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Squamous cell carcinoma or squamous proliferation associated with nivolumab treatment for metastatic melanoma

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Abstract

Nivolumab is a programmed death-1 (PD1) immune checkpoint inhibitor that treats various types of cancers including non-small cell lung carcinoma and melanoma, among others. Although it serves as an effective immunotherapy, there are many associated immune-related adverse events. Even years after the introduction of nivolumab, the breadth of its side effect profile continues to expand. We present a case of squamous cell carcinoma associated with nivolumab treatment for metastatic melanoma.

Keywords: nivolumab, metastatic melanoma, PDL1 inhibitor, squamous proliferation

Introduction

Immune checkpoint inhibitors serve a valuable role in the treatment of various cancers, yielding durable responses in a significant percentage of cancer patients in recent years [1]. This class consists of monoclonal antibodies such as nivolumab that target the programmed death-1 (PD1) receptor present on T cells. When bound by the ligands programmed death-1 and 2 (PDL1 and PDL2), the PD1 receptor negatively regulates T cell effector function. By targeting the PD1 receptor, monoclonal antibodies prevent binding of ligands and help maintain effector activity of T cells [2]. With the broadened usage of immune checkpoint inhibitors for different cancers, numerous immune-related adverse events (irAEs) have been well documented [3]. The most frequent irAEs associated with nivolumab include fatigue, rash, diarrhea, pruritus, and nausea [4]. We report a case of squamous cell

carcinoma (SCC) associated with nivolumab treatment for metastatic melanoma.

Case Synopsis

A 56-year-old man presented for initial evaluation of locally advanced melanoma. After identification of the melanoma on shave biopsy, he subsequently underwent wide local excision with a sentinel node biopsy and was found to have a T4b lesion with one positive sentinel node. Adjuvant immunotherapy with nivolumab was initiated given the patient's locally advanced disease, the depth of invasion of his primary tumor with a Breslow depth of at least 1.6mm, and the size and extranodal extension of his sentinel node deposit. On follow up, the patient reported two pruritic lesions on his left forearm and hand which had been present for about six months since starting nivolumab. Skin examination revealed two erythematous scaly firm plaques on the left dorsal forearm and hand (**Figure 1**). Shave biopsies revealed atypical squamous proliferations with small islands of atypical keratinocytes in the superficial dermis and overlying hyperkeratosis with parakeratosis (**Figure 2**). Nivolumab was continued and treatment with clobetasol was initiated. The lesions subsequently resolved at three months follow-up.

Case Discussion

Nivolumab is a human IgG4 monoclonal antibody that acts as a PD1 immune checkpoint inhibitor. By blocking the PD1 receptor, nivolumab is effective for treating various cancers such as metastatic



Figure 1. 1.2×1.2cm erythematous scaly firm plaque on the left dorsal forearm, and 1×1cm erythematous scaly firm plaque on the left dorsal hand.

melanoma [5]. Since its approval in 2014 as an immunotherapy for unresectable or metastatic melanoma, there have been many well documented irAEs associated with nivolumab. These irAEs have been described to involve many systems such as the skin, respiratory tract, gastrointestinal tract, hepatic, endocrine, renal, and neurological systems [3]. Those that are commonly cited include fatigue, rash, diarrhea, pruritus, and nausea [4,6,7]. Although many irAEs are benign, there have been some cases reported which required discontinuation of nivolumab. Among these cases included erythema multiforme major, dermatomyositis, and toxic epidermal necrolysis in patients being treated with nivolumab for melanoma [8-10]. Immune-related adverse events associated with nivolumab are varied in time of onset, with a majority developing in the first few weeks after treatment is initiated. However, reactions have been reported to occur even after two years [11].

Although many clinical trials and case reports have revealed numerous irAEs associated with nivolumab, there are few which assess different eruption profiles and treatment options. There have been multiple cases associated with nivolumab that describe atypical squamous proliferation in the context of eruptive keratoacanthomas (KA), [12-14]. Many of these KAs have also been reported to occur concomitantly with lichenoid drug eruption-like

changes. These findings are not specific to nivolumab, however, as they have also been reported in other PD1 immune checkpoint inhibitors such as pembrolizumab [15]. The decision as to whether these biopsies are ultimately designated keratoacanthomas or atypical squamous proliferations is based on the extent of atypia and the preference of the dermatopathologist, as well as clinical correlation. Due to the limited number of cases, the pathogenesis of these squamous lesions is poorly understood. Management options have varied with use of imiquimod, cryotherapy, electrodesiccation and curettage, clobetasol, hydroxychloroquine and the Goeckerman regimen (a combination of corticosteroids-under-occlusion “cool down,” UV-B phototherapy, and crude coal tar). Decisions between treatment options should take into account the differing characteristics of these lesions.

