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RECURRENT APHTHOUS ULCER

Recurrent aphthous ulceration (RAU) is an inflammatory condition of unknown etiology characterized by painful, recurrent, single or multiple ulcerations of the oral mucosa. [1]

Introduction

Recurrent aphthous ulcers represent a very common but poorly understood mucosal disorder, with universal occurrence in men and women of all ages, races and geographic regions. The condition is classified as minor, major, and herpetiform on the basis of ulcer size and number. Recurrent Aphthous Stomatitis (RAS) is a disease with worldwide prevalence ranging from 2% to 66% in different populations. [2] Considering oral ulceration, the necessity of a diagnostic criteria is unequivocal. Immunological diseases such as Behcet's disease and Crohn disease, other systemic diseases, such as peptic ulcer, endocrine diseases, anemia, and acquired immune deficiency syndrome, are often accompanied by oral ulcerations. [3] How to treat the oral ulcerative lesion effectively is an issue of common concern for every Dentist and Physician.

Morbidity is quite high in case of RAS; quality of life of RAS patients is affected with complaints of discomfort while eating, drinking, and speaking. Because the exact etiology of RAS is still unknown, most patients with RAS are usually given some medications to relieve their pain only, instead of an etiologic screening and curative treatment. [2] Several types of topical and systemic agents have been used for the treatment of oral ulcers, including corticosteroids, antimicrobials, analgesics, antihistamines, and biologics that promote epithelial repair. This article could help the clinician to improve their diagnostic setup, hone their treatment skills and stress on the importance of prompt referral.

Description and Clinical Forms of Recurrent Aphthous Ulcers

Recurrent Aphthous Ulceration has three different variants—minor aphthous ulcers, major aphthous ulcers and herpetiform ulcers, according to the classification described by Stanley [1]

Minor RAU (MiRAU)

This is the common presentation, which

is characterized by painful round or oval shallow ulcers, regular in outline, usually less than 10mm in diameter, with a grayish white pseudomembranous floor surrounded by a thin zone of erythematous halo. [1] It usually occurs on non-keratinized mucosa. Such as labial mucosa, buccal mucosa and the floor of the mouth, and is uncommon on the keratinized gingiva, palate, or dorsum of the tongue. It appears in the form of “attacks” of single or multiple lesions. These lesions can clearly be differentiated from viral or bacterial infections, dermatologic conditions, and trauma by the normal appearance of adjacent tissues and also the lack of systemic manifestations. [4]

Major RAU (MaRAU)

Previously known as periadenitis mucosa necrotica recurrens, this form occurs in approximately 10% of RAU patients. Lesions are similar in appearance to those of minor RAU, but they are larger than 10mm in diameter, single or multiple and very painful. It has a predilection for the lips, soft palate, and fauces, but can affect any site. The ulcers persist up to 6 weeks or longer and often heal with scarring. [5] It usually has its onset after puberty, is chronic, and persists for up to 20 years or more. In some cases, significant dysphagia can occur. These forms of RAS may be more common in HIV-infected patients because it has been suggested that RAS represents a local breakdown in immunoregulation, a condition that could be amplified by HIV disease. [4]

Herpetiform ulcers

Multiple small clusters of pinpoint ulcers characterize this form of RAS. They occur throughout the oral cavity, tend to be small (2 to 3mm) and numerous (as many as 100

ulcers at once), can fuse together to produce large irregular lesions and can last 7 to 10 days and heal without causing any scar. More often affecting women, it is associated with a later age of onset than other types of RAU. Even though these lesions resemble herpes-like or herpetiform in nature, herpes simplex virus cannot be cultured from the ulcers. Furthermore, the lesions are not preceded by vesicular lesions. [4]

Proposed Causes of Recurrent Aphthous Stomatitis [4]

- Local/oral factors
 - Trauma
 - Salivary gland dysfunction
- Microbial
 - Bacterial: streptococci
 - Viral: varicella zoster, cytomegalovirus
- Systemic factors
 - Behcet’s disease
 - Crohn’s disease
 - Ulcerative colitis
 - Cyclic neutropenia
 - Mouth and genital ulcers with inflamed cartilage syndrome
 - HIV infection
 - Stress
- Nutritional
 - Gluten sensitive enteropathy
 - Iron, folic acid, zinc deficiencies
 - Vitamin B1, B2, B6, B12 deficiencies
- Genetic
- Immunologic
 - Localized T-cell dysfunction
 - Antibody-dependent cellular cytotoxicity

