FEATURE ARTICLE

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Recurrent Aphthous Stomatitis

An Update on Etiopathogenia and Treatment

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ABSTRACT: Recurrent aphthous stomatitis (RAS)—otherwise known as canker sores, aphthous stomatitis, recurring oral aphthae, and recurrent aphthous ulceration—is a common cause of benign and noncontagious mouth ulcers, affecting about 20% of the general population. It is characterized by the appearance of an erythematous macule that develops into a painful, rounded or oval, ulcer covered with a yellow-gray fibrinous membrane with well-defined limits surrounded by an erythematous halo that can be scraped away. Three clinical subtypes of RAS have been established according to the magnitude, number, and duration of the outbreaks. The management of RAS should be based on identification and control of the possible predisposing factors, excluding possible underlying systemic causes. The use of a detailed clinical history is essentially coupled with complementary procedures such as laboratory tests, when needed. The lack of clarity regarding the etiology of aphthous ulcers has resulted in treatments that are mainly empiric, as there is no curative treatment available in most cases. This review examines the existing topical and systemic treatments for RAS and explores its etiology in depth.

Key words: Aphthae, Oral Ulcers, Recurrent Aphthous Stomatitis, Stomatitis

Recurrent aphthous stomatitis (RAS)—otherwise known as canker sores, aphthous stomatitis, recurring oral aphthae, and recurrent aphthous ulceration—is the most common chronic disease of the oral cavity, affecting 5%–25% of the population (Ship, Chavez, Doerr, Henson, & Sarmadi, 2000). It occurs worldwide but is more common in developed countries. Onset peaks between 10 and 19 years old and can persist into adulthood, with no gender predilection. About 80% of people with aphthous stomatitis first developed the condition before the age of 30 years. In addition, there have been reports of ethnic variation. In the United States, for example, aphthous stomatitis may be three times more common in white-skinned people than black-skinned people (Neville, Damm, Allen, & Bouquot, 2008; Ship et al., 2000).

Generally, symptoms may include prodromal sensations such as burning, itching, stinging, and pain, which are worsened by physical contact—especially with acidic foods and drinks. Pain is most intense in the days immediately after the initial formation of the ulcer and then recedes as healing progresses. If there are lesions on the tongue, speaking and chewing can be uncomfortable. Ulcers on the soft palate can also cause odynophagia.

Most aphthae appear on the nonkeratinizing epithelial surface in the mouth—that is, anywhere except the attached gingiva, the hard palate, and the dorsum of the tongue—despite the fact that the more severe forms may also involve keratinizing epithelial surfaces. The thickness of the mucosa may be a crucial factor in this disease. Factors that decrease the thickness of mucosa increase the frequency of ulceration, and factors that increase the thickness of the mucosa (such as smoking tobacco) correlate with decreased occurrence (Figures 1 and 2).

ETIOPATHOGENIC MECHANISMS

Although the underlying etiology remains unclear, it is believed to be multifactorial (Jurge, Kuffer, Scully, & Porter, 2006; Natah, Konttinen, Emattah, 2004). Individuals vary in their observed triggers. Many factors are known to predispose a subject to the appearance of oral aphthae, such as genetic factors, food allergens, local trauma, endocrine alterations, menstrual cycle, toothpaste, psychological stress and anxiety, smoking cessation, certain chemical products, and microbial agents (Belenguer-Guallar, Jiménez-Soriano, & Claramunt-Lozano, 2014; Chavan et al., 2011; Femiano, Buonaiuto, Gombos, Lanza, & Cirillo, 2010; Zhou et al., 2010).

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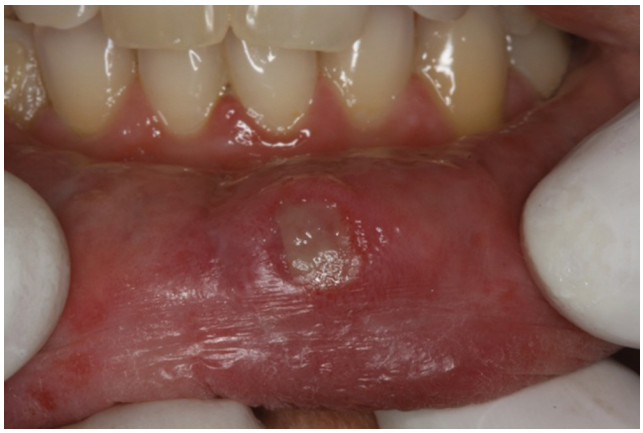

FIGURE 1. Aphtha in oral mucosa.

