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Recurrent Aphthous Stomatitis: A mini - Narrative Review

Review Article

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Abstract

Recurrent aphthous stomatitis (RAS) is a medical term with different meaning for practitioners unclear etiopathogenesis and no definite treatment ladder with lots of challenging issues in over-lap with other disease of oral cavity, for patient recurrent painful lesion in mouth which can im-pact functionally, psychosocially and economically .Diversity of causes and hypothesis each year lead to hundreds of researches to finding out new elements involving patients in this tragic disease but yet pin-pointing a precise etiological factor is difficult.RAS In terms of clinical pres-entation has 3 subtypes: minor (>70% of cases), major (10%), and herpetiform (10%).RAS leads to 25 percent of recurrent oral ulcers in adults and 40 percent in children.Lots of differential di-agnosis for recurrent aphthous ulcerations like idiopathic benign causes, inherited fever syn-dromes, connective tissue disease, gluten-sensitive enteropathy (celiac), ulcerative colitis and Crohn disease should be ruled out by comprehensive history taking and physical exam to find out whether it is related to a systemic inflammatory process or truly idiopathic. More investigation should be done to isolate the etiology of RAS for every case regarding the efficiency of con-ventional and unconventional treatment options, and patients tolerance of side effects.In this re-view of literatures, we trying to summarize results of different studies related to latest break-through and ethiological modalities for RAS to facilitate accurate diagnosis, proper classifica-tion, recognition of provocative factors, and the identification of associated diseases.

Keywords: Aphthous Stomatitis; Oral Ulcer; RAS; Recurrent Aphthous Ulceration.

Introduction

Recurrent Aphthous Stomatitis (RAS) which has another name; canker sores(the Greek word aphthi, which means “to set on fire” or “to inflame) is one of thechronic, inflammatory diseases of the oral cavity(oral mucosa of the lips, cheeks, keratinized palatal,gingival mucosa and ton-gue)with painful oral ulcer without preciseetiologyand with recurrence of one or more erosion or ulcer each year, in the absenceof systemic abnormality or ulcer in other parts of the body [1-4].The ulcers are painful and shallow accompanied by grayish-white pseudomembrane plus an erythematous margin [5]. Simple aphthosis, complex aphthosis, Recurrent Oral Ulcers (ROU), and Recurrent Aphthous Ulcers (RAU) should be regarded as synonyms for RAS [6]. In this review of literature, we are trying to summarize the results of different studies related to the latest breakthrough and etiological modalities for Recurrent aphthous stomatitis (RAS) to facilitate precise diagnosis, appropriate classification, identification of provocative factors, and the recog-nition of related diseases.

Method

This review was conducted using PubMed, SID, ISI Web of Science, Scopus, Scholar in an at-tempt to find all articles relevant to the recurrent aphthous stomatitis published until 2020. Ar-ticles published in English were included. Studies that were similar or duplicated were excluded. We chose the related studies based on the title and abstract of the papers. We checked the refer-ences of selected publications after obtaining the full text to see whether there were any addi-tional studies.

Our search strategy in Pubmed was as follows:

(recurrent Aphthous Stomatitis [Title/Abstract]) OR (Aphthous

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Ulcer[Title/Abstract]) OR (Aph-thous Ulcers[Title/Abstract]) OR (Aphthae[Title/Abstract])) OR (Canker Sore[Title/Abstract]) OR (Canker Sores[Title/Abstract]) OR (Periadenitis Mucosa NecroticaRecurrens[Title/Abstract])

Categories of RAS

Based on morphology,RAS has three categories. After evaluation of its clinical characteristic-spractitioners will decide which type of RAS fired the situation: minor ulcers, major ulcers, or herpetiform Ulcers [7, 8].

Minor RAS: the most common group 75–90% of patients, it is less than 10mm in diameter and typically takes 4-14 days to heal without scarring.Minor RAS appears on non-keratinized mucosa;therefore, it is notcommon on dorsum of tongue, palate or gingiva surfaces. It occurs more frequently in floor of mouth, buccal mucosa, and labial mucosa. Ulcersare concentrated in the anterior part of the mouth and are superficial.

Major RAS: ulcers are less common in comparison with Minor RAS with 10-15 % of cases, deeper, often scarred, maybe with limitation in tongue movements and speech. They exceed 10mm and persist up for weeks.

