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Oral Lichenoid Reactions associated with anti-PD-1/PD-L1 therapies: clinicopathological findings

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Immune checkpoint inhibitors targeting the programmed cell death receptor-1 (PD-1) or its ligand (PD-L1) show broad activity across different tumor types and currently represent one of the keystones of cancer management. Dermatologic toxicities are one of the most frequent immune-related adverse events (irAEs) induced by these new monoclonal antibodies. Maculopapular rash, pruritus, exacerbation of psoriasis or more specific autoimmune disorders (*e.g.* vitiligo, alopecia areata, and bullous pemphigoid) are amongst the most commonly reported AEs.^{1–4} In addition, cutaneous lichenoid reaction has also emerged as one of the most prevalent dermatological toxicities in treated patients.^{4–7} In contrast, sparing of oral mucous membranes is often reported and oral lichenoid reactions (OLR) have only been anecdotally described.^{4–8} Herein, we describe the clinicopathological features of 10 new cases in Table 1. To our knowledge, this is the largest series of patients developing OLRs with immune checkpoint antibodies reported to date.

All patients were treated for advanced cancers, with either pembrolizumab/nivolumab (anti-PD-1, 7 patients) or atezolizumab (anti-PD-L1, 3 patients) therapy. The number of cycles received before OLR diagnosis varied between 2 and 23 cycles. Physical examination mainly revealed symmetric reticulated white streaks consistent with Wickham's striae on the buccal mucosa, tongue, palate, and mucosae of the inner lips/gingiva. Papular, plaque-like, ulcerative or atrophic/erythematous lesions were also observed in some patients (Figs.1, 2). In some cases, these different presentations occurred concurrently. The lesions were generally self-limiting and of low-grade (grade 1, CTCAE V4.0). Three patients, however, experienced tenderness and/or irritation, and associated xerostomia was present in 3 patients. Finally, oral lesions were accompanied by skin, nail or genital lichenoid lesions in only 4 patients. Histopathology findings (n=4) showed patchy-to-florid lichenoid interface dermatitis in the upper lamina propria, with variable degrees of basal vacuolar changes and apoptosis. Of note, and as previously reported in patients developing cutaneous lichenoid reactions with anti-PD-1,⁸ more atypical features such as hypergranulosis and marked parakeratosis were also observed. Ancillary immunostaining demonstrated that the band-like T-cell infiltrate was predominantly CD4/CD8-positive (1:1).

The OLRs did not lead to discontinuation or interruption in oncologic treatment, and in most cases, they improved after several weeks of topical corticosteroid treatment (clobetasol ointment or cream, dexamethasone/prednisolone mouthwash) (Fig.2a,b). Finally, we noted a complete disappearance of the lesions in 2 patients (Fig.2c,d) after treatment discontinuation for tumor progression.

Although reporting of immune checkpoint inhibitor-induced OLR is sparse in literature,⁴⁻⁸ in our clinical practice, these reactions are not uncommon. As OLRs are usually asymptomatic, they may remain undiagnosed. As in previous reports we observed OLRs with both anti-PD-1 and anti-PD-L1 therapy, strongly suggesting a class-effect. Although the pathogenesis remains unknown, we speculate that PD-1/PD-L1 pathway inhibition induces a nonspecific T-cell-mediated autoimmune response that triggers epithelial cell apoptosis and alterations of the basement membrane zone in susceptible individuals. Recent studies have shown that blockade of the PD-1 pathway significantly increases the proliferation of peripheral blood T-lymphocytes in patients suffering from oral lichen planus (OLP), suggesting that PD-1 likely plays a pivotal role in negatively modulating self-reactive T-cell-mediated immune responses in OLP patients.⁹

In conclusion, clinicians should be aware of OLRs occurring in association with anti-PD-1/PD-L1 therapy. This immune-mediated oral toxicity should be added to the wide range of potential dermatologic irAEs observed with these drugs. Regular oral examinations should be offered to treated patients.¹⁰ Finally, a lesional biopsy should be recommended for any persistent or atypical lesions.

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Figure 1.

Reticular streaks consistent with Wickham's striae, involving the buccal mucosa and the palate (fig. 1a–c); lichenoid interface dermatitis (H and E, $\times 40$, fig. 1d) with a mixed CD4+ (fig. 1e)/CD8+ (fig. 1f) T-cell infiltrate.

