Case Reports in Dermatology

Case Rep Dermatol 2018;10:154–157

DOI: 10.1159/000489661
Published online: June 5, 2018

Case Series

Bullous Pemphigoid as an Adverse Reaction to Pembrolizumab: Two Case Reports

Kenneth Thomsen[a] Jon Diernaes[a] Trine Heide Øllegaard[b] Eva Spaun[c] Christian Vestergaard[a]

[a]Department of Dermatology, Aarhus University Hospital, Aarhus, Denmark; [b]Department of Oncology, Aarhus University Hospital, Aarhus, Denmark; [c]Department of Pathology, Aarhus University Hospital, Aarhus, Denmark

Keywords
Adverse drug reaction · Autoimmune bullous diseases · Autoimmune diseases · Bullous pemphigoid · Bullous skin disease · Malignant melanoma · Pembrolizumab · Programmed cell death 1 · Checkpoint inhibitors

Abstract
Checkpoint inhibitors are novel and promising treatment options for different types of cancer. Programmed cell death 1 (PD-1) inhibitors, such as pembrolizumab, have been shown to significantly raise the survival rates of disseminated malignant melanoma (MM). Autoimmune adverse reactions are very common in checkpoint inhibitors. We present 2 cases of bullous pemphigoid, as adverse reactions to pembrolizumab-treated MM.

Introduction

Bullous pemphigoid (BP) is an acquired autoimmune disease, mainly affecting the elderly from the 7th decade [1], with an incidence of 13.4–66:1,000,000 [2] and is characterized by tense bullae on an erythematous background.

KARGER

Kenneth Thomson
Department of Dermatology and Venerology
Aarhus University Hospital
P.P. Oerumsgade 11, bygn. 12, DK–8000 Aarhus (Denmark)
E-Mail kenthoms@rm.dk

The diagnosis is confirmed by typical histopathological signs on the skin, such as inflammatory infiltrate with eosinophils, subepidermal blisters, and linear immunoglobulin G and C3 compliment factor alignment at the basement membrane zone. Eosinophilia is often noticed in the blood [2].

Drug-induced BP may appear up to 3 months after treatment with the culprit medication [3]. Treatment consists initially of high-dose prednisolone 0.75 mg/kg/day and highly potent topical steroid therapy [4].

Pembrolizumab is a monoclonal antibody directed against the programmed cell death 1 (PD-1) receptor used in the treatment of metastatic malignant melanoma (MM). The PD-1 receptor is mainly expressed on activated lymphocytes, and binding of the ligands PD-L1 and PD-L2 results in downregulation of T-cell activity, but also affecting B-cells [5].

Among cutaneous side effects to the anti-PD-1 treatment, the most common are vitiligo and maculopapular rash [6, 7]. BP may be a rare side effect to treatment with pembrolizumab, and so far, only 4 cases have been published [8–10].

We describe 2 patients with metastatic MM treated with pembrolizumab who developed BP as a cutaneous side effect.

Case Reports

Case 1

A 64-year-old male was diagnosed with stage T3a MM in August 2009 and treated with primary excision. The sentinel lymph node biopsy (SLNB) was negative and follow-up was discontinued in 2014.

In November 2015, a CT urography was performed due to intermittent urolithiasis and lateral back pain. Metastatic disease was revealed on the CT urography. A biopsy from a right lung metastasis confirmed MM, BRAF wt, as did an excision of a cutaneous metastasis. In January 2016, therapy with pembrolizumab 2 mg/kg every 3 weeks was initiated.

The patient developed itching with a red and scaly rash following the fourth cycle of pembrolizumab, which was treated with moisturizers only.

In May 2016, the patient was referred to the Department of Dermatology, Aarhus University Hospital, Denmark. The patient had a symmetric and pleomorphic rash with vesiculobullous lesions on the hands and papules on the back, chest, and abdomen. At this point, he had received 7 infusions of pembrolizumab. No other new medications were reported. 3 punch biopsies were performed, 2 FFPE and 1 unfixed for immunofluorescence microscopy. Both FFPE biopsies showed superficial perivascular and interstitial inflammation dominated by eosinophils and a beginning dermoepidermal bulla. Direct immunofluorescence microscopy revealed IgG alignment at the basement membrane as well as eosinophilic inflammation, no alignment of compliment C3 was identified, the histology resembled mostly BP, but dermatitis herpatiformis was suggested as a differential diagnosis. Treatment with pembrolizumab was paused and systemic prednisolone 0.75 mg/kg daily was given, leading to a rapid resolution of both the itching and skin lesions.

In September 2016, an attempt to re-establish treatment with pembrolizumab was made using 5 mg prednisolone systemically daily and topical clobetasol propionate was applied 2–3 times weekly. At the tenth cycle in January 2017, itching had returned. After the fourteenth cycle, the BP re-emerged. Pembrolizumab was discontinued and the eruptions were treated with a short course of systemic prednisolone 0.5 mg/kg and proactive treatment with topical mometasone furoate was started. Since then, no relapse of BP has occurred (Fig. 1).

Case 2

A 71-year-old male was treated with primary surgical excision for stage T3b MM, SLNB negative in January 2011. In November 2012, the first cutaneous in-transit metastases were identified and cutaneous metastases recurred 6 times up to January 2015. Each time, they were treated with surgical excision and all were SLNB negative. All tumors were BRAF wt. By January 2015, a total of 20 cutaneous metastases were identified histologically, and the patient was referred to the Department of Oncology.

Initial therapy was four cycles of ipilimumab 2.7 mg/kg every 3 weeks. Upon progression, pembrolizumab 2 mg/kg every 3 weeks was initiated by September 2015. Adjuvant photon radiation therapy of 27 Gy in three fractions was administered in November 2015. Nine cycles of pembrolizumab were administered without cutaneous adverse effects. The fourth cycle was delayed a week due to pneumonia. In December 2015, an erythematous lesion was noted on the left arm where radiation therapy had previously been performed.

