Photodynamic Therapy for Multiple Eruptive Keratoacanthomas Associated With Vemurafenib Treatment for Metastatic Melanoma

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Background: The development of keratoacanthomas (KAs) and well-differentiated squamous cell carcinomas (SCCs) is a known adverse effect of novel BRAF inhibitors such as vemurafenib. With multiple such neoplasms often arising after BRAF inhibitor therapy, surgical excision is often impractical.

Observations: We describe a patient with stage IV melanoma who received the BRAF inhibitor vemurafenib (recently approved by the US Food and Drug Administration) as part of a clinical trial and developed numerous diffuse, pathology-proven KAs and SCCs. The high number of lesions across a broad area precluded surgical treatment; instead, a noninvasive field approach using photodynamic therapy (PDT) was initiated. Compared with untreated tumors, most lesions demonstrated significant clinical regression following successive cycles of PDT.

Conclusions: Given vemurafenib’s recent approval by the US Food and Drug Administration, we provide a timely case report on the effective use of PDT in the treatment of BRAF inhibitor–associated KAs and SCCs. Although further studies are needed to better understand the biological processes of these secondary neoplasms, our observation provides an alternative noninvasive solution for improving the quality of life for patients receiving BRAF inhibitor therapy.

*Arch Dermatol.* 2012;148(3):363-366

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The Development of Keratoacanthomas (KAs) and Well-Differentiated Squamous Cell Carcinomas (SCCs) is a known adverse effect of novel BRAF inhibitors such as vemurafenib. With multiple such neoplasms often arising after BRAF inhibitor therapy, surgical excision is often impractical; thus, photodynamic therapy (PDT) is a potentially useful choice for initial treatment.

**REPORT OF A CASE**

A 78-year-old white man with stage IV melanoma that was positive for the *BRAF* (OMIM *164757; NCBI Entrez Gene 673) V600E mutation began treatment with the BRAF inhibitor vemurafenib (PLX4032, RO5185426; Hoffmann-La Roche Ltd) as part of a clinical trial (http://clinicaltrials.gov/ct2/show/NCT01474551). Two weeks after initiating therapy, the patient developed an extensive morbilliform eruption beginning on his proximal arms and legs and subsequently extending to involve his trunk. Results of a physical examination revealed confluent erythematous plaques and patches without scale on his trunk and proximal extremities. He denied pain, pruritus, blistering, fevers, or other systemic symptoms. Aside from vemurafenib, the patient denied any new additional medications. Laboratory test results were remarkable only for mild anemia, present before treatment onset. Vemurafenib was withheld for 1 week until the rash improved substantially, and treatment with the trial medication was restarted with a reduced-dose.

Three weeks after restarting his protocol treatment, the patient developed rapidly progressive asymptomatic “growths” on his arms and legs. Physical examination was notable for 2 pink exophytic nodules measuring approximately 1.0 × 1.0 cm, each with a central keratotic plug, located on the right lateral shin and on the left lateral calf (Figure 1A). A surgical biopsy was performed to obtain a histopathologic diagnosis. Analysis of the specimen revealed an atypical endophytic and exophytic squamous cell proliferation with a crateriform architecture, an epidermal collarette, and a large central keratin plug consistent with a well-differentiated, in-

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Invasive, KA-type SCC (Figure 1B). This lesion was reexcised with clear margins. The patient developed additional gritty, mildly indurated, hyperkeratotic papules scattered across his upper back and the dorsum of his hands in areas of extensive sun exposure. Several of these lesions erupted in areas of previous trauma, including the original excision site. The lesions on the dorsum of his hands regressed spontaneously.

Given the 10 to 20 exophytic nodules on his lower extremities that continued to appear, surgical excision was not a feasible strategy. Moreover, because of limitations in the setting of a research protocol, systemic acitretin treatment was not a viable option; therefore, topical agents were considered. We initiated PDT using aminolevulinic acid and red light. A total of 3 treatments were administered during a 5-month period. The skin was prepared with acetone, and the hyperkeratotic lesions were gently curetted. 5-Aminolevulinic acid (Levulan; Dusa Pharmaceuticals, Inc) or methyl aminolevulinate (Metvixia; Galderma Laboratories, LP) was applied to 7 KAs on the bilateral anterior lower extremities and incubated for 3 hours before red light activation at 200 J. The patient tolerated the procedure well, with immediate mild erythema noted at sites of his KAs. Two weeks after treatment, lesions were primarily hyperkeratotic crusts that were easily lifted with gauze.

At the 3-month follow-up visit, most lesions demonstrated clinical regression in response to PDT (Figure 2). Follow-up biopsies were not performed, as there was limited visible evidence of residual disease. Of note, a tumor on the left lateral ankle, which partially responded to the first round of PDT, had greatly enlarged by 2 months after the second PDT treatment (Figure 3). An additional course of PDT resulted in further improvement, but residual tumor persisted (Figure 3C). Unfortunately, the patient developed brain metastases and elected to withdraw from the trial. A few months after stopping vemurafenib treatment, the large keratotic lesion on the left ankle resolved on its own. Six months after the patient ended vemurafenib treatment, no additional KAs were noted.

