

CORRESPONDENCE ARTICLE

Mucous membrane pemphigoid involving palmoplantar lesions that developed during adjuvant nivolumab for malignant melanoma: A rare case and literature review

Mayumi Takata^{1,2}, Shunya Usui^{1,3,*}, Toshiaki Kogame¹, Atsushi Otsuka^{1,3}, Kenji Kabashima¹

¹ Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto 606-8507, Japan

² Department of Dermatology, Kyoto-Katsura Hospital, Kyoto 615-8256, Japan

³ Department of Dermatology, Kindai University Faculty of Medicine, Osaka 589-8511, Japan

* Corresponding author: Shunya Usui, shunyausui19870704@gmail.com

ABSTRACT

Immune checkpoint inhibitors (ICIs), such as nivolumab, which target anti-programmed cell death-1 (PD-1), have been applied to a variety of cancers and have caused immune-related adverse events (irAEs). Although an association between ICIs and bullous pemphigoid and mucosal pemphigoid (MMP) has been reported, the complex mechanisms underlying PD-1 inhibition-induced autoantibody production and autoimmunity remain unelucidated. In this report, we present a unique case of MMP involving the palmoplantar lesions during adjuvant nivolumab therapy. A Japanese woman in her 70s was treated with nivolumab for postoperative vulvar malignant melanoma; after the 12th cycle of treatment, ulcers were seen in the oral cavity, and 4 months later, tense palmoplantar blisters appeared. Microscopic examination of the palmar blister revealed subepidermal vesicles characterized by eosinophil infiltration. Immunofluorescence analysis revealed linear IgG and C3 deposits along the basement membrane; ELISA testing confirmed the presence of anti-BP180 NC16A IgG antibody, and MMP was diagnosed. The patient's condition gradually improved with a therapeutic regimen of corticosteroids and immunoglobulins. A review of 10 cases of ICI-associated MMP, including the present case, revealed clinical similarities to conventional MMP; in cases of persistent oral erosions due to ICI, it is most important to consider mucositis and MMP in the framework of differential diagnosis. Besides, we suggest that we can be more suspicious of MMP by paying attention to examining the palms and soles when the patient receiving ICIs has refractory oral ulcers. This report underscores the importance of careful observation and prompt management of irAE as cancer immunotherapy evolves.

Keywords: adjuvant therapy; BP180; immune checkpoint inhibitors; mucous membrane pemphigoid; palmoplantar lesions

ARTICLE INFO

Received: 7 September 2023

Accepted: 7 October 2023

Available online: 15 December 2023

COPYRIGHT

Copyright © 2023 by author(s).

Trends in Immunotherapy is published by EnPress Publisher, LLC. This work is licensed under the Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0).

<https://creativecommons.org/licenses/by-nc/4.0/>

1. Introduction

Immune checkpoint inhibitors (ICIs), including nivolumab and pembrolizumab, specifically targeting anti-programmed cell death-1 (PD-1), have gained approval for the treatment of various malignancies, encompassing advanced malignant melanoma (MM) and adjuvant therapies for MM^[1]. Conversely, the ICIs elicit nonspecific activation of the immune system, thereby engendering distinctive adverse effects, referred to as immune-related adverse events (irAEs). Cutaneous irAEs induced by anti-PD-1 therapy occur as various manifestations, such as lichenoid reactions, eczema, and vitiligo. In addition, treatment with ICIs has been associated with autoimmune blistering disorders (AIBDs), predominantly bullous pemphigoid (BP)^[2]. While many cases linking mucous membrane

pemphigoid (MMP) with ICIs have been reported, it is noteworthy that no instances of MMP arising during adjuvant ICIs have been previously documented. Thus, the present study provides a comprehensive overview of our unique MMP case, which transpired after the initiation of adjuvant nivolumab, and conducts a systematic review of prior literature.