The patient was referred to the Department of Dermatology in January 2016, at which time he had developed a generalized bullous and reddish eczema with a positive Nikolsky sign. 2 FFPE and 1 unfixed punch biopsies were performed. FFPE material showed changes as in patient 1 with a dermoepidermal bulla consistent with BP; however, direct DIF was negative.

Treatment with systemic prednisolone 0.75 mg/kg and daily topical clobetasol propionate was initiated with excellent response. Pembrolizumab was discontinued due to BP by January 2016, with complete regression of BP as the result. Temozolomide was instead initiated for MM and by May 2016 severe metastases to the lungs were found on CT scan. The patient died of a myocardial infarction in November 2016 with severe metastatic MM.

Discussion

As studies on the safety of pembrolizumab all suggest, autoimmune adverse effects are likely to occur [6, 7]. The biological pathway of the PD-1 and PD-1L axis is a key pathway in activating the apoptosis in cells, and this is considered as the reason for PD-1 inhibitors to result in mainly autoimmune adverse effects [5].

When pembrolizumab was approved by the FDA, there were no reports of BP as an adverse effect to pembrolizumab treatment [7]. However, from 2015 to 2017, including the cases presented here, there are now 6 reported cases [8–10].

Since pembrolizumab has been shown to have effective results in the treatment of MM, it is vital for the quality of life and survival of this patient group that all is done for the treatment to be continued as long as possible.

All BP cases reported responded well to treatment according to BP guidelines if implemented swiftly and aggressively. Pembrolizumab should be paused or discontinued according to the progression and treatment response of PB.

In both our cases, the clinical assessment indicated BP, but DIF only partly supported the diagnoses; in case 2, DIF was negative.

BP230 and BP180 assays would also help to show if disabling a crucial step of the inhibition of the humoral adaptive immune system by pembrolizumab results in BP or if it predisposes to a BP-like skin reaction.

All studies on the safety of pembrolizumab warn physicians to closely watch this patient group for the development of immune response adverse effects. Even though BP is a rare side effect of treatment with pembrolizumab, the skin of the treated patients should be monitored carefully and at signs of cutaneous side effects a dermatologist should be consulted.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

References

1 Nishie W. Update on the pathogenesis of bullous pemphigoid: an autoantibody-mediated blistering disease targeting collagen XVII. J Dermatol Sci. 2014 Mar;73(3):179–86.
2 Schmidt E, Zillikens D. Pemphigoid diseases. Lancet. 2013 Jan;381(9863):320–32.
3 Stavropoulos PG, Soura E, Antoniou C. Drug-induced pemphigoid: a review of the literature. J Eur Acad Dermatol Venereol. 2014 Sep;28(9):1133–40.
4 Khumalo N, Kirtschig G, Middleton P, Hollis S, Wojnarowska F, Murrell D. Interventions for bullous pemphigoid. Cochrane Database Syst Rev. 2005 Jul;(3):CD002292.
5 Okazaki T, Honjo T. PD-1 and PD-1 ligands: from discovery to clinical application. Int Immunol. 2007 Jul;19(7):813–24.
6 Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012 Jun;366(26):2455–65.
7 Martin-Liberal J, Kordbacheh T, Larkin J. Safety of pembrolizumab for the treatment of melanoma. Expert Opin Drug Saf. 2015 Jun;14(6):957–64.
8 Carlos G, Anforth R, Chou S, Clements A, Fernandez-Peñas P. A case of bullous pemphigoid in a patient with metastatic melanoma treated with pembrolizumab. Melanoma Res. 2015 Jun;25(3):265–8.
9 Hwang SJ, Carlos G, Chou S, Wakade D, Carlino MS, Fernandez-Penas P. Bullous pemphigoid, an autoantibody-mediated disease, is a novel immune-related adverse event in patients treated with anti-programmed cell death 1 antibodies. Melanoma Res. 2016 Aug;26(4):413–6.
10 Rofe O, Bar-Sela G, Keidar Z, Sezin T, Sadik CD, Bergman R. Severe bullous pemphigoid associated with pembrolizumab therapy for metastatic melanoma with complete regression. Clin Exp Dermatol. 2017 Apr;42(3):309–12.

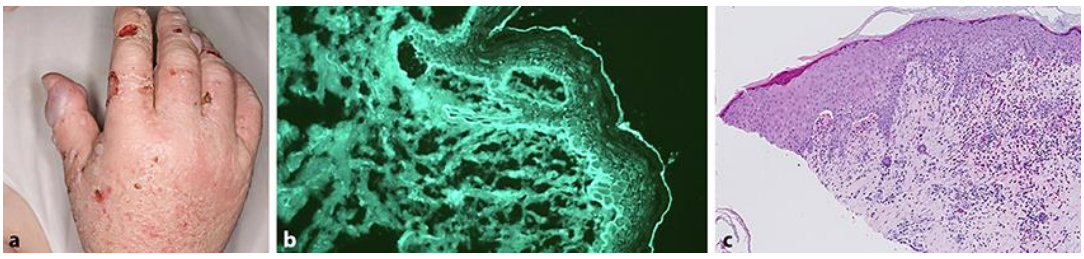

Fig. 1. **a** Clinical picture of the bullous eruption on the hand of the patient. **b** Indirect immunofluorescence of a biopsy from case 1, showing IgG deposition along the dermoepidermal border along the basement membrane. **c** Hematoxylin-eosine staining of a skin biopsy from case 1, demonstrating the split along the dermoepidermal border as well as numerous eosinophils in the inflammatory reaction of the dermis.