Clinical and Experimental Dermatology

Oral ulcers: clinical aspects. A tool for dermatologists. Part I. Acute 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 be 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 the first part of this two-part review, acute oral ulcers are reviewed.

Introduction

Ulcers have several causes and are characterized by a loss of tissue that affects both the epithelium and underlying connective tissue.[1,2] They are very common in the oral mucosa[3] and are generally painful.[2]

In establishing a diagnosis, it is important to know the relative frequency or prevalence of these lesions in the particular time and place. In 1976, Axéll found that the most common lesions of the oral mucosa in Sweden were ulcers (aphthae) associated with recurrent aphthous stomatitis, followed by those associated with recurrent herpes labialis, prosthesis-induced stomatitis and geographical tongue.[4] In 2004, Shulman *et al.*[4] reported that the most common lesions in the USA were related to dental prostheses, although the prevalence of different lesion types varied according to age, gender, ethnicity and tobacco consumption.

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Classification

Oral ulcers are classified into two main groups:[2,5] acute ulcers with abrupt onset and short duration (Table 1), and chronic ulcers with slow onset and insidious progression. There is no consensus about the duration that determines when an oral ulcer has become chronic, but is generally accepted that if the ulcer lasts for > 2 weeks, it can be considered as a chronic ulcer. In this first review, acute oral ulcers are described; chronic oral ulcers will be discussed in the second review.

Acute oral ulcers

Traumatic ulcer

These very common ulcers usually appear in short, painful episodes.[2] The most common causative agents are trauma, chemicals, electricity and heat.

Trauma, such as that caused by sharp teeth and tooth edges, can produce ulcers. Self-inflicted lesions can sometimes be observed in the oral mucosa of children and of patients with mental disorders.[6–8] Self-induced traumatic ulcers can also be caused by incorrect tooth brushing[9] and by postanaesthesia biting of the tongue or lower lip (Fig. 1).[2] Decubitus

Table 1 Acute oral ulcers.

Diagnosis	Clinical features
Traumatic ulcer	Ulcers appear in short and painful episodes. White or yellowish central clear area with erythematous halo
Recurrent aphthous stomatitis	One or multiple recurrent and painful ulcers. Well-defined, round or oval ulcers covered by a white or greyish pseudomembrane and surrounded by an erythematous halo
Behçet's disease	Recurrent oral (aphtae) and genital ulcers, skin lesions and ocular, muscloskeletal, cardiovascular, gastrointestinal and neurological symptoms
Viral infections	Vesicles that readily rupture, giving rise to painful ulcers covered by a yellowish membrane
Bacterial infections	Primary syphilis: deep non-painful ulcers with elevated and indurated borders (chancre). Secondary syphilis: mucosal ulcers and patches
Necrotizing sialometaplasia	Extensive deep ulcers with indurated borders located in hard or soft palate
Allergic reactions	Features range from erythema to ulceration in oral mucosa
Erythema multiforme	Erythema, vesicles and ulcers in oral mucosa. Involvement of the lips in almost all cases, leaving scabs. Typical target skin lesions
Blood disease-related	Ulcers similar to those of recurrent aphtous stomatitis

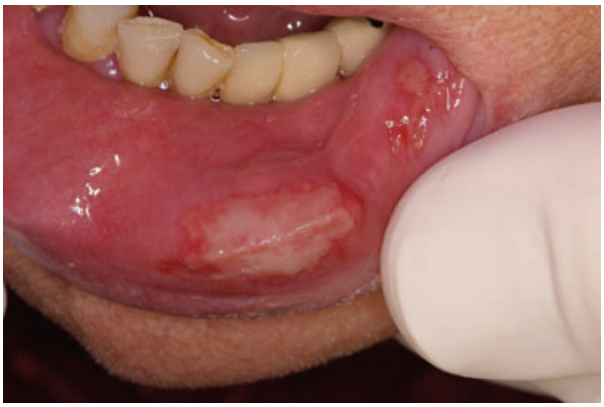

Figure 1 Post-anaesthesia traumatic ulcer on lower lip.

