Inverse lichenoid drug eruption associated with nivolumab

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INTRODUCTION

Nivolumab is a fully human IgG4 anti—programmed cell death protein 1 (PD-1) receptor antibody that is approved by the US Food and Drug Administration for the treatment of metastatic melanoma, refractory non—small cell lung cancer, angiogenesis inhibitor—resistant renal cell carcinoma, and stem cell transplant—resistant classical Hodgkin lymphoma. The blockade of the PD-1 and programmed cell death ligand 1 pathway, as well as other immune checkpoint receptors, functions to inhibit a negative regulator of T-cell activation, thereby activating T cells and promoting antitumor activity.1 Along with pembrolizumab, another PD-1 receptor inhibitor, these agents are promising in the treatment of many different cancer entities but have been associated with a wide array of cutaneous adverse effects. We report an unusual case of a lichenoid drug eruption, with a distinct inverse distribution in the groin area secondary to nivolumab.

CASE REPORT

A 76-year-old woman receiving nivolumab therapy for 6 months before presentation, 3 mg/kg every 3 weeks, for metastatic renal cell carcinoma, presented with a 4-month history of a vulvar eruption. She had no history of inflammatory skin disease such as psoriasis or atopic dermatitis and denied any topical product use before onset of the eruption. She noted vulvar pruritus that progressively worsened to severe and unremitting over the last 4 months. She previously treated the area with topical lidocaine 2% cream, nystatin, vaginal anti-itch cream, and wipes, without significant relief. She noted associated dysuria, urinary frequency, and constipation. Physical examination found erythematous-to-violaceous, confluent patches with peripheral desquamative scale spanning the inguinal creases, labia majora, clitoris, and perineum; the vaginal mucosa was uninvolved, and the perianal area was clear (Fig 1). There were also 3 discrete pink, scaly, 5- to 6-mm round thin papules on the bilateral thighs. There were no other significant mucocutaneous findings on physical examination, such as mucosal erosions or depigmented patches suggestive of vitiligo.

A punch biopsy specimen taken from the vulva showed a lichenoid infiltrate in the superficial papillary dermis, with acanthosis, hypergranulosis, and a superficial bandlike lymphohistiocytic infiltrate with scattered eosinophils and necrotic keratinocytes consistent with a lichenoid drug eruption. There were no associated psoriasiform or spongiotic changes noted, and the typical features associated with a contact dermatitis were not found (Fig 2). Urinalysis and urine culture were negative for any bacterial or yeast growth. An inverse lichenoid drug eruption related to treatment with nivolumab was diagnosed. She was started on clobetasol 0.05% ointment 2 to 3 times daily, and complete resolution of the eruption was noted by 2 weeks. She was able to continue nivolumab without any recurrences of the eruption for the following 4 months after treatment.

Abbreviation used:
PD-1: programmed cell death protein 1

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Conflicts of interest: Dr Jennifer Choi has served on the Advisory Board for Bristol-Meyers Squibb, which is the manufacturer of nivolumab (a PD-1 inhibitor). The rest of the authors have no conflicts to declare.

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DISCUSSION

All checkpoint inhibitors can induce immune-related adverse events, as they all result in the upregulation of the immune response. Of those adverse events reported with PD-1 receptor inhibitors, the skin is one of the most commonly affected organs, with cutaneous eruptions and pruritus of any grade occurring in 28% to 36%. Although cutaneous adverse effects are common with anti–PD-1 therapy, reports that characterize and classify cutaneous adverse effects are limited. Both psoriasiform and lichenoid eruptions have been noted as a manifestation of immune system activation in patients undergoing immune checkpoint inhibitor therapy and are ultimately distinguished by both clinical and pathologic characteristics. Lichenoid eruptions are one of the most common cutaneous adverse effects of PD-1 inhibitors, with a study by Hwang et al noting their prevalence to be 17%. An inverse psoriasiform eruption has been described in response to pembrolizumab. Although lichenoid eruptions and an inverse psoriasiform eruption have been described, the inverse lichenoid drug eruption associated with nivolumab described in this case represents a distinct variant of a cutaneous adverse effect of this drug. The pathogenesis of an eruption that is inverse in distribution is unclear but may be caused by localization of an antigen in the skin to which T cells are reacting that has not yet been identified. Similar cases of anti–PD-1 inhibitor–associated drug eruptions have responded to a course of treatment with complete resolution, without requiring discontinuation of immunotherapy. The development of cutaneous adverse effects during anti–PD-1 therapy may signify greater immune system upregulation and is a positive prognostic factor that may point toward a greater treatment response. In particular, hypopigmentation as a cutaneous adverse effect in melanoma patients may be indicative of a favorable prognosis. As the cutaneous side effects of PD-1 therapies are further classified, additional studies are needed to elucidate the significance of the type of cutaneous adverse effect in relation to tumor progression. Nevertheless, it is important to be aware of the various cutaneous adverse effects of immune-modulating cancer therapy to allow for recognition and appropriate management, leading to improved quality of life for patients with cancer.

REFERENCES


