A diagnostic dilemma: Atypical melanocytic lesions arising in the setting of treatment with the BRAF inhibitor, vemurafenib

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INTRODUCTION

In 2011, the Food and Drug Administration approved vemurafenib, a class 1 RAF inhibitor that is selective for BRAF, for use in unresectable or metastatic malignant melanoma. The BRAF V600E mutation is found in roughly 80%-90% of BRAF-mutated melanomas, and in about 50% of overall melanomas.[1-3] Vemurafenib treatment achieved a response rate of about 50%, a stark improvement from the previous gold standard of dacarbazine chemotherapy (with a response rate around 5%).[2,4] Vemurafenib is also highly effective in patients with relapsed or refractory BRAF-mutated hairy cell leukemia, with overall response rates of 96%-100% in a restrictedstudy.[5]

The use of BRAF inhibitors has come with a wide range of cutaneous side effects, from dermatitides and photosensitivity to atypical squamous proliferations and, more rarely, concerning melanocytic lesions.[1,6] Eruptive melanocytic lesions usually develop within 3 months of treatment with BRAF inhibitors and can also include darkening of preexisting nevi.[7] Here, we present an interesting case of numerous eruptive atypical melanocytic lesions arising in a patient treated with vemurafenib for BRAF-mutated hairy cell leukemia. We suggest that new and evolving melanocytic lesions that are histologically concerning for melanoma should, in the context of vemurafenib treatment, be considered "atypical treatment-related melanocytic proliferations" as opposed to outright melanomas.

CASE REPORT

A 62 year-old man with a history of recurrent hairy cell leukemia (BRAF V600E-mutated) presented 6 weeks after initiating vemurafenib (960 mg twice daily) with multiple new 1-3−mm dark-brown macules and papules on his scalp, trunk, and extremities (Fig 1). An initial biopsy from the posterior aspect of the left shoulder showed an atypical melanocytic lesion concerning for invasive melanoma, demonstrating full-thickness pagetoid migration overlying intradermal epithelioid melanocytic nests with rare mitoses (Fig 2). Molecular testing showed wild-type BRAF. Due to the concerning histologic changes in the initial lesion, 12 additional biopsies of new pigmented lesions were performed. Seven out of 12 subsequent biopsies showed atypical melanocytic lesions with concerning histologic features of early or evolving melanoma, including full-thickness pagetoid migration of atypical melanocytes. All lesions were symmetric at low power and the pagetoid spread did not extend beyond the nested dermal component. After outside consultation and discussion among multiple dermatopathologists, the consensus was that these lesions should be classified as "atypical treatment-related melanocytic proliferations" The remaining lesions sampled

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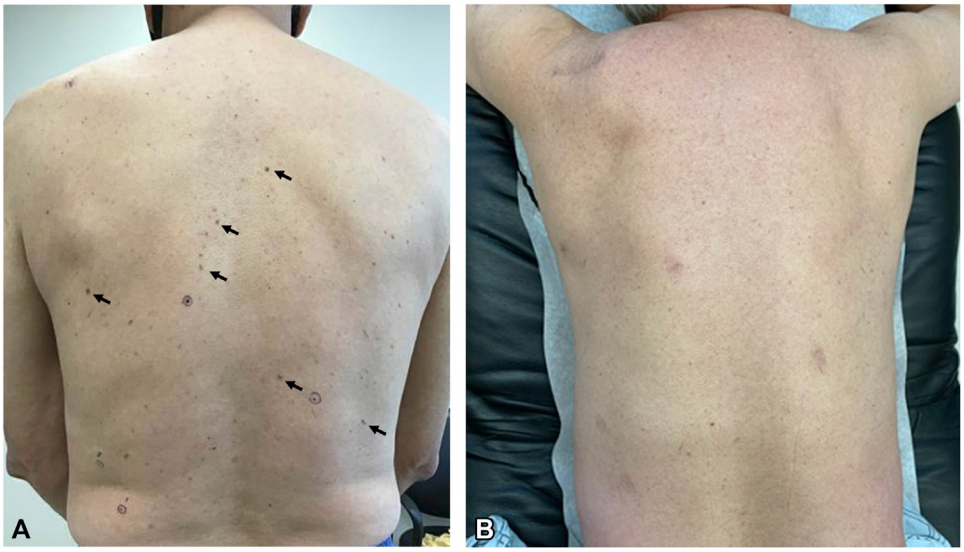

Fig 1. Clinical photos of the patients back before and after stopping vemurafenib. **A,** Appearance at clinical presentation, 6 weeks after starting vemurafenib. Circled lesions indicate those selected for biopsy after the initial biopsy from the posterior aspect of the left shoulder. Some (but not all) of the lesions that later resolved upon stopping vemurafenib are indicated (*black arrows*). **B,** Appearance at follow-up, about a year after stopping treatment with vemurafenib, showing resolution of the pigmented lesions.