Herpetiform ulceration: 5% of cases. A similarity between this term and Herpes Simplex Virus (HSV) herpes labialis (fever blisters, cold sores) infection exists but each one is a distinct entity. 5-100 ulcers with 2-3 mm in diameter may be present at the same time. They are grey and have no delineated erythematous border, therefore it is difficult to visualize them [7, 9, 10].

these groups features are vsummarized in Table 1.

Another method of categorizing RAS is using clinical features of the disease:Mild type is called simple and Severe type is called complex aphthosis [11, 12]. Most patientshave simple ulcers but patients with a history of anemia, Inflammatory Bowel Disease(IBD),celiac,Human Immunodefi-ciency Virus (HIV), systemic lupus erythematous, cyclic neutropenia, Behcet's disease,or other such illnesses experience thecomplex type.

Simple aphthosis types are common, limited to oral cavity, andepisodic. They cause few ulcers, minimal pain, 3-6 episodes per year, little disability and have prompt healing.

Complex aphthosis types are uncommon, continuous or episodic. They cause few to many ulc-ers,marked pain, frequent or continuous ulceration, major disability and have slow healing and-may cause genital aphthae.[12]

RAS is a worldwide known oral ulcer and a patient can be marked with this title only by ruling out other oral ulcerative diseases secondary to systemic diseases, and nutritional or haematologi-caldeficiencies. The estimation of RAS prevalence in each country varies because of the design of studies and number of patients in previous surveys, qualification criteria and origin of the examined subjects.

The prevalence ranges of RAS:

RAS onset is in childhood and the second decade of life considering the peak period. The severity and recurrence tendency to diminish with age may be due to alterations of the immune system(decrease in the neutrophils' chemotactic and phagocytic capacity) [13, 14]. So in patients older than 40 it's not common [15]. Some literature's mentioned that rich people, nonsmokers,women, female dental and medical school students and student nurses are more prone to expe-rience RAS and men are at lower risk [16, 17]. RAS prevalence estimation has a wide range from 2% to 66% in different studies. Konopka in Poland in 2004 reported RAS prevalence near 10 percent. In physical exam of 1281 patients [18]. However in patient history taking in 2009 by Safa-ri in Jordan, RAS prevalence in 13 to 68-year-olds wasclaimed to be near 78.1% [19]. RAS re-currence is about 3 to 6 times each year and lesions which remain for 14 days are categorized as simple

Table 1. Different types of RAS.

Prognosis	Size of ulcers	Number of ulcers	Depth	Distribution	Morphology	Gender predilection	Prevalence	
Lesions resolve in 4–14 days No scarring	<10mm	1–5	shallow	Lips, cheeks, tongue, floor of mouth nonkeratinized area	Round or oval lesions Gray-white pseudomembranes Erythematous halo	Equal 2 life decade	75-90	Minor aphthae (Mikulicz's aphthae; MiRAS)
Lesions persist >6 weeks High risk of scarring	>10mm	1–10	deep	Lips, soft palate, pharynx Keratinized and nonkeratinized area	Round or oval lesions Gray-white pseudomembranes Erythematous halo	Equal 1 and 2 life decade	15-Oct	Major aphthae (Sutton's aphthae; MaRAS)
Lesions resolve in <30 days Scarring uncommon	2–3mm	10–100	shallow	Lips, cheeks, tongue, floor of mouth, gingiva nonkeratinized area	Small, deep ulcers that commonly converge Irregular contour	Female 3 life decade	10-May	Herpetiform aphthae (HeRAS)

aphthosis but if these painful ulcers remain more than 14 daysand emerge in other areas except mouth like genital mucosa,they arecategorized as complex aphthosis [20-25]. If the ulcer of mouth start in childhood rarely accompanies autoimmune diseasebut in third decade, they can be more severe and sometimes the presentation is Herpetiform RAS [26-28].

Oral Ulcerations' Differential Diagnosis:

The first step in approaching a patient's complaint about mucosal aphthous ulcer is listing the differential diagnosis and finding the most matching disease with the patient's presentation. Al-though RAS is common among individuals, lots of diseases have similarities in signs and symp-toms with it. Therefore, before marking patients with RAS, practitioners should rule out diseases which are categorized in Table 2: infections (bacteria, virus,fungi) regularly with vesiculobullous eruptions, trauma due to dental appliances, Hormonal changes, malnutrition, gastrointestinal (GI) diseases, autoimmune diseases with oral manifestations and drugs' side effects. Complete Physi-cal examination and comprehensive history taking are two wings to facilitate diagnosing among differential diagnosis [29] as mentioned in Table 2.

