Case letters

Vemurafenib-associated gingival hyperplasia in patient with metastatic melanoma

To the Editor: Targeted inhibition of activated v-raf murine sarcoma viral oncogene homolog B (BRAF), a driver in a substantial proportion of melanomas, leads to rapid and dramatic clinical responses and improved survival in patients with metastatic melanomas (84% vs 64% 6-month survival).[1] However, this remarkable efficacy, exemplified by vemurafenib, the first Food and Drug Administration–approved targeted BRAF inhibitor, is accompanied by specific toxicities. The most prominent side effect of vemurafenib both in preapproval clinical trials and postmarketing surveillance is the development of keratoacanthoma-like squamous cell carcinomas, induced by paradoxical activation of mitogen-activated protein kinase pathway in cells harboring retrovirus-associated sequence (RAS) mutations, such as keratinocytes on sun-damaged skin.[1,2] Other side effects possibly also representing "RASopathic" effects of vemurafenib include: keratosis pilaris, acanthopapillomas, plantar hyperkeratosis, ultraviolet A–dependent photosensitivity, maculopapular exanthema, pruritus, folliculitis, burning feet, alopecia, curly hair, nail changes, and melanomas.[3] To our knowledge, we describe the first case of vemurafenib-induced gingival hyperplasia.

A 29-year-old woman with a history of metastatic melanoma presented to our clinic in 2011 after having developed many subcutaneous metastases with sequential therapy with radiation followed by paclitaxel and carboplatin. Biopsy specimen and polymerase chain reaction analysis of one of the nodules showed a BRAF V600E mutation and the patient subsequently started vemurafenib. After 2 months of therapy, the patient began to develop keratoacanthomas, acanthopapillomas, xerosis, and gastrointestinal distress. None of the side effects were dose-limiting and the patient continued on vemurafenib. After 3 months of therapy, the patient noted severe gum hyperplasia with bleeding, swelling, and pain (Fig 1, *A*). Multiple cultures were unremarkable and the hyperplasia was refractory to topical steroids, antifungals, and antibacterials. Because of disease progression, vemurafenib was stopped in favor of ipilimumab. Within 1 month of discontinuing vemurafenib, all of the drug-specific side effects, including the gingival hyperplasia, resolved (Fig 1, *B*). Unfortunately, because of accelerated disease our patient died shortly after starting ipilimumab.

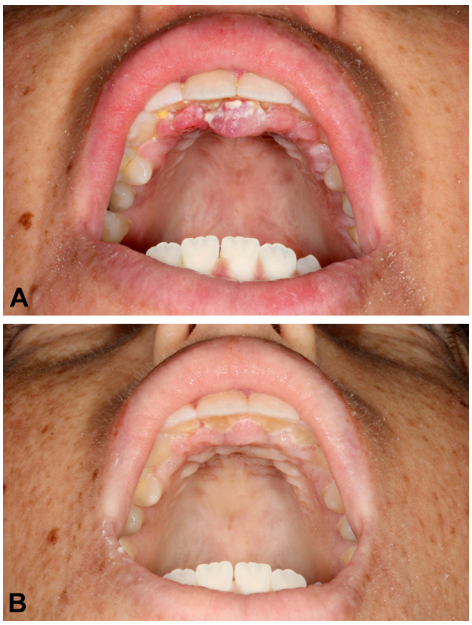

Fig 1. Gingival hyperplasia. **A**, Marked gingival enlargement during vemurafenib treatment. **B**, Rapid resolution of gingival hyperplasia after cessation of vemurafenib.

Our patient represents the first described case of vemurafenib-induced gingival hyperplasia. The refractory nature of the hyperplasia while on vemurafenib and quick resolution with drug cessation implicate vemurafenib treatment as a causative event. Rinderknecht et al[3] argue that activation of germline mutations likely lead to unique toxicities. We can use the germline RASopathies as guidance for possible side effects of RAS/mitogen-activated protein kinase activation. Interestingly, son of sevenless homolog 1 mutations result in the activation of the RAS/mitogen-activated protein kinase pathway and are seen in Noonan syndrome 4 (Online Mendelian Inheritance in Man: 610733) and hereditary gingival fibromatosis 1 (Online Mendelian Inheritance in Man: 135300).[4,5] Noonan syndrome 4 is characterized by congenital anomalies and ectodermal changes: curly hair, keratosis pilaris, and hyperkeratosis skin.[4] Hereditary gingival fibromatosis 1 is characterized by mild hypertrichosis, gingival fibromatosis, and fibro-osseous dysplasia.[5] Therefore, it seems both biologically plausible and clinically supported that our patient's gingival hyperplasia may represent yet another RASopathic side effect of vemurafenib therapy. This and other documented side effects of vemurafenib further illustrate the importance of recognizing and

better understanding the toxicities of targeted agents for improved and more effective patient treatment.

