Severe oral erosive lichenoid reaction to pembrolizumab therapy

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New advances in cancer immunotherapy have been flooding the market at a rapid rate. Pembrolizumab (Keytruda), a programmed cell death protein 1 inhibitor, introduced in 2014, has been used to treat several cancers. Immune-related adverse events associated with pembrolizumab and other immune checkpoint inhibitors are now well-described complications. We describe the case of a 65-year old female with severe oral lichenoid lesions occurring after treatment with pembrolizumab for bladder cancer. To the best of our knowledge, this is the first report of a biopsy-proven oral erosive lichenoid reaction confirmed through direct immunofluorescence. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;130:e301−e307)

Cancer was first described in the *Edwin Smith Papyrus* around 1600 BC.[1] The first cause of cancer was identified in 1775 by a British surgeon, Percivall Pott, in the scrotum of chimney sweepers. Since then, there have been constant endeavors to understand the cause and treatment modalities to cure this disease. Cancers have been treated for over a century by employing various modalities, mainly radiation, chemotherapy, and surgery or a combination of these.[1] Radiation therapy was discovered by Drs. Marie and Pierre Curie at the end of the 19th century.[2]

Chemotherapy, typically in combination with radiation therapy, has been used as a substitute or in addition to surgery for at least 7 to 8 decades. Chemotherapeutics using toxic agents, such as nitrogen mustard and methotrexate, were first used by Dr. Gustaf Lindskog.[3] Dr. William B. Cooley first experimented with immunotherapy for cancer treatment in the 19th century.[4] In the past few years, there have been significant advancements in the use of immunotherapy as a fourth modality in cancer treatment.

Currently, the emerging trends in immuno-oncology include (1) antibody-based therapies (monoclonal: rituximab, trastuzumab, and the immune checkpoint inhibitors ipilimumab, nivolumab, pembrolizumab, atezolizumab, durvalumab, and avelumab); (2) therapies based on interleukin-2 (IL-2), interferons, and other cytokines; (3) Immunosuppression-reducing therapies (depleting M2 type macrophage anti−colony-stimulating factor 1 antibodies); and (4) cancer-prevention vaccines (autologous and allogenic).[4]

In spite of successes in reducing tumor burden, several adverse reactions are seen with the use of immunotherapeutic drugs, especially with immune checkpoint inhibitors. These effects are varied and may present at any time during or even weeks or months after administration of treatment and may persist even after discontinuation of therapy.[5] Some common adverse effects include fatigue, cough, fever, hyperglycemia, pruritus, dermatitis, arthralgia, colitis, pneumonitis, and hepatitis. Nevertheless, oral adverse effects albeit uncommon, may occur and include mucositis, xerostomia, mucosal ulcerations, and lichenoid lesions.[5]

CASE REPORT

A 65-year-old female with a history of urothelial carcinoma of the bladder diagnosed in 2017 presented with a chief complaint of very painful and large sores on her tongue and cheeks. The malignancy had been initially treated with transurethral resection along with 4 cycles of neoadjuvant dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin. This was followed by radical cystectomy with urinary diversion. The above treatment resulted in remission, with no evidence of the disease. At the 1-year follow-up, the patient was diagnosed with metastatic disease, which was confirmed as recurrent urothelial carcinoma. At this point, she was treated with pembrolizumab (Keytruda, Merck) administered at a dose of 200 mg intravenously every 3

Statement of Clinical Relevance

Pembrolizumab (Keytruda), an immune checkpoint inhibitor, is increasingly being used as immunotherapy for treatment of various malignancies. It may result in significant oral adverse effects, including ulcerations and lichenoid lesions. Clinicians should be cognizant of the oral adverse effects of this and the similar fast-growing category of cancer treatment drugs.