The mechanism of the development RAS:

Different studies have been done till now to find out predisposing factors that could trigger the RAS in childhood and adolescence and numerous items claimed to have a major or minor role in this disease. However, the precise etiology is not clear overall. It is assumed that the coincidence of particular trigger factors kicks off the cascade of pro-inflammatory cytokines, directed against sensitive oral mucosa areas, and aphthous will emerge. We should be thankful to our colleagues in all medical research centers for their efforts and here we summarize their findings hope that it could facilitate future studies.

Viral and bacterial infections, stress, malnutrition, hematological deficiencies, Hormonal level fluctuations, genetic predisposition, drugs immune deficiency disorders, trauma and mechanical injuries, and systemic diseases claimed to have role in this mysterious disease [16, 24, 28, 30, 31].

Pathology study of oral RAS samples reported massive leukocytic infiltration with dominancy oflymphocytes (mostly of the T type) and monocytes inthe primary phase and in long-lasting ulcers dominancy of polynuclear leukocytes was reported which is similar to Behcet's disease, lupus erythematous and other inflammatory conditions and it isn't an exclusive feature [32, 33].

Inheritance:

Ship [34] first in 1965 reported the role of genetics in RAS in families and other studies men-tioned that 24-46% of RAS patients have a family history of recurrent aphthous in mouth [35]. Monozygotic vs dizygotic twins have more chance to be affected by aphthous and due to past history their manifestations in recurrence and severity are worse in comparison to those with no family history..[36, 37] DNA polymorphism related to metabolism of interleukins (IL-2, IL-5, IL-1b, IL-6, IL-12, IL-4, IL-10), tumor necrosis factor (TNF) and interferon (IFN)-c, and Human Leukocyte Antigen (HLA)-A33, HLA-B5, HLA-B12, HLA-B35, HLA-B51, HLA-B81, HLA-DR4, and HLA-DR7, have been proved in RAS presentations [38-50].

Table 2. Differential Diagnosis of Oral ulcers.

Inherited	**epidermolysis bullosa, chronic granulomatous disease**
Fungal	Coccidioidesimmitis, Cryptococcus neoformans, Blastomyces dermatitidis
Bacterial	tuberculosis, syphilis
Viral[86]	Coxsackie A, herpes simplex, herpes zoster, cytomegalovirus, epstein-Barr, human immunodeficiency virus
Nutritional Deficiency[87]	iron, folate, zinc, B1, B2, B6, B12
Hematologic	Anemia, neutropenia, hypereosinophilic syndrome
Vesiculobullous disorders	Pemphigus vulgaris, linear igA disease, erythema multiforme
fever syndromes [88-90]	Cyclic neutropenia, PfAPA (periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis), Sweet syndrome
	familial Mediterranean fever, hyperimmunoglobulinemia D with periodic fever syndrome (HiDS)
Trauma	Dental appliances, necrotizing sialometaplasia
recurrent aphthous stomatitis (idiopathic)	
Miscellaneous	MAGiC syndrome, hormonal disturbances, malignancy, smoking, hormonal (menstrual-associated)
Drug induced [91-95]	fixed Drug eruption, linear igA bullous dermatosis, drug-induced bullous pemphigoid, drug-induced pemphigus Stevens-johnson syndrome, toxic epidermal necrolysis
Autoimmune diseases[96-99]	Crohn's (orofacial granulomatosis), Behcet's, Celiac, systemic lupus erythematosus, Lichen planus Linear igA bullous dermatosis, Wegener's granulomatosis

Tobacco:

RAS in smokers has a lower rate due to the reduction of pro-inflammatory cytokines (IL-6, IL-1 and TNF-a).Reactive oral mucosa keratinization also causes a kind of protection against trauma [27, 51].

Drugs:

It was reported that typical aphthous ulcers' clinical description or/and clinical presentation indi-cating the aphthous ulcers' diagnosis have been recorded for eight drugs [8, 52]: Sodium hypochlorite [53], piroxicam [54], phenobarbital [55], phenindione [56] niflumic acid [56], nicoran-dil [57], gold salts [56], captopril [58].

