

APHTHOUS ULCERS AS A MULTIFACTORIAL PROBLEM

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SUMMARY – Recurrent aphthous stomatitis (RAS) is a disorder characterized by recurrent ulcerations limited to the oral mucosa. Many specialists and researchers in the domain of oral medicine and other fields do not recognize a single disease in RAS, but several pathologic states with similar clinical characteristics. Even though the real cause is unknown, there are some predisposing factors such as anemia caused by the lack of iron, folic acid and vitamin B, neutropenia, local trauma, emotional stress, metabolic disorders, hormonal disorders and chronic diseases, which cause immunodeficiency. This disease can appear in three clinical forms: small aphthous ulcers, large aphthous ulcers and herpetiform aphthous ulcers. The treatment of this type of disorder involves local or systemic use of corticosteroids, immunostimulants and vitamin therapy. Due to the association of aphthous ulcers with various other diseases, cooperation among multiple fields of medicine and a multidisciplinary approach are necessary.

Key words: *Aphthae; Recurrent aphthous stomatitis; Oral cavity; Etiology*

Introduction

Recurrent aphthous stomatitis (RAS) is a disorder characterized by recurrent ulcerations limited to the oral mucosa. Many specialists and researchers in the domain of oral medicine and other fields do not recognize a single disease in RAS, but several pathologic states with similar clinical characteristics. The possible etiologic factors in RAS include immune disorders, hematologic diseases, hypovitaminoses and nutritional deficiencies, allergy, psychological disorders, and others. RAS appears in approximately 20% of the general population, its frequency ranging from 5% to 50% in particular ethnic and socioeconomic groups¹.

RAS is classified according to clinical characteristics in three clinical forms: small aphthous ulcers (aphtha minor), large aphthous ulcers (aphtha maior,

Sutton's disease, periadenitis mucosa necrotica recurrens), and herpetiform aphthous ulcers (aphthae herpetiformis). Small aphthous ulcers, which appear in more than 80% of patients, are less than 1 cm in diameter and heal without a scar. Large aphthous ulcers are more than 1 cm in diameter, take longer time to heal (up to a month) and leave scars. Herpetiform aphthous ulcers are rare forms of RAS and are considered a separate clinical entity, which occurs in the form of multiple small erosions that affect the coating mucosa.

Etiology

Once it has been considered that RAS is a form of recurrent herpes simplex virus (HSV) infection, so some still mistakenly call it "herpes". Numerous studies conducted during the past several decades have confirmed that HSV is not the causative agent of RAS, which is additionally corroborated by the fact that the specific and effective antiviral treatment used in HSV has proved useless in the treatment of RAS². The association of RAS with other herpes viruses,

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such as *Varicella zoster* and *Cytomegalovirus*, is still unclear and a subject of numerous researches^{3,4}.

In recent times, RAS is discussed as a clinical syndrome that occurs through the effect of several factors (Table 1). The most important etiologic factors are heredity, mineral and vitamin insufficiencies, allergy, hematologic and immune diseases⁵.

Of all the presumed causes, the best documented is heredity. It has been determined that 30%-40% of patients with RAS have positive family history of RAS⁶. Miller *et al.* studied 1303 children from 530 families and showed that children of RAS positive parents had an increased predisposition to develop this disease⁷. According to research reports, children whose parents are RAS positive have 90% chance to develop RAS, whilst the children of healthy parents have only 20% probability to develop this disease⁸. Numerous studies (offering more evidence speaking for the hereditary etiology of the disorder) have detected specific HLA antigens in RAS patients, especially in certain ethnic groups⁹.

In some patient groups with RAS, the possible causative factors are mineral and vitamin insufficiency, such as the lack of serum iron, folate or vitamin B12, and zinc, and their frequency is estimated at 5%-15%¹⁰. The results have shown that in 75% of patients with RAS, clinical improvement occurs after replacement treatment of the lacking minerals and vitamins¹¹. It is possible that nutritional deficiency is

a consequence of malabsorption syndromes, such as celiac disease, which should also be examined during diagnostic procedure¹².

