ETIOLOGY AND PATHOPHYSIOLOGY OF RECURRENT APHTHOUS STOMATITIS: A REVIEW

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ABSTRACT

Recurrent aphthous stomatitis is the most common oral mucosal ulcer disease. It causes severe pain and occurs repeatedly, causing discomfort in daily routine activities. The description of etiology is varied and none of the explanations given so far are satisfactory. Clinically this condition presents itself in three forms: major, minor and herpetiform ulcers. Causes for the ulcers could be related to host and/or environment. Host factors include genetic, nutritional deficiency, immune dysregulation and stress which can again be multifactorial. Environmental factors include trauma (both physical and chemical) and infections. There are several clinical syndromes which are associated with RAS like Behcet’s syndrome. There are several causes acting together in initiating formation of ulcer unlike a single etiological factor as was thought previously. This means combination of host and environmental factors are essential not only for triggering the ulcer but also for an increase in size. The severity of etiological factors to which an individual is exposed would decide the type of ulcer. Identification of the trigger for a particular individual seems to be important in management of the disease. Hence understanding etiopathogenesis for recurrent aphthous stomatitis would be helpful in formulation of individualized treatment modalities. This review is intended to understand the cause and pathogenesis of recurrent aphthous stomatitis.

Keywords: Recurrent Aphthous Stomatitis, Oral Ulcers, RAS syndromes

INTRODUCTION

Recurrent aphthous stomatitis (RAS) is a disease of the oral mucosa which appears typically as ulcers in the mouth and causes severe pain. Repeated occurrence of ulcers is very debilitating. The prevalence, clinical presentation, etiology and pathogenesis of recurrent aphthous stomatitis will be discussed in this review.

Prevalence of RAS (Recurrent aphthous stomatitis)

RAS is a common oral mucosal condition and has been reported as affecting 20% of the general population at any given time. It reaches a peak of 50% in selected populations such as university students. RAS usually appears first during childhood, with a tendency for ulcers to diminish in frequency and severity with age. In about 80 percent of patients with RAS, the condition develops before 30 years of age.

Clinical Presentation

The ulcers are typically seen on the buccal mucosa, the labial mucosa, the floor of the mouth or the tongue. A prodrome of localized burning or pain for 24 to 48 hours usually precedes the ulcers. The lesions are painful, with well defined margins and shallow necrotic center. All ulcers have yellow-grayish membrane at the base and are surrounded by raised margins and erythematous haloes. The pain is severe and gets aggravated on eating, swallowing and speaking. The pain usually persists for three to four days.
Three clinical presentations of RAS are: Minor aphthous stomatitis (Minor or Mikulicz’s aphthae or mild aphthous ulcers), Major aphthous stomatitis (MjRAS or periadenitis mucosanecrotica recurrence or Sutton’s disease) and Herpetiform ulcers.

**Minor RAS:** This is the commonest type of RAS and 75-85% of RAS are of this type. They typically measure 5-10 mm in size, last for 10-14 days and heal without scarring. Following the healing of the ulcers, there is a variable ulcer free interval of about 3–4 weeks.

**Major RAS:** They typically measure more than 10 mm in size, last for more than two weeks to months and generally heal by scarring. 10-15% of RAS are of this type. MjRAS may produce lesions throughout the entire oral cavity, including the soft palate, tonsillar areas, and oropharynx. The longer duration simulates the malignant ulcer.

**Herpetiform ulcer:** They typically occur as crops of multiple ulcers measuring less than 5mm which may coalesce to form larger confluent areas of ulceration, usually with marked erythema. They last for 10-14 days but severity of pain is more than other forms. 5-10% of RAS are of this type. They resemble ulcers of primary Herpes simplex virus (HSV) infection. The recurrence period may be variable.

**Etiology of Recurrent aphthous stomatitis:**

There are many hypotheses that are put forth for the etiology of RAS. There is no conclusive evidence regarding the etiopathogenesis of RAS.

