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Communication

Oral Toxicities in Cancer Patients, Who Receive Immunotherapy: A Case Series of 24 Patients

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Abstract: The oral problems of 24 cancer patients on immunotherapy between 2017–2022 and referred by their oncologists, were reported. The age range was 49–80 years, and the median was 64 years. Lung cancer was the most common disease. Three patients a had history of autoimmune disease prior to cancer diagnosis. Patients received immunotherapy for two to 48 months. Prior to immunotherapy, 17 patients received cytotoxic chemotherapy, five angiogenesis inhibitors and one1 radiotherapy to head/neck. During immunotherapy, four patients received chemotherapy, one received bevacizumab, and eight received bone targeting agents, either alone or in combination. Presenting symptoms were oral pain (18 patients, 75%), dental pain (five patients), xerostomia (five patients), burning/itching (seven patients), bleeding (three patients), swelling (three patients), and taste problems (dysgeusia) (three patients). One patient was asymptomatic. Immune-related lesions were observed in 15 patients (62.50%), of which three were exacerbations of prior autoimmune disease. Three patients reported severe deterioration and itching after using a mouthwash. We also observed six (25%) infections (four candidiasis and two herpes simplex), and six (25.00%) cases of medication-related osteonecrosis of the jaw (MRONJ). Five of those MRONJ cases developed among the eight patients with the administration of bone targeting agents and one in a patient with bevacizumab. Two patients presented with more than one lesion. In conclusion, immune-related lesions were most common; oral infections and MRONJ were also observed. Various oral complications might be related to the interplay between immunotherapy and other therapies prior or concurrent to immunotherapy.

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1. Introduction

The use of immune checkpoint inhibitors to treat increasing types of cancers is a revolution in oncology. Immunotherapy blocks the T cell receptor-ligand relationships and restores and activates anti-tumor immunity. It prevents tumors from escaping T cell-mediated killing by inhibiting the biological pathways that would otherwise suppress T cell activation and proliferation [1–5]. This enhanced action against tumor cells may also affect healthy tissues, mounting an immune-related inflammatory reaction with variable clinical presentations. This toxicity in known as immune-related adverse events (irAEs), and differs from standard chemotherapy toxicities due to their immune-related pathogenic mechanism [1–9].

Some patients may already have a history of an autoimmune disease in the mouth or in other body systems. In that case, immunotherapy can exacerbate the prior autoimmune disease of the patient [10–12]. Others on immunotherapy may also receive other antineoplastic medications and may be at risk of complications and toxicities related to those other antineoplastic therapies. The synergistic effects, if any, between immunotherapy and other prior or concurrent anticancer therapies have not been studied. Immunotherapy and irAEs may adversely affect patients' quality of life [13].

Dermatologic and gastrointestinal toxicity, polyarthritis, endocrinopathies, and pneumonitis are the most common irAEs that have been described. [1–9,14–18]. In a recent study which compared durvalumab alone to a combination of Durvalumab, fatigue, diarrhea, hypothyroidism, anemia, and constipation were the most common adverse events. No oral toxicity was reported [19].

The primary treatment strategy for those immune-related toxicities is corticosteroid use, systemic or topical, additional immunosuppression, and treatment interruption or discontinuation [1,10,11,14–18].

Reports on oral toxicities related to immunotherapy are sparse. Some clinical trials and reviews have reported xerostomia as the only oral toxicity in immunotherapy, with an incidence between 3% and 7% [2,6,8,15]. No oral mucosal irAEs have been described in other trials and reviews [1,4,5,7,9].

The oral mucosal irAEs have often been described, in case reports and case series, as "oral lichenoid reactions". The mucous membrane pemphigoid, erythema multiforme, Stevens-Johnson syndrome, and Sjogren syndrome are less commonly reported [15,20–28]. The term "oral mucositis or stomatitis" associated with immunotherapy was used in two case reports and a retrospective study by other medical oncology clinics [29–31]. The term "oral mucosal disorders" was used in an analysis of the oral problems of 317 patients from electronic files [32]. Medication-related osteonecrosis of the jaw (MRONJ) has been recently described, in a few case reports, as an additional toxicity in patients who receive immunotherapies of [33–38].