Evidence indicates that genetically mediated disturbances of the innate and acquired immunity play a meaningful role in RAS development. Factors that alter the immunologic response include vitamin and microelement deficiencies, viral and bacterial infections, mechanical injuries and psychological stress, gastrointestinal disorders (celiac disease, Crohn's disease, or ulcerative colitis), hormonal alterations, certain drugs, and food allergies.

The immunopathogenesis of the disease allegedly involves a cell-mediated immune response mechanism involving the production of T-cells, interleukins, and tumor necrosis factor alpha (TNF-α), which is a proinflammatory cytokine associated with the development of RAS (Jurge et al., 2006). In addition, lymphocyte-mediated mechanisms have been proposed in addition to immune complexes (Jurge et al., 2006), and cross-reactivity between streptococci and the oral mucosa has been reported. Immune alterations have been observed, beginning with an unknown antigenic stimulation of the keratinocytes and resulting in the activation of T lymphocytes, cytokine secretion (including TNF-α), and leukocyte chemotaxis. TNF-α is believed to play an important role in the development of new RAS lesions and has been found to increase two- to five-fold in the saliva of affected patients. Changes have also been reported in elements of the salivary defense system such as the enzyme superoxide dismutase, which participates in the inflammatory response of these ulcers (Eguia-del Valle, Martinez-Conde-Llamosas, López-Vicente, Uribarri-Etxebarria, & Aguirre-Urizar, 2011).

An increase in the expression of vascular and keratinocyte adhesion molecules is recognized by the expression of lymphocytes and lymphocyte infiltration of the epithelium, with the induction of ulcer formation (Scully & Porter, 2008). Furthermore, psychological stress has effects on the immune system, which may explain why some cases directly correlate with stress (Scully & Porter, 2008).

At least 40% of people with aphthous stomatitis have a positive family history, suggesting that some people are genetically predisposed to experience oral ulceration. However, these human leukocyte antigen types found in such patients are inconsistently associated with the condition, varying according to ethnicity (Preeti, Magesh, Rajkumar, & Karthik, 2011; Scully, 2013). The inheritance of some specific gene polymorphisms, especially those encoding proinflammatory cytokines that play a role in the formation of aphthous ulcers, may predispose family members to RAS. The role of genetic predisposition was already suggested in 1965 (Ship, 1965) and later again by Miller, Garfunkel, Ram, and Ship in 1977. Miller et al. hypothesized that the autosomal recessive or multigene mode of inheritance interacted with the modulating influence of the environment (Miller et al., 1977). The nutritional deficiencies associated with RAS (B12, iron, folate, and L-lysine) cause a decrease in the thickness of the oral mucosa, which gives rise to ulcers (Neville et al., 2008).

Trauma can decrease the mucosal barrier. Such trauma could occur during injections of local anesthetic in the mouth or otherwise during dental treatments or frictional trauma from a sharp surface in the mouth like a broken tooth or dental prosthesis or from one simply brushing their teeth. Hormonal factors during luteal phase of the menstrual cycle coupled with the use of contraceptive pills are capable of changing the mucosal barrier as well (Preeti et al., 2011).

Aphthous stomatitis is uncommon in people who smoke (Brocklehurst et al., 2012). Tobacco use is associated with an increase in keratinization of the oral mucosa reducing the tendency of ulceration after minor trauma and presenting a more substantial barrier to microbes and antigens. In severe forms, this may manifest as leukoplakia or stomatitis nicotina (smoker's keratosis), which is a response of the palatal oral mucosa to chronic heat. Nicotine is also known to stimulate production of adrenal steroids while reducing the production of TNF-α, interleukin-1, and interleukin-6 (Preeti et al., 2011; Scully, 2013).

