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Recurrent aphthous stomatitis

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Abstract Recurrent aphthous stomatitis (RAS) is the most common acute oral ulcerative condition in North America. RAS is divided into a mild, common form, simple aphthosis, and a severe, less common form, complex aphthosis. Aphthosis is a reactive condition. The lesions of RAS can represent the mucosal manifestation of a variety of conditions. These include conditions with oral and genital aphthae such as ulcus vulvae acutum, reactive nonsexually related acute genital ulcers, and Behçet disease. The mouth is the beginning of the gastrointestinal (GI) tract, and the lesions of RAS can be a manifestation of GI diseases such as gluten-sensitive enteropathy, ulcerative colitis, and Crohn disease. Complex aphthosis may also have correctable causes. The clinician should seek these in a careful evaluation. Successful management of both simple and complex aphthosis depends on accurate diagnosis, proper classification, recognition of provocative factors, and the identification of associated diseases. The outlook for patients with both simple and complex aphthosis is positive.

Introduction

Recurrent aphthous stomatitis (RAS) is also known as canker sores to patients and health care providers. *Aphthous* comes from the Greek word *aphtha,* referring to an ulcer of the mucosal surface. *Stomatitis* refers to an inflammation of the oral mucosa. Other synonyms are simple aphthosis, complex aphthosis, recurrent oral ulcers (ROU), and recurrent aphthous ulcers (RAU). Many patients confuse RAS with recurrent herpes labialis (fever blisters, cold sores), because both are common in young individuals; however, each is a distinct entity. RAS is the most common recurrent acute oral ulcerative condition in North America.[1–4] The lesions of RAS are painful and disabling to many patients, prompting them to seek evaluation and treatment from health care providers.

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Recurrent acute oral ulcers are a common problem in clinical practice.[3] The main causes of recurrent acute oral ulcers to be considered are trauma, RAS, recurrent intraoral herpes simplex virus stomatitis, and cyclic neutropenia. Of these four, RAS is the most common cause of recurrent acute oral ulcers. The practical approach to acute oral ulcers is discussed elsewhere in this issue.[5]

The lesions of RAS develop over several days into the typical aphthous ulcer (Table 1).[6] Initially, the patient will note paresthesia before development of a clinical lesion. A macule develops, which evolves into a papule that subsequently becomes necrotic and ulcerates. The typical lesion of RAS is a round to oval ulcer covered by a yellow-white fibromembranous slough, surrounded by a peripheral halo of erythema. Pain, which reaches its zenith before the ulcerative process, diminishes in the healing phase. Smaller aphthae heal in 4 to 7 days. Larger lesions—major aphthous ulcers—require longer to heal. Smaller lesions heal without scarring, but larger ones may scar.

Table 1 Stages of recurrent aphthous stomatitis

Stage	Time
Premonitory	Hours to 1 day
Preulcerative	1-2 days
Ulcerative	Several days
Healing	Days to weeks

The lesions of RAS characteristically afflict the nonmasticatory, soft oral mucosal surfaces of the cheeks, lips, lateral and ventral tongue, upper and lower nonattached gingivae and sulci, and occasionally the soft palate and fauces. In contradistinction, lesions of recurrent intraoral herpes simplex virus stomatitis afflict the masticatory mucosa of the hard palate and attached gingivae and recur uncommonly in the healthy individual. The lesions of recurrent herpes labialis more characteristically afflict the cutaneous and vermilion lip and spare the intraoral mucosal surfaces. The lesions of cyclic neutropenia may affect both the masticatory and nonmasticatory mucosa but have very specific cyclic periodicity as a differentiating feature, making the distribution of the lesions a key to differential diagnosis.

The lesions of RAS are self-limited, resolving in 1 to 2 weeks in most patients and recurring 3 to 6 times in a year after periods of remission[1] (simple aphthosis). Some patients have almost continuous oral ulcerations, some lesions healing as others develop, with occasional genital aphthae (complex aphthosis).[7]

The lesions of RAS are characteristically noted in childhood and adolescence and recur with decreasing frequency and severity as the patient ages. It is uncommon for an adult older than age 40 to have RAS. The incidence rate varies with the population studied, ranging from 5-60%,[4] with the highest in women student nurses and medical and dental school students and the lowest in men who are hospitalized. In general, younger persons, women, and those of higher socioeconomic classes are more likely to suffer from RAS.

