



Recurrent aphthous stomatitis

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Recurrent aphthous stomatitis (RAS), also known as *canker sores* or *simple* or *complex aphthosis*, is the most common form of painful oral ulcers [1]. RAS affects more than 30% of adults and up to 37% of school-age children [2]. Outbreaks of RAS may take weeks to months to heal, with 50% of individuals having a recurrence within the next 3 months [3]. RAS has been associated with a variety of clinical features, local factors, and systemic associations.

The chief complaint of RAS typically is pain. The painful ulcerations usually develop on freely movable oral mucosa, often the buccal mucosa, vestibules, inner lips, tongue, and soft palate. The ulcers develop after prodromal symptoms of altered sensation or focal erythema or swelling, but without antecedent vesicles or bulla.

Etiology

The cause of RAS is unknown and thought to be multifactorial with many triggers or precipitating factors [4]. Patients with RAS demonstrate increased antibody-dependent cell-mediated cytotoxicity [5]. Neutrophils phagocytize and eliminate antigenic material or damaged tissue in RAS [6]. Neither cell-mediated hypersensitivity nor cross-reactivity to streptococcal or viral antigens has been established. Natural killer T-lymphocyte cell counts and activity levels are lower in patients with RAS than in controls [7].

Patient factors include familial tendencies or genetic predisposition, allergy, medications, hormones,

stress or anxiety, and immunologic abnormalities. A tendency for RAS to occur in families has been observed in approximately 40% [8]. The likelihood of a child developing RAS is influenced by the parents' RAS status [9]. Associations between RAS and specific HLA subtypes suggest a genetic basis for susceptibility for RAS [10]. HIV-associated immunosuppression is associated with RAS or atypical ulcerations as they are also known. Lesions develop because of immunologically cell-mediated cell toxicity of the epithelium [4]. *Helicobacter pylori* have not been shown to have a direct association with oral RAS [11]. Allergens have been reported to play a significant role in the precipitation of new lesions in approximately 35% of RAS patients [12]. It is well recognized that RAS may be associated with sensitivity to gluten. Gluten intolerance with intestinal lesions is known as *celiac disease*. Gluten intolerance with RAS and in the absence of intestinal lesions also occurs [13]. Gluten is a protein found in wheat, barley, oats, and rye.

Other allergens reported to be associated with RAS include benzoic acid, cinnamaldehyde, nickel, parabens, dichromate, mercury, fragrance mix, methyl methacrylate, sorbic acid, phosphorus, colophony, and balsam of Peru. An allergist or dermatologist may be able to conduct skin patch tests or radioallergosorbent tests on blood to identify specific allergens. Alternatively, an elimination diet may be of benefit in identifying food or food additives that precipitate RAS. The elimination diet should be cereal and fruit free and avoid chocolate, nuts, tomatoes, and citrus fruits. Cosmetics and toothpastes also should be eliminated. If there is no improvement of the RAS in 6 to 8 weeks the diet can be stopped. If improvement has occurred, one new food item may be introduced

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every 4 days. If allergens that trigger RAS are identified and the allergens can be avoided, approximately 40% become asymptomatic, 50% demonstrate marked improvement, and 10% remain unchanged [14].

Medications, such as the cyclooxygenase-2 inhibitors celecoxib and rofecoxib, nonsteroidal anti-inflammatory agents used for arthritis, have been associated with the rare occurrence of aphthous-like ulcerations and may contribute to oral dryness, which in turn may promote the development of RAS. The antidepressant sertraline (Zoloft) has been associated with the development of dry mouth and aphthous stomatitis [15].

Clinical features

The painful aphthous ulcers are usually round to oval and covered with a white-yellow fibrinous pseudomembranous cap. An erythematous halo reflecting the mucosal inflammatory reaction surrounds the ulcer [16]. Rogers [17] separates the clinical types of RAS into simple and complex. Simple RAS includes the most common presentation of solitary to few ulcers that heal in 1 to 2 weeks and recur infrequently. Complex aphthosis includes deep, multiple, large ulcers with marked pain and disability, and episodes may even be accompanied by the occasional genital or perianal lesion.

Recurrent aphthous stomatitis is often divided into three distinct morphologic subtypes: (1) minor, (2) major, and (3) herpetiform. Minor RAS is the most common type affecting approximately 80% of individuals with recurrent oral ulcers. Minor RAS exhibits typically solitary ulcers or less than 10 ulcers at one



Fig. 1. This 16-year-old female suffered from frequent simple (minor) aphthous ulcers for 10 years. She reports hypersensitivity to metals. Results of hematologic testing were normal.



Fig. 2. A large, crateriform, painful aphthous ulcer of several weeks duration is present on the soft palate of a 54-year-old male. He has not been free of ulcers for the past 3 months.

time, each less than 1 cm in greatest dimension. These minor RAS ulcers are located usually on freely movable lining mucosa or on the tongue (Fig. 1). The ulcer is usually oval with a white-yellow-gray fibrinous covering surrounded by an erythematous halo on the mucosa. Prodromal tingling or pain may precede ulcer development. Healing occurs within 4 to 14 days without scarring.

