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ORIGINAL ARTICLE

Orofacial complications from immune checkpoint inhibitors: A retrospective analysis from two academic medical centers

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Abstract

Background: Immune checkpoint inhibitors (ICIs) are FDA-approved for various cancers, yet their orofacial immune-related adverse events (irAEs) remain poorly understood. Our two-center retrospective study aims to better understand the prevalence and nature of these orofacial irAEs.

Methods: We retrospectively collected demographics, ICI details, and onset of orofacial irAEs in ICI-treated patients at University of California San Francisco and City of Hope (2013–2021). Orofacial irAEs were identified by ICD-10 codes and data categorized as dry mouth/xerostomia, oral mucosal lesions, and orofacial neuropathies. Patients with pre-existing orofacial conditions resembling the reported irAEs were excluded.

Results: Among 3768 ICI-treated patients, 408 (10.8%) developed 467 orofacial irAEs: oral mucosal diseases (41.4%), dry mouth/xerostomia (41.0%), and orofacial neuropathies (17.6%). Notably, head and neck cancers had the highest incidence of orofacial irAEs.

Conclusions: Orofacial irAEs are relatively common in patients receiving ICIs, necessitating careful monitoring and management of these complications during and after the treatment.

KEYWORDS

cancer treatment side effects, dry mouth, immune checkpoint inhibitors, immune-related adverse events, oral mucosal diseases

1 | INTRODUCTION

Immune checkpoint inhibitors (ICIs) such as antibodies against programed cell death 1 (PD-1), programmed cell death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte antigen 4 (CTLA-4) represent a major breakthrough in cancer treatment.[1] The ability of cytotoxic CD8+ T cells to recognize tumor antigens and attack tumor cells is regulated by co-stimulatory and co-inhibitory signals.[2] ICIs block these co-inhibitory signal pathways and restore the function of cytotoxic CD8+ T cells and subsequent improvement of survival.[3–5]

ICIs are currently approved by the US Food and Drug Administration for the treatment of over 15 malignancies including metastatic head and neck squamous cell carcinoma.[6] This is resulting in increasing use of ICIs in oncology care as a monotherapy or combined with conventional chemo-/radiation therapy.[7]

One of the consequences of ICIs therapy is the reduction of the immune tolerance state which facilitates

antitumor cytotoxic CD8+ T cells to attack normal cells expressing self-antigens that cross-react with tumor antigens, and so it can induce immune-related adverse events (irAEs) with symptoms affecting almost every organ system including the oral cavity.[8–10] Some reported oral irAEs include oral mucositis, characterized by inflammatory changes and ulcerations in the oral mucosa leading to pain and discomfort and oral neuropathies, presenting as neurologically mediated symptoms like altered taste sensation.[10] In one analysis, cranial neuropathies accounted for 7% of the observed irAEs.[11] Other oral irAEs include oral lichenoid lesions, manifesting as white striations or erythema, or oral lichen planus like lesions[12]; and reduced salivary flow or subjective feeling of dry mouth (xerostomia).[6]

The characterization of oral irAEs has been primarily based on case descriptions or clinical trial reports and only one retrospective single-center study.[10] As such, this multi-center study aimed to assess the prevalence and characterize of orofacial irAEs including orofacial neuropathies in two large academic medical centers.

2 | METHODS

We conducted a retrospective study using the PatientExplorer software to identify patients with cancer who received ICIs at the University of California San Francisco (UCSF) between June 2013 and June 2021. PatientExplorer serves as a dynamic visualization dashboard that allows users to query and extract data from EHRs, providing features such as interactive timeline visualizations, multi-domain linked graphs, and the ability to visualize longitudinal patient data, both categorical and numeric.[13]

