Crizotinib-induced oral lichenoid lesions

Sir,

Crizotinib is a first-generation orally active *anaplastic lymphoma kinase* (ALK) inhibitor, also targeting *mesenchymal-epithelial transition factor* (MET) receptor and *receptor of silencing 1* (ROS1) kinases, which is now United States Food and Drug Administration (FDA)- and European Medicines Agency (EMA)-approved for advanced ALK/ROS1-positive non-small cell lung cancer (NSCLC). It is associated with a favorable dermatologic safety profile, with low frequency of all-grade skin toxic effects (about 3%).[1] These dermatologic adverse events, however, have not been characterized until now. Ho and Chen recently described a patient treated for an NSCLC who developed a cutaneous lichenoid eruption induced by crizotinib.[2] We recently observed the development of a severe oral lichenoid reaction with crizotinib therapy.

A patient in her 60s was referred to the dermatology department for recurrent oral ulcerations. She did not report any history of skin disorders. She was treated for an advanced ALK-positive NSCLC with crizotinib for 7 months (500 mg/day). No other medication was reportedly prescribed. Two months after the initiation of treatment, she developed grade 2 stomatitis (according to the National Cancer Institute Common Terminology Criteria, version 4.0), with progressive occurrence of debilitating ulcers on the tongue and oral mucosa. The ulcers interfered with fluid/food intake and had a negative impact on her quality of life. Oral examination revealed a combination of ulcerative lesions with characteristic papular/plaque-like lesions and reticular white streaks involving both keratinized (dorsum of the tongue) and nonkeratinized mucosae (buccal mucosa, lateral aspects of the tongue, mucosal aspect of the lip) [Figure 1a and b]. These oral mucosal changes had developed in an isolated manner, without any involvement of the skin, nails, or genital areas. A mucosal biopsy showed focal parakeratosis with hypergranulosis and a lichenoid interface dermatitis, combining a superficial band-like T-cell infiltrate in the upper lamina propria together with vacuolar basal changes [Figure 2]. Symptomatic management was started with topical high-potency corticosteroids (0.05% clobetasol propionate cream – Dermoval®, twice a day), together with the promotion of optimal oral hygiene. After 1 month of therapy, the oral lesions had returned to grade 1, and the anticancer therapy was continued at the current dose [Figure 3a and b].

Oral adverse events induced by new targeted anticancer therapies remain poorly characterized and are frequently described using nonspecific terminology (e.g. "stomatitis" or "mucositis"). However, targeted-therapy-related oral toxicities often display very characteristic changes that differ significantly from mucositis induced by chemotherapeutic agents [Table 1]. This mainly includes *mechanistic target of rapamycin kinase* (mTOR) inhibitor-associated stomatitis (mIAS), stomatitis, and benign migratory glossitis associated with multitargeted kinase inhibitors of the *vascular endothelial growth factor* (VEGF) and *platelet-derived growth factor* (PDGF) receptors, oral aphthous-like lesions induced by *epidermal growth factor receptor* (EGFR) inhibitors, hyperpigmentation of the palate with imatinib, ibrutinib-related stomatitis, or hyperkeratotic lesions with B-*rapidly accelerated fibrosarcoma* (BRAF) inhibitors in monotherapy.[3] Moreover, oral lichenoid reactions have also been observed with a range of targeted therapies, notably with