The trigger may occasionally be an allergic reaction to certain foods, such as chocolate, coffee, strawberries, eggs, nuts, cheese, highly acidic foods, toothpastes, and mouth rinses. Sodium lauryl sulfate, a component present in some brands of toothpaste and oral healthcare products, may trigger oral ulceration. Certain drugs have been associated

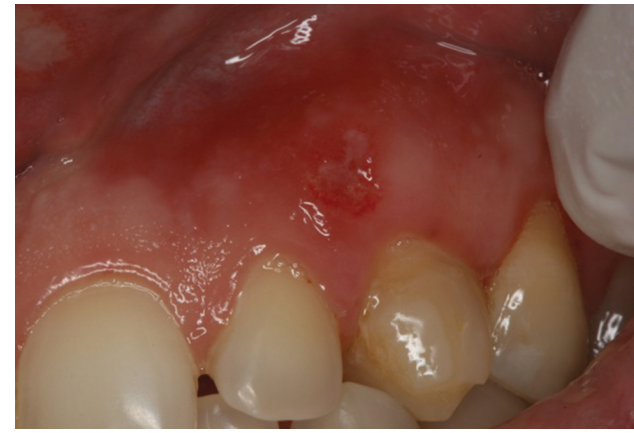

FIGURE 2. Aphtha in gingival mucosa.

with development of aphthous ulcers, including angiotensin-converting enzyme inhibitor captopril, gold salts, nicorandil, phenindione, phenobarbital, and sodium hypochloride. In addition, nonsteroidal analgesic drugs that may cause oral ulceration include propionic acid, diclofenac, and piroxicam (Riera Matute & Riera, 2011).

It has been hypothesized that the condition represents a state of heightened sensitivity to antigenic stimuli—such as streptococci, herpes virus, varicella-zoster virus, cytomegalovirus, and adenovirus—with cross-reactivity to the resulting cell-mediated immune response with epithelium cells. Characteristics of aphthous ulcers, which are indicative of infectious etiology, include recurrent ulceration, lymphocytic infiltration, perivascular cuffing (accumulation of lymphocytes or plasma cells in a dense mass around the vessel), and presence of autoantibodies and inclusion bodies—in the case of herpetiform ulcers. Oral streptococci have been implicated as microorganisms directly involved in the pathogenesis of these lesions or as agents that serve as antigenic stimuli, which in turn provoke antibody production that cross-reacts with oral mucosa. It has been suggested that α-hemolytic streptococci, *Streptococcus sanguis* (*Streptococcus mitis*), was the initiating agent of this disease in some cases. On the other hand, in 1986, Hoover, Olson, and Greenspan showed the low levels of cross-reactivity between oral *Streptococci* and oral mucosal antigens, suggesting that the reactivity is nonspecific (Hoover et al., 1986). A gram-negative bacterium reportedly present in high density within dental plaque, *H. Pylori*, has been implicated as one of the organisms in the etiopathogenesis of RAS (Leimola-Virtanen, Happonen, & Syrjänen, 1995). There have been several viruses implicated in the etiology of RAS, especially Epstein–Barr and human cytomegalovirus. However, no conclusive evidence has yet been presented. It is suggested that, when viral infection occurs in oral epithelial cells, expressing major histocompatibility complex class II molecules, an intense T-cell response is elicited against virus containing oral epithelial cells (Sun et al., 1996, 1998).

Changes have also been reported in elements of the salivary defense system, such as the enzyme superoxide dismutase, which participates in the inflammatory response of these ulcers (Momen-Beitollahi et al., 2010). Many systemic diseases are known to be associated with aphthae-like ulceration, including Behçet's syndrome, hematological disorders, vitamin deficiencies, gastrointestinal diseases, cyclic neutropenia, Reiter syndrome, Magic syndrome, PFA-PA syndrome (periodic fever, aphthous pharyngitis, cervical adenopathy), Sweet syndrome, graft-versus-host disease, syphilis, and immune deficiencies (Baccaglini et al., 2011; Lalla et al., 2012). These aphthae-like lesions are clinically and histopathologically identical to the lesions of RAS, but this type of oral ulceration is not considered to be true aphthous stomatitis as it has a different evolution and etiology. Some of these conditions may cause ulceration on other mucosal surfaces in addition to the mouth, such as the conjunctiva or the genital mucous membranes. Resolution of the systemic condition often leads to decreased frequency and severity of the oral ulceration.