2. Report of a case

A Japanese female in her 70s with vulvar MM (pT4bN1aM0, Stage III C: American Joint Committee on Cancer Staging system for MM 2018) was treated with nivolumab as postoperative adjuvant therapy. After the twelfth course, she complained of tongue dysesthesia and presented with numerous painful oral ulcers (**Figure 1a,b**). The biopsy from the buccal mucosa exhibited ulceration with diffuse lymphohistiocytic infiltration. The clinical impression, along with non-specific histopathological findings, resulted in a diagnosis of oral mucositis due to irAEs. The symptoms persisted in spite of the treatment with a topical dexamethasone ointment, but she completed 15 cycles of adjuvant nivolumab for a year. Four months after the completion of adjuvant therapy, she had similar persistent oral ulcers and newly developed tense blisters on her palmoplantar areas (**Figure 1c–f**). She predominantly presented mucosal lesions, albeit with a few cutaneous lesions. Biopsies were performed on the blisters of the left palm and the erosion of the lower lip. The former biopsy exhibited a subepidermal vesicle with predominant eosinophilic infiltration (**Figure 2a,b**), while the latter biopsy revealed a subepidermal cleavage with mixed inflammatory cells, including eosinophils (**Figure 2c,d**). No acantholysis was observed in either specimen. Direct immunofluorescence (DIF) revealed a linear deposition pattern for IgG and C3 along the basement membrane (**Figure 2e,f**). Indirect immunofluorescence using the salt split technique detected no antibody deposition. Enzyme-linked immunosorbent assay (ELISA) indicated the presence of anti-BP180 NC16A (IgG) antibodies (753 U mL^{-1} [normal range: $< 9 \text{ U mL}^{-1}$]). Blood tests revealed that antibodies of anti-desmoglein-1 and -3 were negative. Upper gastrointestinal endoscopy revealed multiple ulcerations in the pharynx and esophagus without cytomegalovirus infection. Based on these findings, a diagnosis of MMP was established. We considered two possibilities regarding the timing of onset of MMP in this case: the initial mucosal lesions could have been mucositis, followed by the development of MMP, or the lesions could have been MMP from the beginning. We diagnosed the latter, that is, MMP that developed during ICI administration, because the mucosal lesions were consistently similar from the time of onset until the appearance of blisters on the palmoplantar areas. Treatment with oral corticosteroid (1 mg kg^{-1} per day) alleviated the blisters on the palmoplantar lesions in three weeks, but the oral ulcers persisted. Consequently, two courses of intravenous immunoglobulin therapy (12 g per day) were additionally administered, leading to the remission of mucosal lesions within two months. Subsequently, corticosteroid was successfully tapered without relapse of MMP.

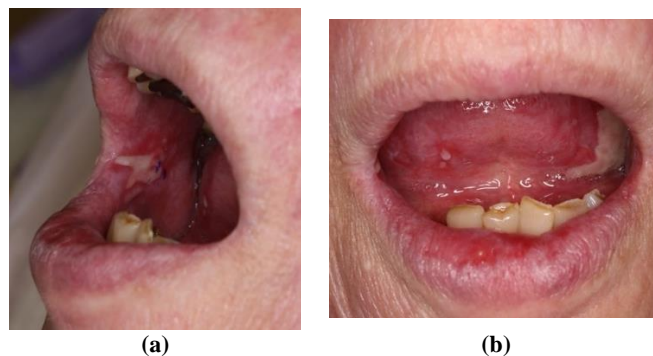


Figure 1. (Continued).



Figure 1. (a, b) clinical presentation. She showed ulcers and erythema on the buccal mucosa, lower lip, and tongue after the twelfth course; (c, d) multiple ulcers and erythema persisted on the lower lip, buccal mucosa, and tongue; and (d, e) new multiple tense bullae developed on the palms and soles; four months after the completion of the adjuvant therapy.

