ISSN 3060-4567

RECURRENT APHTHOUS STOMATITIS – ETIOLOGY, SERUM AUTOANTIBODIES, ANEMIA, HEMATINIC DEFICIENCIES, AND MANAGEMENT

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ABSTRACT. *Recurrent aphthous stomatitis (RAS) is one of the most common oral mucosal diseases characterized by recurrent and painful ulcerations on the movable or nonkeratinized oral mucosae. Clinically, three types of RAS, namely minor, major, and herpetiform types, can be identified. RAS more commonly affects labial mucosa, buccal mucosa, and tongue. Previous studies indicate that RAS is a multifactorial T cell-mediated immune-dysregulated disease. Factors that modify the immunologic responses in RAS include genetic predisposition, viral and bacterial infections, food allergies, vitamin and microelement deficiencies, systemic diseases, hormonal imbalance, mechanical injuries, and stress. Our previous study found the presence of serum gastric parietal cell antibody, thyroglobulin antibody, and thyroid microsomal antibody in 13.0%, 19.4%, and 19.7% of 355 RAS patients, respectively. We also found anemia, serum iron, vitamin B12, and folic acid deficiencies, and hyperhomocysteinemia in 20.9%, 20.1%, 4.8%, 2.6%, and 7.7% of 273 RAS patients, respectively. Therefore, it is very important to examine the complete blood count, serum autoantibody, hematinic, and homocysteine levels in RAS patients before we start to offer treatments for RAS. Because RAS is an immunologically-mediated disease, topical and systemic corticosteroid therapies are the main treatments of choice for RAS.*

Introduction

Recurrent aphthous stomatitis (RAS) is one of the most common oral mucosal diseases characterized by recurrent and painful ulcerations on the movable or

ISSN 3060-4567

nonkeratinized oral mucosa. The prevalence of RAS in the general population varies from 5% to 66% with a mean of 20%.[1] Kleinman et al.[2] reported a point prevalence of 1.23% and a lifetime prevalence of 36.5% for RAS in 40,693 USA school children. In Taiwan, the prevalence of RAS is 10.5% in the general population.[3]

Classification of recurrent aphthous stomatitis

Three types of RAS, namely minor, major, and herpetiform types, are recognized.[1] Minor RAS is the most common type that occurs in 80% of RAS patients. The oral ulcerative lesions of minor RAS measure between 3 mm and 10 mm in diameter. They usually arise from the nonkeratinized oral mucosae with the buccal and labial mucosae being affected frequently. The lesion may be preceded by an erythematous macule with the prodromal symptoms of burning or stinging for a few hours to one or two days. Then, the oral ulceration appears and is subsequently covered by a yellow-white fibrinopurulent pseudomembrane. The oral ulcers heal without scarring in 7–14 days. Although the minor RAS lesion is small, the pain is often out of proportion for the size of the ulceration.[1]

The oral ulcerative lesions of major RAS measure from 1 cm to 3 cm in diameter. They usually take 2–6 weeks to heal and may lead to scarring. The labial mucosa, soft palate, and tonsillar fauces are most frequently involved. In severe cases, the repeated scarring processes may result in a limitation of mouth opening.[1]

Herpetiform RAS has the greatest number of oral lesions and the most frequent recurrences. Their oral ulcerative lesions vary from 1 mm to 3 mm in diameter and some of them may coalesce into larger irregular ulcerations. The oral ulcerations heal between 7 and 10 days. The herpetiform RAS has a female predilection and a typical onset in adulthood. Herpetiform RAS oral lesions may be confused with those of herpes simplex virus (HSV) type 1 (HSV-1 or HHV-1) infection. However, the herpetiform RAS lesions are commonly found on nonkeratinized oral mucosae and the HSV-1 lesions are often present on keratinized oral mucosae such as gingiva and hard palate.[1]

Etiology of recurrent aphthous stomatitis

RAS belongs to the group of chronic, inflammatory, ulcerative diseases of the oral mucosa. Up to date, the etiopathogenesis of this disease remains unclear; however, it is considered to be multifactorial.[4] The results of previous studies indicate that genetically mediated disturbances of the innate and acquired immunity play an important role in the disease development. Factors that modify the immunologic responses in RAS include genetic predisposition, viral and bacterial infections, food allergies, vitamin and microelement deficiencies, systemic diseases, hormonal imbalance, mechanical injuries, and stress.[4]

