

Recurrent Aphthous Stomatitis: A Review

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ABSTRACT

Recurrent Aphthous Stomatitis (RAS) is a disorder characterized by recurring ulcers in the oral mucosa in patients with no other signs of disease. This condition is also called as Sutton's disease, especially in the case of major, multiple or recurring ulcers. RAS appears to represent several pathological states with similar clinical manifestations, including immunologic disorders, hematologic deficiencies and allergic or psychological abnormalities. This article reviews the current data on the etiopathogenesis, diagnosis and management of RAS.

Key words: Oral ulcers, Aphthous stomatitis, Etiopathogenesis, Sutton's disease.

INTRODUCTION

Recurrent aphthous stomatitis (RAS) is defined as the presence of recurring ulcers confined to the oral mucosa in patients with no other signs or symptoms of underlying disease. The types of oral ulcers are diverse, with a multitude of

associated causes including: physical or chemical trauma, infection from microorganisms, medical conditions or medications, cancerous and nonspecific processes. Once formed, the ulcer may be maintained by inflammation and/or secondary infection. The causes of oral ulcers are diverse which includes a multitude of factors¹ (Table-1).

Table 1: Principal causes of oral ulcers

Solitary ulcer	Trauma
Recurrent bouts of one or more ulcers healing spontaneously	Squamous cell carcinoma Infections (e.g. syphilis, tuberculosis) Recurrent aphthous stomatitis (RAS) Behcet's disease 'Aphthous-like' ulcers due to systemic disease or drug therapy.
Single bout of ulceration, preceded by vesicles and affecting multiple oral sites	Recurrent erythema multiforme Viral infections (e.g. herpangina and primary herpetic stomatitis) Erythema multiforme
Persistent oral ulceration affecting different sites	Mucocutaneous disease (e.g. oral lichen planus) Immunobullous disease (e.g. oral pemphigus) Gastrointestinal disease (e.g. Crohn's disease) Haematological (e.g. leukaemia) Drug therapy (e.g. nicorandil)

RAS is the most common type of ulcerative disease of the oral mucosa, and it affects approximately 20% of the general population. Prevalence of RAS varies among different socioeconomic groups and its incidence is strongly affected by family history². Age of presentation is between the second and third decades of life in otherwise healthy individuals. RAS is the most common type of recurrent oral ulceration in the age group of 10 to 19 years. Similar ulcers can be seen in patients with a variety of diseases including systemic lupus erythematosus, Behcet's syndrome, iron deficiency anemia and Crohn's disease. Therefore, RAS patients must be carefully evaluated for associated symptoms to determine whether laboratory evaluation is required.

The worldwide distribution, high frequency and decreased quality of life generated by RAS have resulted in a great deal of research into the etiology and efficient therapy of this disease. However, the etiology of RAS still remains unclear, and the currently available therapy remains inadequate.

DISCUSSION

The exact cause of many aphthous ulcers is unknown, diagnosis is entirely based on history and clinical criteria and no laboratory procedures exist to confirm the diagnosis. Although RAS may be a marker of an underlying systemic illness such as coeliac disease, or may present as one of the features of Behcet's disease, in most cases no additional body systems are affected, and patients remain otherwise fit and well.

Lack of sleep, illness, physical trauma, stress, hormonal changes, sudden weight loss, food allergies, immune system reactions and deficiencies in vitamin B₁₂, iron, folic acid and citrus fruits may contribute to their development³⁻⁵.

Trauma to the mouth is the most common trigger. Physical trauma, such as that caused by toothbrush abrasions, laceration with sharp or abrasive foods such as toast, potato chips or other objects, accidental biting (particularly common with sharp canine teeth), after losing teeth, or dental

braces can cause aphthous ulcers by breaking the mucous membrane.

Oral aphthous ulcers are also commonly seen in celiac disease and Crohn's disease. There is no indication that aphthous ulcers are related to menstruation, pregnancy and menopause, however, smokers appear to be affected less often.

Systemic conditions and aphthous-like lesions

Principal systemic conditions associated with 'aphthous-like' ulcers. These frequently start in adulthood with no previous history of oral ulceration. These conditions may mimic aphthous ulcers which may pose a diagnostic problem⁴. (Table-2)

Table 2: Systemic conditions and aphthous like lesions

Behcet's disease	
Nutritional deficiencies	
Gastrointestinal disorders	
	' Crohn's disease
	' Ulcerative colitis
Cyclical neutropenia	
HIV infection	
MAGIC syndrome	
FAPA syndrome	
Drug reactions	

Clinical presentation

Aphthous ulcers usually begin with a tingling or burning sensation at the site of the future aphthous ulcer. In a few days, they often progress to form a red spot or bump, followed by an open ulcer.

