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Recurrent Aphthous Ulcers: A Review.

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***Abstract**: Aphthous ulceration is a recurrent and painful inflammatory process occurring in the oral cavity due to several predisposing etiologic factors.Trauma,microorganisms,immunology,allergy and nutritional deficiencies are the commonly implicated etiologic factors. Inspite of their higher prevelance,the etiopathogenesis of the condition still remains an enigma.The review presents the clinical features,diagnostic criteria,etiopathogenesis and current management protocols of this exacting condition.*

***Key Words:** Apthous ulcer, Pain ,Trauma ,Microorganisms*

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I. Introduction

Recurrent aphthous ulcers(RAS) is a condition seen from time immetorial.The first mention of this condition was made by Hippocrates (460-370 BC)who used the word "apthai"which means "to set on fire" or to "inflame"[1].Recurrent aphthous stomatitis (RAS ,aphthae, canker sores) is a common condition which is characterized by multiple recurrent small,round or ovoid ulcers with circumcised margins, erythematous halos and yellow or grey flora appearing first in childhood or adolescence[2].Ulcers usually exhibit moderate to intense pain with healing time of 10-14 days for common type and more than two weeks for severe type. Recurrence can occur in intervals within a year or over several years[3].

Epidemiology

Patil et.al[4] in a study of aphthous ulceration in Indian population found 705 of total 3244 patients present with RAS at time of examination giving an overall prevalence of 21.7% .Females (56.3%) were more affected than males (43.7%) with standard significance. Patients in the third (20.7%) and fourth decade (26.5%) were commonly affected. Aphthae may occur for the first time in childhood but the second decade is a peak period of RAS occurrence which usually decrease with age[5].

Clinical Features

Recurrent aphthous ulcers are extremely painful and show prodromal symptoms of tingling or burning before appearence of lesion.It can occur as one or several rounded painful ulcers at intervals of few days to few months in patients who are otherwise well[2].Stanley (1972)[6] classified RAS into three different clinical variants.

1.Minor recurrent aphthae is also known as Miculicz aphthae constitute 80% of recurrent aphthae and vary in size from 8 to 10 mm. It is seen in non keratinized mucosa like labial mucosa,buccal mucosa and floor of the mouth.Ulcers heal within 10 to 14 days without scarring

2.Major aphthae also known as Suttons disease or Periadenitis mucosa necrotica constitute 10-15 percentage of aphthous ulcers.Ulcers exceed 1 cm in diameter.Lips ,soft palate and fauces are involved. Ulcers persist upto 6 weeks and heal with scarring.

3.Herpetiform ulcers:Recurrent crop of ulcers upto 100 in number. Size is 2-3 mm which may coalese to form large ulcers lasting 10-14 days.More common in women.It does not exhibit typical viral prodromal symptoms of herpetic lesions.Herpetiform ulcers involve anterior part of mouth,lip,lateral and ventral tongue,floor of mouth and rarely on lip.

Etiopathogenesis

Trauma

Trauma to oral mucosa due to local anesthetic injection ,sharp tooth ,tooth brush injury and iatrogenic injuries may predispose to development of RAS[2].It has been shown that denture wearers are usually three times more prone to RAS compared to others[7].

Microorganisms

Various microorganisms are implicated as causative agents of RAS.Oral Streptococci was suggested as an important pathogen in recurrent aphthae either as a direct pathogen or as an antigenic stimuli in genesis of antibodies.L-form Streptococci initially typed as Streptococcus sanguis in recurrent aphthae was found to be Streptococcus mutans[2].A study by Hoover et.al (1986)[8] demonstrated low levels of cross reactivity of oral Streptococci and oral mucosal antigens and considered the reactivity to be specific and clinically insignificant. Helicobacter pylori,a gram negative,S- shaped bacteria usually associated with gastritis and chronic duodenal ulcers has been implicated in eitopathogenesis of RAS[9].A study by Porter et.al (1997)[10] which measured the levels of IgG antibodies against H.Pylori in patients with recurrent aphthae showed the frequency of H.Pylori was not elevated significantly in recurrent aphthae patients.The role of viruses have been explored in RAS cases.Sun et.al (1998)[11] used PCR,Slot blot and Southern blot hybridization to show possible presence of EBV-DNA in recurrent aphthae and suggested that pre ulcerative oral aphthous ulceration may be infected with EBV.Stevenson (1967)[12] showed a negative correlation of recurrent aphthae and lactobacillus activity.