Classification

In terms of clinical presentation, RAS is divided into two categories based on severity—mild and severe. The milder type is called simple aphthosis.[1] The more severe, and fortunately less common type, is called complex aphthosis (Table 2).[7] The vast majority of patients have simple aphthosis; however, those with complex aphthosis may have one or more associated conditions, such as anemia, hematinic or mineral deficiencies, inflammatory bowel disease, gluten-sensitive enteropathy, or other conditions in which lesions of RAS are a component (Table 3).[1,2,4,7–13]

Table 2 Types of recurrent aphthous stomatitis

Simple aphthosis	Complex aphthosis
Common	Uncommon
Episodic	Episodic or continuous
Prompt healing	Slow healing
Few ulcers	Few to many ulcers
3-6 episodes per year	Frequent or continuous ulceration
Minimal pain	Marked pain
Little disability	Major disability
Limited to oral cavity	May have genital aphthae

Table 3 Associated systemic disorders

Ulcus vulvae acutum
Reactive nonsexually related acute genital ulcers
Behçet disease
MAGIC syndrome
Cyclic neutropenia
PFAPA syndrome
Aphthous-like ulcerations of HIV disease
Hematinic deficiencies
Celiac disease (sprue, gluten-sensitive enteropathy)
Inflammatory bowel disease (ulcerative colitis, Crohn disease)
Helicobacter pylori disease
Systemic lupus erythematosus

MAGIC, mouth and genital ulcers with inflamed cartilage; *PFAPA,* periodic fever, aphthous stomatitis, pharyngitis, and adenitis.

Another helpful classification of the lesions of RAS is based on morphology (Table 4).[1,2,14,15] Minor aphthous ulcers (MiAU) are small and few in number, occur on the anterior oral mucosa, and are the typical canker sores known to most patients and health care providers (Figure 1). MiAU heal quickly. Major aphthous ulcers (MjAU) are large, few in number, and occur both anteriorly and posteriorly with risk of scarring (Figure 2). MjAU, also known as Sutton ulcers or periadenitis mucosa necrotica recurrens,[16] are the most painful type and heal more slowly due to the larger size. The third subtype is herpetiform ulcer, which is the least common type of RAS. Herpetiform ulcer lesions present as grouped 1- to 2-mm papulovesicles, which coalesce into larger lesions (Figure 3). The term *herpetiform* was selected[17] to describe the grouped morphology (*herpetiform* means grouped). The term is confusing to patients and health care providers, because *herpetiform* is commonly associated with herpes simplex virus infections, which are also characterized by grouped lesions.

Etiology, pathogenesis, and predisposing factors

There are likely multiple immunologically mediated mechanisms that drive the pathogenesis of RAS. Lymphocytic cells

Table 4 Classification of recurrent aphthous stomatitis

Type	Size (mm)	Number	Location	Prevalence (%)
MiAU	<10	Few	Anterior	85%
MjAU	>10	Few	Anterior > posterior	10%
HU	1-2	Many	Both	5%

HU, herpetiform ulcers; *MiAU,* minor aphthous ulcers; *MjAU,* major aphthous ulcers.

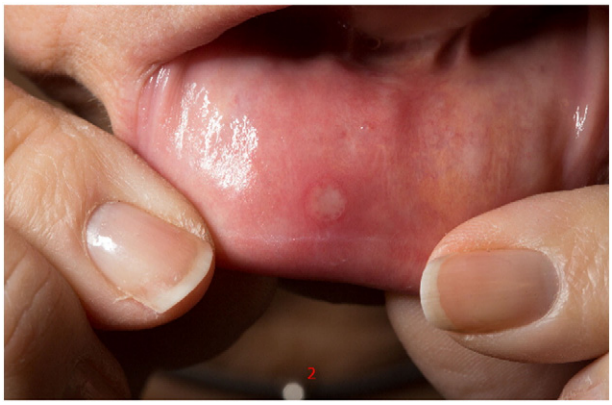

Fig. 1 Minor aphthous ulcers (MiAU), or canker sores, on the anterior oral mucosa.

