

Role of hematinic and zinc deficiencies in recurrent aphthous stomatitis: A Review

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ABSTRACT Hematinic has an essential role in the human body. Suppose its deficiency can cause oral disorders such as aphthous stomatitis. Recurrent aphthous stomatitis is the most common oral lesion. It has three types of clinical appearance, namely minor, central, and herpetiform. The main components of hematinic are folate, vitamin B12, folic acid. Apart from hematinic, another nutrient that can correlate with recurrent aphthous stomatitis is zinc. This review explains the relationship between hematinic deficiency and zinc associated with recurrent aphthous stomatitis.

KEYWORDS: Hematinic Deficiency, Recurrent Aphthous Stomatitis, Zinc

INTRODUCTION

The oral cavity has linked to general health status. Changes that occur in the oral cavity may be an earlier sign and symptoms of underlying systemic diseases.¹ Recurrent aphthous stomatitis (RAS) is the most common oral lesion in the general population that is characterized round or oval, yellowish pseudomembranous cloth, halo erythematous, and may involve both keratinized or non-keratinized mucosa.²⁻³ Recurrent aphthous stomatitis affects approximately 20% of the general population, and the incidence varies from 5% to 50% based on socioeconomic and ethnic groups studied.⁴ The etiology of RAS is unknown, but several factors can predispose to the lesion occurring. Several factors reported RAS diseases, etc. genetic, trauma, microbial, smoking cessation, immunological factors, stress, allergy, and nutritional factors such as hematinic factors.⁴⁻⁶ In this article, we would like to explain more about hematinic deficiencies and RAS association.

Classification of Recurrent Aphthous Stomatitis

The clinical appearance of the RAS has three forms, minor RAS (more than 85% of cases), significant RAS (10% of cases), and herpetiform

(10% of cases). All these forms of RAS significantly impact the patient's quality of life because of pain.⁵ RAS has prodromal burning sensation at least 24 to 48 hours that precede the onset of ulceration. Minor RAS has a small diameter (less than 1 cm in diameter), major RAS has a larger ulcer (more than 1 cm di diameter), the healing process slowly and often causes scarring. The herpetiform manifests as multiple clusters of ulcers that can affect all parts of the oral mucosa. Besides the size, these classification criteria include depth of lesions, the number of lesions in one episode, location, and ulcer duration.⁵⁻⁶

The lesion may precede by an erythematous macule with prodromal, stinging, or burning sensation within a few hours in one or two days. After that, ulceration appears, and it is covered by pseudomembranous yellow-white fibrinopurulent. The lesion heals in 7-14 days. Major RAS take 2-6 weeks to heal and may lead to scarring. The herpetiform RAS has more than ten ulcers that coincide with 1 mm to 3 mm in diameter, and some ulcers may coalesce to large irregular ulcers and heals in 8-10 days.⁵⁻⁸

