Review Article

Recurrent Aphthous Stomatitis

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Abstract

Recurrent aphthous stomatitis (RAS) is commonly known as mouth ulcer. RAS is a very common disease of the mouth. Hence, it is important for dental clinicians to know about the clinical features, causes, diagnostic techniques, and the treatment and management of RAS. Clinically, RAS is seen in three forms minor RAS, major RAS, herpetiform RAS, and in HIV patients, the fourth form is seen. Considerable amount of research has been done to elucidate the causes of RAS; local factors, systemic factors, genetic factors, microbial factors, immunologic factors, etc., but to date, no principal etiology has been discovered. There are three lines of treatment suggested for the treatment of RAS but the treatment generally given is symptomatic. This review gives an up-to-date view of the disease.

Keywords: *Major recurrent aphthous stomatitis, minor recurrent aphthous stomatitis, mouth ulcers, recurrent aphthous stomatitis*

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Introduction

The Greek term "aphthae" was initially used in relation to disorders of the mouth and is credited to Hippocrates (460–370 BC).[1] Today, recurrent aphthous ulceration, or recurrent aphthous stomatitis (RAS), is recognized as the most common oral mucosal disease known to human beings.[2] Epidemiological studies indicate that the prevalence of RAS is between 2% and 50% in the general population; most estimates fall between 5% and 25%[3-6] The peak age of onset for RAS is between 10 and 19 years.[6,7] This may continue throughout their life and this leading to RAS.

Etiologygenetic Basis

Earlier studies by Ship *et al*.[8] found that RAS had a definite tendency to occur along family lines and that the probability of a sibling developing RAS was influenced by the parents' RAS status.[5] A high correlation of RAS has been detected in identical twins but not in nonidentical twins.[9] More recent investigations[10] have detected associations between RAS and specific HLA subtypes, which indicates that RAS in certain persons may have a genetic basis.

Local Factors

The trauma can include anesthetic injection, sharp food causing intraoral trauma, traumatic tooth brushing, and trauma during dental procedure.[2] Many patients with RAS do not develop lesions after trauma though,[11] and edentulous patients are unlikely to have lesions beneath dentures.[12] Polanska *et al*.[13] suggested the role of neutrophil elastase in the process of posttraumatic formation of aphthous ulcer. On the other hand, based on the epidemiological observations, most of the researchers indicate the lower incidence of RAS in smokers in comparison to nonsmoking patients, with a correlation with habit duration and severity;[14,15] that could be explained by a higher level of oral mucosa keratinization in response to smoking, which makes it less prone to injury and irritation.[16,17]

Microbial Factors

It has been suggested that oral streptococci and several viruses may play an etiologic role in RAS, but overall, the results are inconclusive.[10] In general, herpes simplex, varicella zoster, and Epstein–Barr viruses have not been directly isolated from RAS lesions.[18] A recent study[19] demonstrated an association between RAS recurrences and reactivation of varicella zoster virus and cytomegalovirus infection. Pedersen[18] has suggested that the systemic and local cellular immunosuppression associated with RAS is consistent with a viral

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reactivation or is a result of a latent viral infection of oral mucosa. Nevertheless, further research is needed to definitively establish a viral cause.

Systemic Factors

RAS has been observed in several systemic disorders, including Bechet's disease,[20] cyclic neutropenia,[21] mouth and genital ulcers with inflamed cartilage syndrome,[22] nutritional deficiencies with and without underlying gastrointestinal disorders,[23] and immunocompromised conditions including HIV infection.[24] Aphthous-like ulcers have been detected in patients with Crohn's disease and ulcerative colitis and other small bowel changes.[25] The lesions in these patients may occur at any time during the course of the disease, can be present before any intestinal symptoms occur, and may occur more frequently when the intestinal problems become active.[26] These ulcers are histologically similar to the intestinal lesions of the disease. No associations have been established between RAS and the premenstrual period, pregnancy, or menopause. Furthermore, no properly designed study has shown a therapeutic effect of ovarian hormones on RAS, which suggests that the lesions of RAS are not caused by changes in female hormones.[27]

Nutritional Deficiencies

Deficiencies in iron, folic acid, zinc, and vitamins B1, B2, B6, B12[28] have been detected in patients with RAS. Hematological deficiencies in patients with RAS[29] may be related to abnormalities of the small intestine, including celiac disease (gluten-sensitive enteropathy), although these patients may not always have symptoms of bowel disease. Volkovetal *et al*.[30] observed positive effects of the oral vitamin B12 supplementation in RAS patients regardless of the initial serum levels of this microelement.