The different terms which are used to describe oral mucosal immune related toxicity, such as ir-oral lichenoid reactions, or oral mucositis or stomatitis or oral disorders, combined with the lack of reporting of the oral mucosal irAEs in some in clinical trials, point to the difficulties in recognizing and reporting the oral irAEs. At the same time, immunotherapy is increasingly used, combined with other cancer therapies, leading to various other toxicities. The possible synergistic effects on the oral cavity, if any, have not been studied.

The purpose of this manuscript is to report the oral problems/toxicity of 24 cancer patients who received immunotherapy at presentation to the dentist, either as monotherapy or in combination with other cancer therapies.

2. Patients and Methods

Twenty-four cancer patients who received different immunotherapy medications, were referred by their medical oncologists to the private clinic of ONG for oral oncology consultation between the years 2017 and 2022.

Eight patients were referred from public cancer hospitals and 16 were referred from private hospitals. All patients had undergone an oral clinical evaluation by ONG at the private clinic. A smear for Candida species was taken when needed. Panoramic radiographs or Cone Beam Computed Tomography was performed, when needed, by Drs. EG and DG at the private clinic of ONG.

Patients' files were retrospectively assessed, and patients' characteristics and treatments were included in the present series. This assessment was undertaken as a preliminary case series report, within the scope of planning a multicenter research study of oral toxicities of immunotherapy. Oral lesions, treatments, prior and current anticancer therapies, and follow-up information were recorded.

3. Results

There were 19 males and 5 females in the study, with a median age of 64 years. Lung cancer was the most common diagnosis. Eight patients received immunotherapy combined with chemotherapy (n = 4), and/or bone targeting agents (BTA, n = 8), or an angiogenesis inhibitor (bevacizumab) (n = 1). Medications have been described, in detail, in Table 1. Three patients had a history of autoimmune disease prior to cancer diagnosis. One of those cases has been published [28]. Twenty patients had been pretreated with cytotoxic chemotherapy (n = 17) and/or angiogenesis inhibitors (n = 5), alone or in combination with other therapies.

The reasons for referral included oral pain, dental/mandible pain, burning/itching, bleeding, swelling and taste problems, leading to eating difficulties and dysphagia. One patient, although asymptomatic, was referred by his oncologist after reporting a dental extraction two months prior (Table 2).

Immune-related oral lesions were diagnosed in 15 patients. Twelve were consistent with oral lichenoid reactions (Figure 1), while mucosal bullous formation was clinically consistent with benign mucous membrane pemphigoids in three patients (Figure 2).

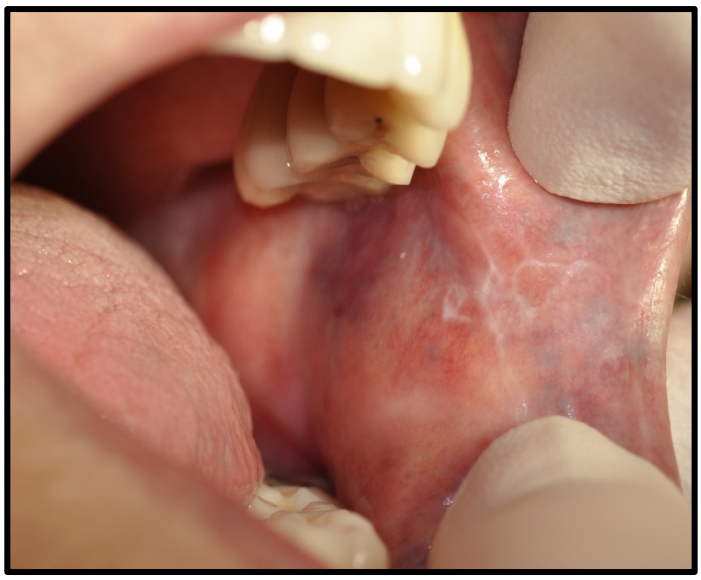

Figure 1. irLichenoid reaction. The patient, on pembrolizumab, presented with oral pain, mild burning/itching, dysphagia, and difficulty in cleaning teeth. White striae are seen on the buccal mucosa.

