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Mini Review on Clinical Images Demonstrating the Healing Steps of Oral Apthous Ulcer

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INTRODUCTION

Recurrent Aphthous stomatitis (RAS) is one of the most frequent forms of the oral ulcerations with a prevalence in the general population ranging between 5% and 60% [1,2]. It's peak age of onset in between 10 and 19 years of age and it can persist into adulthood and throughout the patient's whole lifespan, with no gender predilection [3].

It is mainly classified as primary whose etiology is not well understood till this moment (idiopathic) and as secondary to various well-defined entities. The clinician should always closely investigate through detailed history taking and system wide investigations, whether it is related to a systemic inflammatory process or it is truly idiopathic.

The term aphthae is derived from the Greek word aphthi, which means "to set on fire" or "to inflame" and is thought to have been first used by the philosopher Hippocrates to describe the pain associated with a common disorder of the mouth during his time [4].

Local trauma, genetic factors, nutritional deficiencies, viral and bacterial infections and immune or endocrine disturbances have all been suggested as etiological factors of frequent oral ulcerations. In a subset of patients, no etiology can be identified and a diagnosis of exclusion must be made; such cases are referred to as recurrent aphthous stomatitis (RAS). Three forms of RAS exist: minor (>70% of cases), major (10%) and herpetiform (10%) [5].

These subtypes differ in morphology, distribution, severity, and prognosis **(Table 1)**. Despite their distinct characteristics, all forms of RAS have a significant impact on quality of life and interfere with activities of daily living [6,7].

PATHOGENESIS OF RAS

The pathogenesis of RAS is multifactorial with significant physiological inter relations between the immune system, genetics and environmental factors. Similar to other chronic inflammatory conditions, deoxyribonucleic acid (DNA) damage secondary to oxidative stress is thought to have a major role in recurrent ulcerations.

In a recent case-control study, total oxidative status (TOS), total antioxidant status (TAS) and the TOS:TAS ratio (oxidative stress index, OSI) were used as parameters to assess oxidative damage in RAS patients against unaffected controls and the results strongly suggested that RAS patients have a systemic imbalance in the oxidant-to-antioxidant ratio favoring oxidative damage [8].

New evidence also suggests an immunological basis for the chronic inflammation in RAS patients. Currently it is thought that an unknown antigen stimulates keratinocytes which results in cytokine secretion and leukocyte chemotaxis. TNF-α has been found to be significantly increased in the saliva of RAS patients. A recent study explored the significance of single nucleotide polymorphisms (SNP) in the genes for proinflammatory cytokines IL-1 and IL-6 in RAS. (5) and the average frequency of IL-6.

C-174C haplotype, which is associated with an increase in IL-6 secretion, was detected in higher amounts in affected patients than in controls [9,10].

This also suggests a genetic component to the immunopathogenesis of RAS. Further evidence of a genetic component, it is also suggested in the literature that RAS may be associated with a specific HLA haplotype. HLA haplotype A*038B*07DRB1*13 is the most commonly associated with minor, major and herpetiform RAS [11].

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Table 1. Clinical features of minor, major and herpetiform recurrent aphthous stomatitis (RAS).

	MINOR RAS	MAJOR RAS	HERPETIFORM RAS
Gender predilection	Equal	Equal	Female Predominance
Morphology	Round or oval lesions Gray-white pseudomembranes Erythematous halo	Round or oval lesions Gray-white pseudomembranes Erythematous halo	Small, deep ulcers that commonly converge Irregular contour
Distribution	Lips, cheeks, tongue, floor of mouth	Lips, soft palate, pharynx	Lips, cheeks, tongue, floor of mouth, gingiva
Number of ulcers	1-5	1-10	10-100
Size of ulcers	<10 mm	>10 mm	2-3 mm
Prognosis	Lesions resolve in 4-14 days; No scarring	Lesions persist >6 weeks High risk of scarring	Lesions resolve in <30 days Scarring uncommon

Source: Adapted from [13]

MANAGEMENT OF RAS

The management of RAS can be very challenging, especially in severe cases. When oral aphthous ulcers are secondary to an underlying disease, it is recommended to treat the primary disease to hopefully improve the oral aphthae. In the case of RAS and even some cases of secondary oral aphthous ulcers, the following treatment ladder may be utilized.

