PD1 inhibitor-induced inverse lichenoid eruption: a case series

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Abstract

The increased use of monoclonal antibodies that target the immune checkpoint T cell receptor programmed death-1 (PD1) to treat numerous solid tumors has led to several reports describing associated cutaneous adverse events. Although lichenoid reactions have been well described, we propose that PD1 inhibitor-induced inverse lichenoid eruption (PILE) is a distinct variant. We describe two patients who presented with nearly identical deeply erythematous, malodorous, eroded anogenital plaques with focal crusting. Diagnosis of PILE was established given the biopsy findings and temporal association with PD1 inhibitor therapy. Treatment with clobetasol ointment was successful without necessitating discontinuation of immunotherapy. The findings were consistent with the only other previously published case of inverse lichenoid eruption in the groin secondary to PD1 inhibitors.

Keywords: PD1 inhibitor, inverse lichenoid eruption, immunotherapy

Introduction

Advances in directed immunotherapeutic approaches to cancer have led to the development of monoclonal antibodies that target the immune checkpoint T-cell receptor or ligand, programmed death-1 (PD1) or PDL1. With the emergence of immune checkpoint inhibitors, there have been several reports of cutaneous adverse reactions associated with them [1]. Lichenoid reactions secondary to PD1 inhibitors are well documented [1-4]. However, inverse lichenoid eruption in the groin is a distinct variant that, to our knowledge, has only been reported once [2]. Herein, we describe two additional cases and propose that PD1 inhibitor induced inverse lichenoid eruption (PILE) be recognized as a new entity within the spectrum of adverse cutaneous reactions to immunotherapy agents.

Case Synopsis

Patient 1

An 82-year-old woman with Stage IVB lung adenocarcinoma treated with pembrolizumab every three weeks for 5 months was admitted for worsening perineal and intergluteal rash of 6 weeks' duration. It started as a focal crusted plaque with pruritus, which was initially treated with zinc oxide barrier paste. The patient was switched to nystatin cream and oral fluconazole for 20 days by her oncologist owing to worsening erythema, pruritus, and significant pain. The antifungals led to no improvement. She denied a prior history of inflammatory skin disease. Physical examination showed deeply erythematous, malodorous, eroded plaques with overlying yellow-brown exudative crust in the inguinal folds, labia majora, perineum, and intergluteal folds (**Figure 1A)**.

Skin swabs for fungal and bacterial culture, as well as herpes simplex virus (HSV) 1 and 2 viral polymerase chain reaction were negative. Punch biopsy from the buttock showed superficial perivascular infiltrate of

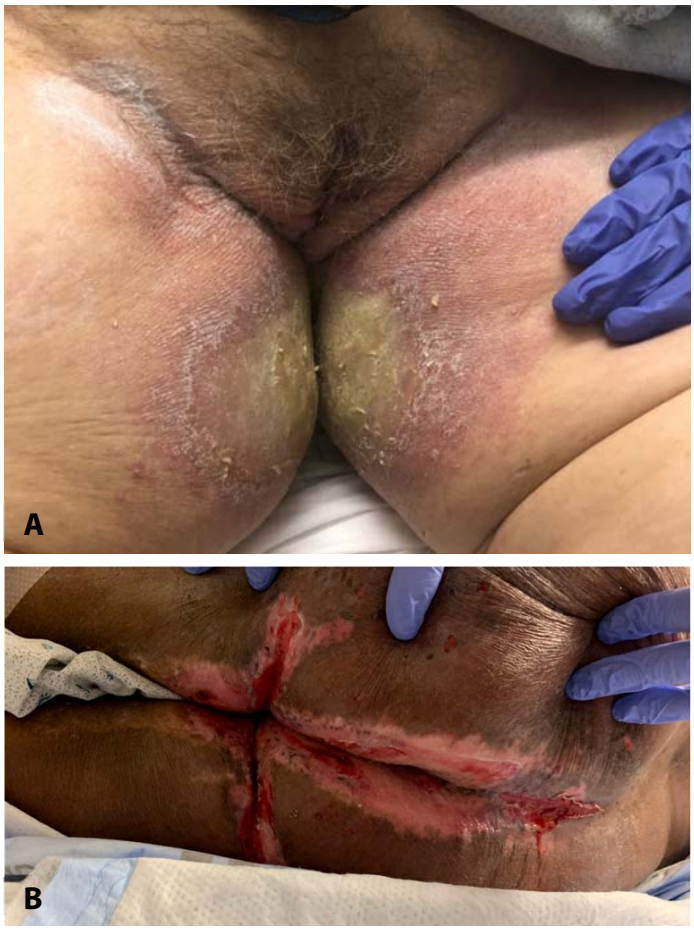

Figure 1. ***A)*** *Patient 1 shows deeply erythematous, eroded plaques with overlying yellow-brown exudative crust in the inguinal folds and labia majora.* ***B)*** *Patient 2 shows erythematous eroded plaques with focal crusting in the gluteal cleft.*

lymphocytes with foci of vacuolar alteration and individual necrotic keratinocytes (**Figure 2**). Twice daily treatment with clobetasol 0.05% ointment led to significant improvement within two weeks. At the time of admission, the patient and her daughters elected to pause the pembrolizumab therapy after a detailed discussion with the oncologist. Pembrolizumab therapy was reintroduced two months later, followed by recurrence of the rash, pain, and pruritus within days. Given the biopsy findings and temporal association with pembrolizumab, a diagnosis of PILE was established. The patient was encouraged to continue pembrolizumab since her symptoms were not life threatening and amenable to topical corticosteroids. Prophylactic application of clobetasol around the time of her infusions prevented future flares.

