REVIEW ARTICLE

Recurrent aphthous stomatitis: Mystery unravelled

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ABSTRACT

Recurrent aphthous stomatitis has been posing a challenge to the field of oral medicine and radiology for the past few decades. This review article throws light and derives clarity in the etiology, clinical features, immunopathology and the management of this entity. Different possibilities in the onset, clinical features are described in detail. Management criteria of this entity has also been described in detail. Henceforth a clarity in this entity in oral medicine and radiology is attained. This article details out the exact the literature available till date about etiology and clinical features of recurrent aphthous stomatitis. It also details the immunopathogenesis in the onset of an ulcer along with the management options needed in the successful treatment protocol for recurrent aphthous stomatitis.

Key words: Recurrent aphthous stomatitis, tumor necrosing factor

INTRODUCTION

Recurrent aphthous ulceration or recurrent aphthous stomatitis (RAS) is the most common oral mucosal disease known to human beings. Despite much clinical and research attention, the causes remain poorly understood, the ulcers are not preventable, and the treatment is symptomatic. The most common presentation is minor recurrent aphthous stomatitis: recurrent, round, clearly defined, small, painful ulcers that heal in 10 to 14 days without scarring. Major recurrent aphthous stomatitis lesions are large (greater than 5 mm), can last for 6 weeks or longer, and frequently scar. The third variety of recurrent aphthous stomatitis is herpetiform ulcers, which present as multiple small clusters of pin point lesions that can coalesce to form large irregular ulcers and last 7 to 10 days. Diagnosis of all varieties are usually made after clinical examination.

The first use of the term aphthai in relation to disorders of mouth is credited to Hippocrates (460–370 BC). To date, the causes remain poorly understood; RAS is not preventable and treatment is symptomatic. The most common presentation is recurrent, round, clearly defined, small painful ulcers with shallow necrotic centres, raised margins and erythematous halos. Diagnosis is usually made on the basis of patient’s health history and clinical examination. Many local and systemic factors have been associated with these conditions, and there is evidence that there may be a genetic and immuno-pathogenic basis for RAS.

Dramatic worldwide increase in patients with immuno-suppression caused by medical treatments, systemic diseases or both, the prevalence of these conditions may be increasing. There is no specific management for RAS, and therefore analgesic, antimicrobial and immune modulatory drugs have been used individually and collectively for symptomatic conditions. As dental clinicians and researchers become better trained in oral medicine and stomatology, it is anticipated that the pathophysiology, prevention and treatment of RAS will improve in the near future.
EPIDEMIOLOGICAL FACTORS

Although Hippocrates is credited with the first use of the term aphthai in relation to disorders of the mouth, the first valid clinical description of RAS appeared in 1888 by von Mikulicz and Kummel.[1]

RAS is most common oral mucosal disease observed in human beings but its prevalence varies widely. In children, RAS is the most common form of oral ulceration seen,[2] and peak age of onset is between 10 and 19 years. After childhood and adolescence, it may continue throughout the entire human life span.

Epidemiological study indicate that prevalence is between 5% and 25% in general population and as high as 50% to 60% in selected groups (e.g., medical or dental students). Ship has also suggested that a greater prevalence of RAS is associated with increasing social class. It is possible that actual prevalence of RAS is greater than reported rates because of the recurrent nature of the condition. Cross sectional clinical surveys probably underestimate the true prevalence because active lesions may not be present at the time of examination.

ETIOLOGY

As the exact etiology of RAS lacks clarity, most patients with RAS are usually given some medications to relieve their pain only, instead of an etiologic screening and curative treatment.

Heredity, hematinc deficiencies, immune dysregulation, some foods, drugs, stress, local trauma, hormonal disturbances, infections, smoking habits, and poor oral hygiene are proposed factors. RAS may be associated with several diseases such as Behcet’s disease, gluten-sensitive enteropathy, pernicious anemia, cyclic neutropenia, inflammatory bowel disease, and FAPA (periodic fever, aphthous stomatitis, pharyngitis and lymphadenitis).[3]

A high incidence of aphthous stomatitis was reported in identical twins compared with nonidentical twins (90% vs 60%). It was indicated about an increased susceptibility to RAS among children of RAS-positive parents. It was also reported that more than 42% of RAS patients had first-degree relatives with RAS.

Serum vitamin status is another proposed predisposing factor for RAS, and it has been shown that up to 20% of RAS patients may have at least one hematinc deficiency. Vitamin B12 replacement therapy shows promising results in the management of RAS.[4]

Cigarette smoking is known to have a protective effect on RAS. This protective effect of smoking may be related to the increased keratinization of the oral mucosa in smokers. Keratin layer may possibly act as a mechanical and chemical barrier of the oral mucosa against minor traumas or microbial agents. Recurrent ulcerations were prevented with the use of 8-mg 7-day Nicorette tablets.[5]

Iron deficiency is another proposed predisposing factor for RAS. It was shown that a significantly low serum ferritin level (11.6%) was found in RAS patients compared with control group (4.9%).

