

# Oral ulcers: clinical aspects. A tool for dermatologists. Part II. Chronic ulcers

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## Summary

Oral ulcers are generally painful lesions that are related to various conditions developing within the oral cavity. They can be classified as acute or chronic according to their presentation and progression. Acute oral ulcers are associated with conditions such as trauma, recurrent aphthous stomatitis, Behçet's disease, bacterial and viral infections, allergic reactions or adverse drug reactions. Chronic oral ulcers are associated with conditions such as oral lichen planus, pemphigus vulgaris, mucosal pemphigoid, lupus erythematosus, mycosis and some bacterial and parasitic diseases. The correct differential diagnosis is necessary to establish the appropriate treatment, taking into account all the possible causes of ulcers in the oral cavity. In this second part of this two-part review, chronic oral ulcers are reviewed.

## Introduction

Ulcers are secondary lesions characterized by a loss of tissue. They affect both the epithelium and underlying connective tissue,<sup>1,2</sup> and are very common lesions of the oral mucosa.<sup>3</sup>

## Classification

Oral ulcers are classified into two main groups:<sup>2,4</sup> acute ulcers with abrupt onset and short duration, and chronic ulcers with slow onset and insidious progression (Table 1). It is generally accepted that if the ulcer lasts for > 2 weeks, it can be considered as a chronic ulcer. In the first part of this review, we discussed acute oral ulcers, and in this second part, we move on to discuss chronic oral ulcers.

## Chronic oral ulcers

### Drug-induced oral ulcers

Although adverse drug reactions present more commonly with cutaneous features, they have also been documented as affecting the oral mucosa.<sup>5,6</sup> Drug-induced oral ulcers are usually single, isolated and located on the side of the tongue, and may be surrounded by an erythematous halo. They are relatively resistant to the usual treatments and can become chronic.<sup>2</sup>

Drugs reported to induce oral ulcers include some beta-blockers (labetabol),<sup>7</sup> immunosuppressants (mycophenolate),<sup>7,8</sup> anticholinergic bronchodilators (tiotropium),<sup>9</sup> platelet aggregation inhibitors (clopidogrel),<sup>10</sup> vasodilators (nicorandil),<sup>5,7,11</sup> bisphosphonates (alendronate),<sup>7</sup> protease inhibitors,<sup>7</sup> antibiotics, nonsteroidal anti-inflammatory drugs, antiretrovirals, antirheumatics and antihypertensives (enalapril, captopril).<sup>5-7</sup> In most cases, the mechanism by which these drugs produce oral ulcers has not been elucidated.<sup>7</sup>

A good differential diagnosis is important in these cases, and doctors should be aware of any new pharmaceutical drugs that may cause this type of

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**Table 1** Chronic oral ulcers.

Diagnosis	Clinical features
Drug-induced ulcers	Single, isolated ulcers, located on the side of the tongue, surrounded by an erythematous halo and resistant to usual treatments
Erosive lichen planus	Areas of atrophy, erosions or painful ulcers, generally resistant to conventional treatments
Pemphigus vulgaris	Bullae appear in oral cavity (posterior region), forming painful ulcers with necrotic fundus and erythematous halo
Mucous membrane pemphigoid	Spontaneous onset of bullae that readily rupture, giving rise to a highly painful ulcerated area (most common areas are palate and gingiva)
Lupus erythematosus	Erythema and oral ulcers, without induration and accompanied by whitish striae and a tendency to bleeding
Reiter's syndrome	Arthritis, urethritis, conjunctivitis and oral ulcers similar to those of recurrent aphthous stomatitis
Tuberculosis	Primary tuberculosis: deep, irregular, persistent and painful ulcer on the tongue, with rolled border and granulation tissue in the fundus Secondary tuberculosis: chronic ulcer, painful and indurated
Mycosis	Mycoses give rise to chronic ulcers on the oral mucosa, most commonly in immunocompromised patients
Other bacterial and parasitic diseases	<i>Klebsiella</i> and <i>Leishmania</i> spp. can produce chronic oral ulcers in HIV-infected patients
Eosinophilic ulcer	Large ulcer, generally in the tongue, with raised, indurated borders and white-yellowish fundus that may resemble a malignant lesion. Persists for weeks or months
Oral squamous cell carcinoma	Can produce ulcers (exophytic, endophytic or mixed). Metastatic lesions can appear as ulcers in the oral cavity

