Recurrent aphthous stomatitis
An update

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Recurrent aphthous ulceration or recurrent aphthous stomatitis is the most common oral mucosal disease known to human beings. Despite much clinical and research attention, the causes remain poorly understood, the ulcers are not preventable, and treatment is symptomatic. The most common presentation is minor recurrent aphthous stomatitis: recurrent, round, clearly defined, small, painful ulcers that heal in 10 to 14 days without scarring. Major recurrent aphthous stomatitis lesions are larger (greater than 5 mm), can last for 6 weeks or longer, and frequently scar. The third variety of recurrent aphthous stomatitis is herpetiform ulcers, which present as multiple small clusters of pinpoint lesions that can coalesce to form large irregular ulcers and last 7 to 10 days. Diagnosis of all varieties is usually made after clinical examination. Many local and systemic factors have been associated with these conditions, and there is evidence that there may be a genetic and immunopathogenic basis for recurrent aphthous ulceration. Management of this condition depends on the clinical presentation and symptoms and includes analgesic, antimicrobial, and immunomodulatory drugs. As dental clinicians and researchers become better trained in oral medicine and stomatology, it is anticipated that the pathophysiology, prevention, and treatment of recurrent aphthous ulceration will improve in the future. (ORAL SURG ORAL MED ORAL PATHOL ORAL RADIOL ENDOD 1996;81:141-7)
50% to 60% in selected groups (for example, medical or dental students). Ship also suggested that a greater prevalence of the disease and severity of expression was associated with increasing social class. It is possible that the actual prevalence of RAS is greater than reported rates because of the recurrent nature of the condition. Cross-sectional clinical surveys probably underestimate the true prevalence because active lesions may not be present at the time of examination.

CLINICAL FEATURES OF RAS

The lesions of RAS are characterized by recurrent ulcerations of the oral mucous membranes that occur either singly or in multiple locations and are usually associated with pain. RAS is divided into three varieties: minor recurrent aphthous stomatitis, major recurrent aphthous stomatitis, and herpetiform ulcers.

The more common form of RAS is the minor variety and is characterized by small round to ovoid lesions with a crateriform base, surrounded by a distinct, raised, and erythematous halo (Fig. 1). These lesions are generally less than 5 mm in diameter and have a grey-white pseudomembrane. These lesions heal within 10 to 14 days without scarring. The most common locations are on nonkeratinized oral mucosa (labial and buccal mucosa and floor of the mouth) with uncommon sites including the gingiva, palate, or dorsal surface of the tongue. They may appear in the form of "attacks" of single or multiple lesions but can clearly be distinguished from primary or secondary viral infections, bacterial infections (necrotizing ulcerative gingivitis), dermatologic conditions (lichen planus, cicatricial pemphigoid, pemphigus), and traumatic episodes (contusions, lacerations, burns) by the healthy appearance of adjacent tissues and the lack of distinguishing systemic features. Diagnosis is generally made on the basis of history and clinical presentation; there are no known laboratory procedures available for definitive diagnosis, and histopathologic examination of biopsy specimens will not provide a definitive diagnosis.

A severe but rare form of this condition is major RAS or periadenitis mucosa necrotica recurrens and occurs in approximately 10% of RAS patients. These lesions are similar in appearance to minor RAS, however, they are larger than 5 mm in diameter, often scar, and can last up to 6 weeks in time (Fig. 2). Major lesions have a predilection for lips, soft palate, and fauces and will cause significant dysphagia. Painful ulcers resembling minor and major aphthous lesions have been associated with human immunodeficiency virus (HIV) infection. The major or minor forms of RAS may be more common in HIV-infected patients because it has been suggested that RAS represents a local breakdown in immunoregulation, a condition that could be amplified by HIV disease.

The third and least common form of RAS is herpetiform ulcers, which will occur in approximately 10% of patients with RAS. Multiple small clusters of pinpoint ulcers characterize this form of RAS, and they occur throughout the oral cavity (Fig. 3). They tend to be small (2 to 3 mm) and numerous (as many as 100 ulcers at once), can fuse together to produce large irregular lesions and can last 7 to 10 days. Although these lesions are herpes-like or herpetiform in nature, herpes simplex virus cannot be cultured from the lesions.