Topical therapies

Currently, the management of RAS is mainly supportive symptomatic treatment. No pharmacological treatment has been curative, although several modalities have been effective in decreasing pain and erythema and increasing the rate of re-epithelialization associated with healing lesions time.

Several topical medications with different mechanisms are effective in managing RAS lesions. Topical treatment is aimed at prevention of super infection, protection of existing ulcers, analgesia, decreasing inflammation and treating active ulcers. It is reasonable to administer chlorhexidine 0.2% rinse to all patients presenting with RAS to decrease the likelihood of super infection with gram-positive and gram-negative bacteria and fungi [5].

Additionally, in vitro, chlorhexidine has been shown to have activity against enveloped viruses (herpes simplex virus (HSV), cytomegalovirus (CMV), influenza and respiratory syncytial virus (RSV)). Chlorhexidine is also effective in eliminating and preventing the formation of biofilms that are commonly found in dental plaque [12].

Topical antibiotics in the form of doxycycline or minocycline mouthwash are also effective, likely secondary to inhibition of metalloproteinases. Protective coating of existing ulcers can be achieved with bioadhesive pastes formulated with benzocaine 20% for pain relief. Lidocaine 5% ointment and lidocaine 10% sprays is also effective for temporary analgesia. The anti- inflammatory properties of diclofenac 3% with hyaluronic acid 2.5% have also been effective. Amlexanox 5% ointment, which has been discontinued in the United States, has been reported to decrease healing time of aphthous ulcers secondary to its anti- inflammatory and immunomodulating properties. Topical corticosteroids (betamethasone mouthwash, fluticasone propionate spray, triamcinolone in an oral preparation) are also successful in the treatment of active ulcers and can be administered with antifungals to reduce risk of oral candidiasis for long term use [5].

Systemic therapies

When there is little to no improvement in frequency or severity of outbreaks with topical therapy, there are a number of oral systemic options that can be suggested. Several systemic medications have been reported as effective for treating RAS in the literature. There is evidence to suggest that oral antimicrobials, such as penicillin G (50 mg QIDx 4 days), decrease ulcer size and pain. Clofazimine, an antimicrobial, in combination with rifampin and dapsone, has been shown to prevent the formation of new ulcers. Zinc at 50 mg/day has also produced beneficial effects on ulcer re-epitheliazation and healing [5].

Pentoxifylline has shown promising results in reducing severity of outbreaks, but has little effect in preventing new outbreaks and unfortunately has numerous GI side effects [10], oral prednisone (initial dose of 25 mg/day with taper) is the first-line systemic therapy and is typically reserved for the acute treatment of severe RAS outbreaks. Systemic

corticosteroids have different side effects and are relatively or absolutely contraindicated in certain patients; for these cases, leukotriene-receptor antagonists are a safer alternative. Montelukast 10 mg daily was found to be equally effective in pain reduction and accelerating healing of lesions when compared to oral systemic corticosteroids. When disease is not adequately controlled with oral corticosteroids, immunomodulators have shown promise in reducing severity of outbreak and preventing further outbreaks. Steroid-sparing agents, such as colchicine at starting at 0.5 mg/day and gradually increasing to 1.5 mg/day or dapsone 25 mg/day and gradually increasing to 100 mg/day may also be effective. Thalidomide at a dose of 50 to 100 mg/day is considered the most effective immunomodulator for RAS, but is obviously limited due to its side effects [5].

Additionally, a recent study explored the effects of daily ascorbic acid 2000 mg/m^2/day for managing minor RAS. A 50% reduction in oral ulcer outbreaks and a significant reduction in pain level were noted in these patients. There is strong evidence to suggest that ascorbate decreases neutrophil-mediated inflammation via modulation of reactive oxygen species (ROS) [10]. Ascorbic acid as an adjuvant therapy to topical should be considered as well because of its relatively low side effects.

Light therapy

Low-level laser therapy at a wavelength of 658 nm may also be beneficial in RAS patients as an adjuvant. It was shown to be equal or even superior to pharmacological treatment in managing pain and inflammation and increasing re-epitheliazation of aphthous ulcers.

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