Aaron R. Mangold, MD,[a] Alan Bryce, MD,[b] and Aleksandar Sekulic, MD, PhD[a]

Departments of Dermatology[a] and Internal Medicine, Division of Oncology,[b] Mayo Clinic, Scottsdale, Arizona

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Correspondence to: Aleksandar Sekulic, MD, PhD, Department of Dermatology, Mayo Clinic, 13400 E Shea Blvd, Scottsdale, AZ 85259

E-mail: sekulic.aleksandar@mayo.edu

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Plaque-like syringoma with involvement of deep reticular dermis

To the Editor: A healthy 28-year-old man presented with an asymptomatic eruption on the penile shaft for 5 years. Physical examination demonstrated multiple 5- to 8-mm, skin-colored, discrete papules coalescing into a plaque on the proximal aspect of the dorsal penile shaft (Fig 1). A 4-mm punch biopsy specimen demonstrated a basaloid ductal proliferation set almost entirely in a dense sclerotic stroma extending into the deep reticular dermis. The ducts were lined by 2 rows of epithelial cells with a bulging outer layer to create a comma-shaped tail (Fig 2). The clinical and histopathologic findings were consistent with a plaque-type syringoma with deep extension.

Syringomas are benign adnexal neoplasms. Eccrine versus apocrine differentiation is still debatable as both variants are reported in the literature. From the histologic perspective, the main differential diagnosis in our case included desmoplastic trichoepithelioma, infiltrating/morpheaform basal cell carcinoma, microcystic adnexal carcinoma (MAC), and syringomatous carcinoma. Despite the extension into the deep reticular dermis that abutted subcutaneous tissue, the anatomic location of the lesion, the lack of infiltrative growth, highlighted by the confinement of the proliferation to the accompanying dense sclerotic stroma, and the lack of perineural growth distinguished it from MAC, desmoplastic trichoepithelioma, and infiltrating basal cell carcinoma. Our case demonstrated follicular induction, but there was no evidence of well-differentiated follicular differentiation within the cystic spaces, which is observed in MAC. MAC is also characterized by bland cytology and low or absent mitotic index, but deep and extensive infiltration with possible perineural involvement is

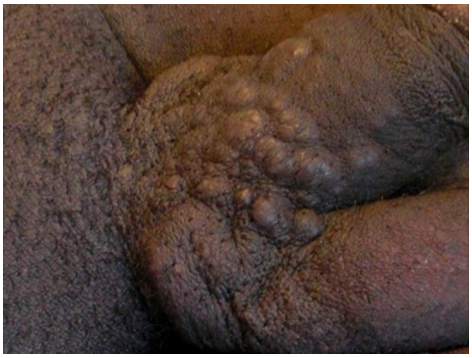

Fig 1. Plaque-type penile syringoma. Multiple, skin-colored, discrete, firm papules coalescing into a large, thick plaque on the proximal aspect of the dorsal penile shaft.

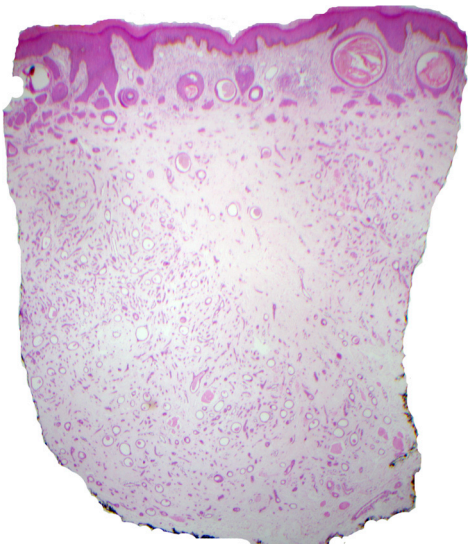

Fig 2. Syringoma. A basaloid ductal proliferation set almost entirely in a dense sclerotic stroma extending into the deep reticular dermis. (Hematoxylin-eosin stain.)