Pembrolizumab-induced lichen planus pemphigoides in a patient with metastatic Merkel cell carcinoma

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INTRODUCTION

Immune checkpoint inhibitors, including pembrolizumab, are novel immunotherapeutic agents that have revolutionized cancer therapy. With increasing use of immunotherapy, early recognition and prompt treatment of associated adverse events are critical to ensure patient safety. Cutaneous toxicities are among the most commonly observed adverse events with this class of drugs. Here we report a novel case of lichen planus pemphigoides (LPP) arising in a patient with metastatic Merkel cell carcinoma treated with pembrolizumab.

Abbreviations used:

BP:	bullous pemphigoid
LPP:	lichen planus pemphigoides
NSCLC:	non–small cell lung cancer
PD-1:	programmed death 1

CASE REPORT

A 65-year-old white woman with widely metastatic Merkel cell carcinoma to the brain, lungs, and subcutaneous tissue, who completed 7 cycles of pembrolizumab, presented to an outpatient dermato-oncology clinic with a diffuse pruritic rash. Her pruritus developed within 1 week of initiating treatment with pembrolizumab (200 mg intravenously, every 3 weeks) and continued to progress with each cycle. She had not experienced any other immune-related adverse events during treatment, with complete radiographic response of metastatic Merkel cell carcinoma to pembrolizumab. At the clinic visit, physical examination was notable for numerous erythematous-to-violaceous, hypertrophic, lichenified papules and plaques scattered on the dorsal hands, forearms, chest, upper back, lower extremities, and dorsal feet bilaterally. There were no vesicles, bullae, or involvement of the scalp, oropharynx, or nails (Fig 1). Conventional histopathologic assessment of lesional skin found lichenoid and vacuolar epidermal interface alteration with associated dyskeratotic keratinocytes and eosinophils (Fig 2, *A*). Direct immunofluorescence of perilesional skin exhibited linear deposits of C3 and faint, discontinuous, linear deposits of IgG along the basement membrane zone (Fig 2, *B*). Indirect immunofluorescence using the patient's serum on salt-split skin showed linear deposits of IgG mapping to the blister roof at a titer of 1:40, and enzyme-linked immunosorbent assay for anti- bullous pemphigoid (BP)180 was positive at 38.

Collectively, in the absence of blisters, the patient's findings were most consistent with a prebullous presentation of LPP, although coexistent hypertrophic lichen planus and evolving bullous pemphigoid could not be excluded. Given the extent and severity of the patient's cutaneous toxicity, after discussing with the oncology team, pembrolizumab was discontinued. The patient was treated with a 3-week course of an oral prednisone taper, starting at 40 mg, supplemented by clobetasol 0.05% ointment

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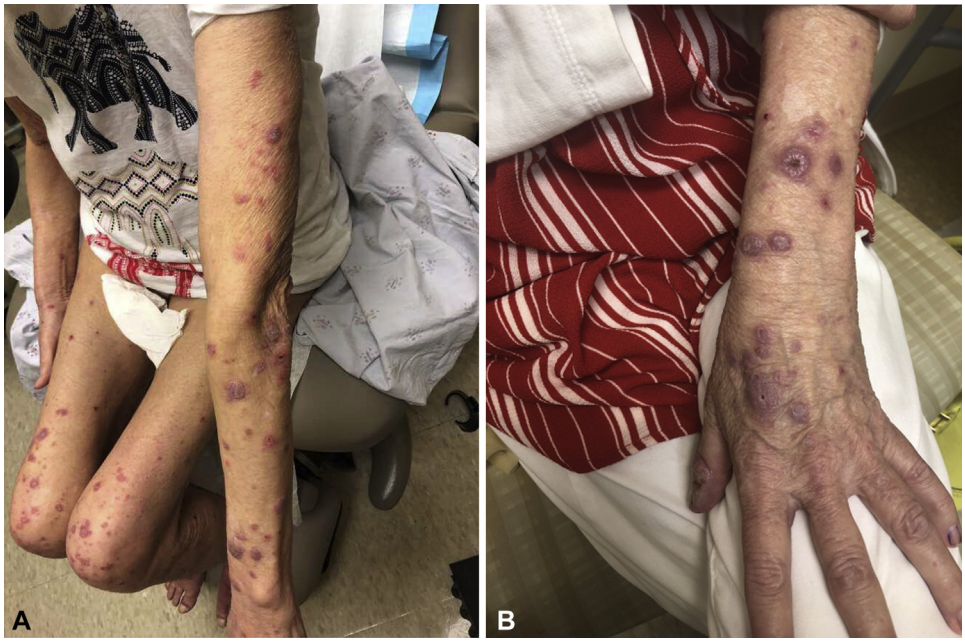

Fig 1. Clinical presentation of LPP. **A**, Multiple erythematous-to-violaceous, hypertrophic, lichenified papules and plaques, some of which have been excoriated, are scattered on the bilateral upper and lower extremities. **B**, Close-up image of the left dorsal hand and forearm highlights the hypertrophic, lichenified papules and plaques.