ulcers can be produced by dental prostheses.[10] They are characterized by acute pain of moderate intensity and by a white or yellowish central clear area with an erythematous halo.[2]

Caustic ulcers are produced by direct contact of the oral mucosa with acids or strong alkalis. Oral mucosal ulcers have been related to topical acetylsalicylic acid, pancreatic supplements, potassium tablets, bisphosphonates, trichloroacetic acid and some oral care products, especially in patients with swallowing difficulties and the resulting prolonged oral exposure to such substances.[11–14] Oral lesions have also been caused by the topical application of cocaine.[13,15]

Electrical burns of the oral cavity are rare, but there have been some rare reports in children after biting or sucking electric cables, sockets or plugs.[16] Ulcers can also be produced by direct contact with excessively hot food (such as food cooked by microwaves) or cold food.[17]

Recurrent aphthous disease

Recurrent aphthous stomatitis (RAS) is an inflammatory disease of unknown origin characterized by ≥ 1 recurrent and painful ulcers (aphthae) in the oral mucosa. RAS affects 20% of the general population and is the most common form of oral ulceration.[2,3,12,18,19]

Various factors have been implicated in the aetiology of RAS, including familial and genetic factors, autoimmune factors, hormonal changes, hypersensitivity to certain foods, drugs, blood deficiency, zinc deficit, stress, tobacco, local traumas, infectious agents and various systemic diseases.[18,19] Aphthae are less common in patients who smoke, suggesting that tobacco plays a protective role.[12,20]

There are three well-differentiated clinical forms: minor aphthae, major aphthae and herpetiform aphthae.[12,18,19]

Minor aphthae are the most common (80%). They are characterized by the formation of 1–5 well-defined superficial ulcers that are round or oval with a diameter < 10 mm, covered by a white or greyish pseudomembrane and surrounded by an erythematous halo. They normally appear in the nonkeratinized mucosa and are rare in the keratinized gingiva, palate or tongue dorsum. Lesions appear over variable time periods and disappear in 10–14 days without leaving scars.[12,18,19]

Major aphthae (10%) (also known as periadenitis mucosa necrotica recurrens or Sutton's disease) are similar to minor aphthae but are larger (> 10 mm) and very painful. They can occur as single or multiple ulcers. They may appear at any site but have a predilection for the lips, soft palate (Fig. 2) and throat. They can persist for ≥ 6 weeks and commonly leave scars.[2,12,18,19]

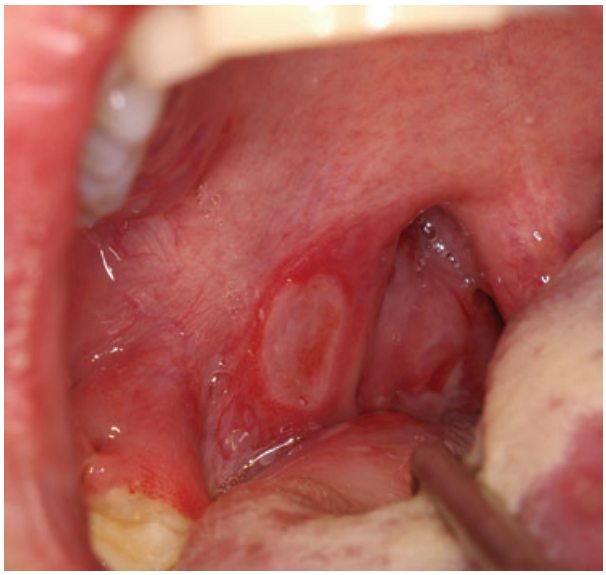

Figure 2 Recurrent aphthous stomatitis, with major aphthae on soft palate.

