

Recurrent Aphthous Stomatitis: Current Concepts in Diagnosis and Management

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ABSTRACT

Recurrent aphthous stomatitis (RAS) is one of the most common oral mucosal condition, but little is known of its etiology or pathogenesis. Several factors have been postulated to be the cause of this condition. Currently, the most widely accepted etiology is that RAS is a localized immunological disorder. The treatment modalities for RAS, till recently, were aimed at providing symptomatic relief. In spite of the fact that the condition is recurrent and common, till date there are no effective and definitive preventive treatment strategies. This article aims to summarize the current concepts of diagnosis and management of RAS.

Keywords: Aphthous ulcer, Diagnosis, Management, Recurrent.

INTRODUCTION

RAS is one of the most common oral mucosal conditions characterized by painful recurring ovoid or round ulcers,¹⁻⁵ but little is known of its etiology or pathogenesis. Currently, the most widely accepted etiology is that RAS is a localized immunological disorder.^{4,7} The incidence of this disease ranges from 5 to 50% of the population, depending on the socioeconomic group or the ethnic group studied.⁵ Almost 80% patients develop RAS before 30 years of age.⁷ Occurrences begin at about 5 years of age and continues throughout life with a peak onset between 10 and 19 years.^{8,9} Similar condition appearing in the early childhood (before 5 years) or after 30 years should alert the clinician to the possibility of recurrent ulceration being part of a more complex disorder.¹⁰⁻¹³ The treatment modalities for RAS, till recently, were aimed at providing symptomatic relief. In spite of the fact that the condition is recurrent and common, there are no effective and definitive preventive treatment strategies.⁴ This article aims to summarize the current concepts in etiopathogenesis, diagnosis and management of RAS.

CLASSIFICATION OF RECURRENT APHTHOUS ULCERS

- *Clinical classification:* RAS can be clinically classified mainly into three groups:
 1. *Minor aphthae (mild aphthae, Mikulicz's aphthae):* This is the most common form of aphthae that accounts for 75 to 85% of all RAS cases.⁷ Minor aphthae is characterized by small ulcers, which typically can be described as well-defined, shallow, round or ovoid

painful ulcers usually, less than 8 to 10 mm, with a necrotic center covered with yellow-grayish pseudomembrane. The ulcers have raised margins and are surrounded by an erythematous halo (Fig. 1). Occasionally, the appearance of ulcers may be preceded by prodromal symptoms, like localized burning sensation or pain. Sometimes there may be associated submandibular lymphadenopathy without the presence of systemic symptoms.^{2,5} Pain and ulcers last for about 3 to 4 days after which reepithelialization begins and the pain starts subsiding.



Fig. 1: Recurrent aphthous minor

Minor aphthae heals without scarring; however, the healing in comparison to the other oral wounds is slightly delayed (10-14 days) probably due to the intensive lymphocytic infiltration.⁷

2. **Major aphthae (periadenitis mucosa necrotica recurrens, Sutton's disease):** A less common variety of RAS which accounts for about 10 to 15% of all RAS cases.⁷ The ulcers are larger, deeper and more painful than minor aphthae and most of them measure more than 10 mm⁷ (Fig. 2). They have a tendency to involve the mucosa overlying minor salivary glands and hence the usual sites of major aphthae are lips, soft palate and throat. The prodromal symptoms are more prominent than minor aphthae and the patients often have fever, malaise and dysphagia.⁷ The ulcers persists for 10 to 20 days and sometimes even months.^{4,7} Scar formation is common when the major aphthae heal. Rarely, major aphthae may present as numerous ulcers affecting a large area, or several giant lesions than persists for months. These lesions often referred to as giant aphthae, relapsing aphthae, or refractory aphthae, are typically seen in immunocompromised conditions (as in HIV), and immune-mediated diseases (like celiac disease, Crohn's disease, cyclic neutropenia, Behcet's disease).⁴
3. **Recurrent herpeticiform ulcers:** Recurrent herpeticiform ulcer is a comparatively rare presentation that accounts for approximately 5 to 10% of all RAS cases. As the name implies, it is characterized by multiple (5-100 in number), each measuring less than 5 mm often similar in appearance to Herpes simplex ulcers^{6,7} (Fig. 3). Unlike its major and minor counterpart, recurrent herpeticiform ulcers do not have any site specificity and can occur anywhere in the oral mucosa. Sometimes the ulcers can coalesce to form large ulcers that can last for about 2 weeks. Healing is usually uneventful and occurs without scarring.⁷ However, some authors are of opinion that recurrent herpeticiform ulcers have a potential for scar formation on healing.⁴