CAUSES OF RAS

There have been numerous proposed etiologic mechanisms for RAS, including local, microbial, systemic, nutritional, immunologic, and genetic factors (Table I). Nevertheless, despite much research, the cause remains idiopathic or a result of a variety of predisposing factors.
Local Factors

Trauma has been often identified as a precipitating factor, including anesthetic injections, sharp foods, toothbrushing, and trauma from dental treatment. However, many patients with RAS do not develop lesions after trauma, and edentulous patients are unlikely to have lesions beneath dentures. Nevertheless, minor trauma should be considered as one of the precipitating factors in RAS. Quantitative or qualitative changes in salivary gland function have been hypothesized to play a role in the pathogenesis of RAS, however, most studies have not found a definitive relationship.

Microbial Factors

It has been suggested that oral streptococci and several viruses may play an etiologic role in RAS, but overall the results are inconclusive. In general, herpes simplex, varicella zoster, and Epstein-Barr viruses have not been directly isolated from RAS lesions. A recent study demonstrated an association between RAS recurrences and reactivation of varicella zoster virus and cytomegalovirus infection. Pedersen has suggested that the systemic and local cellular immunosuppression associated with RAS is consistent with a viral reactivation or is a result of a latent viral infection of oral mucosa. Nevertheless, further research is needed to definitively establish a viral cause.

Systemic factors

RAS has been observed in several systemic disorders, including Behçet's disease, cyclic neutropenia, mouth and genital ulcers with inflamed cartilage syndrome, nutritional deficiencies with and without underlying gastrointestinal disorders and immunocompromised conditions including HIV infection. Aphthous-like ulcers have been detected in patients with Crohn's disease and ulcerative colitis and other small bowel changes. The lesions in these patients may occur at any time during the course of the disease, can be present before any intestinal symptoms occur, and may occur more frequently when the intestinal problems become active. These ulcers are histologically similar to the intestinal lesions of the disease. Deficiencies in iron, folic acid, zinc, and vitamins B1, B2, B6, B12 have been detected in patients with RAS. Hematologic deficiencies in patients with RAS may be related to abnormalities of the small intestine, including coeliac disease (gluten-sensitive enteropathy), although these patients may not always have symptoms of bowel disease. Food sensitivities and allergies to other substances can also cause ulcers in hematologically normal patients with recurrent lesions.

Fig. 3. Herpetiform recurrent aphthous stomatitis ulcers.

Some studies have associated stress with RAS, however, a more recent investigation revealed no association between psychological life stress and recurrences of RAS. Nevertheless, the literature continues to report that stress may play a role in precipitating RAS, and severe emotional or environmental stress should be contemplated in the clinical assessment of RAS. No associations have been established between RAS and the premenstrual period, pregnancy, or menopause. Furthermore, no properly designed study has shown a therapeutic effect of ovarian hormones on RAS, which suggests that the lesions of RAS are not caused by changes in female hormones. In summary, systemic causes should be considered in the evaluation of a patient with RAS, although it is important to know that most lesions occur in patients who are otherwise healthy.

Genetic factors

Earlier studies by Ship et al. found that RAS had a definite tendency to occur along family lines and that the probability of a sibling developing RAS was influenced by the parents' RAS status. A high correlation of RAS has been detected in identical twins but not in nonidentical twins. Nevertheless, there is a clear variability in host susceptibility with a polygenic inheritance but a penetrance dependent on other factors. More recent investigations have detected associations between RAS and specific HLA subtypes, which indicates that RAS in certain persons may have a genetic basis.

Immunopathogenesis

RAS may have primary immunologic abnormalities that result in altered immunoregulatory balances. For example, there are increases in antibody-dependent cell cytotoxicity and greater levels of serum immunoglobulins in patients with RAS.
Table I. Suggested causes of recurrent aphthous stomatitis.

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<th>Local/oral factors</th>
<th>Systemic factors</th>
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<td>Trauma</td>
<td>Behçet’s disease</td>
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<td>Salivary gland dysfunction</td>
<td>Crohn’s disease</td>
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<td>Microbial</td>
<td>Ulcerative colitis</td>
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<td>Bacterial: streptococci</td>
<td>Cyclic neutropenia</td>
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<td>Viral: varicella zoster, cytomegalovirus</td>
<td>Mouth and genital ulcers with inflamed cartilage syndrome</td>
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<td>HIV infection</td>
<td>Stress</td>
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<td></td>
<td>Nutritional</td>
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<td>Gluten sensitive enteropathy</td>
<td>Iron, folic acid, zinc deficiencies</td>
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<td></td>
<td>Vitamin B1, B2, B6, B12 deficiencies</td>
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<td>Genetic</td>
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<td>Immunologic</td>
<td>Localized T-cell dysfunction</td>
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<td>Localized T-cell dysfunction</td>
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Lymphocytes from patients with severe RAS demonstrate increased numbers of T-helper/inducer cells,39 decreased numbers of T-suppressor/inducer cells,39 and depressed responses to mitogens.43 Activated T-lymphocytes aggregate in the periphery of RAS lesions confirming the hypothesis that RAS represents an activated cell-mediated immune response.44 Immunohistochemical studies of lymphocyte subsets in aphthous ulcers of HIV-seronegative patients45 and HIV-seropositive patients46 have yielded similar findings, which strongly indicate that these ulcers represent a cell-mediated immunologic dysfunction in which infiltrating T-lymphocytes play a primary role. It seems likely that in genetically predisposed persons, antibody-dependent cellular cytotoxicity and local immune complex–related reactions are involved in the immunopathogenesis of RAS, but the precipitating factors are unknown. Unfortunately, to date no consistent theory of immunopathogenesis has been accepted. This information will be useful in the future so that more effective treatment and preventive modalities can be identified.

