

REVIEW ARTICLE

Etiopathogenesis, Diagnosis and Recent Treatment Modalities For Recurrent Aphthous Stomatitis: A Review

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ABSTRACT

Recurrent aphthous stomatitis is a disorder characterized by recurring ulcers in the oral mucosa in the patient with no other signs of disease. Recurrent aphthous stomatitis (RAS) are painful lesions that occur within the oral cavity. The incidence of recurrent aphthous stomatitis ranges from 5 to 50% of the population. The underlying etiology of the disease is not clear and no definite treatment modalities are available. The purpose of this article is to review the etiopathogenesis, clinical features, differential diagnosis, diagnosis and recent treatment modalities for recurrent aphthous stomatitis.

Keywords: Recurrent aphthous stomatitis, Oral cavity, Ulcer

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INTRODUCTION

The term “aphthous” is derived from a Greek word “aphtha” which means ulceration. Recurrent aphthous stomatitis (RAS; aphthae;

canker sores) is a common condition which is characterized by multiple recurrent small, round or ovoid ulcers with circumscribed margins, erythematous haloes, and yellow or grey floors, appearing first in childhood or adolescence.^{1,2} RAS has a chronic but self limiting course and mostly manifests in the form of outbreaks. It affects 5-25% of the population, and is the most frequently occurring disease of the oral cavity. The most commonly affected age group is 10-40 years with women and individuals of higher socioeconomic status being affected more commonly.²

CLASSIFICATION

Classification based on nature of recurrence as follows:

- Simple aphthosis – Here the recurrence occurs two to four times in a year.
- Complex aphthosis - Complex aphthosis is usually associated with systemic disease. In this case activity of disease continues throughout the year and as older lesions heal newer lesion develops.

Classification for determining the management strategies:

- Type A: RAS episodes lasting a few days with tolerable pain and a few occurrences in a year.
- Type B: Painful RAS lasting 3 to 10 days recurrence every month.
- Type C: Chronic painful course with disease activity almost continuous throughout the year.

Recurrent aphthous ulcers can also be divided in to three groups:

- Major recurrent aphthous stomatitis.
- Minor recurrent aphthous stomatitis.

- Herpetiform ulcers.³

ETIOLOGY

Immunological reactions

Immunological reactions includes:

- Cytotoxicity of T lymphocytes to oral epithelium.
- Antibody dependent cell mediated cytotoxicity.
- Defects in lymphocyte subpopulations.

Elevated levels of interleukin -2(interleukin-2), interferon gamma & tumor necrosis factor with alteration in CD4+: CD8+ ratio is also noted.

Because levels of serum immunoglobulins and natural killer cells are essentially within normal limits in RAS patients, the focus is on deregulated local cell mediated immune response conducive to accumulation of subsets of T cells, mostly CD8+ cells.

Local trauma

Local trauma is regarded as a predisposing factor for RAS in susceptible individuals. Trauma of minor degree like injection, sharp food, tooth brushing etc. may cause aphthous ulcers. Trauma predisposes to RAS by including edema, early cellular inflammation associated with increased viscosity of oral submucosal extracellular matrix.⁴

Microbial aspect of RAS

Oral streptococci were previously suggested as important in the pathogenesis of RAS, either as direct pathogens or as antigenic stimuli in the genesis of antibodies that may conceivably cross-react with the oral mucosa. An L-form streptococcus isolated from RAS patients was initially typed as *S. sanguis* but later this was found to be *S. mitis*.

In patients with RAS, cross reactivity between a streptococcal 60–65 kDa hsp (heat shock protein) and the oral mucosa has been demonstrated and significantly elevated levels of serum antibodies to hsp have also been detected. As opposed to period of remission, there is a significantly increased lymphoproliferative response to peptide 91-105 in the ulcerative stage .

It has been suggested that there might be a association between RAS and *Helicobacter*

pylori. Certain viruses such as adenoviruses may also play a role but there is no confirmation regarding their role in etiology of RAS.

In some patients, HSV and HSV1 has been detected in circulating mononuclear cells and circulating immune complexes respectively.