Numerous researches of RAS etiology have focused on immune disorders. Earlier works have pointed to an autoimmune disorder or hypersensitivity to microorganisms of the oral cavity, such as *Streptococcus sanguis*¹³. Later researches, with the help of sophisticated immunologic tests, have increasingly proved the role of cellular cytotoxicity dependent on antibodies and disorders of a subpopulation of lymphocytes¹⁴⁻¹⁶. Thomas *et al.* demonstrated increased T-lymphocyte cytotoxicity against oral epithelial cells in RAS patients¹⁴. Studies by Pedersen *et al.* and other authors demonstrated changes of the CD4:CD8 lymphocyte ratio or a disorder in the function of numerous cytokines in the skin and mucosa^{17,18}. In peripheral blood of patients with RAS, a predominance of Th1-cytokines and a decrease in the number of CD4(+)/CD25(+high) regulatory T lymphocytes have been determined, indicating activation of primarily Th1-cytokine immune response¹⁹. Decreased phagocytic functions of salivary and peripheral blood neutrophils have also been proven in RAS patients in comparison to healthy subjects²⁰. However, further research is necessary to determine immune changes in RAS patients.

Also, it has been shown that an allergic reaction to food, especially to cow's milk, takes part in RAS

Table 1. The most significant characteristics of recurrent aphthous stomatitis

Etiology	Related systemic diseases	Therapy
<ul style="list-style-type: none"> - Heredity - Deficiency of vitamins and minerals - Immune disorders - Food allergies - Physical trauma of mucosa - Psychological stress and anxiety 	<ul style="list-style-type: none"> - Behçet's disease (oral/perianal/genital ulcers + eye inflammation + arthritis + skin lesions) - Reiter syndrome (oral changes + polyarthritis + nonspecific inflammation of urogenital tract and intestinal mucosa + ocular changes + mucocutaneous lesions) - MAGIC syndrome (oral/genital ulcers + polychondritis) - Sweet syndrome (oral ulcers + papules and nodules on skin of the head, neck, and extremities) - PFAFA syndrome (elevated temperature + aphthous ulcers + pharyngitis + adenitis) - Cyclic neutropenia - Primary/secondary immunodeficiency 	<p>Local:</p> <ul style="list-style-type: none"> - Neutral preparation, e.g., Orabase - High/low-potent local steroid preparation - Anti-inflammatory agents (amlexanox, benzydamine) - Local tetracyclines, etc. <p>Systemic:</p> <ul style="list-style-type: none"> - Systemic corticosteroids - Immunosuppressants - Appropriate replacement therapy (where necessary) - Laser, etc.

etiology²¹. In cases of refractory forms of the disease, the effectiveness of an elimination diet has been proven in patients with suspect or proven food allergy, such as to cow's milk, cheese, grains and flour²². It has been proven that 33.3% of RAS patients show positive allergic reactions to vanillyn²³. Sodium lauryl sulfate (SLS), a detergent present in tooth pastes, is also mentioned as one of the possible causative agents of RAS²⁴. However, other studies have shown that the application of tooth pastes without SLS does not significantly affect the development of aphthous ulcers²⁵.

In addition, researches on the effect of smoking on RAS were conducted and showed that quitting smoking increased the frequency and intensity of RAS²⁶. However, more recent researches show that the protective effect of smoking is only observed in heavy smokers who smoke more than 20 cigarettes *per* day or longer than 5 years. Still, no significant association between smoking intensity or duration and clinical severity of RAS lesions has been shown²⁷.

According to some researches, a trauma of oral cavity is one of the most frequent triggers. So, RAS can be triggered by physical trauma, such as the one caused by abrasion by a toothbrush, laceration by a sharp or abrasive food (such as toast, chips, and muesli), a bite, or tooth or brace loss. Also, other factors, such as chemical irritation or thermal injury, can lead to ulceration. In addition, gastrointestinal disease should be examined, for example, celiac disease or gluten enteropathy, intolerance to gluten, can also be the cause of RAS²⁸. The role of *Helicobacter (H.) pylori* as a causative agent of RAS remains controversial, although the relationship between *H. pylori* and RAS has been suggested. Because of the histologic similarities between peptic ulcers and RAS and the identified role of *H. pylori* in peptic ulcer, the possibility of bacterial involvement in the progression of RAS has been suggested, but the results obtained did not confirm these assumptions²⁹. Other possible etiologic factors of RAS include psychological stress, anxiety, and others.