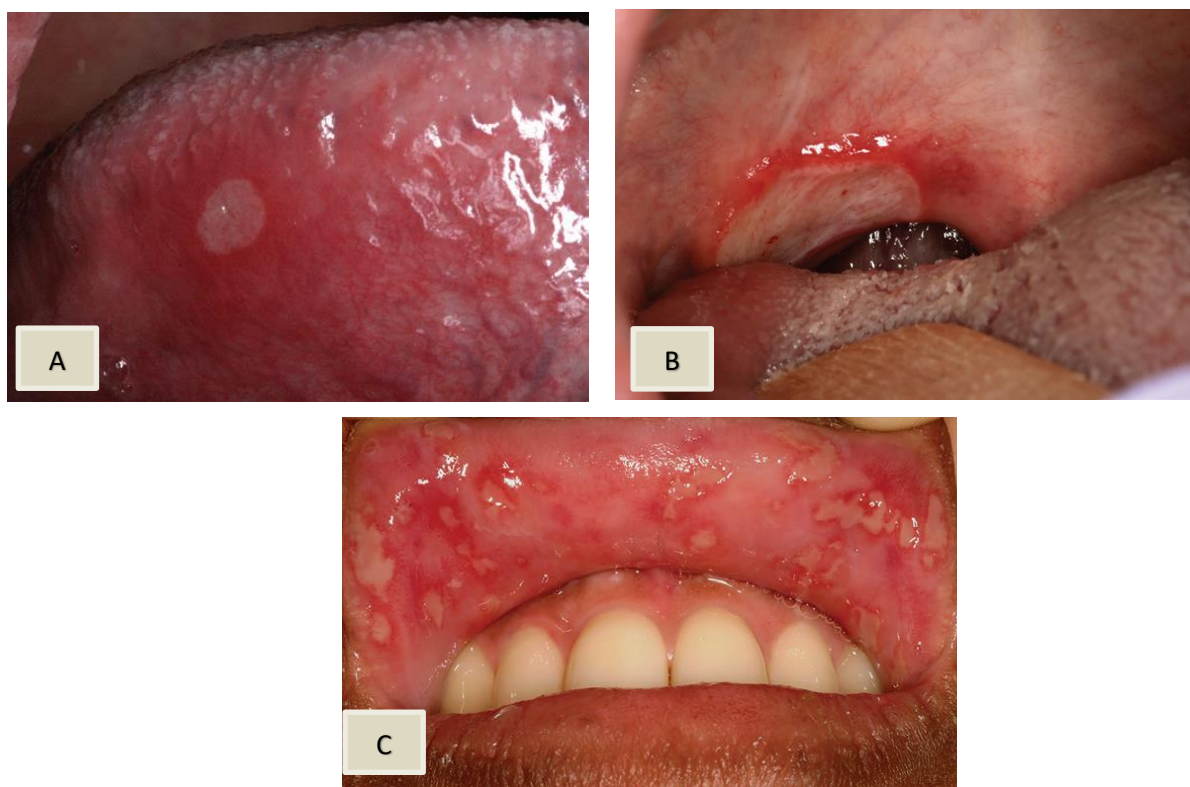


Figure 1. Clinical appearance of recurrent aphthous stomatitis; A: Minor RAS, B: Major RAS, C: Herpetiform RAS (adapted from Neville 2019)²⁴

Hematinic Deficiency, Zinc, and Association to Recurrent Aphthous Stomatitis

Patients with recurrent aphthous stomatitis have been associated with a nutritional deficiency in 5%10% of cases. These nutritional factors may be associated with other diseases such as gluten sensitivity with or without enteropathy. Patients with RAS that have nutritional deficiencies may have immune abnormalities and disruption of the immune system. Hematinic deficiencies are lacking folate, vitamin B12, and ferritin.^{1,8-9} Zinc is an essential factor for biological mechanisms in the human body. Zinc act as a co-enzyme and also acts as an activator for almost 100 human enzymes. Zinc plays a role in the metabolism of protein, lipid, and carbohydrates, regulate DNA and RNA synthesis, modifies the growth and development of epithelium.⁶

The role of zinc in the pathogenesis of RAS is the ability of zinc to stimulate the production of monocyte, IL-1, IL-6, and TNF- α . When patients have a low level of zinc, the cytokine production becomes disrupted, and the low levels of zinc serum correlate with the production of Th1. Th1 plays an essential role in the etiopathogenesis of RAS.⁷⁻⁸ Slebioda Z et al. (2017) reported that serum zinc

concentration did not affect RAS development because when observed from 75 patients, only 10.7% of patients had low serum zinc levels.⁸

Hematinic is needed by the body to help the process of hematopoiesis. The main components of hematinic are serum iron, folate, and B12. Lack of these components can cause anemia, which affects oxygen intake. A low level of oxygen causes atrophy of oral mucosa. Suppose the patient with iron deficiency is affected by the normal function in the oral cavity. The cells will more quickly develop atrophy or produce an immature epithelial layer.¹⁰⁻¹²

Iron has a vital function for organs, such as the hemoglobin synthesis process and oxygen transport throughout the body. It is also an essential element for hemoglobin synthesis. The total amount of iron absorbed by the body in a healthy individual is 1-2 mg, which can compensate for the daily iron loss of 1 mg in men and 1.5-2 mg in women during the menstrual period. Iron deficiency is due to inadequate iron intake, inhibited absorption, or chronic blood loss such as menstruation. Besides, the conditions such as pregnancy, vegetarian diet, consumption of acid-reducing drugs, peptic ulcers, chronic bleeding caused by colon cancer, uterine cancer, gastrointestinal polyps, and hemorrhoids.

