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Letter to the Editor

Nivolumab-related mucous membrane pemphigoid

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To the Editor,

Dermatologic immune-related adverse events (IRaes) are among the most frequent toxicities reported with anti–programmed cell death (PD)-1 or anti–programmed cell death ligand (PD-L1) therapies, affecting up to 40% of treated patients [1,2]. They have been associated with a variety of dermatologic manifestations including eczema-like rash, pruritus, lichenoid reactions, induction or reactivation of preexisting psoriasis, vitiligo and granulomatous reactions [3]. They may also induce or reactivate autoimmune skin diseases [4]. The risk of developing autoimmune blistering disorders with immune checkpoint inhibitors is well established, with approximately 1% of treated patients being affected [5]. Most reported cases are bullous pemphigoid [5–7], but reports of mucous membrane pemphigoid (MMP) in association with pembrolizumab are now emerging [8–10] (Table 1).

Very recently, one of our patients developed a very typical MMP while receiving nivolumab, an immune-related toxicity not reported to date with this anti–PD-1 agent. This strongly suggests that the induction of this adverse event clearly corresponds to a class effect and that it belongs to the wide range of dermatologic IRaes that may occur with monoclonal antibodies targeting PD-1 or its ligand [3].

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Table 1
Characteristics of reported patients developing mucous membrane pemphigoid with anti−PD-1 therapies.

Case No./sex/ age (years)	Underlying malignancies	Anti−PD-1	Time to onset	Oral mucosal lesions	Extra-oral lesions	Perilesional DIF	Standard IIF	Salt-split skin IIF	ELISA	Management	MMP outcome
1/M/62 (10)	Merkel cell carcinoma	Pembrolizumab	13 weeks	Oral erosions, blisters and aphthous ulcers on the tongue and buccal mucosa	None	Linear deposits of C3 along the DEJ	Not done	Circulating IgG and IgA binding the roof of the blister	Positive anti −BP180 NC16A	Pembrolizumab discontinuation Topical steroids and doxycycline	Healing after 6 weeks
2/F/83 (9)	Malignant melanoma	Pembrolizumab	6 months after pembrolizumab discontinuation	Painful gingivitis with blisters, pseudomembrane-covered erosion	None	Linear deposits of IgG and C3 along the DEJ	Negative	Negative	Negative	Pembrolizumab already discontinued Topical steroids and doxycycline	Healing after 6 weeks
3/F/47 (8)	Ovarian clear cell adenocarcinoma	Pembrolizumab	6 weeks	Multiple ulcerative lesions covering oral mucosa (including gingiva)	Fibrosis of the upper respiratory tract Laryngeal stenosis	Linear deposits of IgG along the DEJ	Not done	Circulating IgG binding the roof of the cleavage	Negative	Pembrolizumab discontinuation Rituximab intravenous immunoglobulin therapy Prednisone	Initial improvement with scarring process Death (due to sepsis)
Present case/ F/70	Malignant melanoma	Nivolumab	12 weeks	Painful desquamative gingivitis	None	Linear deposits of IgG, IgA and C3 along the DEJ	Negative	Negative	Positive anti −BP180 NC16A[a]	Nivolumab Continuation Topical steroids	Stable disease

DIF: direct immunofluorescence; DEJ: dermoepidermal junction; IIF: indirect immunofluorescence; ELISA: enzyme-linked immunosorbent microscopy; MMP: mucous membrane pemphigoid.
[a] No detection at treatment initiation.