Classification

According to Bagan, Sanchis, Milian, Penarrocha, and Silvestre (1991), there are three recognized forms:

Minor RAS: This is the most common presentation of the disease, representing 70%–85% of all cases. It manifests as small rounded or oval lesions covered by a grayish-white pseudo membrane and surrounded by an erythematous halo. Each episode involves the appearance of one-to-five ulcers measuring less than 1 cm in diameter, which are self-limiting and resolve within 14 days without scarring (Bagan et al., 1991).

Major RAS: This is the most severe presentation of the disease, representing 10% of all cases. The ulcers measure over 1 cm in size and tend to appear on the lips, soft palate, and pharynx. The lesions can persist for over 6 weeks and can leave scars (Bagan et al., 1991).

Herpetiform RAS: This subtype accounts for 1%–10% of all cases and is characterized by recurrent outbreaks of small, deep, and painful ulcers. Up to 100 aphthae can develop simultaneously, measuring 2–3 mm in size, although they tend to merge to form larger ulcerations with an irregular contour. In contrast to the minor and major RAS subtypes, this presentation is more often seen in female patients and in patients of older age. Lesions resolve within 15 days (Bagan et al., 1991).

Diagnosis

The diagnosis of RAS is based on the clinical manifestations and the patient anamnesis. There is no specific diagnostic test and, in most cases, no need for a biopsy. It is recommended to request laboratory tests, including a complete blood count and evaluations of iron, vitamin B12, and folic acid—particularly in the case of adults who experience sudden outbreaks of RAS; patients with major aphthae; or when lesions are also present in other parts of the body, specifically on the genitals or in the eyes.

Treatments

Treatment is primarily focused on pain relief, aiming to reduce the duration of the disease or the rate of recurrence by reducing the local inflammation. In clinical practice, it is recognized that specific drugs appear to work for individual patients; thus, the interventions are likely to be complex in nature. In addition, it is acknowledged that systemic interventions are often reserved for those patients who have been unresponsive to topical treatments and therefore may represent a select group of patients (Brocklehurst et al., 2012; Table 1).

Topical interventions range from inert barriers to active treatments. Providing a barrier as a mucoadhesive paste for the ulcer should temporarily protect the mucosa, and therefore,

TABLE 1. Treatments for Recurrent Aphthous Stomatitis

Topical Treatments	Systemic Treatments
Chlorhexidine 0.2%	Vitamin C, 2 g/day
Amlexanox ointment 5%	Vitamin B12
Antibiotics (e.g., tetracyclines)	Prednisone, 25 mg/day
Corticosteroids (triamcinolone acetonide)	Thalidomide, 50–100 mg/day
Hyaluronic acid 0.2% gel	Colchicine, 1.5 mg/day
Lidocaine 2% spray or gel	Zinc, 150 mg/day
Benzocaine tablets	Dapsone, 50 mg/day
Triclosan gel or rinse	Potassium penicillin G, 200 mg/day
Diclofenac 3% + hyaluronic acid 2.5%	Pentoxifylline, 1,200 mg/day
Benzidamine hydrochloride rinse	Clofazimine, 100 mg/day
Adhesive toothpaste with polydocanol	Levamisole at 450 mg/day
Laser low frequency	

