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Review Article

RECURRENT APHTHOUS STOMATITIS – A REVIEW

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ABSTRACT

Aphthous stomatitis is a most common condition which affects the oral cavity and it is painful. Aphthous ulcer is characterized by the repeated occurrence of benign and non-contagious mouth ulcers. It can be caused due to triggering of T-cell-mediated immune response, by various factors. This condition is very common, affecting about 15–20% of the population. The lesions generally occur on the cheeks, lips, gums, floor, and roof of the mouth. There are three different types of aphthous stomatitis they are aphthous ulcer major, aphthous ulcer minor, and herpetiform ulcers. It can be also termed as recurrent aphthous ulcer, recurring oral aphthae, and recurrent aphthous ulceration. Informal term is canker sores.

Keywords: Aphthous ulcer, Benign, Non-contagious, Canker sores.

INTRODUCTION

Recurrent aphthous stomatitis (RAS) is spontaneously occurring self-limiting ulceration in the oral cavity. It can be single or multiple lesions present in the non-keratinized parts of the oral mucosa [1]. It is characterized by painful necrotizing ulcers whose etiology is not clearly understood [2]. The lesions are shallow and covered by grayish-white pseudomembrane with an erythematous margin [3]. It is often associated with redness, swelling, and occasional bleeding from the affected areas [4]. These lesions differ from the ulceration produced by the herpes simplex virus [5]. The RAS often causes pain during eating, sleeping, and speaking [6]. In HIV patients, these ulcers are more frequently progressive, destructive, and debilitating [7].

INCIDENCE

Recurrent aphthous ulcer occurs in children as well as in adults. It is common and affects almost 20% of the population [8,9], mostly people belonging to higher socioeconomic status [10,11]. It occurs in adolescence and frequency of the disease decreases with age. Females are more prone to RAS than males and children [12-15]. If the ulcers occur before 5 years of age or after 30 years, then it should be considered as more complex disorder [16-19].

TYPES

Aphthous ulcer minor (MiAU)

This is the most common form, accounting for 80% of all cases. Oral mucosal ulcers which are discrete and <1 cm in diameter characterize this form of aphthous ulcer. MiAU infrequently presents as a small single ulcer. Lesions heal without scarring within 7–10 days. The periodicity varies between individuals, with some having longer ulcer-free episodes and some never being free from ulcers [1]. MiAU; Mikulicz ulcer occur mainly in the 10–40-year-old age group, often cause minimal symptoms. The ulcer floor is initially yellowish in color but assumes a grayish hue as healing and epithelialization proceeds. They are surrounded by an erythematous halo and some edema and are found mainly on the non-keratinized mobile mucosa of the lips, cheeks, floor of the mouth, and sulci or ventrum of the tongue. They are only uncommonly seen on the keratinized.

Mucosa of the palate or dorsum of the tongue and occur in groups of only a few ulcers (1–6) at a time [21].

Aphthous ulcer major (MaAU)

This is formerly known as periadenitis mucosa necrotica recurrens (PMNR). This form is less common than the others and is characterized by oval ulcers >1 cm in diameter. Occasionally, MaAU is a relatively severe form; many major aphthae may be present simultaneously. Ulcers are large and deep, may have irregular borders, and may coalesce. On healing, which may take as long as 6 weeks, ulcers can leave scarring and severe distortion of oral and pharyngeal mucosa may occur [1]. MjAU; Sutton's ulcers; PMNR are larger, of longer duration, of more frequent recurrence, and often more painful than minor ulcers. MjAUs are round or ovoid-like minor ulcers, but they are larger and associated with surrounding edema and can reach a large size, usually about 1 cm in diameter or even larger. They are found on any area of the oral mucosa, including the keratinized dorsum of the tongue or palate, occur in groups of only a few ulcers (1–6) at one time and heal slowly over 10–40 days. They recur extremely frequently may heal with scarring and are occasionally found with a raised erythrocyte sedimentation rate or plasma viscosity [21].

