Recurrent Aphthous Atomatitis : A Comprehensive Review

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RAS is a painful phenomenon, characterized by necrotizing ulcers of the oral mucosa that persist, remit and recur for variable periods of time.[1] RAS indeed is one of the most common lesions seen by the dentist.[2]

RAS is defined as an inflammatory condition of unknown etiology characterized by painful recurrent, single or multiple ulcerations of the oral mucosa.[1]

RAS is sometimes termed as recurrent oral ulceration, but it is important to note there are various causes of recurrent oral mucosal ulceration other than RAS and hence the term RAS is considered more appropriate.[3] RAS was first described in antiquity and since has been the subject of numerous clinical and laboratory investigations.[3] However, the disease still remains poorly understood.[1]

The etiology of the disease is obscure, but small groups of patients can be identified who have definitive predisposing factors.[3] Clinically RAS is classified into three types: **major aphthous ulcers, minor aphthous ulcers** and **herpetiform aphthae**. There is no curative therapy to prevent the recurrence of ulcers, and all available treatment modalities can only reduce the frequency or severity of the lesions.[1]

The disease still remains challenging for the dentist and the patient alike. A more thorough understanding of the underlying etiology, pathogenesis and clinical presentation and differentiation will allow clinicians to make selective and appropriate treatment decisions and hence, broaden the scope of management of this condition.[4]

History And Terminologies

Aphthous stomatitis as a disease entity presents a long and confused history.[5] The first use of the term aphthai in relation to disorders of the mouth is credited to **Hippocrates (460-370 BC).** The term was used in antiquity by **Hippocrates and Celsus,** and their successors to describe certain oral ulcerations in infants and occasionally adults. However their descriptions are not sufficiently clear so that the entity can be recognized with any degree of certainty. In some ways the descriptions are more suggestive of candidiasis.[5,6]

The first reasonable description of the disease was presented by **William Heberden.** He indicated that[7]; "Aphthae are found chiefly in children, in old persons and in tedious fevers. Besides the aphthae which accompany acute fevers in weak constitutions, there are some which may be called chronical: these will sometimes be very troublesome to the mouth, not only for months, but even years, without fever, or any considerable complaint". The first valid clinical description of RAS appeared in **1888 by Von Mickulicz and Kummel**.[5,6,7] These authors were the first to describe the chronic recurrent nature of the disease and described "chronic recurrent aphthae" as a distinct entity.[5]

Over the years RAS has prompted considerable interest and research, and many publications have suggested a variety of synonyms for RAS.[7] These include Periadenitis aphthae, Canker sores, Mickulicz's aphthae, Periadenitis mucosa necrotica recurrences, Sutton's disease, Touraines aphthosis, Aphthous stomatitis, Aphthous ulcers, Recurrent ulcerative stomatitis, Stomatitis aphthosa recurrence cicatricicans.

Epidemiology

RAS is the most common oral mucosal disease known to human beings. The prevalence of the disease varies widely depending on the population studied. It is possible that the actual prevalence of RAS is greater than the 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.[8]

Epidemiologic studies indicate that prevalence of RAS varies between 5% and 25% in general population and is as high as 50% - 60% in selected groups (e.g. medical or dental students).[8] Hence, the cumulative prevalence of RAS varies form 5-66% of population depending on the group studied.[1] Various ethnic factors and gender also tend to influence the prevalence of the disease. Many studies have reported an increased prevalence of the disease in females than in males.[5]

Etiopathogenesis

The literature is replete with reviews and clinical studies directed towards elucidation of the etiology and pathogenesis of the disease. Thus far the cause has remained elusive despite the tabulation of a considerable number of associated variables which demonstrate statistically significant correlations and may predispose patients to the disease. The various causative factors that have been implicated for RAS are hereditary factors, hypersensitivity, endocrine factors, drugs, stress and trauma etc.[10] However, a number of authors make a distinction between etiology and predisposing factors. The latter are important in determining the prevalence, severity and presentation of the disease.[2]