We also recorded information of patients receiving ICIs from electronic medical records at City of Hope Comprehensive Cancer Center (COHCCC) from January 2018 to December 2021. This study was reviewed by Institutional Review Board of the COHCCC (IRB # 22751). Patients at UCSF and COHCCC were identified using keywords corresponding to the generic names of the FDA approved ICIs: pembrolizumab, nivolumab, ipilimumab, atezolizumab, durvalumab, avelumab, cemiplimab, and dostarlimab. IrAEs at both study sites were recorded through keywords reported in the patients' chart as previously reported by Xu et al., and by using the International Classification of Diseases (ICD)-10 codes (Table A1 in Appendix).[10] Oral irAEs were then classified into three categories for the purpose of analysis and reporting: (1) dry mouth/xerostomia (ICD-10: K11.7 and ICD-10: R68.2); (2) oral mucosal lesions: within this category, irAEs encompassed a range of conditions, namely oral mucositis (ICD-10: K12.30), oral stomatitis (ICD-10: K12.1), mouth sores (ICD-10: K12.3), lichenoid drug reactions (ICD-10: L27.0), oral lichen planus (ICD-10: L43.9), and erythema multiforme (ICD-10: L51.9); and (3) orofacial neuropathies included the following conditions: facial numbness (ICD-10: R20.0), unspecified facial numbness (ICD-10: R20.81), facial tingling (ICD-10: R20.2), dysgeusia (ICD-10: R43.9), and glossodynia (ICD-10: K14.6, T28.0).

Data collected included age at the start of ICI therapy, sex at birth, primary cancer diagnosis, type of ICIs (at least one dose), duration of ICIs therapy and the time to onset of orofacial irAEs (in days). Patients with a pre-existing orofacial condition similar to the reported oral irAE before ICI initiation, as well as those who received concurrent chemotherapy and/or radiation therapy to the head and neck, were excluded.

2.1 | Statistical analysis

Descriptive statistics were used to analyze the data, with JMP Pro 17 (SAS Institute Inc., Cary, NC). The Pearson test was used to calculate differences in the age and sex of patients who developed irAEs. The Wilcoxon signed-rank test was applied for nonparametric paired variables. p-values were considered significant at $p < 0.05$.

3 | RESULTS

3.1 | Cohort characteristics

We included 3768 patients who received ICI (1571 females [41.7%]) with a median age of 69 years (range 23–92) (Table 1). The most common cancer diagnoses were lung cancer ($N = 869$; 23.1%) and breast cancer ($N = 664$; 17.6%). Head and neck cancer accounted for 307 patients (8.1%), followed by prostate cancer ($N = 293$; 7.8%). Other cancer types included malignancies of the cecum, colon, and rectum ($N = 240$; 6.4%), hematologic cancers ($N = 235$; 6.3%), cancers of female genital organs ($N = 142$; 3.8%), bladder ($N = 102$; 2.7%), thyroid ($N = 88$; 2.3%), renal cancer ($N = 79$; 2.1%), liver and gallbladder cancer ($N = 67$; 1.8%), brain cancer ($N = 65$; 1.7%), esophagus and stomach cancers ($N = 47$; 1.2%), neuroendocrine tumors ($N = 33$; 0.9%), and pancreatic cancer ($N = 23$; 0.6%).

3.2 | Orofacial irAEs by age, sex at birth and median time to onset

Out of the 3768 patients, 408 (10.8%) experienced 476 orofacial irAEs. The most frequently reported irAEs were oral mucosal lesions ($N = 197/476$; 41.4%), followed by

dry mouth/xerostomia ($N = 195/476$; 41.0%), and orofacial neuropathies ($N = 84/476$; 17.6%).

The median age of the patients was 68 years (range: 23–91) for those with dry mouth/xerostomia, 69 years (range: 25–92) for those with oral mucosal lesions, 63 years (range: 40–91) for those with orofacial neuropathies, and 69 years (range: 27–92) for the overall cohort.

Female patients exhibited a greater number of irAEs ($N = 252/476$; 53.0%) of the observed IrAEs compared to males ($N = 224/476$; 47.0%). The distribution of females and males in various irAEs categories is detailed in Table 2.

