

Case Report

# Intensity-Modulated Radiotherapy Triggers Onset of Bullous Pemphigoid in a Patient with Advanced Melanoma Treated with Nivolumab

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## Keywords

Intensity-modulated radiotherapy · Bullous pemphigoid · Nivolumab · Advanced melanoma

## Abstract

Since the efficacy of ipilimumab on nivolumab-resistant advanced melanoma is extremely low, additional supportive therapy for anti-PD-1 antibody therapy-resistant advanced melanoma is needed. Although several supportive therapies that enhance the antitumor immune response of anti-PD-1 antibodies have already been reported, unexpected immune-related adverse events were detected at the same time. In this report, we describe a patient with advanced melanoma treated with nivolumab followed by intensity-modulated radiotherapy, which might have triggered bullous pemphigoid (BP). Although several cases of BP developing in anti-PD-1 antibody-treated patients have already been reported, in this report, we shed light on the possible pathogenesis of BP developing in a patient treated with nivolumab through M2 macrophages.

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## Introduction

Both sequential and simultaneous administration of ipilimumab significantly enhances the antitumor effects of nivolumab in advanced melanoma patients [1, 2]. On the other hand, the efficacy of ipilimumab in nivolumab-resistant advanced melanoma is only 3.6% [3], suggesting that additional supportive therapy for anti-PD-1 antibody is needed for nivolumab-resistant advanced melanoma. Indeed, although several supportive therapies to enhance the antitumor immune response of anti-PD-1 antibodies have already been reported [3–8], unexpected immune-related adverse events were detected at the same time [8]. In this report, we describe a patient with advanced melanoma treated with nivolumab followed by intensity-modulated radiotherapy (IMRT), which might have triggered bullous pemphigoid (BP).

## Case Reports

A 77-year-old Japanese man visited our outpatient clinic with a slight pain on the neck. He had been treated for acral lentiginous melanoma and had undergone excision of the tumors and left inguinal lymph node dissection (pT4aN3cM0 stage IIIC). In addition, after the surgical treatment, he had received adjuvant chemotherapy (dacarbazine with interferon- $\beta$ ,  $3.0 \times 10^6$  U) for a half year. We screened for possible metastatic lesions with positron emission tomography and found an 11 mm nodule at the second cervical vertebra (Fig. 1a). Since the primary tumor was negative for the BRAF<sup>V600E</sup> mutation, we administered nivolumab at 2 mg/kg q3 weeks. Since a follow-up computed tomography scan 9 weeks after the administration of nivolumab revealed progression of the nodule at the second cervical vertebra, we employed IMRT (45 Gy in 5 fractions) 10 weeks after the administration of nivolumab. Seven weeks after the IMRT irradiation, the patient developed large, tense bullae and erosion arising on erythematous plaque on the trunk and extremities (Fig. 1b). A biopsy specimen revealed prominent interface dermatitis and dense infiltration of eosinophils in the upper dermis (Fig. 1c). Direct immunofluorescent study revealed IgG deposition on the epidermal side of the basement membrane zone. High levels of serum anti-BP180 NC16a antibody (73.1 U/mL) were detected. From the above findings, we made the diagnosis of BP developing in a patient with advanced melanoma treated with nivolumab and IMRT. We treated him with oral prednisolone 20 mg/day with doxycycline (100 mg/day) with nivolumab. Two weeks later, the initial eruptions had disappeared and his disease was under control.

## Discussion

Since the efficacy rate of nivolumab monotherapy for advanced melanoma is approximately 30% [1], enhancing the antitumor immune response induced by nivolumab is necessary to further optimize its use for the treatment of advanced melanoma [2]. Indeed, several successful methods to enhance the antitumor effects of nivolumab by systemic or local therapies have been developed [1–6, 9]. On the other hand, these combination therapies develop unexpected, severe immune-related adverse events [1–3]. In this report, we describe a case of BP in a patient with advanced melanoma treated with nivolumab, probably caused by IMRT.

BP is an autoimmune blistering disease predominantly affecting the elderly. Recent reports have suggested that several immune cells such as regulatory T cells (Tregs), T helper

17 (Th17), and skin-resident M2-like macrophages contribute to the pathogenesis of BP [10–13]. Indeed, the number of Tregs is significantly decreased in the lesional skin of BP patients compared with other inflammatory skin diseases such as atopic dermatitis [10]. In addition, Furudate et al. [12] reported a significant number of M2 macrophages in the lesional BP skin, leading to the recruitment of immune cells in the lesional BP skin [11]. These reports suggested a possible role of M2 macrophages in the pathogenesis of BP [11]. Interestingly, Gordon et al. [14] reported the expression of PD-1 on M2-like tumor-associated macrophages (TAMs) in colorectal cancers in humans and mice, leading to suppressed antitumor functions of M2-like TAMs by PD-1/ PD-L1-dependent pathways. In addition, Rannou et al. [15] reported that radiotherapy increases M1-polarized macrophages in tumor-bearing hosts. Notably, the main population of TAMs is M2-polarized macrophages and one of the main functions of TAMs in tumor microenvironment is to produce various chemokines that recruit Tregs, as well as express immunosuppressive molecules such as PD-L1 [16, 17]. In aggregate, the blocking of PD-1/PD-L1 by nivolumab with IMRT might cause TAMs to abrogate their immunosuppressive function, leading to the development of BP as in our present case. Although several cases of BP developing in anti-PD-1 antibody-treated patients have already been reported [18–20], in this report, we shed light on the possible pathogenesis of BP developing in a patient treated with nivolumab through M2 macrophages.

### Statement of Ethics

The patient gave written informed consent.

### Disclosure Statement

The authors have no conflicts of interest to declare.

### Author Contributions

Taku Fujimura: conception and design, acquisition of clinical data, analysis and interpretation of data, writing, review, and/or revision of the manuscript, and study supervision.

Yumi Kambayashi, Kayo Tanita, Akira Tsukada, Yota Sato, Akira Hashimoto: acquisition of clinical data. Setsuya Aiba: study supervision.

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**Fig. 1.** **a** Positron emission tomography revealed an 11 mm nodule at the second cervical vertebra. **b** Large, tense bullae and erosion arising on erythematous plaque on the trunk and extremities. **c** A prominent interface dermatitis and dense infiltration of eosinophils in the upper dermis. H&E staining. Original magnification  $\times 100$ .