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LETTER TO THE EDITOR

Keratoacanthomas associated with imatinib mesylate

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To the Editor,

Imatinib mesylate, an orally available inhibitor of constitutively activated BCR-ABL tyrosine kinase, platelet-derived growth factor receptor (PDGFR) alpha and beta, and the c-kit receptor tyrosine kinase [1], is approved by the FDA for the treatment of several malignancies. Various dermatologic toxicities have been described in recent years. To our knowledge, squamous cell carcinomas (SCCs) potentially associated with imatinib were only reported once [2]. We report two patients who developed keratoacanthomas (KA) while receiving imatinib.

Case 1

An 89-year-old male had a 3 mm thick melanoma resected on the right sole. Over the following years, subsequent in-transit metastases of the right leg were treated with cryotherapy, topical imiquimod cream and local injections of OncoVEX granulocyte-macrophage colony stimulating factor. His dermatologic history was significant for actinic keratoses (AKs), a KA on the left forearm, and a basal cell carcinoma (BCC) on the right ear. Due to persistent in-transit metastases and because his melanoma harbored an exon 11 L576P and an amplification of KIT (alterations suggesting sensitivity to therapy with a KIT inhibitor), he was enrolled in a clinical trial of imatinib (NCT00470470) 400 mg twice a day for resistant, recurrent melanoma. A mildly pruritic maculopapular rash affecting the trunk and extremities developed after two weeks of therapy. Temporary interruption and reduction of imatinib to 400 mg daily resulted in improvement. Approximately seven months after restarting imatinib, a 7 mm hyperkeratotic nodule developed on the right elbow, followed by another 6 mm keratotic, erythematous papule on the right lower leg, two months later (Figure 1A/B). The histopathologic findings revealed a crateriform squamous proliferation with a central keratin plug surrounded by squamous cells with abundant pink cytoplasm and associated with inflammation (Figure 2) – features typical of a KA. Both lesions were treated surgically, without recurrence. Therapy with imatinib was continued and no new lesions have been noted as of the last follow-up visit 11 months after their surgical removal.

Case 2

A 67-year-old female with metastatic melanoma had progression of disease on temozolomide and was enrolled in the same clinical trial with imatinib. Her dermatologic history was significant for only a few AKs. After two weeks on imatinib, a maculopapular rash necessitated temporary interruption and dose reduction with resultant improvement. A tender keratotic 4 mm papule on the right anterior tibia developed after approximately six months of treatment and proved to be a KA, and was treated surgically without recurrence. Imatinib was discontinued

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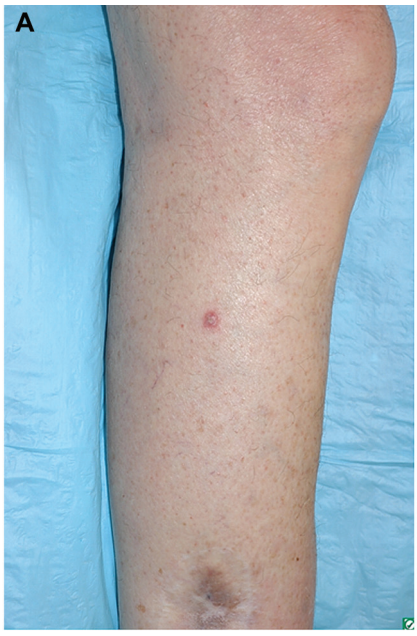

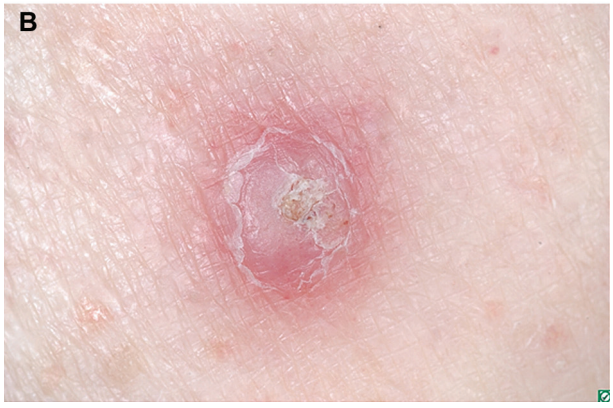

Figure 1A/B. Keratoacanthoma arising on the right lower leg.

one month following surgical intervention due to progression of melanoma.

