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Erythema multiforme major in a patient with metastatic melanoma treated with nivolumab

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Abstract

Nivolumab, a relatively novel immune checkpoint inhibitor with FDA approval in 2014, is gaining greater utilization due to its efficacy in treating metastatic melanoma. Many of the cutaneous immune-related adverse events (irAEs) being catalogued do not necessitate discontinuation of immunotherapy and are managed with supportive therapy. We present a case of erythema multiforme major secondary to nivolumab requiring hospitalization and discontinuation of treatment. This is only the second reported case of nivolumab-induced erythema multiforme in the literature we are aware of, and emphasizes the importance of oncologists working in conjunction with dermatologists for prompt diagnosis and management.

Keywords: nivolumab, erythema multiforme, PD-1 inhibitor, metastatic melanoma, irAEs, check point inhibitor

Introduction

The success in overall survival in treating metastatic melanoma with immune checkpoint inhibitors has led to further investigational studies and approval for use in other malignancies. With broadening treatment indications, there has been a plethora of published literature discussing the significance of immune-related adverse events (irAEs) with these therapies. Nivolumab is one of the two anti-programmed cell death 1 receptor (PD-1) monoclonal antibodies which block a co-inhibitory signal of T cells resulting in increased immune surveillance against solid tumors [1]. The irAEs appear to be less severe compared to cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitors, as the mechanism of action occurs more peripherally [2].

The most common cutaneous irAEs caused by nivolumab are low-grade rash, pruritus, and vitiligo [3]. In most cases, cessation of treatment is not required but there have been reports of palmoplantar erythrodysesthesia, photosensitivity reaction, toxic epidermal necrolysis, and bullous pemphigoid [4]. We describe a case of erythema multiforme major in a patient with metastatic melanoma requiring discontinuation of nivolumab. This case expands on the variety of grade 3 cutaneous reactions and illustrates the importance of dermatologists for prompt diagnosis and management.

Case Synopsis

A 63-year old Caucasian female with primary stage IIIC melanoma of the right lateral lower leg and no other dermatologic history was initiated on nivolumab after being diagnosed with in-transit metastases to the right medial proximal thigh and right anterior shin. She received nivolumab 3 mg/kg every 2 weeks. After two doses of nivolumab, she presented with scattered, pruritic, erythematous and targetoid lesions with central necrotic areas on her bilateral anterior and posterior lower extremities as well as her upper arms (**Figure 1**, **2**). She had not started any other new medications in the 2 months prior. A punch biopsy of the left calf lesion revealed lichenoid dermatitis with scattered necrotic keratinocytes and subepidermal blister consistent with erythema multiforme (**Figure 3**, **4**). Nivolumab

was discontinued and the patient was hospitalized one week later when she developed worsening mucosal and skin involvement (**Figure 5**). Patient was treated with IV methylprednisolone, empiric acyclovir IV and vancomycin IV. Oral swab testing for herpes viruses was negative and patient was transitioned to oral steroids, minocycline, and valacyclovir. The dermatitis subsequently improved and the patient was never rechallenged with nivolumab.

Case Discussion

Immune checkpoint inhibitors are monoclonal antibodies blocking the deactivation of the T cell immune response, specifically T cell co-inhibitory signals, CTLA-4 and PD-1. The first immune checkpoint inhibitor was ipilimumab, which is an IgG1 antibody targeting CTLA-4. More recently, nivolumab, inhibitor of PD-1, has been gaining greater utilization given its superior overall survival and fewer irAEs [5-7]. PD-1 receptors are expressed on T and B cells and bind to programmed death ligand-1 (PDL-1) present on tumor cells resulting in evasion of cellular immunity [4]. Blockade of the PD-1 receptor indirectly leads to increased T cell autoimmunity against solid tumor cells.

Nivolumab is a relatively novel drug, approved by the Food and Drug Administration (FDA) in 2014, and adverse drug reactions (ADRs), including the subset of irAEs, are continuing to be discovered. As of last year, the PD-1 inhibitor data showed adverse dermatologic drug reactions of all grades in up to 37.4% of patients [8]. A meta-analysis found that the most common adverse skin reactions for nivolumab included low-grade rash (morbilliform drug eruption, eczematous or psoriasiform dermatitis), pruritus, and vitiligo [3]. Cutaneous irAEs occur on average 2-3 weeks after initiation of therapy; however, reactions can occur anywhere from 3 weeks to 2 years [1, 3].

The clinical trials of PD-1 inhibitors discovered several adverse skin reactions that included pruritus, rash, dermatitis, erythema, palmoplantar erythrodysesthesia, photosensitivity reaction, toxic epidermal necrolysis, urticaria, and vitiligo [4]. Our case is the second case of which we are aware of erythema multiforme described in the literature; the only other case was also described by our institution in a case series of nivolumab- related bullous dermatoses. Jour et al. presented three cases of bullous pemphigoid and one case of bullous erythema multiforme. All the cases required discontinuation of the immune checkpoint inhibitor, which resulted in resolution of the rash, in conjunction with systemic steroid treatment [9].

Currently, there are no biomarkers that can predict the occurrence of skin toxicities in patients using PD-1 inhibitors [4]. Freeman-Keller et al. has found that the occurrence of some cutaneous irAEs, rash and vitiligo, are associated with a positive prognosis with prolonged overall survival and progression-free survival [10]. It is rare for a dermatological adverse event to warrant discontinuation of immunotherapy. Therefore, it is important for oncologists to collectively work with dermatologists to determine when or if discontinuation is required.

Conclusion

Nivolumab is a PD-1 receptor inhibitor shown to increase survival rates in patients with metastatic melanoma [1,5-7]. The majority of irAEs are mild and do not require discontinuation of treatment. We described one additional case of erythema multiforme major to reinforce that severe cutaneous reactions can occur with PD-1 inhibitors and to expand on the possible cutaneous differential when evaluating a patient on nivolumab [3, 9, 11]. Familiarity with nivolumab's side effect profile will allow clinicians to expeditiously initiate appropriate management with this relatively novel agent.

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