Table 1. Patients and disease characteristics and medications, $n = 24$.

		n	**%**
Gender		**19/5**	**79.2/20.8**
	M/F		
Age/years			
Range/median	49–80/64		
Mean age/standard deviation	65.88/9.20		
Cancer type			
	Lung ca	15	62.50
	Renal Cell ca	4	16.66
	Melanoma	2	8.33
	Urothelial ca	2	8.33
	Oral ca	1	4.16
Immunotherapy		24	100.00
	Nivolumab	11	
	Pembrolizumab	10	
	Atezolizumab	1	
	Ipilimumab switched to Nivolumab	1	
	Pembrolizumab switched to Ipilimumab	1	
Cancer therapy prior to immunotherapy		20	83.33
	CT alone	14	58.33
	CT+Zoledronic acid	1	4.16
	CT+Bevacizumab	2	8.33
	Angiogenesis inhibitors alone	3	12.50
	Sunitinib, $n = 1$ Sunitinib followed by Cabozantinib, $n = 1$ Temsirolimus followed by Sunitinib, $n = 1$		
	Radiotherapy to Head/Neck	1	4.16
Therapy concurrent with immunotherapy		9	37.5
	Cytotoxic CT, 1 alone and 3 combined with other drugs	4	16.66
	BTA alone (zol, $n = 2$, Den = 3)	5	20.83
	BTA in combination ($n = 3$), as following	3	12.50
	CT+Bevacizumab+Zoledronic acid	1	
	CT+Zoledronic acid	1	
	CT+Denosumab	1	
Patients with a history of autoimmune disease		3	12.50
	Oral lichen planus & autoimmune biliary cirrhosis	1	
	Dermal lichen planus	1	
	Vitiligo	1	

M = Male, F = Female, CT = Chemotherapy, BTA = Bone Targeting Agent, Zol = zoledronic acid, Den = denosumab.

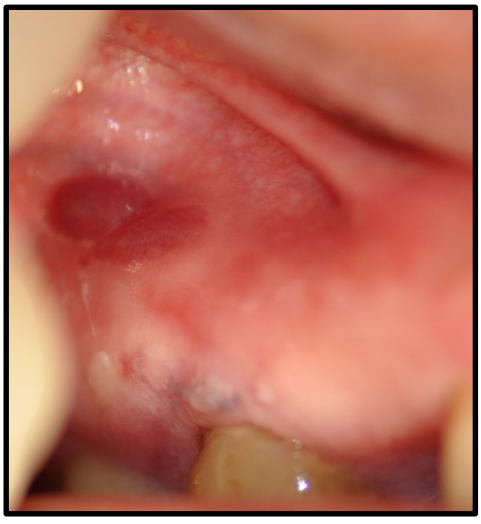

Figure 2. Hemorrhagic blisters, right buccal gingivae, consistent with benign mucous membrane pemphigoid. The patient, on pembrolizumab, presented with pain and dysphagia.