The time to onset for these orofacial irAEs varied with oral mucosal lesions occurring at 105 days (range: 1–1772), dry mouth/xerostomia at 99 days (range: 2–1793), orofacial neuropathies at 189 days (range: 28–1096), and an overall median time to onset of 101 days (range: 1–1793) for all orofacial irAEs (Table 2).

TABLE 1 Patient characteristics.

	***N* (%) (total: 3768)**
Age in years (median; range)	69 (23–92)
Female	1571 (41.7)
Male	2197 (58.3)
Cancer diagnosis	
Lung	869 (23.1)
Breast	664 (17.6)
Head and neck	307 (8.1)
Prostate	293 (7.8)
Skin	245 (6.5)
Cecum, colon, and rectum	240 (6.4)
Hematologic cancers	235 (6.3)
Female genital organs	142 (3.8)
Bladder	102 (2.7)
Thyroid	88 (2.3)
Renal	79 (2.1)
Liver and gallbladder	67 (1.8)
Brain	65 (1.7)
Esophagus and stomach	47 (1.2)
Neuroendocrine tumors	33 (0.9)
Pancreas	23 (0.6)
Other	269 (7.1)

3.3 | Orofacial irAEs by type ICIs

In our study, 3768 patients received eight different ICIs. Pembrolizumab was the most frequently administered ICI ($N = 2265/3768$; 60.13%), followed by nivolumab ($N = 1105/3768$; 29.35%), and ipilimumab ($N = 664/3768$; 17.64%) (for a comprehensive list, please refer to Table 3).

Patients on cemiplimab exhibited the highest incidence of any orofacial irAEs ($N = 23/77$; 29.9%), followed by dostarlimab ($N = 1/8$; 12.5%), pembrolizumab ($N = 279/2265$; 12.3%), and nivolumab ($N = 130/1105$; 11.8%). In contrast, ipilimumab had the lowest incidence at 1.2% ($N = 8/664$).

Patients receiving cemiplimab ($N = 5/77$; 6.5%) had the highest incidence of oral mucosal lesions ($N = 5/77$; 6.5%) followed by pembrolizumab ($N = 122/2265$; 5.4%) and nivolumab ($N = 51/1105$; 4.6%).

Dry mouth/xerostomia was observed in 12.5% patients on dostarlimab at ($N = 1/8$), followed by cemiplimab ($N = 9/77$; 11.7%), nivolumab ($N = 55/1105$; 5.1%), pembrolizumab ($N = 110/2265$; 4.9%), and ipilimumab ($N = 4/664$; 0.6%).

In the orofacial neuropathies category, cemiplimab exhibited the highest incidence at 11.7% ($N = 9/77$), followed by pembrolizumab ($N = 47/2265$; 2.1%) and nivolumab ($N = 24/1105$; 2.2%) (for a comprehensive list, please refer to Table 3).

TABLE 2 Orofacial immune related adverse events by age, sex at birth, and time to onset.

	Dry mouth/xerostomia, *N* (%)	**Oral mucosa lesions, *N* (%)**	**Orofacial neuropathies, *N* (%)**	**Any orofacial irAEs**
Median age (years; range)[a]	68 (23–91)	69 (25–92)	63 (40–91)	69 (27–92)
Sex at birth[b]				
Male	98 (50.3)	97 (49.2)	29 (34.5)	224 (47.0)
Female	97 (49.7)	100 (50.8)	55 (65.5)	252 (53.0)
Median (days; range)	99 (2–1793)	105 (1–1772)	189 (28–1096)	101 (1–1793)

Abbreviation: ir-AE, immune-therapy adverse events.
[a]p for trend = 0.78.
[b]p for trend = 0.73.

TABLE 3 Orofacial immune-related adverse events by immune checkpoint inhibitor (ICI).