Herpetiform aphthae (5–10%) are characterized by the presence of multiple (50–100), small (2–3 mm) and painful ulcers throughout the oral cavity, which tend to coalesce and form ulcers of larger size. They usually heal within 7–10 days without leaving scars.[12,18,19]

The diagnosis of RAS is based on the clinical history of the patient and on clinical findings, but there is no specific diagnostic test.[18] It is important to rule out an association with systemic disease [e.g. Behçet's disease (BD), cyclic neutropenia, coeliac disease, immunodeficiency, FAPA (fever, adenitis, pharyngitis, and aphthous ulcers) syndrome, mouth and genital ulcers with inflamed cartilage (MAGIC) syndrome, Sweet's syndrome or Reiter's disease] and to explore possible causative factors, including blood deficiencies.[2,12,21–23] This disease has unknown origin, therefore there is no specific treatment for it.[18,24]

Behçet's disease

BD is a systemic vasculitis characterized by recurrent oral and genital ulcers, skin lesions and ocular, musculoskeletal, cardiovascular, gastrointestinal and neurological symptoms.[12,25] Onset is usually during the third and fourth decade of life.[25] Genetic, environmental, infectious, immunological and haematological factors have been implicated in its aetiology.[25]

Major, minor and herpetiform aphthae appear in the oral cavity in this disease, generally on oral mucosa, gingiva, lips, soft palate and pharynx. They are commonly the first symptom of the disease and eventually appear in all patients.[12,25]

Infections caused by viruses

The clinical oral features of herpes simplex virus depend on whether the infection is primary or secondary.[2,3,26] The primary infection is called primary herpetic gingivostomatitis. It can be asymptomatic or very mild in very young patients but is associated with more severe general symptoms at an older age of onset.[26] Oral features consist of gingivitis, followed after 2–3 days by the formation of vesicles that readily rupture, giving rise to painful ulcers covered with a yellowish membrane, which tend to coalesce. They are mainly localized to the lips, tongue, oral mucosa, palate and pharynx.[2,26] The ulcers usually heal spontaneously after 10 days with no sequelae,[2,26] and are accompanied by submandibular lymphadenitis, swallowing difficulties and halitosis.[2,26] Herpes labialis is the first feature of secondary infection by type 1 herpes simplex,[2,3,26] which occurs as vesicles and ulcers on the lip and lip vermilion that leave scabs[2] after spontaneous healing within 7–10 days.[26] Recurrent intraoral herpes is the second feature of this secondary infection, with very painful ulcers mainly localized to the keratinized gingiva and hard palate. They spontaneously disappear after 7–10 days.[2]

In varicella zoster virus infection (chickenpox), there is an initial prodromic period, after which papular and pustular skin lesions develop, with vesicles and ulcers on the trunk. Depending upon the severity of the disease, vesicles can appear on the palate.[26,27] Subsequently, the virus remains in nerves and may be reactivated in adulthood, giving rise to mononeuropathies or polyneuropathies[27] that present as herpes zoster (shingles).[2,26] The most common sequela is postherapeutic neuralgia.[26]

Coxsackie virus produces two clinical pictures that involve the oral cavity.[2,26] Herpangina is a systemic disease that is common in childhood, characterized by fever and sore throat followed by vesicles in the oropharynx, mainly in pillars over the soft palate, uvulae, palate and amygdales. These vesicles disappear spontaneously in 4–5 days.[26] Hand, foot and mouth disease, common in school-age children, is characterized by vesicles in the oral cavity, palms of hands and soles of feet.[2] It disappears without treatment within a week.[26]

Epstein–Barr virus produces several clinical pictures, including infectious mononucleosis with fever syndrome, oral ulcers, palatal petechiae and systemic disorders.[2,3,26]

Cytomegalovirus can cause large and chronic oral ulcers in immunodepressed patients.[3]

Measles virus can affect the oral cavity during systemic infection, causing Koplik's spots, gingivitis and pericoronaritis alongside the typical systemic features.[28]

Human immunodeficiency virus causes oral lesions, which can occasionally be the first sign of the disease.[2,26,29] Large, deep ulcers appear, mainly involving the vestibular and pharyngeal mucosae. This ulceration is related to opportunistic pathogens in the oral cavity.[3,29]

