DOI: https://doi.org/10.17921/2447-8938.2023v25n3p188-193

Clinical Aspects and Etiopathogenesis of Recurrent Aphthous Ulcer: Narrative Literature Review

Aspectos Clínicos e Etiopatogenia da Úlcera Aftosa Recorrente: Revisão Narrativa da Literatura

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Abstract

Recurrent aphthous ulcer (RAU) is a common oral mucosal lesion with varied and etiopathogenesis. It presents with pain and clinically manifests as an oval-shaped lesion with regular borders surrounded by an erythematous halo and covered by pseudo membrane. Due to the uncertainty about the possible causative factors, there is a need for studies that seek a better understanding of its pathophysiology. In this context, this study aimed to discuss the etiopathogenesis and clinical aspects of RAU. It was a descriptive study characterized as a narrative literature review. The inclusion criteria were studies relevant to the topic, written in Portuguese and English, without a time limit. The search was conducted between December 2022 and July 2023, through active searching in the Pubmed, LILACS, and SciELO platforms, as well as grey literature from Google Scholar and secondary free search. The Health Sciences Descriptors (DeCS/MeSH) were crossed using a Boolean operator, namely "aphthous ulcers" AND "predisposing factors." RAU has a multifactorial etiopathogenesis and may be associated with immunological, hereditary, nutritional, dietary, psycho-emotional, hormonal, and local trauma factors, although its relationship with microorganisms is controversial. Clinically, it is classified based on its morphology and clinical course. Morphologically, it is classified into minor, major, and herpetiform types, with the minor form being the most common. Therefore, RAU is a frequent oral mucosal lesion, with the minor form being the most prevalent, and despite its uncertain etiopathogenesis, studies indicate that immunological, traumatic, hereditary, hormonal, nutritional, and psycho-social factors are directly related to its development.

Keywords: Aphthous Ulcer. Predisposing Factors. Pathology.

Resumo

A úlcera aftosa recorrente (UAR) é uma lesão frequente da mucosa oral com etiopategia variada. Apresenta dor e clinicamente se manifesta com formato oval, bordas regulares circundada por halo eritematoso e coberta por pseudomembrana. Devido a incerteza sobre os possíveis fatores causais, há uma necessidade de estudos que busquem maior compreensão sobre sua patofisiologia. Diante desse contexto, o presente estudo teve como objetivo discorrer sobre a etiopatogenia e os aspectos clínicos da UAR. Tratou-se de um estudo descritivo, caracterizado como revisão narrativa da literatura. Os critérios de inclusão estabelecidos foram: estudos pertinentes à temática, redigidos em português e inglês, sem corte temporal. O levantamento ocorreu entre dezembro/2022 a julho/2023, através da busca ativa nas plataformas Pubmed, LILACS e SciELO, além da literatura cinzenta do Google Acadêmico e busca livre secundária. Os Descritores em Ciências da Saúde (DeCS/MeSH) foram cruzados com operador booleano, a saber: "aphthous ulcers" AND "predisposing factors". A UAR apresenta etiopatogenia multifatorial, em que pode estar associada com fatores imunológicos, hereditários, nutricionais, alimentares, psico-emocionais, hormonais e traumas locais, todavia sua relação com microrganismos é controversa. Clinicamente, é classificada de acordo com sua morfologia e com sua evolução clínica. Morfologicamente, se classifica em menor, maior e herpetiformes, e a forma menor apresenta maior ocorrência. Portanto, a UAR trata-se de uma lesão frequente em mucosa oral, em que a forma menor tem maior frequência, e apesar de sua etiopatogenia incerta, estudos indicam que fatores imunológicos, traumáticos, hereditários, hormonais, nutricionais e psico-sociais apresentam relação direta com seu desenvolvimento.

Palavras-chave: *Úlcera Aftosa. Fatores Predisponentes. Patologia.*

1 Introduction

The term *aphtae* originates from the Greek "aphtai" and was used by Hippocrates (460-370 BC) to describe disorders of mouth[1] and, in 1898, von Miculicz and Kummel[2] published the first clinical case on recurrent aphthous stomatitis. According to Boras and Savage[3], recurrent aphthous ulcer - RAU is an immunologically mediated and non-vesicular oral mucosa disease, described as the discontinuity of the mucous epithelium associated with exposure of the lamina propria. It is one of the most frequent lesions in the oral cavity, occurring in approximately 20% of the general population.