Squamous cell carcinomas or KAs arising from PD1 immune checkpoint inhibitors have been reported to occur in isolation or in conjunction with lichenoid changes. Hypertrophic lichen planus (HLP) and SCC share many similar characteristics clinically. Hypertrophic lichen planus is a variant of the idiopathic inflammatory disease, lichen planus, which presents with pruritic, thick hyperkeratotic plaques primarily in the lower extremities. As it is inflammatory in nature, there is a question as to

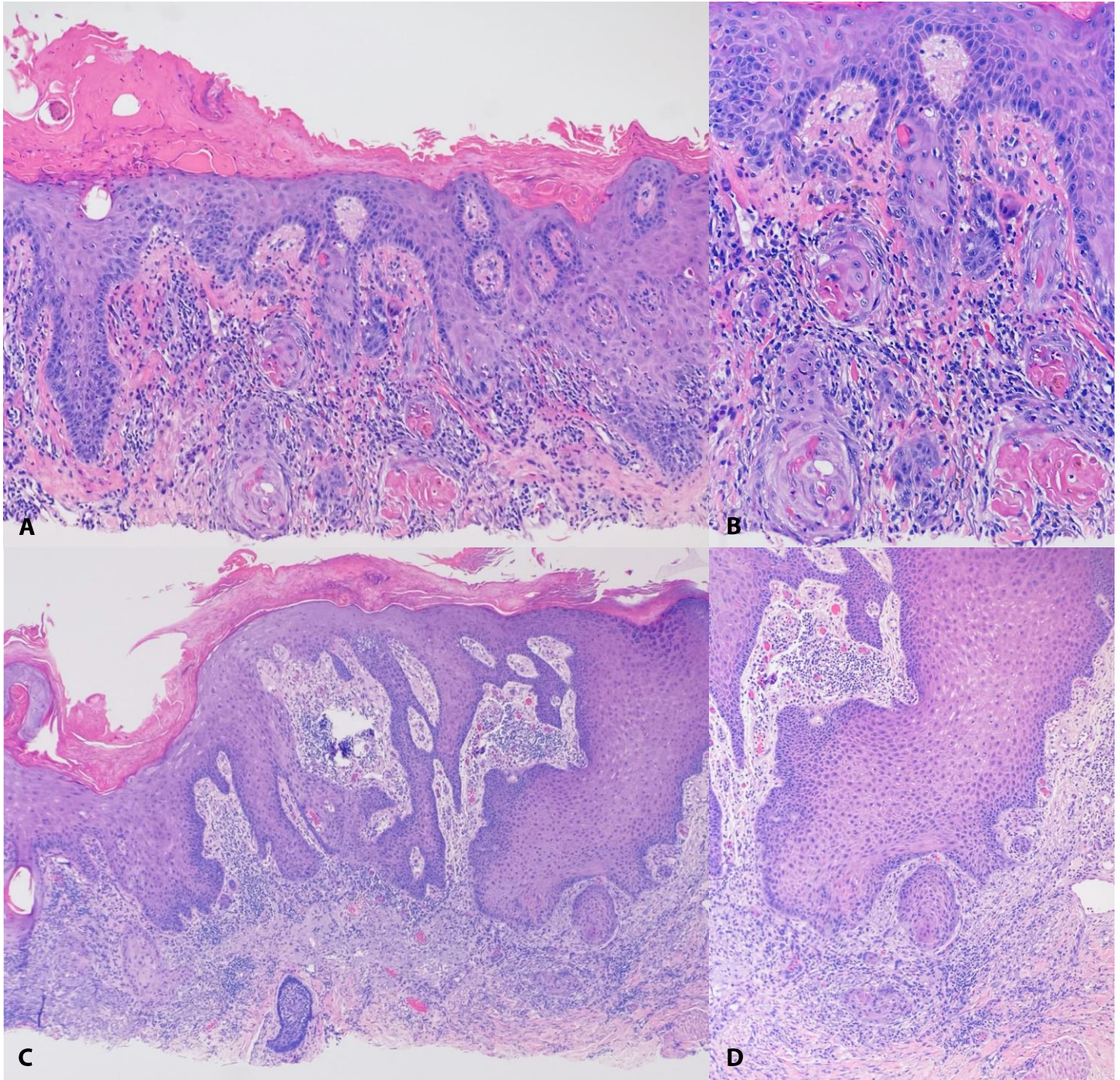


Figure 2. H&E histopathology. Shave biopsy of the left dorsal forearm shows prominent and irregular acanthosis with relatively large keratinocytes, mild atypia, and overlying hyperkeratosis with parakeratosis. Note the foci of necrotic keratinocytes and islands of atypical keratinocytes in the superficial dermis, **A)** 100 \times , **B)** 200 \times . **C)** Left dorsal hand shave biopsy demonstrates irregularly shaped aggregates of atypical keratinocytes suggesting premature cornification with overlying hyperkeratosis and parakeratosis, 40 \times . **D)** There are necrotic keratinocytes present at various levels of the epidermis and islands of atypical keratinocytes in the superficial dermis extending to the base of the biopsy, 100 \times .

whether optimal treatment of concomitant lichenoid eruptions in atypical squamous proliferation is with anti-inflammatory treatments such as intralesional triamcinolone (Kenalog)

injections or topical corticosteroids like clobetasol. Multiple case reports have described resolution of such lesions with treatment of these anti-inflammatory options [16]. Conversely, isolated SCC

or KA has been reported to resolve with other treatments like electrodesiccation and curettage [17]. Hypertrophic lichen planus may be differentiated from SCC through histopathological features. A previous study noted that HLP showed significant differences in hyperorthokeratosis, wedge-shaped hypergranulosis, and irregular psoriasiform hyperplasia, whereas parakeratosis, solar elastosis, deep extension, and perforating elastic fibers were significant for SCC [18]. Recognizing characteristics to make distinctions between isolated SCC, and SCC with lichenoid eruption may be important for guiding optimal treatment options for PD1 immune checkpoint inhibitor induced lesions.

Conclusion

There have been a plethora of noted side effects that are associated with immune checkpoint inhibitors.

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