Case Report

# Transient Eruptive Keratoacanthomas Associated with Nivolumab: A Case Report

Trupti Dongre[1,*], Mahesh Deshmukh[2], Amol Dongre[3], Sushil Pande[4]

[1]Department of Pathology, NKP Salve Institute of Medical Sciences & Research Centre and Lata Mangeshkar Hospital, Nagpur, India
[2]Department of Pathology, Max Super Speciality Hospital, Nagpur, India
[3]Department of Medical Oncology, Max Super Speciality Hospital, Nagpur, India
[4]Department of Dermatology, NKP Salve Institute of Medical Sciences & Research Centre and Lata Mangeshkar Hospital, Nagpur, India

***Correspondence:** dr.truptidongre@yahoo.co.in

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## Abstract

Immune checkpoint inhibitors are increasingly being utilized for the treatment of advanced neoplastic disease and have been associated with cutaneous adverse effects. We are reporting a case of eruptive keratoacanthomas in a patient 24 months after initiation of nivolumab for cHL. Treatment with topical ultra-high potency corticosteroid and third generation retinoid stopped the development of new lesions and healed previous lesions. 5-FU, imiquimod, cryotherapy, and curettage are other methods to treat. Most of these were treated with topical and intralesional corticosteroids, excision, or cryotherapy. Eruptive keratoacanthoma is a rare adverse effect of immune checkpoint inhibitors. Oncologists and dermatologists must be aware of this cutaneous adverse effect as their use has been increased. Appropriate treatment can control and manage the lesions.

*Keywords:* Immune checkpoint inhibitors; Eruptive Keratoacanthoma; Cutaneous adverse effect; Nivolumab

## Introduction

Immune Checkpoint Inhibitors (CPIs) or Programmed Cell Death (PD-1) inhibitors are increasingly being utilized for the treatment of advanced neoplastic diseases like 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 tumour mutational burden. PD-L1 have been associated with wide range cutaneous adverse effects including lichenoid eruption, eczema, vitiligo, and bullous pemphigoid [1].

Dermatologic toxicities associated with immune checkpoint blockade suggested division in 4 categories: inflammatory, immunobullous, alteration of keratocytes, and melanocytes. Also reported are actinic keratosis, seborrheic keratosis, basal cell carcinoma, and squamous cell carcinoma.

We discuss a case of multiple eruptive keratoacanthomas (KAs) arising in a patient approximately 2 years after initiation of Nivolumab for classical Hodgkin Lymphoma (cHL).

## Case Report

A 42-year-old male was diagnosed with EBV +ve classical Hodgkin's Lymphoma (cHL) in 2013. He underwent first-line chemotherapy with ABVD followed by consolidation radiation therapy at the Rt. cervical bulky node region. The patient was in remission from 2014-2018. In March 2018, the patient relapsed. The treatment planned was salvage chemotherapy with GDP followed by high dose myeloablative conditioning (HDCT) with BEAM protocol and autologous stem cell transplant (AHSCT). The patient was in remission from 2018-2021. The patient relapsed again in August 2021. Treatment planned was salvage chemotherapy, followed by second AHSCT transplant and maintenance Immunotherapy with PD-1 CPI. Salvage chemotherapy consisted of Brentuximab, Vedotin and Bendamustine. Transplant treatment plan consisted of HDCT with LACE and second AHSCT. Second transplant was done in Dec 2021. Maintenance immunotherapy was started with PD-1 checkpoint inhibitor nivolumab from 2022-2024. The patient completed 43 cycles after which he developed multiple eruptive keratoacanthomas (KAs) secondary to nivolumab for which the drug was discontinued.

After completion of 36 cycles of nivolumab administered biweekly over 24 months (with temporary withholding of treatment in between for immune-mediated colitis), multiple lesions started erupting on bilateral lower and upper extremities. The lesions increased further without any sign of resolution and reached maximum after 7 cycles administered over the next 4 months thereafter. On physical examination, there were scattered inflamed keratotic papules on legs and hands (Fig. 1). Excisional biopsy of a lesion was done. Histopathology report was of eruptive keratoacanthomas. Pertaining to this, nivolumab was discontinued after 43 cycles and the patient was treated with topical ultra-high potency corticosteroid Clobetasol and third generation retinoid Tazarotene. After a few weeks, development of new lesions stopped and the previous lesions started to heal.

