

Recurrent Aphthous Stomatitis: An Overview

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Abstract

Recurring oral ulcers are among the most common problems seen by clinicians who manage diseases of the oral mucosa. Recurrent aphthous stomatitis is one of the most common oral mucosal pathosis. The cause appears to be 'different things in different people'. This article provides an overview of recurrent aphthous stomatitis including its causes, assessment and treatment.

INTRODUCTION

Recurrent aphthous stomatitis (RAS) is the most common disease affecting the oral mucous membrane. The classic presentation of RAS is recurrent, self-limiting ulcers that mainly affect non-keratinized oral mucosa.[1] It is one of the most painful oral mucosal inflammatory ulcerative conditions and can cause pain on eating, swallowing and speaking[2] in 5% to 50% depending upon the socioeconomic groups.[3] RAS frequently affects patient quality of life as a result of long lasting and recurrent episodes of burning pain.[4] Treatment and management strategies are based on an underlying cause. This article reviews the literature on causes, assessment and treatment of the clinical entity.

ETIOLOGY

Several etiological factors have been implicated in the pathogenesis of RAS. These factors may be conveniently divided into host factors: genetics, nutrition, gastrointestinal diseases, hormones, immunologic and psychological and environmental factors: microbial, trauma, allergy and smoking.

The role of genetic factors is important in the etiology of RAS. Susceptibility to RAS is significantly increased by its presence in one or both parents. Studies of identical twins have also demonstrated the hereditary nature of this disorder. Children with RAS positive parents have a 90% chance of developing RAS at an early age.[5-8]

Nutritional deficiency contributes to RAS. Patients with low

serum levels of iron, folate, zinc, or vitamins B1, B2, B6 and B12, which may be deficient independently or may be secondary to other diseases such as malabsorption syndrome or gluten sensitivity associated with or without enteropathy are more susceptible.[9]

A deficiency of calcium and vitamin C has also been proposed in association with vitamin B1 as a combined nutritional deficiency in RAS patients.[10] Replacement therapy of the deficient nutrient resulted in a remission or improvement of the disease which supports the causative role of nutritional deficiency in a subset of RAS patients.[11] Rowe and Rowe stated that food allergy is a common cause of RAS. Certain food stuffs such as coffee chocolate, potato, nuts, citrus fruits and gluten may act as precipitating factors for food allergy. Foods which can induce histamine release from peripheral blood basophils from patients with aphthae can also induce ulceration.[12]

Inflammatory bowel diseases such as crohn's disease and ulcerative colitis have been associated with oral ulcers. Approximately 10% of patients with crohn's disease have mucosal ulcers which precedes the intestinal symptoms.[13-15]

Female sex hormones are also of etiologic importance. Relationship exists between the occurrence of aphthous ulcer and the menstrual period. Dolby stated that ulceration is maximum in post-ovulation period which is related to the blood level of progesterone. Ferguson et al have shown the efficacy of depoprogesterones in controlling such ulceration.[16-17]

Lehner has proposed that the recurrent aphthous ulcer is the result of an autoimmune response of the oral epithelium. Cohen suggested that RAS is not an autoimmune disease arising from a central immunologic fault but rather represents a local immune response against an antigenically altered mucosa. Studies have shown an association between RAS severity and abnormal proportions of CD4⁺ cells, alteration of CD4⁺:CD8⁺ ratio and elevated levels of interleukin 2, interferon gamma and tumor necrosis factor- α (TNF- α) mRNA in RAS lesions.[18-22]

Stress and psychological factors precipitate the attack of RAS. There is good evidence that stress and anxiety leads to increase in resting levels of cortisol. An increase in biochemical reaction resultant of stress leads to atypical habits that injure the oral mucosa such as bites in cheek and lips, leads to oral ulcer manifestation.[23]

Imbalance between free radicals and antioxidants causes many inflammatory oral soft tissue diseases varying from infections and immunologic diseases to lethal cancers.[24-26] A variety of underlying systemic diseases have been associated with recurrent and multiple ulcerations, some of which may clinically mimic RAS, these include agranulocytosis, cyclic neutropenia, chronic inflammatory and ulcerative bowel diseases, gluten enteropathy, vitamin B-complex deficiency and end stage renal disease.[27] RAS is usually a late finding in AIDS patients with CD4⁺ lymphocyte counts below 100 cells/mm³, but it may occasionally be a presenting sign of HIV infection.