Clinical Characteristics

The first appearance of RAS most commonly occurs during the second decade of life and can be

catalyzed by lesser trauma, menstruation, upper respiratory system infections, or contact with certain foods. The disease begins with prodromal sensation of burning, 2 to 48 hours before the appearance of ulcers. During this initial period, usually local erythema develops. In several hours, small white papules appear, which ulcerate and gradually increase within the next 48 to 72 hours. In RAS, the individual lesions are round, symmetric and shallow (similar to viral ulcers, but without the remainder of epithelium on the lesion edges, which can be noticed after vesicle ruptures) in comparison with the diseases with irregular ulcers (erythema multiforme, pemphigus and pemphigoid)³⁰. Frequently, multiple lesions are present, whose size, number and frequency vary. Lesions appear most commonly on the cheek and lip mucosa, but do not appear on keratinized mucosa, on hard palate and gingival mucosa. In milder forms of RAS, lesions reach the size of 0.3 to 1.0 cm, begin to heal within a week, and heal completely without a scar in 10 to 14 days³¹.

Depending on the size, number and appearance, aphthous ulcers can be classified in three clinical forms: small or minor aphthous ulcers, large or major aphthous ulcers, and herpetiform aphthous ulcers. Small or minor aphthous ulcers are up to 1 cm in diameter, there are several of them simultaneously, and they heal spontaneously within 7 to 10 days, with no scars (Fig. 1)³². Large or major aphthous ulcers are greater than 1 cm in diameter and less in number than small aphthous ulcers (Fig. 2)³². Predisposing locations for the occurrence of large aphthous ulcers are the lip, soft palate and pharyngeal mucosa, and



Fig. 1. Minor aphthous ulcer³².



Fig. 2. Major aphthous ulcer³².



Fig. 3. Herpetiform aphthous ulcers³².

they heal up to a month leaving a scar. Major aphthous ulcers frequently appear in human immunodeficiency virus (HIV)-positive patients, which is explained by a disorder of immunoregulatory abilities and potentiated with HIV disease. Herpetiform aphthous ulcers are the rarest form characterized by a large number of smaller ulcers whose size is several millimeters in diameter, which appear predominantly in the anterior part of oral cavity, most frequently on the vestibule, lip, tongue and sublingual mucosa (Fig. 3)³². These are distributed over larger surfaces of the mucosa and have been named herpetiform, although the only connection to the HSV is their name.

Namely, it is important that aphthous ulcers exclusively appear on less keratinized, coating oral mucosa, and never on the gingiva, hard palate or transitional mucosa (like HSV). Most RAS patients have between 2 to 6 lesions in every episode of the disease, and such episodes occur several times *per year*. This disease is very unpleasant, even in the mild, minor form, and is a real disability for persons with serious and frequent lesions, especially if they appear in the form of large, major aphthous ulcers, where a large surface of the mucosa can be covered with deep and painful ulcers that can merge together. Lesions are excruciating and create problems with speaking and swallowing. They can last for months and consequently are misdiagnosed, as they may be similar to squamous cell carcinoma, chronic granulomatous disease, drug reaction or pemphigoid. Lesions heal slowly and leave scars, which can result in decreased mobility of the uvula and the tongue, and damage to parts of the mucosa.

Diagnosis

RAS is the most common cause of recurrent ulcers of the oral cavity and is diagnosed by exclusion of other conditions. Detailed history and clinical examination should help differentiate RAS from other diseases. So, RAS should be differentiated from primary acute lesions (viral stomatitis), chronic multiple lesions (pemphigoid), and other possible sources of primary recurrent ulcers (connective tissue disease, drug reactions and skin diseases). It is important to examine potential lesions on the skin, eyes, genitals, and the exiting part of the colon, especially if the patient himself mentions these symptoms. Laboratory tests should be done in all cases of disease exacerbation, that is, its appearance after age 25. It is necessary to obtain biopsy of the mucosa in case of suspicion of a granulomatous disease (such as Crohn's disease or sarcoidosis), or if precancerous state, cancer or pemphigus/pemphigoid is suspected^{30,31}.

