

CASE REPORT

Bullous pemphigoid induced by nivolumab in a patient with malignant melanoma

Eriko Adachi*, Erina Yokoyama, Yuna Yamagami, Reiko Koga, Yoshiaki Yoshikawa

Department of Dermatology, Kitano Hospital, the Tazuke Kofukai, Medical Institute, Osaka, Japan.

E-mail: a0081134@kuhp.kyoto-u.ac.jp

ABSTRACT

Immune checkpoint inhibitors, such as nivolumab, have been recognized that the enhanced immune responses often lead to immune-related adverse events (irAEs) in various organs. Although cutaneous toxicity is one of the most common irAEs, bullous pemphigoid (BP) with immune checkpoint inhibitors is rare. Herein, the authors report a case of BP in a patient of the metastatic malignant melanoma of the brain under the treatment of nivolumab. It is notable that this case showed the clear correlation between the status of using of nivolumab and serum levels of anti-BP180 antibody. In addition, the skin eruptions in the case were mainly pruritic erosive or crusted papules and these clinical features may be the clinical characteristics of BP induced by nivolumab.

Keywords: Immune-related Adverse Events (irAEs); Immune Checkpoint Inhibitors; Nivolumab; Bullous Pemphigoid (BP); Malignant Melanoma

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*CORRESPONDING AUTHOR

Adachi, E. Department of Dermatology,
Kitano Hospital, the Tazuke Kofukai,
Medical Institute, Osaka, Japan;
a0081134@kuhp.kyoto-u.ac.jp

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Introduction

Immune checkpoint inhibitors utilizing monoclonal antibodies against programmed cell death protein-1 (PD-1) and programmed cell death ligand-1 (PD-L1), such as nivolumab, are new drugs for many types of solid malignancies^[1,2]. These drugs increase antitumor immune responses and have been demonstrated as effective. However, the increased immune responses often lead to immune-related adverse events (irAEs) in many organs, including the skin. Recently, cases of bullous pemphigoid (BP) associated with nivolumab therapy have been reported, albeit rare. Herein, we report a case of BP induced by nivolumab.

Case presentation

A 67-year-old female, who was treated using nivolumab (3 mg/kg intravenously every 2 weeks) for the local recurrence of malignant melanoma of the brain for seven months, presented with pruritic erosive or crusted papules on erythematous bases, and a few vesicles on the arms, legs and trunk (**Figure 1, 2**). Skin biopsy of the upper extremity revealed subepidermal vesicles with inflammatory cells (**Figure 3**). Direct immunofluorescence microscopy demonstrated linear deposition of IgG and C3 along the dermoepidermal junction (**Figure 4**). Indirect immunofluorescence using human skin with an artificial blister induced by 1 M NaCl incubation was positive for IgG against the epidermal side of the blister (**Figure 5**). On chemiluminescent enzyme assay, there were increased levels of serum anti-BP180 antibody (83.5 U/mL: normal < 9.0 U/mL). The titer of anti-desmoglein 1/3 antibody was below detection limit (< 3.0 U/mL). These findings were consistent with BP. We discontinued nivolumab, considering the possible association between nivolumab and BP, and started oral prednisolone (15 mg/day) and topical steroids. Skin lesions improved and serum

levels of anti-BP180 antibody rapidly decreased to normal; therefore, oral prednisolone was tapered. After five months, skin lesions were completely controlled and nivolumab was restarted. Pruritic erythematous papules reoccurred after three cycles of nivolumab and serum anti-BP180 antibody levels increased to 28.2 U/mL. As the tumor size gradually

increased despite the administration of nivolumab, the chemotherapy was changed to dacarbazine. After the discontinuation of nivolumab, the skin eruptions rapidly improved and the serum level of anti-BP180 antibody decreased to within normal limits. Based on the clinical course, we diagnosed her with nivolumab-induced BP.



Figure 1, 2. Pruritic erythematous papules and a few of vesicles on the arms, legs, and trunk. The black dots indicate the area of skin biopsy.