infiltrate the epithelium and edema develops as a result of transient inflammatory stimuli.[18] Keratinocyte vacuolization and localized vasculitis cause localized papular swelling. The papule ulcerates and is infiltrated by neutrophils, lymphocytes, and plasma cells, followed by healing and regeneration of the epithelium.[19] The immunopathogenesis of RAS likely involves a cell-mediated immune response mechanism, which includes activation of T cells and tumor necrosis factor α (TNF-α) by other leukocytes such as macrophages and mast cells. Initiation of the inflammatory process can be induced by the effect of TNF-α on endothelial cell adhesion and its chemotactic effect on neutrophils.[4]

Elevated TNF-α and interleukin 2 (IL-2) levels (proinflammatory cytokines), as well as lower IL-10 levels (antiinflammatory cytokine), have been detected in the lesional mucosa of patients with RAS.[4] TNF-α is thought to play an important role in the immunopathogenesis of RAS by stimulating expression of major histocompatibility (MHC) class I. Increased levels of class I and class II MHC antigen expression have been reported in both preulcerative and ulcerative stages of the RAS basal epithelial cells.[4] MHC antigen expression was undetected during the process of healing, so they may have contributed to targeting local tissue for attack by cytotoxic

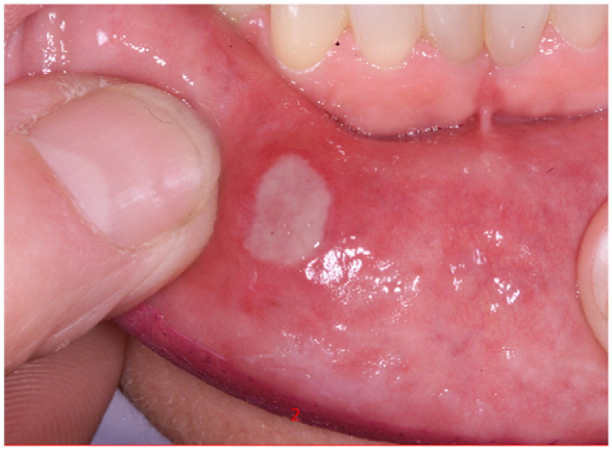

Fig. 2 Major aphthous ulcer (MjAU) on the anterior oral mucosa.

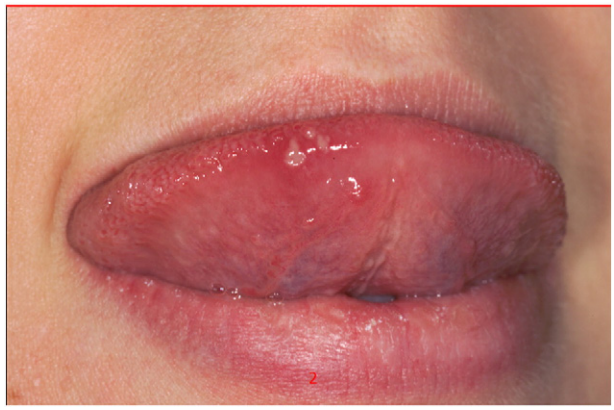

Fig. 3 Herpetiform ulcers (HU) on the tip of the tongue. HU are the least common type of recurrent aphthous stomatitis.

T cells ($CD8^+$ cells) during the ulcerative process. A low IL-10 expression may indicate a prolonged duration of the ulcer, because IL-10 stimulates epithelial proliferation in the healing stage.[4]

Although the pathogenesis of RAS remains unclear despite its high clinical prevalence,[20] there are several predisposing factors linked to RAS. A genetic predisposition for the development of RAS is thought to be likely, because about 40% of patients have a positive family history, and they tend to develop ulcers earlier and with greater severity.[19] Many of the genetic associations are between RAS and genetically determined human leucocyte antigen subtypes.[21]

Trauma to the oral mucosa from mechanical injury is the most common predisposing factor, which can occur due to toothbrushing, local anesthetic injections, and dental procedures that may lead to RAS.[4] Hematinic deficiencies (such as iron, vitamin B_{12}, folic acid) are reported to be twice as common in individuals with RAS compared to control.[1,19,21] Drugs, such as nonsteroidal antiinflammatory drugs and angiotensin converting enzyme inhibitors, have been implicated as triggers for aphthous ulcers. Ulcers usually occur as an adverse side effect and disappear with discontinuation of the offending drug.[21]