Food Allergy

Food sensitivities and allergies to other substances can also cause ulcers in hematologically normal patients with recurrent lesions.[31] According to some researchers, also the exposition to some food ingredients, for example, chocolate, gluten, cow milk, preservatives, nuts, and food coloring agents may induce the pro-inflammatory cascade in RAS.[16,32]

Stress

Some studies[3,33] have associated stress with RAS; however, a more recent investigation[34] revealed no association between psychological life stress and recurrences of RAS. Nevertheless, the literature continues to report that stress may play a role in precipitating RAS, and severe emotional or environmental stress should be contemplated in the clinical assessment of RAS. According to some authors, it rather triggers the onset of the episode than influences its duration.[35,36]

Immunopathogenesis

RAS may have primary immunologic abnormalities that result in altered immunoregulatory balances.[37] For example, there are increases in antibody-dependent cell cytotoxicity[38,39] and greater levels of serum immunoglobulins[40] in patients with RAS. Lymphocytes from patients with severe RAS demonstrate increased numbers of T-helper/inducer cells,[37] decreased numbers of T-suppressor/inducer cells,[37] and depressed responses to mitogens.[41] Activated T-lymphocytes aggregate in the periphery of RAS lesions confirming the hypothesis that RAS represents an activated cell-mediated immune response.[42] Immunohistochemical studies of lymphocyte subsets in aphthous ulcers of HIV-seronegative patients[43] and HIV-seropositive patients[44] have yielded similar findings, which strongly indicates that these ulcers represent a cell-mediated immunologic dysfunction in which infiltrating T-lymphocytes play a primary role.

Clinical Manifestation

It is classified into three types based on clinical manifestation – minor RAS, major RAS, and herpetiform RAS.[8,19,45]

Major Recurrent Aphthous Stomatitis

Major RAS is occasionally referred to as Sutton's disease or periadenitis mucosa necrotica recurrens[1] and is less common (approximately 10% to 15% of all RAS) yet more severe than minor RAS.[46] Major RAS lesions are similar in appearance to those of minor RAS; however, they are larger than 10 mm in diameter, are deeper, often scar, and can last for weeks to months.[1] MaRAS usually has its onset after puberty and is chronic, persisting for up to 20 or more years.[47] They occur on movable nonkeratinizing oral surfaces (labial and buccal mucosa and floor of the mouth), but the ulcer borders may extend onto keratinized surfaces.[48]

Minor Recurrent Aphthous Stomatitis

Minor RAS have been reported to cause 70%–87% of all forms of RAS,[49] with more than 17% of the population being reported to have minor RAS.[50] Minor RAS manifests as recurrent, round, clearly defined, small, painful ulcers with shallow necrotic centers, raised margins, and erythematous halos.[1] These lesions are 5–10 mm in diameter and have a gray-white pseudomembrane[1,51] These lesions heal within 10–14 days without scarring.[51] The most common

location is on nonkeratinized oral mucosa (the labial and buccal mucosa and floor of the mouth).[1] Lesions appear as single or multiple ulcers but can be distinguished from other mucocutaneous diseases based on their history, location, healthy appearance of adjacent tissues, and the lack of distinguishing systemic features.[5]

Herpetiform Recurrent Aphthous Stomatitis

The least common form of RAS is herpetiform aphthous ulcers, which afflict 5% to 10% of patients with RAS.[46] It occurs more frequently in females, and onset is often in adulthood.[48] Multiple small clusters of pinpoint ulcers characterize this rare form of RAS, and they occur throughout the oral cavity.[1] They tend to be small (2–3 mm) and numerous (ranging from 10 to 100 ulcers) but can become confluent to produce larger, plaque-form, irregular lesions.[48] Lesions last 7–30 days and have the potential to scar. Although these lesions are herpes like or herpetic form in nature, herpes simplex virus (HSV) cannot be cultured from these lesion.[52]