The iron deficiency can be accompanied with or without anemia and may progress to anemia¹³⁻¹⁵

Lack of iron can reduce the immune system against infection by reducing bacteriocidal activity against bacteria by PMNs and leukocytes.^{13,14} Another impact is a decrease in the supply of oxygen and nutrients to the cells to inhibit the differentiation and formation of epithelial cells. This process makes the oral mucosa thinner as the epithelium's keratinization disappears, and the epithelium becomes more irritant.¹⁶

Folate (Folic acid and vitamin B9) plays an essential role in DNA synthesis. Therefore oral epithelial turnover is depending on folic acid. Recurrent aphthous stomatitis may manifest in 18% to 28% of patients with B12, folic acid, and iron deficiencies.¹⁷ Ossa (2020) reported two cases of recurrent aphthous stomatitis as symptoms of hematinic deficiency. Two patients with multiple recurrent oral ulcers and from laboratory examination showed iron deficiencies.¹⁶ Jornet (2013) reported the association between RAS and iron, ferritin, vitamin B12, and folic acid deficiency showed that 14.14% hematinic deficiencies in the RAS group compared to 6.39% in the control group ($p=0.086$)¹⁷

Vitamin B12 deficiency can cause megaloblastic anemia and impaired immunity, causing buccal mucosa and tongue. Vitamin B12 plays an essential role in hemoglobin DNA synthesis and cell development. Vitamin B12 deficiency is caused by malabsorption and enteritis disorders or ileal reactions. The deficiency of vitamin B12 leads to pernicious anemia. Folic acid has an essential role in enhancing the regeneration and healing response to an oral ulcer.¹⁸ The precise mechanisms of how hematinic deficiencies can impact RAS still unknown. It can affect the epithelial atrophy, negative impact on the epithelial barrier, and mucous membrane integrity damage speculated on the primary mechanism.¹⁹

CONCLUSION

Recurrent aphthous stomatitis is common in oral lesions. It is one of the earliest signs of hematinic and zinc deficiency. Oral and laboratory

Sun A et al. (2015) reported the relationship between anemia or hematinic deficiencies. RAS showed that the hemoglobin, serum iron, folic acid, and vitamin B12 were detected in 20-43%, 19-36%, 2-6%, and 4-12% of RAS patients, respectively. A patient with anemia and has low hemoglobin levels can reduce the blood's capacity to carry oxygen to oral mucosa and result in mucosa atrophy. Therefore, atrophic oral epithelium in a patient with hematinic deficiencies are prone to have recurrent aphthous stomatitis.^{19,20}

Laboratories Investigation

Laboratory investigation in recurrent aphthous stomatitis aims to exclude underlying diseases. In cases that suggested hematinic deficiency, laboratory investigation can be confirmed, such as complete blood count. A comprehensive blood count examination for assessing hemoglobin, hematocrit, erythrocyte index (Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC)), and red blood cell distribution width. Besides that, serum ferritin, total iron-binding capacity, serum iron, zinc, folic acid, and vitamin B12 can help to rule out particular condition associated with RAS, such as hematinic deficiency.²¹

Normal range of hematocrits in adults is 40-50% (man) and 35%-45% (women), hemoglobin range 13-18 g/dL (man) and 12-16 g/dL (women), erythrocytes $4.4-5.6 \times 10^6$ cells/mm³ (man) and $3.8-5.0 \times 10^6$ cells/mm³ (woman). Normal MCV is 80-100 fL. If the result below the normal range, it is considering iron deficiency conditions.²² If a result more than 100 fL, it is considering to folate deficiency conditions. The normal of MCH is 28-34 pg/cells. The normal of MCH is 28-34 pg/cells. High MCH an indicator of microcytic anemia also if lower MCH sign for macrocytic anemia. Meanwhile, MCHC normal range is 32-36 g/dL.^{23,24}

examinations can help to improve the management of RAS conditions.

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