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weeks in 14 cycles (approximately 10 months). Within 4 cycles, the patient complained of soreness in her mouth, but upon reassurances from her oncologist, she continued with therapy for 10 more cycles. At the end of the 14th cycle of pembrolizumab therapy, the discomfort caused by the oral lesions became significant and concerning to her oncologist, who decided to cease pembrolizumab therapy. The patient expected the oral lesions to resolve as a result of discontinuation of pembrolizumab therapy. However, she saw no changes even after 6 months of cessation, so she decided to seek treatment and was referred to an otorhinolaryngologist for evaluation and treatment of her oral lesions. She presented with a chief complaint of severely painful, nonhealing, large oral ulcers on the tongue, lower lip, and cheeks. The most significant area of involvement was on the dorsum and lateral border of the tongue. The entire left side of the dorsal tongue was covered in a thick fibrinous necrotic zone, with faint white striations radiating from the ulcers (Figure 1A). This ulceration extended to the left lateral border of the tongue, encroaching on the ventral surface. In addition, thick, patchy, white lesions were noted on the right half of the dorsal tongue. White striations on an erythematous background were seen throughout the tongue. Also noted was a 1 × 0.5 cm irregular, shallow ulcer on the mucosal aspect of the left side of the lower lip close to the vermilion border (Figure 1B). Extensive white, striated lesions were seen on the buccal mucosa bilaterally (Figures 1C and 1D). Additionally, the right buccal mucosa demonstrated a zone of ulceration measuring about 1.4 × 0.6 cm that was surrounded by characteristic striated white lines (see Figure 1D).

The patient was prescribed antifungal therapy by her physician. However, her condition failed to resolve or improve. At this point, a consultation with an oral pathologist was requested and a biopsy was recommended. An incisional biopsy of the tongue lesion was performed, but the result was deemed inconclusive because of the complete lack of epithelium on the specimen. The patient returned to the oral pathologist, and a second biopsy specimen was taken from the left buccal mucosa. Tissue from the area was placed in Michel's solution and submitted for direct immunofluorescence testing. Histomorphology revealed a strip of keratinized, stratified squamous epithelium overlying inflamed fibrous connective tissue. The epithelium was covered by a layer of thickened keratin with variably thickened spinous layers (Figure 2A). Occasional saw-toothed rete ridges were noted along with foci of leukocytic exocytosis, a few eosinophilic Civatte bodies, and degeneration of the basement membrane zone (Figure 2B). A dense, band-like infiltrate of lymphocytes was seen in the

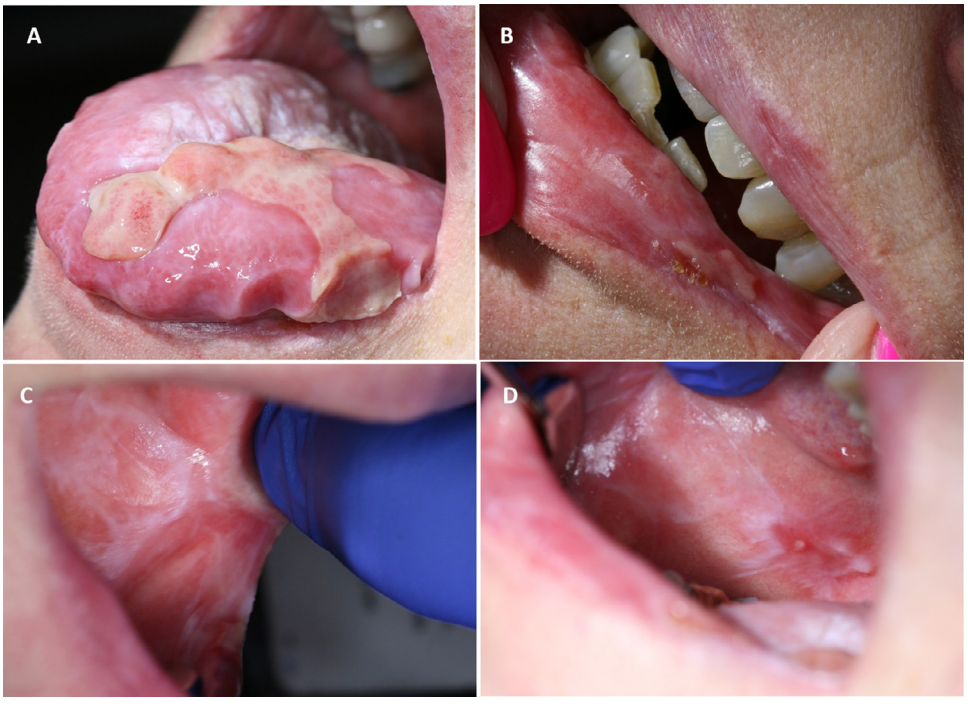

Fig. 1. Composite image of initial presentation. **A,** Large ulceration of the entire left side of the dorsal tongue covered by a necrotic surface, with faint white striations radiating from the ulcers. **B,** Irregular shallow ulcer of the mucosal aspect of the left side of the lower lip. **C,** Extensive white, striated lesions were seen on the left buccal mucosa. **D,** A central ulcerated area on the right buccal mucosa surrounded by white striations.