Figure 2. significant improvement of oral lichenoid lesions after 3-week therapy with topical dexamethasone solution to “switch and spit” (fig. 2 a,b), and after 2 months of nivolumab discontinuation (fig.2 c,d).

and histopathological features of Oral Lichenoid Reactions in patients treated with Anti PD-1/PD-L1 therapy. BMZ, basement membrane zone.

Table 1

Age	Type of malignancy	Immune checkpoint inhibitor	# of Cycles received before diagnosis	Clinical description	Clinical grading (NCI-CTCAE, V4)	Other dermatological lesions	Histopathological aspects	Treatment	Clinical outcome
53	Multiple myeloma	nivolumab	2	-Asymptomatic -Numerous discrete whitish raised papules and reticular streaks (lips, tongue, buccal mucosa)	1	Yes <i>Cutaneous lichenoid eruption, with genital involvement</i>		Dexamethasone mouthwash	Resolved after several weeks
52	Renal cell carcinoma	nivolumab	23	-Symptomatic -Reticular white streaks (buccal mucosa) -Swollen tongue with white plaque-like lesions -xerostomia	1	No	Mucosa <i>Band-like lymphocytic infiltrate in the upper lamina propria; partial disruption of the BMZ; hypergranulosis and parakeratosis</i>	None	Spontaneous resolution after nivolumab discontinuation (for tumor progression)
42	Glioblastoma multiforme	nivolumab	2	-Asymptomatic -Numerous pinkish white coalescing papules (lips, dorsal surface of the tongue and buccal mucosa)	1	No		Topical corticosteroids and anti-fungal lozenges	Unknown
40	Extranodal marginal zone lymphoma of the lung	nivolumab	6	-Symptomatic (erythema and bleeding of the gums) -Reticular white streaks (buccal and labial mucosa, gingiva, floor of the mouth, soft palate and tongue) -Erythema/atrophy (ventral surface of the tongue)	2	Yes <i>Cutaneous lichenoid eruption</i>	Skin <i>Lichenoid interface dermatitis</i>	Topical and oral corticosteroids (given simultaneously for immune-related pneumonitis)	Resolved after several weeks
41	Breast cancer	pembrolizumab	10	-Asymptomatic -White plaque-like lesions (dorsal surface of the tongue)	1	No	Mucosa <i>Moderate band-like lymphocytic infiltrate in the upper lamina propria; partial disruption of the BMZ; hypergranulosis and parakeratosis</i>	None	Unknown

/Age	Type of malignancy	Immune checkpoint inhibitor	# of Cycles received before diagnosis	Clinical description	Clinical grading (NCI-CTCAE, V4)	Other dermatological lesions	Histopathological aspects	Treatment	Clinical outcome
53	Lung carcinoma	nivolumab	3	-Asymptomatic -Reticular white streaks (buccal mucosa and soft palate)	1	Yes <i>Nonspecific maculopapular rash</i>		None	Unknown
56	Renal cell carcinoma	atezolizumab	11	-Asymptomatic -White plaque-like lesions (dorsal aspect of the tongue) -Reticular white streaks (hard palate)	1	Yes <i>Cutaneous lichenoid reaction, with nail involvement</i>	Mucosa and skin <i>Dense band-like lymphohistiocytic infiltrate in the upper lamina propria and superficial dermis; disruption of the BMZ; hypergranulosis and parakeratosis</i>	Topical corticosteroids	Resolution after atezolizumab discontinuation (for tumor progression)
56	Adenocarcinoma of the esophagus	atezolizumab	14	-Asymptomatic -Reticular white streaks (buccal mucosa) -Xerostomia	1	No	Mucosa <i>Very mild band-like lymphocytic infiltrate in the upper lamina propria; hypergranulosis and parakeratosis</i>	None	unknown
54	Renal cell carcinoma	atezolizumab	5	-Symptomatic (sensitive and swollen tongue) -White superficial ulcers (floor of the mouth) -xerostomia	1	No		Topical corticosteroids	Resolved eventually
58	Lung carcinoma	pembrolizumab	12	-Asymptomatic -Reticular white streaks (buccal mucosa)	1	Yes <i>Diffuse cutaneous lichenoid eruption, with genital involvement</i>		Topical corticosteroids	resolved eventually