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# Cutaneous Toxic Effects Associated With Vemurafenib and Inhibition of the BRAF Pathway

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**Background:** The development of a novel BRAF inhibitor, vemurafenib, has been associated with impressive tumor regression in patients with BRAF-positive stage IV melanoma. In the phase 3 clinical trials, dermatologic toxic effects associated with vemurafenib were described, namely, the development of eruptive squamous cell carcinomas. Herein, 3 cases are presented that highlight the development of squamous cell carcinomas and other cutaneous sequelae that have not been previously reported and are reminiscent of those observed with administration of the multikinase inhibitor sorafenib tosylate. In addition, the current understanding of the molecular mechanisms underlying these toxic effects is reviewed.

**Observations:** The development of keratosis pilaris–like eruptions; seborrheic dermatitis–like rashes; and hyperkeratotic, tender plantar papules reminiscent of those seen in sorafenib-associated hand-foot skin reaction, as well as squamous cell carcinomas, is presented in association with vemurafenib-based treatment of metastatic melanoma.

**Conclusions:** The development of sorafenib-like cutaneous sequelae (squamous cell carcinomas, keratosis pilaris–like eruptions, seborrheic dermatitis–like rashes, and hand-foot skin reaction) associated with vemurafenib administration suggests that BRAF inhibition alone may be sufficient to induce these changes.

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THE MITOGEN-ACTIVATED protein kinase (MAPK) pathway is involved in regulating cellular proliferation, survival, and differentiation. Alterations in this pathway are frequently found in solid tumors; BRAF, an upstream activator of MAPK, is the most frequently mutated protein kinase found in human cancers,[1] and, in cutaneous melanomas, mutations are present in approximately 40% to 60% of tumors.[2,3] In these mutants, 90% contain a substitution of glutamic acid for valine at codon 600 (BRAF V600E), making it a rational target for therapeutic intervention. Vemurafenib was developed using a scaffold-based drug design approach and engineered to preferentially bind BRAF V600E.[4] The effectiveness of vemurafenib in treating metastatic melanomas harboring this mutation led to the expedited US Food and Drug Administration approval of this agent in August 2011.

Several dermatologic sequelae are known to occur with inhibition of BRAF. The most significant of these is the development of eruptive squamous cell carcinomas (SCCs) and keratoacanthomas, initially described with sorafenib tosylate[5-7] and most recently reported in 18% to 31% of patients receiving vemurafenib.[8,9] As clinical experience with vemurafenib increases, additional treatment-specific dermatologic manifestations will likely emerge.

To date, 26 patients with metastatic melanoma have received vemurafenib at our institution, several of whom have developed significant dermatologic adverse effects. In total, of 15 patients who continued vemurafenib therapy for at least 1 month, 5 developed SCCs and 3 developed a keratosis pilaris–like eruption. Herein, 3 cases of patients with metastatic melanoma treated with vemurafenib demonstrating exceptional dermatologic adverse effects are presented. Two patients developed a diffuse keratosis pilaris–like rash, a seborrheic dermatitis–like eruption, and a hyperkeratotic hand-foot skin reaction (HFSR) mimicking treatment-related adverse effects reported with sorafenib. Both patients also developed cutaneous SCCs within the first 2 months after starting therapy. Also pre-



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**Figure 1.** Patient 1. A, Extensive metastases on the right groin, hip, thigh, and gluteal region at baseline examination. B, Diffuse keratosis pilaris–like eruption after 1 month of vemurafenib treatment. C, Face at baseline examination without cystic lesions. D, Abundant facial cystic lesions after 1 month of vemurafenib treatment. E, Melanoma after 3 months of vemurafenib treatment. F, Hand-foot skin reaction with hyperkeratotic plaques over the sole after 1 month of vemurafenib treatment. G and H, Eruptive squamous cell carcinomas over the right arm and left nose after 3 months of vemurafenib treatment.

sented is the case of a patient who developed explosive SCCs (17 biopsy-proven lesions during 10 weeks of treatment); this was the only case in our experience in which dermatologic adverse effects led to discontinuation of therapy.

