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Case Report

Steroid-Refractory Lichenoid Eruption Associated with Pembrolizumab in a Patient with Non-Small Cell Lung Cancer

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Abstract

Abstract
Programmed cell death receptor 1 (PD-1) inhibitors are promising and effective treatments for various cancers. Cutaneous adverse events, such as lichenoid drug eruptions, are well-known common side effects associated with PD-1 inhibitors. Lichenoid drug eruptions associated with PD-1 inhibitors show rapid improvement with high potency topical steroids and do not require cessation of the offending drug. We present the case of an 84-year-old female with progressive pembrolizumab therapy-associated lichenoid eruption that was resistant to several treatments and ultimately required discontinuation of pembrolizumab and treatment with methotrexate to resolve. This report includes histological findings of the pembrolizumab-associated lichenoid eruption.

Keywords
lichenoid eruption; pembrolizumab; PD-1 Inhibitors; drug side effects; methotrexate; steroid-refractory; non-small cell lung cancer

Introduction

Programmed cell death receptor 1 (PD-1) inhibitors, including pembrolizumab and nivolumab, represent some of the most promising and effective treatments for various cancer entities, such as metastatic melanoma and refractory, non-small cell lung cancer.[1] Normally, PD-1 serves as a negative regulator of the T cell immune response when bound to its ligand, PD1-L1 or PD1-L2.[2] One well-known mechanism by which cancer cells evade the body's immune response is through overexpression of PD-1 ligands leading to downregulation of T cells.[3] PD-1 inhibitors prevent this downregulation and thus promote antitumor activity through a more robust immune response.[3] However, this upregulated immune response is associated with a number of cutaneous adverse effects, with lichenoid eruptions being the most commonly reported.[2] Of the reported adverse events, up to 36% of patients showed cutaneous involvement.[2–4] In a study conducted by Hwang et al., lichenoid eruption was prevalent in 17% of patients on PD-1 inhibitor therapy with cutaneous adverse events.[5] These patients generally respond well to moisturizer ointments in conjunction with topical corticosteroids. More severe eruptions may require the use of systemic corticosteroids. Generally, pembrolizumab therapy can be continued in conjunction with systemic corticosteroid treatment.[6] We report a novel case of lichenoid drug eruption developed during pembrolizumab therapy that was refractory to topical and oral corticosteroid therapy but responsive to methotrexate and discontinuation of pembrolizumab.

Case Description

An 84-year-old female presented with a three-month history of a pruritic and painful rash of her lower extremities. Her medical history

was significant for metastatic non-small cell lung carcinoma, for which she was receiving pembrolizumab therapy 25 mg/mL every three weeks for four months prior to presentation. The patient denied any history of dermatological conditions. Previous treatment with mupirocin 2% mixed with clobetasol 0.05% did not produce significant relief. A physical examination revealed scattered erythematous papules and plaques, some with flaccid bullae and mild scale, spanning the bilateral anterior lower extremities and posterior right forearm. **(Figure 1)**

Over the past two months, the patient was tested for abdominal pain that yielded negative results for human immunodeficiency virus (HIV) and human T-lymphotropic virus 1 (HTLV-1). A serial assessment of a stool sample was performed for a possible small bowel infection and failed to demonstrate the presence of a parasitic infection. She was diagnosed with enteritis and small bowel infection and was treated with vancomycin via a peripherally inserted central line at a skilled nursing facility.

A punch biopsy of the lower extremity revealed a lichenoid interface dermatitis with scattered eosinophils in the dermis, consistent with lichenoid drug eruption. **(Figure 2)** No associated psoriasiform or spongiotic changes were noted, and typical features associated with contact dermatitis were absent. Direct immunofluorescence of perilesional skin was negative. Pembrolizumab therapy-related lichenoid drug eruption was diagnosed. Despite restarting the topical clobetasol 0.05% ointment for two weeks, the cutaneous manifestations appeared worse at a follow-up evaluation, including new ulcerated and bullous lesions. The topical steroid was discontinued, and treatment was escalated to a low-dose prednisone taper for two weeks. The patient returned three weeks later with continued progression of the eruption, including new mucosal erosions. A biopsy of the mucosal lip also revealed lichenoid interface dermatitis with eosinophils. After discussion with the patient's oncologist, her pembrolizumab infusions were stopped, and a high-dose four-week prednisone taper was initiated. This treatment only provided mild improvement in her cutaneous symptoms. Despite the cessation of her pembrolizumab infusions, the rash continued to progress to her chest and back over the following two months. Extensive involvement of her palms and soles contributed to significant pain and functional impairment. During those two months, subsequent high-dose prednisone tapers showed mild efficacy but were stopped due to side effects of insomnia and weight gain. Following cessation of high-dose prednisone tapers, additional treatment with metronidazole 500 mg twice daily and hydroxychloroquine 200 mg twice daily for six weeks were both ineffective. Upon titration of methotrexate to 20 mg weekly with concomitant folic acid supplementa-