Infections caused by bacteria

Syphilis is a sexually transmitted disease caused by the anaerobic spirochaete *Treponema pallidum*. It is associated with skin and mucosal lesions in its acute phase.[30] A chancre, a deep nonpainful ulcer with increased and indurated borders, appears during the initial stage of primary syphilis. The ulcers can be genital or oral, and heal spontaneously.[30] Secondary syphilis gives rise to several systemic features, including mucosal ulcers and patches; and tertiary syphilis is characterized by the presence of syphilitic gummas (pain-free ulcerated nodular lesions on hard palate or tongue) and nerve and vascular changes.[30]

Gonorrhoea presents with several oral features, ranging from mild erythema to deep ulcers covered by a pseudomembrane.[31]

Necrotizing sialometaplasia

Necrotizing sialometaplasia is an uncommon disease that gives rise to extensive, deep ulcers with indurated borders (Fig. 3), mainly localized to the hard and/or soft palate.[3] It is a benign and self-limiting necrotizing inflammatory disease of the minor salivary glands but can simulate a malignant neoplasm.[32] The cause is believed to be an ischaemia secondary to trauma or to damage from a chemical or biological agent.[3,32]

Allergic reactions

Allergic reactions, ranging from erythma to ulceration, can appear in the oral mucosa after the topical application of numerous substances and medicines (contact stomatis). They are usually late cell-mediated immune reactions that remit when the substance is withdrawn.[13,33]

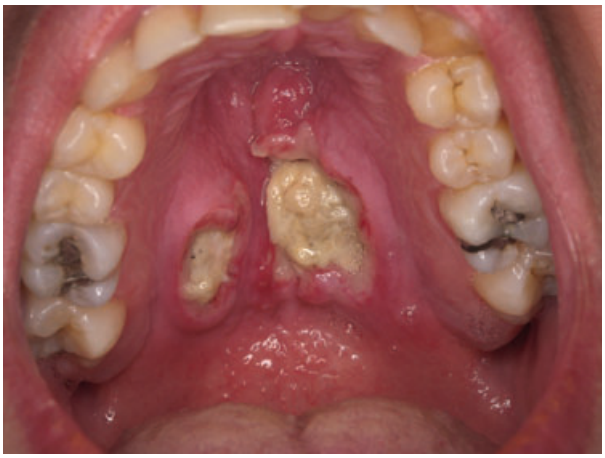

Figure 3 Necrotizing sialometaplasia. Deep ulcers with indurated borders on the palate.

Erythema multiforme

Erythema multiforme (EM) is a vesicobullous mucocutaneous disease that is occasionally life-threatening. The pathogenic mechanisms are not precisely known, but it is believed to be related to infections and drug treatments.[13,33,34] The diagnosis is usually established by exclusion of other diseases, because there is no conclusive specific test.[34]

There are three types of exudative EM: toxic epidermal necrolysis (TEN) or Lyell's syndrome, EM major [commonly identified with Stevens–Johnson syndrome (SJS)] and multiform erythema minor, in decreasing order of severity.[34]

The minor form is acute and self-limiting and can be episodic or recurrent. Typical target lesions symmetrically cover < 10% of the body surface area (BSA). The mucosae are sometimes involved, most commonly the oral mucosa, with erythema, vesicles and ulcers and involvement of the lip in almost all cases, leaving scabs.[34]

The major form is also a self-limiting, occasionally recurrent, disease, characterized by the symmetrical involvement of the skin and at least two different mucosae, again affecting < 10% of the BSA but more severely than in the minor form.[34] SJS is considered by some authors to be the same disease as EM major, whereas others consider it a distinct condition.[34]

TEN is characterized by erythematous patches, skin lesions at atypical target sites, severe mucosal erosions and bullae and epidermal detachment of > 30% of the BSA.[13,34]

Ulcers related to blood diseases

Oral ulcers may appear in diseases associated with blood deficiencies, e.g. anaemias, leukaemias, lymphomas, multiple myeloma and neutropenias,[3] especially cyclic neutropenia, which causes ulcers similar to those of recurrent aphthous disease.[12]

Principles of topical treatment on the oral mucosa

An exhaustive medical history and oral exploration of the patient, in conjunction with complementary diagnostic methods, are essential in order to achieve a specific diagnosis of the oral ulcers. The diagnosis, the severity of the oral disease, and the presence or absence of extraoral lesions are the key factors that determine the selection of a topical treatment.