Immune checkpoint inhibitors	Dry mouth/ xerostomia, *N* (%)	Oral mucosa lesions, *N* (%)	Orofacial neuropathies, *N* (%)	Any orofacial irAEs, *N* (%)	Treatment duration, median (days; range)
Cemiplimab ($n = 77$)	9 (11.7)	5 (6.5)	9 (11.7)	23 (29.9)	70 (1–364)
Dostarlimab ($n = 8$)	1 (12.5)	0 (0.0)	0 (0.0)	1 (12.5)	1 (1)
Pembrolizumab ($n = 2265$)	110 (4.9)	122 (5.4)	47 (2.1)	279 (12.3)	184 (1–1562)
Nivolumab ($n = 1105$)	55 (5.1)	51 (4.6)	24 (2.2)	130 (11.8)	159 (1–2139)
Durvalumab ($n = 148$)	9 (6.1)	6 (4.1)	2 (1.4)	17 (11.5)	231 (13–549)
Avelumab ($n = 22$)	1 (4.6)	1 (4.6)	0 (0.0)	2 (9.1)	43 (43)
Atezolizumab ($n = 244$)	6 (2.5)	8 (3.3)	2 (0.8)	16 (6.6)	106 (1–352)
Ipilimumab ($n = 664$)	4 (0.6)	4 (0.6)	0 (0.0)	8 (1.2)	63 (1–2376)
Total[a] ($n = 4533$)	195 (41.0)	197 (41.4)	84 (17.16)	476 (100.0)	101 (1–1793)

Abbreviation: ir-AE, immune-therapy adverse events.

[a]The total numbers for (*n*) add up to more than the total number of patients 3768 or 100% because some patients received multiple agents at different time points during their treatment.

3.4 | Orofacial irAEs by type of cancer

The cancer type with the highest incidence of any orofacial irAEs was observed in the category of head and neck cancers ($N = 117/476$; 24.6%). Among patients with head and neck cancer, dry mouth/xerostomia was the highest reported irAEs in this category ($n = 59/476$; 12.4%), followed by oral mucosa lesions ($n = 36/476$; 7.6%) and orofacial neuropathies ($n = 22$; 4.6%). Breast cancer displayed the second highest orofacial irAEs incidence ($n = 76/476$; 16%). Among patients with breast cancer, oral mucosa lesions were the highest recorded irAEs ($n = 44/476$; 9.2%) followed by dry mouth/xerostomia (17/476; 3.6%) and orofacial neuropathies (15/476; 3.2%). Skin cancer ranked third highest orofacial irAE rates ($n = 69/476$; 14.5%). Among patients with skin cancer, oral mucosa lesions were the highest recorded irAEs ($n = 30/476$; 6.3%) followed by dry mouth/xerostomia ($n = 26/476$; 5.5%) and orofacial neuropathies ($n = 13/476$; 2.7%) (for a comprehensive list, please refer to Table 4).

No statistically significant differences were found among patients who developed oral irAEs when considering age, sex, and cancer diagnosis.

4 | DISCUSSION

Immune checkpoint inhibitors target programmed cell death-1 (PD-1), PD ligand-1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibodies show potent and durable antitumor effects, especially for patients with advanced cancer. However, these therapies disrupt immune tolerance, allowing CD8+ T cells to target healthy cells with self-antigens that cross-react with tumors, potentially causing irAEs.[14] The present study offers insights into the occurrence and characteristics of orofacial irAEs in a cohort of 3768 patients with cancer treated with different currently available ICIs. Approximately 11% of patients experienced orofacial irAEs. Oral mucosal lesions can present as extensive oral ulcers, oral lichen planus like lesions, mucous membrane pemphigoid/bullous pemphigoid, erythema multiforme, and Stevens–Johnson syndrome/toxic epidermal necrolysis.[12,15,16] Oral mucosal irAEs seem to be secondary to adaptive immunity activation. In particular, PD-1 inhibitors increase CD8+ T cells in tissues, while CTLA-4 inhibitors increase CD4+ T cells in lymph nodes. These events relate to expanded T-cell receptor diversity, early autoantibody detection during ICI therapy, and T- and B-cell clonality, contributing to irAE development.[14,17] In our study, oral mucosal irAEs were the most frequently observed orofacial irAEs, accounting for 41.4% of all irAEs reported in this study. Previous reports have suggested that roughly 8% of patients may develop oral mucosal toxicities caused by ICIs. These complications are frequently accompanied by irAEs affecting other tissues and organs.[10,17,18]

