Subclinical granulomas in benign skin lesions heralding the onset of *BRAF* and *MEK* inhibitor–associated granulomatous dermatitis in a patient with metastatic melanoma

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CASE REPORT

A 48 year-old white woman presented with melanoma, metastatic to the mediastinum. The primary lesion was ulcerated with a Breslow depth of 2.6 mm. The lesion was excised with appropriate margins. Right axillary sentinel lymph node biopsy was positive in 1 node, whereas a full lymph node dissection failed to find additional nodal involvement. She was treated with adjuvant interferon-β2, which was poorly tolerated and discontinued after 2 weeks. One year later, she presented with a 1-cm subcutaneous nodule above the excision scar, a biopsy of which confirmed metastatic melanoma. *BRAF V600E* mutation was detected. Positron emission tomography/computed tomography scan found new pulmonary and mediastinal lymphadenopathy confirmed to be melanoma by biopsy. She completed 4 cycles of ipilimumab, but imaging 5 months later showed enlarging mediastinal nodes. In July 2014, she had diffuse asymptomatic livedo reticularis involving the trunk and extremities. Mild intermittent pruritus developed that improved with moisturizers. Punch biopsy specimen from the right forearm showed a blue nevus, and shave biopsy specimens from the right lateral and medial arm each showed intradermal nevi. After not responding to ipilimumab, the patient was started on dabrafenib/trametinib combination therapy. After completing 1 year of this therapy, 2 suspicious skin lesions were noted, and a punch biopsy specimen of a blue-grey macule on the right buttock showed a blue nevus with associated epithelioid granulomas (Fig 1). A shave biopsy specimen of a tan macule from the left forearm showed a solar lentigo with an associated epithelioid granuloma (Fig 2). After 5 months of dabrafenib/trametinib combination therapy, computed tomography scan of the chest showed no lymphadenopathy and positron emission tomography scan showed interval resolution of hypermetabolic mediastinal lymphadenopathy. Three months later, a shave biopsy specimen of a thin pink scaly plaque from a new eruption on the right forearm showed interstitial granulomatous dermatitis with areas of palisading and mucin deposition resembling granuloma annulare (Fig 3), whereas a second shave biopsy specimen of an erythematous papule from the right second toe also showed granulomatous dermatitis with epithelioid granulomas (Fig 4). She has remained on dabrafenib/trametinib combination therapy with complete response for 30 months.

DISCUSSION

We report a rare case of subclinical granulomatous dermatitis found within benign skin lesions after

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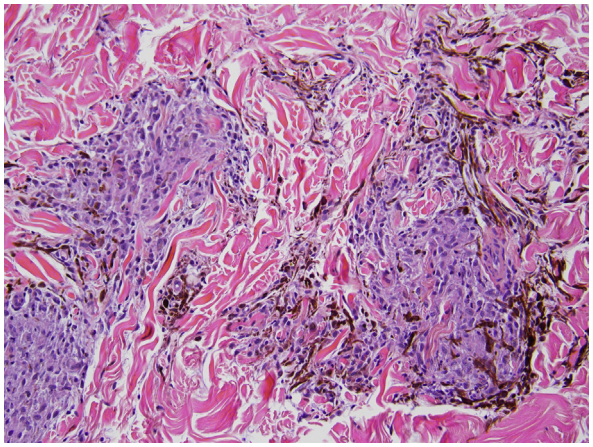

Fig 1. Punch biopsy specimen of a blue gray macule prepared with hematoxylin-eosin stain (H&E) shows epithelioid granulomas in proximity to a blue nevus.

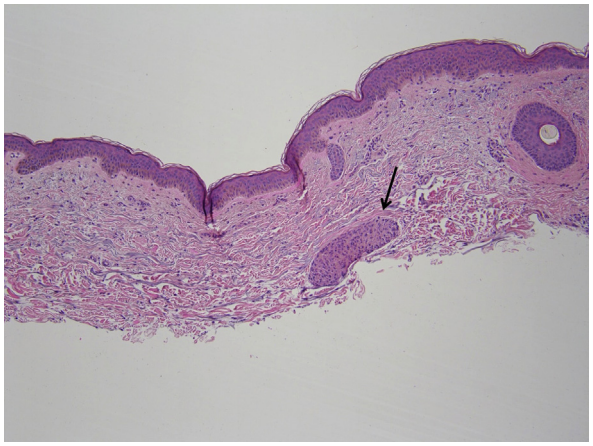

Fig 2. Shave biopsy specimen of a tan macule from the left forearm prepared with H&E shows a solar lentigo with an associated epithelioid granuloma (*arrow*).

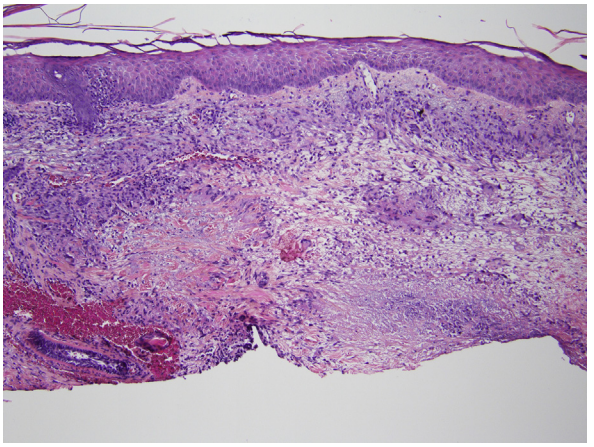

Fig 3. Shave biopsy of a thin pink scaly plaque from the right forearm prepared with H&E shows an interstitial granulomatous dermatitis with areas of palisading and mucin deposition resembling granuloma annulare.