## REPORT OF CASES

### PATIENT 1

A 50-year-old white man was found to have a cutaneous melanoma, Breslow thickness of 2.3 mm, on his right lower back in February 2010. The patient underwent wide local excision and sentinel lymph node examination revealing 2 of 2 right inguinal sentinel lymph nodes positive for metastatic disease. After completion lymphadenectomy, the patient received a treatment course of high-dose interferon that was discontinued at 6 weeks because of melanoma recurrence. The patient received a treatment course of dacarbazine monotherapy; however, he experienced continued growth of the cutaneous and subcutaneous metastases noted on the right groin, hip, thigh, and gluteal region (**Figure 1**A). Eleven months after initial diagnosis, additional subcutaneous metastases developed on the left cheek and right shoulder, and imaging revealed distant metastases found in the bladder and lung. At that time (May 2011), treatment was started with vemurafenib, 960 mg, by mouth twice daily.

Within 5 days of starting therapy, the patient noted arthralgias involving both hands and a generalized hyperkeratotic, follicularly centered eruption resembling keratosis pilaris (Figure 1B). This eruption was associated with pruritus that resolved over the course of 3 to 4 weeks with therapy. Acneiform cysts were noted on both cheeks, also developing in the first week of treatment (Figure 1C and D). Shortly thereafter, the patient reported the development of painful hyperkeratotic papules and plaques over the pressure points of the soles of both feet (Figure 1F). After 1 month of therapy, he experienced dramatic clinical and radiologic improvement in his cutaneous and systemic metastases, as well as his symptoms (Figure 1E). Two months after starting treatment with vemurafenib, the patient developed enlarging hyperkeratotic nodules over the right arm and nose (Figure 1G and H). Biopsies of these lesions were performed, revealing well-differentiated SCC.

### PATIENT 2

A melanoma with a Breslow thickness of 0.8 mm on the back of a 51-year-old white woman was diagnosed in 2001. The patient developed clinically palpable recurrent dis-



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**Figure 2.** Patient 2. A, Presence of a 13-cm metastatic nodule on the left posterior thigh at baseline. B, Melanoma after 1 month of vemurafenib treatment. C, Diffuse keratosis pilaris–like eruption over the abdomen. D, Eruptive squamous cell carcinoma over the left leg.

ease in the left axilla in April 2007. She received a 1-year treatment course of adjuvant interferon that was well tolerated, but in July 2009 she developed metastatic disease on her left flank, which was treated with excision. Bone metastases were then diagnosed by restaging positron emission tomography/computed tomography (PET/CT) in October 2009 and were confirmed by fine-needle aspiration. She received external-beam radiotherapy at an outside institution. Her subsequent treatment included an experimental dendritic cell vaccine, an adoptive immunotherapy trial at the National Institutes of Health, and a 4-dose course of ipilimumab, all with progressive disease. She ultimately developed enlarging subcutaneous nodules in the right gluteal region, soft-tissue masses in the transverse mesocolon, and a pancreatic metastasis that eroded into the duodenum. As a result, she developed anemia that required transfusions. Oral vemurafenib treatment, 960 mg twice a day, was begun in June 2011. She was evaluated by a dermatologist and, on examination, was anemic, ill-appearing, and weak, with an approximately 13-cm subcutaneous nodule of the posterior right thigh without other evidence of cutaneous disease (**Figure 2**A).