Herpetiform recurrent aphthous ulcer

This least common form (5–10% of cases) has the smallest of the aphthous ulcers, commonly <1 mm in diameter in size. The ulcers tend to occur in clusters that may consist of tens or hundreds of minute ulcers. Clusters may be small and localized, or they may be distributed throughout the soft mucosa of the oral cavity [24]. Herpetiform ulceration is found in a slightly older age group than the other forms of RAS and is found mainly in females. They begin with vesiculation which passes rapidly into multiple minute pinhead-sized discrete ulcers, which involve any oral site including the keratinized mucosa. They usually increase in size and coalesce to leave large round ragged ulcers, which heal in 10 days or longer, are often extremely painful and recur so frequently that ulceration may be virtually continuous [21].

ETIOLOGY

The etiology of RAS is still not understood, although many predisposing and precipitating factors have been described, namely, trauma, stress, changes in the immune system, sensitivity to certain types of food or ingested substances such as preservative agents or substances such as cinnamaldehyde or sodium lauryl sulfate present in some toothpaste, and iron, zinc, and vitamin deficiency [26,27]. Alteration of local cell-mediated immunity is often encountered in patients with RAU. Systemic T- and B-cell responses have also been reported as altered in patients with RAU [28]. Histologically, aphthous ulcers contain a mononuclear infiltrate with a fibrin coating [29]. RAS may be also one of the symptoms

of the Behçet's syndrome – a systemic, inflammatory disease, where, apart from oral and genital lesions, various general symptoms may occur. They include anterior or posterior uveitis, retinal vasculitis, erythema nodosum, cutaneous vasculitis and arthralgia, and less commonly – dysfunction of the gastrointestinal tract, nervous system, and kidneys [30-34].

Hypersensitivity reactions to exogenous antigens other than gluten do not have a significant etiological role in RAS [35]. Infectious agents such as *Helicobacter pylori* and herpes simplex virus have been investigated but have not been consistently found in aphthous ulcers [36]. It can also be due to immunological attack as in lichen planus, pemphigoid, or pemphigus; damage because of an immune defect as in HIV disease and leukemia; infections such as herpes viruses, tuberculosis, and syphilis; cancer and nutritional defects such as vitamin deficiencies and some gastrointestinal diseases [21]. There is a genetic basis behind RAS, more than 42% of patients have first-degree relatives with RAS [37]. The occurrence is 90% if both the parents are affected, but only 20% if anyone of them are only affected. It is likely to be more severe and starts at an early age in patients with family history than the ones without [38]. There are few patients whose RAS remits with oral contraceptives or during pregnancy [39]. A minority of women with RAS have cyclical oral ulceration related to the luteal phase of the menstrual cycle [40-43]. A link with autoimmune progesterone dermatitis is most unlikely [44]. Several reports document the negative association between smoking and the occurrence of RAU [6].

TREATMENT

Treatment for RAS is symptomatic; the goals being to decrease pain, healing time, number and size of the ulcer, and to increase disease-free periods because the main etiology is not clearly understood. Current treatment options include topical agents, systemic and topical steroids, corticosteroids, cauterization, antibiotics, mouthrinses containing active enzymes, laser treatments, and combination therapy [45].

Topical treatment

Amlexanox is a topical preparation that is effective in the treatment of RAS. The drug was approved by the US Food and Drug Administration in 1996 as the first treatment for aphthous ulcers in immunocompetent patients. Amlexanox is an anti-inflammatory that inhibits leukotrienes and histamines, although its exact mechanism of action in the treatment of RAS is unknown [46]. Specifically, application of amlexanox as a 5% paste to ulcerations resulted in complete resolution of pain 1.3 days sooner than no treatment and 0.7 days sooner than vehicle alone. Similarly, amlexanox reduced complete healing by 1.6 days compared with no treatment and by 0.7 days compared with vehicle alone. Ointments, unlike gels or creams, do not burn or sting when applied to ulcerations, although they adhere poorly to mucosa. Elixir forms of corticosteroids such as dexamethasone can be used as an oral rinse for patients with multiple ulcerations [5].

Other antimicrobial compounds including the mouthwash Listerine® (Warner–Lambert Consumer Healthcare, Morris Plains, NJ), whose active ingredients include a mixture of essential oils, can be used to decrease the duration and severity of RAS and to possibly reduce the occurrence of ulcerations in susceptible patients [47].