HIV, human immunodeficiency virus.

lesion. Lesions usually disappear when the drug is withdrawn, but this is not always feasible.<sup>2,5,6</sup> Account should also be taken of possible cross-reactions with flavour-enhancing and aroma-enhancing agents in some foods or drinks.<sup>12</sup>

**Lichen planus**

Lichen planus (LP) is a chronic disease that affects the skin and mucosa. It can appear in the oral mucosa as whitish striae (reticular LP), or as areas of atrophy, erosions or painful ulcers (erosive LP) (Fig. 1).



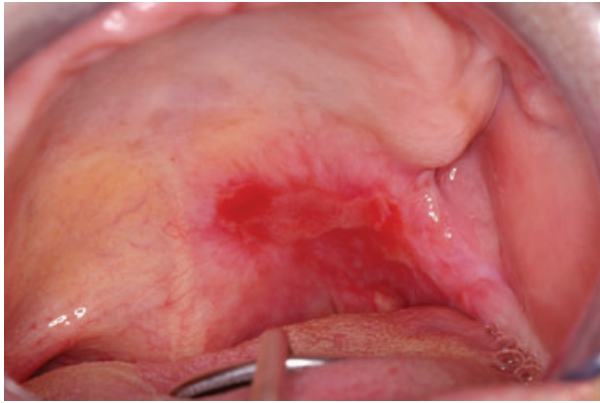
**Figure 1** Erosive lichen planus: ulcers surrounded by whitish striae.

Differentiating LP from pemphigus vulgaris (PV) and mucous membrane pemphigoid (MMP) is difficult, and the final diagnosis requires histological confirmation of a biopsy.<sup>13</sup> The aetiology of this disease has been related to a cytotoxic T cell-mediated attack on basal keratinocytes.<sup>13,14</sup> LP is considered a precancerous lesion or state.<sup>2,13</sup> Initial treatment is usually with corticoids, but erosive LP is commonly resistant to these drugs, requiring the application of topical immunosuppressants (e.g. tacrolimus) that inhibit the response of cytotoxic T cells.<sup>14</sup>

**Pemphigus vulgaris**

PV is an immune-mediated chronic vesiculobullous mucocutaneous disease that almost invariably has oral features. Over half of PV cases have the initial lesions in the oral mucosa. PV is characterized by the onset of acantholytic intraepithelial blisters caused by the action of antibodies (IgG) against specific proteins (desmogleins) located in desmosomes.<sup>15,16</sup>

Bullae appear in the oral cavity, preferentially on the posterior oral regions. They readily rupture, forming painful ulcers with a necrotic fundus and erythematous halo. If the gingiva is involved, chronic desquamative gingivitis is usually observed. The final diagnosis requires histological examination of a biopsy, which shows acantholytic intraepithelial vesicles and Tzanck cells. Direct immunofluorescence study of the tissue



**Figure 2** Mucous membrane pemphigoid: ulcer on the soft palate.

reveals the presence of IgG or IgM and complement fragments in intercellular spaces.<sup>15,16</sup>

### Mucous membrane pemphigoid

This group of immunological diseases mainly affects mucosae, with subepithelial bullae and deposits of immunoglobulin G, immunoglobulin A or complement fraction C3 throughout the basal membrane. MMP occasionally involves the skin, oral and ocular mucosa, oesophagus, nasopharynx and larynx. Patients with MMP produce antibodies that attack several autoantigens of the mucosal or epidermal basal membrane. The most common autoantigens are laminin-5, type IV collagen, laminin-6, subunit  $\beta 4$  of integrin, uncein, and bullous pemphigoid antigens 1 and 2.<sup>17</sup>