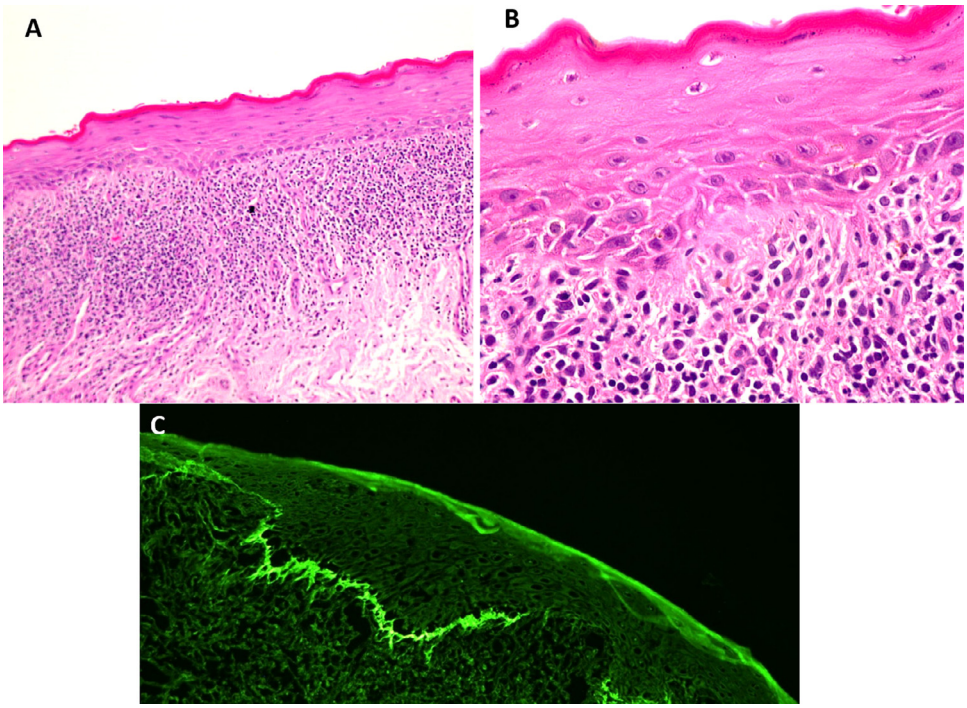

Fig. 2. Composite image of photomicrographs from biopsy specimen taken from the right buccal mucosa. **A,** A hematoxylin and eosin (H&E)−stained section demonstrating classic histomorphologic features of lichenoid mucositis. Keratinized stratified squamous epithelium overlying inflamed connective tissue containing a band-like lymphocytic infiltrate immediately subjacent to the epithelium (magnification × 100). **B,** Degeneration of the basement membrane and the lymphocytic infiltrate are evident (magnification × 200). **C,** Prominent positive linear band-like fibrinogen along the basement membrane zone.

superficial lamina propria immediately subjacent to the epithelium (Figure 2C). The specimen submitted for direct immunofluorescence demonstrated a prominent positive linear, band-like fibrinogen along the basement membrane zone throughout the specimen. A diagnosis of lichen planus was rendered, and a comment raising the possibility of pembrolizumab therapy−associated lesions was provided.

At this stage, the patient was prescribed clobetasol propionate 0.05% ointment to be applied topically 2 times daily directly on the lesions for 2 weeks to 1 month. The patient reported significant improvement upon re-evaluation at 2 weeks (Figures 3A and 3B). The frequency of application of topical clobetasol (0.05%) was then reduced to once a day. The treatment was continued for an additional 2 weeks, and the patient reported further reduction in lesions and symptoms (Figure 4). Intermittent (1 to 3 times a week) applications continue to date, and the patient has had no major recurrence of lesions. Significant reduction in symptoms has been maintained as well. In addition, the patient remains under close clinical follow-up to monitor for recurrence of lesions. To date, she has reported only minor symptoms (small zones of erythema). In addition, the patient continues to be in remission and semiannual re-evaluations with her oncologist are ongoing.