RAU is considered the second ulcerated lesion with the greatest occurrence in the oral cavity, in which it loses only for traumatic ulcer. It is predicted for the second decade of life and the region of non-keratinized mucosa, especially labial and jugal mucosa, which are the most frequently involved[4]. It presents painful symptomatology and clinically manifests itself with a round or ovoid shape, with regular and well-defined borders, surrounded by an erythematous halo and

covered by a white or yellow pseudo membrane. The initial symptoms manifest with burning in about two to 48 hours before the onset of the lesion, followed by the appearance of the localized area of erythema. In a few moments, a small ulcerated white papule develops and gradually increases between 48 and 72 hours[1].

Clinically, the aphthous ulcers are divided into smaller, larger and herpetiform ulcers. The smaller form is the most common, manifesting as a circular, ovoid or elongated lesion in the region of the jugal and labial mucosa, or as a more elongated lesion in the vestibule bottom. The larger form presents about 10-50 millimeters (mm) in diameter, is deeper and can extend to the gum and pharyngeal mucosa. Whereas the herpetiform pattern is the most unusual, presenting multiple small lesions (<2 mm) in non-keratinized mucosa[5].

Its etiology is not well elucidated, however, local, nutritional, hormonal, hereditary, immunological and psycho-emotional correlate with lesion development[4]. Individuals with nutritional deficits, especially iron, folate, zinc and B-complex vitamins, can more frequently manifest RAU. Furthermore, it is believed that these lesions may also be associated with syndromes of bad absorption or sensitivity to gluten, microbial factors, T-cell-mediated cross-reactions and *Streptococcus sanguis antigens*, as well as to the mitochondrial Heat Shock Protein (HSP)[1].

The role of specific cells in RAU has already been determined through the use of sensitive labeling forms for mast cells, which are cells responsible for the production of inflammatory markers[6]. Nathan et al.[7] have shown that these cells are 65% more diverse in RAU than in normal mucosa and have demonstrated signs of activation and degranulation, which suggests activity in the pathogenesis of this lesion. Furthermore, immunohistochemical studies have demonstrated the participation of inflammatory cells of varying conformities and $CD4^+$ and $CD8^+$ T lymphocytes present a prominent role in the clinical manifestation and in the duration of the lesions[1,4,6].

It is noted that the diversity and uncertainty of etiological factors make it difficult to develop a specific therapy for RAU and highlights the need for studies that seek a greater understanding of the pathophysiology of the lesion. In this context, the present study aimed to address a narrative review of the literature on etiopathogenesis and clinical aspects of RAU, with emphasis on understanding the causes of the disease and related physiological changes.

2 Development

2.1 Methodology

This was a descriptive and exploratory study, developed through the narrative review of the literature, carried out on the basis of electronic platforms: *PubMed*, Scientific Electronic Library Online (*SciELO*) and Latin American and Caribbean Health Sciences literature *(Lilacs),* as well as the gray literature of Google Academic, in the period from December 2022 to July 2023. The search took place at the intersection as a Boolean AND operator, with the following descriptors in Health Sciences (DeCS/MeSH): "*aphthous ulcers*" AND "*predisposing factors*" AND "*Pathology*", and in Portuguese "úlceras aftosas" AND "fatores predisponentes" AND "patologia". Articles addressing clinical characteristics related to RAU, as well as its etiopathogenesis, were selected.

Table 1 summarizes the identified and selected studies.

Table 1 - Crossing of DeCS/MSM descriptors and studies identified and selected

Database	Crossing	Sample Identified	Excluded	Final Sample
PubMed	"*aphthous ulcers*" AND "*predisposing factors*" AND "*Pathology"*	3	3	0
Scielo	"*aphthous ulcers*" AND "*predisposing factors*" AND *"Pathology*"	0	0	0
Lilacs	"*aphthous ulcers*" AND "*predisposing factors*" AND *"Pathology"*	4	3	1
Google Acadêmico	"úlceras aftosas" AND "fatores predisponentes" AND "Patologia"	3,040	3,026	14
Busca Livre	-	10	-	10
Total		1,376	1,347	**25**

Source: resource data.

Initially, three articles were identified in *PubMed*, four in Lilacs and 3,040 in Google Acadêmico The inclusion of articles that evidenced the topic addressed, in the English, Portuguese, and without a defined period of publication, in addition to all types of studies, was carried out. Papers that did not contain contextualized information were automatically excluded, as well as studies without their receptive abstracts in the electronic bases.

After initial critical analysis of the titles and abstracts, 15 articles were included. In a secondary way, a free search was performed with a view to complementing the theoretical rationale, by searching articles in the references selected in the first step of refinement, with the addition of 10 manuscripts, which totaled 25 studies in the final sample.