For the genetic predisposition, the positive family history of the RAS was reported in 24%–46% of RAS cases.[5, 6] The patients with a positive family history of RAS suffer more frequent recurrences and more severe course of the disease compared to those with a negative RAS family history.[7, 8, 9] Furthermore, in both RAS and Behcet's disease, the risk of the disease development was higher in monozygotic twins than in dizygotic twins,[9, 10] The genetic risk factors that modify the individual susceptibility to RAS include various DNA polymorphisms in patients, especially those related with the alterations in the metabolism of interleukins (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12), interferon (IFN)-γ, and tumor necrosis factor (TNF)-α, can modify the individual susceptibility to RAS.[4] Our previous studies showed a strong association of HLA-DRw9 with RAS in Chinese patients and a strong association of anti-epithelial cell antibodies with HLA-DR3 or DR7 phenotype in RAS patients.[11, 12]

In addition, our previous study also demonstrated that the phenotype frequencies of HLA-DR5, -DRw8 and -DQw1 as well as the haplotype frequencies of HLA-DR5/DQw1 and HLA-DRw8/DQw1 in patients with the mucocutaneous type of Behcet's disease are significantly higher than those in RAS patients. Moreover, the relative risks of HLA-DR5/DQw1 and HLA-DRw8/DQw1 haplotypes are greater than the relative risks of HLA-DR5, HLA-DRw8, and HLA-DQw1 antigens. These results suggest that some specific HLA-DR/DQ haplotypes may be more important than the individual HLA-DR and HLA-DQ phenotypes in the disease

shift from RAS to the mucocutaneous type of BD.[13] In RAS patients, higher incidences of HLA-A33, HLA-B35 and HLA-B81,[14] HLA-B12,[15] HLA-B51,[16] HLA-DR7 and HLA-DR517, 18 are observed when compared to healthy control subjects.

Bacterial (Streptococcus oralis, Helicobacter pylori) and viral (HSV, varicella-zoster virus, cytomegalovirus, and adenoviruses) antigens have been reported to be potential factors that may modify the immunologic response and subsequently induce recurrent aphthae in predisposed subjects. However, the results of these studies are ambiguous and conflicting.[4] In addition, Greenspan et al.[19] concluded that neither cell-mediated hypersensitivity to streptococcal or viral antigens nor cross-reactivity between oral mucosal and streptococcal antigens is likely to play a role in the pathogenesis of RAS.

Deficiencies of hematinics (iron, vitamin B12, and folic acid) and zinc have been demonstrated in some RAS patients, but it has not been well explained why the hematinic deficiencies may influence on the course of immune response in RAS.[4] We tried to explain why anemia and hematinic deficiencies might cause the occurrence of RAS.[20] Deficiencies of iron, vitamin B12, or folic acid may lead to anemia in RAS patients. Because RAS patients with anemia have reduced capacity of the blood to carry oxygen to oral mucosa, finally resulting in atrophy of oral mucosa.[20] Moreover, iron is essential to the normal functioning of oral epithelial cells,[21] and both vitamin B12 and folic acid play important roles in DNA synthesis and cell division.22, 23 Oral epithelial cells have a high turnover rate. Therefore, deficiencies of iron, vitamin B12, and folic acid may result in oral epithelial atrophy. Atrophic oral epithelium in hematinic-deficient patients may explain why some patients with deficiencies of hematinics are prone to have RAS.[20] Furthermore, high blood homocysteine level (due to deficiencies of mainly vitamins B6 and B12 and folic acid) in some RAS patients may result in an elevated frequency of thrombosis in the feeding arterioles that supply the oral epithelial cells.24, 25, 26, 27, 28 This in turn leads to a breakdown of oral epithelium and finally produces an oral ulceration. Taken these together, anemia, hematinic deficiencies, and a high blood homocysteine level can decrease oral epithelial barrier and thus increase the

frequency of RAS occurrence.[20] In addition, Volkov et al.[29] found that oral vitamin B12 supplementation can improve the symptoms and signs of RAS regardless of the initial serum levels of vitamin B12. This finding also confirms the role of vitamin B12 deficiency in the development of RAS.

Some previous studies mentioned that exposure to some specific ingredients (e.g., chocolate, gluten, cow milk, preservatives, nuts, and food coloring agents) may induce RAS.[4] However, a previous double-blind study did not confirm the role of specific food ingredient allergy in the development of RAS.[30]

Some patients with systemic diseases, especially the Behcet's disease, inflammatory bowel diseases (Crohn's disease, ulcerative colitis), celiac disease, and immunodeficiency virus (HIV) disease, are prone to have RAS.[1, 4] Moreover, RAS is one of the criteria for the diagnosis of Behcet's disease.[1] Patients with inflammatory bowel diseases or celiac disease are more likely to have the complications of nutrient deficiencies due to the malabsorption of nutrients. Moreover, these patients tend to have autoimmune reactions that result in oral aphthous ulcerations.[4] HIV-infected patients are immunocompromised and also have more chance to develop RAS due to the decrease of CD4 lymphocytes and the increase of CD8 lymphocytes.[3]

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