Recurrent Aphthous Stomatitis

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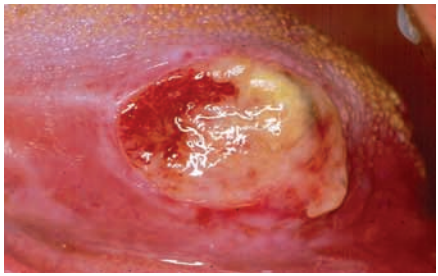
Introduction

Recurrent aphthous stomatitis (RAS) is defined by the presence of ulcerous lesions in the oral mucosa, with well defined clinical characteristics, highly prevalent in the general population and with a favorable prognosis. Recurrent aphthous stomatitis has received different names over time, such as aphtha or common aphtha, vulgar aphtha, Miculicz' aphtha, Sutton's aphtha, periadenitis mucosa necrotica recurrens, recurrent aphthous ulceration and others. As the manifestation occurs quite often in the buccal mucosa and has uncertain etiologic bases, lay people have a distorted view of its reality, so they often suggest causes that have no foundation in fact, and suggest totally innocuous treatments or even harmful treatments that can delay treatment of more aggressive lesions. It is important to remember that the lesions of RAS are very similar to early ulcers in spindle cell carcinoma, the most frequent malignant tumor in the mouth. Lesions in RAS usually resolve in five to seven days, while the carcinomatous ulcer evolves both in extension and depth and results in a hardening at the base of lesions. It can be concluded that characteristics of both of these common lesions must be very well known.

For the general population, the term aphtha refers to any lesion in the oral cavity, whatever the symptoms or other clinical aspects. Actually, various ulcerous lesions in oral mucosa can have similar clinical aspects but some characteristics that lead to evident clinical differentiation. **Traumatic ulcers**, for example, caused by high- intensity, instantaneous, physical mechanical trauma, present a single lesion with clinical characteristics different from those of RAS. The traumatic lesion is wider and deeper, has irregular borders, and its clinical cycle varies from seven to 15 days, depending on its dimensions and location (**Figure 1**). **Herpes simplex** lesions are always preceded by multiple vesicles. In **pemphigus vulgaris** the ulcers are shallow and wide, recovered by a membrane formed by some of the epithelium detached after the vesicles and/or blisters were developed. **Lichen planus**, on the other hand, shows ulcers with white streaks, and this is the aspect that the clinician should examine with a magnifying glass. In cases of **Leishmaniasis**, borders of the ulcers have a "sun ray" aspect. Deep ulcers with whitish areas alternating with scattered red petechiae are found in **Paracoccidioidomycosis**.

Figure 1. Traumatic ulcer



Etiology

Aphthous ulcers, among the most common causes of recurrent oral lesions, must be distinguished from other conditions such as viral herpes simplex and viral coxsackie infection, agranulocytosis, and Behçet´s disease. The etiologic basis of aphthous ulcers remains uncertain, although a number of infectious agents, including virus, have been implicated. The most prevailing hypothesis suggests that the mechanism for mucosal ulceration is autoimmune in nature.

No defined etiopathogenesis has been identified and several beliefs have thus been developed, relating RAS to causes that have no scientific logic as a basis. **Very often, patients believe that their aphtha is caused by "*oral acidity*" originated in the stomach or resulting from acid substances in contact with the oral mucosa.** Although pH of the oral cavity is usually around 7, slight alterations are observed and are controlled by the buffering effect of saliva, as it has high levels of calcium carbonate. **In order to cause lesions in the oral mucosa, this "acidity" should have very low pH values, which does not happen.** It is the opposite that actually occurs. When caustic soda, extremely alkaline, is accidentally ingested and comes in contact with the mucosa it causes deep necrotic ulcers, showing that alkaline substances can be more aggressive in the mucosa than the assumed effect of acids.

It is quite complex to establish a plausible explanation to understand the direct cause-effect relationship between RAS and gastrointestinal aspects of an individual. The pH of gastric juices does not have the potential to cause chemical trauma in oral mucosa, and the anatomy of the digestive tract and its sphincters make this contact more difficult. **This contact can occur when there is reflux, but the chemical aggression on oral mucosa will not result in ulcers. Patients with varied systemic pathologic conditions who vomit quite often do not develop RAS for this reason.**

Several theories have been proposed for the etiopathogenesis of RAS, some of the more convincing being:

- ***inheritance***: genetic predisposition.
- ***hormone factors***: it has been shown that women developing aphthae in certain periods of their cycle have no aphthae during pregnancy, which indicates a possible association.
- ***nutritional deficiencies***: a deficiency of vitamin B12 and folic acid could be associated with the occurrence of RAS.