Local traumatic factors which includes oral surgical procedures, tooth brushing, dental procedures, needle injuries and self inflicted bites and dental trauma were the precipitating factors in nearly 75% of cases according to a study by Greycovaski and his coworkers.[28] Microbiological agents such as the L form of streptococci, herpes simplex virus, varicella zoster virus, adenovirus and cytomegalovirus have been associated with RAS.

CLINICAL PICTURE

The onset of RAS is usually during childhood with the tendency of ulcer to diminish in intensity and frequency with age. Female predominance is seen, white people are more affected than black, and children of higher socioeconomic status are more commonly affected than those of lower socioeconomic group.[29, 30]

The clinical picture of RAS is defined by small, shallow,

round or ovoid ulceration with well defined, circumscribed margin with an erythematous halo around it. Three distinct forms of RAS can be distinguished clinically categorized by size, location and sequelae as minor, major and herpetiform.[31]

Minor aphthae are the most common affecting 80% of the patient population. Recurrent aphthous minor occurs more frequently in women than in men and majority of the patients report the onset of disease between the age of 10 and 30 years. Patients with minor aphthous ulceration experience the fewest recurrences and the individual lesions exhibit the shortest duration of the three variants. The ulcers arise almost exclusively on the non-keratinized mucosa. The buccal and labial mucosa are the most commonly involved sites followed by the ventral surface of tongue, mucobuccal fold, floor of mouth and soft palate. Involvement of keratinized mucosa is rare and usually represents the extension from the non-keratinized mucosa. The lesion may be preceded by prodromal symptoms of burning, itching with the development of erythematous macule. The macule develops an ulceration which is covered by yellowish-white removable fibrinopurulent membrane and is encircled by an erythematous halo. The ulceration is shallow, painful, well circumscribed and measure between 3mm and 10mm and heal without scarring in 7 to 14 days. [32]

Major aphthae are a severe variant characterized by chronicity and scarring. The onset of major aphthae is after puberty and recurrent episodes may continue to develop for around 20 years or more. Labial mucosa, soft palate and tonsillar fauces are the most commonly affected sites but any oral surface area may be involved. Approximately 10% to 15% cases of RAS are major aphthae.[33] The prodromal symptoms are more intense than those of minor aphthae, the ulceration are deeper and larger with raised irregular borders and frequently measure from 1 to 3 cm in diameter. The number of lesions varies from 1 to 10 and last for weeks or months and often leave a scar after healing. The onset of disease may occur with manifestation such as fever, dysphagia and malaise.[33] Patients with severe major aphthae also occasionally show similar lesion of vagina and penis, rectum and larynx with associated rheumatoid arthritis or conjunctivitis.

Herpetiform ulcers are rare constituting only 5-10% of RAS.[33] Ulcers tend to appear in women and generally have a later age onset. The ulcers are characterized by crops of multiple, small, rounded, shallow, painful ulcers with 1-3 mm in diameter and often up to 100 in number. Lesions

begin as small, pinhead sized erosion that gradually enlarge and coalesce clinically similar to the primary herpiform gingivostomatitis. Lesions are present almost continuously for one to three years with relatively short remissions. Ulcerations heal within seven to ten days but the recurrences tend to be frequent.[34,35]