The aphthous ulcer appears as a white or yellow oval with an inflamed red border. Sometimes a white circle or halo around the lesion can be observed. The gray-, white-, or yellow-colored area within the red boundary is due to the formation of layers of fibrin, a protein involved in the clotting of blood. The ulcer, which itself is often extremely painful, especially when agitated, may be accompanied by a painful swelling of the lymph nodes below the jaw, which can be mistaken for toothache, another symptom is fever. A sore on the gums may be accompanied by discomfort or pain in the teeth.

Minor ulceration

“Minor aphthous ulcers” indicate that the lesion size is between 3 mm (0.1 in)-10 mm (0.4 in). The appearance of the lesion is that of an erythematous halo with yellowish or grayish color. Extreme pain is the obvious characteristic of the lesion. When the ulcer is white or grayish, the ulcer will be extremely painful and the affected lip may swell. They may last about 1 week.

Major ulcerations

Major aphthous ulcers have the same appearance as minor ulcerations, but are greater than 10 mm in diameter and are extremely painful. They usually take more than a month to heal, and

frequently leave a scar. These typically develop after puberty with frequent recurrences. They occur on movable non-keratinizing oral surfaces, but the ulcer borders may extend onto keratinized surfaces. They may last about 10 to 14 days.

Herpetiform ulcerations

This is the most severe form. It occurs more frequently in females, and onset is often in adulthood. It is characterized by small, numerous, 1–3 mm lesions that form clusters. They typically heal in less than a month without scarring. Palliative treatment is almost always necessary.

Table 3: Classification of RAS

Type	Features	Treatment
Type A	RAS episodes lasting for only a few days, occurring only a few times a year	*Medication may not be indicated *Topical anesthetics to relieve pain
Type B	*Frequent and painful RAS, lasting between three and 10 days. *The patient might have changed diet and oral hygiene habits because of the pain	*Medication is needed in this type of RAS *Treated by topical corticosteroids or systemic corticosteroids
Type C	Painful, chronic courses of RAS in which by the time one ulcer heals, another develops.	Best treated by topical corticosteroids, systemic corticosteroids, azathioprine or other immunosuppressants such as dapsone, pentoxifylline and sometimes thalidomide

Classification

To help determine management strategies, Crispian Scully divided RAS in three clinical presentations: type A, type B and type C⁵. (Table-3)

include topical and systemic corticosteroids, topical antibiotics, immunomodulators and others. Numerous randomized control trials have been reported discussing their efficacy in the treatment of RAS (Table-4).

Management

The treatment of recurrent aphthous stomatitis (RAS) still remains nonspecific and is based primarily on empirical data. The goals of therapy include the management of pain and functional impairment by suppressing inflammatory responses, as well as reducing the frequency of recurrences or avoiding the onset of new aphthae. Non therapeutic treatment includes proper maintenance of oral hygiene, trauma prevention, avoidance of certain foods/drinks, use of straws, relaxation techniques. Therapeutic options for RAS

Topical therapy

Medication prescribed to treat RAS should relate to the severity of the disease. In mild cases, with two or three small lesions, use of topical coating agents such as Orabase or Zilactin is appropriate. Pain relief can be obtained with the use of a topical anesthetic agent, such as benzocaine in Orabase. In more severe cases, the use of a high potency topical steroid preparation, such as fluocinonide, betamethasone or clobetasol, placed directly on the lesion shortens healing time and the size of the ulcer.

Table 4: Randomized control trials for RAS (table-4)

Study	Subjects	Treatment	Results	Adverse effects
Binnie <i>et al.</i> , 1997 ⁽⁶⁾	1133 healthy subjects with history of minor RAS and mean age of 27.5	5% Amlexanox oral paste	Better healing, pain relief	No adverse reactions reported
Khandwala <i>et al.</i> , 1997 ⁽⁷⁾	1335 healthy subjects with history of minor RAS and Mean age of 28.6	5% Amlexanox oral paste	Decreased healing time	No adverse reactions reported
Ylikontiola <i>et al.</i> , 1997 ⁽⁸⁾	31 healthy subjects with history of minor RAS and Mean age of 38	150 mg doxymycine 0.9% NaCl 1 drop cryo	Decreased pain	No adverse reactions reported
Kerr <i>et al.</i> , 2003 ⁽⁹⁾	110 healthy subjects with history of minor RAS	Topical 50mg penicillin G potassium troches applied 4 times a day for 4 days	Better healing and pain relief	No allergic reactions reported
Alidaee <i>et al.</i> , 2005 ⁽¹⁰⁾	97 healthy subjects with history of minor RAS and Mean age of 26	Silver nitrate sticks gently painted on ulcer leading to chemical cauterization	Significant reduction of pain	Must be done by trained professional
Murray <i>et al.</i> , 2005 ⁽¹¹⁾	46 healthy subjects with history of minor RAS and associated prodromal symptoms. Mean age of 37	0.5cm of 5% Amlexanox paste applied 4 times a day to check the prevention of ulcer and healing	Decreased ulcer size and extent of pain	Mild and transient side effects
Martin H Thornhill <i>et al.</i> , 2007 ⁽¹²⁾	26 subjects were randomized to placebo or treatment	Pentoxifyline 400 mg 3 times daily, or matching placebo	Decreased healing time less pain	Dizziness, headaches, stomach upset, increased heart rate, and nausea
Porter SR <i>et al.</i> , 2009 ⁽¹³⁾	63 healthy subjects with history of minor RAS and Mean age of 25	HybenX versus an occlusive covering device (Salicept oral patches; Carrington Laboratories) (HybenX is normally used as plaque biofilm remover)	HybenX safely and effectively reduced the painful symptoms	Nausea
Volkov I <i>et al.</i> , 2009 ⁽¹⁴⁾	58 healthy subjects with history of minor RAS	Sublingual dose of 1000 mcg of vitamin B ₁₂	Duration of outbreaks, the number of ulcers and the level of pain were reduced significantly	No known significant toxic effects

