Nivolumab-induced psoriasis successfully treated with risankizumab-rzaa in a patient with stage III melanoma

George D. Glinos, MD,[a] William Steele Fisher, BS,[b] Claudia S. Morr, MD,[a] and Lucia Seminario-Vidal, MD, PhD[a,c]
Tampa, Florida

Key words: cutaneous toxicity; nivolumab; psoriasis; risankizumab-rzaa.

INTRODUCTION

Nivolumab is a fully humanized, monoclonal, IgG4 antibody targeting the programmed cell death protein 1 (PD-1) indicated for use as adjuvant therapy for advanced melanoma. Despite its efficacy in treating advanced melanoma it is associated with a variety of cutaneous toxicities, which are the most frequently reported adverse events.[1,2] Psoriatic eruptions are well-described cutaneous reactions to PD-1 and programmed death-ligand 1 inhibitors.[3-5] Standard therapies for these eruptions have consisted of topical and systemic agents, which are either only appropriate for short-term use, not entirely effective, or palliative.

Risankizumab-rzaa is a highly efficacious novel treatment for moderate-to-severe psoriasis in adults. It is a humanized IgG1 monoclonal antibody targeting the p19 subunit of interleukin 23 (IL-23).[6,7] In contrast with older biologic medications, risankizumab-rzaa is not contraindicated in patients with recent malignancy. Here, we present the case of a patient who developed nivolumab-induced psoriasis successfully treated with risankizumab-rzaa.

CASE DESCRIPTION

A 61-year-old woman presented with a history of stage IIIB (T2aN1cM0) invasive melanoma on the right side of the back initially treated with radical resection, right axillary sentinel lymph node biopsy, and adjuvant therapy with nivolumab. One out of 2 sentinel lymph nodes were positive for melanoma, and no evidence of distant active metastases was reported on imaging. Two weeks after the first infusion of nivolumab, the patient developed a generalized pruritic rash with mild improvement after topical clobetasol. This eruption worsened after a second infusion, evolving into generalized erythematous plaques with overlying scale, involving 80 % of her body surface including the neck, trunk, upper and lower extremities, but sparing the face and mucosal surfaces (Fig 1). There were no nail findings or lymphadenopathy. Punch biopsies showed acanthosis, parakeratosis, mixed superficial perivascular inflammation, mild spongiosis, and subcorneal pustulation (Fig 2), consistent with drug-induced psoriasis. This eruption lasted much longer than 5 half-lives after nivolumab was discontinued—around 133 days. Extensive medication history failed to identify any other suspected drug or supplement. The patient did not have a personal or family history of psoriasis.

Nivolumab therapy was discontinued after 2 cycles. She was initially treated with low-dose systemic corticosteroids by her oncologist with poor response. She was given high-dose prednisone (1 mg/kg/day) with improvement, but subsequently, flare was observed after tapering. She was restarted on prednisone with concomitant acitretin (25 mg/day) but did not tolerate this regimen due to transaminitis after 2 months of therapy initiation. She declined phototherapy due to her history of melanoma and declined treatment with apremilast due to

Abbreviations used:

ICI:	immune checkpoint inhibitors
IL:	interleukin
PD-1:	programmed cell death protein 1

From the Department of Dermatology & Cutaneous Surgery[a] and Morsani College of Medicine[b], University of South Florida; Cutaneous Oncology Program, H. Lee Moffitt Cancer Center.[c]
Funding sources: None.
Correspondence to: Lucia Seminario-Vidal, MD, PhD, 13330 USF Laurel Drive, 6th Floor, Tampa, FL 33612 E-mail: luciasem@gmail.com.