CLINICAL FEATURES

Recurrent aphthous ulceration (RAU) has three different variants—minor aphthous ulcers, major aphthous ulcers and herpetiform ulcers, according to the classification described by Stanley (1972).[6]

Minor RAU (MiRAU) is the common variety, affecting about 80% of RAU patients.[7] It is characterized by painful round or oval shallow ulcers, regular in outline, less than 10 mm in diameter, with a grey–white pseudomembrane surrounded by a thin erythematous halo. Minor RAU usually occurs on non-keratinized mucosa such as labial mucosa, buccal mucosa and the floor of the mouth, and it is uncommon on the keratinized gingiva, palate, or dorsum of the tongue. MiRAU is the most common form of childhood RAU53. The lesions recur at varying frequencies (from every few years to almost constantly) and heal within 10–14 days without scarring.[7]

Major RAU (MaRAU), also known as periadenitis mucosa necrotica recurrens, occurs in approximately 10% of RAU patients. The lesions are similar in appearance to those of minor RAU, but they are larger than 10 mm in diameter, single or multiple and very painful. Major RAU has a predilection for the lips, soft palate, and fauces, but can affect any site. The ulcers of MaRAU persist for up to 6 weeks or longer and often heal with scarring. MaRAU usually has its onset after puberty.
The third and least common variety of RAU is herpetiform (HuRAU). The name is derived from the supposed resemblance to the intraoral lesions of primary herpes simplex (HSV) infection, but HSV cannot be isolated from HuRAU lesions or from any other forms of RAU. Furthermore, HuRAU lesions are not preceded by vesicular lesions, but develop—like all RAU lesions—directly as ulcers. This form is characterized by multiple recurrent crops of small, painful ulcers that are widely distributed throughout the oral cavity. As many as 100 ulcers may be present at a given time, each measuring 2–3 mm in diameter, although they tend to fuse, producing large irregular ulcers.

They usually heal without scar formation, the healing time of an individual lesion being 7 to 10 days. The condition occurs more often in women and is associated with a later age of onset than other types of RAU.

Recurrence is the hallmark of RAU, and patients generally present with only one variant of the disease, but two forms may coexist, or a change in clinical expression may be seen with time.

**IMMUNOPATHOGENESIS**

Immunological aberrations involving both cell-mediated and humoral immunity have been reported in previous studies of RAU. Both class I and II MHC antigens have been found to be expressed on the epithelial basal cells in preulcerative RAU lesions and more diffusely within the epithelium at the ulcer stage, consistent with active cell mediated inflammation. Studies carried out *in vitro* have shown that peripheral blood lymphocytes from patients suffering from RAU are cytotoxic against oral epithelial cells which, however has not been confirmed by others. Patients with RAU have significantly increased antibody dependent cellular cytotoxic (ADCC) activity in the early stage of the disease. However, ADCC values such as those assessing effector function of polymorphonuclear neutrophils have been found to be higher during acute RAU when compared with those of controls.

Immunofluorescence studies have demonstrated deposits of IgG, IgM, IgA and C3 in and along mucosal blood vessels and in the cytoplasm of stratum spinosum cells in aphthous ulcer lesions in patients with RAU and Behcet’s disease. Some researchers have reported a decrease in the number of circulating CD4+ cells, but normal or reduced numbers of CD8+ cells and a normal or slightly reduced CD4/CD8 ratio in RAU patients. Comparison of major and minor types of RAU suggests that CD8+ cells are more common in the major type than in the minor type. The CD4+/CD8+ ratio in the major type was lower than in the minor type. In oral mucosa, the percentage of CD4+ lymphocytes has been shown to be increased in ulcerative lesions and the proportion of CD8+ cells has also been shown to be significantly increased in the lesion sites. Previous studies on peripheral NK-cells in patients with RAU have been contradictory, as their percentages have been reported to be either increased or similar to that of controls. Furthermore, it was found that depletion of CD-16+ positive NK-cells produced no change in cytotoxicity towards the oral epithelial target cells. Another report demonstrated that among patients with major RAU, NK-cell activity is increased when active oral lesions are seen, depressed during periods of resolution and becomes normal in patients in remission. In contrast, a significant depression in NK-cell activity has been observed in patients with acute RAU as well as in the remission period, when compared with controls.

Formation of perivascular lymphocyte infiltrates is probably in part mediated by endothelial intercellular adhesion molecule-1 (ICAM-1) and lymphocyte function-antigen-3 (LFA-3) binding to their counterpart ligands lymphocyte function-antigen-1 (LFA-1) and CD-2 on lymphocytes, respectively. ICAM-1 is expressed on the epithelium and submucosal capillaries and venules, suggesting that it may support T-cell adhesion and control the trafficking of leucocytes into the submucosa and epithelium. LFA-3 and its counterpart ligand CD-2 are likely to be involved in T-cell activation in RAU. Increased numbers of CD1+ Langerhans cells have been found in the epithelium and lamina propria in BD and RAU. Moreover, factor XIIIa+ dendrocytes, dendritic cells which seem to be involved in regulatory functions and/or antigen handling in the subepithelial connective tissue have been found to be enlarged and increased in numbers in the subepithelial compartment of RAU lesions. It is thus evident that there is no unifying theory of the immunopathogenesis of RAU.