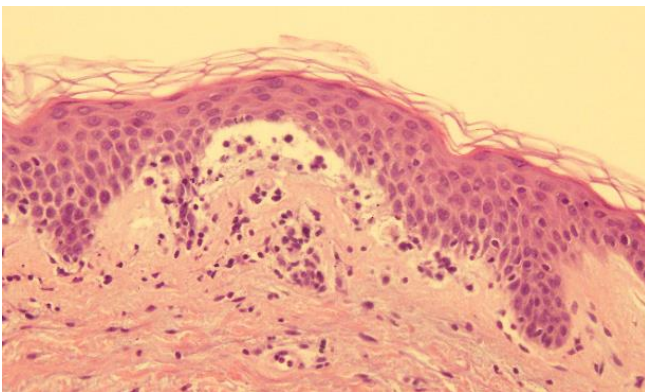


Figure 3. Histopathological findings of the skin lesion (hematoxylin and eosin staining, $\times 200$).

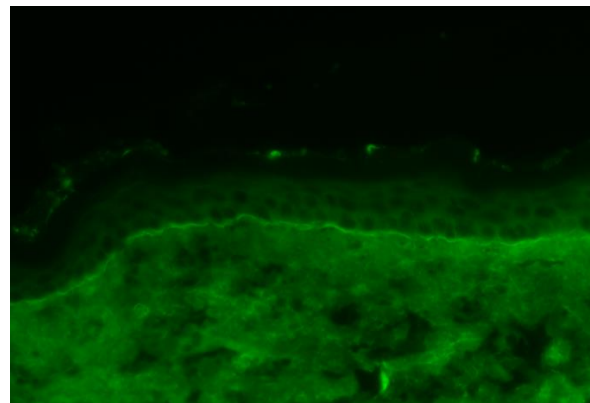


Figure 4. Direct immunofluorescence demonstrated linear deposition of IgG at the basement membrane zone.

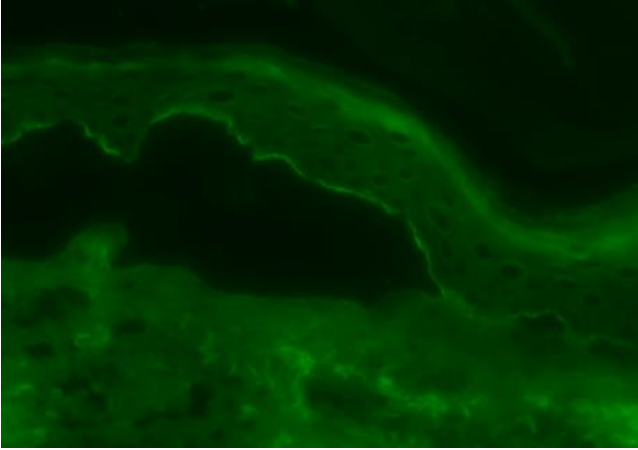


Figure 5. Indirect immunofluorescence was positive for IgG against the epidermal side of the blister.

Discussion

To our knowledge, BP is a rare cutaneous irAE and there are 16 previous cases of BP developing during nivolumab-therapy^[3-7]. In oncologic patients, BP may be idiopathic, paraneoplastic or related to medication, including cancer therapy. Although it is generally difficult to distinguish immunotherapy-induced BP from other types of BP, a clear correlation between the status of using nivolumab and serum levels of anti-BP180 antibody was noted in our case, and we are able to exclude the possibility of idiopathic or paraneoplastic BP. Of note, the skin eruptions in our case were mainly pruritic papules, and these clinical features are similar to non-bullous type BP and may be the clinical characteristics of BP induced by nivolumab. Although the pathogenesis and clinical characteristics of BP induced by nivolumab have not been elucidated, clinicians should be aware of the possibility of BP associated with anti PD-1/PD-L1 antibodies and consider further examinations for BP even if vesicles or bullae are not found.

Conflict of interest disclosure

None declared

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