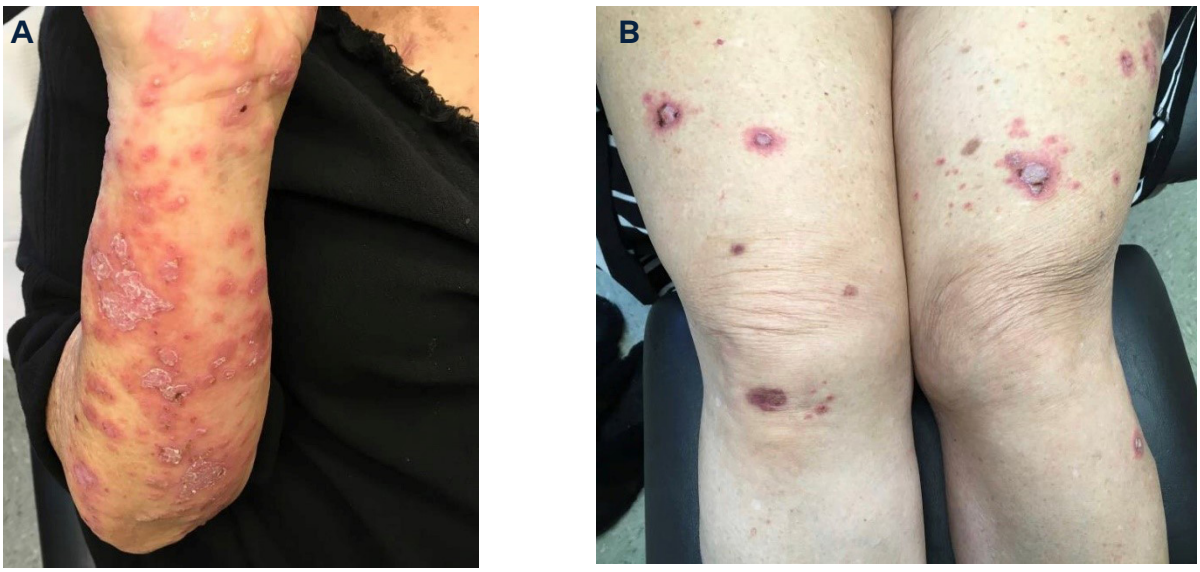

Figure 1. A. Erythematous papules and plaques with mild scale shown on the anterior right forearm. **B.** Erythematous-to-violaceous papules and flaccid bullae scattered on the anterior lower extremities.