Major RAS, representing 5% to 10% of all cases of RAS, exhibits large, deep, crateriform ulcers. The outline of the ulcers may be irregular. These ulcers are found on freely movable lining mucosa or the dorsal tongue (Figs. 2–4). The lesion of major RAS may take weeks to months to heal, and healing may be accompanied by scarring (Fig. 5).

Herpetiform RAS represents 5% to 10% of all cases of RAS [18]. The herpetiform ulcerations are



Fig. 3. Same patient as in Fig. 2. Lesion healed after treatment with prednisone, topical fluocinonide and chlorhexidine rinses in addition to increasing water intake due to dry mouth. See Figure 4.



Fig. 4. Same patient as in Figs. 2 and 3. Salivary flow rate measurement using Modified Schirmer test is zero/31 mm in three minutes, consistent with profound dry mouth. Salivary pH was 5.0, normal 7.0–7.4.

characterized by successive crops of dozens of exquisitely painful ulcerations usually 1 to 3 mm in diameter. The ulcers typically develop in a bilateral distribution on nonkeratinized mucosa, although the dorsal tongue may be involved. Like minor and major RAS, vesicles do not precede the development of ulcerations. There is no known relationship of herpetiform RAS to herpes simplex virus infection (Figs. 6 and 7).

Differential diagnosis

The differential diagnosis of RAS includes recurrent intraoral herpes simplex virus, herpes varicella zoster virus, herpangina, hand-foot-and-mouth disease, erythema multiforme, oral lichen planus, cicatri-



Fig. 5. This 19-year-old male has had severe aphthous ulcerations for 12 years. Mucosal scarring is present. Results of hematologic testing were normal. Low levels of gliadin antibody IgA were detected.



Fig. 6. A 46-year-old female experienced multiple crops of exquisitely painful shallow cluster of ulcerations in a bilateral distribution for the past 5 months. This cluster of herpetiform ulcerations is present on the right side of the lower lip.

cial pemphigoid, pemphigus vulgaris, Behçet's disease, Wegener's granulomatosis, and pyostomatitis vegetans [17,19]. In most instances, a careful history and clinical examination result in the establishment of a definitive diagnosis. Viral infections, acute oral ulcers, pseudo-Beçet's disease, and complex aphthosis and Beçet's disease are discussed elsewhere in this issue.

Diagnosis

The diagnosis of RAS may be accomplished by careful history and clinical evaluation, with adjunctive procedures of biopsy, cytology [20], and culture if necessary for lesions that fail to heal or respond to treatment. Although the microscopic features of RAS ulcerations are nonspecific, biopsy may help



Fig. 7. Same patient as in Fig. 6. A cluster of shallow painful ulcerations on the left ventral tongue.

to eliminate other specific disease from the differential diagnosis. Culture may rule out specific viral infections that may also cause oral ulcerations, such as herpes simplex, herpes varicella zoster, or cytomegalovirus. The clinical evaluation and history includes attention to complicating local and systemic factors that must be considered in developing treatment recommendations.

Local factors

Local factors influencing the frequency of RAS include chemical and mechanical injury, such as the use of sodium lauryl sulfate contained in dental health care products; traumatic injury; inadequate saliva; and cessation of tobacco use. Sodium lauryl sulfate is an anionic detergent, desirable in oral health care products for its foaming properties, but which decreases mucin and increases oral mucosal antigen exposure. Avoidance of sodium lauryl sulfate-containing mouthwash and dentifrices has been shown to decrease aphthous ulcers by 64% [21,22]. Interestingly, the antibacterial, anti-inflammatory chemical triclosan has been demonstrated to prevent the chemotoxicity of sodium lauryl sulfate and reduce aphthous ulcers by 96% [23,24]. Colgate Total, (Colgate-Palmolive, New York, NY) is a commercially available dentifrice containing triclosan.

Mechanical injury, such as with a toothbrush or sharp, dry food, may precipitate the development of RAS. Lack of adequate saliva to lubricate and protect the oral mucosa from injury and antigenic exposure may contribute to the development of RAS (see Figs. 2 and 3) [19].

Cessation of tobacco use may be accompanied by the onset of frequent RAS. Tobacco use induces a mild hyperkeratosis that reduces antigen exposure [25]. As the hyperkeratosis resolves with tobacco use cessation, painful mouth ulcers may develop within a week or more. Although it is likely that the hyperkeratosis associated with tobacco use is responsible for reduction in RAS for most patients, nicotine has been demonstrated to be protective against the development of oral aphthae for a few patients [25].