INVESTIGATIONS AND HISTOPATHOLOGIC APPEARANCE

A detailed history taking and examination are characteristic of RAS. Complete blood count, measurement of the levels of red cell folate, serum vitamin B12 and serum ferritin is useful if finding suggest a nutritional deficiency or a hematologic disorder. Serologic test for rheumatologic diseases, cultures and other specific tests for infectious disease such as herpes simplex virus, cytomegalovirus or HIV and evaluation for gastrointestinal diseases are advised if the features are suggestive of these disorders. A biopsy should be considered for solitary or multiple ulcers lasting for more than three weeks. The microscopic picture of aphthous stomatitis is characteristic but not pathognomic. The pre-ulcerative lesions demonstrate subepithelial inflammatory mono nuclear cells with abundant mast cells.[36] The early ulcerative lesions demonstrate a central zone of ulceration covered by a fibrinopurulent membrane. Deep to the area of ulceration, the connective tissue exhibit an increased vascularity and a mixed inflammatory cellular infiltrate that consist of lymphocyte histiocytes and polymorphonuclear leukocytes. The epithelium at the margin of lesion demonstrates extravasated erythrocytes, subepithelial neutrophils, numerous macrophages loaded with phagolysosomes and the non-specific binding of stratum spinosum cells to immunoglobulins may be a result of vascular leakage and passive diffusion of serum proteins.[37,38]

DIFFERENTIAL DIAGNOSIS

RAS is the most common cause of recurring oral ulcers and is essentially diagnosed by exclusion of other diseases. A detailed history and clinical examination distinguish RAS from primary or secondary viral infections, bacterial infections, dermatologic conditions, traumatic episodes, various syndromes, immunologic disorders and other systemic diseases.

Multinucleated epithelial giant cells in cytologic smears and presence of herpes simplex virus seen on culture and electron microscopic examination are the differentiating factors of herpes simplex infection. Like viral ulcers, RAS

ulcers are symmetric but do not have tissue tags as seen in irregular ulcers such as erythema multiforme, pemphigus and pemphigoid. [35]

Oral ulcers in RAS and Bachel's syndrome appear clinically indistinguishable, but the presence of at least two of the classic triad of the disease: recurrent oral ulcers, recurrent genital ulcers and ocular inflammation is diagnostic of Bachel's disease.

Large aphthous like ulcers may be seen in HIV-positive patient and in non-HIV-infected patients with other immunodeficiency, myelodysplastic syndrome, benign neutropenia and other forms of neutropenia such as cyclical neutropenia. Hematological screening and subsequent systemic investigation help in differential diagnosis.[39-41]

Features such as persistent diarrhea that are suggestive of systemic disease should raise the possibility of Crohn's disease or ulcerative colitis. Weight loss or other signs of malabsorption may suggest gluten-sensitive enteropathy, although this disease is present in less than 5% of patients with RAS attending the clinic.[9]

TREATMENT

The choice of treatment for RAS depends on the severity of the disease, the frequency, size, and the number of ulcerations. In the absence of a clearly defined cause the treatment is aimed primarily at pain relief and the reduction of inflammation. Effective treatment of the underlying disorder or condition results in the remission of the ulcers. Oral trauma caused by hard tooth brushes or foods such as toast, acidic foods or drinks that may exacerbate pain or precipitate ulcers should be avoided.[24]

Topical antibiotics have been advocated as a therapy for RAS for a long time.[42-44] Clinical studies suggest that topical analgesics such as benzidamine or 1% lidocaine [45] and protective bioadhesive such as carmellose or cyanoacrylate can help relieve the pain. Other topical agents that can minimize patient discomfort and painful symptoms include 5% amlexanox, dexamucobase, diclofenac, Hyben X, and M Lexanox paste which has been also shown to decrease the healing time of minor aphthae.[46-48]

In patients with mild disease the mainstay of therapy is topical corticosteroids. Although topical therapy is sufficient treatment for most of the patients of RAS but it does not decrease the formation of new lesions and may not be sufficient treatment for patients with major RAS or patients

who have frequent episodes of multiple minor RAS. These patients are best treated with potent topical corticosteroids (such as betamethasone, beclomethasone, clobetasol, fluticasone or fluocinonide), systemic corticosteroids, azathioprine or other immunosuppressant such as depstone, pentoxifylline and sometimes thalidomide.[49, 50]

In recent years, natural anti-oxidant products have been used for management of RAS. These preparations include extracts and/or oils of medicinal plants which have effects on reducing the severity of pain and shortening the healing time.[51,52] Laser ablation is of limited practical benefits, though it shortens the duration and decreases associated symptoms.[53]

CONCLUSION

Treatment plans should be tailored in each patient individually depending upon the severity and frequency of outbreaks of the disease. In all patients with RAS it is important to rule out the predisposing factors and treat the etiological factors before introducing more specific therapy.

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