Other predisposing factors include gluten-sensitive enteropathy,[22] inflammatory bowel disease,[4] sodium lauryl sulfate–containing toothpaste,[4] hormonal changes,[23] stress,[24] and microorganisms such as *Helicobacter pylori*,[25,26] *Streptococcus mitis*,[27] or Epstein-Barr virus.[28] Interestingly, tobacco has been documented to have a negative association with RAS. This is believed to be due to increased mucosal keratinization, which provides a protective barrier against injury and microbes.[29–31]

Associated systemic disorders

Successful management of patients with aphthosis, particularly complex aphthosis, depends on an accurate diagnosis, classification of the disease, recognition of causative factors, and the identification of associated disorders, which permit

the clinician to address the treatment of the patient suffering from lesions of RAS.

Because aphthosis is a multifactorial condition, the lesions of RAS can be the mucosal manifestations of a variety of conditions, which need to be considered in patient evaluation and management (Table 3). Aphthous lesions may involve the anogenital tissues in associated conditions such as ulcus vulvae acutum,[32] reactive nonsexually related acute genital ulcers,[33] complex aphthosis,[1,4,7–13] and Behçet disease (BD).[34–36] Aphthous ulcers also occur in other inflammatory disorders such as systemic lupus erythematosus and periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome. PFAPA is discussed in detail in this issue of *Clinics in Dermatology*, and BD will be discussed in a future issue.[37–39]

Complex aphthosis

Complex aphthosis occupies a position on a continuum from simple aphthosis with involvement limited to the soft oral mucosa, to systemic involvement with oral and genital aphthae and a variety of other clinical manifestations, including gastrointestinal conditions.[1,4,7–13] This is not surprising, because the mouth is the beginning of the gastrointestinal tract and aphthosis is a reactive process. Several associated systemic disorders may present with oral lesions of RAS (Table 3).[1,4,7] These include patients with rare and unusual combinations of clinical findings plus aphthosis such as mouth and genital ulcers with inflamed cartilage (MAGIC) syndrome,[40] cyclic neutropenia, and PFAPA syndrome.[36,37]

BD is an important consideration in patients suffering from complex aphthosis. The relationship between BD and complex aphthosis was addressed in the urban legend series in the journal *Oral Diseases*[36] and will be addressed in an article on BD that will appear in a future issue of *Clinics in Dermatology*. BD is a trisymptom complex of oral and genital aphthae and ocular inflammation (uveitis, iritis) often affecting young patients of Mediterranean, Middle Eastern, and Eastern Pacific descent. The geographic area of higher risk is the famed ancient "Silk Road." On the other hand, patients with complex aphthosis in Western Europe and North America are unlikely to develop BD.[11–13,36,39,41] The diagnosis of BD should be made cautiously and after careful evaluation.[42]

Patients with complex aphthosis should be evaluated carefully for underlying correctable causes.[1,11–13] Laboratory investigations should include a complete blood cell count and levels of iron and zinc, as well as vitamins B_1, B_2, B_6, B_{12}, and folic acid. Identification of a deficiency and appropriate supplementation can lead to complete remission of complex aphthosis.

In addition, gastrointestinal diseases should be considered. The aphthae may be a sign of inflammatory bowel disease such as ulcerative colitis and Crohn disease, as well as celiac sprue (gluten-sensitive enteropathy).[1,4,36] As many as 5% of patients with gluten-sensitive enteropathy may present with aphthosis.[43,44]

Complex aphthosis thus requires appropriate investigation to identify any associated systemic conditions that are amenable to therapy, which can ultimately result in a dramatic reduction in the severity and frequency of the lesions of RAS.

Simple aphthosis

The vast majority of patients suffering with lesions of RAS have simple aphthosis (Table 2).[1,4] These patients are otherwise healthy and are unlikely to have an associated systemic condition. They have a few episodes per year with a few days of painful lesions during each episode. The prognosis is excellent, with fewer episodes and diminishing severity over time and an eventual remission to minimal disease activity.

