

## SHORT COMMUNICATIONS

### Pruritic Rash and Oral Erosions During Nivolumab Treatment for Melanoma

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*To the Editor:* A 76-year-old man with a history of stage 3 melanoma treated with nivolumab presented with a persistent eruption of intensely pruritic papules on the trunk that started six months after initiating immunotherapy. He denied skin blistering. The patient also reported recurrent blood-filled blisters in the mouth that ruptured to form painful erosions. Physical examination revealed scattered erythematous papules without vesiculation on the back (Figure 1A), excoriated papules on the chest (Figure 1B), and several shallow erosions of the buccal mucosa (Figure 1C). Immunohistochemical (IHC) staining of the skin biopsy showed linear deposition of complement protein C3d along the dermal-epidermal junction (Figure 2) and enzyme-linked immunosorbent assay (ELISA) revealed anti-BP180 antibodies, confirming a diagnosis of bullous pemphigoid.

Bullous pemphigoid (BP) is a rare autoimmune skin disease that typically affects elderly patients. Although BP is usually idiopathic, numerous medications have been reported as suspected causative agents. More recently, cases of BP have been associated with inhibitors of programmed cell death 1 (PD-1) receptor and its ligand (PD-L1)<sup>1</sup>, which are now widely used in the treatment of various cancers, including nivolumab for advanced

melanoma. While intense pruritus and tense bullae are the typical skin findings in BP, patients can also present with non-blistering urticarial papules, as in this case (Figure 1A). Moreover, oral erosions are an under-recognized feature of BP despite their presence in approximately 17% of cases.<sup>2</sup>

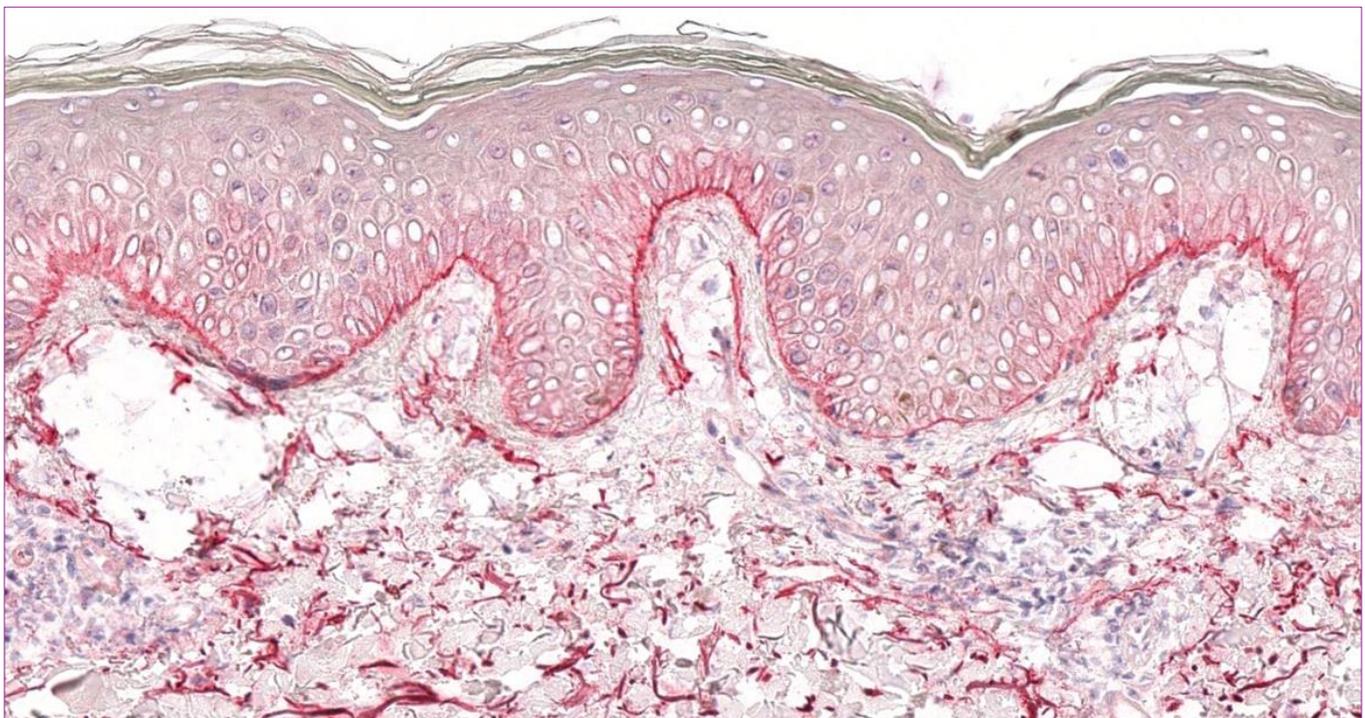
BP is caused by auto-antibodies that bind to hemi-desmosomes, which adhere epidermal keratinocytes to the basement membrane zone (BMZ); auto-antibody deposition results in an inflammatory infiltrate at the dermal-epidermal junction and subsequent subepidermal blistering. Diagnosis of BP is confirmed by identifying auto-antibodies recognizing hemi-desmosome proteins (BP180 and/or BP230); circulating auto-antibodies can be detected in the serum using ELISA or indirect immunofluorescence while tissue-deposited auto-antibodies at the BMZ can be visualized by direct immunofluorescence of unfixed peri-lesional skin or by IHC staining of fixed lesional tissue sections for complement protein C3d.<sup>3</sup>

Treatment of idiopathic BP varies depending on illness severity and patient performance status, relying heavily on expert opinion due to the limited number of prospective randomized studies. While severe cases often require systemic corticosteroids, ultra-

**Figure 1.** (A) Scattered non-bullous erythematous papules were noted on the back. (B) Excoriated papules were present on the chest. (C) Shallow erosions were present on the buccal mucosa.



**Figure 2.** Immunohistochemistry staining of a punch biopsy of lesional skin from the back showed linear deposition of complement protein C3d (red) along the dermal-epidermal junction (200x).



potent topical corticosteroids and doxycycline<sup>4</sup> are effective for treating BP without systemic immunosuppression. Therapeutic decisions in oncology patients with BP are challenging because standard immunosuppressive therapies may carry unacceptable risks in the setting of active

malignancy. Targeted depletion of B-cells (and auto-antibodies) with rituximab has been reported to be effective in immunotherapy-related BP<sup>5</sup> and may offer a more favorable risk profile than traditional immunosuppressive agents, though controlled studies are lacking.

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In sum, the diagnosis of BP should be considered in patients treated with anti-PD-1 or anti-PD-L1 therapy who develop a pruritic rash,<sup>1</sup> which should prompt a skin biopsy and evaluation for auto-antibodies. Only one case of non-bullous pemphigoid in association with anti-PD-1 therapy has been previously reported.<sup>6</sup> Our case further supports that immunotherapy-related BP may present with non-bullous skin lesions and additionally emphasizes the need to monitor closely for oral erosions.<sup>2</sup>

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