Involution of Eruptive Melanocytic Nevi on Combination BRAF and MEK Inhibitor Therapy

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Eruptive melanocytic nevi (EMN) have been described as the sudden-onset development of numerous melanocytic nevi in association with bullous diseases or conditions of immunosuppression, including patients with human immunodeficiency virus, or those who have undergone chemotherapy or organ transplantation. In the recent literature, EMN have been described in patients receiving sorafenib, a multikinase inhibitor, vemurafenib, a selective BRAF inhibitor. No case reports, to our knowledge, have characterized the initial eruption and subsequent involution of EMN in patients receiving combination targeted therapies. Herein, we report involution of EMN in a patient receiving dual BRAF inhibitor, cobimetinib. Within months, we noted clinical involution of many of her EMN. In addition, numerous preexisting nevi were noted to fade in color on the dual regimen. Over a year after initiating this combination therapy, most of the patient’s EMN were no longer clinically evident.

Conclusions and Relevance: Our case report describing the involution of EMN supports data from previous clinical trials indicating that combination BRAF and MEK inhibition may reduce cutaneous proliferative effects that arise on BRAF inhibitor monotherapy. Further studies are necessary to characterize the biological mechanisms underlying this phenomenon.
sum. Within the first 3 months of BRAFi therapy, the patient was noted to have developed numerous, small, eruptive, banal-looking nevi, particularly on her trunk, which stabilized in number by 6 months of BRAFi therapy, per total-body mole mapping comparison (Figures 1B, 2B, and 3B). In terms of her baseline preexisting nevi, some were noted to have become darker in appearance and some lighter during treatment with the BRAFi, although no clinical or dermoscopic features were evident to suggest malignant transformation.

The patient achieved complete response with vemurafenib on clinical and radiologic grounds for a total of 18 months until April 2012, when she developed an enlarging right posterior auricular lymph node that was pathologically confirmed as melanoma. Imaging with positron emission tomography–computed tomography (PET-CT) in May 2012 showed pulmonary metastases and metastatic lymphadenopathy in the head and neck, mediastinum, and portacaval region. She was subsequently enrolled in a clinical trial combining vemurafenib with a MEKi, cobimetinib, with the first dose of the drug in May 2012.

Cobimetinib, or GDC-0973, was administered on a regimen of 21 days on and 7 days off at a dose of 60 mg by mouth daily, with continuous use of twice-daily vemurafenib at 960 mg. The patient demonstrated gradual complete response to the combination BRAFi-MEKi regimen with serial PET-CT and CT scans (to date, the last was in June 2014) demonstrating no evidence of recurrence or metastatic disease.

Her adverse effects while receiving the BRAFi-MEKi combination included pyrexia, facial flushing, headache, and gastrointestinal tract symptoms (nausea, vomiting, diarrhea, and abdominal pain), all of which were more severe early in the treatment course. The patient’s periodic erythema nodosum lesions persisted on the combination regimen. However, her other BRAFi-associated cutaneous findings largely abated, including marked reduction in scalp scale and diffuse xerosis; full regrowth of scalp, eyebrow, and eyelash hair; and significantly less photosensitivity.

In October 2012, 4 months after starting the BRAFi-MEKi trial, the patient’s EMN were observed to be fading in color, with clinical involution of most of the tan to brown nevi that developed while she was receiving vemurafenib monotherapy (Figures 1C, 2C, and 3C). Many of her preexisting nevi were also noted to have faded in color while she was receiving the dual regimen. Nearly all of the patient’s nevi, both preexisting and eruptive, underwent some degree of involution on clinical and dermoscopic grounds and seemed to be similar...
larly affected by the addition of MEKi therapy. Sixteen months following initiation of combination targeted therapy, most of her eruptive nevi had faded on clinical and dermoscopic evaluation, although the patient declined a biopsy to confirm whether complete nevus involution had occurred histopathologically. Serial clinical and dermoscopic evaluation every 3 months, as well as photographic comparison and updated total-body mole mapping, did not demonstrate features of severe dysplasia or early melanoma in any of the patient’s baseline or eruptive nevi. Likewise, no clinical halo phenomenon or dermoscopic regression structures (eg, peppering [granularity] or white scarlike areas, were noted).

Discussion

Eruptive melanocytic nevi have been described in association with kinase inhibitors, including sorafenib and vemurafenib, and typically develop within 3 months of treatment with BRAF inhibitors.2 Patients exposed to BRAF inhibitors can also develop darkening of existing nevi, atypical melanocytic proliferations, or second primary melanomas.3–5 This patient experienced variable color changes in her baseline nevi (per photodocumentation pretreatment and during therapy), with some nevi becoming darker while others became lighter. More notable was her development of multiple, small, uniform, and banal-appearing EMN while she was receiving vemurafenib monotherapy, which clinically regressed following the use of combined targeted vemurafenib and cobimetinib therapy.