● ***psychosomatic factors***: in daily practice, it is observed that in individuals with mild and sporadic RAS and even in those who have never had a single episode, lesions of RAS can appear as a result of an emotional disorder with variable degrees of intensity or after prolonged stress; sometimes the lesions are very aggressive while the emotional cause persists. Signs and symptoms tend to disappear when the psychological process is controlled. An attempt to explain this situation is related to Merkel cells normally found in oral epithelium. When an intense emotional disorder occurs, these cells can rupture, releasing catecholamines and causing vasoconstriction, which can result in ischemia and posterior necrosis, clinically favoring the occurrence of RAS.

● ***microbiological agents***: another possibility is the relationship between RAS and Lancefield streptococcal group L, which could be inoculated into epithelium with a infiltrative local anesthesia or some other trauma. Herpes simplex virus, varicella zoster virus or even cytomegalovirus can be present in oral epithelium without causing an evident infection, especially in carriers of HIV, and could then be inoculated.

● ***traumatic factors***: a low-intensity mechanical trauma can be associated with the development of RAS when the epithelium is ruptured.

● ***immune factors***: in some individuals there seems to be an interaction between several factors associated with the development of RAS. However, the fundamental and major role of **loss of immune balance** should be stressed, as it is present in most cases. Patients who are immunologically depressed in prolonged recovery after surgery or in convalescence after a chronic consumptive disease very often develop ulcerous lesions compatible with RAS. In the same manner, patients who for some reason are receiving immunomodulatory treatment do not have these ulcers with the same frequency.

In some cases, the triggering agent can be more easily identified. However, **in order to establish a cause-effect relationship, the patient should be asked to fill in a diary, writing down everything used as food, personal hygiene products, cosmetics, drugs, emotional instabilities, among other things. The diary should also include everything not routine, such as the day when RAS appeared, its evolution, the number and sites of lesions. It is thus possible to identify triggering and modifying factors using this information, obtaining parameters for its control and perhaps cure.**

Diagnostic methods

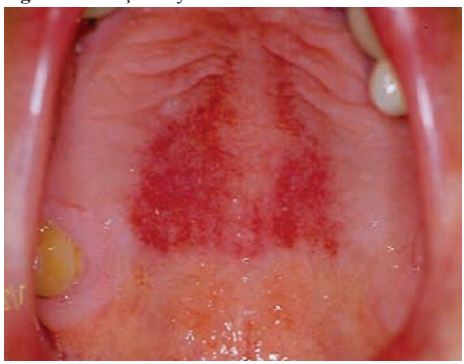
Complementary examinations such as a hemogram, exfoliative cytology, biopsy and serology are not very helpful in the diagnosis of RAS, which is eminently clinical. The diagnosis is established a few days after the first visit to the physician by the behavior of the lesion, as it has a characteristic cycle of manifestation, and there is no laboratory test that identifies the pathologic conditions, whether serological, cytological or biopsy.

Clinical aspects

Recurrent aphthous stomatitis is always presented as a painful ulcer developed in the oral mucosa, that tends to recur. It can be present in the clinical course of some rheumatologic, infectious, and immune diseases such as Crohn's

disease, Behçet's syndrome (**Figure 2**), idiopathic ulcerative colitis, Reiter's disease and others. In general, patients indicate prodromal symptomatology such as pain, burning, itching, mild edema, local hyperthermia, a sensation of roughness, erythema. If it is recognized, this can help in early treatment. No other previous signs are observed, such as vesicles and/or blisters, which differentiate it from a diagnosis of other lesions such as those of herpes.

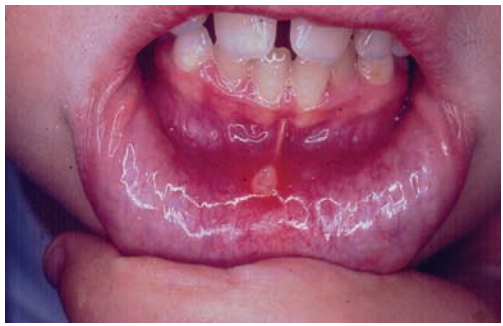
Figure 2. Behçet's syndrome



Three major clinical variants are recognized: (1) minor aphthous ulcers, (2) major aphthous ulcers, and (3) herpetiform aphthous ulcers. The lesions of RAS are polymorphous and can be clinically classified as follows.