corruptive stimulants are less likely to sensitize nerve endings while providing pain relief. The addition of active compounds to the barrier can potentially give an immunomodulatory effect. Because of the nature of the mucosal layer, there is great variability in the penetration of active compounds through the mucosal barrier, and as such, there is great variability as to the efficiency of such topical treatments. A broad range of topical medications is available, including antiseptics such as chlorhexidine 0.2% in rinses or gel three times a day for as long as the lesions persist, which comprises the first line of treatment. Anti-inflammatory drugs can also be added such as amlexanox ointment 5%, applied two-to-four times a day; antibiotics (tetracyclines); corticosteroids (triamcinolone acetonide); hyaluronic acid 0.2% gel, which is applied twice a day over the course of 2 weeks; topical anesthetics such as 2% lidocaine (spray or gel); adhesive toothpaste containing polydocanol; or benzocaine tablets. Triclosan can also be used in gel or rinse format three times a day (without swallowing), for as long as the lesions persist and afford anti-inflammatory, antiseptic, and analgesic effects (Meng et al., 2009).

In addition, topical 3% diclofenac with 2.5% hyaluronic acid can be applied to lessen the pain. There have also been reports of oral rinses with benzidamine hydrochloride providing temporary pain relief (Scully & Porter, 2008). In the last few years, new technology using low-level laser therapy has been reported to have an analgesic effect reducing the pain and the inconvenience of eating, drinking, and brushing teeth in patients with RAS, compared with placebo. This is delivered as wavelength of 809 nm, power of 60 mW, pulse frequency of 1800 Hz, duration of 80 seconds per treatment, and dose of 6.3 J/cm^2 (Albrektson, Hedstrom, & Bergh, 2014; Anand, Gulati, Govilla, & Anand, 2013).

Because of the relationship between RAS and vitamin deficiencies, treatment with vitamin B12, which has low risk, proves effective in these cases, even independently of the serum vitamin B12 levels of the patient (Baccaglini et al., 2011; Volkov et al., 2009). Treatment with ascorbate (vitamin C) of 2 g/day during 3 months has also been shown to be effective (Yasui et al., 2010).

In patients with constant and major aphthae outbreaks, or when topical treatment is unable to afford symptoms relief, systemic therapy is indicated in the form of corticosteroids (prednisone) or thalidomide, among other drugs. Corticosteroids are the first choice of systemic treatment, which are used as rescue therapy. Oral prednisone has been used at a starting dose of 25 mg/day, followed by stepwise dose reduction, during 2 months, with disappearance of the pain and reepithelization of the lesions in the first month of therapy (Brocklehurst et al., 2012; de Abreu, Hirata, Pimentel, & Weckx, 2009; Femiano et al., 2010; Pakfetrat et al., 2010).

Other systemic pharmacological treatment includes colchicine of 1.5 mg/day; thalidomide of 50–100 mg/day; zinc of 150 mg/day; dapsone of 50 mg/day; systemic antibiotics such as potassium penicillin G of 200 mg/day over 4 days, which helps to reduce the size of the ulcers and lessen the pain; pentoxifylline of 400 mg three times a day for 1 month; clofazimine of 100 mg/day for 6 months; levamisole of 450 mg/day for 6 months; and an oral antipoliomyelitic vaccine (Hello, Barbarot, Bastuji-Garin, Revuz, & Chosidow, 2010; Scully & Porter, 2008; Sharquie, Najim, Al-Hayani, Al-Nuaimy, & Maroof, 2008; Weckx, Hirata, Abreu, Fillizolla, & Silva, 2009; Yazdanpanah et al., 2008; Zhou et al., 2010).

Finally, other systemic treatments have been described, including homeopathic medicines containing borax, mercurius solubilis, natrum muriaticum, phosphorus, sulfuric acid, nitric acid, arsenicum album, nux vomica, and lycopodium (Mousavi, Mojaver, Asadzadeh, & Mirzazadeh, 2009).

CONCLUSION

All three clinical types of RAS are associated with varying degrees of morbidity, including pain and difficulties in function. RAS is a chronic episodic oral mucosal condition, which can impact on the quality of life. Given its high prevalence, treatment strategies must be directed toward providing symptomatic relief by reducing pain, increasing the duration of ulcer-free periods, and accelerating ulcer healing. It is essential to recognize and control possible triggers for these patients. The clinician must exclude potential underlying systemic causes. The use of a detailed patient's medical history in addition to any needed laboratory tests is vital for the care of these patients. ■

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