DISCUSSION

Pembrolizumab (Keytruda)

Tumor growth depends on the tumor cells as well as the tumor microenvironment (TME). The TME includes ground substances and cells, some of which promote and others inhibit tumor progression. Promoter cells include macrophages (M2 type), T-regulatory cells, myeloid-derived suppressor cells, and CD4 type 2 helper T cells.[6] During tumorigenesis, these TME promoter cells show upregulation of immune checkpoint molecules, helping the tumor cells to evade the host's immune system.[7] Immune checkpoints are regulatory pathways, and they render immune tolerance to a specific target or a set of targets. Immunotherapy in cancer treatment inhibits these immune checkpoints and aids the host's immune system in targeting antigens, such as viral particles and cancer cells.[8] Some of the most studied immune checkpoint molecules include cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed cell death-1 (PD-1) and its ligands (PD-L1 and PD-L2).[9] PD-1 is expressed on T lymphocytes, natural killer (NK) cells, B cells, dendritic cells, and monocytes during antigenic stimulation. The ligands corresponding to PD-1 are PD-L1 and PD-L2. PD-L1 is expressed on a wide variety of cells, including nonhematogenic and hematogenic cells. PD-L2 has a higher affinity for PD-1 and is

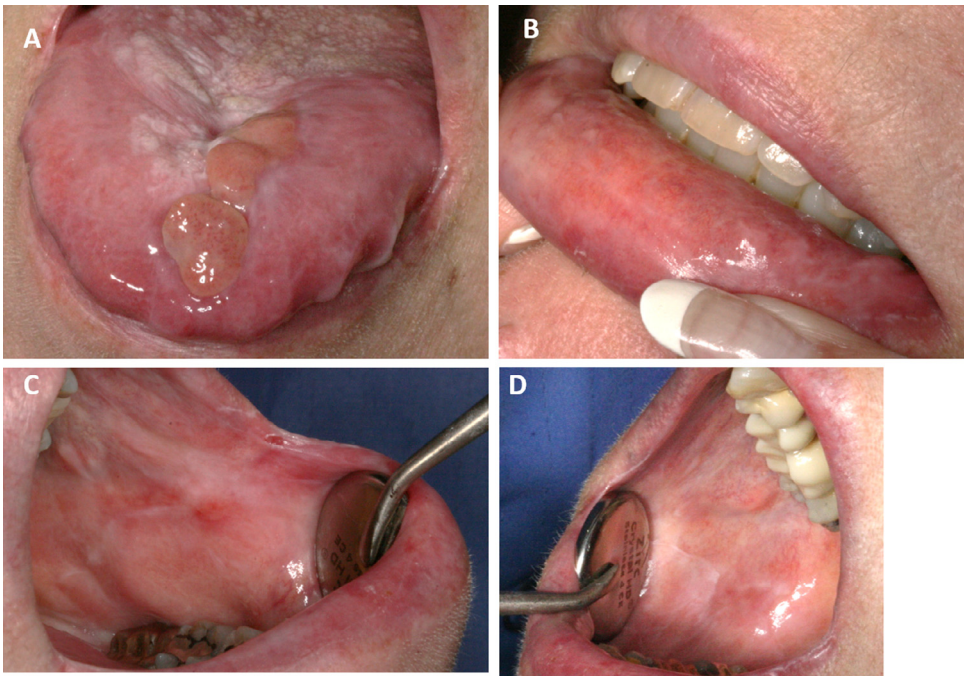

Fig. 3. Composite clinical photographs from 2-week follow-up after topical steroid therapy. **A,** Dorsal tongue demonstrates significant improvement of ulcerations. **B,** Lower lip ulceration is almost completely resolved. **C, D,** Bilateral buccal mucosa exhibiting significant improvement in lichen planus–like lesions.

expressed chiefly on dendritic cells, macrophages, and some B cells.[9] When PD-1 engages with its ligand(s), it stimulates an inhibitory signal and reduces the production of cytokines, cytotoxic activity, and lymphocyte proliferation. The blockage of this pathway results in the host's immune system being enhanced.[7]

Tumors also use some of the same pathways to avoid immune surveillance. These tumors are thought to