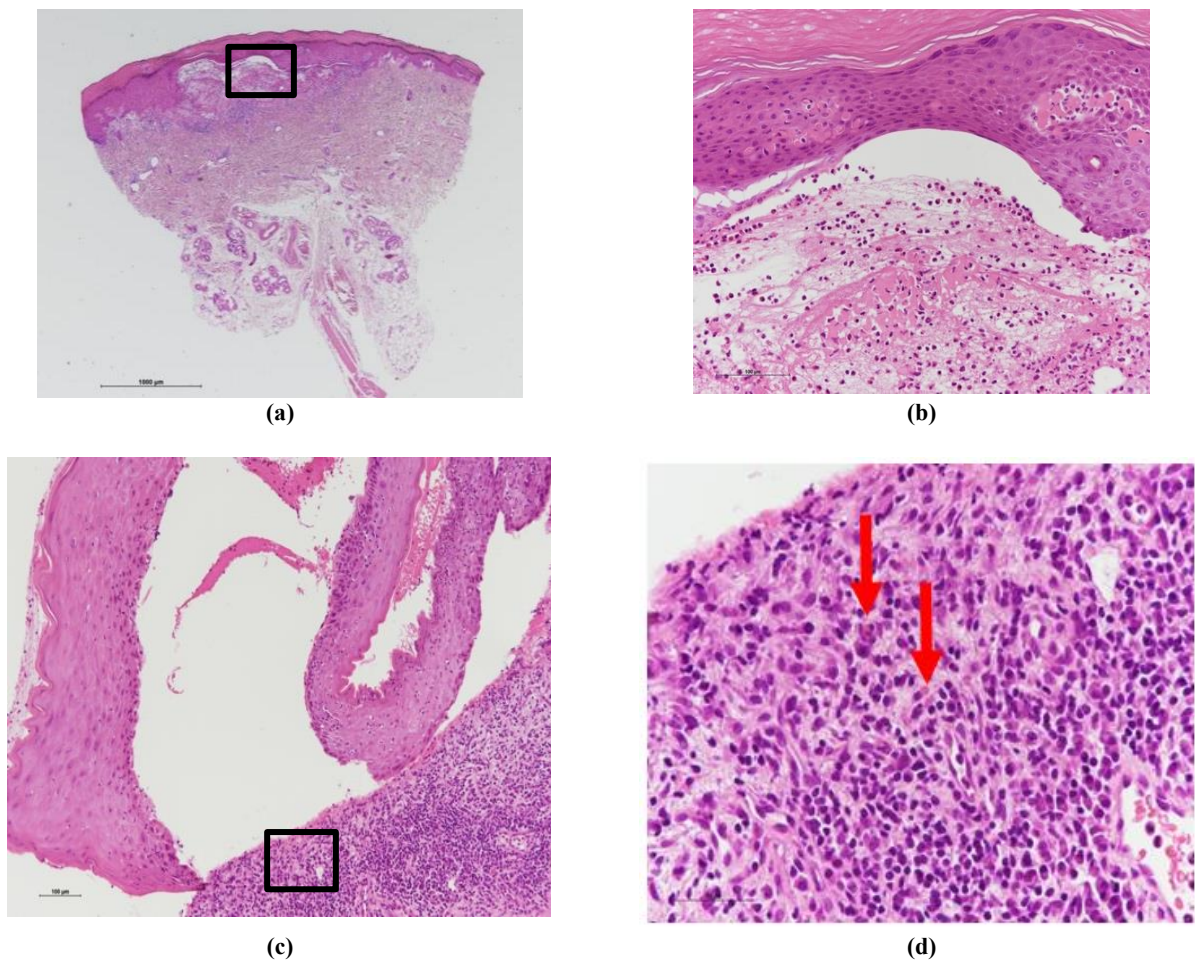


Figure 2. (Continued).