In patients with a more severe form of aphthous ulcers, one should determine the levels of iron, folate, vitamin B12, ferritin, serum zinc, and exclude connective tissue disease. Patients should also be referred to an internist to exclude malabsorption syndrome, food allergy, gluten-sensitive enteropathy (celiac disease), etc.²². Also, it is necessary to examine the possibility of HIV infection because these patients are predisposed to develop large aphthous ulcers. Thereby, a multidisciplinary approach is necessary³¹.

The influence of drugs as the causes of oral ulcers is also possible, particularly in differential diagnosis of RAS. Thereby, direct contact between drugs and

oral mucosa may induce chemical burn or local hypersensitivity, or sometimes drug-induced oral ulcerations, possibly with cutaneous or systemic manifestations. Thus, oral ulcerations following the symptoms of burning mouth, metallic taste, dysgeusia or ageusia are strongly suggestive of a pharmacological origin. Most of the drugs able to induce solitary oral ulcerations are commonly prescribed in rheumatology, cardiology, psychiatry, etc.³³. There is also the possibility of oral manifestations with drug-induced leukopenia, e.g., due to analgesics, antibacterial agents, phenothiazines, antithyroid and cytotoxic agents, carbamazepine, etc. Cyclic neutropenia is a rare cause of recurrent oral ulceration and periodontitis that most frequently starts in infancy or childhood. During neutropenic episodes, the most common symptoms are fever and oral ulceration.

It is significant that aphthous ulcers exclusively appear on less keratinized, coating oral mucosa, and never on the gingiva, hard palate and transitional lip mucosa (as in HSV infection). Because the appearance of RAS is possibly one of the first signs and characteristics of multiple disorders (e.g., Behçet's disease and Reiter syndrome), it is recommended to pay attention to other disease symptoms (ocular, genital, arthritic and others). Thus, RAS is usually the first sign of Behçet's disease, the ulcers may precede other symptoms by several years, and the patients usually have perianal and genital ulcers, which are deeper and more painful. Recurrence of aphthous ulcers is possible in Reiter syndrome (an autoimmune, recurrent, nonsuppurative polyarthrititis with nonspecific inflammation of urogenital tract and intestinal mucosa, ocular changes and mucocutaneous lesions)². RAS can sometimes be a manifestation of other systemic diseases such as the mouth and genital ulcers with inflamed cartilage (MAGIC) syndrome, Sweet syndrome, periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome, and others⁶. Oral ulcers similar to aphthous ulcers are possible in Sweet syndrome (febrile neutrophilic dermatosis), which appear idiosyncratically or with numerous conditions (malignant carcinomas, infections, systemic disorders, drugs) in the form of confluent skin papules and nodules, with possible pustules and bullae. The PFAPA syndrome is a rare clinical syndrome of unknown etiology, which usually occurs in children.

When finding recurrent oral ulcers, on differential diagnosis it is also necessary to consider skin diseases such as erythema multiforme, pemphigus and pemphigoid, drug eruptions, contact reactions, squamous cell carcinoma, and infectious diseases, such as lesions caused by HSV, Cocksackie stomatitis, and syphilis (ulcus durum)^{30,31,34}. In addition to this, it is necessary to consider granulomatous diseases (e.g., Crohn's disease, sarcoidosis).

Treatment

Although the majority of RAS cases spontaneously enter remission, it is necessary to treat the patients because the disease is very unpleasant. Most commonly used RAS therapy are local corticosteroids, which decrease pain and duration of ulcers, but have no effect on future occurrence of new lesions.

Therapeutic approaches for RAS depend on disease severity. In mild cases with 2-3 small lesions, protective therapy with preparations that have the ability of adhesion to oral mucosa (for example, Orabase) is sufficient. If there is pain accompanying small lesions, it can be removed by use of local anesthetics or local diclofenac. In patients with more developed disease, local steroid preparations (such as hydrocortisone, fluocinonide, betamethasone, triamcinolone or clobetasol) can be used to cover the lesions, to decrease the size of ulcers and to shorten the time of healing. They are applied 2-3 times *per* day (after meals and before bedtime), most frequently mixed in Orabase, which prevents quick washout of the medicine through saliva and improves therapeutic effect due to longer contact with larger lesions. Thereby, hydrocortisone and triamcinolone preparations are popular because neither causes significant adrenal suppression, but they often fail to stop recurrence. On the other hand, betamethasone, fluocinonide, fluocinolone, fluticasone and clobetasol are more potent and effective, but they carry the possibility of some adrenocortical suppression and predisposition to candidiasis³⁵. Longer contact with large lesions can also be achieved by the application of pieces of gauze soaked for 15-30 minutes in local steroids.