Management of Recurrent Aphthous Stomatitis

Once a diagnosis of RAS is reached, patients with frequent or severe outbreaks of aphthae should be counselled, regarding the advisability of a medical screening for anemia, gastrointestinal disease, food “allergies,” and other diseases potentially affecting the immune system. The first step towards effective management of RAS is to identify and appropriately treat any modifiable predisposing factor before introducing therapy. It is warranted to reassure RAS patients on the benign nature of this ulcer, reduce stress, eliminate trauma or bad habit (e.g., cheek bite); any iron or vitamin deficiency should be corrected. If an obvious relationship to certain foods is established, these should be excluded from the diet. Possible causal drugs should be excluded. In case aphthous ulcers are the expression of systemic disease, treatment should be first directed to the underlying conditions. [7]

For treatment planning, patients can be classified according to their clinical characteristics as follows:

- Type A: Brief episodes occurring only a few times during the year, and characterized by tolerable pain levels. Predisposing factors should be identified and controlled. It is generally advisable to avoid hard foods, nuts, chocolate, acidic beverages or foods, salty or spicy foods and alcoholic or carbonated beverages.

- Type B: Episodes develop on a monthly basis, lasting 3-10 days, and pain causes the patient to modify habits of hygiene and diet. Apart from identifying and controlling predisposing factors, enquire about prodromal manifestations (itching or swelling), in order to provide topical treatment when these occur.

- Type C: The episodes are very painful, with chronic aphthae. Some lesions develop while others heal, and the patient does not respond to topical treatment. In such cases systemic therapy is indicated. [9]

Topical Therapies

Treatment should always start with topical medication, which range from inert barriers to active treatments. Providing a barrier for the ulcer (for example a mucoadhesive paste) should allow the breach in the mucosa to temporarily be protected and therefore noxious stimulants are less likely to sensitise nerve endings. The addition of active compounds to the barrier can potentially give an immunomodulatory effect.

Topical Steroids

Corticosteroids have anti-inflammatory and immunomodulatory effects that shortens healing time and reduces the size of lesion. Drugs most commonly adopted are hydrocortisone hemi succinate (as pellets of 2.5 mg) and triamcinolone acetonide (in an adhesive paste containing 0.1% of the steroid), applied four times daily. In severe RAS, high potency topical steroid such as fluocinonide, betamethasone or clobetasol gel can be carefully applied directly to the lesion after meals and at bedtime 2-3 times a day or mixed with an adhesive such as orabase prior to application. Larger lesions can be treated by placing a gauze sponge containing the topical steroid on the ulcer and leaving it in place for 15-30 minutes to allow for longer contact. Ulcerations located in the areas that make them difficult to see or reach can be controlled by topical dexamethasone elixir, 0.5mg/5ml held over the area or applied with a saturated gauze pad to the ulcers, four times per day for 15 minute (Lo Muzio 2001)

and betamethasone sodium phosphate rinse (dissolve 0.5 mg in 5 mL of water and rinse for 2–3 min), steroid aerosol (e. g. beclometasone dipropionate, 100 lg/puff), or a high-potency topical corticosteroid, such as clobetasol 0.05% in orabase or fluocinonide 0.05% in orabase. [10]

Amlexanox

Amlexanox is a topical anti-inflammatory, anti-allergic drug. Wenxia et al used 5% amlexanox four times daily in 216 participants, and reported 91.67% pain reduction, and 86.11% of subjects had faster reduction in size compared with control. Another study by Katti and Darsha, 2011 reported lower pain scores and significant difference on 3rd, 6th and 9th day regarding ulcer size. It is currently the only clinically proven product approved by the US FDA for the treatment of aphthous ulcers. [11]

Aloe Vera Gel

Aloe Vera (AV) is a tropical plant with anti-inflammatory and immunostimulant effects, with wound healing properties. Clinical trial by Babaee et al shows AV gel to be effective in terms of alleviating the patient’s pain score and lesion diameter compared with the placebo. [12]