The Suggested Causes of Ras Are

1) Local factors : Trauma, Smoking, Salivary gland dysfunction

2) Microbial factors: Bacterial, Viral

3) Exposure to certain drugs

4) Systemic factors: Allergy, Stress, HIV disease, Behcet's disease, Hormonal influences, Coeliac disease, Crohn's disease, Neutropenic ulcers, PFAPA syndrome, MAGIC syndrome, Sweet's syndrome

5) Nutritional and Hematological Deficiencies : Iron, Zinc, Folic acid, Vitamin B_1, Vitamin B_2, Vitamin B_6 and B_{12} deficiency.

6) Genetic factors

7) Immunological factors

Local Factors

Trauma

A subset of patients with RAU are predisposed to develop aphthae at the sites of trauma.[1] The local trauma may be from anesthetic injections, sharp foods, tooth brushing and trauma from dental treatment. However many patients with RAS don't develop RAS or fail to show convincing evidence of increased ulceration at the site of trauma. Nevertheless, minor trauma should be considered as one of the precipitating factors in RAS.[2]ulation with higher SES.[4]

Sodium Lauryl Sulfate And RAS

Sodium lauryl sulfate (SLS), is a synthetic agent commonly used in dentifrices. Previous studies have reported the role of SLS in the etiology of RAS.

Salivary Gland Dysfunction :

Quantitative and qualitative changes in salivary gland function have been hypothesized to play a role in the pathogenesis of RAS. However most studies have not found a definitive relationship.[8]

Exposure To Certain Drugs

Over the years various drugs have been associated with occurrence of RAS, the list of these drugs include: Captropril, Gold salts, Nicorandil, Niflumic acid, Phenidone, Phenobarbital, Piroxicam, Sodium hypochloride.[1]

Microbial Factors And RAS

It has been suggested that oral streptococci and several viruses may play an etiologic role in RAS, but overall results are inconclusive.[8] In general herpes simplex virus, varicella zoster virus and Epstein-Barr virus have not been directly isolated from RAS lesions.[11] While streptococci have been cited as potential etiologic pathogens, possibly as a result of streptococcal antigens cross-reactivity with oral mucosa. However, studies based on antibody levels and lymphocyte blast transformations refute streptococcal relationship. Hence, researchers disagree about the role of microorganisms in RAS.

Systemic Factors

Allergic Disorders :

The raised serum IgE levels in some patients suffering with RAS together with a positive family history of RAS might be suggestive of an atopic state.[3] Food induced allergic reactions are well recognized. In recent years there has been considerable interest in food induced allergies in the mouth. Some investigators have correlated the onset of ulcers to exposure to certain foods such as Cow's milk, gluten, chocolate, nuts, cheese, azodyes, flavoring agents and preservatives. However, the involvement of components of food in causation of RAU is controversial.[1]

Stress

Stress and Psychological factors have long been recognized to play a role in causing RAS. Certain personality traits are said to be common in RAS patients.

Several mechanisms can be postulated for a cause and effect relationship between trait anxiety and RAS. There could be an as yet unknown biochemical effect, or a possibility of a self induced traumatic injury as a predisposing factor.[3]Severe emotional and environmental stress must be contemplated in clinical assessment of RAS.[8]

Hiv Infection

Patients with HIV infection have an overall prevalence rate of RAS ranging form 1-4%. Severe episodes of RAU have been observed in patients infected with HIV. Even though HIV DNA has been identified in buccal mucosal scrapings from apparently healthy mucosa of HIV seropositive subjects; there are no studies that have demonstrated the presence of HIV in oral ulcers. It is unknown whether such lesions represent a localized autoimmune reaction, developing in response to an undefined antigen which triggers a normal immunological response, or whether they represent overactive HIV in the mucosa of T-cell deficient hosts.[1]