BRAF inhibitors are promising agents in the treatment of advanced, surgically unresectable melanoma. However, multiple mechanisms trigger resistance to BRAF inhibitors through both MEK-dependent and MEK-independent signaling, resulting in high rates (50%) of disease progression, typically by 6 to 7 months after BRAFi or MEKi monotherapy.6 The combination BRAFi-MEKi therapy has demonstrated improved progression-free survival in patients with metastatic melanoma.6

Multiple cutaneous adverse effects have been characterized in patients receiving BRAFi therapy, most notably, profound UV-A–induced photosensitivity and squamous cell carcinoma (SCC) of the keratoacanthoma (KA) type. Apart from acneform dermatitis, the pivotal trial of combination BRAFi-MEKi therapy demonstrated reduced skin toxic effects, including reduced cutaneous SCC-KA, alopecia, hyperkeratosis, and papillomas.6 Eruptive melanocytic nevi have been less commonly described in patients receiving vemurafenib, accounting for only 10% of cases in one prospective study.2 In addition to EMN, a recent review7 described changes in baseline, pretreatment melanocytic nevi, and onset of new primary melanomas in patients receiving vemurafenib. These changes included involution of preexisting nevi, alteration of nevus color and size, and transformation of nevi into melanoma. New primary melanomas have also been reported to develop in patients receiving BRAFi therapy, occurring both de novo (in 2 cases) and from preexisting nevi.7

Preliminary assessments of the mechanism underlying EMN following BRAF inhibition have centered on the notion of paradoxical mitogen-activated protein kinase (MAPK) activation. There are a few models that explain this phenomenon. Typically, in cells with a BRAF V600E mutation, abnormal signaling from BRAF causes elevated downstream extracellular signal-regulated kinase (ERK) signaling within the MAPK pathway.8 Normally, BRAF inhibition will attenuate activation of ERK. However, in wild-type BRAF cells with upstream NRAS mutations, the CRAF isoform of BRAF becomes a primary modulator. When exposed to BRAF inhibition, wild-type BRAF dimerizes with CRAF, which causes transactivation and paradoxically increased downstream MAPK signaling.9 This model has been applied to and verified as a definitive explanation for cutaneous SCC and KA formation.10

BRAF mutations have not been identified in biopsied nevi from patients receiving BRAF inhibitors,7 supporting the hypothesis that it is wild-type BRAF cells that undergo paradoxical MAPK activation when exposed to BRAF inhibitors. Zimmer et al9 found that no nevi or new primary melanoma biopsied during treatment with BRAF inhibitors had BRAF mutations, while NRAS mutations were present in 2 of the nevi (20%) and 1 of the new primary melanoma lesions (9%). This finding supports the concept that upstream RAS mutations may drive this activity in wild-type BRAF cells.

The downstream signaling that occurs in paradoxical MAPK activation has direct implications on nevus development.
Transgenic zebrafish with activated BRAF mutations have developed dramatic patches of ectopic melanocytes, indicating that alterations in this pathway are sufficient to promote nevus formation. These BRAF mutations initially stimulate melanocyte proliferation, but in both in vitro and in vivo studies, oncogenic BRAF signaling later caused a growth-inhibitory response that models the classical pattern of senescence.

Nevi are dynamic and are believed to undergo 3 phases in their natural history: inception to growth, senescence, and involution. Nevus involutio may involve a halo phenomenon, regression pattern, or gradual involutio without either of these features, the latter of which we favor in our patient's case. Nevus are thought to regress from mechanisms related to immune surveillance. Histologically, nevi are believed to be effaced from the epidermis by the degeneration and atrophy of nevus cells, which are then replaced by fibrous stroma and melanophages. Terushkin et al recently characterized the dermoscopic features associated with different types of involutio. It seems that the most of our patient's nevi, including both her EMN and preexisting nevi, regressed during combination BRAFI-MEKI therapy. Although we were unable to obtain tissue biopsy specimens of nevi from our patient, the involutio of her EMN in particular was clearly temporally related to the concomitant use of a MEKI.

We propose 2 distinct mechanisms that may explain this involutio. First, in a melanocyte “intrinsic” model, EMN may have become dependent on continuous MAPK signaling. The combination therapy was designed to bypass resistance mechanisms and block downstream signaling in the MAPK pathway. Thus, it is reasonable to expect that the eruption of nevi on BRAFI monotherapy was counteracted by the addition of a MEKI. The concurrent involutio of her preexisting nevi may also be explained by this hypothesis. Just as BRAF activation has been shown to cause nevus formation, blocking downstream signaling through a MEKI may lead to involutio of all types of nevi. Second, in a melanocyte “extrinsic” model, preexisting nevi or EMN may express new cell-surface signals in the presence of combination BRAFI-MEKI therapy that identify them for subsequent immune-mediated destruction. A recent study showed that treatment with BRAFI or combination BRAFI-MEKI therapy led to an increased expression of melanoma antigens on tumor biopsies, with a corresponding increase in CD8+ T-cell infiltrate. This antigen expression may be shared by nevi, leading to an immune-mediated response from melanophages and T cells.

### Conclusions

To our knowledge, we report the first case in which a patient demonstrated fading and apparent involutio of EMN on combination BRAFI-MEKI therapy. A limitation is the lack of histopathologic assessment of both EMN and regressing nevi owing to patient preference to forego skin biopsy. This report underscores the importance of close dermatologic surveillance for patients receiving both BRAF and MEK inhibitors. In addition, it highlights the importance of using the skin as a model for elucidating the effects of targeted therapies on normal cells. Further study of these biological mechanisms may shed light on why adverse events occur in other tissues. In addition, as novel melanoma therapies are increasingly combined, attention to associated skin findings may promote understanding of the mechanisms by which multiple agents act in synergy.