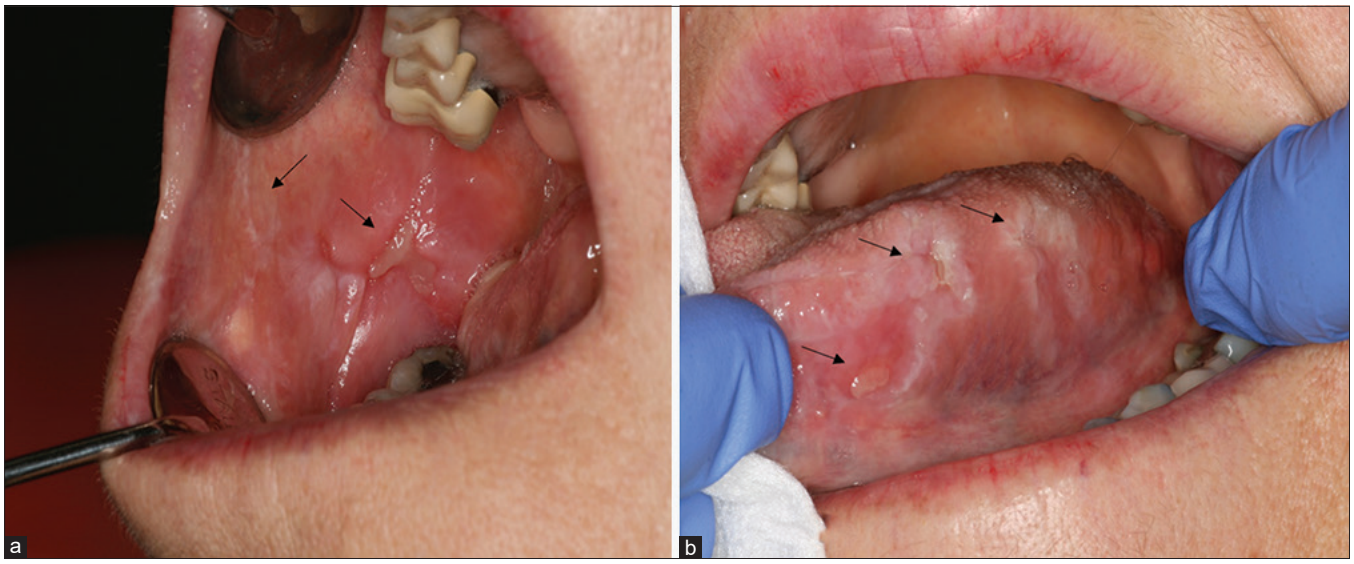

Figure 1: Buccal mucosa (a) and lateral aspect of the tongue (b) with visible reticular white streaks (arrow) and ulcerative lesions (arrow)

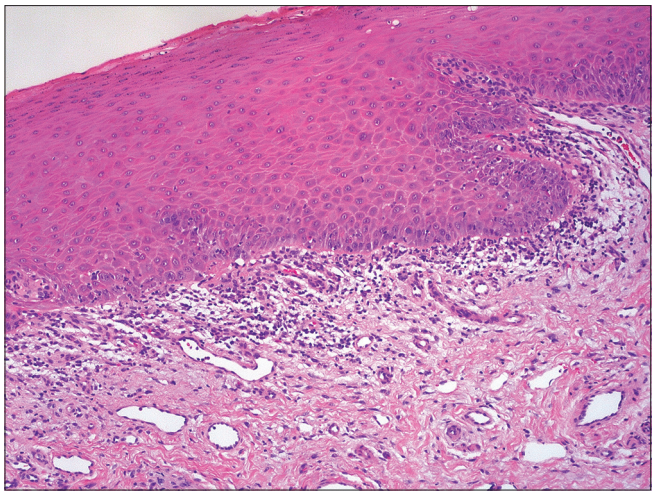

Figure 2: Superficial band-like infiltrate with interface dermatitis (H and E, ×100)

imatinib and to a lesser degree with rituximab. The overall incidence of such oral lichenoid lesions appears even higher with the newly developed immune checkpoint inhibitors. In this context, oral lichenoid reactions may occur alone or in association with cutaneous or nail involvement, as we have recently described with *anti-programmed cell death* 1 (PD-1) or *anti-programmed cell death-ligand* 1 (anti-PD-L1) therapies.[4]

The only emergent oral mucosal toxicity associated with crizotinib is dysgeusia, which affects approximately 20% of patients treated with this drug.[3] Nonspecific stomatitis has been only reported sporadically in a subset of patients treated with this drug. Our case, as well as that recently reported by Ho and Chen, shows that a subset of eruptions induced by crizotinib may be due to a lichenoid reaction, either with skin or oral mucosal involvement.[2] However,