Sodium Lauryl Sulphate(SLS) Free Dentifrices

Sodium Lauryl Sulphate is an anionic detergent that has been used as the major or sole surfactant in most dentifrices for more than 20 years. Study done by Y J Shim et al in 2012 showed that even though the number of ulcers and episodes did not differ significantly, the duration of ulcers and mean pain score was decreased on using SLS-free dentifrices. [13]

Topical Therapies [14]

Drug	Dose	Mechanism of Action	Benefits
Therapeutic options to reduce the frequency of recurrence and/or the number of ulcers			
0.4% w/w zinc sulphate, Triclosan 0.15% in 15.6% w/w ethanol	10ml for 30 s b.i.d.	Antibiotic	Reduction of number of ulcers in 43%, of pain by 45%, increase in ulcer-free days vs. controls
2.5% tetracycline solution	5 mL rinse in mouth for 1 minute q.i.d.	Antibiotic	Increase (over 40%) in ulcer-free or pain-free days
Therapeutic options to reduce pain			

Diclofenac 3% in 2.5% hyaluronic acid gel	200 µL once	Anti-inflammatory	Less pain 2–6 hours after application
CO2 laser (2–5 mW)	Once	Modulating action and reparative effect on tissues	Reduction of pain immediately after treatment, relief lasting 96 hours
Nd:YAG laser	Once	Modulating action and reparative effect on tissues	Less pain immediately and on days 4 and 7. Less exudation
Minocycline 0.2% in aqueous solution	5 mL q.i.d.	Antibiotic	Less pain starting with day 2
Therapeutic options to reduce the duration of illness and size			
Amlexanox 5% paste	b.i.d.	Anti-inflammatory	Reduction in size and Erythema
Amlexanox 2mg patch	q.i.d	Anti-inflammatory	Reduction in pain and size on days 4 and 6
5-aminosalicylic acid 5% cream	t.i.d.	Anti-inflammatory	Reduction in duration (7 vs. 11 days) and pain
Sucralfate solution	Apply 5 mL solution with applicator q.i.d.	Antacid, ulcero-protective	Reduction in frequency and duration
Triamcinolone acetonide 0.1% in oral paste	t.i.d	Anti-inflammatory, immunosuppressant	86.7% response rate
Dexamethasone 0.1% in oral paste	q.i.d	Anti-inflammatory, immunosuppressant	Quicker healing

Systemic Therapies

For the purpose of the review, the interventions have been grouped into two categories: immunomodulatory/anti-inflammatory and uncertain.

Levamisole

Levamisole is an anti-helminthic drug that acts apparently as an immunomodulator. Eight trials compared levamisole with placebo, with the dose of levamisole being 150mg per day in all studies, but the duration of treatment varied from 3 consecutive days per episode (with a minimum of 2 weeks between each treatment period) to 11 consecutive days followed by 11 days of no levamisole (for a total of 9 weeks). Patients receiving levamisole reported more adverse effects than those receiving placebo, but did not require withdrawal. [15]

Montelukast (leukotriene receptor antagonist)

In a trial conducted by Femiano, 20 participants received 10mg montelukast orally daily for 1 month followed by alternate days for the second month. Time in days to resolution of first ulcer was shorter, along with a significant reduction in total number of new lesions over the 2-month treatment period. [16]

Rebamipide

Rebamipide, a gastro protective agent, acts by the decrease in oxygen radicals, increase in blood flow and production of protective prostaglandins in ulcer mucosa, which accelerates the process of healing. In a study comparing rebamipide with levamisole, the efficacy of both in improving both aphthae count and pain score were found to be almost similar. However, rebamipide was suggested to be well tolerated and easily administered,

and hence recommended as a long-term treatment for recurrent oral aphthous ulcers. [17]

Systemic Steroids

Major aphthous ulcers often require systemic treatment as an initial approach. Systemic prednisone therapy should be started at 1.0 mg/kg a day (40 mg/day) as a single dose in patients with severe RAS and should be tapered after 1-2 weeks. Intralesional steroids can be used to treat large indolent major RAS lesions. [10]