Table 2. Reason for referral, diagnosis of oral lesion and management, $n = 24$.

		n	%
Reason for referral			
	Oral pain	18	75.00
	Dental/mandible pain	5	20.83
	Burning/itching	7	29.16
	Xerostomia	5	20.83
	Gingival bleeding	3	12.50
	Swelling	3	12.50
	Taste problems	3	12.50
	Dental extraction follow-up	1	4.16
Oral mucosal lesions			
Immune Related		15	62.50
	OLP/lichenoid reaction (3 were exacerbations of previous autoimmune disease)	12	50.00
	Benign mucous membrane pemphigoid	3	12.50
Management	Costicosteroid mouthwash, with good response		
Infections	Candidiasis, pseudomembranous (3), & erythematous (1), managed with oral fluconazole	4	16.66
	Herpes simplex, lip ulcers, managed with oral acyclovir & topical cream on lip	2	8.33
Osteonecrosis of the mandible, exposed type		6	25.00
Medications with known ONJ risk, prior or concurrent with Immunotherapy			
	Prior bevacizumab	1	
	Concurrent zoledronic	1	
	Prior sunitininb, followed by cabozantinib, concurrent denosumab	1	
	Concurrent bevacizumab & zoledronic acid	1	
	Prior & concurrent zoledronic acid	1	
	Concurrent denosumab	1	
Management	Conservative, antibiotics	6	
Patients with more than one lesion at presentation		2	8.33
	Lichenoid reaction+candidiasis+herpes	1	
	MRONJ + Candidiasis	1	

OLP = oral lichen planus, ONJ = osteonecrosis of the jaw.

Three patients had lesions which were exacerbations of previous oral and dermal lichen planus, and one had vitiligo. (Figure 3). Three patients presented with painful ulcers following the use of mouthwash (Figure 4). The mouthwash was used to alleviate mild oral mucosal symptoms after the initiation of immunotherapy.

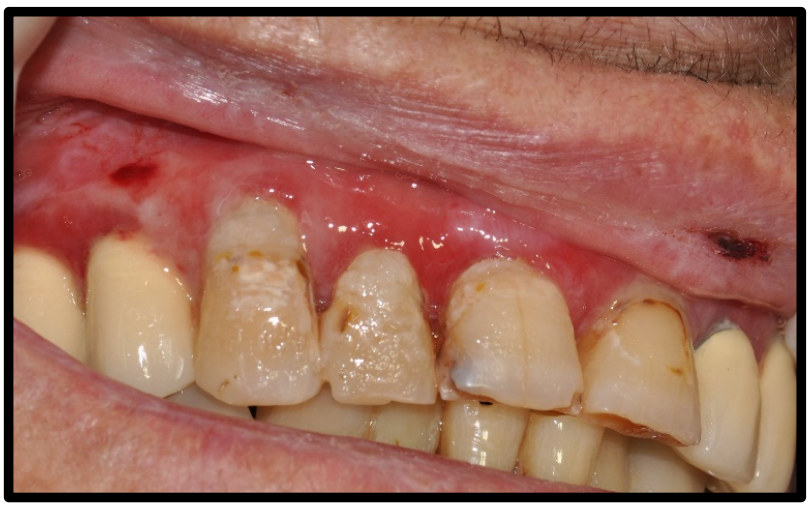

Figure 3. Exacerbation of oral lichen planus; the biopsy was documented years before the cancer diagnosis. The patient, on pembrolizumab and switched to ipilimumab, presented with oral/gingival pain, bleeding, and the inability to perform oral hygiene.