Treatment

The natural history of an individual aphthous ulcer is healing without further sequelae.[6] While present, the lesions are most painful until covered by the fibromembranous slough. Symptomatic relief can be gained by applying over-the-counter products that contain an anesthetic preparation or a coating substance such as Orabase© or sucralfate[45] to individual lesions. Treatment with escharotics converts the lesion to a painless wound that heals quickly. Similar results are obtained with laser treatment (Table 5).[46]

Trauma has been implicated by patients, providers, and investigators[47] as a predisposing factor. Accidental dental trauma from toothbrushing, flossing, chewing food and gum, malocclusions, and talking while chewing can be reduced with therapeutic benefit. Sodium lauryl sulfate (SLS)–containing toothpaste should be avoided, because the duration of ulcers and mean pain score was found to be significantly higher in patients using SLS-containing, compared with SLS-free, toothpaste during the ulcer-healing process.[48]

It is likely that the lesions of RAS are mediated by immunologic mechanisms.[1,2,4] As a result, topical fluorinated corticosteroids such as 0.05% fluocinonide in Orabase applied every

Table 5 Topical and systemic treatments for recurrent aphthous stomatitis

Topical	Systemic		
	Specific	*Nonspecific*	
Corticosteroids Orabase	Vitamin B_{12}	Corticosteroids	Montelukast
Sucralfate		Dapsone	TNF-α inhibitors
Escharotics		Colchicine	Levamisole
Laser treatment		Tetracycline	Cyclosporine A
		Thalidomide	

TNF, tumor necrosis factor.

1 to 2 hours while awake to symptomatic areas may prevent the full-blown development of the lesions of RAS.[45]

Systemic therapy can be specific or nonspecific (Table 5). Specific therapy can be directed at the underlying condition associated with aphthosis, such as treating gluten-sensitive enteropathy and inflammatory bowel disease or replenishing vitamin and mineral deficiencies.[1,4,44,49–51]

Many investigators have attempted to implicate infectious agents as a cause of aphthosis. The most recent has been *Helicobacter pylori*. A recent study[52] with 18 *H pylori*–eradicated patients and 12 *H pylori*–noneradicated patients noted that vitamin B_{12} levels were increased ($P = .001$) and mean number of aphthous lesions was decreased ($P = .0001$) after eradication of *H pylori*. This study emphasizes the need to carefully assess each patient for correctable causes such as anemia, mineral and hematinic deficiencies, and gut disease.

In another study, researchers treated patients with a sublingual dose of 1000 μg of vitamin B_{12}. They reported that the duration of outbreaks, number of ulcers, and level of pain were all significantly reduced ($P < .05$) at 5 and 6 months of treatment. During the sixth month of treatment, 74.1% of 31 interventional group participants achieved the "no aphthous ulcers status" ($P < .01$). Researchers concluded that vitamin B_{12} treatment is inexpensive, low risk, and appears to be effective in treating patients with RAS, regardless of their initial serum vitamin B_{12} levels.[53]

Nonspecific systemic therapy involves the use of numerous immunomodulatory drugs such as corticosteroids, dapsone, colchicine, tetracycline, thalidomide, biologic agents (such as TNF-α inhibitors), and levamisole (Table 5).[54,55]

The use of systemic corticosteroids provides a temporary remission of the oral ulcerative process. A 3-week tapering course of prednisone in a single morning dose of 0.75 mg/kg body weight in the first week and reducing by 0.25 mg/kg in each of the next 2 weeks induces clinical remission. The long-term use of systemic corticosteroids for aphthosis is contraindicated.[54]

Should systemic therapy be indicated, treatment with an antiinflammatory drug such as dapsone or colchicine can be initiated concurrently with the tapering course of systemic corticosteroids and continued for maintenance of remission. This regimen has worked well for patients requiring systemic treatment.[13,54] Treatment with colchicine alone has yielded variable success (28%[54] versus 71%[56]), and treatment with dapsone alone has been reported to be unsuccessful with a 7% complete or partial improvement rate, although the authors' experience has suggested that dapsone alone can be very effective[54]; however, a combination of colchicine and dapsone increased the complete or partial response rate to 57%, a vast improvement from separate administrations of the drugs.[54] Tetracycline, when used as a 250-mg oral rinse and swallow treatment, reduced the size and pain of ulcers but did not affect the frequency of flaring and thus was not recommended for use in clinical practice.[55]