HIV-associated Recurrent Aphthous Stomatitis

Large aphthous-like ulceration are seen associated with HIV-positive patients with the prevalence of approximately 2%–3%.[53] Frequently major RAS is found in patients infected with human immunodeficiency virus (HIV)[26,54-56] perhaps because of the amplification of local immune imbalance secondary to HIV disease.[57]

Diagnosis Serologic, Chemical, Hematologic Finding

Full hematologic screening of patients with RAS has been proposed to reveal deficiency states of serum ferritin, iron, folate, and Vitamin B.[29,58] Deficient levels of serum ferritin or iron are the most common findings occurring in 11% to 36% of patients with RAS.[31,58-60] Hematologic screening of children with RAS is also recommended because it has been reported that 21% of patients have some type of hematologic abnormality, most notably latent iron deficiency without anemia.[61]

Histopathologic Finding

A histopathologic specimen is rarely required for the diagnosis of RAS because of the nonspecific nature of the ulcer. However, if another oral mucocutaneous condition is suspected, then a biopsy may be necessary. In the preulcerative phase, there is a mild infiltrate of T4 helper-inducer lymphocytes, which becomes an infiltrate of T8 cytotoxic-suppressor cells in the ulcerative phase.[62]

Immunoflourescence Finding

Direct and indirect immunofluorescence studies are not sensitive or specific diagnostic tests for RAS, and therefore should not be utilized except to rule out other oral mucosal diseases (e.g., pemphigus and pemphigoid).[1]

Differential Diagnosis

The diagnosis of RAS is typically established from the history and clinical presentation.[1] Usually, these conditions can be differentiated from RAS by the location of the lesion and/or the presence of an additional symptom. HSV infections may have similar-appearing lesions; however, primary HSV infections present with a diffuse gingival erythema and fever preceding oral mucosal vesicles and ulcers.[63] Furthermore, recurrent HSV lesions are found primarily on attached keratinized mucosa, such as the hard palate or gingiva,[64] Recurrent aphthous lesions can be differentiated from varicella-zoster virus infections (shingles) based on the clinical presentation (extraoral and intraoral distribution pattern) and other burning symptoms. Less common oral viral infections, such as herpangina and hand-foot-and-mouth disease, should also be included in the differential diagnosis of RAS when initial symptoms occur.[64] Erythema multiforme presents with painful oral ulcers, but unlike RAS, erythema multiforme lesions occur on both attached and movable mucosa and usually involve crusting of the lips with skin macules and papules.[65]

Treatment

Goals of treatment Treatment of RAS has 4 major goals; (1) ulcer management (to promote healing and reduce duration), (2) pain management (to reduce morbidity and enhance function), (3) nutritional management (to ensure adequate food and fluid intake), and (4) disease control (to prevent recurrence or reduce frequency). The relative importance and priority of each goal depends on the severity of the condition.[46]

Primary line of treatment

Topical gels, creams, and ointments. The primary treatment of RAS lesions utilizes topical anti-inflammatory agents. Strong topical corticosteroids when compounded with mucosal adherents (e.g., Orábase, Bristol-Myers Squibb; isobutyl cyanoacrylate or Iso-Dent, Ellman International) are effective despite limited contact time.[26,66]

Secondary line of treatment

For the patient whose symptoms are not relieved by the primary line of treatment or whose signs and symptoms

warrant a more aggressive treatment modality, prednisone should be considered for both HIV-negative[67-69] and HIV-positive patients,[26,70,71] Prednisone, an anti-inflammatory and an immunosuppressive agent, can be used in combination with topical gels and rinses.

Tertiary line of treatment

Thalidomide, an inhibitor of tumor necrosis, can be used. Factor-K, has been shown to be an effective treatment for severe RAS, despite the potential for significant side effects.[72,73] Use of thalidomide in children has been documented with some success, but long-term effects have not been established.[74]

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Conflicts of interest

There are no conflicts of interest.

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