Critical review of the etiopathogenesis of recurrent aphthous stomatitis

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Abstract

Background: Recurrent aphthous stomatitis is one of the most common diseases affecting the oral mucosa, and one of its variants is the most painful affliction of the oral mucosa.
Aim: To search for new immunologic pathways of the disease for the purpose of developing an accurate treatment and simplifying diagnostic procedures.
Methods: A literature search was made of the PubMed, Cochrane, and Scopus databases, limited to articles published between 2020 and 2026, with scientific levels of evidence 1 and 2 (meta-analyses, systematic reviews, phase I and II randomized clinical trials, cohort studies, and case-control studies), and conducted in humans.
Results: The present article provides a detailed review of the current knowledge of the etiology and pathogenesis of recurrent aphthous stomatitis.
Conclusions: Recurrent aphthous stomatitis (RAS) is a complex condition with no single identifiable cause. It is considered multifactorial, involving interactions between genetic predisposition, immune dysregulation, environmental triggers, and systemic factors. Genetic factors, particularly HLA variants and cytokine polymorphisms, influence disease susceptibility and severity, while immune mechanisms—such as increased pro-inflammatory cytokines and abnormal T-cell responses—play a key role in mucosal damage. (**TCM-GMJ August 2026; 11 (3): P25-P29)**

Keywords: Recurrent Aphthous Stomatitis, Etiology, Pathogenesis, Immune Dysregulation, Genetic Factors, Nutritional Deficiencies, Microbial Factors.

Introduction

Recurrent aphthous stomatitis (RAS) is the most common oral ulcerative disease with unknown etiology. Its prevalence in the general population varies between 5 and 25%, with its peak appearance in the second decade of life. (2) Hippocrates (460 to 370 BC) is credited with the first use of the word "aphthai" regarding oral diseases, although he was probably referring to thrush. The term aphthae is derived from the Greek word *aphthi*, which means “to set on fire” or “to inflame.” (21) In the writings of William Shakespeare, some characters averred that they would be cursed with blisters of the tongue·for speaking an untruth: "If I prove honey mouth'd, let my tongue blister" (Paulina, The Winter's Tale 2.2.32). Juliet was not above cursing her nurse for shaming Romeo: "Blister'd be thy tongue for such a wish!" (Juliet, Romeo and Juliet 3.2.90). These references to "blisters of the tongue" might well refer to RAS, as the tongue is commonly involved (19)

The first valid clinical description of RAS was published by Mikulicz and Kummel in 1888 (12). Sutton described the first case of major aphthous ulcers in 1911 and coined the phrase “periadenitis mucosa necrotica recurrens,” which is considered “major aphthous ulcers” nowadays (5). Cooke described “herpetiform” ulcers, whose clinical appearance was very similar to herpesvirus, but cytologic, serologic, cultural, or histopathologic methods could not detect a virus (3). Cooke was the first to classify RAS into 3 clinical forms: minor aphthous ulcer, major aphthous ulcer, and herpetiform ulcers (Table 1)

Minor aphthous ulcers are the most commonly encountered form. This type usually appears as a single, painful, oval ulcer that is less than 0.5 cm in diameter on nonkeratinized mucosa, covered by a yellow fibrinous membrane and surrounded by an erythematosus halo (Figure 1). Minor aphthous ulcers generally last 7 to 10 days and heal without scar formation.

Major aphthous ulcers are larger (>0.5 cm) and more painful and persist longer than minor aphthae (Figure 2). Because of the depth of inflammation, major aphthous ulcers clinically appear crateriform and heal with scar formation. Lesions may take as long as 6 weeks to heal. The

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predilection for movable oral mucosa is as typical for major aphthous ulcers as it is for minor aphthae (18).

Herpetiform aphthous ulcers present clinically as recurrent crops of small ulcers (Figure 3). Although the movable mucosa is predominantly affected, the palatal and gingival mucosa may also be involved. Pain may be considerable, and healing generally occurs in 1 to 2 weeks. Unlike herpes infection, herpetiform aphthous ulcers are not preceded by vesicles and exhibit no virus-infected cells (Table 2).

