Recurrent Aphthous Stomatitis Caused by Food Allergy

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ABSTRACT

Reccurent Aphthous Stomatitis (RAS) is one of the most common oral lesions which occur either in single or multiple forms in oral mucosa. The mouth is subjected to a wide spectrum of antigenic agents, including foodstuff, and allergic reactions to such antigens may manifest in a number of diverse ways. Food allergy, however, has not been widely investigated as the cause of RAS. The main complaint of RAS typically is pain, and the main therapy is still corticosteroids, besides avoiding allergenic foodstuff. In RAS, there is often a genetic basis. More than 42 percent of patients with RAS have first-degree relatives with RAS. The likelihood of RAS is 90 percent when both parents are affected, but only 20 percent when neither parent has RAS, and it is also likely to be more severe and to start at an earlier age in patients with a positive family history.

The primary goals of therapy of RAS are relief of pain, reduction of ulcer duration, and restoration of normal oral function. The secondary goals include reduction in frequency and severity of recurrences and maintenance of remission. Diagnostic elimination diets are frequently utilized both in diagnosis and management of RAS caused by food allergy. Patients with RAS may have increased levels of $CD8^+$ T-lymphocytes and/or decreased $CD4^+$ T-lymphocytes. There may be a reduced percentage of "virgin" T-cells and an increased of "memory" T-lymphocytes. Patients with active RAS have an increased proportion of $\gamma\delta$ T-cells compared with healthy control subjects and RAS patients with inactive disease. The $\gamma\delta$ T-cells may play a role in ADCC and it is believed that $\gamma\delta$ T-cells play a role in immunological damages.

Preventive treatment is a consideration for patients with RAS caused by food allergy who report regular exacerbations of their condition. It focuses on dietary modifications, the earliest stage, the prodromal stage, and attempts to intercept ulcer development again by the use of topical immunosuppressant and particularly corticosteroids.

Key words: *recurrent aphthous stomatitis, food allergy.*

INTRODUCTION

Recurrent aphthous stomatitis or recurrent aphthous ulcers, frequently refered as canker sores, is one of the most common oral mucosal diseases encountered in children and adults. This chronic, incurable condition can be painful for the patient, making it uncomfortable to speak, eat or drink. It can also be frustrating for the patients and the clinicians to manage.[1,2] The cause of RAS is unkown and thought to be multifactorial with many triggers or precipitating factors. Patient factors include familial tendency or genetic predisposition, allergy, medications, hormones, stress or anxiety, and immunologic abnormalities.[3]

Recurrent aphtous stomatitis occures world wide and it affects 2 – 66 percent of the international population. In one study performed in Malaysia by Zain RB, from 11,697 randomly selected Malaysian, the average prevalence of RAS during oral examination was found 0.5 percent (64 subjects).[4] A short report in 1986 by Wright A, et al in Sheffield, found that among 11 patients with severe RAS, 6 patients responded to a dietary withdrawal dramatically within a week of avoiding the incriminated food and after prolonged and relentless periods of ulcerations, so that a causal relation the food seems likely.[5] A study between January and June 2004 in Turkey, performed by Gonul M, et al, on 27 patients with RAS and 25 patients without RAS as control with matching ages and socioeconomics, came with the result that the occurence of RAS was associated with eating several kinds of foods.[6] Sensitivity to foods, preservatives, or other agents has been indentified in 35 to 50 percent of patients with RAS, and the strict elimination diets resulted in improvement and/or resolution of otherwise persistent ulcers in 25 to 75 percent of patients. A study performed by Nolan A, et al in Sweden, showed that among 21 patients with RAS undertaking patch test using food substances considered clinically relevant,

there were 12 patient who gave positive results.[7]

In RAS, there is often a genetic basis. More than 42 percent of patients with RAS have first-degree relatives with RAS. The likelihood of RAS is 90 percent when both parents are affected, but only 20 percent when neither parent has RAS, and it is also likely to be more severe and to start at an earlier age in patients with a positive family history.[8] An increase in the frequency of the human leukocyte antigen types A2, B12, DR2, DR5, and A28 in Greek people, DR7 and MT3 in Sicilian people, and DRw9 in Chinese people has been noted in patients with RAS.[8]

PATHOPHYSIOLOGY

Pathologic observations of early RAS lesions provide circumstantial evidences for the thesis that there are immunopotentiating activities. The association between allergy and mucosal diseases, including RAS, may influence disease expression or severity in a number of ways: type I hypersensitivity, type III hypersensitivity, and type IV hypersensitivity or cell mediated damage.[9] A cell mediated immunopathogenesis has been suggested by the histopathogenesis appearance of early lesions of RAS which fulfills the histologic criteria of Coe, Feldman, and Lee for a delayed hypersensitivity reactions. There are at least 3 clusters of mononuclear cells per cross section perivascularly or perineurally, dispersed mononuclear cells in the dermis without obvious pattern, polymorphonuclear leukocytes constituting less than 5 percents of the inflammatory infiltrates, and absence of necrosis or smudging of the wall of venules.[10] The present evidence implies that a B-lymphocytes-mediated immunopathogenic mechanism with antibodies, immune complexes, antibody-dependent cel-mediated cytotoxicity (ADCC), and K (killer) cells possibly play key roles.[11]