JAAD Case Reports 2021;11:74-7.
2352-5126

https://doi.org/10.1016/j.jdcr.2021.03.029

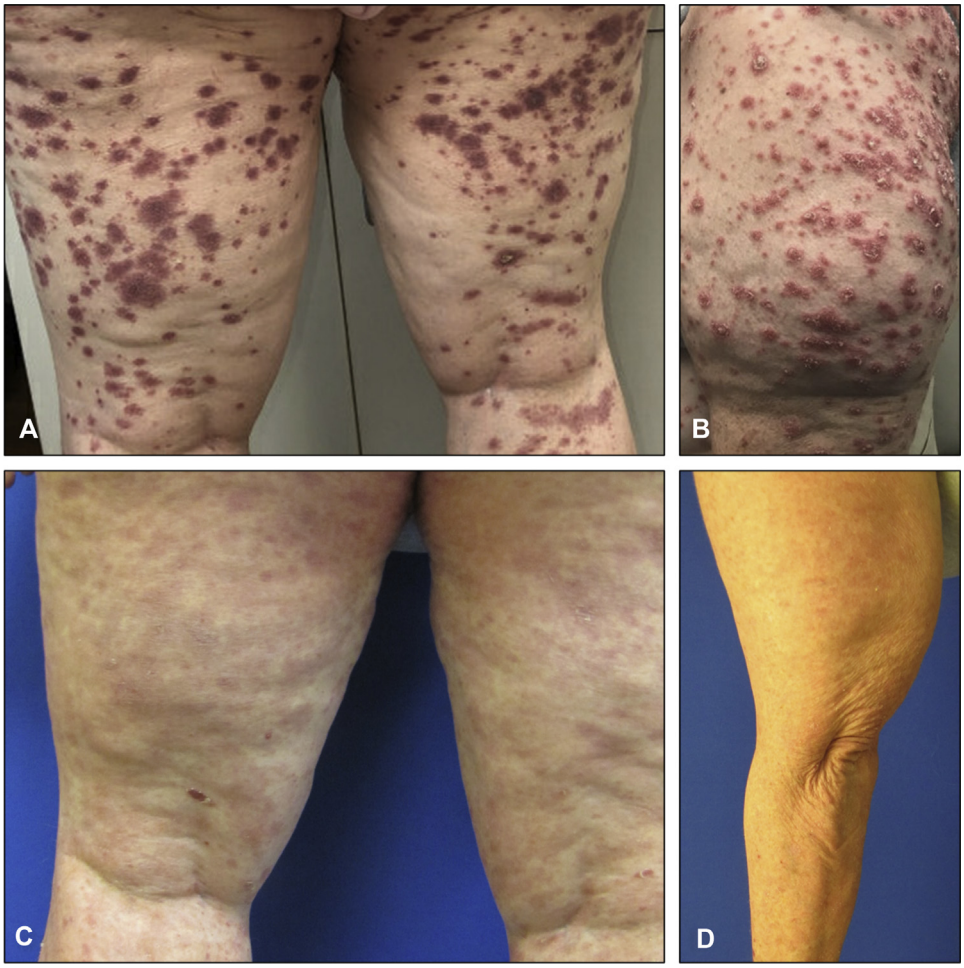

Fig 1. Response of drug-induced psoriasis to risankizumab-rzaa at week 0 (**A** and **B**) and after 2 doses at week 6 (**C** and **D**).

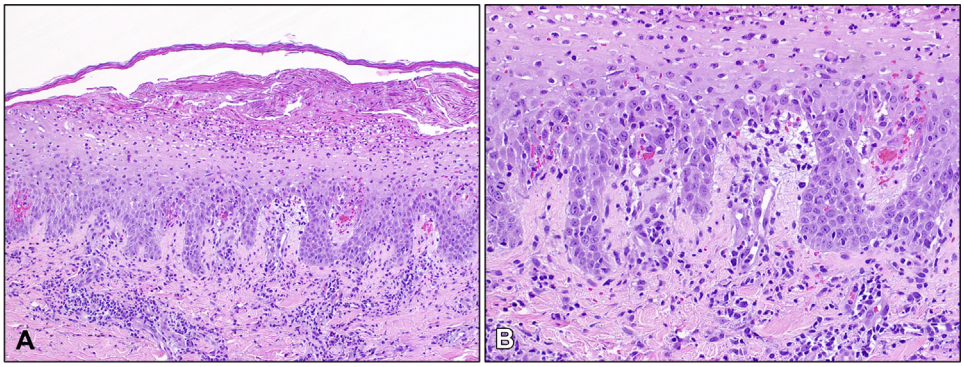

Fig 2. Histopathologic findings of drug-induced pustular psoriasis including acanthosis, confluent parakeratosis, and hypogranulosis of the epidermis associated with a mixed superficial and perivascular infiltrate and subcorneal pustule (**A** and **B**, Hematoxylin-eosin stain; original magnifications, **A**, ×100; **B**, ×400). Periodic-acid—Schiff and Gram stains were negative for infectious organisms.

lower response rates compared with newer biologic agents.

Finally, this patient's drug-induced psoriasis was treated with risankizumab-rzaa with the Food and Drug Administration (FDA)-approved loading and maintenance dosage for plaque psoriasis (150 mg injected subcutaneously on week 0, week 4, and every 12 weeks thereafter). She experienced a rapid response of her psoriatic eruption at 6 weeks (Fig 1) and maintained a durable clinical response. She has been clear for the last year. The patient and her oncologist decided to not restart nivolumab despite clearance of her rash. This patient's melanoma remains in remission, and she is being monitored with surveillance scans every 6 months.

DISCUSSION

Immune checkpoint inhibitors (ICIs), such as nivolumab, are vital components of modern regimens for patients with advanced stage malignancies, and it may be a difficult decision for patients and oncologists alike to discontinue immunotherapies despite the development of cutaneous adverse events, given their well-documented benefits in treating a variety of cancers. Therefore, management of immunotherapy-related cutaneous toxicities is an area that requires attention, and if they are managed effectively, it may increase compliance and thus improve patient prognosis.