One month after vemurafenib was started, there was marked regression of the nodule on the patient's right posterior thigh (Figure 2B). She also developed diffuse asymptomatic eruption of hyperkeratotic, follicularly centered papules across the chest, abdomen, and upper and lower extremities (Figure 2C). The patient reported that the eruptions had started 2 to 3 weeks after the initiation of therapy. At her 4-week follow-up visit, a pruritic erythematous patch was noted across the forehead, cheeks, and chin, sparing the periorbital skin in a seborrheic distribution. Desonide cream, 0.05%, to be applied twice daily as needed was prescribed at that time, and her pruritus improved during the next 3 weeks. The patient also noted the development of tender areas at the fifth metatarsal-phalangeal joints bilaterally within the first month of treatment. At her 4-week follow-up, there were callous-like thickenings of the plantar skin overlying these areas. In addition, a new scaly red 3-mm papule was noted on the left distal medial thigh that was biopsied and identified on histologic testing as a well-differentiated and superficially invasive SCC arising in a verruca vulgaris (Figure 2D).

## PATIENT 3

A dermal metastatic melanoma was diagnosed on the left leg of a 79-year-old white woman in October 2009, with no known primary site. A wide local excision with sentinel lymph node mapping was undertaken, revealing 1 of 3 inguinal lymph nodes containing metastatic melanoma. The patient declined completion lymphadenectomy at that time. In April 2010, she noted small nodules on her left leg. Imaging with PET/CT revealed multiple FDG (fluorodeoxyglucose)–avid nodules with inguinal lymphadenopathy. The patient received 3 cycles of granulocyte macrophage colony-stimulating factor and a 4-dose treatment course of ipilimumab. However, restaging PET/CT performed in February 2011 revealed bone metastases to the L5 vertebral body. In May 2011, vemurafenib treatment was begun.

Two weeks after the initiation of therapy, the patient was hospitalized with fatigue and nausea. Laboratory tests on admission revealed a serum potassium level of 2.4 mEq/L (1:1 conversion to millimoles per liter). Dose reduction of vemurafenib was undertaken per the study protocol from 960 mg twice daily to 720 mg twice daily with partial normalization of her serum potassium level. After 1 month of treatment, the patient developed scaly, indurated red papules on the arms, legs, and torso that were clinically suspicious for SCCs. Six lesions were biopsied, with the lesions on the arms and legs revealing well-differentiated SCCs that were subsequently excised. The lesions on the chest were superficially consistent with verrucae vulgaris but had irregular, infiltrative nests of keratinocytes in the superficial dermis, worrisome for a superficially invasive SCC. Two months after initiation of treatment with vemurafenib, the patient developed more lesions suspicious for SCCs across the torso as well as keratoacanthomalike lesions on both forearms, the dorsum of the nose, and the right dorsal hand (**Figure 3**A-C). Histologic characteristics were similar to those seen in the lesions on the chest (Figure 3D and E). A total of 17 well-differentiated SCCs were diagnosed by week 10 of therapy, as well as hyperkeratotic actinic keratoses and 2 verrucae vulgaris. Vemurafenib was discontinued and the patient was treated with excision of the SCCs in combination with Mohs surgery for the SCC on her nose.

## COMMENT

Investigations into the contributions of BRAF mutations to the development and propagation of human cancers have led to several targeted therapies, including vemurafenib and sorafenib. Vemurafenib was developed in a structure-guided manner as an inhibitor of BRAF. In vitro studies[4] have demonstrated that vemurafenib is a



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**Figure 3.** Patient 3. A through C, Eruptive squamous cell carcinomas over the left forearm, dorsal nose, and right dorsal hand. D, Histopathologic analysis revealing a well-differentiated squamous cell carcinoma ([hematoxylin-eosin, original magnification ×2. E, Histopathologic analysis of the squamous cell carcinoma (hematoxylin-eosin, original magnification ×20).

potent inhibitor of BRAF, with specificity for oncogenic BRAF V600E compared with wild-type BRAF and a panel of 200 other kinases. Sorafenib, on the other hand, was initially identified as a BRAF inhibitor; however, it was later found to inhibit multiple other kinases, including vascular endothelial growth factor receptors 2 and 3 (VEGFR-2 and VEGFR-3), platelet-derived growth factor receptor (PDGFR)-β, FMS-like tyrosine kinase 3 (FLT-3), c-Kit protein (c-Kit), and RET receptor tyrosine kinase.[10-12] Despite the success of vemurafenib in clinical trials, initial studies[13] evaluating sorafenib as single-agent therapy in the treatment of metastatic melanoma revealed no efficacy. It is possible that toxic effects related to its multikinase inhibition prevented appropriate dosing of sorafenib to achieve sufficient BRAF inhibition in these studies.

