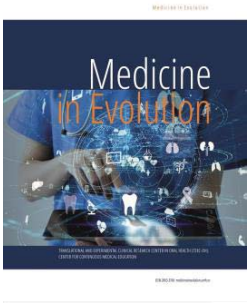
Recurrent aphthous ulcers (RAU) and recurrent aphthous stomatitis (RAS) enigmatic etiopathology



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Abstract

Oral aphthous ulcer is a well-known condition that significantly affects the quality of life for patients by producing intense pain and difficulties in speaking and chewing. When recurrence is present we refer to them as recurrent aphthous ulcers (RAU) and recurrent aphthous stomatitis (RAS). Mouth ulcers are typically uncomfortable sores that can occur as a result of a variety of local and general disorders. It is one of the most prevalent oral ulcerative conditions.

Keywords: aphthous ulcers, aphthous stomatitis, etiopathology

INTRODUCTION

A frequent condition known as recurrent aphthous ulcers (RAU) or recurrent aphthous stomatitis (RAS) causes repeated, excruciating sores on the non-keratinized oral mucous membranes [1, 2, 3]. Recurrent aphthous ulceration (RAU) and recurrent aphthous stomatitis (RAS) are terms used when recurrence is frequent [4]. This pathologies manifested as oral ulcers are commonly known as aphthae or canker sores [1, 2, 3].

The term "aphthous" is derived from a Greek word "aphtha" which means ulceration, syntagma which was initially used by Hippocrates to describe disorders of the mouth [5, 6, 7]. Aphthous ulcer can be described as a painful inflammatory condition of the mouth mucosa, developed on its own or as a result of various different disease conditions [4].

Believed to be one of the most prevalent oral lesions in the general population, aphthous ulcers affect 20–25% of the population. It is considered that the prevalence is higher in developed nations and women are slightly more susceptible [8]. Even though it is the most prevalent oral mucosa disorder, the etiopathology is still unclear [1, 2, 3].

It can reoccur any time, with a frequency that varies up to 3 months. These type of ulcers can be extremely painful and may make it difficult to chew, speak or swallow, affecting people's daily lives. Although the majority are benign and self-healing, a tiny fraction of ulcers are malignant [9].

Clinically, this lessions are characterized by circular or oval ulcers with circumscribed margins and floors that are slightly below the level of the surrounding mucosa [10]. They are usually found on the buccal and labial mucosa as well as the tongue. A white fibrous layer protects the ulcers, which contrasts with the reddish edge [11]. According to Stanley's 1972 classification of RAS, three distinct clinical variations have been recognized: minor RAS, major RAS and herpetiform ulceration [12].

Aim and objectives

Considering the most recent papers in the specialized literature, the aim of this research is to attempt to elucidate the etiopathology of recurrent aphthous ulcers (RAU) and recurrent aphthous stomatitis (RAS) in the oral cavity.

ETIOPATHOLOGY

The origin of this conditions occurrence has not been defined precisely. Aphthous ulceration of the oral mucosa has an idiopathic, complex etiology that also involves the activity of the cell-mediated immune system. Being unrelated to acute infections, recurrent aphthous ulcers (RAU) and recurrent aphthous stomatitis (RAS) are non-contagious illness [13, 14, 15].

Although the exact causes of aphthous ulcers remain unknown, it is believed that one or more extrinsic triggers are responsible for sores. Local trauma, emotional or physiological stress can all cause aphthae [16].

Minor mouth injuries, such as those caused by cuts, burns or bites while eating, incorrect dental work, improperly fitting dentures or vigorous brushing can also be responsible for the appearance of ulcers [16].

Mouth ulcers frequently develop because of stress. While stress does not directly cause ulcers, it can raise the likelihood of them happening and can influence how quickly they heal. By limiting what and how a person can eat and drink, mouth ulcers can also lead to stress creating what is called a never-ending vicious circle [17, 18].

It is well acknowledged that both local and systemic immunological, genetic and environmental variables are responsible [10, 19]. Given that 40% of those who develop ulcers have a family history of the disease, it may potentially be partially genetic [16].

In some patients, general associated causes, such as malabsorption, enteropathy or celiac disease, have been identified. About 20% of cases are related to hematinic or other deficiencies (iron, zinc, thiamine – vitamin B1, folic acid - vitamin B9, vitamin B6, vitamin B12, vitamin D) [13, 14, 15].

Rarely, recurrent aphthous ulceration (RAU) may be a symptom of a number of serious illnesses, such as Crohn's disease, Celiac disease, Behcet disease or AIDS [16]. To determine if a condition is caused by a systemic disease process or is truly idiopathic, a complete history and systemic examination are necessary [4]. Menstruation and hormonal disorders associated with pregnancy were also mentioned as a possible cause of mouth ulceration [13, 14, 15, 16].

One of the crucial environmental factors has been identified as heterogeneity in microbiota composition [20]. It is considerd that oral aphthous ulcers microbiology is made up of a variety of bacteria, authors even incriminating changes in the oral microbiome [4].

Another cause of aphthous ulcers can be an allergic reaction or sensitivity to certain excipients present in toothpastes or mouthwashes (sodium lauryl sulfate), in food (cinnamon, cheese, citrus fruits, figs, pineapple) or exposure to toxins (nitrates in water) [13, 14, 15].