Anti-inflammatory agents can help and a spectrum of topical agents such as benzydamine and amlexanox may decrease the time necessary for healing of RAS lesions. Thus, amlexanox paste and local tetracyclines

can be applied as solutions for the mouth (250 mg capsule in 10 mL of water as a solution for mouth rinsing) or soaked in gauze. On doing so, caution is necessary when locally applying tetracyclines because they are contraindicated in children younger than 12 years due to their effect of tooth discoloration. However, topical tetracyclines may reduce the severity of ulceration, but they do not alter the recurrence rate. Refractory large aphthous ulcers demand intralesional/perilesional corticosteroid instillation. It is also necessary to maintain good mouth hygiene, mouth solutions on the basis of chlorhexidine or triclosane being of help.

Chlorhexidine gluconate mouth rinses reduce the severity and pain, but not the frequency of ulceration.

When RAS does not respond to the mentioned local therapy and measures, it is necessary to consider systemic therapy, for example, immunomodulators under physician control, who estimates the potential benefits against the risks of application concerning the side effects of these medications.

Few, if any, of other medications used for RAS have undergone serious scientific evaluation³⁵. These include transfer factor, gamma-globulin therapy, sodium cromoglycate lozenges, dapsone, colchicine, pentoxifylline, levamisole, colchicine, azathioprine, prednisolone, azelastine, alpha 2-interferon, cyclosporin, deglycerinated liquorice, 5-aminosalicylic acid (5-ASA), prostaglandin E2 (PGE2), sucralfate, diclofenac, aspirin, etc. Thalidomide 50-100 mg daily is effective against severe RAS, although ulcers tend to recur within 3 weeks, but adverse effects dissuade most physicians from its use (teratogenicity, neuropathy, and others).

Aside from the supervising dentist and family medicine specialist, on administering therapy specialists who monitor patients for the possible side effects and who adequately respond to their occurrence should be involved. Research on the effectiveness of laser on RAS lesions demonstrated faster pain decrease and complete lesion regression in 75% of patients, in comparison to patients on corticosteroids³⁶.

It is also necessary to correct the potential causative factors or systemic disorders that could be in the background of RAS. If the patients are predisposed to develop RAS, it is necessary to warn them not to traumatize oral mucosa while brushing the teeth (by using soft toothbrushes with a small head), and avoid hard

and sharp food and other traumas of the mucosa. In case that oral hygiene products contain SLS, it is necessary to change them. In patients with proven deficiency of iron, folate, vitamin B12 or zinc, appropriate replacement therapy should be introduced. If an association with a certain type of food has been observed, it is necessary to avoid it and possibly undergo allergologic testing (skin tests)³⁴. In patients whose aphthous ulcers occur cyclically with menstrual cycles or as a reaction to the hormonal system established by oral contraceptive, it should be discontinued or switched to another one. It is necessary to exclude drugs that are a potential cause of RAS occurrence. Also, it is required to treat any systemic diseases related to oral aphthous ulcers.

Discussion

Aphthous ulcers or recurrent aphthous ulcers, recognized by the occurrence of round or oval recurrent painful ulcers on the oral mucosa, are characteristic of the disease. According to literature data, they affect every fifth person at least once in their lifetime. Although the disease is of a benign character, the greatest challenges are subjective disturbances which appear and recur. Apart from other complications, it should be noted that RAS can sometimes lead to facial edema or elevated temperature, or even difficulty with swallowing, speaking or chewing. This can be partially attributed to the usual specific localization of aphthous changes on the mucosa, which is involved in many functions such as chewing, speaking, swallowing, thus causing painful speech and mastication.