Genetic Factors

Family history of aphthous stomatitis is seen in 24-36% of RAS patients[13].The presence of aphthae in parents significantly influences the risk of RAS development and course of disease in offspring.Risk of aphthae reaches 90% in patients with both parents affected compared to 20% in children with healthy parents[14].Alteration in cytokine metabolism including interleukins(IL-1β,IL-2,IL-4,IL_5,IL-6,IL-10,IL-12) ,Interferon-γ and TNF- α,serotonin transporter gene and endothelial nitric oxide synthetase gene was analyzed. Elevated concentration of m-RNA corresponding with IL-2,IFN-ϒ and TNF-α and decreased m-RNA levels corresponding with IL-10 was detected in aphthous patients[15].Certain HLA groups identified with RAS include HLA-A2,HLA-B5,HLA-B44,HLA-B12,HLA-B51,HLA-B52,HLA-DR2,HLA-DR7 and HLA-DQ series. Since no HLA is consistently associated with RAS,studies are inconclusive[16].

Immunologic Factors

Immunologic factors has often been implicated in etiopathogenesis of RAS.Savage et.al used monoclonal antibodies directed against T-lymphocyte surface antigens (OKT,OKT4 and OKT8) to investigate changes in T-cell sub population in RAS.Ulcerative lesions contained a large number of OKT8 positive suppressor/cytotoxic cells and a very small number of OKT4 positive cells supporting the role of lymphotoxicity in establishment of RAS.Bachtiar et.al[18] analysed propotions of CD3+(T cell),CD4+(helper T cell),CD8+(suppressor/cytotoxic cell),CD19+(B cell) and CD 16+/CD56+(NK cell) groups.RAS was associated with abnormal population of CD4+ and CD8+ cells.

Allergic Factors

Allergy has been suspected as a cause of RAS especially due to hypersensitivity to certain food substances. Foods like milk and milk products[19] ,almonds ,tomatoes and wheat flour are implicated in RAS.[20].Sequential elimination of milk,cheese and wheat has been found beneficial for some patients.Quian et.al[22] investigated the occurrence of RAS among college students and its potential effect on dietary habits in students at Beijing University of Chinese Medicine. They concluded that students using frequent carbonated beverages or had frequent thirst had a higher incidence of RAS while use of nuts afforded protection. A study to investigate the effects of sodium lauryl sulfate(SLS),a synthetic detergent in dentifrices on RAS patients for 3 months followed by dentifrice without sodium lauryl sulfate showed a statistically significant decrease in number of aphthous ulcers in patients using SLS free dentifrice.It is suggested that effect of SLS on the oral mucin layer with exposure of the underlying epithelium induces RAS[23].Another recent study showed that the number of ulcers and episodes did not differ between SLS free dentifrice and SLS containing dentifrice[24].

Nutritional Deficiency

RAS can also result from a nutritional deficiency particularly lack of iron,vitamin B3,vitamin C,folic acid or vitamin B12[25].Some nutritional deficiency can occur along with other diseases such as malabsorbtion syndrome or gluten sensitivity with or without enteropathy[26].Full hematologic screening of RAS patients should be done to identify latent deficiency states so that the underlying causes can be elucidated and corrected especially in vitamin B12 deficiency[27].

Psychologic factors

Stress has been proposed as an important cause of RAS.Gallo et.al in their study in RAS patients supported the role of stress in RAS patients[28].Psycological stress may act as a trigger or modifying factor rather than an emotional factor in RAS.Miller et.al[29] in a study of 1788 professional students from the University of

Pennsylvania showed prevalence rate of 48.3% in men and 57.2% in women during their period of study but decreased considerably once they became practicing professionals.

II. Allied Medical Conditions

Behchets syndrome

It is similar to RAS but with multiple system involvement including recurrent genital ulceration,ocular and cutaneous diseases and a range of renal,GIT,,joint and hematologic abnormalities.Both genetic and environmental factors are involved in development of Behchets syndrome.The disease is assumed to stem from an autoimmune response which in turn may be triggered by infection or other environmental agents in genetically susceptible individuals[30].