In our study, dry mouth/xerostomia was the second most common reported orofacial irAE accounting for 41.0% of all irAEs reported in this study. Dry mouth/xerostomia in ICI-treated patients may resemble Sjögren syndrome, primarily involves autoreactive T cells and T cell-mediated salivary gland inflammation.[19] Lip mucosa salivary gland biopsies in ICIs-treated patients showed increased CD3+ T cell infiltration and acinar damage, but limited CD20+ B cells and few patients have anti-

TABLE 4 Orofacial immune-related adverse events by cancer type.

Cancer type	Dry mouth/ xerostomia, *N* (%)	Oral mucosa lesions, *N* (%)	Orofacial neuropathies, *N* (%)	Any orofacial ir-AE, *N* (%)
Bladder ($N = 102$)	4 (0.8)	3 (0.6)	0 (0)	7 (1.5)
Brain ($N = 65$)	0 (0)	1 (0.2)	0 (0)	1 (0.2)
Breast ($N = 664$)	17 (3.6)	44 (9.2)	15 (3.2)	76 (16)
Cecum, colon, and rectum ($N = 240$)	6 (1.3)	7 (1.5)	0 (0)	13 (2.7)
Esophagus and stomach ($N = 47$)	3 (0.6)	5 (1.1)	0 (0)	8 (1.7)
Female genital organs ($N = 142$)	10 (2.1)	10 (2.1)	2 (0.4)	22 (4.6)
Head and neck ($N = 307$)	59 (12.4)	36 (7.6)	22 (4.6)	117 (24.6)
Liver and gallbladder ($N = 67$)	3 (0.6)	4 (0.8)	0 (0)	7 (1.5)
Lung ($N = 869$)	10 (2.1)	17 (3.6)	10 (2.1)	37 (7.8)
Neuroendocrine tumors ($N = 33$)	2 (0.4)	2 (0.4)	2 (0.4)	6 (1.3)
Other ($N = 269$)	52 (10.9)	35 (7.4)	20 (4.2)	107 (22.5)
Pancreas ($N = 23$)	1 (0.2)	1 (0.2)	0 (0)	2 (0.4)
Renal ($N = 79$)	2 (0.4)	2 (0.4)	0 (0)	4 (0.8)
Skin ($N = 245$)	26 (5.5)	30 (6.3)	13 (2.7)	69 (14.5)
Total	195 (41.0)	197 (41.4)	84 (17.16)	476 (100.0)

Abbreviation: ir-AE, immune-therapy adverse events.

Sjögren syndrome-related autoantibodies.[17] Previous study reported that approximately 5%–6% of patients develop dry mouth/xerostomia induced by ICIs.[10,20]

Neurologic irAEs appear to stem from damage to peripheral nerves through cell-mediated processes and antibody responses that specifically target elements like compact myelin, Schwann cells, or nodal antigens.[11,17,21] These responses are part of an abnormal immune reaction. Additionally, there is a potential mechanism involving the cross-reactivity between tumor antigens and similar components on healthy cells, which contributes to the development of neurologic toxicity linked to ICIs. Several studies have reported that neurologic irAEs occur in 1%–12% of patients undergoing ICI therapy, with cranial nerves being affected in approximately 7% of these cases.[11,17,21] Orofacial neuropathies were the less common irAEs, accounting for only 17.7% of all irAEs documented in this study. Our study found that the median time-to-onset for orofacial irAEs after ICI therapy was 101 days. This closely matches the previously reported data of 100 days post-ICI treatment, as published by Xu et al., indicating a consistent pattern in the timing of orofacial irAEs.[10] The onset of neurologic change appeared to develop later, after a mean of 189 days (range: 28–1096).