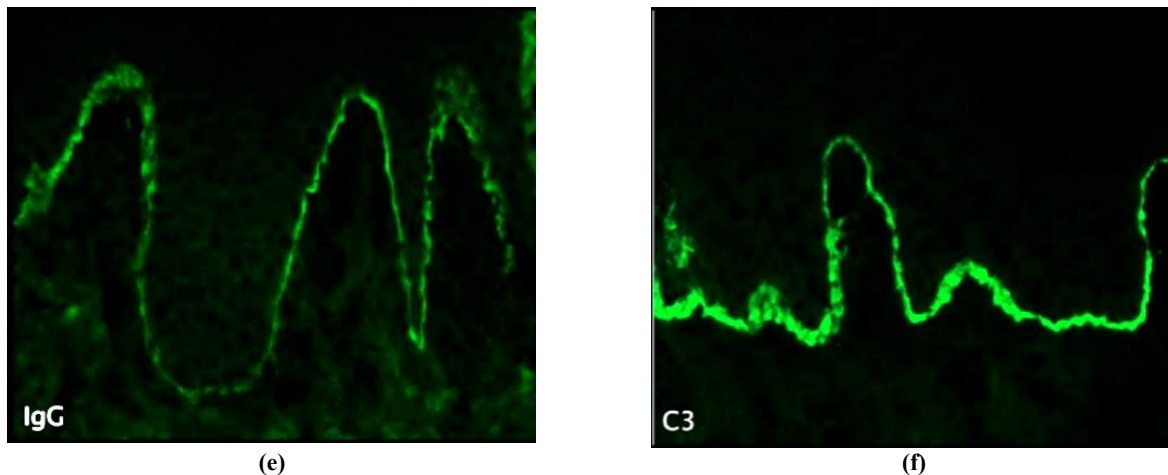


Figure 2. Histological findings. **(a)** histological examination of the left palm biopsy showing a subepidermal vesicle with predominantly eosinophilic infiltration. [Magnification: $\times 20$]; **(b)** magnified view of the rectangular area in **Figure 2a**. [Magnification: $\times 100$]; **(c)** histology of the lower lip showing subepithelial cleavage with mixed inflammatory infiltrate, including eosinophils. [Magnification: $\times 100$]; **(d)** magnified view of the rectangular area of **Figure 2c**. Arrowheads show eosinophils. [Magnification: $\times 400$]; **(e, f)** direct immunofluorescence of the left palm demonstrating linear deposition of IgG and C3 along the basement membrane.

3. Discussion and literature reviews

MMP belongs to the group of autoimmune blistering diseases (AIBDs), characterized by the presence of autoantibodies against components of the dermo-epidermal junction. It predominantly affects the mucous membranes, with or without concurrent cutaneous lesions. The onset of MMP typically occurs between the ages of 60 and 65, whereas BP onset occurs between 75 and 79 years^[3]. Several target antigens of MMP have been identified, such as BP180 (approximately 75% of patients), BP230 (25%; usually along with BP180 reactivity), and laminin 332 (25%)^[3]. Although MMP predominantly affects mucous membranes, 25–30% of the patients manifest concomitant skin lesions that appear primarily on the upper trunk and head areas^[3,4]. Additionally, around 25%–30% of MMP patients with anti-laminin 332 antibodies have been reported to have an association with malignant tumors^[5], whereas no such association has been observed in patients with anti-BP180 antibodies, to the best of our knowledge. Therefore, these findings suggest that the development of MMP in our case may not be linked to malignancy.

As the use of ICIs has increased, reports of AIBDs by ICIs also have increased. More than 100 cases have been reported to date by many authors^[6,7]. On the other hand, only 9 cases of MMP were reported to associate ICIs (**Table 1**)^[8–15]. Five out of nine patients were female. The mean age at diagnosis of MMP was 69 years old (range, 47–84 years old), and the median time from the introduction of ICIs to the diagnosis of MMP was 7.4 months (range, 1–18 months). Approximately 50% of the patients were detected with anti-BP180 NC16A (IgG) antibodies. In all cases, ICI therapy was introduced for advanced malignancy. Clinical features of ICI-related MMP resembled conventional MMP. Extramucosal lesions were observed in one patient on the face and scalp. Only in our case, MMP developed after the introduction of adjuvant ICI therapy, and palmoplantar lesion appeared as extramucosal lesion. All patients were treated with oral or topical steroids. In one patient, the skin lesion improved after discontinuing ICI and did not recur. The drug was not restarted. Regarding nivolumab related BP, there has been a case report in which the skin lesion and serum BP180 autoantibodies improved after discontinuation of ICI, but both relapsed upon re-administration^[16].

Table 1. Characteristics of reported cases of mucous membrane pemphigoid associated with immune checkpoint inhibitor therapy.

