Bullous pemphigoid secondary to pembrolizumab mimicking toxic epidermal necrolysis

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Key words: bullous pemphigoid; pembrolizumab; toxic epidermal necrolysis.

INTRODUCTION

Pembrolizumab is an anti–programmed death receptor-1 (PD-1) antibody effective as an antineoplastic agent by reversing T-cell suppression.[1] Similar to other biologic therapies targeting immune system checkpoints,[2] pembrolizumab has also been linked to several immune-related adverse events, the most common of which are lichenoid reactions, eczema, and vitiligo.[3] More recently, cases of pembrolizumab-induced bullous pemphigoid (BP) have been described in the literature.[4,5]

BP is an autoimmune blistering disease caused by autoantibodies against the collagen XVII (BP180/BPAG2) and the BP230 (BPAG1) components of the hemidesmosome.[6] Drug-induced BP is similar to idiopathic BP both clinically and histologically, both presenting with subepidermal blisters with direct immunofluorescence showing a linear deposition of IgG at the dermoepidermal junction.[4,7] Here we describe a patient presenting with BP mimicking toxic epidermal necrolysis (TEN) after treatment with pembrolizumab.

Abbreviations used:

BP:	bullous pemphigoid
ELISA:	enzyme-linked immunosorbent assay
PD-1:	programmed death receptor-1
SJS:	Stevens-Johnson syndrome
TEN:	toxic epidermal necrolysis

CASE

A 79-year-old woman had metastatic lung adenocarcinoma diagnosed in October 2018. Her first cycle of 200-mg infusions of pembrolizumab was started in November 2018. After the 13th cycle in October 2019, an erythematous, pruritic papular eruption developed on her lower abdomen. Treatment with triamcinolone and cetirizine was initiated. Acute worsening of the rash occurred in November 2019 after cycle 14, with multiple pruritic tense bullae spreading to her neck, trunk, and upper and lower extremities with 50% body surface area involvement. The patient reported both severe pain and pruritus. On physical examination, there were tense bullae on an erythematous base on the face and neck (Fig 1) and tense bullae and widespread erosions on the trunk and extremities (Fig 2). A punch biopsy of the left thigh showed lichenoid dermatitis with subepidermal blister formation, and direct immunofluorescence results showed IgG and C3 staining along the basement membrane zone, consistent with pemphigoid. BP 180 (BP180) NC16A enzyme-linked immunosorbent assay (ELISA) assay was positive at 44 U/mL ($\geq$ 9.0 U/mL being a positive result). BP230 ELISA was less than 9 U/mL.

Treatment with prednisone, 50 mg, was initiated then switched to methylprednisolone sodium succinate, 70 mg intravenously (1 mg/kg) per oncology recommendation after 1 day. Pembrolizumab was held. The oncology team recommended that the patient likely should not receive further immunotherapy given the severity of the eruption. Intravenous immunoglobulin was not considered because of ventilation-perfusion scan findings concerning for pulmonary embolism. After 18 days on methylprednisolone, involvement improved from 50% to 12% body surface area. Four weeks

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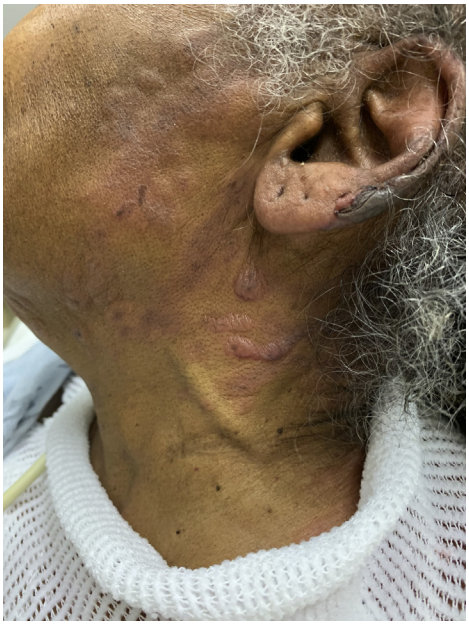

Fig 1. Tense bullae on an erythematous base.

Fig 2. Tense bullae and widespread erosions on the trunk and extermities.

after initiation of corticosteroids, only a single bulla on the patient's right foot remained, with evidence of diffuse healing of erosions.

DISCUSSION

Through the dysregulation of T-regulatory cells, anti—PD-1 therapies have been implicated in the development of humorally mediated autoimmune disease, including BP.[2] A systemic review of 10 cases of pembrolizumab-induced BP and a case report of 2 cases describe a range of 4 to 84 weeks from initiation of pembrolizumab to clinical presentation of cutaneous toxicity.[4,5] Similar to the 2 case reports and several patients in the systemic review, this patient had erythematous papules before bullae development. Our patient's confluent bullae led to large areas of denuded epidermis, mimicking the epidermal sloughing classically seen in TEN. Accurate diagnosis depends on supportive studies showing the presence of circulating autoantibodies and their pattern of epidermal deposition. Direct immunofluorescence, with a sensitivity of 90.8%, is more sensitive than ELISA, with sensitivities ranging from 73% for BP180 to 59% for BP230. Both direct immunofluorescence and ELISA have specificities close to 100%.[8]

BP can typically be distinguished from TEN clinically. BP initially presents with urticarial papules or eczematous plaques, whereas TEN begins with tender, dusky, ill-defined erythematous patches. As blisters develop, the classic BP lesion is a 1- to 3-cm tense bulla on an erythematous base, differentiating BP from the rapidly coalescing bullae of Stevens-Johnson syndrome (SJS)/TEN. Additionally, the acute phase of SJS/TEN is 8 to 12 days, whereas BP has a more insidious course with a mean diagnostic delay of 6 months.[9] The presence of pruritus offers a diagnostic clue for BP, whereas skin tenderness and a fever greater than 38°C should alert to the possibility of TEN.[10] Mucosal involvement occurs in 90% of cases of TEN with almost invariable involvement of the oral mucosa and vermilion border.[11] Mucosal involvement is an unusual manifestation of BP but has been observed in up to 20% of BP patients.[12] A careful audit of the timing of new medications can also provide diagnostic clues, as the time duration between drug intake and onset of symptoms is about 2 to 4 weeks in SJS/TEN[13] and 4 to 84 weeks in pembrolizumab-induced BP.[4,5] Although around 50 medications have been implicated in drug-induced BP,[14] less is known about the delay of symptom onset from initiation of the culprit medication; reports have ranged from 6 weeks to several years.[15]

Similar to other cases of BP secondary to pembrolizumab, our patient was successfully treated with systemic steroids. Because of the unpredictable timeline of the development of BP secondary to pembrolizumab, it is important to monitor for cutaneous symptoms while a patient is receiving the drug. It is also important to understand the course of clinical presentation of pembrolizumab-induced BP and that widespread bullae development can lead to confluent denuded patches, mimicking TEN. Although much remains to be discovered about the adverse effects of anti—PD-1 drugs, the number of reported cases of these medications precipitating SJS/TEN in patients is similar in number to reports of BP.[4,5,16] Because of stark differences in the prognosis of BP and SJS/TEN, early differentiation of BP from SJS/TEN could lead to a drastic improvement in patient outcome. In the context of pembrolizumab-induced BP, the most helpful distinguishing features are serology/

histopathology, the presence of pruritus, the absence of fever, and chronicity, especially in relation to pembrolizumab treatment initiation.

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