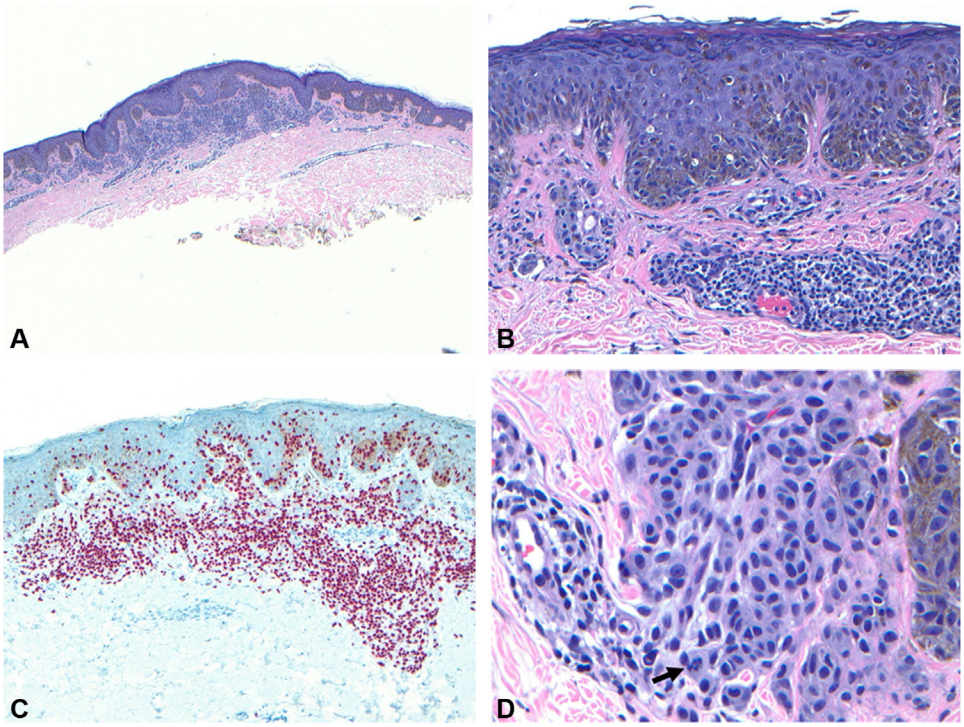

Fig 2. Shave biopsy of the posterior aspect of the left shoulder showing an atypical melanocytic proliferation with histologic features concerning for malignant melanoma *in situ* with possible invasion. **A,** Compound melanocytic proliferation with relative symmetry at low power (hematoxylin-eosin stain; magnification ×40). **B,** Atypical junctional melanocytes with significant pagetoid spread (hematoxylin-eosin stain; magnification ×200). **C,** Prominent full-thickness pagetoid spread of melanocytes (Sox10 immunohistochemical stain, magnification ×100). **D,** Dermal nests of epithelioid melanocytes with rare deep dermal mitotic figure (*black arrow*) (hematoxylin-eosin stain; magnification ×400).

showed compound nevi with mild or moderate atypia. Vemurafenib was discontinued after 10 total weeks of treatment, due to the development of these concerning melanocytic lesions. The most atypical lesions were treated with conservative re-excision. At follow-up 5 months and 12 months after stopping vemurafenib, the patient had resolution of many of the remaining eruptive melanocytic lesions clinically.

DISCUSSION

Cutaneous adverse events occur in roughly 50% of patients treated with BRAF inhibitors for metastatic melanoma.[4] These side effects include benign entities, such as acneiform facial eruptions, other dermatitidis, follicular eruptions, Grover disease, hair changes with alopecia, palmoplantar erythrodysesthesia, panniculitis, keratotic or verrucous papules, and photosensitivity. They also commonly include squamous cell carcinoma (keratoacanthoma-type commonly), as well as changing or atypical nevi and even melanoma.[5,8] Eruptive melanocytic nevi have been described in about 10% of patients receiving vemurafenib.[7] New primary melanomas as a result of vemurafenib treatment have been reported in approximately 2% of patients treated for metastatic melanoma and are invariably BRAF wild-type.[4] While eruptive melanocytic lesions in patients treated for metastatic melanoma are well documented, there are only few reports of new melanomas developing during the treatment of non-melanoma malignancies.[5,8] A single case of cutaneous melanoma was reported by Tiacci et al in a study of patients treated with vemurafenib for hairy cell leukemia.[5] The changes seen in new or evolving melanocytic lesions are thought to arise not from direct tumor promotion but from a paradoxical activation of the MAPK pathway in RAS-mutated or BRAF wild-type cells.[1,2] Combination therapies with BRAF and MEK inhibitors may help limit the development of secondary tumors caused by this paradoxical activation.[7,9]

What has not been sufficiently studied is the criteria for diagnosing melanoma in patients treated with these drugs. Studying the natural progression is difficult, as standard of care indicates excision of worrisome lesions. However, in order to prevent unnecessary wide excisions, pathologists should be aware that, in the context of vemurafenib treatment, some microscopic features otherwise associated with melanoma, such as pagetoid spread or a mitotic figure, may not be sufficient, unless additional evidence (eg, marked asymmetry, nuclear pleomorphism, positive ancillary test results) support the diagnosis of melanoma. If there is uncertainty as to whether a lesion represents true melanoma, we recommend reporting it as an "atypical treatment-related melanocytic proliferation." While larger studies are needed to create usable guidelines for diagnosing and treating these emerging lesions, with borderline cases, a conservative re-excision may be preferable to the standard wide local excision.

Clinicians using BRAF inhibitors should be aware of these melanocytic side effects and the diagnostic and treatment challenges that might arise. Documentation of skin appearance prior to treatment and appropriate sequential follow-up over the course of treatment continues to be crucial for management.

Conflicts of interest

None disclosed.

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