

## Short Case Report

# Nivolumab-induced oral and cutaneous bullous pemphigoid: A case report

Julie Sturque<sup>1,\*</sup>, Franck Boralevi<sup>2</sup>, Jean-Christophe Fricain<sup>1</sup>

<sup>1</sup> Odontology Department, Pellegrin Hospital, Bordeaux, France

<sup>2</sup> Dermatology Department, Pellegrin Hospital, Bordeaux, France

(Received: 17 September 2018, accepted: 11 January 2019)

**Keywords:**  
pemphigoidbullous /  
nivolumab / mouth

**Abstract – Introduction:** Nivolumab-induced oral and cutaneous bullous pemphigoid have been rarely reported in the literature. **Observations:** A 64-year-old male patient was treated with nivolumab for melanoma. He presented with oral lesions in the palatal and gingival mucosal lesions. Nine months after the initiation of nivolumab therapy, a cutaneous bullous pemphigoid was found on his right forearm. The level of anti-BPAG2 (or anti-BP 180) was positive with a rate of 83 AU/mL, thereby confirming the diagnosis of bullous pemphigoid. His oral mucosa, first in the posterolateral area of the palate and then in the gingiva, was affected 3 months later. Histological examination revealed a subepidermal bulla with few eosinophils. **Comments:** Nivolumab is a novel monoclonal human antibody used to potentiate T cell responses, particularly anti-tumor responses. The first diagnosis considered was lichen planus, and it has been excluded from this study based on histological results. Right from lesion onset after treatment initiation, nivolumab was strongly suspected to cause these mucocutaneous lesions. To investigate the causes and effects of nivolumab-induced oral and cutaneous bullous pemphigoid, it would be necessary to record the regression of these lesions at the end of treatment; however, this is not possible due to ethical reasons. The treatment of lesions primarily involves corticosteroid usage; however, rituximab is also used. **Conclusion:** Oral surgeons must consider the oral side effects of novel targeted therapies, including those of immunological checkpoint inhibitors.

A 64-year-old male with a history of nivolumab-treated melanoma presented with palatal and gingival mucosal lesions. His medical history indicated high blood pressure levels, childhood asthma, herpes labialis, and ocular migraines. He also had a history of long-term treatment with trandolapril.

The patient had acral lentiginous melanoma in the right ungual region (T4N2M0). The lesion was surgically treated by amputating the fifth finger with a negative sentinel node in October 2013. The lesion recurred in December 2015 and was unresectable with no distant metastasis. First-line therapy with ipilimumab was initiated in February 2016, and progression of cutaneous lesions was noted. Second-line therapy with nivolumab (one intravenous injection every 15 days) was prescribed in June 2016 due to which complete clinical skin lesion response was obtained.

In March 2017, the patient demonstrated recurrence of an inflammatory bullous lesion on his right forearm. Pathological analysis of the lesion matched the indications for bullous pemphigoid (continuous and intense deposition opposite to the dermoepidermal junction of IgG and C3). Anti-BPAG2 (or

anti-BP 180) antibodies at a level of 83 AU/mL were detected using enzyme-linked immunosorbent assay (ELISA), thereby confirming the diagnosis of bullous pemphigoid.

Secondary oral lesions appeared 3 months later. Examination of those lesions revealed a yellowish bullous and two large, well-defined bilateral post-bullous erosions with raised margins and flesh-colored background. These lesions were located within the erythematous mucosa at the posterolateral level of the hard palate (Fig. 1).

Gingival involvement manifested as marginal gingival erythema with a tendency to extend to adherent gingiva, which presented with a whitish border. The sign of the forceps was negative, characterized by the absence of epithelial detachment during mucosal traction using fine forceps. The lesions were painful, making it difficult to brush the teeth, thereby resulting in desquamative gingivitis combined with biofilm-induced gingivitis marked by the presence of inflammatory papillae and plaque (Fig. 2).

A novel assay for anti-BPAG2 antibodies was performed. The results of this assay were again positive, and doubling of the level (161 AU/mL) between the two serum samples at 1 month intervals was noted. Pathological analysis of a palatal mucosa specimen revealed a subepidermal bulla with few eosinophils;

\* Corresponding author: [julie.sturque@gmail.com](mailto:julie.sturque@gmail.com)



**Fig. 1.** Bullous and erosive post-bullous palatal involvement.



**Fig. 2.** Erosive gingivitis and biofilm-induced gingivitis.

this result matched the indications for bullous pemphigoid. Direct immunofluorescence examination was not helpful owing to the lack of epithelium on the biopsied tissue fragment.

The clinical and paraclinical presentations helped confirm the diagnosis of bullous pemphigoid. Treatment with local corticosteroids (clobetasol) was initiated, and partial response was observed.

Nivolumab is a human immunoglobulin G4 monoclonal antibody that potentiates T cell responses, including anti-tumor responses. It binds to programmed death-1 (PD-1) receptor, a negative regulator of T cell activity [1]. It is the most specific checkpoint-inhibitor immunotherapy among all PD-1 inhibitors and is followed by pembrolizumab. Immune-related side effects of anti-PD-1 have already been described, particularly at the cutaneous level. A literature review found that 39% of all patients taking anti-PD-1 presented with rash [1]. Bullous pemphigoid was a frequently reported skin lesion; however, reportedly, only three cases had both oral and cutaneous bullous pemphigoid [1]. Of note, the oral side effects of nivolumab can also manifest as lichen planus [1].

Lichen planus, the primary oral manifestation of checkpoint-inhibitor immunotherapy, was the first differential diagnosis to be considered before bullous pemphigoid [2] and could be eliminated through biopsy. Other differential diagnoses included pemphigus vulgaris, paraneoplastic pem-

phigus, bullous lupus erythematosus, and pemphigoid lichen planus. In our patient, clinical, biological, and histological evidence led to the diagnosis of oral and cutaneous bullous pemphigoid.

Based on the currently available knowledge, right from lesion onset after treatment initiation, nivolumab was strongly suspected to cause these lesions. Also, to confirm the imputability of nivolumab, it would be interesting to evaluate lesion evolution upon withdrawal and recommencement of nivolumab from a scientific point of view. In contrast, this diagnostic approach is ethically questionable in this context.

No therapeutic consensus has been defined for autoimmune bullous diseases induced by checkpoint inhibitors, and corticosteroids are frequently prescribed for these conditions [1]. Treatment with rituximab (anti-CD 20) is reportedly effective for corticosteroid-resistant bullous pemphigoid [3].

In conclusion, the present case indicates that oral surgeons must consider the oral side effects of novel targeted therapies, including those of immunological checkpoint inhibitors.

## References

1. Curry JL, Tetzlaff MT, Nagarajan P, Drucker C, Diab A, Hymes SR, *et al.* Diverse types of dermatologic toxicities from immune checkpoint blockade therapy. *J Cutan Pathol* 2017;44:158–176.
2. Sibaud V, Eid C, Belum VR, Combemale P, Barres B, Lamant L, *et al.* Oral lichenoid reactions associated with anti-PD-1/PD-L1 therapies: clinicopathological findings. *J Eur Acad Dermatol Venereol* 2017;31:464–469.
3. Sowerby L, Dewan AK, Granter S, Gandhi L, LeBoeuf NR. Rituximab treatment of nivolumab-induced bullous pemphigoid. *JAMA Dermatol.* 2017;153:603–605.