The diagnosis of aphthous ulcers is usually established on the basis of a characteristic clinical picture and history, and subsequently, a wider work-up is undertaken to examine the possible association with some other disease. In the diagnostic procedure, it is significant that RAS lesions are round, symmetric and shallow (similar to viral ulcers, but without the remainder of epithelium on the lesion border, which can be observed after vesicle rupture), by which they differ from the diseases with irregular ulcers (e.g., erythema multiforme, pemphigus and pemphigoid). It should be emphasized that the appearance of RAS may be linked to some systemic disease, and sometimes with the appropriate work-up some related disease or syndrome can be discovered. Also, in case of

precancerous state or carcinoma in the differential diagnosis, biopsy is indicated or excision of the change with histopathologic analysis, as well as in non typical changes of granulomatous disease, pemphigus, pemphigoid, etc.

Due to the association of manifestations of aphthous ulcers with various other diseases, cooperation between a number of specialties and a multidisciplinary approach are necessary. So, the topic has been researched and written about by oral pathologists, oral surgeons, immunologists, dermatologists, ENT specialists, pediatricians, gastroenterologists, allergologists, rheumatologists, infectologists, and various other specialties. Because the occurrence of RAS is possibly one of the first signs and features of multisystem disorders, in patients with RAS it is recommended to always pay attention to other related symptoms (primarily ocular, genital and arthritic, and others). So, for example, RAS may be the first sign of Behçet's disease, with the possible existence of ulcers several years before other symptoms. Also, the possibility of Reiter syndrome should be examined, which includes changes on multiple organs and changes in the oral cavity. Additionally, RAS can sometimes be a manifestation of some rarer syndromes, such as MAGIC, Sweet and PFAPA syndromes, and others. Also, there is a possibility of a rare condition, the PFAPA syndrome, which is a clinical syndrome of unknown etiology and usually occurs in children.

On the differential diagnosis, one should keep in mind the association with skin changes and the possibility of a primarily dermatologic disease, such as Sweet syndrome (febrile neutrophilic dermatosis), which can be an idiopathic disease or secondary to numerous conditions like malignant carcinomas, infections, systemic disorders, drugs, etc. On finding recurrent oral ulcers, on the differential diagnosis it is also necessary to consider skin diseases, which can have a similar clinical picture, such as erythema multiforme, pemphigus and pemphigoid. Additionally, in oral ulcers, the possibility of squamous cell carcinoma should be examined, especially if there are larger individual lesions. Furthermore, clinically similar can be infectious diseases, for example, lesions caused by HSV, Coxsackie stomatitis and syphilis (ulcus durum). It is necessary to think of granulomatous diseases (Crohn's disease, sarcoidosis). Because of the

multifactorial etiology of oral changes that point to aphthous ulcers and the association with a number of other disorders, a multidisciplinary approach to the disease is necessary.

There is a need for public and patient education about the possibilities of work-up and treatment of RAS to decrease patient concern and improve their quality of life³⁷. Health services that encompass medical workers and pharmacists should organize better education on the diagnostic procedures and treatment of oral diseases, including RAS. Also, a lot is expected from randomized clinical researches, which are necessary to examine the potential use of different therapeutic possibilities.

Conclusion

In the diagnosis of the disease, it is important to differentiate RAS from other oral ulcers, which are a manifestation of serious, even life-threatening diseases. Considering that aphthous ulcers are accompanied by painful sensations and frequently have a recurrent course, the disease is very unpleasant. Therapeutic approach to the patient with aphthous ulcers is symptomatic having no possibilities to prevent disease recurrence. Yet, the disease prognosis is good at long term as the recurrences usually resolve at older age.

References

1. ROGER RS. Recurrent aphthous stomatitis: clinical characteristics and associated systemic disorders. *Semin Cutan Med Surg* 1997;16:278-83.
2. BRAUN-FALCO O, PLEWIG G, WOLFF HH, BURG-DORF WHC, editors. *Dermatology*, 2nd rev. edn. Berlin, Heidelberg, New York: Springer-Verlag, 2000.
3. PETERSON A, HORNSIETH A. Recurrent aphthous ulceration: possible clinical manifestations of varicella zoster in cytomegalovirus infection. *J Oral Pathol Med* 1993;22:64-8.
4. GHODRATNAMA F, RIGGIO MP, WRAY D. Search for human herpesvirus 6, human cytomegalovirus and varicella zoster virus DNA in current aphthous stomatitis tissue. *J Oral Pathol Med* 1997;26:192-7.
5. SCULLY C, PORTER S. Recurrent aphthous stomatitis: current concepts of etiology, pathogenesis and management. *J Oral Pathol Med* 1989;18:21-7.
6. JURGE S, KUFFER R, SCULLY C, PORTER SR. Mucosal disease series. Number VI. Recurrent aphthous stomatitis. *Oral Dis* 2006;12(1):1-21.