Behcet's Disease

Behcet's disease is a multisystem disorder that predominantly affects young men of Mediterranean, Middle East and Japanese descent.[111]The disease is traditionally described as a triad consisting of RAS, genital ulcerations and ocular disease. Behcet's disease (BD) is now recognized as a multisystem disorder, the clinical expression of which may be dominated by mucocutaneous, articular, neurologic, urogenital, vascular and intestinal or pulmonary manifestations. Nonetheless RAS occurs virtually in all patients of BD, and according to some authors it is frequently the first systemic manifestation, of the disease.[12]A high frequency of RAU has been found among relatives of patients with BD. RAU has some, but not all immunological abnormalities that arise in BD. In this respect, it has been suggested that RAU and BD might represent different degrees of the same disease spectrum.

Hormonal Influences

It appears from different and sometimes conflicting studies that a minor subset of women with RAU has cyclical oral ulcerations related to the onset of menstruation or the luteal phase of the menstrual cycle. Complete remission during pregnancy has also been reported.[1] There are also few patients whose RAS remits with oral contraceptives. These findings strongly implicate a hormonal basis in these instances.[3]

Coeliac Disease And Ras

Coeliac sprue, also called as coeliac disease or gluten sensitive enteropathy, is a condition related to the small intestines intolerance to gluten. Some authors have reported that individuals with RAS have an increased prevalence of Coeliac Disease and have suggested that the oral aphthae may be an early indicator or sign of Coeliac Disease. [13] However some investigators have failed to demonstrate any benefit from gluten free diet in aphthous ulcer patients, and have suggested that the benefit if any may be due to a placebo effect.

Immunological markers like anti transg- lutamininase and antiendomysium antibodies have been used for identifying

Coeliac Disease however; no studies have used these markers for screening RAS patients for presence of Coeliac Disease.

Crohn's Disease And RAS

Since 1969 when Dudeney first described an oral manifestation of Crohn's disease, it has been shown that this granulomatous inflammation of unknown origin can involve any part of the gastrointestinal tract. Characteristic lesions in the oral mucosa may also precede the other gastrointestinal involvements or appear without them. The frequency of non-specific lesions such as aphthous stomatitis and oral ulcerations is reported to be 4% to 9% in patients with Crohn's disease in the small or large bowel. Therefore; the clinician must obtain a careful history of gastrointestinal tract dysfunction for every patient with RAS.[14]

Pfapa Syndrome

The syndrome of periodic fever, aphthous ulcers, pharyngitis and cervical adenitis or PFAPA was first recognized in 1987 in a group of children and shares some features with cyclic neutropenia.[14]

Sweet's Syndrome

Sweet's syndrome (acute febrile neutrophilic dermatosis), which was first described in 1964 by Sweet, is characterized by 4 cardinal features : 1) fever, 2) a relative increase of neutrophils in the peripheral blood, 3) skin lesions such as tender erythematous plaques, nodules, vesicles, and pustules on the face and extremities and 4) a dense dermal infiltrate with mature neutrophils seen histologically. It has been reported that Sweet's syndrome is often accompanied by oral lesions.

Nutritional And Hematological Deficiencies

Haematinic deficiencies have been found in about 20% of patients with RAU. In several studies, deficiencies of iron, vitamin B_{12} and folate have been reported, although in many cases the deficiencies were marginally low. Also improvement of RAU with zinc sulphate supplementation has been described in an open trial however such improvement has not been confirmed,