- Classification based on the nature of recurrence as follows:
 1. **Simple aphthosis:** Here, the recurrence occurs two to four times a year.
 2. **Complex aphthosis:** Here, the disease activity is almost continuous throughout the year with newer lesions developing as older lesions heal. Usually, complex aphthosis is associated with systemic diseases.
- Classification for determining the management strategies:
 1. **Type A:** RAS episodes lasting a few days with tolerable pain and few occurrences a year.
 2. **Type B:** Painful RAS lasting 3 to 10 days with recurrence every month.
 3. **Type C:** Chronic painful course with disease activity almost continuous throughout the year.

ETIOPATHOGENESIS

Recurrent aphthous ulcer is an ulcerative oral disorder with uncertain etiopathogenesis. Even though several factors like; trauma,^{6,7} heredity,¹⁴⁻¹⁶ gastrointestinal factors,¹⁶ bacterial,^{6,14} protozoal,¹⁴ hormonal imbalances, stress and menstrual cycle,^{6,7,17} food,^{7,18,19} viral,²⁰⁻²² and hematologic^{5,22-24} have been suggested no conclusive evidence exist as to their relationship with RAS.^{6,14}

Of late immunologic etiology for RAS has gained importance. Early workers suggested an autoimmune etiology or hypersensitivity reaction to oral microflora as the etiologic factor for RAS.⁵ Subsequent research into the immunological aspects of RAS suggests lymphocytotoxicity, antibody-dependent cell-mediated cytotoxicity and defects in the lymphocyte cell subpopulation as the etiological factors.⁵ Cytokines, such as interleukin-2 (IL-2) and interleukin-10 (IL-10) and depression of natural killer cell (NK cells) activity, are also believed to play a role in the development of RAS.⁷ The current concept of immunological factors involved in the etiopathogenesis of RAS revolves predominantly around cell-mediated immune response in which tumor necrosis factor α (TNF α) plays a major role. Even though the exact mechanism is not known, the formation of RAS probably involves



Fig. 2: Recurrent aphthous major



Fig. 3: Recurrent herpeticiform ulcers

cell-mediated immune response involving T cells, macrophages and mast cells and TNF α production by these cells. TNF α subsequently can induce inflammatory changes due to its effect on the endothelial cell adhesion and neutrophil chemotaxis.⁷ Identification of the role of TNF α in RAS has been helpful in controlling RAS by using TNF α synthesis inhibitors, like thalidomide and pentoxifylline.⁷

A lower prevalence rate and severity in RAS has been observed among heavy smokers.²⁵ Nicotine tablets and smokeless tobacco use are associated with lower prevalence of RAS.⁷ Some patients have often reported an increase in RAS on cessation of smoking.⁷ However, these findings cannot be used as an excuse for smoking as the ill effects far outweighs the benefits.

DIAGNOSIS OF RECURRENT APHTHOUS STOMATITIS

The diagnosis is primarily based on the history and clinical criteria. A multitude of serologic and histopathologic tests may be helpful in establishing a diagnosis by a process of elimination^{4,7} (Table 1). Along with these tests that help in the diagnosis of the disease, a comprehensive series of serologic tests like alanine aminotransferase (ALT), aspartate aminotransferase (AST), venereal disease research laboratory test (VDRL), fluorescent treponemal antibody tests (FTA), G6PD test and blood counts (to monitor bone marrow) may be performed to screen the patient, for evaluating the contraindications to medications and to monitor during the pharmacotherapeutic treatment.

MANAGEMENT OF RECURRENT APHTHOUS STOMATITIS

The cyclic nature of the disease, unknown etiologic factors make recurrent aphthous stomatitis a difficult disease to treat.

Variations in the clinical presentation demands a predominantly symptomatic treatment regime tailored to suit each patient individually. The goals of the treatment are namely: (1) To decrease the symptoms (2) To reduce the number and size of the ulcers (3) To increase the duration of the disease-free state with minimal adverse effects. The patient's medical history, severity of pain, frequency/flare-ups, and the patient's ability to tolerate medication are some factors that determine treatment. It is mandatory that all the predisposing factors be treated or ruled out prior to specific treatment for RAS.