7. MILLER MF, GARFUNKEL AA, RAM CA, SHIP JJ. The inheritance of recurrent aphthous stomatitis observations on susceptibility. *Oral Surg* 1980;49:409-12.
8. SHIP JJ. Epidemiologic aspects of recurrent aphthous ulcerations. *Oral Surg* 1972;33:400-6.
9. EVERSOLE LR. Immunopathogenesis of oral lichen planus and recurrent aphthous stomatitis. *Semin Cutan Med Surg* 1997;16:284-94.
10. CHALLACOMBE SJ, BARKHAN P, LEHNER T. Hematologic features and differentiation of recurrent oral ulcerations. *Br J Oral Surg* 1977;15:37-48.
11. ROGERS RS, HUTTON KP. Screening for haematinic deficiencies in patients with recurrent aphthous stomatitis. *Aust J Dermatol* 1986;27:98-103.
12. FERGUSON MM, WRAY D, CARMICHAEL HA, *et al.* Coeliac disease associated with recurrent aphthae. *Gut* 1980;21:223-6.
13. DONATSKY O, BENDIXEN G. *In vitro* demonstration of cellular hypersensitivity to Strep 2A in recurrent aphthous stomatitis by means of leukocyte migration test. *Acta Allergol* 1972;27:137-44.
14. THOMAS DW, BAGG J, WALKER DM. Characterization of the effector cells responsible for the *in vitro* cytotoxicity of blood leucocytes from aphthous ulcer patients for oral epithelial cells. *Gut* 1990;31:294-9.
15. HOOVER CI, OLSON JA, GREENSPAN JA. Humoral responses and cross-reactivity to viridans streptococci in recurrent aphthous ulceration. *J Dent Res* 1986;65:1101-4.
16. GREENSPAN JL, GADOL N, OLSON JA, *et al.* Lymphocyte function in recurrent aphthous ulceration. *J Oral Pathol* 1985;14:592-602.
17. PEDERSEN A, KLAUSEN B, HOUGEN HP, STENVANG JP. T-lymphocyte subset in recurrent aphthous ulceration. *J Oral Pathol Med* 1989;18:59-60.
18. BRUNO IJ, HUFF JC, WESTON WL, *et al.* Elevated levels of interferon gamma, tumor necrosis factor alpha, interleukins 2, 4, 5, but not interleukin 10, are present in recurrent aphthous stomatitis. *Arch Dermatol* 1998;134:827-31.
19. LEWKOWICZ N, LEWKOWICZ P, BANASIK M, KURNATOWSKA A, TCHORZEWSKI H. Predominance of type 1 cytokines and decreased number of CD4(+) CD25(+high) T regulatory cells in peripheral blood of patients with recurrent aphthous ulcerations. *Immunol Lett* 2005;99(1):57-62.
20. KUMAR BP, KELUSKAR V, BAGEWADI AS, SHETTI A. Evaluating and comparing phagocytic functions of salivary and blood neutrophils in patients with recurrent aphthous ulcers and controls. *Quintessence Int* 2010;41(5):411-6.
21. RENNU JS, READE PC, HAY KD, SCULLY C. Recurrent aphthous stomatitis. *Br Dent J* 1985;159:361-7.
22. HAY KD, READE PC. The use of elimination diet in the treatment of recurrent aphthous ulceration in the oral cavity. *Oral Surg* 1984;57:504-7.
23. TORGERSON RR, DAVIS MD, BRUCE AJ, FARMER SA, ROGERS RS 3rd. Contact allergy in oral disease. *J Am Acad Dermatol* 2007;57:315-21.
24. CHAHINE L, SEMPSON N, WAGONER C. The effect of sodium lauryl sulfate on recurrent aphthous ulcers: a clinical study. *Comp Cont Educ Dent* 1997;18:1238-40.
25. HEALY CM, PATERSON M, JOYSTON-BECHAL S, *et al.* The effect of sodium lauryl sulfate-free dentifrice on patients with recurrent oral ulceration. *Oral Dis* 1999;5:39-43.
26. AXELL T, HENRICSSON V. Association between recurrent aphthous ulcers and tobacco habits. *Scand J Dent Res* 1985;93:239-42.
27. SAWAIR FA. Does smoking really protect from recurrent aphthous stomatitis? *Ther Clin Risk Manag* 2010;6:573-7.
28. BUCCI P, CARILE F, SANGIANANTONIA, D'ANGIO F, SANTARELLI A, Lo MUZIO L. Oral aphthous ulcers and dental enamel defects in children with celiac disease. *Acta Paediatr* 2006;95(2):203-7.
29. MANSOUR-GHANAIE F, ASMAR M, BAGHERZADEH AH, EKBATANINEZHAD S. *Helicobacter pylori* infection in oral lesions of patients with recurrent aphthous stomatitis. *Med Sci Monit* 2005;11(12):576-9.
30. BUDIMIR J, LUGOVIĆ MIHIĆ L, ŠITUM M, BULAT V, PERŠIĆ S, TOMLJANOVIĆ-VESELSKI M. Oral lesions in patients with pemphigus vulgaris and bullous pemphigoid. *Acta Clin Croat* 2008;47(1):13-8.
31. GREENBERG G. *Burketova oralna medicina, dijagnoza i liječenje*. Zagreb: Medicinska naklada, 2006. (translation of *Burket's Oral medicine*, 10th edition)
32. LASKARIS G. *Color atlas of oral diseases*, 3rd edn. Stuttgart-New York: Thieme Verlag, 2003.
33. MADINIER I, BERRY N, CHICHMANIAN RM. Drug-induced oral ulcerations. *Ann Med Interne (Paris)* 2000;151(4):248-54.
34. BAKULA A, LUGOVIĆ-MIHIĆ L, ŠITUM M, TURČIN J, ŠINKOVIĆ A. Contact allergy in the mouth: diversity of clinical presentations and diagnosis of common allergens relevant to dental practice. *Acta Clin Croat* 2011;50(4):553-61.
35. PREETI L, MAGESH K, RAJKUMAR K, KARTHIK R. Recurrent aphthous stomatitis. *J Oral Maxillofac Pathol* 2011;15(3):252-6.
36. De SOUZA TO, MARTINS MA, BUSSADORI SK, *et al.* Clinical evaluation of low-level laser treatment for recurring aphthous stomatitis. *Photomed Laser Surg* 2010;28(Suppl 2):85-8.
37. KRISDAPONG S, SHEIHAM A, TSAKOS G. Impacts of recurrent aphthous stomatitis on quality of life of 12- and 15-year-old Thai children. *Qual Life Res* 2012;21(1):71-6.