1. Case report

A patient in her 60s was referred to the oral medicine department for a mildly painful desquamative gingivitis. She did not report any dermatological history. She was managed for a stage IV BRAF wild-type melanoma with multiple skin metastases (T3 N0 M1a). Five months before presentation, she had begun treatment with nivolumab as a single agent, with a flat dosing schedule (480 mg every 4 weeks). Two months after treatment initiation, she developed grade II stomatitis with the progressive onset of ulcerative lesions on the mandibular and maxillary gingivae. The non-keratinised mucosae were spared (buccal mucosa, soft palate, ventral aspect of the mouth, labial mucosa), as was the dorsal aspect of the tongue and the hard palate. Oral examination revealed erythematous patches on the gingiva (Fig. 1a) that progressed to desquamation with the formation of a pseudomembrane, erosions and oral ulcers. No other cutaneous or mucosal sites such as the conjunctiva or genital/nasopharyngeal mucosae were involved. A mucosal punch biopsy for routine histology revealed a subepidermal cleft with a mixed inflammatory infiltrate composed predominately of lymphocytes and plasmocytes (Fig. 1b). No intraepidermal cleft formation or acantholysis was noted. A perilesional biopsy performed for direct immunofluorescence microscopic analysis showed the intense linear deposition of IgG, IgA and complement along the epithelial basement membrane zone (Fig. 1c and d). Standard indirect immunofluorescence microscopy on monkey oesophagus did not detect any circulating anti-basement membrane zone antibodies. Conversely, enzyme-linked immunosorbent assay (ELISA) revealed isolated circulating antibodies targeting bullous pemphigoid antigen 2, with an anti–BP180 NC16A (IgG) antibody titre >40 U mL^{-1}. Circulating antibodies to desmoglein 1/3, collagen VII and BP 230 were negative. The patient tested negative for antinuclear antibodies and anti–extractable nuclear antigen. Absolute blood eosinophil count was within normal limits. Of note, ELISA testing was negative for BP180 just before nivolumab initiation (upper limit of normal <20 U mL^{-1}). Symptomatic management was started with very-high-potency topical corticosteroids (0.05% clobetasol propionate cream, twice a day). After one month of therapy, the oral lesions were similar, and anti–PD-1 therapy was continued with the same regimen. Over the next three months, the mucosal condition did not worsen with a prolonged course of topical corticosteroid therapy. Skin metastases remained stable.

2. Discussion

MMP consists of a heterogeneous group of rare subepithelial autoimmune blistering diseases thought to result from the linear binding of IgG/IgA or