Management of Type A Aphthous Stomatitis

Type A aphthae may not require any specific medication as they are associated with tolerable pain. Here, attempts are made to identify and eliminate the precipitating factor(s) along with an evaluation of the nature of the disease, its outbreak and the patient's efforts to manage the situation. Self-management strategies, if found effective, may be encouraged.

Management of Type B Aphthous Stomatitis

For Type B, every effort should be made to identify and eliminate precipitating factors. Patients with prodromal symptoms should be identified and may be encouraged to use corticosteroid (topical/systemic) to prevent the ulcerations that follows. Several treatment regimes have been suggested once the ulcers appear:

1. Cauterizing drugs/escharotic agents drugs, like phenol, chromic acid, alum, silver nitrate, have been used for alleviating pain as they destroy the nerve endings and initiate fibrosis at the base and the sides of the ulcer. But, they prolong healing time due to their destructive activity.⁶

Table1: Tests to rule out other conditions in aphthous ulcer

S no.	Tests	Conditions to be ruled out
1.	Biopsy	When mucocutaneous lesions are suspected
2.	Full blood picture	
3.	Hemoglobin	To rule out iron deficiency
4.	Total and differential count	To rule out cyclic neutropenia
5.	Red cell indices	To rule out iron and folic acid deficiency
6.	Iron studies: Serum ferritin levels	To rule out iron deficiency
7.	Red cell folate assay	To assess deficiency of folic acid
8.	Serum vitamin B12 levels	
9.	Fungal culture/periodic schiff test (PAS)	Candidiasis
10.	Microimmune-diffusion test: Blastomyces A-antigen enzyme immunoassay	Blastomyces
11.	Direct immunofluorescence	Pemphigus, cicatrical pemphigoid, lichen planus, dermatitis herpetiformis
12.	Indirect immunofluorescence	Systemic lupus erythematosus
13.	Endoscopy, laryngoscopy, small bowel series colonoscopy, sigmoidoscopy	Crohn's disease, Behcet's syndrome, ulcerative colitis
14.	Serum autoantibodies to desmoplakin I and II	Erythema multiforme
15.	Antigliadin, antireticulin, antiendomysial antibody tests	Celiac disease, glutensensitive enteropathy
16.	pp65 CMV antigenemia test, CMV culture and antibody test	For EB virus
17.	Virus neutralization test	Coxsackie virus
18.	HSV culture and antibody test	For herpes simplex virus (HSV)

2. *Vitamins*^{26,27}: Even though previous studies with B1, B2 and B6 were inconsistent, recent studies especially on sublingual administration of B12 or its bioactive form has concluded that B12 can be effective in controlling RAS, regardless of the level of serum B12 levels.
3. *Milk of magnesia*: Used as a mouthwash, may provide relief from pain, but it provides only temporary relief.
4. Mucous membrane adhering compounds, like orabase, 2-octyl cyanoacrylate bioadhesives, methylcobalamin bioadherent disks, may be used topically.²⁷
5. Vaccinations with cowpox virus, lactobacillus containing materials and nutrient supplements have been tried.⁶
6. Nonsteroid anti-inflammatory agents and antihistamines used as oral rinses have been found to be effective in reducing pain and discomfort (Kaopectate, Maalox, diphenhydramine, etc. used as mouth rinses).
7. *Topical corticosteroids*: Topical corticosteroids which should be applied thoroughly and frequently to the ulcer considered to have only minimal penetration into the systemic circulation. They may be prescribed alone or in combination with other agents. Some of the topical preparations are:
 - Dexamethasone 0.05 mg/ml rinse (prepared by mixing 1 ml of 4 mg/ml injection dexamethasone in 400 ml water), for rinsing three times a day
 - Dexamethasone 0.05 mg/ml rinse, with 0.2% chlorhexidine mouthwash for rinsing thrice a day
 - Clobetasol ointment 0.05% in orabase (1:1) for topical application thrice daily
 - Fluocinonide ointment 0.05% in orabase (1:1) topically three times a day
 - Triamcinolone acetonide 0.1% oral paste.
8. *Systemic corticosteroid therapy*: Recommended for patients with recalcitrant cases of RAS. It involves corticosteroid tablet, hydrocortisone 20 mg tab or triamcinolone 4 mg tab orally upto a maximum of 50 mg/day for five days. The dose requirements are variable and requires individualization for which such cases are best referred to an oral medicine specialist. They may also need a maintenance treatment protocol because of the constant recurrent pattern. Most often systemic steroid therapy has been found to be less effective when used alone and has the disadvantage of steroid resistance.⁴