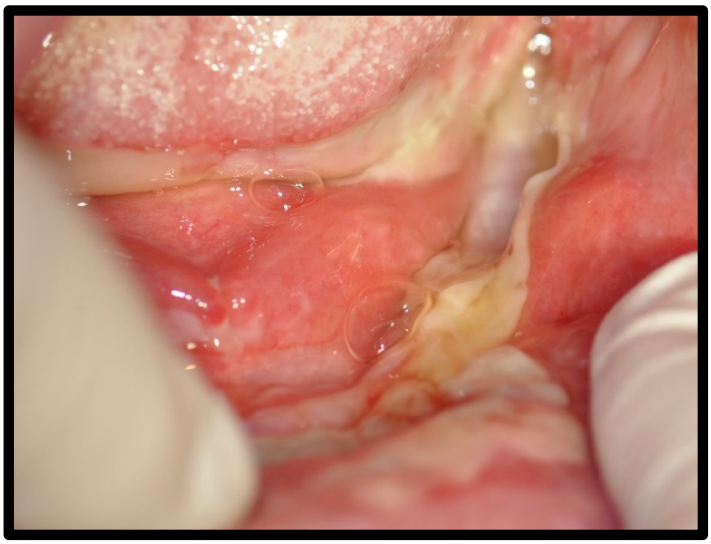

Figure 4. Oral mucosal ulcers on the floor of mouth, the mandible, and the lip mucosa. The patient used itching/burning mouthwash. The patient, on pembrolizumab, presented with severe oral pain.

Six patients had oral infections; four were candidiasis (Figure 5), and two were herpes simplex recurrent infections, presenting as blisters and ulcers, with crusting on the vermillion border and commissures (Figure 6). Five patients reported xerostomia, which was related to oral candidiasis (n = 3), an irLichenoid reaction (n = 1), and mouthwash use (n = 1).

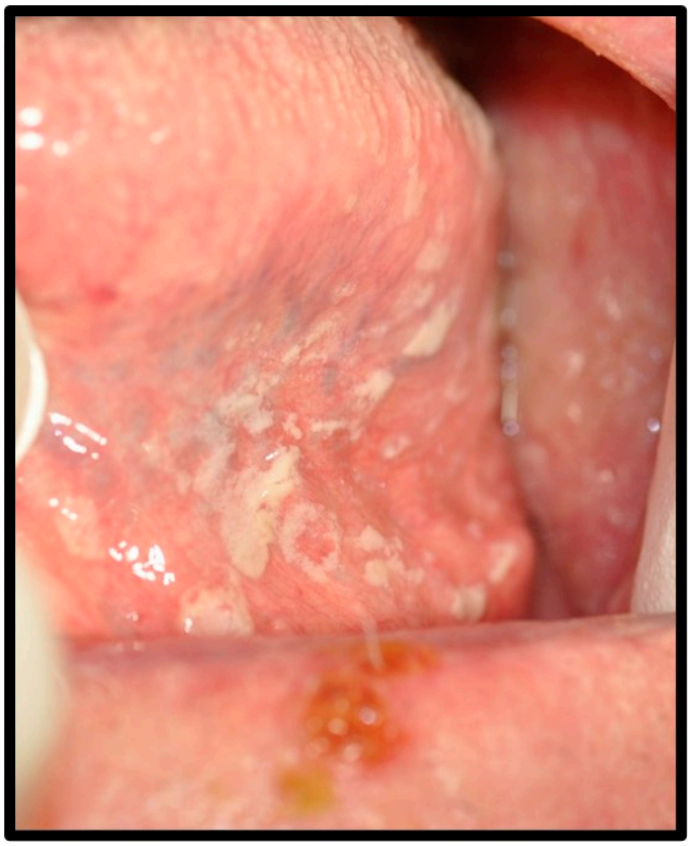

Figure 5. Oral pseudomembranous candidiasis, with positive Candida albicans, on the ventral and lateral tongue. The patient, on pembrolizumab, presented with xerostomia and dysphagia. Herpes labialis was also seen on the lower lip.

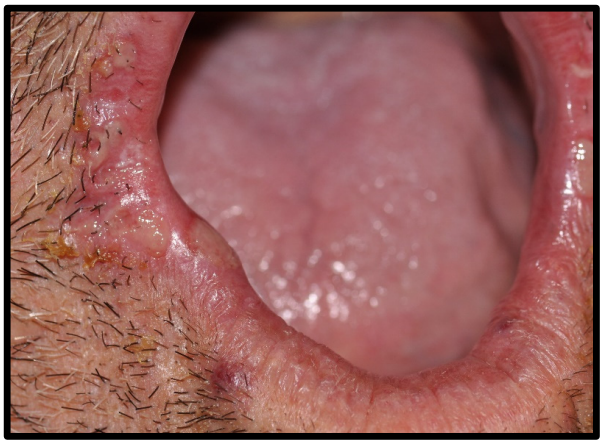

Figure 6. Herpes simplex virus infection on both lip commissures, presenting with blisters and crusting. The patient, on nivolumab, was in pain for more than one month.

