

BRIEF ARTICLES

Verrucous Keratoses Associated with Checkpoint Inhibitor Immunotherapy

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ABSTRACT

Introduction: Checkpoint inhibitor immunotherapy is associated with numerous adverse events, including eruptive keratoacanthomas and squamous cell carcinomas. However, no cases of immunotherapy-associated verrucous keratoses (VKs) have been reported. VKs are proliferative lesions generally considered benign, although they have been suggested to represent premalignant lesions.

Cases: We present the first case series of three patients with immunotherapy-associated VKs. The patients were receiving nivolumab for renal cell carcinoma, combination ipilimumab/nivolumab for non-small cell lung carcinoma, and pembrolizumab for malignant melanoma. The VKs appeared 3-7 months after initiation of immunotherapy. Lesions were treated with shave removal or cryosurgery without recurrence. This report adds to the spectrum of cutaneous squamoproliferative lesions induced by checkpoint inhibitor immunotherapy.

INTRODUCTION

Immune checkpoints act as a normal brake on immune activation and response. Cytotoxic T lymphocyte associated antigen 4 (CTLA-4) regulates the activation of naïve T cells.¹ In contrast, programmed cell death protein 1 (PD-1), expressed on T cells, B cells, NK cells, and macrophages, binds to programmed death-ligand 1 and 2 (PD-L1, PD-L2) leading to downregulation of the adaptive immune response.¹ Many cancers have been shown to co-opt these immune checkpoints to evade detection and destruction by the immune system.² Immune checkpoint inhibitors have been developed to block this downregulation of the immune response, facilitating an immunologic

response to cancers.¹ The first approved checkpoint inhibitor, ipilimumab, is a humanized anti-CTLA-4 immunoglobulin monoclonal antibody (mAb).¹ Nivolumab is a fully human anti-PD-1 immunoglobulin G4 (IgG4) mAb, whereas pembrolizumab is a humanized anti-PD-1 IgG4 mAb.¹

Increasing clinical use of checkpoint inhibitors has led to the recognition of immune-related adverse events (irAEs).¹ The most common irAEs include skin eruptions and itch, fatigue, diarrhea, and endocrinopathies.¹ The skin eruptions include maculopapular, papulopustular, lichenoid dermatitis, vitiligo, bullous disorders, and eruptive keratoacanthomas.^{3,4} Here we present, to our knowledge, the first

January 2020 Volume 4 Issue 1

reported cases of verrucous keratoses (VKs) associated with checkpoint inhibitor immunotherapy.

REPORT OF CASES

Case 1. An 87-year-old man with a history of psoriasis, prostate cancer (diagnosed 17 years earlier), metastatic clear cell renal carcinoma (initial diagnosis 13 years prior, metastasis found 5 years ago), and infiltrating ductal breast carcinoma (diagnosed 1 year ago) presented with a 2-month history of a non-pruritic eruption over the upper body. The patient had begun treatment with nivolumab after failing pazopanib for his metastatic renal cell carcinoma. After receiving 6 cycles over 3 months, nivolumab was discontinued due to the development of profound arthralgias as well as flares of psoriasis. Treatment with topical corticosteroids and vitamin D analogues was unsuccessful, leading to initiation of narrowband UVB phototherapy. Despite nivolumab being held for 4 months, his metastatic renal tumors continued to regress, demonstrating an ongoing immunologic response to the malignancy.

Seven months after initiating nivolumab, physical exam revealed several discrete erythematous papules and plaques diffusely over the upper and lower extremities and trunk (Figure 1A). Dermoscopy of the lesions showed exophytic hyperkeratotic papules with central white keratin horns containing thrombosed vessels and an erythematous halo peripherally (Figure 1B). Biopsies were performed on four representative lesions which showed marked hyperkeratosis and acanthosis, and a dermal lymphohistiocytic infiltrate; koilocytosis and features of invasive growth were absent. Overall, biopsies were consistent with an inflamed VK (Figure 2). The lesions did not recur after the shave

removals were performed, and other smaller similar papules resolved with cryosurgery.

Case 2. A 71-year-old woman with a history of metastatic large cell neuroendocrine lung carcinoma initiated treatment with combination ipilimumab and nivolumab after previous treatments with carboplatin, etoposide, and pemetrexed. Five months after beginning immunotherapy, she presented with a growth on the medial cheek. It had been enlarging over the last two weeks, with intermittent pruritus and bleeding. Physical exam demonstrated a 2-cm fusiform, stuck-on plaque with yellow and heme crust and surrounding erythema. Biopsy of the lesion demonstrated an inflamed VK without atypical cells.

Case 3. A 59-year-old woman with a history of stage IIIB melanoma undergoing initial treatment with pembrolizumab presented with a one-week history of a sudden growth on her chest three months after initiating immunotherapy. Physical exam demonstrated a 6-mm inflamed, stuck-on papule with hemorrhagic crust and surrounding erythema. Biopsy of the lesion demonstrated an inflamed VK.