The patient should avoid precipitant factors if they are present (e.g. in traumatic ulcers). Infectious diseases (of viral, bacterial or fungal aetiology) must be managed with the appropriate (antiviral, antibiotic or antifungal) topical and/or systemic treatment available. For oral ulcers of unknown origin or related to autoimmune diseases, topical corticosteroids (TC) are currently central to their treatment.

The basic rule is that a TC of a potency appropriate to the severity of the clinical symptoms should be used, at the lowest possible concentration and frequency compatible with maintaining the effectiveness of the treatment, in a vehicle that minimizes the area exposed to the drug. Mild and moderate potency steroids such as 1% hydrocortisone hemisuccinate or 0.1–0.2% triamcinolone acetonide are generally considered appropriate for the treatment of clinically unimportant autoimmune diseases of the oral mucosa, and for maintenance treatment in more severe diseases that have responded to systemic corticosteroids and/or high-potency TCs. High-potency steroids such as 0.025–0.05% clobetasol propionate, 0.05% fluocinonide acetonide or 0.025–0.1% fluocinolone acetonide are considered appropriate for the treatment of clinically severe diseases.

In cases of oral ulcers confined to single locations, use of TC in an adherent vehicle such as orabase (carmellose sodium) or denture adhesive paste is indicated. Patients prescribed TC in an adherent vehicle should be instructed to apply a small amount to the target area after meals (3–4 times per day), and not to eat or drink for at least 30 min after application.

In cases of multiple oral ulcers affecting several locations, aqueous TC solution mouthwashes are preferred. These are recommended to be used 3–4 times per day, after meals, and patients should not to eat or drink for at least 30 min after use. The patient should hold the liquid in the mouth without swallowing for as long as possible, generally for 10–15 min. Patients must be clearly informed about the need to avoid ingesting the drug. If pain is present, 2% lidocaine can be added to the formulation. In cases of long-term treatment, the addition of nystatin 1×10^6 IU/mL to the formulation is recommended to prevent oral candidiasis.

Finally, patients should be given clear instructions on oral hygiene. The pain, inflammation and bleeding from the ulcers may often lead to inadequate oral hygiene, resulting in poor plaque control and exacerbation of erosive disease.[24,35–37]

Learning points

- Oral ulcers are very common lesions in the oral mucosa, and are generally painful. They are characterized by a loss of tissue (epithelium and underlying connective tissue).
- The most common diseases that may develop acute oral ulcers are recurrent aphthous stomatitis, BD, bacterial and viral infections, EM, necrotizing sialometaplasia, allergic reactions and blood diseases.
- Traumatic ulcers are very common acute oral ulcers, often caused by trauma, electricity, chemicals and heat.
- Recurrent aphthous stomatitis is an inflammatory disease of unknown origin characterized by ≥ 1 recurrent and painful ulcers (aphthae) in the oral mucosa. There are three clinical forms: minor aphthae, major aphthae and herpetiform aphthae.
- BD is a systemic vasculitis characterized by oral recurrent ulcers among other symptoms. Minor, major and herpetiform aphthae may appear.
- In viral infections, the principal symptom is the appearance of vesicles and ulcers that heal spontaneously in 5–10 days.
- Syphilis and gonorrhoea give rise to several oral features depending on the stage of the disease.
- Necrotizing sialometaplasia is a benign and self-limiting necrotizing inflammatory disease of the minor salivary glands, but can simulate a malignant neoplasm.
- There are many substances and medicines that may produce contact stomatitis. This reaction decreases when the substance is withdrawn.
- There are three types of erythema multiforme: TEN or Lyell's syndrome, erythema multiform major (commonly identified with SJS) and EM minor, in decreasing order of severity.

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