Multivitamin Therapy

Lalla et al in 2012 compared a daily multivitamin with placebo in patients who had a validated history of at least three episodes of RAS within the previous 12 months. No statistically significant difference was found between groups with regard to mean number of new lesions, duration of episodes, or average mouth pain during RAS episodes. Clinicians should not recommend multi-vitamin supplementation routinely as prophylaxis for RAS. [18]

Vitamin B12

In 2009, Volkov et al randomised a total of 58 participants to sublingual vitamin B12 (1000mcg daily for 6 months) and compared with placebo. At completion of treatment at 6 months, compared to placebo, the treatment group reported lower pain scores, a shorter average duration of RAS episode (number of days) and lower frequency of outbreaks per month. During the last 2 months of treatment, statistically significantly more participants receiving vitamin B12 reached a 'no ulcer' status. No adverse events were reported. [19]

Bee Propolis

Propolis is an over-the-counter, flavonoid-containing food supplement, known to possess antimicrobial activity, free radical scavenging ability, immune system activation, and numerous antioxidant properties. Samet et al studied patients who took a 500mg

supplement of propolis daily were shown to have a statistically significant decrease in the frequency of outbreaks of RAS, suggesting that propolis may be used for patients who do not respond to other forms of treatment. [20]

Systemic Therapies [14]			
Drug	Dose	Mechanism of Action	Benefits
Therapeutic options to reduce the frequency of recurrence and/or the number of ulcers			
Prednisolone	5mg daily p.o.	Anti-inflammatory, immunosuppressant	Reduction of pain and number of lesions after 3 months
Rebamipide	300mg daily p.o.	Decrease in free radicals, increase in blood flow and production of protective prostaglandins	Reduction in number of ulcers and pain in 65%
Colchicine	0.5-2mg daily p.o. for 6 weeks	Inhibiting chemotaxis, mobilization, adhesiveness, and lysosomal degranulation	Reduction of pain and number of lesions
Azathioprine	2.5mg/kg BW daily p.o.	Immunosuppressant	Reduction in frequency from 43% to 11%
Thalidomide	100 or 300mg daily p.o.	Immunomodulatory and anti-inflammatory - inhibit the production of tumor necrosis factor alpha	Reduction in frequency of ulcers after 4 weeks

Levamisole	150mg per day for 3 consecutive days per episode (with a minimum of 2 weeks between each treatment period)	Immunomodulator	Increased disease-free intervals
Cyclosporine	10mg/kg BW daily p.o.	Immunosuppressant	Ulcers improved by 70%
Doxycycline	20mg b.i.d. p.o.	Inhibition of prostaglandin production, leukocyte suppression, and inhibition of collagenase and gelatinase	Reduction in days with new aphthous ulcers
Clofazimine	100mg daily p.o. for 30 days, then 100 mg p.o. q.o.d.	Inhibitory effects on neutrophil migration, increases synthesis of lysosomal enzymes and phagocytic capacity	More ulcer-free intervals
Therapeutic options to reduce duration of illness and size of ulcers			
Sucralfate	1g q.i.d.	Locally binds with proteins at the base of ulcer to provide a protective covering	More rapid healing and less pain in 80%
Pentoxifylline	400mg daily p.o.	Immunomodulatory and anti-inflammatory	Reduction in ulcer size
Montelukast	10mg daily for 1 month and then q.o.d. for 1 month p.o.	Mast cell stabilizer	More rapid healing and reduction in frequency of flares
Dapsone	100mg daily p.o.	Inhibit migration of polymorphonuclear leukocytes (PMNs)	Reduction in number, duration and frequency
Zinc sulphate	300mg daily p.o.	Promotion of wound healing and maintenance of epithelial integrity	Smaller and fewer lesions

Conclusion

Until RAS etiology is discovered, treatment options will remain few and only partially effective, so patients must be made aware of the limitations of treatment. It is essential to review the patient to assess their progress and response to any treatment instituted. Depending upon the response to treatment, alternatives could be trialled. Future research should focus on identifying RAS etiology, developing standardized diagnostic criteria for RAS, and improving the design and reporting of clinical trials.

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