Genetic Factors

It is possible that more than 40% of patients may have a familial history of RAU. Patients with a positive family history of RAU develop oral ulcers at an earlier age and have more severe symptoms than individuals with no family history of RAU. Nevertheless, there is clear variability in host susceptibility which can be explained by the way of polygenic inheritance, with penetrance being dependent on environmental factors.[1] Genetic factors have been implicated in numerous studies on association between RAU and genetically determined human leukocyte antigen (HLA) subtypes. An increased frequency of HLA2, B12, B51 and CW7 in Jewish patients, DR2 and DR4 in Turkish patients DR5 and A28 in Greek patients and DRW9 in Chinese patients have been reported. Some investigators have reported a variety of associations or absence of associations between RAU and a particular HLA antigen. This could be explained by different ethnic background or by multiple etiological basis for RAU. These reported studies suggest that RAU has a genetic basis at least in some patients.[1]

Immunological Factors

RAS patients may have primary immunologic abnormalities that result in altered immunoregulatory balances. For eg, there are increases in antibody dependent cell cytotoxicity, and greater levels of serum immunoglobulins in patients with RAS. Activated T-lymphocyte aggregate in the periphery of RAS lesions confirming the hypothesis that RAS represents an activated cell-mediated immune response.[8] Studies have also noted that patients with RAU have aberrations in the proportion of lymphocytes. Some researchers have reported a decrease in the number of circulating CD_4 + cells but normal or reduced numbers of CD_8 + cells and a normal or slightly reduced CD_4 / CD_8 ratio; an increase in the number of T-helper / inducer cells (CD4, CDW 29+); and a decrease in the number of Tsuppressor / inducer cells (CD_8, $CD_{45}R$).

The following simplistic outline can explain the occurrence of RAU.[14]

- Some patients affected by RAU have a mild systemic immune deregulation that may have a genetic basis.
- In the presence of local or systemic stimulus the epithelial cells become targets for lymphocyte monocyte and neutrophils. Epithelial cells are destroyed, and acute phase reactants are released.
- Current evidence suggests that while immune mediated destruction of the epithelium is the final common pathway, in the pathogenesis of RAU, it is not an autoimmune phenomenon. No specific antigens have been identified irrefutably and most of the histologic and immunologic findings are non specific.

Clinical Features

The lesions of RAS are characterized by recurrent ulcerations of the oral mucous membranes that occur either singly or in multiple locations and are usually associated with pain.[8] The lesions are painful, clearly defined, round or oval with shallow necrotic centre covered with a yellow grayish pseudo membrane and is surrounded by raised margin and erythematous halo.[15,16]

Age Distribution

The onset of RAS is usually during the childhood, with a tendency of ulcers to diminish in frequency and severity with age. In about 80% of patients with RAS, the condition develops before the age of 30 years and onset in later years suggests a possibility of definable predisposing factors leading to RAS.[15] The peak age of onset is the second decade of life.[1] Most of the studies have shown a general trend of low RAS prevalence in first decade with an increase in prevalence in 2nd and 3rd decade. Following the 3rd decade, prevalence decreases.[17]

Sex Distribution

Many studies world wide have shown higher RAS prevalence in women as compared to men.[10] Data indicates 57% lesions occur in females and 43% in males.

Site

Aphthous ulcers may occur in any area of the oral cavity; however, they commonly occur on the freely movable oral mucosa. Ulcers most often involve the labial and buccal mucosa but also occur on the tongue, mucobuccal fold, floor of the mouth and soft palate. The keratinized lip mucosa, hard palate and gingiva are rarely involved.[2]

Clinical Presentation

Symptoms

A prodrome of localized burning or pain for 24-48 hours can precede the ulcer.[15] An aphthous probably is the most painful of all ulcerative lesions involving the oral mucosa and the pain may be variable. As the tissue undergoes necrosis and an ulcer forms, there is severe pain.[16] The pain and ulceration disable the patients and prevent

them from performing their daily activities, which can include eating and talking.[1] The pain lasts for 3-4 days at which point early eptihelialization can occur.[15] Constitutional involvement is absent in RAS.

Signs

Following the prodromal period, a localized area of erythema develops. Within hours, a small white papule forms, ulcerates and gradually enlarges over the next 48-72 hours.[18] The individual lesions are round, symmetric and shallow, but no tissue tags are present.[5]Multiple lesions are seen, but the number, size and frequency of these varies considerably.