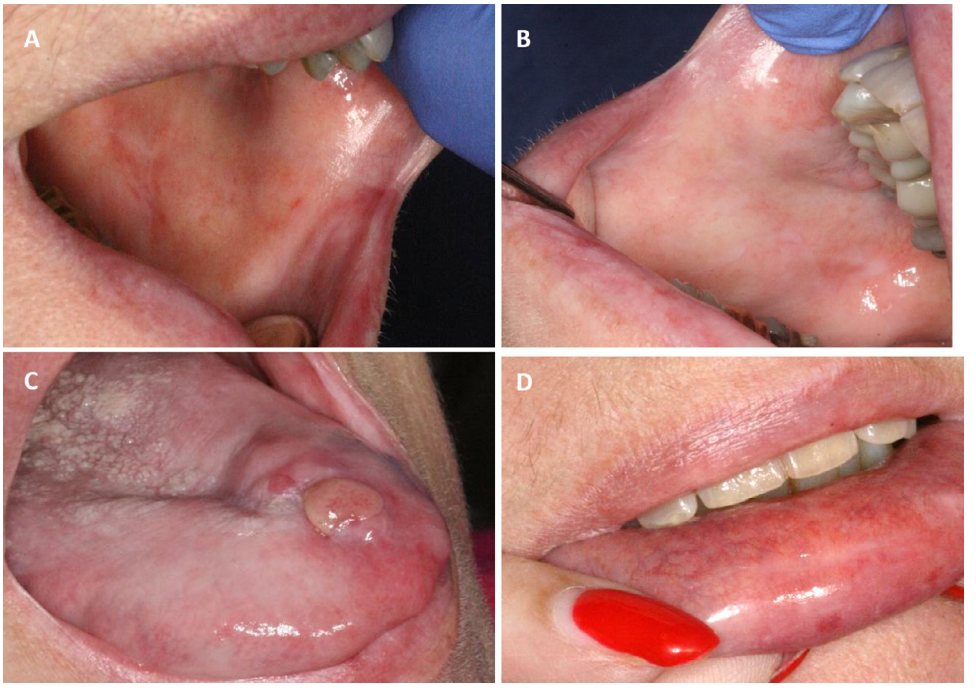

Fig. 4. Composite of clinical photographs 1 month after initiation of topical steroid application. All areas exhibit significant improvement. The tongue dorsum displays a persistent but shrinking area of ulceration, with reduction in symptoms.

express PD-L1 and are associated with a poorer prognosis.[9] Immune checkpoint blockers are immunoglobulin G4 (IgG4) antibodies, which act against immune checkpoint molecules.[9] Pembrolizumab (humanized IgG4 monoclonal antibody) targets PD-1 and hence is helpful in maintaining the host's immune system.[7] Other checkpoint inhibitors include Ipilimumab (Yervoy); nivolumab (Opdivo); avelumab (Bavencio); durvalumab (Imfinzi); and atezolizumab (Tecentriq). These are used alone or in combination with other medications in the treatment of metastatic cancers.

Checkpoint inhibitor molecules may cause adverse reactions because checkpoint molecules are needed to balance the immune system. The exact pathophysiology is still not fully understood, but many possibilities have been hypothesized. These include the following:

1. *Breakdown of immune tolerance, leading to autoimmune reactions:* Immune tolerance is the unresponsiveness of the host immune system toward certain antigens. The mechanisms resulting in immune tolerance are varied, but the result is the same. Upregulation of the immune checkpoint molecules in the cells of the TME can result in breakdown of immune tolerance, resulting in adverse effects by causing T-cell dysregulation.[10]
2. *Shared antigen on both tumor cells and healthy tissue:* Immunotherapeutic drugs result in the development of an immune reaction against tumor cells as well as healthy cells, resulting in an adverse reaction.[11]
3. *Neurologic adverse reactions:* Antineuronal antibodies (SOX 2, anti-Hu, and anti-Yo) are produced against shared neuron- specific antigens resulting adverse reactions.[12]

These mechanisms lead to systemic as well as oral adverse effects. Immunoregulatory modalities help regulate the immune system and are considered the gold standard for treating these reactions.

Table I lists the very few cases of oral adverse reactions reported in the English language literature.