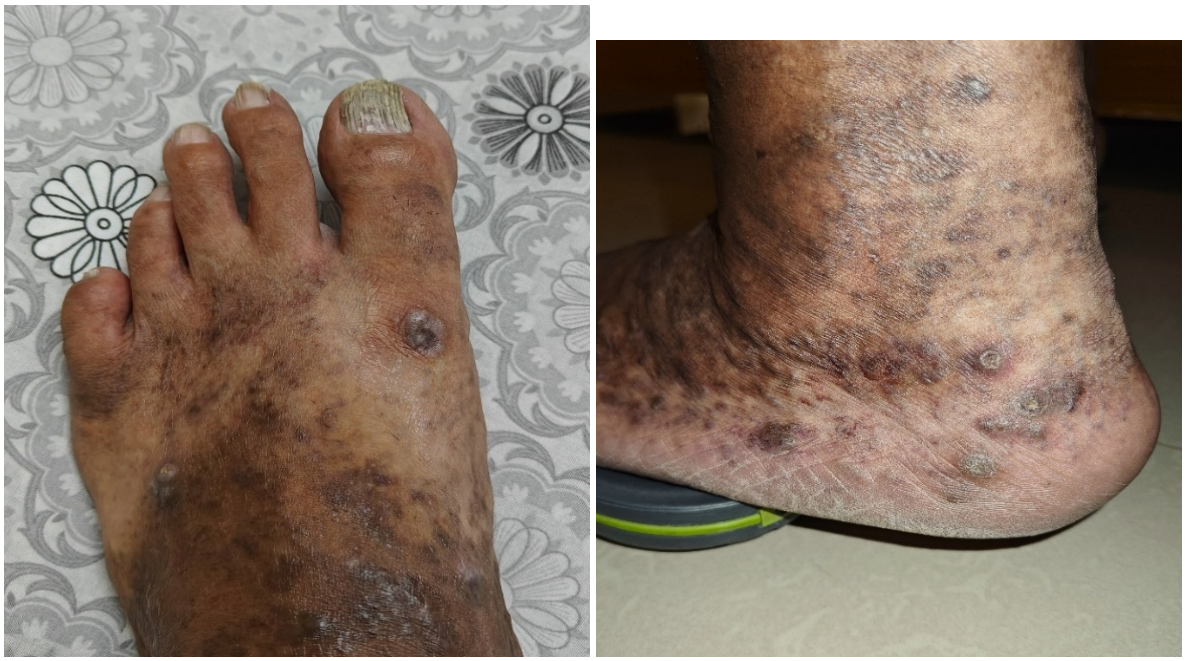

**Figure 1:** Eruptive lesions on the leg.

## Discussion

KAs are tumours originating from keratinocytes in the follicular infundibular/isthmic region or in the outer layer of the skin and are commonly found in sun-exposed areas of the body (Fig. 2). They follow a three-phase pattern of development: a proliferative phase (early), a stabilized phase (well-developed), and a regressive phase (late), resembling the respective hair cycle [2]. KAs appear on areas exposed to the sun, the hands, arms, legs, faces, and trunk. In rare cases, they may occur in a non-sun-exposed area such as the nasal vestibule. Fair-skinned people are more prone to this skin condition [3]. The initial size is about 1-2mm; over a period of a couple of weeks, it grows to a diameter of 1-3cm. It can have a hard keratin core. At some point within this period, the lesion will stop growing. The skin lesion takes about 2-12 months to heal completely. The period differs from person to person. A scar will remain at the site of the lesion after healing. They can appear 1-18 months after starting PD-1 inhibitor therapy [4].

Eruptive keratoacanthomas are a recently described rare cutaneous side effect of PD-L1 inhibitors. Our case is of a 42-year-old male having cHL with two AHSCT followed by maintenance therapy with PD-1 CPI. Timing of onset of eruptive keratoacanthomas range from 1 to 18 months after initiation of PD-1 inhibitor therapy with a mean of 5 months. Our patient