However, serum levels of interferon are not increased in RAS. IgM and IgG antibodies to VZV may be elevated in some RAS patients suggesting an association between reactivation of VZV and RAS. Furthermore VZV-DNA can be detected in lesional tissue by PCR, but contamination is possible and may underlie these observations.

Elevation of antibodies to CMV has also been noted in ill defined oral ulcerations in non HIV infected persons.

Many theories have been put forward regarding the etiology of RAS but there is no definitive evidence regarding these theories. Cross reactivity between bacterial heat shock proteins and epithelial components is a new theory which has come forward these days.⁵

Stress

Stress and psychological imbalance have been associated with recurrent aphthous ulcers. Patient often manifest increased stress with onset of aphthous ulcers and several studies have reported higher occurrence. Fergusson et al in 1984 suggested that antidepressant therapy reduces the incidence of ulcers. Several mechanisms can be postulated for a cause and effect relationship between trait anxiety and recurrent aphthous stomatitis. There could be an as yet unknown biochemical effect or trait anxiety that could lead to parafunctional habits including lip and cheek biting and physical trauma which might initiate the ulcerative process in susceptible individuals.^{4,6,7}

Systemic diseases

Several medical disorders are associated with oral ulcerations that resemble RAS. These systemic conditions are summarized in table 1.⁵

Genetic factors

In some individuals RAU may have familial basis. Certain genetically specific HLAs have been identified in RAS patients. They are HLA-

1	Behcet's disease	RAS is an important feature Behcet's disease. The ulceration may be more severe. Patients also suffer from recurrent genital ulceration, cutaneous disease, (papulopustular lesions or), ocular disease (posterior uveitis) and variety of other gastrointestinal, neurological, renal, joint and haematological abnormalities.
2	MAGIC syndrome	Comprises major aphthae and generalized inflamed cartilage. A variant of Behcet's disease.
3	Sweet's syndrome	Also termed acute neutrophilic dermatosis. Affected patients have superficial ulceration similar to RAS. In addition, there is sudden onset fever, leucocytosis and well demarcated cutaneous, plum-coloured papules or plaques. Usually arises in middle-aged females. In 50% of patients there is an associated malignancy (e.g. acute myeloid leukaemia).
4	PFAPA syndrome	Comprises periodic fever, aphthae like oral mucosal ulceration, pharyngitis and cervical adenitis. Although rare, PFAPA tends to occur in young children. This is a self limiting, non recurrent disease and may respond to cimetidine.
5	Cyclic neutropenia	Patient suffering from cyclic neutropenia develop oral ulceration, fever, cutaneous abscesses, upper respiratory tract infections and lymphadenopathy. Other oral complications include severe gingivitis and aggressive periodontitis. Treated with recombinant granulocyte colony stimulating factor (rG-CSF). Other neutropenias (e.g. chronic neutropenia) can give rise to superficial oral mucosal ulceration without any significant periodicity.
6	HIV disease	Aphthous-like ulceration may occasionally arise in HIV disease. However, it remains unclear, if there is a significantly raised frequency of recurrent idiopathic oral ulceration in HIV disease

Table-1: Several medical disorders are associated with oral ulcerations

A2, HLA-B5, HLA-B12, HLA-B44, HLA-B51, HLA-B52, HLA-DR2, HLA-DR7, HLA-DQ series.

Allergic factors

RAS can also be caused by allergy or hypersensitivity reaction to certain food substances. The possible causative factors are oral microbes such as *S. sanguis* and microbial heat shock protein.⁴

Nutritional factors

Roger et al reported clinical improvement in 75% of patients with RAS when a specific haematological deficiency was detected and corrected with specific replacement therapy.⁸