(1) Minor form (common aphtha) is the most frequent, found in approximately 80% of all cases. It occurs mainly in children from ten to 14 years of age as a shallow ulcer with maximum diameter of five millimeters, uniformly circular, with a clear outline (**Figure 3**). The ulcers appear gray-yellow, often with a raised and erythematous margin, and are exquisitely painful. It has an erythematous halo around a single lesion or several halos around various smaller lesions, distributed in the non-keratinized mucosa that lines the oral cavity.

Figure 3. Minor aphta

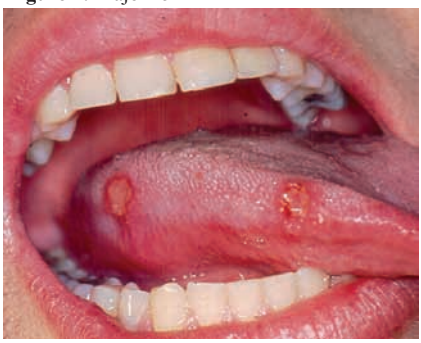


Minor aphthous ulcers appear as a number of small ulcers on the buccal and labial mucosa, the floor of the mouth, or the tongue. The palatal soft tissues, pharynx and tonsillar fauces are rarely involved. Enlargement of lymph nodes is seen only with secondary bacterial infection. A prodromal stage is usually present. The course of ulceration varies from a few days to several weeks, usually disappearing after seven days, followed by spontaneous healing. A very important clinical finding is that the minor form of RAS occurs mainly in little-keratinized or non-keratinized mucosa. This aspect helps or even defines the diagnosis. Another fact, no less interesting, is that mucosa in smokers tends to be more keratinized, which makes outbreaks of RAS more difficult.

(2) Major form (periadenitis mucosa necrotica recurrens) occurs in 10% of all cases, mostly in women and at an older age. Major aphthous ulcers are more protracted and last up to several months. All areas of the oral cavity, including the

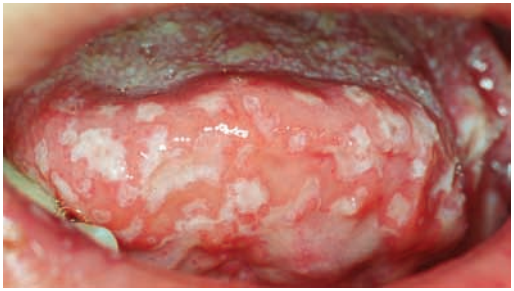
soft palate and tonsillar areas, may be involved. It presents as a deep and extensive ulcer, single or a few, distributed throughout the lining mucosa. It can also be present in the masticatory mucosa (more keratinized) and is larger (one or more centimeters in diameter) and has irregular borders **(Figure 4)**. As these lesions are deeper and more extensive, the pain is more intense and repair takes longer, 15 to 20 days or more, and can leave a scar after healing. Since the lesions are more severe, patients find it difficult to eat and their general condition can make it more difficult to control the lesions. Prolonged periods of remission may be followed by intervals of intense ulcerous activity.

Figure 4. Major form



(3) Herpetiform aphthous ulcers occur in fewer than 8% of cases, in the group between 20 and 30 years old. The ulcers are morphologically similar to the minor form, occurring in large numbers in groups close to each other, similarly to herpetic lesions. They are small and multiple, and they characteristically affect the lateral margins and tip of the tongue. The ulcers are gray with a delineating erythematous border and are extremely painful, making eating and speaking difficult (**Figure 5)**. Despite the name of this variant, there is little clinical resemblance to acute herpetic gingivostomatitis. Although intranuclear inclusions have been demonstrated in herpetiform aphthous ulcers, there is no evidence to suggest that these inclusions bear any relationship to the presence of viruses. They are located both in the lining and in the masticatory epithelium.

