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Letter

Agminated melanocytic nevus status post dabrafenib therapy for metastatic melanoma

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Abstract

Agminated melanocytic nevus is an uncommon type of mole, characterized by a local group of macular or papular pigmented lesions, well demarcated, without a common pigmented background. This pattern has also been associated with Spitz nevi, dysplastic melanocytic nevi, and non-melanocytic lesions.

We describe the onset of an acquired agminated melanocytic nevus after dabrafenib treatment. Our case highlights paradoxical MAPK activation in the setting of single-agent BRAF blockade and underscores the importance of characterizing the diverse side effects of selective BRAF inhibitors. This is the first case, to our knowledge, of agminated melanocytic nevus in association with dabrafenib.

Keywords: Melanoma, agminated melanocytic nevus, Dabrafenib

Dabrafenib is the second selective Class I RAF inhibitor approved by the US Food and Drug Administration for the treatment of metastatic or unresectable melanoma with BRAFV600E mutation. Verrucous keratosis, Grover disease, squamous cell carcinoma, photosensitivity, and plantar hyperkeratosis are relatively common, recently enumerated cutaneous adverse effects with BRAF monotherapy [1]. In contrast, the clinical and microscopic changes within preexisting melanocytic nevi, and similarly, characterizations of de novo melanocytic proliferations secondary to BRAF inhibition continue to be elucidated. Herein, we report a patient in whom an acquired agminated melanocytic nevus developed status post dabrafenib treatment for metastatic melanoma.

Case synopsis

A man in his 40s was diagnosed with primary cutaneous melanoma pT3 M1a with paratraqueal lymph node macrometastases diagnosed approximately three years prior. BRAF V600E mutation was identified with molecular testing at the time of diagnosis. Approximately two years later the patient developed new lymph node and lung metastases. Dabrafenib was initiated at 150mg/ 12 hours. Four months later, the patient noticed the abrupt onset of numerous new melanocytic nevi on the trunk and extremities. Specifically on the right shoulder, fifteen brown papules were compactly arranged and lacked a uniformly pigmented background (Figure 1).

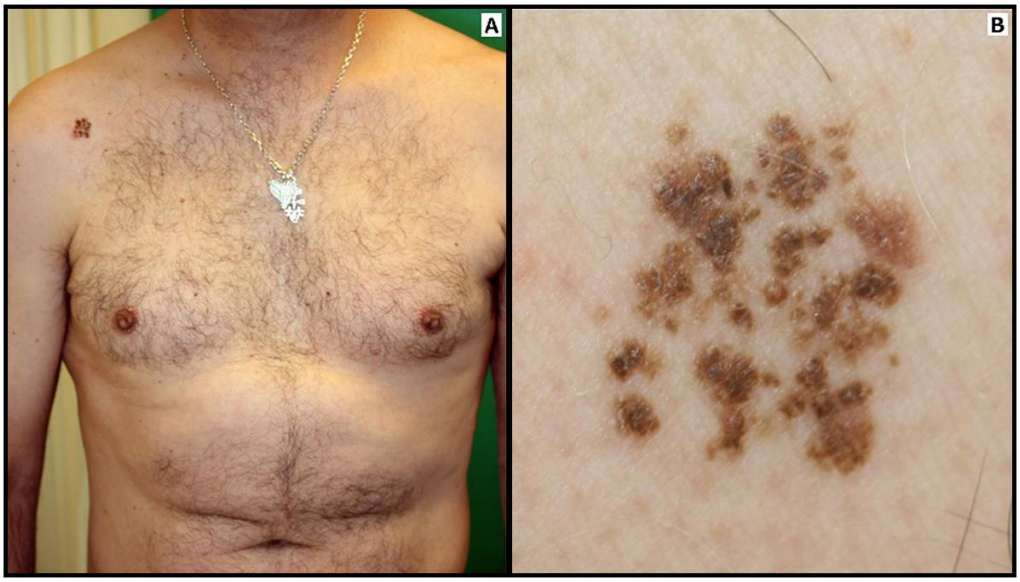

Figure 1. Agminated melanocytic nevi on the right shoulder (a) and detail (b).