MMP develops in the oral mucosa with the spontaneous onset of bullae that readily rupture, giving rise to a very painful ulcerated area. The most commonly involved areas are the palate (Fig. 2) and gingiva, commonly in the form of chronic desquamative gingivitis.<sup>17</sup>

### Lupus erythematosus

Lupus erythematosus (LE) is an autoimmune disease of the connective tissue that appears in two forms: systemic LE and discoid LE. Both forms give rise to oral features similar to those of lichen planus, and they may precede or follow the cutaneous features. Discoid lesions and facial erythema in a 'butterfly' pattern appear on the skin, and erythematous and ulcerated areas develop on the oral mucosa, without induration and with the onset of whitish striae and a tendency to bleeding.<sup>18,19</sup>

### Reiter's syndrome

Reiter's syndrome is characterized by arthritis, urethritis, conjunctivitis and oral ulcers similar to those of recurrent aphthous stomatitis.<sup>1</sup> It is an uncommon disease, and the main diagnostic criterion is a positive reaction for human leucocyte antigen B27.<sup>20</sup>

### Tuberculosis

Tuberculosis (TB) is a chronic granulomatous infectious disease, mainly caused by *Mycobacterium tuberculosis*, which has regained prevalence as a severe complication of human immunodeficiency virus (HIV) infection.<sup>21–24</sup> Oral lesions are rare, resulting from primary tuberculosis of the oral cavity, or secondary to active pulmonary tuberculosis. In the former case, the disease presents as a deep, irregular, persistent and painful ulcer, commonly located on the side of the tongue, with a rolled border and granulation tissue in the fundus.<sup>21,22</sup> Secondary tuberculosis of the oral cavity presents as a chronic ulcer, generally painful and indurated.<sup>24</sup> Diagnosis requires histological examination of a biopsy.<sup>21,24</sup>

### Infections caused by fungi

The most common mycoses in the oral cavity are candidiases, which typically give rise to nonulcerous types of lesion, but other mycoses can also present as oral ulcers.

*Cryptococcus neoformans* is a fungus that usually affects patients with acquired immunodeficiency syndrome. Oral ulcers are rare and generally secondary to an infection in other organs, but nevertheless must be taken into account in the differential diagnosis.<sup>25</sup>

*Histoplasma capsulatum* is responsible for histoplasmosis, generally in immunocompromised patients, which is an infection produced by inhaling the spores of this fungus. It is a rare but severe disease, commonly appearing in the form of chronic oral ulcers. The final diagnosis requires histological examination of a biopsy.<sup>3,26</sup>

Exposure to the fungus *Aspergillus fumigata* can also produce a disease associated with chronic oral ulcers. This rare condition also mainly affects immunocompromised patients.<sup>3,27</sup>

Fungi of the genera *Absidia*, *Rhizopus*, *Rhizomucor* or *Mucor* produce zygomycosis, a fungal infection that can give rise to ulcers with a necrotic halo on the palate. Diabetes and immunodeficiency diseases have been related to a higher risk of this infection.<sup>28</sup>

### Other bacterial and parasitical diseases

*Klebsiella rhinoscleromatis* is an aerobic cocobacillus that causes a chronic granulomatous infection known as oral or respiratory scleroma, which can involve the oral cavity.<sup>29</sup>

Leishmaniasis is a parasitical disease caused by protozoa of the *Leishmania* genus. It is transmitted by mosquitoes and may occasionally produce ulcers on the hard or soft palate. It is rare in developed countries and is most commonly observed in patients with HIV infection.<sup>30</sup>

### Eosinophilic ulcer

Eosinophilic ulcer of the oral mucosa is an uncommon, benign, self-limiting and generally asymptomatic lesion that heals spontaneously. Its aetiology is uncertain, but it is associated with traumas. It presents as a large ulcer, generally on the tongue, with wide indurated borders and a yellowish-white fundus that may resemble a malignant lesion. It develops rapidly and can remain for weeks or months. Histologically, a leucocyte-rich inflammatory infiltrate confirms the diagnosis and excludes the possibility a malignant tumour such as squamous cell carcinoma (SCC).<sup>31</sup>