Authors Year of report	Sex Age (year)	Cancer type	Name of anti- PD-1 treatment Reason for treatment	Onset of MMP after starting ICIs (months)	Extramuco- sal lesions	Autoantibo- dies	Treatment for MMP	Tumor response
C. Zumelzu et al. ^[8] 2018	F 83	Malignant melanoma	Pembrolizumab For metastasis	18	None	Laminin332	Doxycycline Topical steroid	CR
V. Haug et al. ^[9] 2018	M 62	Merkel cell carcinoma	Pembrolizumab For metastasis	3	None	BP180	Doxycycline Topical steroid	PR
L. Bezinelli et al. ^[10] 2019	F 47	Ovarian adenocarcinoma	Pembrolizumab For metastasis	1	None	Negative	Oral steroid Immunosuppressant	PD Dead
V. Sibaud et al. ^[11] 2019	F 60s	Malignant melanoma	Nivolumab For metastasis	2	None	BP180	Topical steroid	SD
Ö. Durmus et al. ^[12] 2020	F 54	Hodgkin's lymphoma	Nivolumab For first line	12	None	NA	Oral steroid	PR or CR
M. Fassler et al. ^[13] 2020	M 78	Malignant melanoma	Pembrolizumab For metastasis	6	None	BP180	Doxycycline Topical steroid	CR
M. Fassler et al. ^[13] 2020	F 82	Malignant melanoma	Pembrolizumab For metastasis	6	Ulcer of the face and scalp	Negative	Doxycycline Topical steroid	CR
S. Duan et al. ^[14] 2021	M 75	Urothelial carcinoma	Toripalimab, then Pembrolizumab For metastasis?	5	None	BP180	Topical steroid	Poor response
A. Lagos-Villaseca et al. ^[15] 2023	M 84	Urothelial carcinoma	Pembrolizumab For metastasis	13.5	None	BP180, Desmoglein 1	Oral steroid Methotrexate	CR
Present case	F 70s	Malignant melanoma	Nivolumab For adjuvant	9	blisters on the palmoplantar areas	BP180	Oral steroid IVIg	

Footnotes: Anti-PD-1 = anti-programmed cell death-1, MMP = mucous membrane pemphigoid, ICIs = immune checkpoint inhibitors, CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, IVIg = intravenous immunoglobulin.

Although the pathophysiology of ICI-related AIBDs such as BP and MMP is largely unknown, some hypothesized the possible underlying mechanisms. Zhao et al. hypothesized that the activation of pathogenic B cells may cause ICI-related BP in patients who possess normally suppressed pathogenic B cells, and furthermore, T-follicular regulatory cells dysregulated by anti-PD1 may activate indirectly the pathogenic B cells^[17]. Sibaud et al. argued that in the case of nivolumab-related MMP, the findings of a negative ELISA test for BP180 just before nivolumab initiation and elevated serum BP180 autoantibodies detected only after nivolumab initiation strongly suggested the therapeutic inhibition of the PD-1 pathway may also trigger B-cell activation^[11].

In conclusion, despite an extensive review of the existing literature, no discernible differentiating features between ICI-related MMP and conventional MMP were identified. Although the possibility of conventional MMP developed during nivolumab therapy cannot be completely ruled out in our case, nivolumab likely played a role in triggering MMP. This case is unique that MMP developed in a patient receiving adjuvant nivolumab therapy and extramucosal bullae appeared on palmoplantar area. Extramucosal bullae are a reason to be more suspicious of MMP than oral mucositis due to irAE. Therefore, we also should pay attention to

examining the palms and soles when the patient receiving ICIs has refractory oral ulcers. The underlying mechanism responsible for ICI-related MMP remains elusive, necessitating further investigation and analysis.

Conflict of interest

The authors declare no conflict of interest.