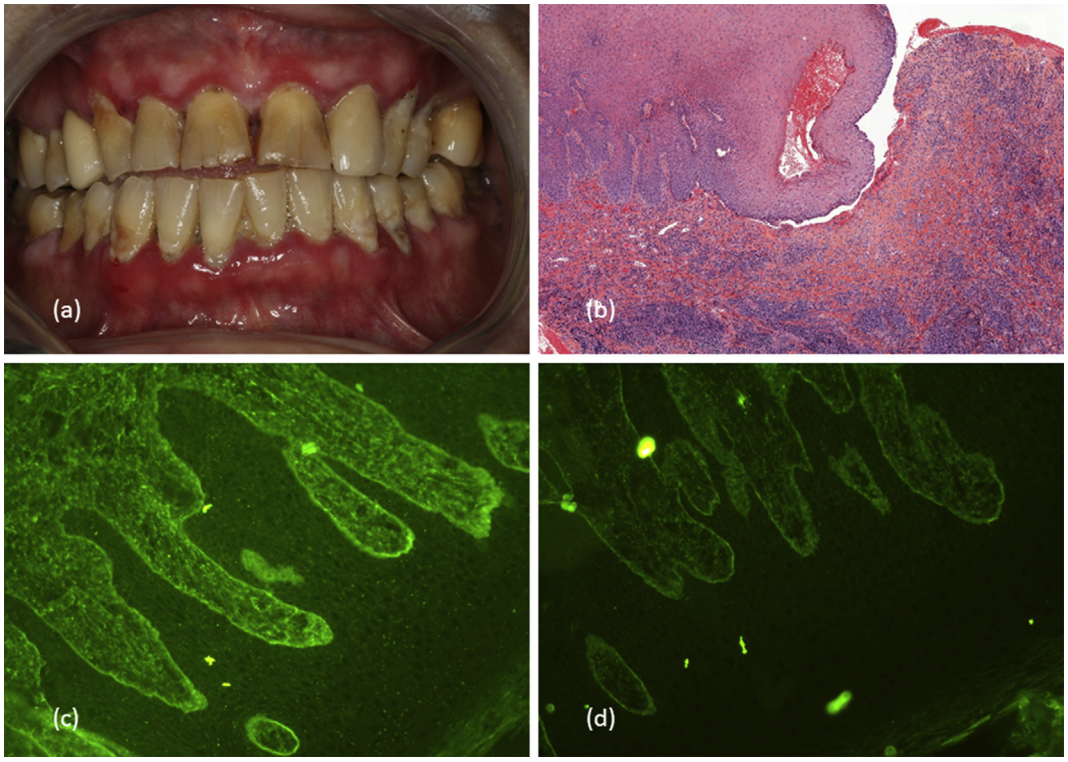

Fig. 1. (a–d): a, diffuse desquamative gingivitis; b, subepithelial cleavage with mixed inflammatory infiltrate (haematoxylin and eosin staining); c and d, direct immunofluorescence demonstrating linear deposition of IgG (c) and IgA (d) along the basement membrane zone.

complement along the basement membrane zone [11,12]. It has been previously demonstrated that B cells and T cells, especially Tregs, play a critical role in its pathogenesis. However, the exact pathophysiology of anti–PD-1–related MMP remains to be elucidated. Although IRaes are assumed to be largely T cell–mediated, PD-1 blockade therapy might also modulate humoral immunity in some cases and may stimulate the overproduction of specific autoantibodies [13]. The occurrence only after nivolumab/pembrolizumab initiation of circulating autoantibodies targeting the hemidesmosomal protein BP180, which is the most frequently targeted antigen in bullous pemphigoid or MMP, has not been described until now in treated patients who developed such autoimmune blistering disorders [5–10]. In our case, ELISA testing was negative at baseline and elevated serum BP180 autoantibodies were detected only after nivolumab initiation. This finding strongly suggests that the therapeutic inhibition of the PD-1 pathway may also trigger B-cell activation in addition to promoting autoreactive T-cell proliferation and to restricting Treg activity.

The oral mucosa is the most frequently involved site in MMP, and as with our patient, the gingiva may be the only site of disease activity [11,12]. Unlike previously published cases [8–10], immunotherapy was not discontinued in our patient, yet there was no subsequent worsening. She had a very typical BP180-positive MMP with exclusive gingival involvement, which is the most common presentation [11,12]. Although MMP may be associated with significant morbidity and severe complications such as tissue destruction, fibrosis and loss of function (e.g. laryngeal stenosis, ocular scarring with trichiasis and symblepharon), disease limited to the oral mucosa is classified at low risk and has a favourable prognosis and a better response to treatment [11,12]. Therefore, we suggest that discontinuation of potentially life-saving anti–PD-1 therapy should not be systematic if an MMP develops and should be discussed case by case on a multidisciplinary basis.

As previously described, oral lichenoid lesions combining ulcerations and reticular streaks represent the most frequent oral mucosal toxicities observed with immune checkpoint monoclonal antibodies [14,15]. Clinicians should be aware, however, that the diagnosis of autoimmune bullous disorders (MMP or more exceptionally lichen planus pemphigoides and linear IgA bullous dermatosis) should be considered in all patients treated with immune checkpoint inhibitors [5,8,9,16] who have recalcitrant oral erosions, blistering or long-lasting desquamative gingivitis. Moreover, gingival MMP may be initially indistinguishable from a gingival lichenoid reaction or from gingivitis due to inadequate oral hygiene practices [12]. Consequently, a mucosal biopsy with direct immunofluorescence should be performed systematically in patients developing chronic gingivitis or recurrent oral mucosa ulcerations under anti–PD-1/anti–PD-L1 therapies. Early detection of MMP may be critical for the prompt management of this life-threatening or scarring blistering disease.

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Conflict of interest statement

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