### Oral squamous cell carcinoma

All oral cancers can produce ulcer. The most common malignancy in the oral cavity (90% of tumours) is



**Figure 3** Oral squamous cell carcinoma: exophytic ulcer on the lateral border of the tongue.

oral SCC, and hence this is also responsible for the most cancer-associated tumours. These ulcers can be exophytic (Fig. 3), endophytic or mixed.<sup>2</sup> Additionally, metastatic lesions of primary tumours at other sites can appear as ulcers in the oral cavity.<sup>1</sup> The detection of this type of ulcer is of great importance because the tumour has a good prognosis if accessible and diagnosed at an early stage. Health professionals should educate patients to recognize suspicious lesions and to know the risk factors (e.g. tobacco and alcohol use for such malignancies). A biopsy (or second opinion) should be obtained for suspicious lesions and ulcers that persist after the removal of possible causal agents, as these are the only reliable methods for establishing a definite diagnosis.<sup>2,32</sup>

### Indications for biopsy of an oral ulcer

A biopsy is indicated in case of ulcer (i) of unknown origin that remains without signs of healing after 2 weeks; (ii) of probable known aetiology (after clinical examination and diagnostic tests) that do not respond to appropriate treatment after 2 weeks; and (iii) believed to be caused by precipitant factors, which do not show signs of healing 2 weeks after removal of these factors. In small ulcers (< 5 mm in diameter) an excisional biopsy is recommended (including 2 mm of perilesional tissue), whereas in larger ulcers (> 5 mm in diameter) an incisional biopsy is preferred. The specimen must include part of the ulcer and the perilesional tissue, including the unaffected surrounding epithelium. The centre of the ulcer alone usually does not show diagnostic features. Scalpel or punch biopsies are preferred; other techniques (e.g. lasers, electrical scalpels) are not recommended.

### Conclusion

Oral ulcers are lesions occurring in the oral mucosa. Aphthae and traumatic ulcers are the most common, but the most serious are those associated with oral cancer. In many cases, it is not possible to establish a definitive diagnosis without histological examination of a biopsy, and thus a biopsy should be taken from any lesion persisting for > 2 weeks or any with a suspicious appearance. Histological examination of a biopsy should confirm whether the ulcer is a possible malignant lesion, and establish both the definitive diagnosis and correct treatment.

### Learning points

- The most common diseases associated with chronic oral ulcers are erosive LP, PV, MMP, LE, Reiter's syndrome, TB, some mycoses, eosinophilic ulcers and oral cancer.
- Among the drugs reported to induce chronic oral ulcers are beta-blockers, immunosuppressants, anticholinergic bronchodilators, platelet anti-aggregants, vasodilators, biphosphonates, protease inhibitors, antiretrovirals, antibiotics and antihypertensives.
- LP is considered to be a precancerous lesion or state, and its aetiology has been related to a cytotoxic T cell-mediated attack on basal keratinocytes.
- Around 50% of cases of PV begin in the oral mucosa, and its aetiology is related to the action of antibodies against specific proteins (desmogleins) located in desmosomes.
- MMP mainly affects mucosae. Patients produce antibodies that attack several autoantigens of the mucosal or epidermal basal membrane.
- Systemic and discoid LE can give rise to oral features similar to those of LP, and they may precede or follow cutaneous features.
- Oral lesions in TB are rare, resulting from primary TB of the oral cavity or secondary to active pulmonary TB.
- Mycoses of the oral cavity (excluding candidiasis) give rise to chronic oral ulcers mainly in immunocompromised patients.
- Eosinophilic ulcer of the oral mucosa is uncommon, benign, self-limiting and generally asymptomatic. It may resemble a malignant lesion, but a biopsy will exclude a malignant tumour.
- All oral cancers can produce ulcers, and the detection of this type of ulcer is important because the tumour has a good prognosis if it is diagnosed at an early stage.

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