Patient 2

A 61-year-old woman with stage IIB lung adenocarcinoma treated with lobectomy and four cycles of adjuvant carboplatin/paclitaxel in 2011 had recurrence of her cancer in 2015. She was started on nivolumab in 2016 and switched to atezolizumab (PDL1 inhibitor) in 2017 owing to worsening disease. She developed a painful perineal and intergluteal rash about 30 months after the initiation of nivolumab, while on atezolizumab. The patient denied oral lesions and a prior history of inflammatory skin disease. Physical examination showed erythematous, malodorous, eroded plaques with focal crusting in the lower abdominal as well as inguinal folds, labia majora, mons pubis, perineum, and intergluteal folds (**Figure 1B)**.

Skin swab for HSV and serum desmoglein 1 and 3 antibodies were negative. Punch biopsy from the left inguinal fold showed a dense lichenoid infiltrate in the superficial papillary dermis with lymphocytes, plasma cells, and neutrophils (figure not included because of acute necrosis and sloughing off of the epidermis, secondary to acute interface dermatitis from both biopsy specimens taken from the patient).

Immunostaining for cytomegalovirus and HSV 1 and 2 were negative. The nearly identical clinicopathologic findings as Patient 1 led to the diagnosis of PILE. The patient was successfully treated with twice daily application of clobetasol 0.05% ointment. Atezolizumab was not discontinued secondary to the cutaneous eruption. **Table 1** summarizes both these cases along with the previously published case by Guggina et al. [2].

Case Discussion

Cutaneous eruptions are commonly reported with PD1 inhibitors, occurring in close to one-third of patients [2]. Generalized dermatitis, pruritis, vitiligo, and lichenoid eruptions are among the most frequently described [1-6]. There is evidence that cutaneous adverse effects during anti-PD1 treatment may serve as a positive prognostic factor [4,5,7].

