

Transient eruptive keratoacanthomas associated with nivolumab



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INTRODUCTION

Programmed cell death 1 (PD-1) inhibitors show efficacy in the treatment of metastatic melanoma, non-small cell lung cancer, urothelial cancers, head and neck squamous cell carcinoma, cervical cancer, and various malignancies with microsatellite instability and high tumor mutational burden. PD-1 inhibitors are reported in association with various cutaneous adverse effects including lichenoid eruption, eczema, vitiligo and bullous pemphigoid.^{1,2} The development of keratinocyte neoplasms such as actinic keratosis, seborrheic keratosis, basal cell carcinoma, and squamous cell carcinoma have also been reported.¹ A recent review of dermatologic toxicities associated with immune checkpoint blockade suggested they be divided into 4 categories: inflammatory, immunobullous, alteration of keratinocytes, and alteration of melanocytes.³ We report a case of eruptive keratoacanthomas (KAs) seen in association with nivolumab therapy, which resolved without intervention and despite continuation of immunotherapy.

CASE REPORT

A 92-year-old man with axillary apocrine adenocarcinoma presented to his dermatologist with new crusted lesions on the arms. Eight months prior, the patient had a painful mass in his right axilla with adjacent lymphadenopathy. Pathology findings of the cutaneous mass showed small glandular structures filling the dermis and infiltrating the subcutaneous tissue and showed pagetoid involvement of the epidermis. Pathology findings of the lymph node were consistent with metastatic apocrine carcinoma. Tumor cells were positive for periodic acid-Schiff and mucicarmine and negative for cytokeratin 20,

Abbreviations used:

KA: keratoacanthoma
 PD-1: programmed cell death 1

thyroid transcription factor 1, and napsin A. Genomic studies showed the tumor to be negative for human epidermal growth factor receptor 2 (immunohistochemistry 1 positive; fluorescent in situ hybridization negative), epidermal growth factor receptor mutation, and PD ligand 1. Positron emission tomography scan found enlarged hypermetabolic right axillary and mediastinal lymph nodes. Fine-needle aspiration of the mediastinal nodes via endobronchial ultrasound scan confirmed metastatic disease. In view of the patient's advanced age, his refusal to participate in clinical trials, and paucity of effective chemotherapeutic agents for this entity, treatment with nivolumab was started after obtaining informed consent.

The patient reported that new lesions on the arms first appeared shortly after his third nivolumab infusion. On physical examination there were scattered inflamed keratotic papules on the left arm and left dorsal hand (Fig 1, A). Curette biopsy of a representative lesion showed squamous cell carcinoma, KA type (Fig 2). At his follow-up appointment 2 weeks later, the patient had more lesions, now with greater than 20 keratotic papules and plaques on the bilateral arms and dorsal hands. The largest lesion was treated with complete curettage, and pathology findings were consistent with squamous cell carcinoma. Per patient report, he subsequently had several similar-appearing lesions on the legs. At his

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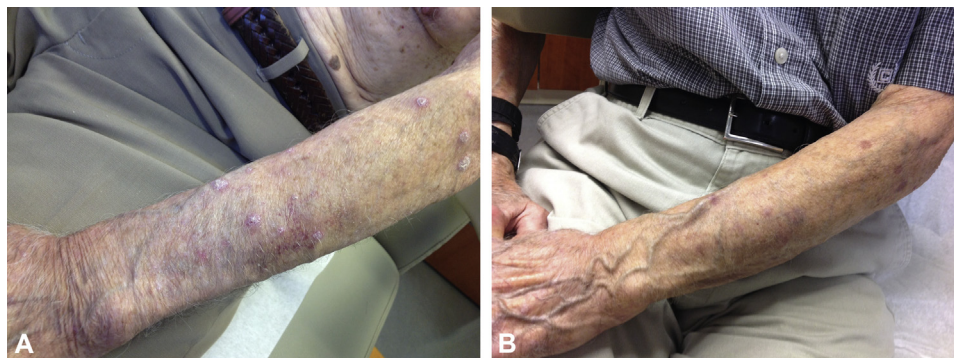


Fig 1. **A**, At time of initial presentation to the dermatologist, with many inflamed keratotic papules on the left arm and hand. **B**, At follow-up visit 8 weeks after initial presentation, with resolution of keratotic lesions.

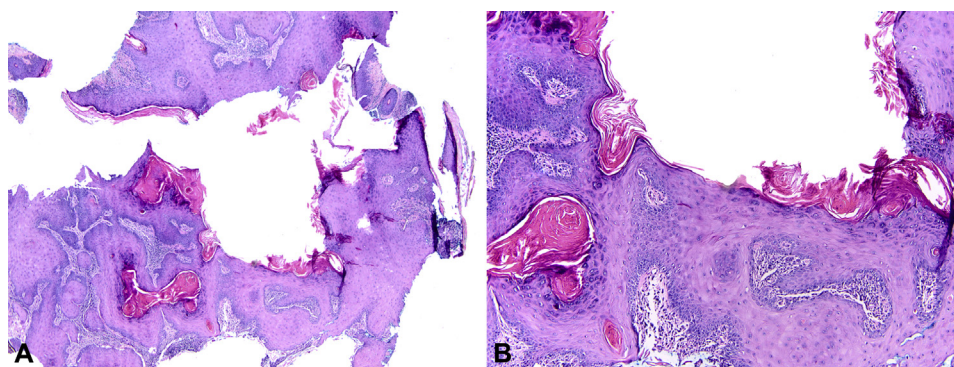


Fig 2. **A**, A curette biopsy of a representative keratotic lesion shows fragments of an atypical squamous proliferation with a crateriform invagination (hematoxylin and eosin, $\times 4$). **B**, Higher power shows an atypical squamous proliferation. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**, $\times 4$; **B**, $\times 10$.)

follow-up visit 6 weeks later, there was complete resolution of all lesions (Fig 1, B). Nivolumab treatment was continued, and the patient did not use any topical or systemic medications for his skin lesions.