PATHOGENESIS

The pathogenesis of RAS involves a predominantly cell mediated immune response in which TNF TNF- α plays a major role. A mononuclear (lymphocyte cell) infiltrate in the epithelium in pre ulcerative stage followed by a localized popular swelling due to keratinocyte vacuolation surrounded by a reactive erythematous halo representing

vasculitis. The painful papule then turns in to a vesicle which ulcerates and fibrinous membrane covers the ulcer, which is mainly infiltrated by neutrophils, lymphocytes and plasma cells. Finally there is healing with epithelial regeneration. The immunopathogenesis probably involves cell mediated responses involving T-cells and TNF- α production by these and other leukocytes (macrophages and mast cells). TNF- α induces inflammation by its effect on endothelial cell adhesion and neutrophil chemotaxis.⁹

CLINICAL FEATURES

Major recurrent aphthous stomatitis

(Periadenitis mucosa necrotica recurrens, Sutton's disease)

- Rare and severe form.
- Accounts for 10 to 15% of all RAS cases.
- Ulcers are larger deeper and painful.
- These lesions are oval and may exceed 1 cm in diameter; indeed, they may approach 3 cm.
- They have tendency to involve mucosa overlying the minor salivary glands and

hence usual sites of major aphthae are lips, soft palate and throat.

- The prodromal symptoms are prominent than minor aphthae and patient have fever, malaise and dysphagia.
- Ulcers persist for 10 to 20 days and sometimes even months.
- Scar formation is common.
- Rarely major aphthae may present as numerous ulcers affecting a large area or several giant lesions that persists for month. These lesions often referred as giant aphthae, relapsing aphthae or refractory aphthae (Figure-1).

Minor recurrent aphthous stomatitis

- Also known as mild aphthae or Mikulicz's aphthae
- Minor RAS is common form of and it accounts for 75to85% of all cases.
- These ulcers are usually oval or round in shape, less than 5mm in diameter and enveloped by thin erythematous halo with grey-white pseudomembrane.
- The labial and buccal mucosa and the floor of the mouth are predominant sites affected by minor RAS. Gingiva, palate, or dorsum of the tongue is rarely affected.
- Prodromal symptoms like localize burning sensation and pain may occur before the appearance of ulcers.
- At times, submandibular lymphadenopathy may be present in absence of disease.
- Ulceration and pain lasts for about 3 to 4 days, and then re-epithelialization begins after which pain starts subsiding. (Figure-2)

Herpeti form ulcers

- Rare presentation.
- Accounts for 5 to 10 % of all RAS cases.
- Characterized by multiple recurrent crops of small, painful ulcers (5-100) that are widespread and may be distributed throughout the oral cavity.
- They tend to fuse, producing large irregular ulcers. (Figure:3)
- These ulcers have later age of onset with more predisposition for women.

- Herpeti form ulcers do not have any site specificity and can occur in anywhere in oral mucosa.
- Healing is usually uneventful and without scarring.^{3,5,10}



Figure-1: Recurrent aphthous major; **Figure 2:** Recurrent aphthous minor; **Figure 3:** Recurrent herpetiform ulcers

DIFFERENTIAL DIAGNOSIS

Herpes zoster

Lesions in herpes zoster appear 1 to 7 days after the onset of pain and hyperesthesia. New crops of vesicles can appear for 3to 5 days and then dry and form crusts that take about 3 weeks to heal and lesions are seen unilaterally.

Traumatic ulcer

In traumatic ulcer there will be history of trauma like that of injury from tooth brush, contact with sharp cusp or food stuffs, improper dental restorations or denture irritation. Traumatic ulcers are usually single, irregular, deep and covered with slough.

Herpes simplex infection

Aphthous lesions initiated by local discomfort at the site while in herpes simplex infection there is lack of tactile or sensory perception that may progress to tingling, burning, or throbbing sensation. Local lesions proceeded by 1to 2 days with systemic symptoms like fever, malaise, headache, nausea, vomiting. Generalized marginal gingivitis, enlarged submandibular and cervical lymphnodes are present in HSV not in RAS. Lesions in RAS tend to be larger, spread over a large area of mucosa and usually occur in labile mucosa that is tongue, buccal mucosa, labial mucosa and floor of the mouth.