Clinical Types [19] :

CHARACTERISTICS OF CLINICAL PRESENTATIONS OF RAS

CHARACTERISTIC	TYPE OF PRESENTATION		
	Minor aphthous	Major aphthous	Herpetiform ulcers
Number of ulcers	1 - 10	1 - 5	5 - 100
Size (mm)	5 - 10	>10	<5
Pain	None to moderate	Severe	Mild to moderate
Duration(days)	10 - 14	>2 weeks	10 - 14
Scarring	No	Yes	No
Location	Buccal mucosa, labial mucosa, lateral tongue, floor of the mouth.	Labial mucosa, soft palate, oropharynx.	Any site with non-keratinised oral mucosa.
Incidence	75 - 85 %	10 - 15 %	5 – 10 %

Patients with few lesions that heal in 1-2 weeks and recur infrequently are diagnosed to have **simple aphthosis**.[15]In contrast; patients are diagnosed to have **complex aphthosis** when they have numerous large severely painful lesions that may be associated with genital or perianal ulcers. In these patients new lesions develop as older lesions resolve, [20]

Diagnosis

There are no known laboratory procedures available to establish a definite diagnosis of RAS and also the histopathological examination of biopsies does not provide a definitive diagnosis for RAS.[1] A detailed history and examination help in distinguishing RAS from primary acute viral stomatitis or from chronic multiple lesions such as pemphigoid, as well as other possible causes of recurring ulcers, such as connective tissue disease, drug reactions, and dermatologic disorders. Detailed virological investigations of lesional tissue or serum are usually not warranted unless to exclude atypical herpetic involvement.[1]

Histopathology of R.A.U

Overall the histopathologic picture is non specific. There is initial lymphocytic infiltration followed by destruction of the epithelium and infiltration of the tissues by neutrophils. Mononuclear cells may also surround blood vessels (perivascular cuffing).These changes are said to be consistent with either type III or IV reactions, but true vasculitis is not seen.[21]

Management

There is no specific management for RAS patients. The symptoms can be reduced, but it may be not possible to permanently cure RAS in these patients.[8] The general goals of treatment while treating an RAS patient are to : **Decrease symptoms, Reduce ulcer number and size, Increase disease free periods**. The best treatment is that which controls ulcers for the longest period with minimal adverse effects. The treatment approach should be determined by the disease severity, patient's medical history and frequency of flare ups and patients ability to tolerate the medication. In all patients with RAS it is important to rule out any predisposing factor and treat any such factor, where possible, before introducing more specific therapy.[15]

Many treatment modalities have been used in RAS patients these include: -

1) Elimination of local factors

2) Topical therapy

- Analgesics and anti-inflammatory drugs
- Antimicrobials
- Corticosteroids

Others : Amlexanox, KNO_3, Sodium cromoglycate, Cromoglycic acid, carbenoxolone sodium, Prostaglandins, Azathioprine, Cyclosporine, Sucralfate, 5-amino salicylic acid, Bioadhesive patches.

3) Systemic Therapy

Immunomodulators : Levamisole, Thalidomide, Colchicine, Pentoxyfylline, Azelastine, Dapsone and Azathioprine, Longovital

Others : Corticosteroids (Prednisolone, Triamcinolone, Betamethasone, Dexamethasone etc), MAO inhibitors, Systemic zinc sulphate, Acyclovir

4) Other Therapies

- Ultrasound and Lasers

Elimination of Predisposing Factors

1) If trauma is detected as a predisposing cause then prophylactic smoothening of the sharp cups, restorations or prosthesis and protection from orthodontic appliances can at times be beneficial. [3]

2) If nutritional or vitamin deficiency is detected then replacement therapy can be of benefit. 14.9% patients with RAS have been found to be deficient of folic acid, vitamin B_{12} or iron in some studies and correction of these deficiencies results in favorable response in some patients.[3]

