**, Large nodular collection of heavily pigmented melanophages in the dermis. No viable melanoma cells were identified. **B**, Immunohistochemistry shows strong positive staining for CD68 and **C**, negative staining for S100. (**A**, Hematoxylin-eosin stain; **C**, red chromagen; original magnifications: **A**, x20; **B** and **C**, x100.)

lesion, the patient's history, the dermoscopic appearance, and the fact that the lesion was cutaneous rather than subcutaneous like the back and axilla metastases, suggest the original lesion was a primary melanocytic neoplasm, possibly a melanoma evolving in a preexisting nevus or a blue nevus which regressed with therapy, rather than a metastatic deposit. Furthermore, although this is the second reported case of tumoral melanosis occurring with dabrafenib-trametinib, the tumoral melanosis in our patient presented alone rather than admixed with granulomatous inflammation.⁴ Lastly, the clinical presentation of tumoral melanosis as a large nodule is rare in the literature.

Increasing atypia and regression of melanocytic nevi is a reported effect of *BRAF* inhibitors and is hypothesized to be caused by the presence of mutated nevus cells, which respond to treatment in the same way as the primary melanoma.⁸ In our patient, there was no change in his nevi on serial imaging, which could suggest other nevi did not share the same mutation as the tumoral melanosis or his primary melanoma.

Several reports suggest that in the setting of immunotherapy and targeted therapy, the presence of tumoral melanosis represents disease regression and favorable treatment response. However, in our patient, this was not the case.^{7,9} With continued use of therapy for metastatic melanoma, the incidence of tumoral melanosis will likely increase, and its possible role as a prognostic factor may become clearer.

We acknowledge the generous support of the Princess Alexandra Hospital Private Practice Trust Fund in purchasing the VECTRA WB360 3D total body imaging system.

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