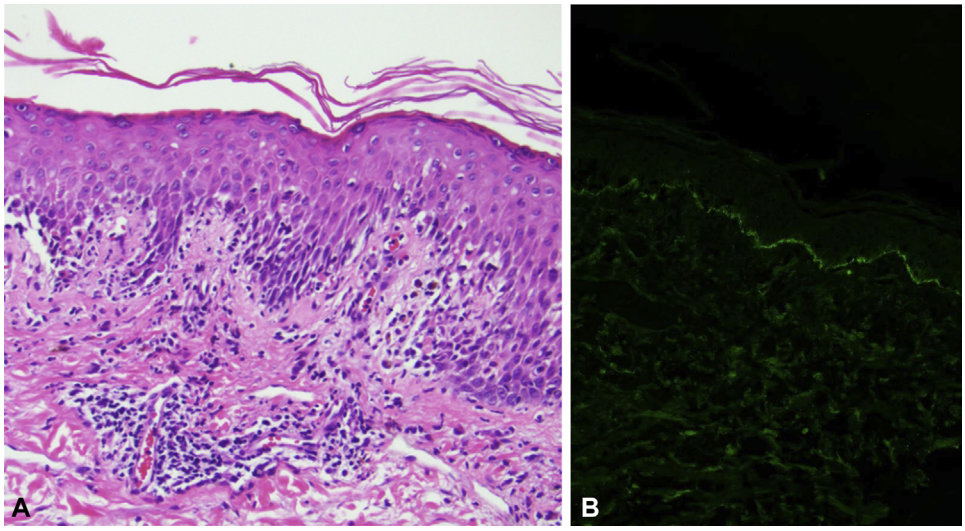

Fig 2. Histopathologic findings of LPP. **A**, A punch biopsy of lesional skin shows lichenoid and vacuolar interface epidermal alteration with dyskeratotic keratinocytes and scattered eosinophils. **B**, Direct immunofluorescence of perilesional skin shows linear deposition of C3 at the basement membrane zone. (**A**, Hematoxylin-eosin stain; **B**, direct immunofluorescence; original magnifications: **A**, ×100; **B**, ×200).

twice daily. Her pruritus rapidly resolved, and her skin lesions began to resolve rapidly, with secondary changes gradually fading over 6 months. Fifteen months since discontinuing the pembrolizumab, the patient remains stable, with no evidence of disease on surveillance imaging studies, thus obviating the need to reinitiate immunotherapy. There was also no recurrence of the skin eruption.

DISCUSSION

There is a rapidly growing list of indications approved by the Food and Drug Administration for

immune checkpoint inhibitors. Cutaneous toxicities are among the most common adverse events that can arise with these immunotherapeutic agents. The most frequently observed toxicities include eczematous dermatitis, lichenoid reactions, and vitiligo. Development of de novo BP has also been reported.[1-4] Recognizing that patients on immunotherapy can present with occult immunobullous diseases, particularly BP, often without tense blisters, immunofluorescence and enzyme-linked immunosorbent assay studies can yield valuable information in the workup of atypical clinical presentations, and we routinely perform them.

In cases of severe cutaneous toxicities, current guidelines recommend withholding immunotherapy and treating with systemic steroids.[3-5] However, even after cessation of the checkpoint inhibitors, these toxicities may persist, warranting steroid-sparing immunosuppressive agents for longer treatment. Unless the cutaneous toxicity is life-threatening, however, immunotherapy does not need to be permanently discontinued, although the toxicity may recur upon resuming the checkpoint inhibitor.

LPP is a rare, subepidermal blistering disorder with characteristics of both lichen planus and BP in which bullous lesions can arise on either lichenoid or normal skin. To our knowledge, this is the first reported case of LPP associated with pembrolizumab treatment for metastatic Merkel cell carcinoma. During a phase II clinical trial in Germany, a 64-year-old man with metastatic melanoma had LPP after completing 9 cycles of pembrolizumab (unspecified dosing, every 3 weeks).[6] Pembrolizumab was discontinued, and LPP resolved with a 6-month course of dapsone. The patient's complete tumor response, achieved with pembrolizumab, was sustained at 2-year follow-up.

Two reported cases of LPP also exist in which another approved programmed death 1 (PD-1) inhibitor, nivolumab, was implicated. There are no reported cases of LPP associated with the remaining, approved PD-1 inhibitor, cemiplimab. In 1 case, an 87-year-old woman with metastatic non—small cell lung cancer (NSCLC) had LPP after completing 9 cycles of nivolumab (3 mg/kg, every 2 weeks).[7] Nivolumab was discontinued, and LPP was treated with a 2-week course of an oral prednisone taper, starting at 40 mg. At 1-year follow-up, the NSCLC remained clinically stable without progression. In the other case, a 57-year-old man with NSCLC had LPP after 3 months of treatment with nivolumab (unspecified dosing, every 2 weeks).[8] Nivolumab was discontinued, and the LPP cleared with a 2-week course of oral prednisolone and doxycycline. The report does not comment on his tumor response. No extracutaneous toxicities were reported in these 3 cases.

The pathomechanism by which PD-1 inhibitors induce LPP remains unclear. LPP has not yet been reported to occur with cytotoxic T-lymphocyte antigen inhibitors. Moreover, preliminary observations have intimated that cutaneous toxicities may serve as surrogate markers for the efficacy of treatment with immune checkpoint inhibitors. Multiple studies report statistically significant associations between the development of dermatologic adverse events and superior clinical outcomes including tumor response rate, overall survival, and progression-free survival.[9] This association is also supported by our case, along with the other immunotherapy-induced LPP cases referenced here, but further research is needed to validate this relationship.

With such a small sample size, it is also unclear if LPP induced by pembrolizumab and nivolumab differs from LPP encountered outside of this context. Immunotherapy-induced LPP may follow a different course than de novo LPP, in a manner similar to drug-induced BP exhibiting a distinct clinical course and therapeutic response compared with conventional BP. With increased recognition of immunotherapy-induced LPP, more data can be collected about patient outcomes, including identification of treatments that allow for the resolution of LPP while maintaining the tumor response achieved by the immunotherapeutic agents.

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