3) In a small proportion of patients with menstrually related RAS the disease can be controlled by appropriate hormonal therapy.[3]

4) If dietary factors or allergies are suspected. Then these factors should be identified and this may require the use of

elimination diet. After determination of the cause, the patient should be advised to avoid that agent e.g. in 3% of patients suffering from RAS a gluten-sensitive enteropathy is suggested. In these cases a gluten free diet and folate replacement are necessary to produce resolution.[3]

5) If stress is considered as a predisposing factor then its management has shown to benefit RAS patients. E.g. Relaxation and imagery training in RAS patients has shown to produce significant decrease in ulcer recurrence.[8]

Topical Therapy

Topical agents are the first line of treatment for RAS. They are effective, safe and economical.[1] A variety of topical agents have been used in RAS with variable success. The commonly used topical agents include topical analgesics, antimicrobials and glucocorticoids.

Topical Analgesics

Topical analgesics are widely employed in RAS for pain control.[14] There have been many topical anesthetic agents which have been used in RAS patients, these include:

Lidocaine HCl viscous 2%, Dyclonine HCl 0.5 to 1% , Diphenhydramine HCl elixin 12.5 mg/5 ml, Benzydamine HCl 0.15, 3% Diclofenac, Benzocaine20%, Milk of Magnesia.

Antimicrobials

Use of antimicrobial agents in RAS is intended to control microbial contamination and secondary infection.[1] A number of studies have reported efficacy of topical antibiotics (in terms of a reduction in duration of ulcers and/or pain relief). Primarily various tetracycline preparations, chlorhexidine gluconate preparations, and Listerine antiseptic mouth rinse have been used. Although the exact mechanism of using antibiotic agents in treatment of RAS remains unclear, it is hypothesized that a concentration of antibiotics high enough to inhibit bacterial flora at the site of the ulcer may be beneficial in accelerating ulcer healing and pain relief.

A wide variety of antimicrobial agents have been tried these include:

Chlorhexidine gluconate (0.12%-0.2%), Listerine Antiseptic mouth rinse, Tetracycline, Doxycycline, Mysteclin (tetracycline hydrochloride and amphoterecin), Penicillin G.

Topical Corticosteroids

Topical corticosteroids are probably the mainstay of RAS treatment.[22] They are effective in that they help reduce inflammation and, more specifically, to reduce exudation of leucocytes and formation of soluble inflammatory mediators, while helping to maintain cellular membrane integrity, inhibit phagocytosis and release of lysozymes from granulocytes and stabilize the membranes of lysozymes that contain hydrolytic enzymes.[23] Corticosteroids may also directly act on the T lymphocytes and alter the response of effector cells to precipitatants of immunopathogenesis.[1]

The commonly used topical glucocorticoids are[8]:

Creams and ointments

Triamcinolone acetonide (0.1% or 0.5%), Fluocinonide 0.05%, Betamethasone valerate 0.1%, Clobetasol propionate 0.05%

Elixirs

Dexamethasone elixir 0.5 mg/5 ml, Hydrocortisone hemisuccinate (0.25 mg)

Injections

Triamcinolone diacetate 25 mg/ml, Betamethasone sodium phosphate 6 mg/ul

The efficacy of these topical agents can be increased markedly if they are administered during the early phase of the ulceration (i.e. when lymphocyte activity is at its maximum). Clinicians should be cognizant of the potential of topical glucocorticoids to cause acute pseudo membranous candidiasis. However, the use of topical glucocorticoids will diminish the risk of suppressing the hypothalamic-pituitary adrenal axis system a frequent complication due to use of systemic glucocorticoids.[24] Topical glucocorticoids may also be helpful in patients with ulcers who are immunocompromised. HIV-infected patients with minor and herpetiform ulcers as well as some major lesions can experience resolution from topical glucocorticoids with out notable side-effects.[8]

Amlexanox

Amlexanox is 2-amino-7-isopropyl-5-oxo5H-(1)benzopyrano-pyridine-3-carboxylic acid also denoted as CHX3673. It has been shown to have both antiallergic and anti-inflammatory properties. The beneficial effects of 5% amlexanox oral paste in accelerating the healing of aphthous ulcers has been demonstrated in well controlled clinical studies.[25] Also no side effects have been reported following treatment with this agent.

