

UC Davis

Dermatology Online Journal

Title

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

Permalink

<https://escholarship.org/uc/item/2513974h>

Journal

Dermatology Online Journal, 23(9)

Authors

Sundaresan, Swami
Nguyen, Kathleen T
Nelson, Kelly C
[et al.](#)

Publication Date

2017

DOI

10.5070/D3239036484

Copyright Information

Copyright 2017 by the author(s). This work is made available under the terms of a Creative Commons Attribution-NonCommercial-NoDerivatives License, available at <https://creativecommons.org/licenses/by-nc-nd/4.0/>

Peer reviewed

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

Swami Sundaresan¹ BA, Kathleen T Nguyen² MD, Kelly C Nelson³ MD, Doina Ivan^{3,4} MD, Anisha B Patel³ MD

Affiliations: ¹The University of Texas McGovern Medical School at Houston, Houston, T Texas, ²The University of Texas Health Science Center at Houston - UT Health, Department of Dermatology, Houston, Texas, ³M.D. Anderson Cancer Center, Department of Dermatology, Houston, Texas, ⁴M.D. Anderson Cancer Center, Department of Pathology, Houston, Texas

Corresponding Author: Kathleen T. Nguyen MD, Department of Dermatology, The University of Texas Health Science Center at Houston, 6655 Travis Street Suite #980, Houston, TX 77030, Email: Kathleen.T.Nguyen@uth.tmc.edu.

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.

References

1. Gelao, L., Criscitiello, C., Esposito, A., Goldhirsch, A., & Curigliano, G. Immune checkpoint blockade in cancer treatment: a double-edged sword cross-targeting the host as an "innocent bystander". *Toxins*, 2014 Mar 3;6(3):914-33. [PMID: 24594636].
2. Robert, C.; Soria, J.C.; Eggermont, A.M. Drug of the year: Programmed death-1 receptor/programmed death-1 ligand-1 receptor monoclonal antibodies. *Eur. J. Cancer*, 2013 Sep;49(14):2968-71 [PMID: 23907003].
3. Belum, V. R., Benhuri, B., Postow, M. A., Hellmann, M. D., Lesokhin, A. M., Segal, N. H.,... & Lacouture, M. E. Characterisation and management of dermatologic adverse events to agents targeting the PD-1 receptor. *European Journal of Cancer*, 2016 Jun;60:12-25. [PMID: 27043866].
4. Eigentler, T. K., Hassel, J. C., Berking, C., Aberle, J., Bachmann, O., Grünwald, V.,... & Zimmer, L. Diagnosis, monitoring and management of immune-related adverse drug reactions of anti-PD-1 antibody therapy. *Cancer treatment reviews*, 2016 Apr;45:7-18. [PMID: 26922661]
5. Robert, C., Long, G. V., Brady, B., Dutriaux, C., Maio, M., Mortier, L., & Savage, K. J. Nivolumab in previously untreated melanoma

- without BRAF mutation. *New England Journal of Medicine*, 2015 Jan 22;372(4):320-30. [PMID: 25399552].
6. Weber, J. S., D'Angelo, S. P., Minor, D., Hodi, F. S., Gutzmer, R., Neyns, B.,... & Linette, G. P. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. *The Lancet Oncology*, 2015 Apr;16(4):375-84. [PMID: 25795410].
 7. Topalian, S. L., Sznol, M., McDermott, D. F., Kluger, H. M., Carvajal, R. D., Sharfman, W. H.,... & Leming, P. D. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. *Journal of Clinical Oncology*, 2014 Apr 1;32(10):1020-30. [PMID: 24590637].
 8. Villadolid, J., & Amin, A. (2015). Immune checkpoint inhibitors in clinical practice: update on management of immune-related toxicities. *Translational lung cancer research*, 2015 Oct;4(5):560-75. [PMID: 26629425].
 9. Jour, G., Glitza, I. C., Ellis, R. M., Torres-Cabala, C. A., Tetzlaff, M. T., Li, J. Y.,... & Drucker, C. R. Autoimmune Dermatologic Toxicities from Immune Checkpoint Blockade with anti-PD-1 Antibody Therapy: A Report on Bullous Skin Eruptions. *Journal of Cutaneous Pathology*. 2016 Aug;43(8):688-96. [PMID: 27086658].
 10. Freeman-Keller, M., Kim, Y., Cronin, H., Richards, A., Gibney, G., & Weber, J. S. (2016). Nivolumab in resected and unresectable metastatic melanoma: characteristics of immune-related adverse events and association with outcomes. *Clinical Cancer Research*, 2016 Feb 15;22(4):886-94. [PMID: 26446948].
 11. Carlos, G., Anforth, R., Chou, S., Clements, A., & Fernandez-Peñas, P. A case of bullous pemphigoid in a patient with metastatic melanoma treated with pembrolizumab. *Melanoma research*, 2015 Jun;25(3):265-8 [PMID: 25831416].