DISCUSSION

Eruptive keratoacanthomas are a recently described and rare cutaneous side effect of PD-1 inhibitors (Table 1). Ten cases have been reported, including 4 associated with pembrolizumab and 6 associated with nivolumab. Affected patients have had various metastatic malignancies including melanoma, head and neck squamous cell carcinoma, pancreatic cancer, renal cell carcinoma, and apocrine adenocarcinoma. Timing of onset of eruptive KAs has ranged from 1 to 18 months after initiation of PD-1 inhibitor therapy, with a mean of 5.5 months. Although suggested to represent a delayed onset dermatologic adverse effect,⁴ our patient had eruptive KAs after only 1 month (third infusion) of nivolumab. KAs tend to occur in

photodistributed areas on the hands (5 cases), arms (4 cases), legs (6 cases), and trunk (2 cases).

In 4 cases, PD-1 inhibitor therapy was discontinued shortly after the development of KAs. Treatment strategies include topical and intralesional steroids, cryotherapy, imiquimod, and curettage. Although systemic retinoids are first-line therapy for eruptive KAs associated with syndromes, their side-effect profile and potential interactions make them a less suitable choice for patients with metastatic cancer treated with immunotherapy. Notably, all of our patients' KAs resolved within 8 weeks of initial presentation, without intervention, and while nivolumab therapy was continued. Similarly, Fujimura et al⁵ have recently reported a case of eruptive KAs associated with nivolumab resolving without intervention within 6 weeks, highlighting the transient nature of PD-1 inhibitor-associated eruptive KAs.

Several reported cases noted KAs to occur in the setting of recent or concomitant lichenoid skin toxicity^{4,6} or bullous pemphigoid-like disease,⁶

Table I. Cases reported to date of eruptive keratoacanthomas associated with PD-1 inhibitors

Reference	Age y/sex	PD-1 inhibitor	Malignancy	Time to onset of KAs	Distribution of KAs	PD-1 inhibitor discontinued?	Therapy and response	Other dermatologic adverse events
Bandino et al ⁶	73/M	Pembrolizumab	Metastatic melanoma	After sixth infusion (4 mo)	Bilateral lower extremities	Yes	Doxycycline and niacinamide for concurrent bullous pemphigoid-like eruption; KAs regressed spontaneously	Bullous pemphigoid-like eruption
Bandino et al ⁶	90/M	Nivolumab, previously pembrolizumab	Metastatic melanoma	6 mo after initiation of PD-1 inhibitor	Trunk	Yes	Electrodesiccation and curettage	Bullous pemphigoid-like eruption, Actinic keratosis, basal cell carcinomas
Freites-Martinez et al ⁴	M	Pembrolizumab	Metastatic melanoma	18 mo	Extremities	No	Clobetasol ointment, intralesional triamcinolone, cryotherapy; Complete response after 1 mo	Lichenoid skin reaction
Freites-Martinez et al ⁴	F	Pembrolizumab	Metastatic melanoma	13 mo	Legs	No	Clobetasol ointment, intralesional triamcinolone, cryotherapy; Complete response after 1 mo	None
Freites-Martinez et al ⁴	M	Pembrolizumab	Metastatic scalp SCC	4 mo	Dorsal hands	No	Clobetasol ointment, intralesional triamcinolone; Complete response after 1 mo	Lichenoid skin reaction
Feldstein et al ⁷	78/F	Nivolumab	Metastatic anal SCC	6 mo	Arms, legs, upper chest	Yes	Imiquimod; Complete response at 6 months	None
Feldstein et al ⁷	85/F	Nivolumab	Pancreatic cancer	After fifth infusion (2 mo)	Dorsal hands and palms, lower legs	Yes	Cryotherapy; Complete response at 4 month follow up	None

Bednarek et al ⁸	79/F	Nivolumab	Metastatic clear cell renal carcinoma	4 mo	Dorsal hands, forearms, lower leg	No	Clobetasol ointment, intralesional triamcinolone; Complete response at 3 mo	None
Fujimura et al ⁵	73/M	Nivolumab	Cervical SCC	1 mo	Dorsal hands	No	Spontaneous resolution after 6 wk	Grade 3 fever and skin eruption
Antonov et al (current case)	92/M	Nivolumab	Metastatic apocrine adenocarcinoma	After third infusion (1 mo)	Bilateral arms and dorsal hands	No	Curettage of 2 lesions; Spontaneous resolution after 8 wk	None

SCC, Squamous cell carcinoma.

although an eruptive KA may occur as an isolated phenomenon, as the case reported here. Many reports noted a lichenoid or interface dermatitis seen on skin biopsy of KAs. Some suggest that the lichenoid milieu and the enhanced T-cell response caused by PD-1 inhibitors may encourage the development of KAs in predisposed individuals,^{7,8} although the mechanism is poorly understood.

We report a tenth case of eruptive KAs in association with PD-1 inhibitor therapy; in this case, KAs were transient and showed rapid resolution despite continuation of immunotherapy. Based on the cases reported to date, eruptive KAs may not be an indication to discontinue immunotherapy and may be treated conservatively. Given the increasing usage of PD-1 inhibitors to treat malignancies, dermatologists and oncologists should be aware of this troublesome, but usually self-limited adverse effect.

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