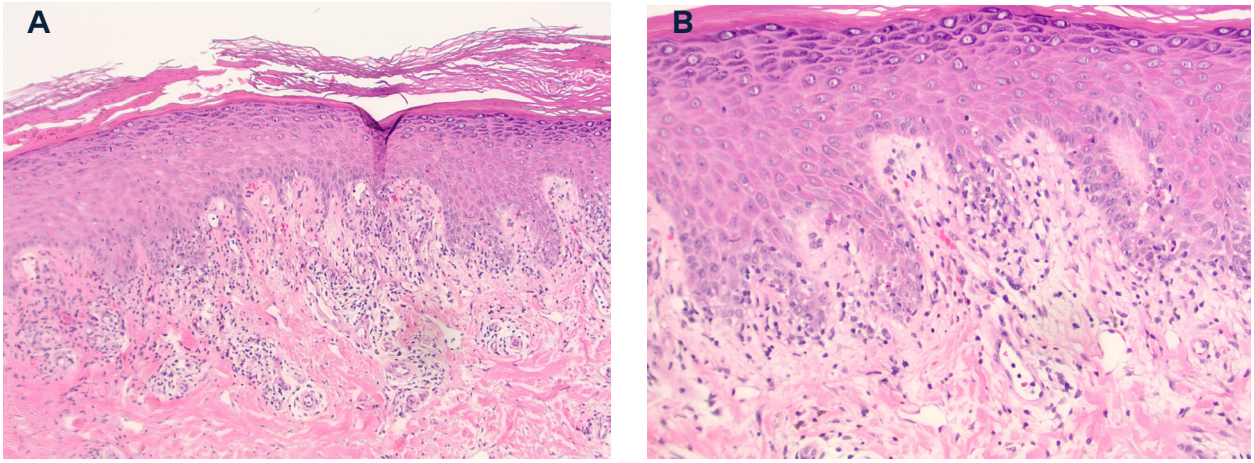

Figure 2. Histopathology findings revealed a lichenoid interface dermatitis with hypergranulosis and scattered eosinophils in the dermis. (Hematoxylin-eosin stain; original magnification X 10 in **A** and X 20 in **B**)

tion, the patient began to show a considerable reduction of pain symptoms and a decrease in the surface area affected by the eruptions. Due to this significant adverse drug reaction, the patient was unable to resume pembrolizumab therapy upon resolution of the lichenoid drug eruptions. For further treatment of non-small cell lung carcinoma, she was switched to nivolumab.

Discussion

The use of immune checkpoint inhibitors, such as PD-1 inhibitors, have shown to be highly effective in patients with metastatic malignancies, such as non-small cell lung cancer. Unfortunately, despite their therapeutic effect, their mechanism of action can induce immune-related adverse events. Due to the timing between initiating pembrolizumab therapy and the development of a lichenoid eruption, in conjunction with the known association between the two, we believe pembrolizumab to be the culprit of our patient's cutaneous lesions. Interestingly, the presence of cutaneous adverse effects during pembrolizumab therapy is indicative of a positive response to therapy and traditionally a positive prognosis factor.[1]

Although both pembrolizumab and nivolumab are PD-1 inhibitors, our patient was switched to nivolumab for continued treatment for non-small cell lung carcinoma due to a slightly lower risk of adverse events. A systemic review by Martins et al. showed that among PD-1 inhibitors, atezolizumab had the lowest risk of adverse events at 66.4% as compared to 71.8% with nivolumab and 75.1% with pembrolizumab.[7] Atezolizumab may be the next option if our patient develops new side effects or if steroid-refractory lichenoid eruptions recur with nivolumab treatment.

Although steroid-responsive lichenoid eruptions during pembrolizumab therapy have been observed, lichenoid eruptions unresponsive to both corticosteroid therapy and cessation of the offending immunotherapy have not been reported. This refractory case allows for a distinct management plan for a common cutaneous adverse effect.[8] In most cases, lichenoid drug eruptions rapidly improve with high potency topical steroids and do not require cessation of the offending drug. This patient, however, required more aggressive treatment, including methotrexate and discontinuation of pembrolizumab therapy. In the few reported cases in the literature of steroid-refractory lichenoid drug eruptions, pembrolizumab therapy did not require discontinuation. One case showed that a single 15 mg dose of methotrexate yielded a significant improvement of steroid-refractory lichenoid drug reaction due to pembrolizumab. That patient was advised to continue the methotrexate for a total of three weeks.[9] Another case showed that cyclosporine 100 mg with prednisone 40 mg daily showed dramatic improvement. In that case, prednisone was tapered off and cyclosporine was increased to 125 mg daily for four months with complete resolution and no remission of the lichenoid eruption.[10] This case serves as evidence to further support the role of methotrexate

and other immunosuppressing agents in the management of adverse cutaneous effects of PD-1 inhibitor therapy.

Conclusion

With the rarity of immunotherapy cessation and steroid-refractory lichenoid drug eruptions, we hope that the unique treatment plan in our case serves to expand the management of cutaneous immune-related adverse effects seen in PD-1 inhibitor therapy.

Conflicts of Interest

Dr. Krishnamurthy reports personal fees from Regeneron, Sanofi-Genzyme, Abbvie Janssen and Eli Lilly outside the submitted work.

Dr. Kou is an employee of St. Petersburg Hospital, a hospital affiliated with the journal's publisher.

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