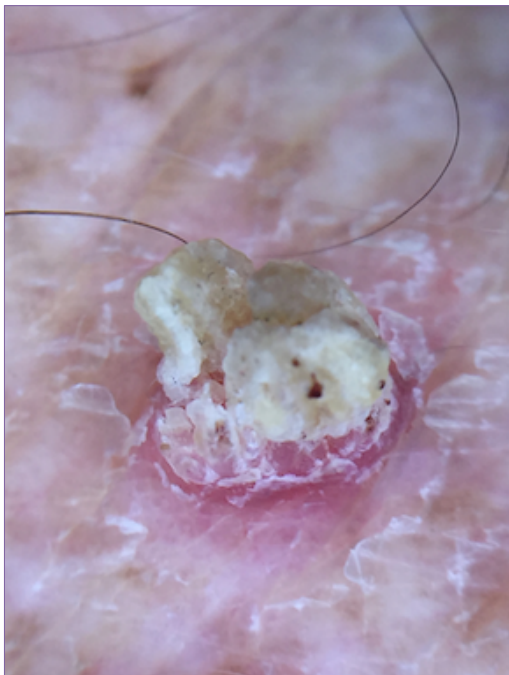
DISCUSSION

VKs are squamoproliferative lesions that lie on a spectrum of epithelial hyperplasia. Though generally benign, there are concerns that VKs may represent premalignant lesions if new in onset in the context of anticancer therapy.⁵ Studies of BRAF inhibitors (e.g., vemurafenib and dabrafenib) in the treatment of melanoma have documented the development of verrucae vulgaris, verrucous keratoses, actinic keratoses, KAs, and squamous cell carcinomas (SCCs) in up to 79% of patients.⁶ The mechanism for this is

Figure 1. (1a) Clinical image demonstrating numerous discrete erythematous verrucous papules on the back. (1b) Dermoscopic image demonstrating an exophytic hyperkeratotic papule with central white keratin horns containing thrombosed vessels and an erythematous halo peripherally.

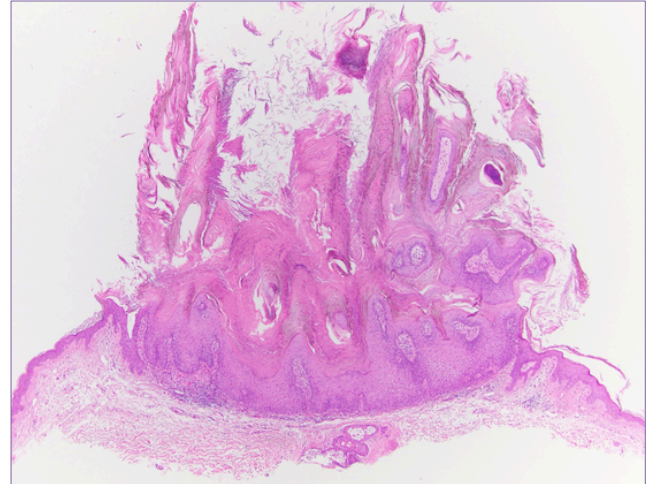


(1a)



(1b)

Figure 2. Histopathologic image demonstrating marked hyperkeratosis and acanthosis, and a dermal lymphohistiocytic infiltrate. Koilocytosis and invasive growth are absent (hematoxylin and eosin stain, 40x original magnification).



thought to occur via paradoxical activation of the mitogen-activated protein kinase (MAPK) pathway in cells which do not harbor the V600E BRAF mutation, leading to proliferation and tumorigenic growth of keratinocytes.⁷

This would be, to our knowledge, the first report of immunotherapy-induced VKs. Previous reports have documented the occurrence of eruptive KAs and eruptive SCCs during immunotherapy.^{4,8-10} Therefore checkpoint inhibitor immunotherapy may serve to exaggerate a squamoproliferative pathway in some patients, leading to the development of eruptive VKs, KAs, or SCCs.

We cannot completely rule out the possibility of pre-existing or incipient verrucous or seborrheic keratoses (SKs) that subsequently enlarged and became inflamed with immunotherapy. It is also possible that the lesions represented a precursor to a developing KA or SCC-like growth that have previously been reported, although we believe this is less likely given their clinical

and benign histopathological appearance. Patient 1 had a more diffuse, multi-lesional presentation which might argue for a broad inflammatory response to preexisting keratoses. However, patients 2 and 3 each presented with one inflamed VK at sites that were clearly documented with recent photos as having no previous SK or other lesion at the site. Each VK biopsied demonstrated a lymphohistiocytic dermal infiltrate, similar to previous reports of immunotherapy induced KAs.^{4,8-9} Whether this represents a non-specific inflammatory response or a targeted immune response remains an open question.

While the pathophysiology of immunotherapy-induced VKs is unknown, an intriguing observation seen in Patient 1 was a continued development of VKs and reduction in tumor burden despite cessation of anti-PD-1 therapy. The persistent immunological response despite discontinuing anti-PD-1 therapy is a hallmark of immune checkpoint inhibition.¹

Anti-PD-1 therapy is now approved for the treatment of advanced cutaneous squamous cell carcinoma.¹¹ It will be important to surveil these patients for the development of new keratinizing skin lesions, which may cloud the clinical picture. Clinicians should be aware of the possible development of any kind of new cutaneous squamoproliferative lesion, both benign and atypical, in the context of immunotherapy that are unrelated to the primary cancer.

Conflict of Interest Disclosures: None

Funding: None

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