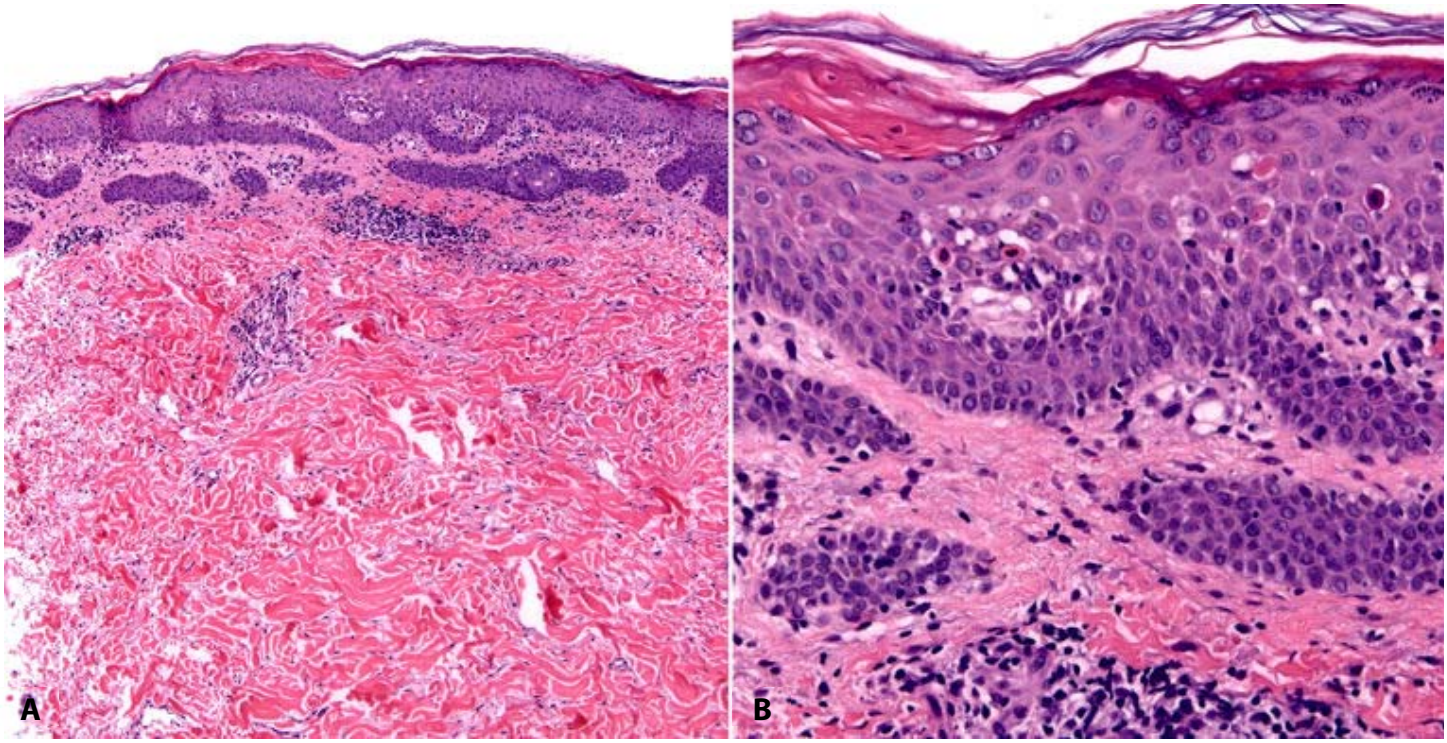

Figure 2. ***A)*** *Punch specimen histopathology from Patient 1 showing superficial perivascular infiltrate of lymphocytes with foci of vacuolar alteration. H&E, 100×.* ***B)*** *Punch specimen from Patient 1 higher-power view (H&E, 400×) showing individual necrotic keratinocytes.*

Lichenoid reactions while on PD1 and PDL1 inhibitor immunotherapy present as discrete, erythematous, scaly papules or plaques on the trunk and extremities. Mucous membranes are usually spared [3]. Histopathologically, they show a greater lymphohistiocytic lichenoid infiltration, increased spongiosis, and increased epidermal necrosis when compared to non-drug related cases of lichen planus [1]. Although diffuse lichenoid and inverse psoriasiform eruptions have been reported with PD1 inhibitors, the intertriginous presentations described in this case series are unique. There has only been one other report of a similar presentation, which was associated with nivolumab treatment for metastatic renal cell carcinoma [2]. We would therefore like to classify this PD1 inhibitor induced inverse lichenoid eruption (PILE) as a distinct entity. Based on our cases, it may manifest anywhere from 5 months to more than two years after initiation of immunotherapy. The pathogenesis of PILE is hypothesized to result from a localized T cell immune response [2]. A similarly distributed intertriginous eruption referred to as symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) is postulated to be a type IV hypersensitivity involving CD4+ helper T cells. A type IV hypersensitivity might also explain why PILE does not occur after the first exposure without prior sensitization. The flexural predilection of both PILE and SDRIFE might result from occlusion, sweating, or the excretion of certain medications or their metabolites from eccrine glands [8]. Additionally, although this clinical presentation can be seen as part of toxic erythema of chemotherapy, neither of the patients received any chemotherapy. It should be noted that all patients identified with PILE thus far were female. However, the limited number of cases makes it is hard to postulate whether this occurred by chance or represents a true gender predisposition.

High potency topical corticosteroids successfully treated both our patients. The only other report of a patient with PILE similarly noted complete resolution with clobetasol use and no recurrence despite continuation of nivolumab [2]. Thus, interruption of the PD1 inhibitor is not necessary. Prophylactic use of topical corticosteroid around the time of infusions is another option to prevent flares.

Table 1. *Characteristics of the three cases and therapeutic response.*

Case No./ Sex/Age, y	Immunotherapy	Underlying Cancer	Duration of Immuno-therapy Prior PILE	Anatomical Distribution of Eruption	Pathology Findings	Treatment
1/F/82	Pembrolizumab	Stage IVB lung adenocarcinoma	5 months	Inguinal folds, labia majora, perineum, intergluteal folds	Superficial perivascular infiltrate of lymphocytes with foci of vacuolar alteration and individual necrotic keratinocytes	Clobetasol ointment
2/F/61	Nivolumab switched to Atezolizumab	Stage IIB lung adenocarcinoma	30 months	Inguinal folds, labia majora, mons pubis, perineum, intergluteal folds	Base of a subepidermal blister with dense lichenoid infiltrate in the superficial papillary dermis with lymphocytes, plasma cells and neutrophils	Clobetasol ointment
3/F/76 [2]	Nivolumab	Metastatic renal cell carcinoma	6 months	Inguinal folds, labia majora, clitoris, perineum	Lichenoid infiltrate in the papillary dermis, with acanthosis, hypergranulosis, superficial bandlike lymphohistiocytic infiltrate with scattered eosinophils and necrotic keratinocytes	Clobetasol ointment

Conclusion

With the increasing use of PD1 and PDL1 inhibitors, dermatologists should be cognizant of the variable presentations of cutaneous adverse events and their management so as to ensure proper diagnosis, optimal treatment, and better health-related quality of life for their patients. Further investigation is required to better understand the pathogenesis of this distinct variant.

Potential conflicts of interest

The authors declare no conflicts of interest.

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