Approximately 60% of human melanomas harbor mutations in the BRAF gene, of which 90% have a substitution of glutamic acid for valine at amino acid 600 (V600E).1 The BRAF gene encodes a serine/threonine kinase that plays a key role in the mitogen-activated protein kinase (MAPK) signaling pathway and has emerged as an important therapeutic target for melanoma. Given the high prevalence of V600E mutations, therapeutic agents such as vemurafenib, a potent inhibitor of V600E BRAF, have been designed and shown to demonstrate complete or partial metastatic melanoma regression in 81% of phase 1 study patients and, more recently, a 63% reduction in risk of death and a 74% improvement in progression-free survival in patients with metastatic melanoma.2,3 However, cutaneous adverse effects are a common finding with these novel inhibitors. In 2 trials,2,3 approximately 20% of all patients developed either KA-like or SCC lesions, and 10% to 12% of trial patients experienced grade 2 rashes after initiating treatment—both evident in our patient. Keratoacanthomas are well-differentiated squamous neoplasms that are characterized by rapid growth and spontaneous resolution. The lesions typically present on sun-exposed areas as solitary dome-shaped papules with a keratinaceous core.4,5 Although KAs are difficult to differentiate histologically from well-differentiated SCC, their characteristic clinical evolution—rapid appearance often in association with antecedent trauma2 and self-regression—suggest a separate biological process from that of traditional SCCs.
The use of systemic retinoid therapy has been effective in the treatment of multiple eruptive KAs. However, retinoid therapy may have unknown interactions with targeted chemotherapeutic agents such as vemurafenib and therefore alternative treatment modalities were considered; further evaluation of the compatibility of BRAF inhibitors and retinoids is warranted. Topical PDT represents a promising therapeutic option for eruptive KAs, having been used to effectively treat superficial nonmelanoma skin cancers, such as basal cell carcinoma and SCC in situ, as well as large areas of actinic damage. However, there is no consensus regarding the efficacy of PDT for treating KAs, with anecdotal data suggesting both improvement and exacerbation of PDT-treated tumors. Our patient underwent 3 interval treatments with aminolevulinic acid and red light, after which most treated lesions demonstrated clinical improvement. This was in contrast to untreated tumors on his lower extremities, which persisted during treatment. Although KAs have been documented to develop at sites of trauma, we found it interesting that no new KAs developed in the treatment field. One lesion grew larger during the 2 months after the second treatment; therefore, it is difficult to determine whether the increased size was caused by PDT or incomplete treatment. The lesion improved after the third and final treatment. Although the natural history of KAs may be to regress spontaneously, their behavior when induced by BRAF inhibitors remains to be classified. In general, treatment of KAs is preferred given the potential risk of metastasis, as there are currently no biomarkers to determine biological behavior. As such, the case described herein illustrates the potential utility of PDT in treating eruptive and extensive KAs in similar patients. The worsening of one tumor suggests that close follow-up is necessary and that frequent serial treatments are likely required because the limitations of PDT are the depth of penetration of the topical agent as well as of the light source. We believe that

Figure 2. The right medial shin with several keratoacanthomas before (A) and after (B) treatment demonstrates significant resolution after 3 cycles of photodynamic therapy.

Figure 3. A single keratoacanthoma on the left lateral ankle. A clinical photograph shows the keratoacanthoma (A), which was enlarged 2 months after the second course of photodynamic therapy (PDT) (B) but demonstrated significant regression after additional PDT treatment (C).
the improvement in our patient’s KAs was a result of multiple treatments, with greater penetration of the photosensitizer with each treatment; nevertheless, it remains to be determined whether agents such as methyl aminolevulinate, which is composed of a lipophilic base, may better penetrate these hyperketotic lesions and make them more responsive to fewer treatments.

Our patient illustrates eruptive KA development after the initiation of treatment with a BRAF inhibitor for metastatic melanoma and represents the first report, to our knowledge, of a case in which PDT is used for the treatment of these lesions. Recent evidence in vitro and in vivo suggests that selective BRAF inhibitors can induce activation of downstream elements of the MAPK pathway in BRAF wild-type cancer cells.11–13 This raises the possibility that vemurafenib is acting on genetically abnormal keratinocytes in stimulating the de novo appearance of lesions such as those seen in our patient. Further patient reports and clinical follow-up will aid in characterizing the biological processes and natural history of BRAF inhibitor–induced KAs, as well as their long-term response to treatment such as PDT. We believe that the keratinocytic proliferations seen in response to BRAF V600E inhibitors represent a reactive process, especially in light of complete resolution of these lesions once treatment with the medication was stopped. As such, measures to improve quality of life will be important because we anticipate that many of these patients will need to receive targeted therapy for extended periods.

Accepted for Publication: December 5, 2011.

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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Financial Disclosure: None reported.

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