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Atypical manifestation of an afta in the hard palate: A case report

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Abstract

Recurrent aphthous stomatitis is the most common oral mucosal disorder and its etiology is multifactorial but still not clear. Most of the recent articles underline that the immunological factors play an important role in the etiopathogenesis of recurrent aphthous stomatitis (RAS). Nicotine can prevent the occurrence of RAS modulating the expression of pro-inflammatory and anti-inflammatory cytokines. There is evidence that autoimmune disease are related to RAS as autoimmune thyroiditis. This case report is a description of a rare clinical condition of recurrent aphthous stomatitis in a patient suffer from hypothyroidism.

Keywords: recurrent aphthous stomatitis, autoimmune diseases, hypothyroidism, nicotine, ulcerations, Hashimoto's syndrome

1. Introduction

Aphthous stomatitis is a common disease, idiopathic in nature, with recurrent painful aphthous ulcers on the non-keratinized oral mucous membranes. Aphthous stomatitis affects approximately 20% of the general population. It is slightly more common in girls and women, instead race does not appear to be a factor in the disease^[1]. Age of onset may be during childhood, but more commonly in the second and third decade of life, becoming less common with advancing age. Aphthous ulcers occur on non-keratinized oral mucosae such as along the labial or buccal surfaces, soft palate, the floor of the mouth, the ventral or lateral surface of the tongue. The ulcers of aphthous stomatitis are present as well-circumscribed lesions with central necrotic ulcer with gray, fibrinous exudate surrounded by an erythematous halo. The most common form of aphthous stomatitis are minor aphthous ulcers that are less than 1 cm in diameter, round or oval in shape and heal typically within 7-14 days^[2]. Major aphthous ulcers are deeper than 1 cm, may have irregular raised borders, and can take many weeks or months to heal, sometimes with scarring. Herpetiform aphthae are characterized by multiple, small (2-3 mm) and painful ulcers which tend to coalesce and form ulcers of larger size. They usually heal within 7-10 days without leaving any sequelae^[1, 2]. Since, the non-keratinized mucosa is more commonly involved, this type of lesions are seen on the soft palate, an important point which differentiates it from herpetic stomatitis that involves chiefly the keratinized part of the mucosa^[3]. In this case report we present an unusual manifestation of RAS in the hard palate in a patient suffering from hypothyroidism.

2. Case Report

A 36-year-old woman was referred to our clinic with a complaint of a burning sensation due to multiple aphthous lesions. She went to our observation with a diagnosis of RAS for which she resulted affected for 4 years. The patient reported positive medical history of hypothyroidism, in particular she has Hashimoto's thyroiditis, also known as chronic lymphocytic thyroiditis, diagnosed 1 year before the appearance of RAS. The patient assumes Levothyroxine 125 mcg (1/day) as a pharmacologic treatment for Hashimoto's thyroiditis. Laboratory tests including a blood count analysis were performed to determine the erythrocyte sedimentation rate, serum b12, red cell folate and anti-endomysial autoantibody levels of vitamin b and iron all of which showed normal results. She does not suffer of infective pathologies as HIV and hepatitis C and present no hematologic disorders, nutritional deficiencies, vesiculobullous disease or other infections. The other aspects of the patient's medical history were insignificant.

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No family medical history is relevant. She referred us that she had smoked moderately (5-10 cigarettes per day) for 5 years but in the last six months she stopped smoking. She did not use nicotine replacement treatment to quit smoking.

Clinical examination of the oral cavity has revealed the presence of several aphthous ulcers in the tip of the tongue (figure 1), in alveolar mucosa (figure 2), in the cheek (figure 3) and a single ulcer in the hard palate (figure 4). The patient refers to us that she has never presented aphthous ulcers in the hard palate.

The consistency of the base of the ulcer has been evaluated by palpation and the dimension assessed with a probe.

We carried out a palpation of the cervical lymph nodes, no signs of hypertrophy.

The patient has never suffered from herpes simplex type 1 but has had an episode of genital herpes two years ago.



Fig 1: Single ulcer in the tip of the tongue more than 10 mm covered by a grey fibro-membranous slough with erythematous halo and a straight edge



Fig 2: single ulcer in the left alveolar mucosa with a size less than 10 mm with circumscribed margin and yellow floor



Fig 3: ulcer in the right mucosa of the cheek, irregular edges and a erythematous halo with fibrin bottom, greater than 10 mm



Fig 4: single ulcer minor than 10mm, in the hard palate. The tissue surrounding the ulcer is erythematous