Methods

This literature review was conducted to evaluate current evidence on the etiopathogenesis of recurrent aphthous stomatitis (RAS). A comprehensive search of electronic databases, including PubMed, Cochrane, and Scopus, was performed for studies published between January 2000 and December 2025.

Search terms included combinations of keywords such as "recurrent aphthous stomatitis," "etiology," "pathogenesis," "immune dysregulation," "genetic factors," "nutritional deficiencies," and "microbial factors."

Inclusion criteria comprised:

- Peer-reviewed original research articles, systematic reviews, and meta-analyses
- Studies focusing on etiological or pathogenic mechanisms of RAS
- Articles published in English

Exclusion criteria included:

- Case reports, editorials, and conference abstracts
- Studies not directly addressing etiopathogenesis

Two independent reviewers screened titles and abstracts for relevance, followed by full-text assessment of eligible articles. Discrepancies were resolved through discussion or consultation with a third reviewer.

Data extracted from selected studies included study design, sample size, investigated etiological factors (e.g., immunological, genetic, nutritional, microbial), and key findings related to disease mechanisms.

Results and discussion

Although the cause of aphthous ulcerations is unknown, several possibilities have been postulated. Several theories describing the etiopathogenesis of RAS have been described in the literature. The nature of the initiating stimulus remains a mystery. The causative agent could be an endogenous (autoimmune) antigen or an exogenous (hyperimmune) antigen, or it could be a nonspecific factor, such as trauma, in which chemical mediators may be involved. The pathogenesis of RAS is multifaceted, with significant physiological interplay between the immune system, genetics, and environmental factors. Genetic factors include certain human leukocyte antigen variants and cytokine gene polymorphisms that influence immune responses, impacting susceptibility and recurrence patterns. The role of genetic predisposition in recurrent aphthous stomatitis was first suggested by Miller *et al.* in 1977 and by Ship in 1965, who proposed an autosomal recessive or multigene mode of inheritance with a modulating influence of the environment. Patients with a positive family history of RAS may develop oral ulcers at an earlier age and exhibit more severe symptoms than those without a family history of oral ulceration (20). The probability of a sibling developing RAS is influenced by the parents' RAS status (Ship, 1972), and there is a high correlation of RAS in identical twins (13)

Hila Yousefi and Morteza Gholami conducted a systematic review and meta-analysis of the role of genetic polymorphisms in recurrent aphthous stomatitis. They identified six polymorphisms in four genes: IL-1β-511, IL-1β+3954, IL-6-174, IL-10-592, IL-10-1082, and serotonin transporter. (24).

Lee and co-authors performed a retrospective review of medical records from 1203 patients treated at a tertiary hospital between June 2012 and June 2017. Data regarding HLA-B51 status and clinical conditions were extracted, and patients were classified according to the "Revised Japanese Diagnostic Criteria for Behçet's disease (1987)", resulting in 878 patients diagnosed with complete (n = 250) and incomplete (n = 628) BD. Among these patients, 400 (45.6%) tested positive for HLA-B51, with the positivity rate increasing progressively with symptom severity. (9).

Immune mechanisms involve heightened pro-inflammatory cytokine activity, abnormal T-cell responses, and programmed keratinocyte death pathways such as PANoptosis, which collectively lead to mucosal damage. It is currently thought that an unknown antigen stimulates keratinocytes, resulting in cytokine secretion and leukocyte chemotaxis. TNF-α has been found to be significantly increased in the saliva of RAS patients. Surboyo et al performed a systematic review and meta-analysis about the expression of TNF-α in recurrent aphthous stomatitis, and they found that healthy individuals showed significantly lower TNF-α than RAS (SMD = -1.517, 95% CI [-2.25, -0.78]). Although there is a significant difference between the samples, and TNF-α was concluded as a useful diagnostic marker for RAS (i.e., saliva, serum) and detection type (i.e., cytometry bead array, ELISA), both methods can detect a significant difference in TNF-α between healthy individuals and RAS patients (23).