2.2 Etiopathogenesis of the Recurrent Aphthous Ulcer (RAU)

The etiopathogenesis of RAU is multifactorial, resulting from the interaction of local and systemic factors[6]. It is believed that there is a correlation between RAU and immunological, genetic, nutritional deficiency and food

allergy factors, in which there is also a possible association with the presence of immunological and (or) physiological stress, hormonal changes and oral hyperacidity[1,6,8]. Table 2 compiles the possible etiopathogenic factors related to RAU, according to the current literature.

Table 2 - Summarizing the etiopathogenic aspects related to RAU

Nutritional Deficiencies	Vitamin deficiency of complex B (B1, B2, B6 and B12), vitamin D, iron, folate and zinc[5,9].
Food	Cow's milk, hard-mass cheese, chocolate, nuts (nuts, peanuts and almonds), acid fruits, wheat flour and coffee[5].
Psycho-emotional	Psychological stress is considered a major trigger, due to the increased cortisol level considered the "*stress hormone*"[5,15].
Immunologic	The relationship between sores and immunological dysfunctions has been presented when lymphocyte intensification is observed, as demonstrated by the reduction of effective CD4 + lymphocytes and the increase of the CD4 + lymphocytes in memory[6,8].
Local trauma	Dental brushing, malocclusion and orthodontic braces[5,8,10].
Female sex hormones	Hormone imbalance phases, such as menstrual cycle and menopause[5,21,22].
Hereditary factors	Individuals who have a family history with oral ulceration tend to commit the same clinical signs[10,16,17].

Source: resource data.

The relationship between aphthous ulcers and immunological dysfunctions has been presented in the literature when observing lymphocyte intensification, proved by the reduction of T CD4 + lymphocytes and the increase of the T CD4 + lymphocytes in memory[8]. The auxiliary T cell (Th1) also plays a prominent role in its etiopathogenesis, with a more frequent presence in patients with autoimmune disease, who present oral ulcers[6]. In addition, the Tumor Necrosis Factor alpha (TNF-α) may be related to the development of RAU, since it stimulates the expression of the fundamental complex of histocompatibility and, consequently, causes a cytotoxic response and ulceration of the mucosa[6,8].

The role of neutrophils in the occurrence of RAU is still not well elucidated. The chemotactic and phagocytic functions, as well as the elaboration of toxic oxygen radicals, were not exacerbated in relation to healthy patients, however, an immense concentration of these defense cells was observed in the ulcerative phase of the lesion, which may suggest an active participation[4,7]. It is assumed that neutrophils produce matrix metalloproteinases 8 (MMP-8), since these proteolytic enzymes were found intracellularly in the ulcer area and in the extracellular basal membrane, laterally to the ulcer, in a way that collaborated with the destruction of local tissue[7].

It is believed that macrophages act through the mechanism of "cleaning" of remaining neutrophils in the ulcerated area, since in histopathological studies, the presence of macrophages loaded with foligosomes containing granulocyte neutrophil residue was verified[4,7].

Nutritional deficiencies, especially of B-complex vitamins (B1, B2, B6 and B12), vitamin D, iron, folate and zinc may be associated with RAU[5,9]. Thus, a large deficiency of iron, folic acid or even vitamin B12 can cause anemia, which consequently reduces oxygen transport to the mucosa of the oral cavity and promotes degeneration of this region. Furthermore, these same constituents have as their characteristic to act in cell division and DNA synthesis, functions that aid in the normal performance of epithelial cells[5].

Otherwise, eminent blood homocysteine levels of RAU patients were found in association with vitamin deficiency of complex B (B6 and B12) and folic acid. That is, this high level can cause epithelial damage, which favors ulceration[9].

Trauma is considered a local etiological factor triggering RAU lesions. Dental brushing, malocclusion, orthodontic and prosthetic devices may be considered as the main responsible factors[8,10]. In addition, certain types of food may favor the appearance of RAU, especially cow's milk, hard-mass cheese, chocolate, nuts (nuts, peanuts and almonds), acid fruits, wheat flour and coffee. Ulcers are believed to occur due to a strong association between levels of anti-milk proteins of cow immunoglobulin A (IgA), IgE and IgG and the clinical manifestation of RAU[5].

Syndromes are capable of causing lesions that resemble RAU lesions. In Sweet's Syndrome, also called acute neutrophilic dermatosis, the affected patients present superficial ulcerations similar to RAU, in addition to fever, leukocytosis and well-demarcated papules or skin plaques with plum color[11]. Behcet's Syndrome is a vasculitis that is evidenced by ulcerations in oral and genital mucous membranes, in addition to ocular lesions. These ulcerations may be more severe through the herpetiform pattern[5,11].