Other topical preparations that have been shown to decrease the healing time of minor RAS lesions include amlexanox paste and topical tetracycline.

Systemic therapy

Systemic therapy for RAS is usually advised to patients with chronic lesions and multiple painful lesions. Vitamin B₁₂ is a simple, effective, and low-risk therapy to prevent recurrent aphthous stomatitis¹⁵. Zinc deficiency has been reported in people with recurrent aphthous ulcers. Zinc supplementation had reported positive results in these individuals¹⁶.

For patients with major aphthae or severe cases of multiple minor aphthae who do not respond to topical therapy the use of systemic therapy should be considered. Pentoxifylline (PTX) can be used systemically to control ulcers that do not respond to topical medication. PTX is a methylxanthine compound related to caffeine and theophylline. It is used chiefly to treat peripheral vascular disease because it increases the flexibility of red blood cells and enhances blood flow to ischemic limbs. It also increases neutrophil chemotaxis and motility, and decreases the clumping of neutrophils. And it has anti-inflammatory properties by decreasing the production of cytokines and by decreasing the effect of the cytokines on leukocytes. Several reports suggest that PTX is effective in preventing aphthous ulcers¹⁷.

Levamisole is a safe drug. When compared with the placebo, levamisole is not effective in the prophylactic treatment of recurrent aphthous stomatitis. The placebo effect is important in diseases where emotional factors affect recurrence or expression of symptoms¹⁸.

Dapsone(100mg/day) can be used for oral and genital aphthae, however, rapid relapses can occur after discontinuation of treatment¹⁷.

Colchicine is another systemic medication that has been used with success in treating ulcers that are unresponsive to topical medication. Colchicine is an anti-inflammatory agent that limits leukocyte activity by binding to tubulin, a cellular microtubular protein, and, therefore, inhibiting

protein polymerization¹⁹. It also inhibits lysosomal degranulation and increases the level of cyclic AMP, which decreases both the chemotactic and the phagocytic activity of neutrophils.

Alkylating Agents like chlorambucil on orogenital ulcerations in ABD demonstrated a good response when administered at an initial dose of 0.1mg/kg, followed by a low maintenance dose of 2mg/day.

Thalidomide has been shown to reduce the incidence and severity of RAS. The drug was first marketed in Europe in the 1950s as a non-addictive sedative agent, but it was withdrawn from the market nearly 40 years ago after the discovery of its teratogenicity. Several reports have been published reporting positive results when treating severe recurrent ulcers with thalidomide. Thalidomide has many serious adverse effects, including teratogenicity, peripheral neuropathy, and other minor adverse effects, such as dizziness and somnolence. To minimize the risk of teratogenicity, the System for Thalidomide Education Prescribing Safety (S.T.E.P.S.) program has been instituted to control and monitor the use of thalidomide¹⁷.

Application of 5-aminosalicylic acid 5% cream (applying a small amount to cover the aphthae 3 times/day), or a toothpaste containing amyloglucosidase and glucose oxidase can reduce pain and lessen the duration of oral aphthae¹⁷.

CONCLUSION

RAS is a common oral mucosal disorder with uncertain etiopathogenesis. The diagnosis of this condition is made on clinical grounds alone. Several factors such as trauma, diet and stress are known to trigger the disease. The most important factor in the treatment of RAS is to identify underlying precipitating factors and try to eliminate them. Given its painful presentation and inflammatory nature, RAS responds quite well to the use of topical or systemic anti-inflammatory drugs, particularly corticosteroids. Since the advent of high potency topical steroids, most patients with RAS can be managed this way. Topical steroids, when used for a short period, have a very safe

profile and should be the first line of treatment for recurrent oral stomatitis. Medications such as immunomodulators and other agents like

thalidomide should be used with care. The use of these high end medications should be reserved for treating major, multiple and recurring ulcers.

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