PFAPA syndrome

The syndrome of periodic fever,aphthous stomatitis,pharyngitis and cervical adenitis is the most common cause of periodic fever in childhood.Usually PFAPA syndrome resolves during adolescence but there is increasing evidence that the condition may persist into adulthood[31].

Sweet syndrome

Originally described by Dr.Robert Douglas Sweet,it is characterized by acute febrile neutrophilic dermatosis syndrome characterized by pyrexia ,elevated neutrophil count,nodules ,plaques,painful red papules and an infiltrate consisting of predominantly mature neutrophils in upper dermis.It is seen usually im middle aged females,50% of patients develop associated malignancy(AML)[32].

MAGIC Syndrome

MAGIC syndrome (Mouth and Genital ulcers with inflamed Cartilage) has been proposed to describe patient with clinical features of both relapsing polychondritis and Bechets disease[33].

HIV

In HIV patients,persistent,painful ulcers can occur on soft palate,buccal mucosa,tonsillar pillars or tongue with symptoms more severe than non HIV patients.RAS is usually delayed in patients with CD4+ lymphocyte count below 100 cells/mm3 but it can also be a pointer to an impending HIV infection[34].

Chrons disease

60% of patients with Chrons disease present with oral manifestations including chelitis,oral ulcerations fissuring and glossitis and this can be the first sign of disease in 5-10% cases[35].

Treatment

The treatment of RAS depends on the frequency ,number and size of ulcers.The treatment should be governed by the disease severity,frequency of occurence and medical history of the patient[36].Small lesions are usually treated by lidocaine 1% cream ,polidocanol paste and benzocaine lozenges.Mouth wash of Benzocaaine and Cetylpyridinium has shown good results.Other topical agents that can minimize patient discomfort include diclofenac,a NSAID or amelxanox paste which has been shown to decrease healing of minor apthae[37].Topical antibiotics such as tetracycline and their derivatives like minocycline and doxycycline in gel or rinse form often decreases the pain due to local inhibition of collagenases and metalloprotienaeses[38].Most widely used drugs in RAS is topical corticosteroids because it suppresses the pain,reduces healing time and eliminate symptoms.Triamcinolone acetonide ,Flucocinolone acetonide and Clobelastol propionate are used[39]. Pentoxifylline ,inhibitor of TNF-α and of neutrophil function and chemotaxis has been beneficial in patients with RAS.Due to several side effects especially in GIT,it should be used as a second line treatment option in patients that fail to respond to other therapies[40].Immunomodulators like thalidomide have been used for treatment of RAS at a dose of 50-100 mg/day and has shown complete remission in 85% of patients in a study.Thalidomide however exhibits many adverse effects like teratogenicity ,polyneuropathy ,drowsiness ,headache,nausea and gastric pain[41]. Levimasole ,another immunomodulator restores normal phagocytic activity among macrophages and neutrophils and modulates T cell mediated immunity.Drug dose of 150 mg,three times a week for six months reduce the number,size and frequency of attacks.Adverse effects include nausea,dysguesia and agranulocytosis[42].

For better management stratergies,RAS may be classified in three clinical presentations: TypeA,Type B and Type C.

Type A: Usually occur sporadically in a year with tolerable pain levels.The dietary history of the patient should be analysed.Hard foods,all types of nuts,chocolate,acid beverages ,alcohol and spicy foods should be

avoided.Predisposing factors like local trauma,tooth brush injury should be prevented and the patient adviced regarding this matter[43].

Type B: Episodes lasting 3-10 days occur monthly.The predisposing factors should be identified and controlled along with diet and habit modification.It is important to identify prodromic manifestations like itch or swelling and provide topical treatment as and when it occurs[43].

Type C: Chronic aphthae with painful episodes.While some lesions heal others develop and the patient is never free of lesions.Systemic therapy is usually indicated since topical therapy is unsuccessful[43].

III. Conclusion

Even though aphthous stomatitis is a widely studied lesion lot of grey areas exist in the etiopathogenesis and diagnosis of this condition.Even though topical and systemic medicaments are useful in controlling RAS symptoms, it often interferes in the well being of the patients.A treatment protocol may aid the clinicians in determining the appropriate treatment for the patient.

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