Non-bullous pemphigoid associated with immune checkpoint inhibitor treatment

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December 30, 2021

Abstract

Though a variety of immune-related adverse events of immune checkpoint inhibitors (ICIs) including bullous pemphigoid have been reported, non-bullous pemphigoid (NBP) associated with ICI therapy was scarcely reported. We present a case of NBP with a long latent disease course without diagnosis during nivolumab, an ICI therapy.

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Informed consent: Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

Statement of all funding sources: None declared

Conflict of interest disclosure: None declared

Word count: 488 words

Figure: 1 figure

Key words: non-bullous pemphigoid, bullous pemphigoid, immune checkpoint inhibitor, melanoma, nivolumab, immune-related adverse event

Running head : **Non-bullous pemphigoid by nivolumab**

Introduction

Nivolumab is an immune checkpoint inhibitor (ICI) that facilitates T cell activation by counteracting the suppressive effect of programmed death 1 signaling on T cells, which results in great efficacy in various cancers including melanoma (1). Thus far, a variety of cutaneous immune-related adverse events (irAEs) have been reported, including bullous pemphigoid (BP) (2). However, only one report previously described non-bullous pemphigoid (NBP) associated with ICI treatment (3). Here, we describe a second case report of an insidious presentation of NBP during nivolumab treatment.

Case Report

A 68-year-old male presented with metastatic recurrent uveal melanoma in liver and sacral bone 17 years after from the removal of left eye. Nivolumab/ipilimumab combination therapy was introduced. After three cycles of the combination therapy, we switched to nivolumab monotherapy (240 mg/body, every two weeks) because of colitis as irAE (grade 1, according to CTCAE criteria v.4.0). After 9 cycles of nivolumab, erythematous, urticarial pruritic papules and plaques developed on his back and extremities (Fig. 1a). We suspected cutaneous irAE and initiated topical clobetasol propionate 0.05% ointment without success. Skin biopsy was performed after 14 cycles of nivolumab (3 months from the onset of skin symptoms). Histological analysis revealed interface dermatitis and dermal lymphocyte infiltration (Fig. 1b), which were compatible with drug eruption. Thus, we continued nivolumab treatment with concurrent oral prednisolone (20 mg/day). His skin symptoms worsened with some small blisters (7 months from the onset of skin symptoms) (Fig. 1c). Skin biopsy of the bullous lesion showed subepidermal blister formation and neutrophil infiltration in the dermis (Fig. 1d). Direct immunofluorescent (DIF) study showed linear C3 and IgG deposition at the basement membrane (Fig. 1e and data not shown). Serum anti-BP180 antibody was elevated (47.1 U/mL; normal range, <9.0 U/mL). Eosinophil counts were not elevated (2.0%; normal range, 3.0-5.0%). Total IgE level was below normal range. We diagnosed the patient with NBP associated with nivolumab treatment.

Discussion

Generally, NBP is recognized as non-bullous pruritic skin lesions and difficult to diagnose (2). Thus far, various cutaneous irAEs have been reported including about 60 cases of BP associated with ICI treatment (3). However, only four cases in one report of NBP associated with ICI were reported so far (4). A retrospective analysis indicates that about 20% of conventional BP cases without ICI were originally manifested as NBP (5). We can therefore estimate that there may be more undiagnosed or under-reported NBPs associated with ICIs.

About 10-20% of NBP are reported to accompany bullous lesions later during follow-up (2). In our case, bullous lesions developed seven months after the onset of skin symptoms. Persistent non-blistering pruritic plaques, combined with positive anti-BP180 antibody test, DIF findings and late onset of blister formation fulfilled the previously reported diagnostic criteria of NBP (5). Our case emphasizes the importance of publicizing the existence of NBP, a phenotype of BP that is difficult to diagnose, and exemplifies the diagnostic utility of serum anti-BP180 antibody and DIF in evaluating patients undergoing ICI with chronic pruritus.

Author's contribution

Akiyoshi Senda: Drafting the manuscript and patient management. Yoshihiro Ishida, Teruasa Murata, Atsushi Otsuka, and Kenji Kabashima: Scientific revision of manuscript. Takaya Komori: Drafting the manuscript, patient management and corresponding author.

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Figure 1. Clinical and pathological findings of the patient

(a) Initial presentation of the eczematous plaques on his back (b) Hematoxylin & eosin (H & E) staining of a specimen from the back of the patient revealed interface dermatitis and dermal lymphocyte infiltration. Scale bar, 100 μm. (c) The eczematous plaques on his back exacerbated. () H & E staining of a specimen from the chest of the patient revealed subepidermal blister formation. Scale bar, 100 μm. () Direct immunofluorescent study showed linear C3 deposition on the basement membrane of the skin.