Chlorhexidine gluconate, a widely prescribed oral rinse used to reduce plaque and gingivitis, increases ulcer healing and intervals between episodes of RAS but not the recurrence rate of oral ulcerations [48].

The commonly used agents are betamethasone, fluocinonide, fluocinolone, fluticasone, and clobetasol. These agents are found to be more effective than hydrocortisone and triamcinolone, but higher risk for adrenocortical suppression and predisposition to candidiasis. So in clinical practice, triamcinolone or fluocinonide dental paste is used as topical application over the ulcers 2–3 times daily for 5 days [6].

Sodium cromoglycate lozenges may provide mild symptomatic relief (Dolby and Walker, 1975; Kowolik *et al*., 1978), [49] but cromoglycate-containing toothpaste is not beneficial [50]. Carbenoxolone sodium mouthwash reduced the severity of RAS in one study [51].

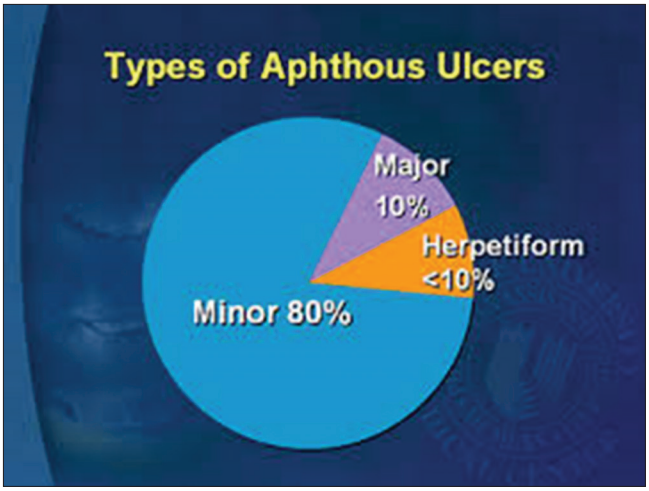

Fig. 1: [20]

Fig. 2: [22]

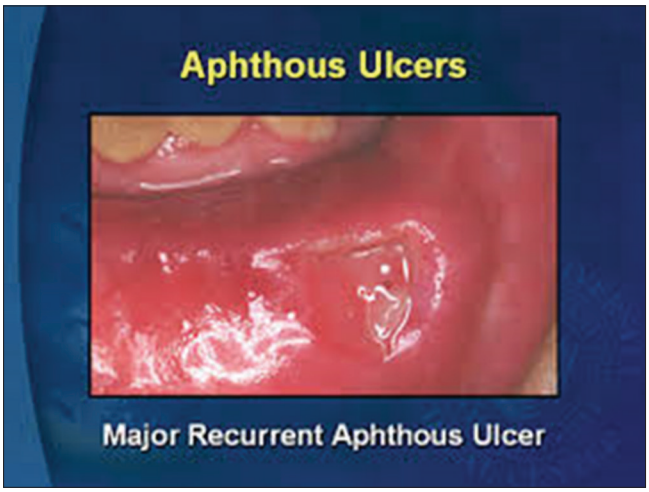

Fig. 3: [23]

Pain relief may be achieved with 2% viscous lidocaine applied with a cotton swab several times daily, as needed [24,52]. Over-the-counter benzocaine preparations (e.g., Anbesol and Oragel) may also be used.

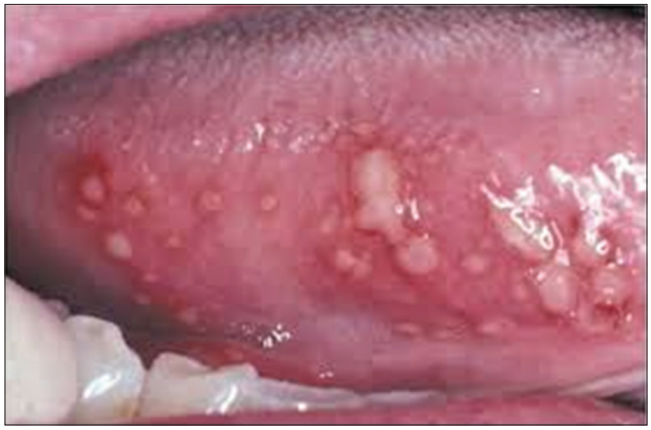

Fig. 4: [25]

Over-the-counter agents such as orabase or zilactin-B coat aphthous ulcers and provide local protection [52].