Treatment

The goals of treatment of RAS include control of pain, promotion of healing, and decreased numbers of future ulcers [26]. Many cases of RAS can be managed with the careful control of local factors and the judicious use of over-the-counter preparations or

prescription topical medications, such as amlexanox, corticosteroids, or chlorhexidine. Over-the-counter preparations include covering agents, such as Orabase (Colgate Pharmaceuticals Canton, MA); Zilactin (Zila Pharmaceuticals Phoenix, AZ); local anesthetics; oxygenating agents; antiseptics; and chemical cautery agents [27].

Prescription options include the nonsteroidal anti-inflammatory agent topical amlexanox 5% paste applied four times a day to the ulcers to enhance healing and reduce pain with minimum side effects [28–30], and topical glucocorticoids. Topical triamcinolone, fluocinonide [31], and clobesterol have demonstrated efficacy in the treatment of RAS. The topical corticosteroids may be used alone or mixed with Orabase mucosal adherent, although the dilution may affect the strength. In general, for topical corticosteroid use, the patient should dry the area gently and apply a thin film of the corticosteroid up to four times daily until the ulcer has healed [32].

Tetracycline rinses may be helpful in the patient with RAS. Tetracycline is antimicrobial and reduces collagenase activity [26]. The use of topical medications, such as glucocorticoids or tetracycline, can be problematic in the patient with diminished salivary flow. Corticosteroids and tetracycline may promote the growth of endogenous fungal *Candida albicans*, resulting in an opportunistic infection. Additionally, tetracycline is extremely acidic and may cause tooth erosion and mucosal soreness if used topically, especially in patients with diminished salivary flow characteristic of salivary gland hypofunction. Chlorhexidine mouthwash 0.12%, 0.5 oz, for 30 seconds twice daily (after brushing and flossing in dentate patients) may help to decrease the duration of the ulcer and pain with RAS [33] in addition to reducing the chance of oral candidiasis [34,35].

The treatment of simple aphthosis includes attention to the role of local factors to reduce recurrences and topical medication to minimize the discomfort and to promote healing of painful ulcers. Patients with complex aphthosis, major RAS, or herpetiform RAS should have evaluation of local and systemic associations. Hematologic testing for folate, iron, serum ferritin, and vitamin B₁₂ is recommended [4,36,53]. Remission or marked improvement of RAS is seen in 70% of patients with replacement therapy for nutritional-hematologic abnormalities.

Debridement with the removal of the fibrinous pseudomembrane and necrotic plug from the ulcer base has been reported to stimulate healing and decrease discomfort [37], perhaps by allowing endogenous protein secretory leukocyte inhibitor to reach

the base of the ulcer [38]. The debridement can be accomplished more easily and with greater patient comfort after the application of a topical anesthetic. Bioadhesive 2-octyl cyanoacrylate has been recommended as a topical, nonprescription treatment for RAS to reduce pain [39].

Oral corticosteroids may be used for the management of severe RAS [40]. Burst therapy of 20 to 40 mg daily may be given for 5 to 10 days, or an initial higher dose may be followed by a taper over 2 weeks [3]. Other systemic treatments for RAS include thalidomide [41], levamisole [42], colchicine [43], cyclosporine [44], axelastine [45], dapsone [46], and pentoxifylline [47].

The uncommon albeit clinically distinctive RAS variant seen in some children is known as *periodic fever, aphthous stomatitis, pharyngitis, and adenopathy syndrome* [48,49]. It has been shown to respond within 2 to 4 hours to a single oral dose of prednisone, 2 mg/kg [50], or cimetidine therapy [51]. Rebound phenomenon has been observed following the single oral dose of prednisone.

Control of local factors

The clinician should identify and control local factors influencing recurrences of aphthae:

1. Consider an empirical clinical trial of sodium lauryl sulfate-free toothpaste and mouthwash. Commercially available products include Biotene toothpaste (Laclede, Rancho Dominguez, CA) and Rembrandt's Canker Sore toothpaste (DenMat, Santa Maria, CA).
2. Measure the salivary flow rate using objective volumetric, gravimetric, or calibrated paper [52] methodology to determine adequacy of saliva objectively and accurately. In patients with a low salivary flow rate, management with palliative and therapeutic options including adequate water ingestion daily and sialogogue medications, such as pilocarpine (Salagen, MGI Pharma Bloomington, MN; 5 mg, three to four times daily) and cevimeline (Evoxac, Daiichi, Montvale, NJ; 30 mg, three times daily), may be indicated.
3. Avoid or minimize mechanical injury to oral mucosa. Soft toothbrushes are desirable to minimize injury.
4. If the patient has onset with smoking cessation the clinician may consider a trial of nicotine gum or a nicotine patch.

Summary

Recurrent aphthous stomatitis remains a commonly occurring cause of oral pain and ulceration. Although the ulcerations of RAS are multifactorial and of unknown cause, recognition of the role of patient and environmental factors may be helpful in developing recommendations for treatment and prevention of future ulcers.

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