The cutaneous adverse effects of sorafenib have been described[14-19] in several reviews and case reports and include HFSR, alopecia, facial erythema, generalized keratosis pilaris–like eruptions, and eruptive keratoacanthomas and SCCs. Given the multitude of targets affected by sorafenib, the molecular pathogenesis of these cutaneous sequelae has been the subject of much speculation. Comparison of adverse effect profiles with the similar multikinase inhibitor sunitinib (inhibitor of VEGFR-1, VEGFR-2, PDGFR-α, PDGFR-β, FLT-3, and c-KIT but not serine/threonine kinases such as RAF) has offered some insights. For example, facial erythema was reported in one observational study[18] to have occurred in 27 of 43 patients treated with sorafenib but was not associated with those treated with sunitinib, suggesting that inhibition of RAF, rather than other targets, was responsible for this finding.[18,19] Similarly, sorafenib-induced alopecia (26%) was much more common than alopecia associated with sunitinib malate (6%).[19] However, HFSR has been reported in 48% of patients treated with sorafenib and 36% of patients treated with sunitinib.[15] For these reasons, speculation centered on VEGFR or FLT-3 inhibition as the molecular mediator of this often dose-limiting adverse effect. Indeed, the frequency and severity of HFSR was increased when sorafenib was paired with the VEGF antagonist bevacizumab.[20] It is hypothesized that VEGF inhibition leads to vessel regression and negative effects on vascular repair in areas of trauma.[15,16]

The development of keratosis pilaris–like eruptions associated with facial erythema and HFSR in patients treated with vemurafenib validate the association of facial erythema with the BRAF pathway and call into question VEGF inhibition as the sole molecular mechanism responsible for HFSR. The specificity of vemurafenib for BRAF suggests that inhibition of the BRAF pathway alone is sufficient to induce HFSR; however, the initial pre-



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clinical specificity screens of vemurafenib demonstrated inhibitory effects on additional kinases, including ACK1, an Akt activator; KHS1, which is hypothesized to regulate stress responses; and SRMS, the function of which is thus far unknown.[4] To date, no cellular assays have been performed examining the effect of inhibiting these non-RAF kinases.

The paradoxical phenomenon of vemurafenib-induced SCCs also finds parallels in an increasing number of case reports documenting a similar phenomenon in patients treated with sorafenib. Recent biochemical studies[21-23] have revealed a mechanism by which BRAF inhibitors can simultaneously suppress RAF-MAPK signaling while paradoxically activating this pathway in cells carrying an oncogenic mutation in *RAS*. Mutated *RAS* promotes the dimerization of RAF isoforms, thus forming BRAF-CRAF, BRAF-ARAF, and CRAF-CRAF dimers. This dimerization allows downstream signaling through isoforms of RAF not bound by small molecule inhibitors. In this manner, it is hypothesized that vemurafenib can induce transactivation of CRAF despite inhibition of its BRAF partner in a RAS-dependent manner. Of note, *RAS* mutations are detected in some actinic keratoses as well as some SCCs.[24,25] In fact, mutational analysis undertaken of lesions arising in the setting of sorafenib treatment revealed mutations in *HRAS*, *TGFBR1*, and *TP53*.[26] This suggests that a population of cells predisposed to transformation by clinically silent *RAS* mutations may be driven by BRAF-inhibitor–induced MAPK signaling via noninhibited RAF isoforms. The observed cases of cutaneous SCC in the context of sorafenib may function by a similar mechanism.