The complex role of vitamin D in the regulation of immune system function, deficiency of vitamin D in autoimmune disorders, and epidemiological studies suggest that the deficiency of vitamin D is an important environmental factor in the pathogenesis of immune mediated disorders.
The relationship between the immune system dysregulation and the pathogenesis of RAS, and the results of our study may also prove the role of vitamin D deficiency in the pathogenesis of RAS.[17]

MANAGEMENT

There is a multitude of therapies for recurrent aphthous ulcers. The goals of therapy are 3-fold: (1) control the pain of the ulcer, (2) promote ulcer healing, and (3) prevent recurrence. Because there is no consensus regarding the cause of RAU, it is difficult to have completely effective treatment or prevention.

For the short-term goal of decreasing the pain of these ulcers, viscous lidocaine or dyclonine hydrochloride may be used. Although this has no effect on the natural course of the disease, this treatment is important because the extremely painful nature of these ulcers can prevent a patient from eating. In the case of major aphthous ulcers, which take 4 to 6 weeks to heal, weight loss can be substantial. Zilactin (Zila Inc, Phoenix, AZ) is a non-prescription topical medication that has mucosal adherence properties (hydroxypropyl cellulose) and provides an impermeable barrier to protect ulcerations from further trauma or irritation.

This coating can provide hours of relief. Users should be warned that its application causes a severe burning sensation for several seconds.

Following the theory of an infectious cause of RAU, chlorhexidine and tetracycline have been used.[18] In 1968, it was showed that tetracycline (5 mL tetracycline suspension [250 mg]) reduced the severity of ulcerations but had no effect on recurrence. Matthews et al In 1987, it was found that chlorhexidine (0.1% to 0.2% with mouthwash) decreased ulcer days, reduced secondary infections, and increased the interval between ulcer recurrences. It did not, however, stop recurrences.

Topical corticosteroids are considered the mainstay of therapy.[18] Triamcinolone (0.1% mixed with Orabase (Bristol-Myers Squibb Company, Stamford, CT) and fluocinonide gel in Orabase have been used to decrease the duration of ulcers and increase the time between episodes. No adrenal suppression has been noted.[19] Systemic steroids will heal most ulcers within a week and will control severe outbreaks, but not recurrences. The use of systemic steroids should be avoided because of its systemic side effects. In general, it is indicated only for persistent major ulcers.

Other agents shown to be effective in smaller studies are thalidomide, 5-aminosalicylic acid, sulfasalazine, colchicine, and cromolyn. In 1990, it was found that thalidomide (100 mg QD for 2 months) induced remission within 7 days. It was very effective for severe RAU, but lesions recurred after stopping the drug. Thalidomide is believed to decrease TNF levels, thereby decreasing the immune system’s attack on normal mucosa.[21] This is supported by evidence that thalidomide reduces RAU in HIV patients, who frequently have increased TNF levels.[22] Aside from the well-known teratogenic effects, side effects such as drowsiness, headache, constipation, and xerostomia can be significant.

Topical 5-aminosalicylic acid (5% cream 3 times daily for 2 weeks) was shown by Collier et al[22] to cause significant reduction in the number and duration of ulcers. The mechanism of action is largely unknown but is thought to be reduction of prostacyclin synthesis, inhibition of oxygen metabolite production by polymorphonuclear cells, or inhibition of the release of leukotrienes from mucosa. The mechanism is similar to that proposed for its action in ulcerative colitis.

Cromolyn[23] has been used with modest results in managing RAU. It is used as drops or lozenges (20 mg 4 times daily) to decrease ulcer days and increase time between recurrences. Cromolyn is a mast cell stabilizer and inhibits the release of histamine and leukotrienes from mast cells. Its exact mechanism of action in RAU is unknown. Colchicine (0.5 mg 3 times daily for 2 months) has been shown to decrease the subjective pain score reported by patients. The mechanism is prevention of polymorphonuclear leukocyte recruitment. This drug is relatively safe for control of major RAU. Side effects include myopathy and neuropathy.

Several other agents have been used in small studies. These include levamisole, azothiaprim, dapsone, and pentoxifylline.[24] These and several of the previously mentioned agents will require larger clinical studies in order to establish their efficacy.

CONCLUSION

RAS is a very common oral disease that can be extremely painful and debilitating for patients. It must be differentiated from other causes of oral
ulcers by a careful history and physical examination. The etiology of RAS is established by now. There are several therapies that reduce the pain associated with RAS and modestly reduce duration and recurrence. Larger clinical studies are necessary to show the efficacy of the many therapies that have been proposed. Topical corticosteroids remain the mainstay of therapy for severe attacks.

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