TREATMENT AND MANAGEMENT OF RAS

There is no specific treatment for RAS, and management strategies depend on the symptoms, duration, severity, and when applicable, associated systemic conditions (Table II). The value of physical debridement of these lesions is unknown.47 Surgical removal of ulcers has traditionally been ineffectual, yet recently carbon dioxide laser therapy was shown to be useful for RAS.48

Patients with RAS as a result of systemic conditions should be referred to the appropriate health care provider to treat the underlying disease. If stress is felt to be a strong cofactor, consultation with behavioral medicine, psychology/psychiatry, or both is warranted. For example, relaxation and imagery training in patients with RAS produced a significant decrease in ulcer recurrence and influenced patients’ reports of their overall psychological distress.49 Concomitant topical treatment with many agents may help diminish pain, hasten healing, and improve oral-pharyngeal function. If there is a nutritional or vitamin deficiency, replacement therapy can be useful.32 When a food sensitivity is demonstrated from patch testing, avoidance of the allergen can improve oral symptoms.34 A gluten-free diet has been suggested for patients with RAS and gluten sensitive enteropathy, however, a recent report50 indicated that it is not superior to placebo for RAS patients without gluten enteropathy.

Topical therapies include antimicrobial and anal-
giec mouth rinses, topical glucocorticoids, immunomodulators, and hormones. The most common topical therapy uses glucocorticoids, including hydrocortisone, triamcinolone, fluocinonide, betamethasone, and flumethasone. These medications can reduce symptoms and will not cause hypothalamic-pituitary-adrenal axis suppression when used for less than 3 weeks. Topically, greater efficacy can be achieved with stronger glucocorticoids that should be administered for long-lasting, nonhealing, or major RAS lesions. For example, clobetasol propionate ointment 0.05% in adhesive paste was used twice to three times daily in patients with persistent major RAS, and five of seven patients experienced complete remission without major side effects. This potent topical corticosteroid can be used if lesions are refractory to weaker medications, and if effective, it may alleviate the need to administer systemic glucocorticoids.

Topical glucocorticoids may also be helpful in patients with ulcers who are immunocompromised. HIV-infected patients with minor and herpetiform ulcers as well as some major lesions can experience resolution from topical glucocorticoids without notable side effects. Alternatively, severe cases of major RAS may require systemic prednisone. When systemic prednisone is used for severe recalcitrant RAS in HIV-seronegative and HIV-seropositive patients, a 2-week tapering dose is recommended starting with 60 mg. Administration of glucocorticoids in single daily doses compared with multiple daily doses and on alternate-day regimens will help minimize hypothalamic-pituitary-adrenocortical suppression. Furthermore, the use of a combination of immunosuppressant (for example, azathioprine) and glucocorticoid may be effective in these patients.

Other immunosuppressive drugs including colchicine, which blocks the ability of serum to enhance neutrophil migration, cyclosporin, which suppresses lymphocyte-dependent antibody response, and thalidomide, which inhibits histamine-induced circulating immune-complex mediated damage have been used for patients with RAS; all require more extensive testing before clinical recommendations can be made. An 8-week trial of topical cyclosporin mouth rinses was helpful in eight patients with severe RAS. Another multicenter crossover randomized trial used 100 mg/day thalidomide versus placebo for 2 months in patients with severe RAS. Complete remission was obtained in 32 of 67 patients, and thalidomide patients experienced a diminution in number of ulcers despite significant side effects (drowsiness, constipation, headache, and xerostomia).

Immunopotentiating agents such as levamisole, which enhances cell- and humoral-mediated immunity, may be beneficial in patients with RAS. Similar drugs include transfer factor (extract of immunocytes), gammaglobulin, and LongoVital (food supplement that may increase T-lymphocytes), but all require comprehensive clinical testing before routine use in patients with RAS.