3. Discussion

The clinical feature of RAS is that it occurs on non-keratinized mucous membranes because the keratin layer acts as a chemical and mechanical barrier against antigens, microbial agents and trauma [4]. On the other hand, non-keratinized mucosa is more permeable to bacteria, virus and antigens and this is because RAS is more frequent in the lining mucosae [4]. To our knowledge, this is the first case report of a patient present an aphthous ulcer in the keratinized mucosa of the hard palate. *Immunological features of RAS and autoimmune diseases* Etiological factors implicated in the occurrence of RAS are local trauma, nutritional deficiencies, bacterial and viral infections, immune and endocrine disturbances and genetic factors [1]. RAS pathophysiology seems to be associated also with a disorder in immunomodulation [5]. The immune-pathogenesis in RAS has been reviewed 14 years ago in which authors affirm that the ulceration results from the activation of a cell-mediated immune response [6]. T lymphocytes, that seem to be the predominant cells in RAS, produce TNF-alfa and other cytokines that lead to epithelial cell necrosis and ulceration [7]. In particular, data suggest that the dominant cells of the

inflammatory process are T lymphocytes (80%) with an increment in the expression of TNF-ALFA, IL-2 and IFN- γ and decrement in the expression of IL-4, IL-5 and IL-10 that are anti-inflammatory cytokines [2]. Autoimmune disease related to RAS are Crohn's disease, Behcet's disease, celiac, systemic lupus erythematosus, lichen planus, linear IgA bullous dermatosis and Wegener's granulomatosis [1]. However, a recent article underlines that thyroid autoimmunity could be associated with recurrent aphthous stomatitis proving that the frequency of thyroid autoimmune-related problems was higher in patients with RAS [8]. Our patient suffers from Hashimoto's disease. Hashimoto's disease is an autoimmune disease in which the thyroid gland is gradually destroyed due to a combination of environmental and genetic factors. The thyrocyte destruction is carry on by the activation of CD8 + T-cells in response to cell-mediated immune response affected by CD4+ T cells (Helper T-lymphocytes) [9]. The same T-helper Type 1 cytokines involved in the autoimmune pathogenesis of Hashimoto's disease are associated with the etiopathogenesis of RAS [8]. The immunological factors play an important role in the etiopathogenesis of RAS. The author hypothesizes that sensitised T lymphocytes may attack against the oral mucosa that lead to epithelial cell death and cause aphthous ulcerations [8]. Moreover, increased amounts of IL-2, TNF-ALFA and IFN- γ were found in the serum of patients with autoimmune thyroiditis. All of these findings corroborate the hypothesis of a correlation between RAS and autoimmune thyroiditis and the important role of autoimmune disease in the etiopathogenesis of RAS. *Immunological features of RAS and the role of nicotine*

The patient was a moderate smoker and in the last 6 months she stopped smoking. She not used any smoking cessation medications as nicotine replacement therapy (NRT). After quitting smoking she reported to us a ulcerations in the non-keratinized oral mucosa and a ulceration in the hard palate.

Recurrent aphthous stomatitis rarely occur in smokers and a multitude of articles demonstrates that the incidence of RAS is lower in smokers compared to non-smokers [4, 10].

The explanation of this clinical observation is caused by direct and indirect factors. In the first case, smoking induces tissue keratinization which, in this way, is less permeable to antigens, bacteria and more resistant to trauma [4].

It has been hypothesized that nicotine has a protective role in the occurrence of RAS.

Nicotine and its metabolites decrease the levels of pro-inflammatory cytokines as TNF-alfa, IL-1, IL-6 and increase anti-inflammatory cytokines as IL-10 [11]. In addition nicotine and cotinine, its metabolite, reduce circulating levels of immunoglobulins causing immunosuppression and reduction of inflammatory response [4].

In literature, we found that even the articles that studied the correlation between smoking habit and RAS underline that the immunological mechanisms are involved in the development of the aphthous lesions [4, 11, 12]. Actually, Nicotine can activate the nicotinic acetylcholine receptors on macrophages reducing the production of TNF-alfa and IL-1 and 6 [13]. Nicotine may also activate the hypothalamus-pituitary-adrenal axis as Sopori et al hypothesize, inducing the production of glucocorticoids and activation of the autonomic nervous system to reduce the level of inflammation [14].

Smokers experience an increase of RAS upon cessation of this habit [10, 15, 16] and 40% of patients developed mouth ulcers, mostly in the first 2 weeks [15].

Our observation confirms that mouth ulcers are common

results of stopping smoking and ras manifestation affects 2 in 5 quitters [10, 17] as the study of Chen and McRobbie affirm.

In this clinical case, smoking may partially protect the mucosae on the onset of aphthae and quitting smoking may have led to the presence of this palatine disease.

We can consider all of these findings to partially explain why an aphthous ulcer may occur in the keratinized mucosae. Palatal ulceration is a consequent of a loss of tissue, both the epithelium and the connective tissue and may involve also keratinized mucosa. Only the major (more than 10 mm) and the herpetiform variants are seen on the palate but usually in the soft palate.

Our patient not use any Nicotine replacement therapy. A considerable number of articles demonstrate that patients under NRT therapy have lower incidence of RAS [17-19].

4. Conclusion

RAS is the most common oral mucosal disorders however its etiology remains unclear.

With this case report, we want to underline that many studies have investigate the immunological role in the etiopathogenesis of RAS. Lesions are in fact a consequence of immunological cytotoxicity of T-helper type 1 that lead to increase of pro-inflammatory cytokines and a decrease of expression of anti-inflammatory cytokines. Nicotine has a preventive role on the onset of RAS due to its down-regulation of pro-inflammatory cytokines in favor of anti-inflammatory cytokines.

Based on these considerations, it may be worth developing a strategy that, by inducing tissue keratinization, reduces the frequency and duration of lesions in patients with RAS.

In addition we want to underline that T Helper type 1 cytokines may be the common immunological features causing RAS and autoimmune thyroiditis. However, there is a need for new studies that can detect relationships between autoimmune diseases and RAS.

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