Sažetak

AFTOZNE ULCERACIJE KAO MULTIFAKTORIJALNI PROBLEM

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Recidivirajući aftozni stomatitis (RAS) je poremaćaj obilježen recidivima ulceracija ograničenih na oralnu sluznicu. Mnogi specijalisti i istraživači iz područja oralne medicine i drugih područja u RAS-u ne prepoznaju jednu bolest, nego nekoliko patoloških stanja sa sličnim kliničkim značajkama. Iako je pravi uzrok nastanka nepoznat, postoje neki predisponirajući čimbenici kao što su anemija zbog nedostatka željeza, folata i vitamina B skupine te cinka, neutropenija, lokalna trauma, emocionalni stres, metabolički poremećaji, hormonski poremećaji, kronične bolesti koje dovode do imunodeficijencije. Bolest dolazi u tri klinička oblika: male afte, velike afte i herpetiformne afte. Liječenje ovoga poremećaja uključuje lokalnu ili sustavnu primjenu kortikosteroida, imunostimulansa i vitaminsku terapiju. Zbog povezanosti manifestacija afti s različitim drugim bolestima potrebna je suradnja više struka i multidisciplinarni pristup.

Ključne riječi: *Afte; Recidivirajući aftozni stomatitis; Usna šupljina; Etiologija*