In an epidemiological study carried out in Kuwait by Favaro[12], the predominance of RAU between urban and desert populations was assessed, and it was observed that the prevalence of ulcers in Bedouins is lower (5%) than in urban inhabitants (22%). This result was credited to the quality of life and to the stressors of urban places. In 2004, Araya et al.[13] demonstrated that the degree of stress in patients with RAU is almost double (61%) that found in the control group. However, in the study of[14], no patterns of association between stress and the immune system were identified.

Psychological stress can cause RAU development[15]. Stress binding and the appearance of aphthous ulcers are presented by several causes. In a stress situation, the increase in cortisol in serum, urine and saliva is identified, which generates stimulation of immunoreaction and increase in the number of leukocytes in the inflammation region. As a result, the parasympathetic nervous system and the regulation of the sympathetic branches, with changes in the HPA axis (hypothalamus-pituitary-adrenal), is modified because of stress. The autonomous increase of hormones produced by the HPA axis and cortisol stimulation promote leukocyte increase

in regions of inflammation associated with psychological stress, characteristic in the pathogenesis of RAU[5].

In some individuals, RAU may have a hereditary basis[16]. Approximately 40% of patients with these lesions have a family history and develop oral ulcers at an earlier age[17]. The probability of a child developing RAU is influenced by parents and there is also a high probability that identical twins will acquire these lesions. However, a direct association of RAU with serology by human leukocyte antigen (HLA) or haplotype is controversial. According to Kuntz et al.[18], the HLA-B12 antigen is present in patients with aphthous ulcers. However, according to[10,17], HLA-B5 antigen is not increased in these patients, although individuals diagnosed with Behçet syndrome present this same antigen in 75% of the cases. The same authors found that combinations of HLA-A2 with HLA-A29 and HLA-B12 were constant in patients with RAU, suggesting a possible relationship between RAU and haplotypes[10,17].

When it comes to the correlation between RAU and microorganisms, the literature is controversial. Strong association between *Streptococcus viridans* and these ulcers could be verified, since this bacterium proceeded as antigen and promoted immunologic reaction[19]. However, it is worth pointing out that *Streptococcus viridans* is not specific for patients with RAU. According to Scully et al.[20], *Helicobacter pilori* was located in 72% of the ulcers examined by Polymerase Chain Reaction (PCR). However, other studies have shown that the frequency of IgG antibodies to *Helicobacter pilori* has not been increased in RUA patients[10,19].

Female sex hormones (estrogen and progesterone) can act in the development of RUA[21]. Hormone imbalance phases, such as menstrual cycle and menopause, would be favorable to the onset of lesions[22]. In fact, it was detected that in the period of the menstrual cycle, ulcers appear a few days before menstruation (during the luteal phase: seven days after ovulation). In another way, ulcer remission was observed in women under hormonal contraception or during pregnancy[5].

Although RUA is a frenzy lesion with multifactorial etiopathogenesis, there is still no consensus in the literature in force on all the aforementioned causal factors, which requires studies with this focus, since this may facilitate the determination of possible therapeutic agents for this purpose.

2.3 Clinical aspects of Recurrent Aphthous Ulcer (RAU)

Cooke and Lehner[24] classified the canker sores from the morphological point of view according to size, in larger, smaller and herpetiformes, in addition to duration and residual healing (Table 3). The most common lesions are the smaller ones, diagnosed in approximately 80% of the population, followed by the larger ones, with a preponderance of 10% and herpetiformes, with a frequency of less than 10%.

Table 3 - Morphological classification according to RUA size, based on the proposal of Cooke 1960[24]

Classification	General Characteristics
Smaller	More frequent – 80% of cases; Individuals between 10 and 40 years; Ulcer in oval or round shape; After the appearance of the ulcer, a gray or yellowish pseudo membrane is formed in the center of the lesion, between seven and 10 days; Diameter: Up to four mm; Main sites: floor, labial and oral mucosa, tip and ventral surface of the tongue; Pain, prodrome mentioned with burning or hypersensitivity; They do not form scars.
Larger	More unusual – 10% of cases; More frequent in puberty; Diameter: >1 cm - deep; They affect any oral mucosa site; Recurrent and pain of higher intensity; They may form scars.
Herpetiformes	More unusual – 10% of cases; More often in women of advanced age; They preferentially affect the region of mouth, apex, lateral and ventral surfaces of the tongue; Diameter: 1-3 mm that aggregate; Numerous (10 to 100 sores per episode), recurrent and painful; fast tissue repair, which occurs between seven and 10 days.