MRONJ on the mandible was diagnosed in six patients (Figure 7). Five of those patients had received bone targeting agents during immunotherapy, combined either prior or concurrent with angiogenesis inhibitors, and one had received bevacizumab prior to nivolumab (Table 2). The patient with MRONJ, with prior bevacizumab, was included in our review on MRONJ related to non-antiresorptives [33].

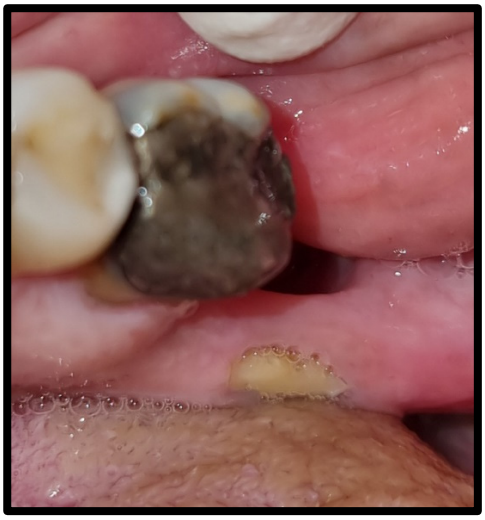

Figure 7. MRONJ, right lingual mandible. The patient, on atezolizumab and zoledronic acid and chemotherapy, presented with pain in the jaw two months after dental extraction due to dental pain.

Two patients presented with more than one oral lesion: one with a lichenoid reaction at first visit and oral candidiasis and herpes labialis at the re-examination one week later, and a second patient presented with MRONJ and oral candidiasis.

The reasons for referral: oral mucosal diseases, MRONJ and medications, are shown in Table 2.

Topical corticosteroids, oral fluconazole, miconazole topical cream and oral and/or topical acyclovir were administered. The patients responded well. Immunotherapy was discontinued in five patients who had irPneumonitis (n = 2), thrombosis (n = 1), irHepatitis (n = 1), and disease progression (n = 1). The BTA was discontinued in all patients, and MRONJ was managed conservatively, since their medical oncologists and the patients themselves did not consent to surgical management.

4. Discussion

Reports on the oral problems in patients who receive immunotherapy are sparse and have been described in patients who have received single agent checkpoint inhibitors [15,22,25,27,32]. However, patients who receive immunotherapy, may have also received other cancer therapies, either prior to or concurrently with immunotherapy.

The oral problems have often been defined as irLichenoid reactions, mucous membrane pemphigoid, and xerostomia. Recently, a few cases of osteonecrosis of the jaw in patients who received immunotherapy either alone or combined with other therapies have been published [33–38]. In the present series, 9 of the 24 patients, while on immunotherapy, received other anticancer or cancer supportive care medications, such as cytotoxic chemotherapy, angiogenesis inhibitors, and/or bone targeting agents. Twenty of our patients were also pretreated with cytotoxic chemotherapy and/or angiogenesis inhibitors or zoledronic acid.

Immune-related lichenoid reactions and mucous membrane pemphigoid were common in our study, and were observed in 15 patients. Most lesions were low-grade and were relieved with topical corticosteroids, as reported by other investigators [21–25,27,28]. Extensive and painful oral ulcerations were attributed to the use of a mouthwash in three patients who reported the worsening of mild oral symptoms following immunotherapy. Mouthwash was introduced following immunotherapy in order to relieve mild oral symptoms.