Erythema multiforme

Has explosive onset and extensive lesions occur in less than 24 hours, RAS begin with prodromal burning any from 2 to 48 hours before ulcer appears. RAS confined to oral mucosa but

erythema multiforme have typical skin lesions (target lesions) along with oral lesions. Lesions of erythema multiforme are deep, irregular and often bleed, crusted lesions on vermillion border of lip and drooling of blood tinged saliva is characteristic of EM.

Pemphigus

Chronic mucocutaneous disorder occurring in older age group. RAS is characterized by round symmetrical ulcers but lesions in pemphigus are shallow, irregular and spread peripherely.

Mucous membrane pemphigoid

Occurs in adults above age of 50 years. MMP may involve skin, eyes, genital mucosa, along with oral lesions. Desquamative gingivitis is most common manifestation of MMP.

HISTOPATHOLOGIC FEATURES

Sub-epithelial inflammatory, mononuclear cells with abundant mast cells, connective tissue edema and lining of the margins with neutrophils can be demonstrated in pre-ulcerative lesions.

Damage to the epithelium usually begins in basal layer and progresses through the superficial layers, leading eventually to ulceration and surface exudates. Characteristic changes in nuclei of epithelial cells taken by cytological smear from around recurrent aphthous ulcers.

The cell consists of elongated nuclei, containing a linear bar of chromatin with radiating process of chromatin extending towards the nuclear membrane referred as "anitschkow cells".^{4,8}

INVESTIGATIONS

Blood investigations- Serum iron, folate, vitamin B12, and ferritin levels should be checked.

Immuno Histochemistry - The epithelial basal cells in pre-ulcerative RAS lesions and epithelium at the ulcer stage contain Class I and Class II MHC antigens, both being consistent with active cell mediated inflammation. RAS biopsy tissue on immunological study reveals numerous cells with variable ratios of CD4+:CD8+T lymphocytes depending on ulcer duration.

Immunofluorescence – Immunofluorescence studies demonstrated deposits of IgG, IgM, IgA, and C3 in along mucosal blood vessels and in the cytoplasm of stratum spinosum cells.^{4,8,11}

TREATMENT

In order to facilitate definition of the best treatment option, the patients can be classified according to their clinical characteristics as follows:

Type A: Characterized by brief episodes of tolerable pain levels only a few times during the year. Identification and control of the predisposing factors are essential. To evaluate the association between the disease outbreaks and certain foods, patient should be questioned about his or her eating habits. Avoidance of hard foods like hard toasted bread, all types of nuts, chocolates, acid beverages or foods, salty foods, very spicy food and alcoholic and carbonated beverage is advisable.

Type B: Monthly episodes of pain lasting for 3-10 days, the patient had to modify the habits of hygiene and diet. Identification of predisposing factor (trauma, stress, diet, hygiene etc.) should be evident and need to be controlled. Questioning about the prodromic manifestations (itching or swelling) is important to provide topical treatment for the same.

Type C : Characterized by painful episodes with chronic aphthae. No response to the topical treatment by the patient as some lesions develops while others heal. Systemic therapy is indicated in such cases.

Topical preparation - Symptomatic treatment with appropriate topical therapy containing 2% viscous lidocaine gel. Other agents include Diclofenac, amlexanox also decrease the healing time topical corticosteroid such as clobetasol proprionate 0.05% in Orabase, halobetasol proprinate 0.05% or fluocinonide 0.05% in Orabase (1:1). Steroids have an anti-inflammatory action and they decrease both the size and healing time of the ulcers. Larger lesions can be treated by placing gauze sponge having topical steroid on ulcer and leaving it in place for 15-30 minutes to allow longer contact of medication.^{8,9}

Topical Hyaluronic Acid - Hyaluronic acid gel 0.2% applied is beneficial. Main function of hyaluronic acid is activation and moderation of angiogenesis, promoting re-epithelization via proliferation of basal keratinocytes and reducing collagen disposition and scarring.¹²

Mouthwashes - Tetracycline mouth rinses decrease both the healing time and pain of lesions. Aqueous preparation of 0.1% to 0.2% triamcinolone, 0.3% hydrocortisone and dexamethasone elixir 0.5 mg/ 5ml can also be used as rinse and spit for 3 to 4 times a day as mouthwashes.