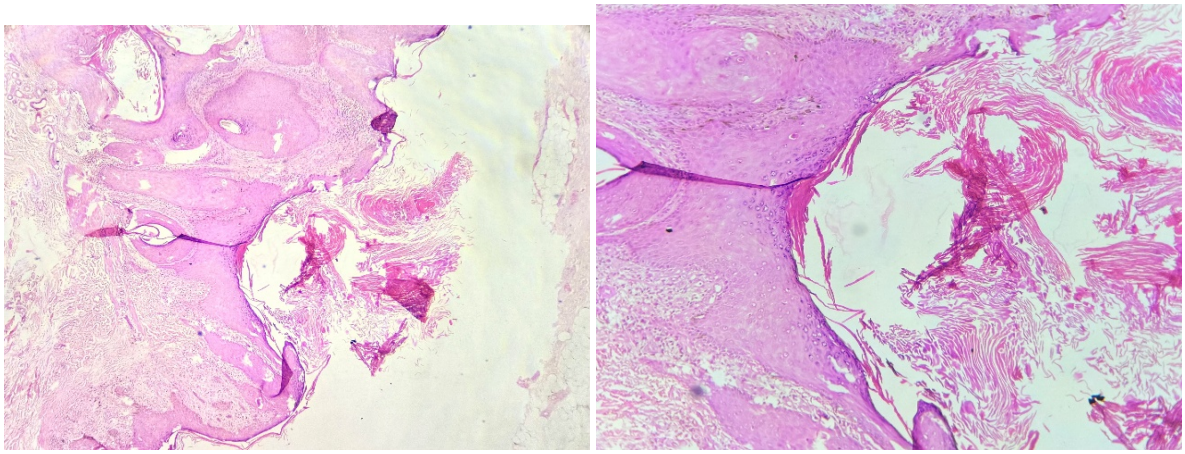

**Figure 2:** Histopathology image showing fragments of an atypical squamous proliferation with a crateriform invagination. (A) 100X magnification. (B) 400X magnification.

started to develop it after 2 years. The patient had taken a 2 months break in between due to other adverse events.

KAs tend to occur in photo distributed areas on the hands, arms, legs, trunk, and head.

Treatment strategies include topical and intralesional steroids and or 5-FU, imiquimod, cryotherapy, and curettage. Systemic retinoids are first-line therapy for eruptive keratoacanthomas associated with syndromes, but its side effects and interactions make it a less suitable choice for patients with cancer and on immunotherapy. Cryotherapy involves freezing the lesion using liquid nitrogen or carbon dioxide snow. The treatment is relatively safe, reliable, and cost-effective. Once the tumour is removed, the KA is considered cured as long as the dermatologist does not leave behind any of the core material. The neoplasm is unlikely to recur. If it is found out to be SCC, additional treatment is required.

Fujimura et al. reported a case of eruptive KAs associated with nivolumab resolving within 6 weeks without any intervention, highlighting the transient nature of PD-1 inhibitor associated eruptive KAs. Keratoacanthoma is a fast-growing skin tumour that can be observed as a solitary lesion or rarely as multiple lesions in the context of rare genetic syndromes, Ferguson-Smith syndrome, eruptive KA of Grzybowski, multiple familial KA of Witten and Zak, Muir-Torre syndrome, and Incontinenti-Pigmenti [5, 6].

KA and SCC are rare side effects of PD-L1 inhibitors that can disrupt therapy. There is no consensus on optimal treatment. IHC of atypical keratinocytes revealed PD-1/PD-L1 positivity, high p53, and low bcl-2 for all cases with differential expression of CD44 and $\beta$-catenin for KA versus SCC. The most common treatment was excision/destruction followed by topical and/or intralesional steroids. Therapy was definitely withheld in 22% of KA patients and in 9% of SCC cases. The expression of PD-L1 by atypical keratinocytes helps to explain the effects of nivolumab on the development of cutaneous neoplasms. Few can be managed without interference of therapy [7, 8].

## Conclusion

Discontinuation of immunotherapy due to development of eruptive KAs presents a challenge in the treatment of underlying malignancies. In our patient, we had to discontinue nivolumab, even though he underwent 43 cycles of the drug. If we are better able to treat eruptive KAs, then the patient can remain on immunotherapy for the treatment. Although treatment modalities help in speedy recovery, our patient had to discontinue the drug for regressing the lesion [9, 10]. Given the increasing usage of PD-1 inhibitors to treat malignancies, dermatologists and oncologists should be aware of this troublesome adverse effect [11, 12].

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## Conflicts of Interest

The authors declared no conflict of interest.

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