Oral infections at presentation were diagnosed in six patients. This is the first report of oral infections, as a presenting symptom, in patients who received immunotherapy, although infections are common in the cancer patient setting. Xerostomia, dysgeusia or ageusia and burning were the reasons for referral in patients with oral candidiasis. Oral pain was the presenting symptom in patients with herpes. All six patients responded well to oral and topical antifungal and antiherpetic therapy. Urinary tract infections, pneumonia and sepsis were the most common cause of the discontinuation of immunotherapy in a study of patients who received atezolizumab or pembrolizumab [5]. In another study of 459 dermatology patients with irSkin problems, the authors reported the diagnosis of 24 skin infections [18]. No oral candidiasis or other oral infection or any kind of oral ir problem was observed in any of the above studies [5,18].

Xerostomia was one of the main complaints in five of the patients. It was related with an ir-lichenoid reaction in one patient and with mouthwash use in another patient. Xerostomia was the main complaint in three patients with oral candidiasis. Xerostomia is a risk factor of candidiasis and, on the other hand, xerostomia is one of the first symptoms of oral candidiasis. Michot et al., in their review of immune related adverse events, reported that about 5% of patients who receive an immune checkpoint blockade have symptoms of dry mouth [6]. They recommend, however, that oral candidiasis must be firstly ruled out in this context. Ir-xerostomia has been reported in a small case series and in several clinical trials of immunotherapy, and ranged from 6.0% to 24% [2,6,8,39]. In a review of the electronic medical records of 4683 patients who received immunotherapy, xerostomia was the most common oral disorder (68.5%), followed by oral mucosal disorders (33.4%) and dysgeusia (24.0%) [31]. The authors commented that additional studies are warranted to better characterize oral irAEs and their biologic basis.

Medication related osteonecrosis of the jaw was diagnosed in six patients, all on the mandible and all of the exposed type. Five patients presented with dental pain or pain in the mandible, and one presented with an asymptomatic non-healing post-dental extraction socket. All six patients received medications, with a known risk for MRONJ, such as angiogenesis inhibitors and/or bone targeting agents, either prior to or concurrent with immunotherapy. MRONJ has emerged as another, although rare, oral toxicity in patients on immunotherapy [33–38]. The first report was associated with ipilimumab therapy [33]. Another case was related to nivolumab with the prior administration of bevacizumab, and three more cases of MRONJ were related to pembrolizumab and epacadostat, to nivolumab, and to ipilimumab with the implication of a role for targeted therapy [34–37]. Recently, a case of MRONJ was related to the combined treatment with pembrolizumab and deno-

sumab [38]. The knowledge on the role of immunotherapy in the development of MRONJ, beyond the few case reports, either alone or combined with other medications, with a known risk for osteonecrosis of the jaw, is limited, and it remains to be explored. Xu et al. [32] noted in their study that cytotoxic chemotherapy may exacerbate the risk of oral adverse events. Recently, cytotoxic chemotherapy was found to increase the risk of exacerbations of periodontitis [40], while dental/periodontal infection is the most important local risk factor for MRONJ [41]. Furthermore, the dental/periodontal infection, when associated with histologically necrotic periodontal bone, may be an early stage of MRONJ [42–44].

Twenty of the 24 patients in the present study, had been pretreated with cytotoxic chemotherapy and/or angiogenesis inhibitors or a BTA prior to immunotherapy. Four patients were receiving chemotherapy at presentation, concurrently with immunotherapy, while eight were receiving bone targeting agents; four patients were receiving zoledronic acid and four were receiving denosumab.

In conclusion, oral mucosal irAEs were observed in 15 of a series of 24 patients on immunotherapy, who were referred by their oncologists for different oral symptoms. Furthermore, six oral mucosal infections and six MRONJ cases were observed.

The rapidly increasing use of immunotherapy, the increasing types of cancers treated with immunotherapy, and the need for therapy combinations, in the real world, highlight the necessity for physician awareness of the potential for oral irAEs. Prospective studies should examine the possible synergistic effects of therapy combinations on the oral mucosa. Educational programs may help raise awareness and improve the communication between the members of the multidisciplinary team, resulting in the timely and successful management of the patient.

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