Potassium Nitrate / Dimethyl Isosorbide (KNO_3/DMI)

KNO_3 has been used to treat aphthous ulcers. This remedy has lessened pain and made the healing period shorter. The problem with this approach is that it does not always penetrate the deeper basal layers of mucosa or skin. When Dimethyl isosorbide is added to KNO_3 hydroxyethyl cellulose gel, it enhances the capacity of KNO_3 to penetrate tissues. KNO_3 routinely and predictably promotes pain control and healing is hastened. It does this by inhibiting the CNS nerves from emitting and conducting pain, and the ANS from initiating an inflammatory response.

Sodium Cromoglycate Tooth Paste

Sodium cromoglycate has been used in treatment of RAS and is shown to cause reduction in pain and number of the lesions. Sodium cromoglycate is believed to act by stabilizing the mast cell membranes, and numerous mast cells have been demonstrated in RAS biopsy. The drug has been employed in lozenges and tooth paste form and has shown significant improvement in RAS patients, while a few studies have failed to show this effect.

Cromoglycic Acid

Cromoglycic acid has been shown to be effective in RAS and it acts mainly by causing reduction in pain. This action of CGA may be due to inhibition of release of pharmacological mediators in a possible 'second phase' immune component in the development of an ulcer, the one associated specifically with pain.

Carbenoxolone Sodium (Liquorice)

Liquorice derivatives have been widely used for their antiulcer and anti-inflammatory properties. The mechanism of action of the drug in RAS may be related to the antiviral activity or ulcer healing property of the drug similar to that seen in patients with peptic ulcer. Carbenoxolone sodium is a Liquorice derivative that has been used in managing RAS patients.

Prostaglandins

Prostaglandins are biologically active lipids, which the body produces from unsaturated essential fatty acids. They

mediate a host of biological effects, including modulation of inflammatory response. Some prostaglandin effects on mucosa are clinically useful in prevention of aphthous ulcers.

Azathioprine

Azathioprine is an extensively used immuno suppressive drug. The suppression of emigration of lymphocytes to the site of inflammation is a factor by which it can inhibit ulcer formation. The drug has been successfully used topically in treatment of skin disorders but when tried in aphthous ulcer patients it did not demonstrate any beneficial effects.

Cyclosporine

Topical cyclosporine therapy has been successfully tried for various oral mucosal disorders. The drug may exert local immunomodulatory effects in the oral cavity and hence finds use in various immune mediated disorders including RAS.

Hydroxyquinoline And Zinc Salts

Both hydroquinoline and zinc salts have long been used as antiseptics. The inhibition of glucose stimulated acid production by indigenous bacteria is achieved by hydroquinoline and Zn salts when combined with salivary peroxide system. A mouth wash containing Zn, H_2O_2 and hydroquinoline has also been shown to be beneficial in RAS patients.

Sucralfate

Sucralfate, which acts locally by binding with the proteins at the base of an ulcer to provide a protective covering has been suggested as a treatment for aphthous ulcers.

Systemic Therapy

Immunomodulators

Colchicine

Colchicine has been successfully used in RAS. Its exact mechanism of action is not known. However the drug prevents recruitment of polymorphonuclear cells and interferes with their microtubular function, this immunomodulatory action of the drug may be of benefit in RAS patients.

Pentoxifylline

Pentoxifylline is a methyl xanthine derivative and has an immunomodulating and anti-inflammatory action, which seem to be related, to the inhibitory effect of PTX on TNF- production which may be of benefit to RAS patients as the drug has been successfully used in treating RAS.