### Host Factors:

- Genetic factors
- Food allergy
- Vitamin deficiency
- Immune dysregulations
- Physical or emotional stress

### Environmental factors:

- Microtrauma
- Local trauma
- Chemical injury or physical trauma
- Infections
- Smoking

1. **Genetic Factors:** Field and Allan in 2003 described that there is a genetic predisposition for RAS and more than 40% of affected individuals have first degree relatives with RAS. Scully et al 2004 found that the likelihood of RAS is 90% when both parents are affected, but only 20% when neither parent has RAS. A family history of recurrent aphthous ulcers is evident in some patients. A familial connection includes a young age of onset and symptoms of increased severity. Recurrent aphthous ulcers are highly correlated in identical twins. HLA subtypes like HLA B-51, HLA-B52, HLA-B44, HLA-DRW10 and DQW1 antigens were found to be closely associated with RAS.

2. **Nutrition:** Foods such as chocolate, coffee, peanuts, cereals, almonds, strawberries, cheese, tomatoes (even the skin of the tomatoes) and wheat flour (containing gluten) may be implicated in some patients. In one study of patients with RAS who previously were diagnosed in patch tests as reactive to agents such as benzoic acid, 50% showed clinical improvement when certain foods were excluded from the diet.

3. **Vitamin Deficiency:** Hematinic (iron, folic acid, vitamins B-6 and B-12) deficiencies were twice as common in patients with RAS. As many as 20% patients with RAS had a hematinic deficiency. Lower dietary intake of folate and vitamin B-12 is more common among persons with aphthous ulcers and treatment with 1000 mcg/d has shown benefit in individuals regardless of serum vitamin B-12 levels. A small group of adolescents were shown to have reduced incidence and pain from RAS when given 2000 mg/d of ascorbic acid.

4. **Immune Dysregulations:** Immune dysregulations may play a significant role but no conclusive evidence has been noted.
Cytotoxic action of lymphocytes and monocytes on the oral epithelium seems to cause the ulceration, but the trigger remains unclear. Upon histologic analysis, RAS consists of mucosal ulcerations with mixed inflammatory cell infiltrates. T-helper cells predominate in the pre-ulcerative and healing phases, whereas T-suppressor cells predominate in the ulcerative phase. There is reduced response of patients' lymphocytes to mitogens. There may be alterations in the activity of natural killer cells in various stages of disease. Increased adherence of neutrophils and reduced quantities and functionality of regulatory T cells in tissue with lesions and release of tumor necrosis factor-alpha (TNF-alpha) is seen. There is significant involvement of mast cells in the pathogenesis of RAS. Reduced cellular expression of heat shock protein 27 and interleukin 10 is seen in aphthous lesions. There is significant involvement of mast cells in the pathogenesis of RAS. Reduced cellular expression of heat shock protein 27 and interleukin 10 is seen in aphthous lesions.

5. **Trauma:** Local trauma may play a role in initiating the mucosal injury which leads to ulcers in patients with RAS. This study was initiated to determine whether standardized mechanical injury would lead to ulcers in patients prone to aphthous stomatitis when compared with normal controls. In this study experimental biopsies failed to disclose any histological differences between mechanically induced and spontaneous ulcers.

6. **Physical or Psychological stress:** Psychological stress may play a role in the manifestation of recurrent aphthous stomatitis as a trigger or a modifying factor. No studies have conclusively proved stress as a causative or precipitating factor for RAS.

7. **Infections:** The possible immunopathological destruction of oral mucosa by viridian streptococci was under consideration until 1986 but was disproved. *Streptococcus sanguis* or its L-form has been implicated, as has autoimmunity to the oral mucosal homogenate. A common or cross-reactive antigen between streptococci and oral epithelium has been suggested and demonstrated between the streptococcal 60–65 kD heat shock protein (HSP) and oral mucosal tissue. Significant increase in serum antibodies to HSP has been detected in patients with RAS. *Helicobacter pylori* has been detected in lesions of oral ulcers, but the frequency of serum immunoglobulin G antibodies to *H pylori* is not increased in recurrent aphthous ulcers, and the organisms have never proven causative.