Local Techniques- Triamcinolone tablets can be used as local technique by directly dissolving it over the lesion. Beclomethasone dipropionate aerosol spray can be used in tonsillar pillar areas.⁴

Intralesional Steroids- Lesions may be injected with corticosteroids such as betamethasone, dexamethasone or triamcinolone to enhance or boost the local response.

Systemic Steroid Therapy- Systemic prednisone must be started at dose of 1mg/kg single dose in patient with RAU and should be tapered after 1 to 2 weeks. Long-term prednisone therapy can cause adverse effects. In patients with recalcitrant RAS, a short course of systemic corticosteroid therapy may be required, never exceeding more than 50 mg per day (preferably in the morning) for 5 days.⁹

Levamisole - Have immunostimulatory effects. Levamisole has the ability to normalize the CD4+ cell/ CD8+ cell ratio and improve symptoms in recurrent aphthous ulcers. 150 mg of levamisole is given for 3 consecutive days every fortnightly.¹³

Thalidomide - It is a potent anti-inflammatory and immunomodulatory drug. Thalidomide is effective at dosages of 100 and 300 mg/day but this drug must be used with extreme caution in women during childbearing years as it can cause teratogenesis. Other side effects include peripheral neuropathy, gastrointestinal complaints and drowsiness.⁸

Pentoxifylline - Plays an immunosuppressive action by interfering with neutrophil adherence and inhibition of lymphocyte activation. Pentoxifylline (Trental) 400 mg three times a day for one month is effective in reducing the number of recurrent aphthous stomatitis.

Colchicine - Used for decades to manage gouty arthritis. It is given systemically 0.6 mg three times daily. It causes decrease in the pain and mean ulcer count.¹⁴

Zinc sulphate - Systemic zinc treatment causes an improvement or remission in patients with RAS. It is given systemically, a total of 660 mg of zinc sulphate per day in divided doses.¹⁵

Laser Therapy - Patients who have severe disease or frequent recurrences may benefit from referral to a laser treatment centre or specialist. Laser therapy of most aphthae immediately relieves pain, speeds healing, and reduces recurrences. The mechanism assumes noninvasive way of action without unfavourable thermal side effects. Tissues reaction depends on the amount of energy absorbed. Effective doses of laser light in the treatment of RAS were estimated to be around 2-12 J/cm². Inhibition of the increased blood vessels permeability that prevents as early swelling was observed as well as inhibition of the formation of granulation tissue in area. Laser biostimulation is an effective method of pain relief. A complete healing process was observed after 2-3 sessions of laser biostimulation. Compared to when low laser is used. Laser enhances epithelisation, stimulates angiogenesis and fibrillogenesis, and thus accelerates tissue healing.⁹

Bioadhesive Patches - Bioadhesive hydrogel patches, made of pharmaceutical grade cellulose derivative are also used to control pain and as an aid to healing of recurrent aphthous ulceration. The mechanism of action of the patch is probably by mechanical protection. The dry patch in contact with mucin coated epithelium forms a swolled bioadhesive hydrogel layer that directly adheres to the ulcer site.¹⁶

Moghadamnia AA evaluated the efficacy of licorice bioadhesive hydrogel patches to control the pain and reduce the healing time of recurrent aphthous ulcer on 15 patients and he concluded that, licorice bioadhesive can be effective in the reduction of pain and of the inflammatory halo and necrotic centre of aphthous ulcers.¹⁷⁻²⁰

CONCLUSION

Recurrent aphthous stomatitis is the most common inflammatory ulcerative condition of the

oral mucosa, it occur as painful ulcers and recur from time to time. The etiology of this disease is unclear. The possible predisposing factors, including trauma, emotional stress, hormonal state, family history, food hypersensitivity, viruses, bacteria, and immune dysregulation. The severity of etiological factors to which the patient is exposed would decide the type of ulcer. Proper identification of etiological factor for the triggering of the disease plays an important role in the management of the disease.

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