Management of Type C Aphthous Stomatitis

Type C RAS is best dealt with by oral medicine specialist. Here, the treatment may be started with topical steroids as in Type B RAS followed by systemic therapy. To avoid the ill effects of prolonged systemic steroid therapy, a part of the steroid dose may be supplemented with drugs like azathioprine.²⁸ Drugs like dapsone, levamisole, pentoxifylline, colchicine and even thalidomide have been tried in the treatment of type C aphthae.²⁸

Azathioprine: An imidazolyl derivative of mercaptopurine often used for immunosuppression in humans. Azathioprine supplementation in the management of Type C RAS has been tried with limited success.⁴ Azathioprine is started at 50 mg/day and can be escalated up to 150 mg/day. The toxic effects of azathioprine include bone marrow depression, (manifested as bleeding, leukopenia, thrombocytopenia, anemia) hepatic dysfunction (with high serum alkaline phosphatase levels, jaundice), gastrointestinal disturbances and nephrotoxicity.²⁸ Hence, complete blood count examination before and during azathioprine treatment is mandatory.²⁸

Dapsone: Diaminodiphenyl sulphone (dapsone) a widely used drug in the long-term treatment of leprosy and some dermatologic conditions have been tried with limited success in the management of major aphthae.⁴ Dapsone is given 100 mg orally in divided doses and may be increased at the rate of 50 mg/day per week to a maximum of 300 mg/day.⁴ Dapsone, a potentially toxic drug, can precipitate hemolytic anemia, hence, the patients should be monitored for hemolysis, methemoglobinemia, anemia and agranulocytosis.⁴

Levamisole: Levamisole (150 mg/day), an immunotherapeutic drug is believed to reduce pain, number, duration and the frequency of ulceration in major RAS.⁴ This drug is believed to have an immunomodulatory effect which makes it useful in controlling RAS.

Pentoxifylline: A drug, used in the treatment of peripheral vascular disease, has been effectively used in the treatment of RAS.⁴ Pentoxifylline is believed to inhibit TNF α production like thalidomide, and like colchicines it inhibits neutrophil function and chemotaxis, without the well-known side effects of these drugs and has a fairly good safety record even in long-term use.³² It may be administered 400 mg orally three times a day. Pentoxifylline has been found to reduce pain, size and number of ulcers.⁴ However, pentoxifylline is considered only as a second line drug in the management of RAS.²⁹

Thalidomide: TNF α blocker, may be effective in the treatment of RAS.^{4,30} Thalidomide may induce healing and reepithelialization as it can improve human keratinocyte migration and proliferation.⁴ The recommended dosage is 100 to 200 mg/day to start with and to be continued till remission. The treatment may be restarted as per the initial regimen until remission followed by a maintenance dose of 50 to 100 mg daily or 50 mg every other day.⁴ Maintenance dose itself may be tapered off to reduce side effects. Since, thalidomide is a well known teratogen, strict precautions to the use of drugs should be taken. The FDA (United States food and drug administration) has strict guidelines for prescribing thalidomide known as STEPS (System for Thalidomide Education, Prescribing Safety oversight program).⁴ In this program, the patients undergo training regarding (i) drug (ii) screening procedures (iii) therapy under close observation, prior to thalidomide usage.

CONCLUSION

RAS is little understood in spite of, being a common, painful, recurrent disorder. Currently, RAS is considered to have a localized immunological etiology. Even though the role of several immunologic factors ranging from hypersensitivity to cytokines have been discussed, the role of TNF α in the etiology of RAS has gained importance recently. This has paved the way for the use of TNF α inhibitors like pentoxifylline and thalidomide in the treatment of recalcitrant cases of RAS. However, these drugs are not without any pitfalls. We are yet to develop effective and definitive preventive strategies in the management of RAS.

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