Infectious factors:

Bacteria like (Helicobacter pylori, Streptococcus oralis)and viral (HIV-infected per-sons, cytomegalo virus, herpes simplex virus, varicella-zoster virus, adenoviruses) antigens in dif-ferent studies were proved to have prominent ties with RAS.In higher B12 serum level the RAS after eradicatin of H.pyloriRAS tend to be reduced which served as a significant document that H.pylori role in RAS should be a target point [28, 59-63].

Diet component role in RAS:

Food and microelement deficiencies such as vitamins and minerals (vitamin B12, zinc, folic acid, microelement, iron) were proved to be in relation to more prevalence of RAS and excessive exposure to some food elements like date, raisin, gluten, preservatives, food coloring agents, chocolate,cow milk, and nuts can lead to RAS [5, 28, 64-69]. A meta-analysis by Al-Maweri et al.[70] suggests that there is a significant relation between low levels of vitamin D and RAS.

Systemic Diseases:

Celiac disease and chronic inflammatory bowel diseases (ulcerative colitis, Crohn's disease) by two pathophysiologies tend to present RAS in the mouth; 1-food and microelement deficiencies, 2-autoimmune reactions [3, 28, 63, 71].

Hormonal Imbalance:

Serum levels of sex hormones in the luteal phase and Oral Contraceptive Pills (OCPs) in case of contraceptive will lead to RAS [28, 72].

Minor trauma:

A majority of patientswho suffered from RAS claim that lesions often appear following trauma without disclosed reason till now [28, 72, 73].

Stress:

Tention playsa key role in the occuranceof RAS by modifying immune response system [28, 74-76].

Immunological mediated mechanisms in RAS:

It was proved by lots of recently studies that Immunologic response disruption has footprints in RAS and drives the pathogenesis. For better management of such disabling disease having a comprehensive concept of immune response is necessary. Increase in Pro-inflammatory cytokine-soriginated byT helper 1 (Th1)(IFN-c, IL-12, IL-2, TNF-a),known as trigger factors of autoim-munization by cellular type, and decrease of anti-inflammatory cytokines with the source of Th2(IL-13, IL-5, IL-4 and IL-10) and (TGF)-bwork by immunoglobulin E (IgE) in humoral re-sponse system have been implicated as triggers of RAS [14, 42, 43, 77-82]. As lymphocyte im-migrate to themucosa of the mouth, pro-inflammatory cytokines'secretion by activation of T cells and TNF-α will affect some specific areas of buccal mucosa ends to neutrophils migration to the lesions with ulcer manifestation [83]. In patients with lower IL-10 level, RAS ulcers last more than others due to its role inhealing process [40, 42, 71]. Higher secretion of Th1 cytokines, neutrophils' reactivation, increased NK cells and B lymphocytes disproportion CD4/CD ratio lead to RAS [80, 84, 85].

In some papers DNA polymorphism was proved to have different effect on RAS as mentioned in Table 3.

Conclusion And Future Perspectives

This review was designed to explore the precise mechanisms of RAS (which occurs as round, shallow, recurrent, oral ulcerations surrounded by inflammation). Since it is the most common oral mucosal lesion in the general population,therefore, it will be of great interest to de-velop a list of specific factors influencing the development of oral ulcers. The specific etiology of RAS remains unclear despite extensive researches, but several systemic, genetic, nutritional, microbial, local, immunologic, and allergic factors have been suggested in different studies. Re-cent studies suggest

Table 3. DNA role in RAS.

DNA polymorphism	Thr role in RAS
interleukins (IL-1b, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12)	Affect susceptibility to RAS[10]
interferon (IFN)-g	Affect susceptibility to RAS[10]
tumor necrosis factor (TNF)-a	Affect susceptibility to RAS[10]
HLA-DR5, -DRw8 and -DQw1	mucocutaneous type of Behcet's disease[100]
HLA-DR5/DQw1 and HLA-DRw8/DQw1	Increase relative risk of RAS[100]
of HLA-A33, HLA-B35 andHLA-B81,14 HLA-B12,15 HLA-B51,16 HLA-DR7 and HLADR517,18	Increase relative risk of RAS[100]

that genetics plays a prominent part in combination with environmental fac-tors in the development of RAS so we tried to prepare a brief review of all factors which havea role in this disease.By a deep evaluating of different studies, it will be disclosed that genetics besides environmental modalities has a great impact on the incidence and morbidities of RAS. Therefore, in future studies all these factors must be regarded in a unique structure, not as different isolated items, otherwise, no remedy could eradicate RAS.

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