Our study highlighted the variability in the occurrence of irAEs incidents across the eight different ICIs included in this research. Specifically, we found that cemiplimab accounted for 29.9% of all irAEs reported in our study. Furthermore, our study revealed that ipilimumab exhibited the lowest incidence of irAEs, standing at 1.2%. This observation closely aligns with a previously reported incidence of 2.2%.[10]

Moreover, the examination of orofacial irAEs based on the type of cancer diagnosis unveiled variations in irAE rates across different cancer categories. Head and neck cancers displayed the highest incidence of any orofacial irAEs, accounting for 24.6% of all irAEs reported in this study. Within this group, dry mouth/xerostomia was the most frequently reported adverse event. The specific mechanisms underlying the development of irAEs in patients with head and neck cancer may involve the presence of tumor antigens in these areas, which can trigger immune responses and contribute to the observed higher incidence of orofacial irAEs in this patient group. Furthermore, this study found that breast cancer and skin cancer patients also showed notable high rates of orofacial irAEs, although the specific types of adverse events within these categories varied.

The management of irAEs depends on their severity grade. Alongside the National Cancer Institute Common Terminology Criteria for Adverse Events v5, other guidelines exist. For instance, the European Academy of Dermatology and Venereology task force has comprehensive recommendations for diagnosing and managing dermatological and mucosal irAEs, including evidence-based guidelines.[22,23] In addition, Klein et al. introduced a new grading system specific for orofacial irAEs.[15]

Treatment options for oral lesions is usually with topical and or systemic steroids with maintaining optimal oral hygiene practices. In severe orofacial mucosal irAEs, the consideration of suspending ICI therapy might be necessary. When managing dry mouth, remedies vary from moisturizers and sialagogues to possible discontinuation of ICI therapy, depending upon the severity of the condition.[15,17,22,23] Peripheral neuropathies follow a similar pattern, with interventions aligning with symptom severity as per the American Society of Clinical Oncology Clinical Practice Guideline.[24]

Our study had some limitations due to its heterogeneity and retrospective design, which relied on data from different providers and may result in variations in the collected data and the overall prevalence of orofacial irAEs. Additionally, as a retrospective study, the incidence of irAEs might be underestimated or overestimated if graded by clinicians with no oral medicine expertise. While all the orofacial irAEs reported in this study required medical attention, one of the limitations that we did not assess their severity or impact in patients' quality of life.

5 | CONCLUSION

In summary, our study described the orofacial irAEs in a large cohort of patients with cancer treated with eight ICIs. Overall, we found that 10.8% of patients experienced orofacial irAEs, although this varies with different ICIs. The orofacial irAEs included oral mucosal lesions, dry mouth/xerostomia, and orofacial neuropathies being the most common. Careful monitoring of patients receiving ICIs for orofacial complications is crucial during and after treatment. Early detection and management of these adverse events can improve outcomes and reduce long-term complications. Clinicians should remain vigilant in assessing for orofacial irAEs and use appropriate grading criteria to determine the best treatment plan.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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APPENDIX A

TABLE A1 Categories of orofacial adverse events.

Categories	
Oral mucosa lesions	Oral mucositis (ICD-10: K12.30), oral stomatitis (ICD-10: K12.1), mouth sores (ICD-10: K12.3), lichenoid drug reactions (ICD-10: L27.0), oral lichen planus (ICD-10: L43.9), erythema multiforme (ICD-10: L51.9)
Dry mouth	Dry mouth (ICD-10: R68.2), xerostomia (ICD-10: K11.7)
Orofacial neuropathies	Facial numbness (ICD-10: R20.0), unspecified facial numbness (ICD-10: R20.81), dysgeusia (ICD-10: R43.9), numbness and tingling of the face (ICD-10: R20.2), burning mouth sensation (ICD-10: K14.6, T28.0)

Abbreviation: ICD-10, International Classification of Diseases-10th revision.