



Letter to the Editor

A Fortunate Eruption of Malignancies: Nivolumab-Induced Squamous Cell Carcinomas

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Dear Editor,

Nivolumab is an anti-cancer immunotherapy checkpoint inhibitor targeting PD-1 which frequently results in cutaneous immune related adverse events (irAE).^[1] Cutaneous squamous cell carcinoma (cSCC) is a common malignancy predominantly driven by chronic ultraviolet light exposure, typically presenting as a solitary lesion.^[2] Keratoacanthomas are similar but benign cutaneous tumours which typically spontaneously resolve. Here we report a case of nivolumab-induced cSCCs and keratoacanthomas.

An 82-year-old woman was initiated on first-line single-agent nivolumab 480mg 4-weekly for de novo metastatic melanoma. During cycle 1, the patient developed a grade 1 diffuse macular dermatitis on her lower limbs, initially managed with topical corticosteroids. The rash gradually progressed through cycles 2-6, requiring 50mg of oral prednisolone daily, resulting in temporary improvement. By cycle 6, the rash had transformed into an eruption of 30 to 40 scattered erythematous hyperkeratotic ulcerating papules and nodules (Fig. 1). Punch biopsies revealed multiple moderately-well differentiated squamous cell carcinomas and keratoacanthomas. Nivolumab was withheld and the larger lesions were surgically excised, while the smaller lesions were managed with cryotherapy. This resulted in clearance or a reduction of size of all lesions, with one further lesion arising in the weeks following. At this time,

restaging of the metastatic melanoma demonstrated complete radiological remission.

Eruptive cSCCs and keratoacanthomas have been associated with anti-PD-1 therapy in case reports and series, typically occurring 1-18 months post immunotherapy in sun exposed areas.^[3] Their association appears paradoxical given the anti-tumour effect of PD-1 inhibitors, which have efficacy in treating metastatic cSCC.^[4] It has been hypothesized off-target T-cell driven immune reaction at sites of prior UV-induced dysplasia may result in cellular proliferation, possibly akin to pseudoprogession associated with checkpoint inhibitors.^[5] PD-1 inhibitor induced cSCCs have an excellent prognosis, with response noted to excision, topical therapies such as 5-fluorouracil, intralesional corticosteroids and even oral niacinamide (vitamin B3) alone.^[3] Resolution has been demonstrated regardless if the provoking anti-PD-1 agent has been ceased or continued. Given self-resolution is not a feature of typical cSCC, PD-1 inhibitor induced cSCC may have an intrinsically benign nature similar to traditional keratoacanthoma, or may be induced to resolve due to the anti-tumour effect of the PD-1 inhibitor. Cutaneous irAEs, particularly vitiligo, are a positive prognostic factor for the targeted malignancy, indicative of an anti-tumour effect.^[6] As demonstrated in our patient, PD-1 inhibitor induced cSCCs have a similarly positive impact, with 86% of cases experiencing stability

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Figure 1. Lower limb eruption of squamous cell carcinomas and keratoacanthomas.

or improvement of their metastatic disease at the time of follow-up.^[3]

While an eruption of malignancies may be initially concerning, PD-1 inhibitor induced cSCCs may be exceptionally benign and portend a positive prognosis for the targeted metastatic disease.

Disclosures

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