Table I. Oral manifestations reported with pembrolizumab use

Author	*Year*	*Age*	*Gender*	*Oral manifestation*
Robert et al.[16]	2015	–	–	Xerostomia
Owosho et al.[13]	2016	61	Male	Chronic graft-versus-host disease–like/lichen planus–like lesion
Schmidgen et al.[15]	2017	64	Male	Lichen planus
Brand et al.[14]	2018	69	Male	Mucositis and oropharyngeal ulcers
Bezinelli et al.[17]	2019	47	Female	Gingival mucositis, oral ulcers
Our case	2020	64	Female	Mucositis and oral ulcers and lichenoid lesions

Oral adverse effects of pembrolizumab

The first report of oral manifestations related to pembrolizumab therapy was by Owosho et al.[13] These authors reported the case of a patient with chronic graft-versus-host disease–like and lichen planus–like oral lesions that developed after administration of 6 doses of pembrolizumab. The lesions were characterized by lichenoid–keratotic mucosal changes, erythematous areas, and pseudomembranous ulcerations involving the buccal and palatal mucosae, the gingiva, and the tongue.[13] Although uncommon, varied oral manifestations have been reported as a result of immune checkpoint inhibitor therapy and are seen more frequently in PD-1 inhibitor therapy than with CTLA-4 inhibitors.[14] These adverse reactions include mucositis, lichenoid mucositis, lichen planus, dysgeusia, and xerostomia.[14-16] A rare case of mucous membrane pemphigoid with severe widespread involvement of the oral mucosa, upper respiratory tract, and conjunctiva was reported by Bezinelli et al.[17] In this case, the authors reported that the lesions persisted even after discontinuation of pembrolizumab therapy and that the oral lesions were the only manifestations present, similar to our case.[17]

Table II summarizes the most commonly reported adverse effects of immune checkpoint inhibitors.

Treatment of adverse effects of pembrolizumab

Xerostomia was reported in approximately 4% to 7.2% of patients. Patients should be advised to keep themselves well hydrated; use salivary stimulants, such as sugar-free gum and candy; and maintain impeccable oral hygiene. In severe cases, sialagogues may be prescribed.[18]

Mucositis and oral ulcers can be successfully treated with topical or systemic corticosteroids, depending on the severity of the lesions. In cases of oral ulcerations causing severe discomfort during ongoing treatment with pembrolizumab, the patient's physician may be consulted regarding substitution or discontinuation of the immunoregulatory agent.[18] The patient with severe mucous membrane pemphigoid, reported by Bezenelli et al., developed refractory and progressive vesiculobullous lesions and required significant immunosuppressive therapy, including steroids and rituximab, but finally succumbed to sepsis related to the severe oral and laryngeal lesions.[17] Lichen planus or lichenoid lesions may also be treated successfully with topical or systemic corticosteroids.[13,18]

Table II. Adverse effects of other immune checkpoint inhibitors[13,17,18]

Name of medication	*Adverse effects*
Ipilimumab	Fatigue
	Diarrhea
	Colitis
	Pruritus
	Myalgia
	Dermatitis
	Hepatitis
Nivolumab	Fatigue
	Myalgia
	Dermatitis
	Diarrhea
	Hypothyroidism
	Colitis
	Hepatitis
	Pneumonitis
Avelumab	Fatigue
	Myalgia
	Colitis
	Dermatitis
	Hypothyroidism
	Hyperglycemia
	Hepatitis
	Nephritis
Durvalumab	Fatigue
	Colitis
	Fever
	Myalgia
Atezolizumab	Fatigue
	Diarrhea
	Fever
	Myalgia
	Hepatitis
	Pruritus
	Dermatitis
	Pneumonitis
Pembrolizumab	Fatigue
	Dermatitis
	Arthralgia
	Cough
	Hyperglycemia
	Hepatitis
	Pruritus
	Oropharyngeal mucous membrane pemphigoid
	Chronic graft-versus-host disease–like/lichen planus–like lesion

In our case, clobetasol 0.05% ointment, a topical high-potency steroid, was instrumental in providing symptomatic relief and resolution of the majority of lesions. The patient continues to have a small area of ulceration on the dorsum of the tongue, but the lesion is significantly reduced in size. The patient remains in remission from her prior malignancy.

CONCLUSIONS

Oral adverse reactions to immunotherapy with immune checkpoint inhibitors are far less common compared with cutaneous adverse reactions. Treatment of the oral adverse reactions is of paramount importance to improve the patient's quality of life. Patients receiving immunotherapy for advanced malignancies already are under considerable stress, which may be compounded by the severe discomfort caused by their oral lesions. Clinicians should be cognizant of the possibility of oral adverse effects of this fast-growing category of anticancer drugs.

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