Patients with RAS may have increased levels of $CD8^+$ T-lymphocytes and/or decreased $CD4^+$ T-lymphocytes. There may be a reduced percentage of "virgin" T-cells and an increased of "memory" T-lymphocytes. Patients with active RAS have an increased proportion of γδ T-cells compared with healthy control subjects and RAS patients with inactive disease. The γδ T-cells may play a role in ADCC and it is believed that ãä T-cells play a role in immunological damages.[12] There is an elevation of serum levels of IL-6 and IL-2R, and soluble intercellular adhesion molecules (ICAM), although their pathogenic significance remains unclear.[11]

In the pre-ulcerative phase of RAS, there is a local mononuclear infiltrate consisting initially of large granular lymphocytes (LGL) and T4 ($CD4^+$) helper-induced lymphocytes. The ulcerative phase is associated with the appearance of $CD4^+$ cytotoxic suppressor cells, but these are replaced by $CD4^+$ cells during healing. Polymorphonuclear lymphocytes (PMNL) also appear in the lesions. Their chemotactic function is normal and the phagocytic function is also not significantly defective.[11,12]

The aggregation of lymphocytes is probably mediated by the adhesion molecules- ICAM-1 and lymphocyte function-antigen-3 (LFA-3)- binding to their counterpart ligands LFS-1 and CD2 on lymphocytes. Intercellular adhesion molecule-1 is expressed on the sub-mucosal capillaries and venules, suggesting that it may control the trafficking of leukocytes into the sub-mucosa, while LFA-3 and its counterpart ligand CD2 are likely to be involved in T-cell activation in RAS.[11,12]

Human Leukocyte Antigen (HLA) class I and II antigens appear on basal epithelial and then perilesional cells in all layers of the epithelium in early phases of ulceration, presumably mediated by gamma interferon released by T-cells. Such MHC antigens may target these cells for attack by cytotoxic cells.[13] Activated mononuclear cells infiltrate the epithelium, especially the prickle cell layer, and are in close contact with apoptotic prickle cells, which they and PMNL sometimes phagocytose. Immune deposits do occur in lesional biopsy specimens, especially in the stratum spinosum, and there can be evidence of leukocytoclastic or immune complex vasculitis, leading to the non-specific deposition of immunoglobulin and complements. It seems probable that immune-complex-mediated tissue damage is of secondary importance in the etiopathogenesis of RAS.[11,12]

Serum immunoglobulin levels are generally normal, though increases in serum IgA, IgG, IgD, and IgE have all been reported in RAS. Serum C9 have been reported to be raised in some patients and together with elevated serumlevel of $â_2$ microglobulin, may represent a non-specific acute phase response.[14-16]

CLINICAL PRESENTATION

The accepted classification of RAS is based on three parameters of lesion size, duration, and the present of residual scarring. Each lesion tends to follow a set presentation and course, albeit with variation in the duration and size of lesions. Clinically, patients and clinicians are often able to map the sequence of presentation through to resolution into following stages: prodromal-symptoms but without any

visible clinical sign, pre-ulcerative-initial presentation usually erythema and slight edema, ulcerative-formation of the epithelial defect, healing-symptom abatement and progressive healing, and remission-no evidence of lesions.[17] The distribution site of ulceration in the patients with RAS are 45 percent at the internal labial mucosa, 19 percent at tongue, 19 percent at gingival, 11 percent at buccal, 3 percent at palatal, and 3 percent at larynx.[18]

Recurrent aphthous stomatitis is one of the most painful oral mucosal inflammatory ulcerative condition and can cause pain on eating, swallowing, and speaking. Three clinical presentation of RAS: minor aphthous stomatitis (Mikulicz's aphthea or mild aphthous ulcers), major aphthous stomatitis (periadenitis mucosa necrotica recurrence or Sutton's disease), and herpetiform ulcers.[18,19]

Minor recurrent aphthous stomatitis is the most common variety, affecting about 75 – 80 percent of RAS patients and recent study places its frequency rate at 17.7 percent in general population.[20] It usually involves every non-keratinized mucosa of the oral cavity (labial, buccal, the floor of the mouth, and the cenral or lateral surface of the tongue). The lesion appears as discrete, painful, shallow, covered by a yellow-grey pseudomembrane (fibrinous exudates), and surrounded by an erythematous halo. The ulcers usually are smaller than 8 to 10 cm in diameter and tend to heal within 10 to 14 days without scarring, but it heals more slowly than other oral wounds, possibly because of the intensive lymphocytic infiltrates may play a role in this process.[20,21] (**Figure 1**)