Additionally, treatment with thalidomide has been reported to have improved results compared with traditional treatments with dapsone or colchicine, with 59% having complete or partial improvement.[13] Thalidomide has also been found to be effective in treating aphthous ulcerations of the mouth in patients with HIV. In a study with 29 patients in the thalidomide group and 28 controls, 55% of patients in the thalidomide group had complete healing of their aphthous ulcers after 4 weeks, compared with 7% in the control group. Pain due to ulcers also diminished and the ability to eat was improved; however, side effects of thalidomide treatment included somnolence and dermatitis (7 patients each), toxicity (6 patients), and increased HIV RNA levels ($P = .04$).[57] Regardless of the success of reported clinical trials, the previously mentioned drugs should be used in select patients suffering from debilitating disease, given their potential for adverse effects.

Pentoxifylline has also been administered at a dose of 400 mg three times a day for 1 month to suppress TNF-α levels and neutrophil function and chemotaxis, pathogenic factors in RAS. Positive results were reported in 63.6% of men and 61.5% of women[58]; however, the recurrence of ulcers occurred in every patient when drug administration was discontinued.[58] As a result, pentoxifylline was suggested to be a second-line treatment option for patients who do not respond well to other therapies or to be used in conjunction with other treatments.[19]

Other TNF-α inhibitors that have been tested in patients with complex aphthosis include etanercept, adalimumab, infliximab, and golimumab. Eighty-nine percent of patients had complete or partial clearance of orogenital aphthous ulcerations soon after the onset of therapy with these drugs, but the actual duration of treatment ranged from 3 to 77 months.[59] Fifty percent of patients received a combination of different TNF-α inhibitors during the course of their treatment. Twenty-eight percent of patients experienced adverse effects that are possibly linked to TNF-α inhibitor treatment.[59] Although TNF-α inhibitors appear to be a good option for patients with severe complex aphthosis who do not respond well to standard treatments, randomized controlled trials are needed before a recommendation can be made.[59]

Prednisone and montelukast were also evaluated for their effectiveness in reducing the number of lesions, ulcer healing capabilities, and pain relief.[60] Prednisone was found to be more effective than montelukast in relieving pain ($P < .0001$) and in ulcer healing rate ($P < .0001$), but adverse effects were more common in patients treated with prednisone (30%) compared with montelukast (10%).[60] Montelukast was well tolerated without significant side effects and did not require dose reduction during the course of treatment[60]; therefore, it could be considered as a viable treatment option, especially for long-term use.

The effectiveness of prednisone was improved when combined with levamisole. Thirty patients with chronic oral ulcers were treated with topically applied dexamethasone in Orabase, 150 mg/day of levamisole and 15 mg/day of prednisolone for 3 consecutive days each week.[61] Within 2 weeks, all patients had either complete or partial remission of oral ulcerative lesions. Additionally, almost none of the patients had evidence

of lesions after 4 to 8 weeks of treatment. All patients remained free of lesions for more than 6 months and only one developed a minor skin rash.[61]

Cyclosporine A has been used to treat aphthosis in patients with Behçet disease. In one study, oral administration of 10 mg/kg/day of cyclosporine A was noted to be useful in treating oral aphthous ulcers, skin lesions, and genital ulcerations.[62] In a more recent study, a dosage of 3 to 6 mg/kg was found to be effective in 50% of the patients, but sudden withdrawal of the therapy was suspected to lead to a rebound phenomenon. Severe adverse effects may be associated with cyclosporine A, and therefore it should be used with caution.[63]

Conclusions

Most patients with lesions of RAS suffer from mild disease, simple aphthosis, with a few lesions per episode, few episodes per year, and a good prognosis for a spontaneous remission. Other patients suffer from severe disease or complex aphthosis. Fortunately, most patients with complex aphthosis have one or more correctable causes for their disease that are amenable to treatment. For those with aphthosis without an underlying correctable cause, nonspecific immunomodulating treatment can induce and maintain a relative remission. For all patients with aphthosis, the outlook is positive.

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