Dermoscopic examination showed a globular pattern. A skin biopsy revealed a junctional melanocytic proliferation with single melanocytes arrayed at the sides and bases of rete ridges to form nests; BRAF VE1 stain was negative (Figure 2).

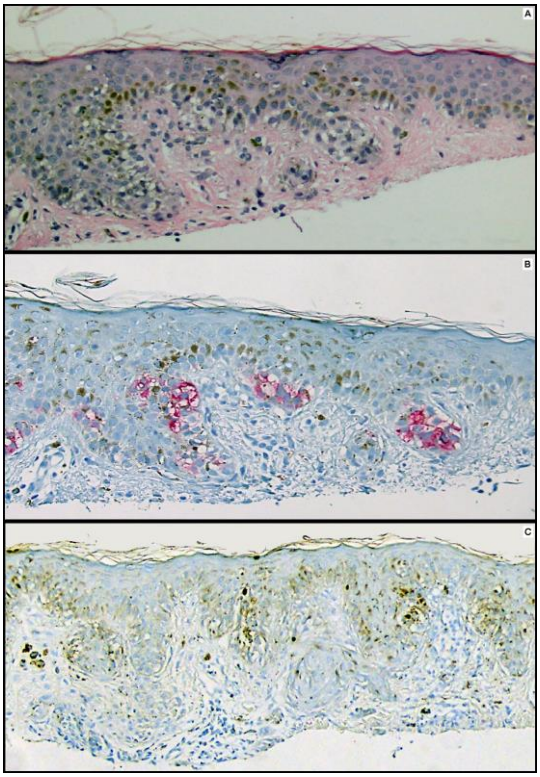

Figure 2. Nest of melanocytic cells at dermoepidermal junction (a). The melanocytes were positives for Melan A stain (b) and negatives for BRAF-VE stain (c). Original magnifications: X20 (H&E and Melan A) and X10 (BRAF-VE).

Unfortunately, despite the chemotherapy regimen, the patient died of metastatic disease a few months later.

Discussion

Compared with keratinocytic proliferations, which are observed in more than 60% of patients treated with selective BRAF monotherapy, the frequency data and characterization of de novo melanocytic proliferations in the setting of BRAF blockade are lacking [1,2]. Eruptive nevi, new common or dysplastic nevi, and new primary melanomas constitute the majority of such reports in the literature. These side effects secondary to BRAF inhibition appear overrepresented in vemurafenib patients versus dabrafenib patients [3]. Similar in etiopathogenesis to anti-BRAF induced keratinocytic neoplasia, the paradoxical activation of MAPK in the presence of a UV-induced RAS mutation drives melanocyte growth [4]. As a result, BRAF-inhibitor associated melanocytic proliferations invariably lack the BRAF V600E mutation, in contrast to conventional acquired nevi arising on sun-exposed skin [3,4]. Moreover, combination therapy with BRAF/MEK inhibition has led to involution of eruptive melanocytic nevi [5]. Our case provides the first observation of an acquired agminated melanocytic nevus following either selective or non-selective BRAF blockade. Agminated melanocytic nevi are rare and characterized by

discrete macules, patches, or papules, coupled with intervening areas of normal skin that lack a tan or taupe background. The accentuation of background pigmentation would be seen in speckled lentiginous nevus (aka nevus spilus) rather than agminated melanocytic nevus. The term agminated refers to clustering of lesions of the same kind, similar to sheep in a herd. Agminated clinical morphology may be seen in melanocytic (blue nevus, Spitz nevus, lentigo simplex, Clark nevus) and non-melanocytic tumors (xanthogranuloma, angiofibroma, schwannoma, neurothekeoma) neoplasia [6]. Specifically, agminated melanocytic nevi can also be categorized into congenital or acquired types, with the latter being far less common, especially when excluding an association with dysplastic nevus syndrome [6,7].

Conclusion

This is the first case, to our knowledge, of agminated melanocytic nevus in association with dabrafenib. The case highlights paradoxical MAPK activation in the setting of single-agent BRAF blockade, and subsequently, the potential for development of eruptive melanocytic nevi and an unconventional variant, agminated melanocytic nevus. Our case underscores the importance of characterizing the diverse side effects of selective BRAF blockade, which may contribute to better understanding of conventional and unconventional melanocytic tumor biology in the future.

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