8. **Tobacco smoking:** Patients suffering from RAS usually are nonsmokers, and there is a lower prevalence and severity of RAS among heavy smokers as opposed to moderate smokers. Some patients report an onset of RAS after smoking cessation, while others report control on re-initiation of smoking. The use of smokeless tobacco is associated with a significantly lower prevalence of RAS. Nicotine-containing tablets also appear to control the frequency of RAS.
Recurrence of aphthous stomatitis Associated Syndromes

i. Behcet’s disease (BD) is a multisystemic, chronic, relapsing vasculitis that affects nearly all organs and systems. It is associated with multiple oral, genital ulcers, arthritis, hematemesis, melena, and epigastric pain as predominant manifestations. Seung-Ho Rhee et al 2005 in their study described that RAS and BD had similar presenting symptoms like oral lesions and abdominal pain. There was no clinical, endoscopic, histopathological or serological difference between patients with intestinal BD, RAS and healthy volunteers in Anti-Neutrophil Cytoplasmic Antibodies (pANCA) 28.

ii. RAS is a part of PFAPA syndrome which includes the Periodic Fever, Aphthous stomatitis, Pharyngitis and cervical Adenitis. PFAPA syndrome is regarded as a non-hereditary disease of unknown etiology although the clinical observation is that, in a small proportion of cases, one of the parents or a more distant relative had similar symptoms in childhood 29.

iii. MAGIC syndrome: Mouth And Genital ulcers with Inflamed Cartilage syndrome (also known as “MAGIC syndrome”) is a cutaneous condition 2.

iv. Imerslund-Grasbeck syndrome (IGS) is characterized by Juvenile megaloblastic anemia due to vitamin B_{12} deficiency and proteinuria. All the three cases of Imerslund-Grasbeck syndrome described in the study ArnonBroides et al 2006 were associated with RAS. Though it was described that defective neutrophil phagocytosis and neutropenia caused by the Vitamin B_{12} deficiency may be the possible mechanism for the causation of stomatitis, none of the patients had neutropenia. The cause of RAS in IGS was inconclusive 30.

v. Sweet’s syndrome, also known as acute febrile neutrophilic dermatosis, is characterized by fever, neutrophil leukocytosis, erythematous skin plaques or nodules and, often, classical RAS. It may occur in conjunction with malignant conditions, such as leukemia 2.

vi. Celiac disease (CD) is caused by gluten sensitivity of the small intestines. According to study by SelimAydemir et al 2004 the CD prevalence (40%) in patients with RAS is higher than in the normal population. It is also described that RAS may be the presenting sign of the disease and may be used as a marker for the CD 31.

vii. Crohn’s disease: The intraoral involvement in Crohn’s disease (CD) is observed in approximately 9% of cases and oral inflammation precedes intestinal symptoms in about 60% of these patients. Hence it is important to consider the differential diagnosis of Crohn’s disease in subjects with intestinal symptoms and RAS 32.

Pathophysiology of Recurrent aphthous stomatitis:
The complex interactions of various etiological factors together can trigger ulcer formation. Etiological factors can be classified into predisposing factors and precipitating / triggering factors. The factors like HLA associations, immune dysregulation, nutritional deficiency, personality type A are the predisposing factors. Microtrauma, infections, stress could be the initiating or triggering factor for ulcer formation.

Those individuals who are susceptible when exposed to the triggering factors for certain duration tend to develop ulcers. Based on the intensity and duration of the triggering factors, ulcer starts growing till the factors are removed. Pain suffered by the patients is directly proportional to the size of the ulcer and severity of the triggering factors. For example the serum cortisol level: which is a biomarker of the stress was increased in the
subjects with RAS and the increase was directly proportional to the ulcer size.  

CONCLUSION

Recurrent aphthous stomatitis or aphthous ulcers are more common in younger adults. There are several causes that have been explained for ulcer formation but no single cause is definitive. The cause is still non-specific. There are multiple factors which may be acting together in a complex manner in initiating the formation of ulcer unlike a single etiological factor as was thought previously. This means a combination of host and environmental factors are essential not only for triggering the ulcer but also for an increase in size. The severity of etiological factors to which an individual is exposed would decide the type of ulcer. Underlying mechanisms relating to pathogenesis need to be explored in order to establish the treatment protocol.

ACKNOWLEDGEMENT

Authors acknowledge the immense help received from the scholars whose articles are cited and included in references of this manuscript. The authors are also grateful to authors / editors / publishers of all those articles, journals and books from where the literature for this article has been reviewed and discussed.

REFERENCES


