

Essentials of recurrent aphthous stomatitis (Review)

CÉSAR RIVERA

Oral Medicine and Pathology Research Group, Department of Basic Biomedical Sciences,
Faculty of Health Sciences, University of Talca, Talca, Maule 3460000, Chile

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Abstract. Recurrent aphthous stomatitis (RAS), also known as canker sores, is the most common disease of the oral mucosa. Unlike caries and periodontal disease, patients with RAS are unable to prevent it. The clinical picture of RAS is characterized by recurrent episodes of solitary or multiple painful ulcerations without association with systemic diseases. The objective of this review is to present the essential characteristics of RAS, including its definition, pathogenesis, clinical and microscopic characteristics, proposed experimental models and recommended pharmacological management. This understanding can serve as a theoretical framework for research proposals.

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1. Introduction

Recurrent aphthous stomatitis (RAS), also known as canker sores, is the most common disease of the oral mucosa (1). This review presents key aspects of RAS, integrating clinical, histological and molecular concepts that are important for

every medical professional that encounters this disease to understand.

The clinical picture of RAS is characterized by recurrent episodes of solitary or multiple painful ulcerations (2) without an association with systemic diseases (3). The latter is relevant to ensure that RAS is not confused with aphthous ulcerations.

2. Differential diagnosis and epidemiology

Aphthous ulcerations (or RAS-like ulcerations) have an underlying systemic cause; therefore, they should be considered as a distinct medical condition (3). The differential diagnoses should be established with autoinflammatory syndromes, including periodic fever with adenitis, pharyngitis and aphthae (PFAPA) syndrome, Behçet's syndrome and Crohn's disease; and immunodeficiency states, including nutritional defects (such as celiac disease and other gastrointestinal disorders), immune defects (such as human immunodeficiency virus infection/acquired immune deficiency syndrome) and neutrophil defects (such as cyclic neutropenia) (4). The term RAS should be used for ulceration present in the absence of systemic disease.

The prevalence of RAS varies between 0.9 and 78% in different groups examined. In the US, for the period of 1988-1994 the prevalence was 0.89% in adults (5) and 1.64% in children (6). In Iran (2005), Jordan (2008), India (2010-2012) and China (2013-2017) reported prevalence was 25.2% (7), 70% (8), 21.7% (9) and 27.17% (10), respectively. Its onset appears to peak between 10 and 19 years of age (11) and its frequency decreases with advancing age (12).

3. Pathogenesis

The etiology and pathogenesis of RAS remain unclear. Multiple factors are associated with the establishment of this disease, including a positive family history, food hypersensitivity, smoking cessation, psychological stress and immune disturbance (11,13). However, for this evidence, there is often an absence of statistical risk analysis. Immune dysregulation linked to several triggers may facilitate the development of RAS. The roles of the immune system and inflammatory processes have been confirmed in recent large-scale bioinformatics analyses (14,15). It is known that a Th1-type hyperimmune response favors the appearance of inflammatory reactions that precede ulcerations (Fig. 1) (16,17). In addition, genetic risk factors can determine individual susceptibility

Correspondence to: Dr César Rivera, Oral Medicine and Pathology Research Group, Department of Basic Biomedical Sciences, Faculty of Health Sciences, University of Talca, Campus Norte, Avenida Lircay S/N, Talca, Maule 3460000, Chile
E-mail: cerivera@utalca.cl

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to RAS; in particular, several DNA polymorphisms of the NOD-like receptor 3 (18), toll-like receptor 4 (19), interleukin (IL)-6 (20), E-selectin (21), IL-1 β and TNF- α genes (22). However, despite the large number of factors examined, the underlying cause triggering the episodes of ulcers remains to be elucidated. Therefore, clinically, the emergence of new lesions cannot be avoided at present.

4. Clinical characteristics

RAS is known to be particularly painful (15). These idiopathic ulcerations are oval lesions of different sizes with clean edges surrounded by an erythematous halo. At the center of the ulceration, the necrotic fundus is covered with a yellow-white fibrinous exudate (23). The ulcers typically present in the non-masticatory mucosa of the cheeks, lips, ventral and lateral surfaces of the tongue, non-attached gingiva, and occasionally, the soft palate (24). RAS lesions are self-limiting (simple aphthosis), resolving within 1-2 weeks in the majority of patients (25). In those affected by the disease, the ulcers can compromise important daily functions, including nutrition, speech and oral hygiene (26), and affect quality of life (27). This is important, considering that the lesions can last >2 weeks, with recurrent episodes in a period of 1-4 months (11). RAS occurs in three morphological presentations: Minor-type (Mikulicz ulcers, 2-10 mm in diameter), which is the most common (Fig. 2); major aphthous, also termed Sutton ulcers or periaadenitis necrotic mucosa (>10 mm in diameter); and herpetiform ulceration, which consists of multiple small ulcers (28). Some patients have continuous oral ulcerations; in these cases, some ulcers heal as others develop, with occasional genital ulcers. This corresponds to a clinical state known as complex aphthosis (11). Complex aphthosis has an underlying systemic cause, which does not correspond with the RAS diagnosis.