Discussion

Maculopapular eruptions and edema are the most common dermatologic adverse events of imatinib [3]. To our knowledge there have been only a few reports of cutaneous neoplasms in patients receiving imatinib. Malpighian epithelioma and hyaline-cell chondroid syringoma have been reported in two patients undergoing long-term treatment with imatinib, exceeding 50 weeks [4]. The development of new squamous cell carcinomas (SCCs) and a rapid progression of a pre-existing lesion with subsequent ulceration were reported in two patients with chronic myeloid leukemia receiving imatinib [2]. However, in this report the true association is difficult to ascertain, since lesions developed in photo-exposed

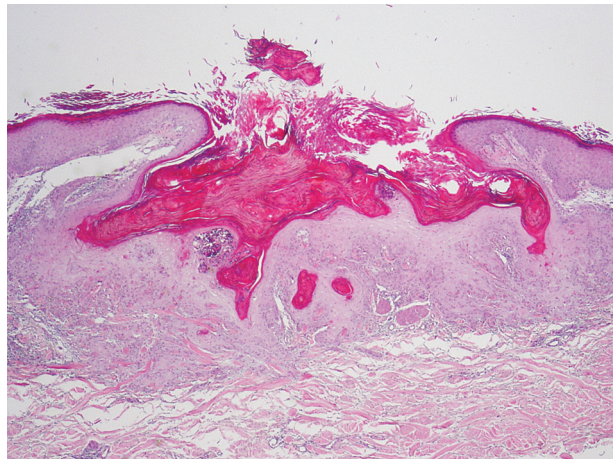

Figure 2. Biopsy of the right lower leg lesion demonstrated a crateriform squamous proliferation with a central keratin plug surrounded by squamous cells with abundant pink cytoplasm and associated with inflammation, consistent with a keratoacanthoma.

areas and one patient had numerous AKs. More importantly, both patients had previously received hydroxyurea, which is a risk factor for development of SCCs on sun-exposed areas [2]. In one of our patients with previous history of AKs, BCC and a KA, new KAs developed on relatively photoprotected areas. The second patient had only few previous AK's and no history on non-melanoma skin cancers, suggesting that imatinib may be a potential culprit.

The underlying mechanism that may explain the occurrence of KAs in association with imatinib is unknown. However, development of AKs, KA's and SCCs in association with sorafenib, a targeted agent approved for treatment of advanced renal cell and hepatocellular carcinoma, has been well documented [5]. Sorafenib, initially designed to inhibit a RAF kinase, has multiple other targets including vascular endothelial growth factor (VEGFR)-2 and -3, PDGFR-beta, c-Kit, ret proto-oncogene, and FMS-like tyrosine kinase 3 [6]. Similarly, a novel selective mutant RAF inhibitor PLX4032 has also been associated with the development of KAs and SCCs [7]. The underlying pathogenesis has not yet been elucidated but one proposed hypothesis is that RAF inhibition may result in activation of upstream, parallel, alternative pathways such as PI3K/Akt with subsequent inhibition of apoptosis and cell proliferation [8]. Additionally, recent investigations of RAF inhibitors demonstrated that although significant inhibition of mitogen-activated protein kinase (MAPK) signaling is observed in cells harboring BRAF mutations, a paradoxical activation of RAF-MEK-ERK pathway occurs in cells with wild-type BRAF [9]. Therefore, it is plausible that tendency to develop cutaneous neoplasms with agents that inhibit BRAF may stem from enhanced signaling of the MAPK

pathway in skin. However, the same does not apply to imatinib, which is not known to target BRAF.

In vitro studies of head and neck squamous carcinoma cells demonstrated the ability of imatinib to indirectly induce activation of the epidermal growth factor receptor (EGFR) and downstream signaling of the MAPK pathway, which was attributed to the release of endogenous EGFR-activating ligands [10]. It has also been shown that there is an overexpression of the EGFR in KAs, SCCs, and AKs [8,11]. Based on these studies, enhanced EGFR activity may be a potential underlying mechanism that may explain increased growth of KAs in our patients. However, other in vitro studies have demonstrated significant imatinib-induced inhibition of head and neck squamous cell carcinoma cells either alone or in combination with chemotherapy and radiation [12–14]. Furthermore, regression of SCC in a patient with CML after several months of imatinib treatment has also been reported [15]. If an association between imatinib mesylate and growth of cutaneous squamous neoplasms does exist, further investigations are necessary to elucidate the underlying mechanisms and explain the differences in clinical behavior among different patients. It is likely that the development of KAs in our patients is multifactorial in nature, but direct molecular effects of imatinib on signaling pathways regulating cellular growth may be involved as well.

Familiarity with this potential toxicity is therapeutically relevant and can facilitate earlier recognition and treatment. If the induction of KAs is truly associated with imatinib, patients undergoing such therapy may benefit from routine dermatologic screening.

Declaration of interest: Dr. Carvajal is a consultant for Novartis and is on advisory board for Novartis and Baxter. He has received honoraria from Novartis and Baxter. There are no funding sources to declare.

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