The finding of similar dermatologic sequelae in patients who received vemurafenib and those who received sorafenib suggests that inhibition of the BRAF pathway alone may explain several of these phenomena. However, the paradoxical development of cutaneous SCCs demonstrates the complexity and redundancy of kinase signaling. Indeed, the recognition of the role of the RAS/MAPK pathway in the pathogenesis of several congenital syndromes, including cardio-facio-cutaneous syndrome, Noonan syndrome, and Costello syndrome (collectively referred to as *RASopathies*), highlights the limits of our understanding. Cardio-facio-cutaneous syndrome, which is associated with a constitutive activation of BRAF in approximately 60% of cases, is also characteristically associated with alopecia, keratosis pilaris, and palmoplantar hyperkeratosis reminiscent of that associated with BRAF inhibitors.[27,28] Whether this seeming contradiction is a product of undefined feedback mechanisms or effects associated with specific mutations to BRAF remains to be seen. Despite these limitations to our current knowledge, these observations provide an opportunity to dissect the molecular basis of BRAF inhibitor–induced toxic effects. Furthering this understanding is important not only for the development of second-generation agents that have improved toxicity profiles but also in elucidating the role of the MAPK pathway in cutaneous homeostasis.

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## Notable Notes

### Plica Polonica: Confusion, Confabulation, and the Death of a Disease

As evidence-based medicine becomes the norm, precisely defining dermatologic disease is increasingly critical for both determining prognosis and assessing therapeutic efficacy. While contemporary dermatologists rightly focus on novel diseases and advanced therapeutics, appreciating the history of dermatology may serve to better inform our thinking, especially as patients present with putatively novel diseases and expect immediate therapeutic decision making; indeed, the value of accurate and precise diagnosis far outweighs rapid therapeutic intervention.

For half a millennium, physicians and scholars have investigated the etiology of and therapeutic options for a disease known as plica polonica, described originally by Johannes Schenck von Grafenberg[1] in 1584 as an irreversible plaiting of the hair accompanied by lice, headache, mutilating arthritis, scoliosis, and onychogryphosis. Referred to variously as *trica incubarus* (devil's hair), *weichselzopf*, and *plica polonica*, early descriptions of this entity focused as much on its perceived spiritual roots as its medical origins.

Plica polonica was indeed considered a major dermatologic problem, and early medical texts invariably included a discussion of this entity. Tobias Cohn,[2] after training at the University of Padua in Italy in the late 17th century and while serving as court physician to Turkish Sultan Mehmet II, included an extensive discussion of this disorder in his *Ma'aseh Tuviya*, a medical text aimed at the Hebrew-reading lay public. He dedicated more pages to plica polonica than to any other disease, reflecting its ubiquity among the Eastern European Jews, who represented his target audience. Echoing the thoughts of eminent 17th-century medical writers such as Daniel Sennert, he discussed the role of evil spirits and devils as causative factors but also noted that poor hygienic practices in Poland might be responsible for the endemic nature of this process. His extensive discussion of this disease, coupled with widespread ignorance of contemporary Latin-language medical scholarship, led to numerous erroneous assertions that his work represented the first description of this disorder.

In 1850, however, French dermatologist Pierre Louis Alphée Cazenave,[3] after an exhaustive exploration of the myriad opinions on this entity and whether it represented a disease sui generis, concluded that it is merely a form of seborrhea. This theory was echoed and expounded on by no less than Moritz Kaposi, in a text published with Hebra, who stated categorically that plica polonica represents a common end point resulting from neglect.[4] While articles published even in this century continue to refer to plica polonica as a discrete dermatologic disease, a thorough review of the literature, coupled with an understanding of the historical and social context of these descriptions, confirms Cazenave's prescient assertion. A half millennium after its first description, plica polonica is dead.

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