Aphthous ulcers are more common in non-smokers and smokers who quit smoking, and less common in people with good oral hygiene practices [13, 14, 15].

DISCUSSIONS

Recent studies have linked bacterial and fungal dysbiosis to recurrent aphthous stomatitis (RAS). In RAS patients and healthy controls, Stehlikova et al. looked at microbial shifts during RAS manifestation at an ulcer site, in its environs and at an unaffected site in comparison with healed mucosa. The area with the most obvious variations in microbial alpha and beta diversity between RAS patients and healthy controls was found to be the lower labial mucosa. This author shows how active RAS ulcers alter the types of bacteria and fungi that colonize healthy oral mucosa and how this transformation continues in some form even after the ulcer has healed [21].

In RAS patients, microbiological analyses showed that active ulcers are associated with *Fusobacterium*, *Leptotrichia*, *Cardiobacterium*, *Lachnoanaerobaculum*, *Clostridia*, *Malassezia*, *Streptococcus*, *Haemophilus* and *Porphyromonas*, while healed zones revealed strict association with *Selenomonas*. Moreover, compared to healthy controls, RAS patients had higher serum levels of IgG against *Mogibacterium timidum*, emphasizing the immunological component of this disease [21].

Yun-ji et al. also demonstrated that RAS is linked to dysbiosis of the mucosal and salivary microbiota, *Streptococcus salivarius* and *Acinetobacter johnsonii* being two of the RAS associated species. A mechanism that could explain why ulcers take longer to heal is the fact that *Acinetobacter johnsonii* significantly decreased gingival epithelial cell growth and displayed increased cytotoxicity against the cells [22]. Yang et. al proposed *Escherichia coli* and *Alloprevotella* colonisation as a cause of RAS and concluded that limiting this bacteria growth promotes healing [23].

Slebioda et. al indicated that although no unique gene has been found, twin studies have provided some indication of a familial component with early onset and increased severity. The study illustrates a higher prevalence of aphthae among family members, pointing the condition's hereditary origins. Family members may be more susceptible to RAS

if they inherit certain gene variants, particularly those that produce pro-inflammatory cytokines, which are involved in the development of aphthous ulcers [24].

Thus, immunologically mediated processes is significantly contributing to the pathogenesis of oral aphthous ulcers. A theory that could explain why ulceration gets worse after local injury, after the cessation of smoking or both, suggests that it may be caused by an unchecked or excessive production of interleukin-1 (IL-1) or interleukin-6 (IL-6), crucial factors for its development [25].

Some toothpastes and mouthwashes contain sodium lauryl sulfate, a chemical that has not been confirmed to be a trigger for ulcers, but is known to delay their healing [16].

It is considered that diet has a significant impact on the appearance of mouth ulcers, which is why the relationship between dietary habits and RAS appearance has been intensively investigated. Several foods and beverages, including acidic or spicy dishes, coffee, chocolate, eggs, cheese, cow's milk, almonds and gluten are accused [16]. Researchers have shown a link between the consumption of this specific foods and the development of RAS, but no substantial correlation between RAS and three particular incriminated foods - tomatoes, strawberries, walnuts - was discovered by Eversole et al [26].

According to Du et al. regular consumption of carbonated beverages or frequent thirst will raise the probability of this condition, whereas a preference for nuts offers protection [27]. The lack of fluid consumption causes an imbalance between free water and bound water in oral mucosa, with consequences such as changes in local energy metabolism, explaining the appearance of local heat and burning symptoms specific to aphthous ulcers [28]. Nuts rich content in vitamin A, vitamin B, vitamin E and proteins explain the protective effect on RAS [29, 30]. Fruit consumption is believed to have no good effects [27]. Consuming sugary foods and citrus fruits alters the pH of the oral cavity, encouraging the development of stomatitis and explaining why ulcers appear [31]. Because to its glycosides, which stimulate the oral mucosa, and its protease, which can cause allergic reactions in some people, pineapple may cause or worsen mouth ulcers [32]. However, according to Xu et al. eating fruits and drinking water may be useful as daily preventive strategies against RAS [33].

Although diet has a minimal part in the pathophysiology of RAS, it can have a function in the development of RAS by inducing hypersensitivity or by depleting the body of certain vitamins and minerals [34].

When a person stops smoking, their risk of developing RAS rises, presumably as a result of the loss of nicotine's protective effects or the mucosal keratinization that tobacco smoke promotes [35]. Furthermore, Hill et al. demonstrated that nicotine replacement treatment is effective in healing ulcers brought on by quitting tobacco use [36]. Mohamed et al. considered that cigarette smokers experience aphthous ulceration less frequently, while other authors suggested that this effect of smoking on RAS is time-dependent and dose-dependent [37, 38].

CONCLUSIONS

Within the limitation of this research and literature provided, it is safe to say that recurrent aphthous ulcers (RAU) and recurrent aphthous stomatitis (RAS) etiopathology is multifactorial and a single etiological factor cannot be specified.

A number of factors, including genetic, immunological, traumatic and environmental ones, contribute to the development of oral aphthous ulcers.

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