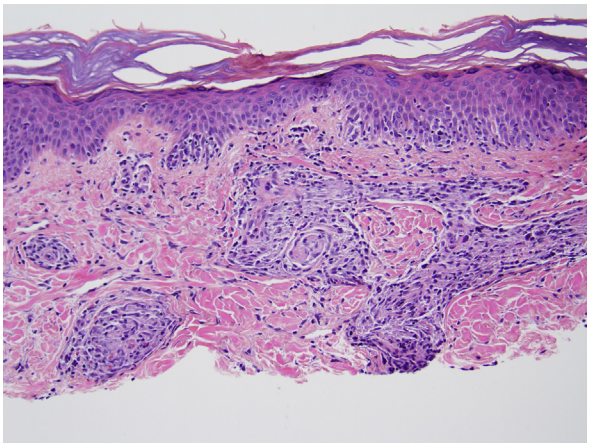

Fig 4. Shave biopsy specimen of an erythematous papule on the right toe prepared with H&E shows superficial dermal epithelioid granulomas.

initiation of *BRAF* and *MEK* inhibitors for metastatic malignant melanoma, which heralded the onset of clinically apparent granulomatous dermatitis. Mitogen-activated protein kinase is a signaling pathway that regulates cell growth, differentiation, and survival via the sequential phosphorylation of mediators including *ERK*, *MEK*, *RAS*, and *RAF*.[1] Mutations in the mitogen-activated protein kinase pathway are key in the pathogenesis of melanoma. In particular, *BRAF* mutations are present in about 50% of melanomas, with *V600E* being the most common mutation. Vemurafenib and dabrafenib are 2 *BRAF* inhibitors that have been approved by US Food and Drug Administration for the treatment of metastatic melanoma with mutated *BRAF*. Trametinib, a MEK inhibitor, and dabrafenib, are approved by the US Food and Drug Administration in combination for patients with advanced melanoma *V600E*-mutated *BRAF*.[2]

Cutaneous side effects of *BRAF* inhibitors are common, occurring in up to 95% of patients on vemurafenib.[3] The most common manifestations are actinic keratoses, alopecia, hand-foot skin reactions, morbilliform eruptions, photosensitivity, keratoacanthoma, keratosis pilaris, pruritus, squamous cell carcinoma, and xerosis.[1] In addition, melanocytic lesions including nevi and melanoma have been reported with *BRAF* inhibitors.[4]

Granulomatous skin eruptions with *BRAF* inhibitors are quite rare. The first case report described 2 patients with metastatic melanoma undergoing treatment with combination *BRAF* (dabrafenib) and *MEK* (trametinib) inhibitor therapy.[5] One patient experienced regression of nevi with biopsy of 1 lesion

revealing a nevus with underlying sarcoidal-type granulomatous inflammation. The other patient experienced an eruption of erythematous papules and plaques, the biopsy of which found interface dermatitis with increased dermal mucin deposition with foci of sarcoidal-type granulomas. Two other reports described a total of 3 patients with metastatic melanoma also treated with dabrafenib and trametinib.[6,7] In the first report, both patients had erythematous and violaceous papules and plaques. In the first patient, 2 biopsies were performed, 1 finding sarcoidal granulomatous inflammation with foreign body–type giant cells, and the second finding granulomatous inflammation surrounding a focus of melanoma. The eruption resolved with topical corticosteroid treatment. In contrast, a biopsy specimen in the other patient found granulomatous dermatitis with focal necrosis, not related to melanoma. The lesions resolved 3 weeks after therapy cessation. In the second report, 1 patient had sarcoidal granulomatous inflammation in association with tumoral melanosis and other areas of sarcoidal granuloma associated with metastatic melanoma deposits. The lesions resolved spontaneously.

Another a patient with metastatic melanoma undergoing the same treatment had simultaneous sarcoidal granulomatous inflammation with admixed giant cells of the skin and the kidney.[8]

Patients with granulomatous dermatitis after initiation of *BRAF* inhibitor therapy with or without a *MEK* inhibitor have presented with diffuse eruptions of erythematous to violaceous papules or scaly plaques or localized in close association with sites of metastatic melanoma undergoing involution. However, in our patient, subclinical granulomatous dermatitis was seen in multiple benign skin lesions while on *BRAF/MEK* inhibitor therapy and is further notable for subclinical granulomatous dermatitis heralding the onset of clinical granulomatous dermatitis. Previous reports of cutaneous granulomatous reactions have noted predominantly sarcoidal granulomas with some admixed foreign body-type giant cells. However, our case expands the spectrum of granulomatous dermatitis associated with *BRAF/MEK* inhibitor therapy with the presence of granuloma annulare–like lesions. Our patient has been disease free for 30 months, suggesting a possible correlation of the granulomatous dermatitis with a positive chemotherapeutic response to *BRAF/MEK* inhibitor combination therapy.

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