It has been postulated that RAS may be due to reactivation of one or more members of the herpesvirus family, and several immunomodulatory drugs that also have nonspecific antiviral activities have been tested in patients with RAS. Low-dose human interferon alpha treatment (1200 IU/day, 1 minute rinse + swallow) was used in a double-blind study in 19 patients with chronic minor RAS, and within 2 weeks all patients achieved total remission. After drug withdrawal, 11 of 19 patients did not experience any recurrence during a 6-month observation period. Interferon has been shown to have potent activity against several infectious agents and possesses significant immune regulatory functions, which could explain its potential usefulness with RAS.

Acyclovir (400 mg twice a day for 1 year) was used in a double-blind study in 25 patients with RAS without any benefit in the prevention of ulcers. Alternatively, higher dosages (800 mg twice a day for 8 weeks) of acyclovir were used in one study of eight patients with recurrent RAS, and six patients experienced either total regression of existing ulcers or relief of symptoms within 2 days of therapy. As with other immunomodulatory and antimicrobial medications, further investigations are required to identify reliable and safe drug treatment strategies before treatment recommendations can be supported.

A variety of other medications may have direct beneficial effects on the ulcers of RAS and should receive further research attention. Tetracyclines have recently been demonstrated to inhibit collagenase activity, and oral rinses were effective in alleviating the discomfort caused by lesions. Sucralfate is believed to act primarily at ulcer craters to form a protective coat that shields the lesion and promotes healing. A prospective randomized, double-blind placebo-controlled, cross-over clinical trial with 21 patients reported that after 2 years of follow-up, sucralfate was superior to both placebo and antacid with respect to duration of pain, reduction of healing period, and duration of remission. Azelastine hydrochloride helps stabilize cell membranes and suppresses reactive oxygen generation; 1 mg oral administration twice daily for 3 weeks significantly diminished the frequency of occurrence, the ulcer duration, and oral irritation in 43 patients.

There has also been interest in developing hormonal medications for inflammatory conditions. Patients who used prostaglandin E-2 gel (0.3 mg twice a day for 10 days) over a 10-day trial experienced significantly fewer new lesions compared with placebo in one study.
ternatively, no differences were observed in the duration of healing and the pain of lesions.68

Antimicrobial rinses have some clinical efficacy for the treatment of RAS. In addition to tetracycline, a commonly used medication is chlorhexidine gluconate. Several studies have reported that this rinse reduces the number of ulcer days, increases ulcer-free days and the interval between bouts of ulceration, but does not prevent recurrence.22 Topical tetracyclines can also reduce the severity of ulceration21 but do not alter the recurrence rate of RAS.22 Another potential oral rinse is Listerine (Warner Lambert Co., Morris Plains, N.J.). Twice-daily rinsing with Listerine over a 6-month period reduced the duration and severity of RAS in one study.69 Interestingly, both the Listerine and the hydroalcoholic control mouth rinse significantly reduced the incidence of RAS occurrences from baseline.59

Finally, oral analgesic rinses can be prescribed if patients have considerable pain. Because protracted RAS-associated pain can cause dysphagia and eventual nutritional impairment, especially in young patients and immunocompromised persons, these rinses may prevent systemic sequelae. Dexamethasone elixir (0.5 mg/5 ml), diphenhydramine elixir (12.5 mg/5 ml), and dyclonine hydrochloride 0.5% or 1.0% can be used 3 to 4 times daily. They can be combined with sucralfate, Kapectate (Upjohn, Kalamazoo, Mich.), or Maalox (Rhone-Poulenc Rorer, Ft. Washington, Pa.) to improve drug adherence to ulcers. Patients should be instructed that these rinses may reduce the gag reflex, and therefore caution should be exercised during eating and drinking to avoid possible airway compromise.

SUMMARY AND CONCLUSIONS

Much progress has been made over the last three decades on the epidemiologic information, complete description, causes, and treatment of recurrent aphthous ulcers. RAS remains the most common oral mucosal disorder and is found in men and women of all ages, races, and geographic region. The three classic forms of the lesions are minor, herpetiform, and major. Considerable research attention has been devoted to elucidating the causes of these conditions, and local and systemic conditions, genetic, immunologic, and microbial factors all may play a role in the pathogenesis of RAS. However, to date, no principal cause has been discovered. Treatment of RAS includes the use of topical and systemic glucocorticoids, topical analgesics, and antimicrobial drugs, and immunomodulatory and hormonal medications.

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REFERENCES