References

1. Seidel JA, Otsuka A, Kabashima K. Treating tumors with immune checkpoint inhibitors: Rationale and limitations. *Trend Immunother* 2017; 1(1): 2–9. doi: 10.24294/ti.v1.i1.20
2. Siegel J, Totonchy M, Damsky W, et al. Bullous disorders associated with anti-PD-1 and anti-PD-L1 therapy: A retrospective analysis evaluating the clinical and histopathologic features, frequency, and impact on cancer therapy. *Journal of the American Academy of Dermatology* 2018; 79(6): 1081–1088. doi: 10.1016/j.jaad.2018.07.008
3. Schmidt E, Zillikens D. Pemphigoid diseases. *Lancet* 2013; 381(9863): 320–332. doi: 10.1016/S0140-6736(12)61140-4
4. Chan LS, Ahmed AR, Anhalt GJ, et al. The first international consensus on mucous membrane pemphigoid. *Archives of Dermatology* 2002; 138(3): 370–379. doi: 10.1001/archderm.138.3.370
5. Goletz S, Probst C, Komorowski L, et al. A sensitive and specific assay for the serological diagnosis of antilaminin 332 mucous membrane pemphigoid. *The British Journal of Dermatology* 2018; 180(1): 149–156. doi: 10.1111/bjd.17202
6. Aggarwal P. Disproportionality analysis of bullous pemphigoid adverse events with PD-1 inhibitors in the FDA adverse event reporting system. *Expert Opinion on Drug Safety* 2019; 18(7): 623–633. doi: 10.1080/14740338.2019.1619693
7. Irie K, Kikuchi N, Ishikawa M, et al. Six Cases of Bullous Pemphigoid after Administration of Anti-PD-1 Antibody. *Japanese Journal of Dermatology* 2023; 133(10): 2373-2384.
8. Zumelzu C, Alexandre M, Le Roux C, et al. Mucous membrane pemphigoid, bullous pemphigoid, and anti-programmed death-1/ programmed death-ligand 1: A case report of an elderly woman with mucous membrane pemphigoid developing after pembrolizumab therapy for metastatic melanoma and review of the literature. *Frontiers in Medicine* 2018; 5: 268. doi: 10.3389/fmed.2018.00268
9. Haug V, Behle V, Benoit S, et al. Pembrolizumab-associated mucous membrane pemphigoid in a patient with Merkel cell carcinoma. *The British Journal of Dermatology* 2018; 179(4): 993–994. doi: 10.1111/bjd.16780
10. Bezinelli LM, Eduardo FP, Migliorati CA, et al. A severe, refractory case of mucous membrane pemphigoid after treatment with pembrolizumab: Brief communication. *Journal of Immunotherapy* 2019; 42(9): 359–362. doi: 10.1097/cji.0000000000000280
11. Sibaud V, Vigarios E, Siegfried A, et al. Nivolumab-related mucous membrane pemphigoid. *European Journal of Cancer* 2019; 121: 172–176. doi: 10.1016/j.ejca.2019.08.030
12. Durmus Ö, Gulseren D, Akdogan N, Gokoz O. Mucous membrane pemphigoid in a patient treated with nivolumab for Hodgkin's lymphoma. *Dermatologic Therapy* 2020; 33(6): e14109. doi: 10.1111/dth.14109
13. Fässler M, Rammelmair A, Feldmeyer L, et al. Mucous membrane pemphigoid and lichenoid reactions after immune checkpoint inhibitors: Common pathomechanisms. *Journal of the European Academy of Dermatology and Venereology* 2020; 34(2): e112–e115. doi: 10.1111/jdv.16036
14. Duan S, Zhang X, Wang F, et al. Coexistence of oral mucous membrane pemphigoid and lichenoid drug reaction: a case of toripalimab-triggered and pembrolizumab-aggravated oral adverse events. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology* 2021; 132(3): e86–e91. doi: 10.1016/j.oooo.2021.05.012
15. Lagos-Villaseca A, Koshkin VS, Kinet MJ, Rosen CA. Laryngeal mucous membrane pemphigoid as an immune-related adverse effect of pembrolizumab treatment. *Journal of Voice* 2023; in press.
16. Adachi E, Yokoyama E, Yamagami Y, et al. Bullous pemphigoid induced by nivolumab in a patient with malignant melanoma. *Trends in Immunotherapy* 2020; 4(1): 15. doi: 10.24294/ti.v4.i1.1210
17. Zhao CY, Hwang SJE, Consuegra G, et al. Anti-programmed cell death-1 therapy-associated bullous disorders: A systematic review of the literature. *Melanoma Research* 2018; 28(6): 491–501. doi: 10.1097/cmr.0000000000000500