Azelastine

Azelastine is an immunomodulator and has been used in RAS patients. The drug causes suppression of leukocyte function, reactive oxygen generation and cytokines. The drug also increases resistance of epithelial cells to cell impairing circumstances.

Thalidomide

Thalidomide is an immunomodulator and inhibits the production of various cytokines (eg. TNF-) and has been shown to be effective in treatment of RAS patients.[1]

Azathioprine

Azathioprine is a purine analog and is currently used for its immunosuppressive properties. This drug is classified as an antipurine and acts to inhibit DNA synthesis and replication. The drug has been used in a wide variety of autoimmune diseases including RAS.

Dapsone

Dapsone has been found to be useful in managing RAS. The drugs effect on aphthous ulcers in patients with Behcet's disease is also well documented. Dosages of 50-100 mg have been used to suppress ulcer formation.[19]

Levamisole

Levamisole is now recognized as a compound that possesses a wide variety of immunological effects both in vitro and in vivo. Since, levamisole acts apparently as an immunosuppressant at prolonged doses and as an immunopotentiator at lower dosages or on intermittent administration, it has been designated as an immuno modulator.[26] In July 1990, United States FDA, approved levamisole as a helpful agent in selected autoimmune and inflammatory diseases. Levamisole has been demonstrated to improve symptoms in RAS patients. The drug can significantly reduce pain intensity, ulcer number, ulcer size, ulcer duration and frequency of ulcers in patients with RAS.[1]

Systemic Steroids

Systemic glucocorticoids in the form of prednisolone have been widely used for the control of a variety of acute and chronic oral inflammatory ulcerative diseases because of the anti-inflammatory and immuno-suppressive action. Systemic prednisolone therapy can be started at a dose of 1.0 mg/kg a day as a single dose in patients with severe RAU and should be tapered after 1-2 weeks.[1] Patients on a course of prednisolone have fewer if any ulcers while receiving treatment; however, the ulcers often recur on withdrawal of the steroid.[31] Because the long term use of prednisolone carries the risk of adverse effects it can be combined with another immunosuppressive agent.

An adequate therapeutic management should address both healing of ulcers present initially as well as prevention of new lesions. Present data indicates that currently available treatments for RAS are inadequate, and don't provide health care practitioners with a means by which they can cure the disease.[27] Analgesics, antimicrobials, corticosteroids and immunomodulator drugs have been individually and collectively used for treating RAS.[8] However, most of the available therapies are largely symptomatic and are either entirely empiric or based on the clinician's perception of the cause of the disease.

Other Therapies

Ultrasound

Low intensity ultrasound therapy has also been shown to be beneficial in RAS patients. The mechanism underlying the therapeutic response to this form of ultrasound has not been confirmed, although evidence supports a modification of the inflammatory response.[28]

Laser Therapy

Laser therapies have been successfully used in RAS. Clinical studies have focused on lasing the ulcer with the He-Neon or "soft" laser. CO_2 laser therapy has also been successfully used to treat RAS as it reduces or eliminates the pain and inflammation with normal would healing.[29]

Conclusion

Recurrent Aphthous Stomatitis (RAS) is an inflammatory condition of unknown etiology characterized by painful, recurrent single or multiple ulcerations of the oral mucosa.[1] RAS is the most common oral mucosal disease and is found in men and women of all ages, races and geographic regions.[8] The disease affects up to 20% of the population at sometime in their lives.[1] RAS has been a subject of considerable clinical and research attention. However, despite this the cause of RAS remains poorly understood, the ulcers are not preventable and the treatment is symptomatic.[8] The management of chronic patients with RAS remains a challenge, therefore the authors advocate use of various above mentioned therapies in combination while removing the predisposing factor for remission.

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Illustrations

Some Varied Clinical Presentations of RAS: