Case Report

Bullous lichen planus-like reactions in a patient with renal cancer after receiving anti-programmed cell death-1 therapy

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Abstract

Anti-programmed cell death 1 (anti-PD-1) agent is a promise in cancer immunotherapy for various advanced malignancies, but dermatologic toxicities are common during therapy. We report one advanced transitional cell carcinoma patient who developed multiple bullous skin lesions over bilateral lower extremities after anti-PD-1 antibody pembrolizumab treatment. Skin biopsy revealed subepidermal cleft, wedge-shaped hypergranulosis, saw-tooth acanthosis, and presence of interface band-like lymphohistiocytic infiltrate compatible with bullous lichen planus-like reactions. Potent topical steroid and temporary cessation of pembrolizumab relieved the skin eruptions. Early recognition and appropriate management of rare bullous dermatologic toxicities are critical in patients receiving immune checkpoint blockade therapy.

Keywords: Anti-programmed cell death 1, bullous lichen planus, immunotherapy, lichenoid interface dermatitis, pembrolizumab

Introduction

Immunotherapy based on the blocking of intrinsic down regulators of immunity represents a major breakthrough in cancer treatment. Several types of immune checkpoint-directed antibodies targeting cytotoxic T-lymphocyte antigen 4 and programmed cell death 1 (PD-1) or its ligand, PD ligand 1 (PD-L1) have been approved for various cancer therapies.[3,4] Pembrolizumab was the first PD-1 inhibitor approved for treating advanced melanoma. The indications for this inhibitor were subsequently extended to other types of cancer, including advanced transitional cell carcinoma.[5]

Dermatologic and gastrointestinal toxicities are the most frequent side effects of immune checkpoint inhibitors.[3,4] Among dermatologic adverse reactions, nontypical maculopapular rash and pruritus are the most common clinical manifestations.[3] Moreover, a wide range of other dermatologic reactions, including psoriasis, vitiligo, autoimmune skin disorders, reactivation of varicella-zoster or herpes simplex virus infection, and severe life-threatening cutaneous drug reactions have been reported.[3,6] Early recognition and appropriate management are critical to prevent the deterioration of dermatologic toxicities and minimize treatment interruption.

We present a case who exhibited bullous lichen planus (BLP)-like reactions after receipt of anti-PD-1 therapy for renal transitional cell carcinoma.

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**Case Report**

A 77-year-old woman with a history of the right renal nonpapillary transitional cell carcinoma was referred to our dermatologic department after exhibiting multiple scattered bullae over the bilateral lower limbs for 1 week. She received robotic-assisted nephroureterectomy with bladder cuff excision and local radiotherapy for the pelvis. However, multiple sites of metastases, including the lung, liver, bones, and right adrenal gland, were detected during the follow-up. The patient’s medical history included hypertension treated with carvedilol, amlodipine, and valsartan.

Immunotherapy with pembrolizumab (100 mg every 3 weeks) was initiated for the patient’s advanced malignancy, but she developed many clustered vesicles over erythematous bases on the right dorsal thigh 3 weeks after the first dose. It is noteworthy that the result of the antinuclear antibody test before the initiation of immunotherapy was positive (1:320 with nucleolar and speckled pattern). Subsequently, Sjögren’s syndrome was diagnosed by a rheumatologist based on a positive anti-Ro antibody and symptoms of dry eyes and dry mouth for several years.

Herpes zoster involving right S1 dermatome was diagnosed, and famiciclovir was prescribed. However, the patient subsequently exhibited progressive multiple painful and scattered new bullous skin lesions along the bilateral lower limbs during her 4th week of using pembrolizumab. On examination, erythematous to violaceous papules and plaques with multiple tense bullae were observed on the bilateral lower extremities [Figure 1]; however, no oral mucosal lesions were observed. Results of Tzanck smear obtained from tense bullae were negative for multinucleated giant cells. Our clinical differential diagnosis included disseminated herpes zoster, BLP, lichen planus pemphigoides, paranephrotic pemphigus, bullous pemphigoid, and bullous erythema multiforme.

An incisional biopsy was obtained from a tense bulla overlying an erythematous plaque on the left heel. Histopathology revealed a subepidermal cleft with characteristics of lichen planus-like lichenoid interface dermatitis, including hyperkeratosis, wedge-shaped hypergranulosis, and saw-tooth acanthosis. The major cells of band-like infiltrate at the dermoepidermal junction were lymphocytes and histiocytes; no eosinophils were identified. In addition, a few focal parakeratosis and numerous cytoid bodies were observed over the lower part of the epidermis [Figure 2]. However, no deposition of IgG, IgA, IgM, or C3 was detected through direct immunofluorescence (DIF).

In addition, no circulating autoantibodies against the basement membrane zone or intercellular substance were detected. Based on the clinicopathological correlation, BLP-like reaction was diagnosed. The patient was treated with potent topical steroids (clobetasol propionate), and treatment with pembrolizumab was temporarily ceased; the lesions improved gradually without novel eruptions. Other regular medications for hypertension were maintained throughout this treatment course. No more of pembrolizumab was administered to our patient after BLP-like reactions due to her deteriorated clinical status thereafter.

**Discussion**

Lichen planus is the prototype of lichenoid interface dermatitis, and it encompasses several variants. BLP is a rare variant of lichen planus, and extreme T-cell-mediated inflammation plays a major role in its pathogenesis. The major clinical manifestations of BLP are tense bullae developing near or on pre-existing lichen planus lesions on the lower extremities and oral mucosa. Cutaneous bullae may contain clear or hemorrhagic fluid. These bullae are histological subepidermal blisters, which are large Max Joseph spaces resulting from massive vacuolar degeneration. The other histological findings of BLP are typical features of lichen planus. Only one previous case series have reported PD-1 inhibitor-induced BLP-like reactions, and these were similar to the findings of our case. In that case series, two patients had advanced non-small cell lung cancer, and another one had metastatic melanoma. All three patients were treated with pembrolizumab. Similar to our patient, two of the three patients developed skin eruptions approximately 1 month after immunotherapy. In addition, only one of the patients developed painful oral erosions. In contrast to the simultaneous bilateral symmetrical eruptions observed in the aforementioned cases, our patient developed cutaneous adverse effects over the lower extremities from one side to the bilateral sides. BLP has no established treatment of choice; however, potent topical corticosteroids have been used empirically. Systemic corticosteroids are considered second-line treatments for severe refractory cases. Other medications such as dapsone, antimalarial drugs, and topical or systemic retinoids have also been used.

BLP should be distinguished from lichen planus pemphigoides and bullous pemphigoid. In contrast to BLP, lichen planus pemphigoides is a rare autoimmune disease characterized by concurrent lichen planus and bullous pemphigoid. All three of these diseases present with clinically tense bullae with predilection over the extremities, consistent with histological
subepidermal bullae. Notably, eosinophilic spongiosis can be found in bullous pemphigoid and lichen planus pemphigoides but not in BLP. Furthermore, DIF study has revealed only linear IgG and C3 deposition along the dermoepidermal junction in lichen planus pemphigoides and bullous pemphigoid, compared with negative findings or globular IgM deposition in BLP.\[^{5,6}\] Vesiculobullous eruptions have been reported in patients who had received anti-PD-1 treatment, and bullous pemphigoid is the most common diagnosis.\[^{15-19}\] Hence, testing for circulating autoantibodies against BP180 and BP230 is critical for confirming diagnoses of bullous skin lesions in patients during anti-PD-1 therapy.

**Lichenoid interface dermatitis during anti-PD-1 therapy (pembrolizumab and nivolumab)** has been sporadically reported, and diagnosis is generally based on the histological analysis.\[^{5,6}\] Pembrolizumab and nivolumab are structurally similar, and no significant difference is observed between the clinical appearance and histological analysis of related lichenoid drug eruption. In addition, most patients who presented lichenoid mucocutaneous eruptions due to anti-PD-1 or anti-PD-L1 were taking concurrent medications related to drug-induced lichenoid interface dermatitis.\[^{20}\] Although amlodipine is a reported cause of lichenoid interface dermatitis, it was used continuously before the onset and after the resolution of skin eruptions in our case. Moreover, patients with lichen planus have significantly higher prevalence of Sjögren’s syndrome than do healthy controls,\[^{21}\] but our patient did not develop similar episodes of BLP until initiation of anti-PD-1. Furthermore, cancer patients with pre-existing autoimmune diseases, including Sjögren’s syndrome, were at a significantly increased risk of immune-related adverse events when treated with immune checkpoint inhibitors.\[^{22}\] Although the mechanism of anti-PD-1-induced drug eruptions remains to be elucidated, unmasked T-cell-mediated immune response of skin to medication or autoantibody, which was previously tolerated, has been implicated.\[^{5,20}\]

In conclusion, many cutaneous side effects are related to anti-PD-1 therapy. The present case demonstrates that BLP-like reaction should be included in the differential diagnoses of cancer patients with vesiculobullous skin lesions after receipt of anti-PD-1 therapy. Early recognition and timely intervention for such dermatologic side effects are critical for the ever-growing population of cancer patients with anti-PD-1 immunotherapy.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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