Source: Oliveira[1]; Pereira[4]; Alves[8]; Curvelo[14]; Cooke[24].

Minor sores affect individuals between 10 and 40 years of age, have an oval or round shape, measure up to four mm in diameter and are associated with pain. They occur preferentially on the floor, labial and oral mucosa, tip and ventral surface of the tongue, and keratinized mucosa is rarely affected. They may be preceded by a prodrome mentioned with burning or hypersensitivity in the two days preceding the appearance of erythematous papule or "white dot"[14]. After the appearance of the ulcer, a gray or yellowish pseudo membrane is formed in the center of the lesion, between seven and 10 days after the first signals.

The larger sores have a dimension >1 centimeter (cm) and are characterized by a longer evolution and pain of greater intensity, with the possibility of causing facial edema[4]. They are more common in puberty and can recur again chronically for more than 20 years. They affect any site of the oral mucosa and involute between 10 to 40 days, or even months later, while new lesions manifest. Unlike the smaller sores, which are limited to the superficial region of the lamina propria in the submucosa, the larger sores reach the submucosa in a deep way and the adjacent tissues, which may cause scars. Clinical signals of dysphagia and fever may be present in cases of secondary infection by bacteria and/or fungi, and otalgia or odynophagia may be reported when the aphthous lesion is located close to the oropharynx region. The larger ulcers in the tongue and in the mouth floor are capable of presenting a slight regional, ipsilateral adenomegaly[8].

Herpetiform sores are numerous, recurrent and painful,

with clinical manifestation of 10 to 100 sores per episode and may present different proportions, ranging from one to three mm in diameter and coalesce forming larger and regular lesions. They affect women of advanced age more often and occur preferentially in the oral floor region, as well as apex, lateral and ventral surfaces of the tongue. Despite numerous, the herpetiform pattern is characterized by a fast tissue repair, which occurs between seven and 10 days [4].

RUAs were also classified according to the phases of clinical evolution. According to Stanley[25], there are four fundamental clinical stages of the evolution of aphthous lesions, namely: prodromic, pre-ulcerative, ulcerative and cicatricial. The first stage is transitory and corresponds to the initial 24 hours, characterized by the recruitment of blood-stream lymphocytes. The individual may experience tingling, burning, pain and local hyperemia, with no perceptual signal at physical examination of the mucosa. The second stage, however, lasts from 18 hours to three days and is marked by the appearance of a small hardened erythematous macula or papule, involved by an erythematous halo. In this stage, pain can be moderate to severe and ulcers have an oval shape, when they preferentially affect the oral and labial grooves, or a rounded shape when present in the jugal and labial mucosa[1].

The histological analysis of the second stage indicates the presence of lymphocytes in the basal layer of the epithelium, whose cytotoxicity will gradually culminate in the ulcerative stage. The third stage lasts from one to 16 days and is characterized by an increase in the size of the lesions, acquiring the largest diameter between the fourth and sixth days. It is at this stage that the aphthous ulcer will assume one of the three morphological characteristics previously mentioned (larger, smaller or herpetiformes). The death of epithelial cells and consequent exposure of the underlying connective tissue will give rise to ulcer itself. Gradually, the lesion will be covered by a gray or yellowish membrane, surrounded by an erythematous halo with associated painful symptomatology. Finally, two to three days after the appearance of the ulcer, pain suddenly ceases and the lesion resumes for healing or last stage[6].

Healing of the aphthous lesions can last between four to 35 days. A granuloma is formed on the exudative surface and, from the marginal epithelium, a new epithelial tissue is progressively proliferating into the center, where it binds the lesion borders, normally without residual scar. It should be emphasized that, because they deeply affect the tissue, the larger aphthous ulcers can cause scars. The literature also mentions a fifth stage, called remission, that covers the free periods of lesion, with the potential to naturally evolve to the pre-ulcerative phase, or after an potentiating event. The relationship between ulcers and immunological dysfunctions has been presented in the literature when observing lymphocyte intensification, proved by the reduction of T CD4 + lymphocytes and the increase of the T CD4 + lymphocytes of memory[1].

3 Conclusion

RUA is a common lesion, with a predilection for non-keratinized mucosa and that, according to its morphological classification, the lower pattern presents a higher occurrence. Although its etiopathogenesis is not yet completely elucidated, studies affirm that its appearance has a relationship with immunological, hormonal, nutritional, nutritional, psycho-emotional and hereditary factors. Moreover, there seems to be the participation of defense cells through neutrophils and macrophages in this process, but the role of microorganisms and haplotypes is still controversial.

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