Topical tetracyclines (e.g., aureomycin, chlortetracycline, and tetracycline) may reduce healing times and/or reduce the associated pain of RAS [53-57], but they may cause dysgeusia, oral candidosis, and a burning-like sensation of the pharynx, and they are not suitable for young children who might ingest them, with resultant tooth staining [58].

Topical immunomodulatory agents that have been suggested to be of some benefit in the management of RAS include azelastine [59], human alpha-2-interferon in cream [60,61], topical cyclosporine [62], deglycyrrhizinated licorice [63], topical 5-aminosalicylic acid [64], and prostaglandin E2 gel [65].

Other topical treatments such as sucralfate have also been proposed, which act by forming a protective film on the bottom of the oral ulcers, reducing pain, and shortening healing time [66].

Systemic treatment

The use of systemic agents should be reserved for patients with frequent episodes of painful and multiple ulcerations. An exception is the use of systemic corticosteroids as an acute treatment for patients [5].

Pentoxifylline is an anti-inflammatory, immunomodulatory, methylxanthine derivative that blocks neutrophil adherence and is indicated for RAS. The mode of action for pentoxifylline appears to be due to the inhibition of tumor necrosis factor and other inflammatory cytokines [67,68]. Pentoxifylline, 400 mg 3 times daily, have reported excellent results, some with long-term benefits [69,70].

Colchicine therapy is indicated in the prevention of RAS [71,72]. Doses of 0.6 mg, administered 3 times daily, appear to not only decrease the severity of RAS but also increase the intervals between episodes. At least 50% of patients appear to respond to treatment, and responders may be maintained on therapy chronically. Colchicine can cause gastrointestinal side effects, especially diarrhea, which may limit its use. Some patients can tolerate only 1 or 2 doses daily, which may limit its use as suppressive therapy. Colchicine-induced myopathy and neuropathy require monitoring for patients on long-term therapy. Bone marrow depression also has been reported, primarily in cases of acute colchicine intoxication [73].

Prednisone, at doses of 40–60 mg administered daily for 3–4 days, usually relieves inflammation and pain. Severe ulcerations may require 2 full weeks of treatment with tapering doses with ulcerations [5].

The use of dapsone in the management of RAS is especially valuable for patients who require suppressive therapy. Like colchicine, dapsone may exert its effects primarily through suppression of inflammatory cell migration. Daily doses of 50–150 mg may be used chronically to suppress ulcer formation. Dapsone should not be administered to patients with a glucose-6-phosphate dehydrogenase deficiency and careful monitoring for hemolytic anemia is also essential. A hypersensitivity to dapsone characterized by fever, hepatitis, cholestatic jaundice, and rash is rare [74]; and agranulocytosis, another uncommon complication of dapsone, typically develops 8–12 weeks after initiation of therapy.

Thalidomide has proven to be effective at doses of 100–200 mg/day for treating RAS in patients infected with HIV and has become the drug of choice for patients with severe disease [7,75]. Less severe adverse effects, including sedation, headache, weight gain, nausea, constipation, and rash, are reversible when the drug is discontinued. Patients started on thalidomide therapy may require 2–3 months of treatment before a response is observed. A daily dose of 100–150 mg will usually suppress ulcer formation, although some patients may require higher doses. Once controlled, the dose may be tapered to alternate-day or every 3rd-day therapy [5].

Levamisole rarely causes objective clinical improvement [76], and the associated adverse effects (nausea, hyperosmia, dysgeusia, and agranulocytosis) discourage its use [77-83].

Transfer factor [84] and gammaglobulin therapy [85] have been suggested to be beneficial, but more detailed studies are needed to confirm these preliminary observations.

The reported clinical benefit of monoamine oxidase inhibitor therapy in the treatment of three patients with RAS [86,87] was probably due to accompanying dietary modifications rather than any alteration in psychological status.

CONCLISION

Recurrent aphthous ulcer is the most common ulcer of the oral cavity, whose etiology is not well known. However, there are many treatments available for the prevention as well as for the cure of ulcers.

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