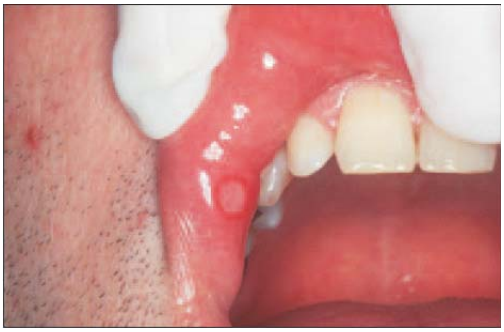

Figure 1. Minor aphthous stomatitis[19]

Major recurrent aphthous stomatitis is a rare and severe form of RAS. It often produces coalescent ulcers, and tends to involve mucosa overlying minor salivary glands. Approximately 10 to 15 percent of RAS cases are major RAS.[19] It usually appears after puberty. The lesions are oval, painful, with raised clear defined margins, usually are larger than 1 cm in diameter, and tends to involve mucosa on lips, soft palate, and throat. The prodromal symptoms are more intense, and the ulcers usually are deeper, larger, and last longer than those with minor ones. Fever, dysphagia, and malaise sometimes can occur early in the disease process.[20] (**Figure 2**)

Herpetiform aphthea is the least common variety of RAS. It approximately about 5 to10 percent of RAS. It is characterized by painful ulcers, 1 to 3 mm in diameter, and occurs in crops of 5 to 100 ulcers at a given time anywhere on the mucosa. They tend to fuse and produce larger ulcers lasting 10 to 14 days. It tends to appear in women and has a later onset of age than other types of RAS.[19] (**Figure 3**)

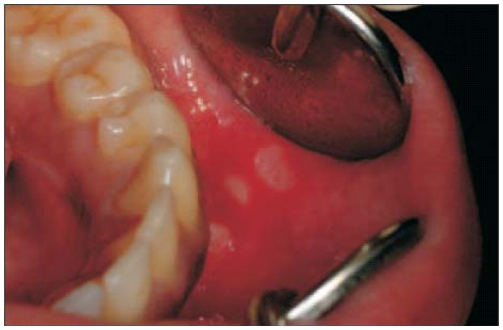

Figure 2. Major aphthous stomatititis[19]

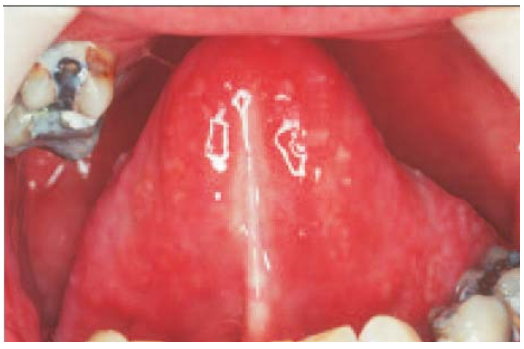

Figure 3. Herpetiform aphthea[19]

DIAGNOSTIC PROCEDURES

The diagnosis of RAS caused by food allergy is made on the basis of clinical history and physical examination, diagnostic laboratory tests include biopsy and cytology for the ulcers that last for more than 3 weeks, and culture or other specific tests for rolling out infectious agents such as herpes simplex virus, cytomegalovirus, or HIV.[20]

The clinical history and physical examination are the foundation for the diagnosis of RAS caused by food allergy. The first goal is to rule out whether the patient's reaction has an immunologic or non-immunologic basis. Immunologic reactions include immediate type or IgE mediated reactions and cell-mediated food hypersensitivity. A clinical history should be taken also to rule out other ulcerative disorders and conditions such as Chron's disease, celiac disease, neutropenia, HIV infection, and Bechcet's syndrome.[20,21]

Complete blood cell count, hematinic estimation, and test anti-endomysial antibodies are indicated to rule out immune disturbances, vitamin and iron deficiencies and malabsorption. Specific IgE testing against causative food has become vital to the evaluation of food allergy. It is providing quantitative values that can aid in predicting with high certainty the presence of clinically significant food allergy, and thereby decreasing the need for food challenges.[21,22]