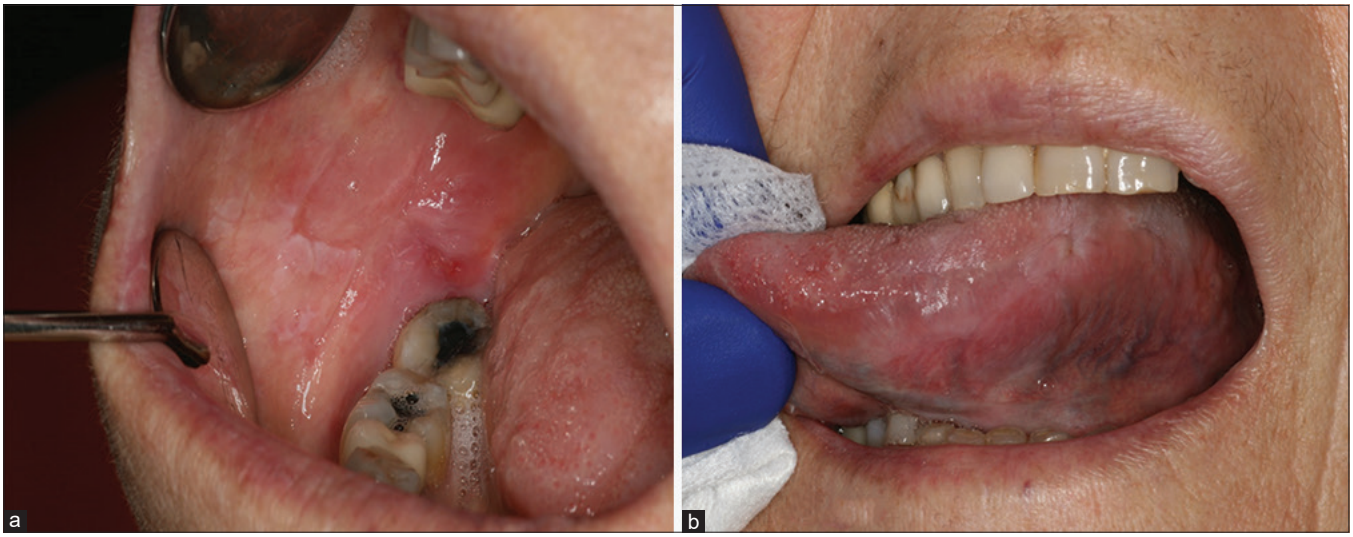

Figure 3: Significant improvement of oral lichenoid lesions after 1-month therapy with topical clobetasol (a and b)

Table 1: Main oral changes induced by newly developed targeted anticancer therapies

Class of targeted therapies	Drugs	Oral clinical presentation
mTOR inhibitors	Everolimus, temsirolimus	mIAS: mTOR inhibitor-associated stomatitis
EGFR (or HER1) inhibitors	Erlotinib, gefitinib, cetuximab, panitumumab	Limited mucositis and aphthous-like lesions
HER inhibitors	Afatinib, dacomnitinib, lapatinib	Limited mucositis and aphthous-like lesions
Angiogenesis inhibitors	Sunitinib, cabozantinib, sorafenib, pazopanib, axitinib, bevacizumab	Nonspecific stomatitis
		Oral dysesthesia
		Aphthous-like lesions
BCR-ABL inhibitors	Imatinib	Lichenoid reactions
		"Blue-gray" hyperpigmentation (hard palate)
		Dysgeusia
BRAF inhibitors	Dabrafenib, vemurafenib, encorafenib	Mucosal hyperkeratotic lesions (linea alba, hard palate, gingiva)
		Gingival hyperplasia
		Secondary oral squamous cell carcinoma
ALK inhibitors	Crizotinib	Dysgeusia, lichenoid reaction
Hedgehog pathway inhibitors	Vismodegib	Dysgeusia, ageusia

mTOR: mechanistic target of rapamycin kinase, EGFR: epidermal growth factor receptor, HER1: human epidermal growth factor receptor 1, BCR-ABL: breakpoint cluster region-Abelson, BRAF: B-rapidly accelerated fibrosarcoma, ALK: anaplastic lymphoma kinase

the description of these lichenoid toxicities with crizotinib remains isolated until date and this must be confirmed over time. It may also be hypothesized that esophageal ulcerations, which have been described recently with this drug in several patients, may be related to a lichenoid inflammation.[5] The available histopathological analyses, however, do not support this theory.[5] Finally, although the overall incidence of skin rash seems to be higher, no skin or mucosal lichenoid reactions have been reported so far with the next-generation ALK inhibitors (e.g. alectinib, brigatinib).[1]

In conclusion, practitioners should be aware of oral lichenoid reactions occurring in association with targeted therapies, including the ALK inhibitor crizotinib, which may require specific management with topical or systemic corticosteroids.[3,4] Moreover, the follow-up of treated patients should include a systematic and regular oral examination. Finally, prospective evaluation of the oral region in patients treated with new-generation ALK inhibitors should also be promoted, to check whether this observation corresponds to a class effect or not.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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References

1. Camidge DR, Kim HR, Ahn MJ, Yang JC, Han JY, Lee JS, *et al.* Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer. N Engl J Med 2018;379:2027-39.
2. Ho YH, Chen CL. Crizotinib-induced lichenoid drug eruption in a patient with lung cancer. Cutis 2018;102:403-6.
3. Vigarios E, Epstein JB, Sibaud V. Oral mucosal changes induced by anticancer targeted therapies and immune checkpoint inhibitors. Support Care Cancer 2017;25:1713-39.
4. Sibaud V, Eid C, Belum VR, Combemale P, Barres B, Lamant L, *et al.* Oral lichenoid reactions associated with anti-PD-1/PD-L1 therapies: Clinicopathological findings. J Eur Acad Dermatol Venereol 2017;31:e464-9.
5. Sawada T, Maeno K, Joh T. Esophageal ulcer in a lung cancer patient. Crizotinib-induced esophageal injury. Gastroenterology 2015;149:e6-7.

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