PD-1 and programmed death-ligand 1 inhibitors are increasingly being used to treat a variety of cancers including melanoma, renal cell carcinoma, lung carcinomas, and more. However, inherent to their mechanism of action, these ICIs are also associated with immune-related adverse events. The most commonly adversely affected organ with the use of these drugs is the skin,[5] and there are many reports documenting psoriasis in patients taking either class of medication.[8] While most patients had a history of psoriasis,[5,8] there are also rare reports of *de-novo* psoriasis in patients on this therapy,[4] and this patient's case is another such example.

The safety profile of risankizumab-rzaa is overall quite good. Infections are the most common adverse events reported, most of which are considered not to be severe.[7] Use of the drug has been associated with rare adverse cardiovascular events. Of particular interest is the fact that this medication, along with the other FDA-approved IL-23 inhibitors, guselkumab and tildrakizumab, does not contain a warning on its labeling regarding the risk of development or progression of malignancies as many older monoclonal antibody medications do. No malignancies other than nonmelanoma skin cancers were reported in the group treated with risankizumab-rzaa for the duration of the phase III clinical trial.[7] Murine models with loss of IL-23 function show conflicting evidence regarding the development of new cancers. Some studies have shown decreased rate of epidermal tumor development, growth, and metastasis. However, the models are variable, showing an increase, decrease, or no difference in melanoma development.[9] Concomitant use of IL-23 inhibitors and ICIs has not yet been studied. However, recent studies suggest that systemic immunosuppressants in patients with autoimmune diseases at ICI start do not affect response rates.[10] Further investigation is needed to better understand whether IL-23 inhibition may affect response rates to ICIs.

As demonstrated by this case, psoriatic drug eruptions in cancer patients may be managed with risankizumab-rzaa. Although an IL-23 inhibitor was selected for treatment in this patient's case, other classes of biologic drugs such as tumor necrosis factor-alpha inhibitors, which are commonly used to treat PD-1 inhibitor colitis, may be considered. IL-23 inhibitors are more immunomodulatory than broadly immunosuppressive and are potential viable therapies for psoriatic cutaneous toxicities, including those in patients with active or recent malignancies on anticancer systemic therapies, such as nivolumab, in whom immunosuppressive medications may be contraindicated or worsen overall prognosis. Although the initial safety profiles for risankizumab-rzaa are reassuring, longer-term safety data is needed, especially regarding the development or progression of malignancies, before generalized treatment recommendations can be made.

The authors would like to thank the patient who participated in this study.

Conflicts of interest

None declared.

REFERENCES

1. Long GV, Weber JS, Larkin J, et al. Nivolumab for patients with advanced melanoma treated beyond progression: analysis of 2 phase 3 clinical trials. *JAMA Oncol*. 2017;3(11):1511-1519.
2. Ascierto PA, Long GV, Robert C, et al. Survival outcomes in patients with previously untreated braf wild-type advanced melanoma treated with nivolumab therapy: three-year follow-up of a randomized phase 3 trial. *JAMA Oncol*. 2019;5(2):187-194.
3. Bonigen J, Raynaud-Donzel C, Hureaux J, et al. Anti-PD1-induced psoriasis: a study of 21 patients. *J Eur Acad Dermatol Venereol*. 2017;31(5):e254-e257.
4. Voudouri D, Nikolaou V, Laschos K, et al. Anti-PD1/PDL1 induced psoriasis. *Curr Probl Cancer*. 2017;41(6):407-412.

5. De Bock M, Hulstaert E, Kruse V, Brochez L. Psoriasis vulgaris exacerbation during treatment with a PD-1 checkpoint inhibitor: case report and literature review. *Case Rep Dermatol*. 2018;10(2):190-197.
6. Reddy V, Yang EJ, Myers B, Liao W. Clinical evaluation of risankizumab-rzaa in the treatment of plaque psoriasis. *J Inflamm Res*. 2020;13:53-60.
7. Gordon KB, Strober B, Lebwohl M, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. *Lancet*. 2018;392(10148):650-661.
8. Matsumura N, Ohtsuka M, Kikuchi N, Yamamoto T. Exacerbation of psoriasis during nivolumab therapy for metastatic melanoma. *Acta Derm Venereol*. 2016;96(2):259-260.
9. Ergen EN, Yusuf N. Inhibition of interleukin-12 and/or interleukin-23 for the treatment of psoriasis: what is the evidence for an effect on malignancy? *Exp Dermatol*. 2018;27(7):737-747.
10. Xie W, Huang H, Xiao S, Fan Y, Deng X, Zhang Z. Immune checkpoint inhibitors therapies in patients with cancer and preexisting autoimmune diseases: a meta-analysis of observational studies. *Autoimmun Rev*. 2020;19(12):102687.