5. Disease phases

The disease sequence comprises the following stages: Premonition (24 h), comprising symptoms but no visible signs of disease; pre-ulcerative (between 18 h and 3 days), comprising erythema and mild edema; ulcerative (1-16 days), comprising active ulceration; healing (4-35 days, usually <21 days), involving a decrease in symptoms and progressive healing; and remission, in which there is no evidence of ulcers (29). The ulcerative and remission phases are those that can be evaluated with greater objectivity on dental examination. Disease recurrence is established with the appearance of new ulcers. Disease severity can be determined based on the number, size and location of the lesions, pain, duration, ulcer-free periods (30) and the impact on patient quality of life (27,31).

6. Microscopic characteristics

The diagnosis of RAS is eminently clinical and is based on careful examination. The incisional or excisional biopsy of ulcers is recommended only in cases of uncertainty, when the presence of an oral disease producing ulcers or a malignancy is suspected (32). The microscopic characteristics of RAS are nonspecific. The pre-ulcerative lesion shows subepithelial

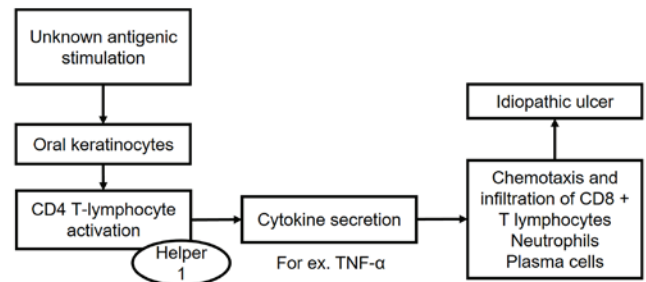


Figure 1. Cell-mediated immunity in the pathogenesis of recurrent aphthous stomatitis. Lymphocytic cells infiltrate the oral epithelium and edema develops as a result of inflammatory stimuli. Keratinocyte vacuolization and localized vasculitis cause a papular swelling. The papule ulcerates and is infiltrated by neutrophils, lymphocytes and plasma cells, followed by healing and regeneration of the epithelium. Adapted from Cui *et al* (24).

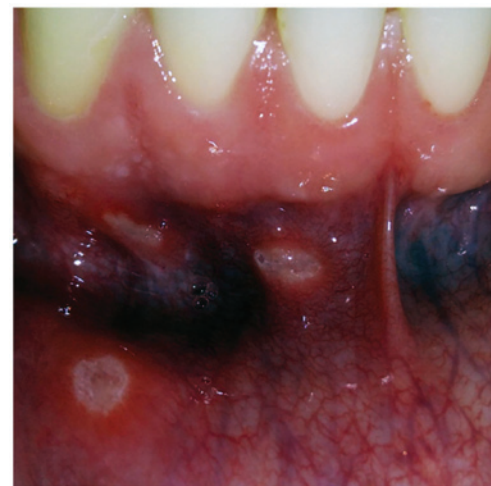


Figure 2. Small ulcers of recurrent aphthous stomatitis minor-type (Mikulicz ulcer). These ulcers are painful.

inflammatory mononuclear cells with abundant mast cells, edema of the connective tissues and neutrophils lining the margins. Damage to the epithelium usually begins in the basal layer and progresses through the superficial layers, ultimately leading to ulceration and surface exudation (2,11).

7. Experimental models

At present, the only way to examine this disease has been in those patients who suffer from it. In the English literature, two models for the experimental evaluation of RAS have been proposed, both using rabbits. One of the models induces ulcers with 50% acetic acid (33,34) and the other by surgical incision in the oral mucosa (35). Neither registered methods are involved in the inflammatory processes described in RAS. As RAS is an immunologically-mediated disease, the chemical and mechanical induction of ulcers cannot be considered valid models.

8. Treatment

Therapeutic alternatives focus on reducing painful symptoms (36). Clinically, dental surgeons at present can advise patients that the ulcers are likely to heal in 2 weeks, and in

more complex cases, treatment based on topical corticosteroids can be implemented (37), which is the same approach used for several diseases of unknown cause, including pemphigus, pemphigoid and oral lichen planus. Despite the use of topical corticosteroids over several years for RAS, there is a lack of high-quality evidence for their efficacy (38) and even less for systemic interventions (31). However, the recommended protocol is a combination of a topical corticosteroid plus a topical anesthetic and a buccal antiseptic (38). The combination includes triamcinolone (0.1% paste, up to four times daily) in addition to topical lidocaine (2% viscous solution, maximum 8 doses/day) and oropharyngeal chlorhexidine (0.12%, 15 ml as a mouthwash twice daily) as an adjuvant (4). Patients should be instructed to avoid recognized trigger foods, and acidic foods and drinks (39).

9. Conclusions

The key concepts associated with RAS are as follows: Its cause is unknown, it cannot be prevented, it is immunologically mediated, diagnosis is clinical, there are no experimental models for its investigation, and recommended treatment includes a combination of corticosteroids and topical anesthesia plus an antiseptic. Taking these key concepts into account, several questions require further biomedical research. These include determining what the molecular differences are between a healthy individual and a patient with RAS, determining which molecules are involved in the ulcerative phase of disease and the phase of disease remission, and establishing whether there are molecules that can predict the clinical course and the severity of ulcers. Answering these questions can open up novel therapeutic and preventive possibilities.

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CR conceived the review and analyzed the relevant literature. CR sourced the literature and wrote the manuscript. CR critically revised the manuscript, produced the figures and have read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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