Figure 5. Herpetiform aphtous ulcers



Treatment

Many different treatments for RAS have been tried. Although results are not totally satisfactory, patients have benefited from their relative success. As patients generally feel frustrated by the existing non-specific therapy and because lesions respond poorly to the drugs usually administered, new empirical and innocuous attempts are constantly presented. However, they can mask symptoms or worsen the clinical evolution of the lesions of RAS. Quite often patients who are disappointed with the therapy instituted use caustic agents in an attempt to minimize the pain caused by RAS; this then results in necrosis with destruction of tissue. The ulcer of RAS becomes more extensive, deep and long-lasting, but the pain is alleviated because nerve-endings are also degraded.

The use of caustic agents to relieve pain should be contraindicated, as these do not always eliminate pain and when they do, damage of varied intensity is caused even though the pain is minimized. Caustic agents are substances that precipitate (coagulate) or dissolve (liquefy) proteins as a result of their physical-chemical action. Their effect can reach the deeper tissues of the oral mucosa, and not be restricted to the more superficial layer. Formaldehyde, arsenic and acids and bases in general are included in this category, as well as certain metal compounds such as silver nitrate. Thus, certain substances derived from formaldehyde and arsenic are used in endodontics, for the devitalization of pulp for example, and also to alleviate pain caused by aphthae.

Some of the medications that have been used over time can be listed as follows:

- aerosol corticoids;
- mouthwashes: benzidamide, chlorhexidine, xylitol;
- systemic drugs: colchicine, prednisolone;
- topical steroids: hydrocortisone, triamcinolone, betametasone;
- immunomodulators: levamisole, thalidomide;
- mucosal protectors: carboxymethyl cellulose.

In principle, it is recommended to wait for spontaneous cure, using medications for the symptoms such as topical and systemic analgesics and anti-inflammatories, which are not always satisfactory. The important point is to make the patient feel that he was "treated," minimizing pain and the emotional component. Very often, an open and honest orientation will help the patient to understand his health problem better and learn to accept it, knowing that new episodes can occur, with different degrees of intensity, but they will disappear after a short period of time. It is important to know that the disease is benign, that it does not lead to other organic alterations and that new episodes can be faced with tranquility as long as the patient is tolerant and does not potentiate the symptoms. Although it is difficult to chew and swallow, the patient should maintain good nutritional status, avoiding as much as possible any physical and emotional stresses.

The use of topical anesthetics such as xylocaine is valid, especially when used a few minutes before meals. Besides the analgesia, this will help the patient to eat, avoiding the organic weakness resulting from shortage of nutrients.

Using an adhesive, a triamcinolone-based oral paste can be applied in thin layers, without rubbing but using some compression to prevent it from detaching. It has an anti-inflammatory function. It should be used four times per day while the ulcer is present, generally five to seven days. Liquid dexamethasone can also be used as a mouthwash. Both help to improve pain-relief but they delay the healing process. Benzidamide can be used as a mouthwash four times per day, before meals, with immediate effect. The undesirable side effects of corticoids used in this way are practically innocuous, as there is minimum swallowing and the treatment is of short duration. We have seen that the associated use of oral anti-inflammatory drugs is valuable for patients with intense symptoms of pain.

Treatment for herpetiform aphthous ulcers is primarily symptomatic, using antiseptic mouthwashes and local anesthetic lozenges or gels. Topical or systemic steroids may be beneficial in selected individuals with extensive disease.

Over time it has been shown that the use of ascorbic acid (vitamin C) by oral administration, two to four grams per day, is an efficient therapeutic adjuvant for RAS, resulting in shorter and milder episodes, with longer periods between them. It seems that vitamin C can modulate the generation of oxygen-reactive species and increase neutrophilic apoptosis, which could prevent neutrophil-mediated inflammation. The use of vitamin B12 has been recommended as a possible adjuvant in the treatment of RAS, reducing the duration of episodes, the number of ulcers and the level of pain, independently of serum-levels of vitamin B12. That is, the vitamin shortage is not the triggering factor of a episode, but its use in treatment has been very efficacious. The use of vitamin E has also been suggested as a protective agent for oral mucosa.

It has been shown that the use of thalidomide as an agent to improve RAS is efficient.

Since in day-to-day activities in the clinic it is observed that smokers tend to develop RAS less often, the use of nicotine with therapeutic objectives has been considered.

In conclusion, it should be kept in mind that although the etiologic bases of RAS are not fully known, an immune factor is present in most cases and corticoid agents should always be included in the therapy. It is quite possible that RAS is not a single pathological entity but rather a lesion manifested in several pathologic conditions. Its favorable prognosis and short course will allow research to proceed.

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