Skin prick testing, in conjunction with the history and physical exam, diagnostic skin testing is a cornerstone in the evaluation of food allergy and it is a tool to investigate type I hypersensitivity involvement. Skin prick testing which can only be suggested on the presence of clinical food allergies with negative predictive accuracy is greater than 95 percent.[22] Skin patch testing is also a useful diagnostic tool in the food allergy to investigate the type IV hypersensitivity involvement. It is used where a history of food allergy exists but the skin prick testing result is negative. In this case, skin patch testing may be of help in order to make specific diagnosis. Recent advances have allowed for the identification and cloning of specific food epitopes. The identification of specific IgE epitopes with immunoblot analysis may theoretically be used to better define the likelihood of clinical reactivity and/or natural history of food allergy than traditional allergen specific IgE measurement.[22-24]

The double blinded, placebo controlled food challenge (DBPCFC) has been long considered for the diagnosis of food allergy and as a "gold standard" test from which to judge the diagnostic performance characteristics of clinical history, skin testing, and IgE antibody serology.[23] The selection of the foods to be tested in are generally based on history and/or skin prick testing. The practical approach to diagnosing food allergy is an exclusion diet, eliminating all foods implicated by history and/or skin prick testing, which is conducted for 1 to 2 weeks in suspected IgE mediated. If no improvement is noted, it is unlikely that food allergy is involved.[21,23]

THERAPY

The primary goals of therapy of RAS are relief of pain, reduction of ulcer duration, and restoration of normal oral function. The secondary goals include reduction in frequency and severity of recurrences and maintenance of remission.[24] Diagnostic elimination diets are frequently utilized both in diagnosis and management of RAS caused by food allergy. Once certain foods are suspected of provoking allergic disorders, they are completely omitted from the diet. The success of these diets depends on the identification of the correct allergens, the ability of the patient to maintain a diet completely free from all forms of the offending allergen, and the assumption that other factors do not provoke similar symptoms during the same period.[24]

Treatments of RAS caused by food allergy consist of topical and/or systemic treatments. In topical treatment, topical corticosteroids remain the mainstay of the treatment. There are many available topical corticosteroids with different potency, and all can reduce symptoms but can not stop the recurrent of the ulcers (**Table 1**).[19] The major concern of the use of topical corticosteroids is adrenal suppression with long-term and/or repeated applications, but there is evidence that 0.005 percent fluocinonide in adhesive paste and betamethasone-17-valerate mouthrinse do not cause this problem. The patients with corticosteroid use should be monitored for yeast superinfection. Another topical treatment is 5 percent Amlexanox in prodromal stage, that has "triple action" in the form of preventing recurrence, decreasing healing time, and accelerating pain resolution.[24,25]

For the recalcitrant ulcers, systemic corticosteroids can be used, including the administration of intralesional injections of corticosteroid such as betamethasone,

Table 1. Examples of readily available topical corticosteroids[19]

Steroid	UK trade name	Dosage every six hours
Low potency		
Hydrocortisone hemisuccinate pellets	Corlan	2.5 mg pellet dissolved in mouth close to ulcers
Medium potency		
Triamcinolone acetonide 0.1% in carmellose gelatin paste	Adcortyl in Orabase	Apply paste to dried lesions
Betamethasone phosphate tablets	Betnesol	0.5 mg; use as mouthwash
High potency		
Beclomethasone (Beclomethasone) dipropionate spray	Becotide 100	1 puff (100 micrograms) to lesions

dexamethasone or triamcinolone to enchange or boost the local response, thus allowing for shorter systemic treatment. Levamisole was a possible treatment because it has wide immune-stimulatory effects and there have been several studies of its efficacy with 100-150 mg of levamisole daily for 2-3 months. The possible side effect of levamisole is the decreasing of white blood cell count.[25] Thalidomide therapy should be considered when patients have episodes of profound ulceration, because of its immune-modulating and angiogenesis-inhibiting activities. The 200 mg of thalidomide for entire 4 weeks will heal enhance the ulcers completely. The possible side effects of thalidomide are teratogenicity, polyneuropathy, and mood change. Another systemic agents that can be used with their side effects can be seen in **Table 2**.[25-26]

Table 2. RAS therapy: Common adverse effects of drugs to be used systemically[25]

Drug	Possible adverse effect(s)
Colchicine	Painful gastrointestinal symptoms, diarrhea, male infertility
Dapsone	Methemoglobinemia
Levamisole	Decreased white blood cell count
Pentoxifylline	Nausea
Thalidomide	Teratogenicity, polyneuropathy, mood change

CONCLUSION

Preventive treatment is a consideration for patients with RAS caused by food allergy who report regular exacerbations of their condition. It focuses on dietary modifications, the earliest stage, the prodromal stage, and attempts to intercept ulcer development again by the use of topical immunosuppressant and particularly corticosteroids. Clinical experience shows that many patients with RAS caused by food allergy will enter a phase of complete remission following the medium use of corticosteroid mouthrinse on daily basis initially and then on a minimal maintenance dose over one to two months.[17,25]

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