Similar to other chronic inflammatory conditions, deoxyribonucleic acid (DNA) damage secondary to oxidative stress is thought to play a large role in recurrent ulcerations. In order to cleanse the radicals produced by the generation of reactive oxygen species (ROS), the body develops antioxidant systems. Antioxidants regulate ROS production under normal physiological circumstances so that it does not affect the tissues and organs; however, oxidative stress induces an imbalance in these antioxidant mechanisms. As a result, components in the body, like lipids, DNA, and proteins, are harmed by oxidation (10) For example, superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) are erythrocyte antioxidant enzymes that play a crucial role in the oxidative stress defense system and have been linked to RAS. Ghasemi et al found that erythrocyte superoxide dismutase and Glutathione peroxidase activity were significantly lower in patients with RAS compared to healthy controls (SMD = − 1.00, 95%CI = -1.79 to -0.21, p = 0.013, and SMD = − 1.90, 95%CI = -3.43 to -0.38, p = 0.01, respectively) and the total antioxidant status (TAS) level, in serum was significantly lower in RAS patients than healthy controls (SMD = − 0.98, 95%CI = -1.57 to -0.39, p = 0.001) (6).

Light and electron-microscope examination of oral aphthous ulcers showed a penetrating, early, lympho-monocyte infiltration of the epithelium. Mononuclear cells normally infiltrate the basal -cell and prickle-cell layers of the epidermis, and they are most commonly lymphocytes and monocytes, but superficial to and immediately adjacent to the ulcer, neutrophil polymorphs were also found. The immuno-fluorescent studies showed predominantly IgG and IgM binding only in autologous tissues from

patients with aphthous ulcers (1)

Bacterial (Streptococcus oralis, Helicobacter pylori) and viral (HSV, varicella-zoster virus, cytomegalovirus, and adenoviruses) antigens have been reported to be potential factors that may modify the immunologic response and subsequently induce recurrent aphthae in predisposed subjects. However, the results of these studies are ambiguous and conflicting (22). In addition, Greenspan et al. concluded that neither cell-mediated hypersensitivity to streptococcal or viral antigens nor cross-reactivity between oral mucosal and streptococcal antigens is likely to play a role in the pathogenesis of RAS (7)

Deficiencies in iron, zinc, and B vitamins impair the mucosa's ability to repair and defend against oxidative stress, worsening tissue damage. Moreover, iron is essential for the normal functioning of oral epithelial cells, and both vitamin B12 and folic acid play important roles in DNA synthesis and cell division. Oral epithelial cells have a high turnover rate. Therefore, deficiencies of iron, vitamin B12, and folic acid may result in oral epithelial atrophy (15). Khan et al.48 evaluated deficiencies of Hb, hematocrit, serum vitamin B12, serum ferritin, and red blood cells (RBC) folate levels in 60 RAS and 60 age- and sex-matched healthy control subjects without RAS. They found that the hematocrit ($P < 0.001$), serum ferritin (P Z 0.001), RBC folate ($P < 0.001$), and serum vitamin B12 ($P < 0.001$) levels are significantly lower in the RAS patients than in the healthy control subjects without RAS. Combined deficiency state (including Hb, hematocrit, serum ferritin, serum vitamin B12, and RBC folate deficiencies) is identified in 8 (13%) of 60 RAS patients (8). Piskin et al.56 investigated the serum iron, ferritin, folic acid, and vitamin B12 levels in 35 RAS patients and 26 healthy controls. They demonstrated significantly lower vitamin B12 levels in RAS patients than in healthy controls (16)

Anxiety, stress, and depression are more common in patients with a history of RAS than in healthy people, which suggests that negative emotions may promote the recurrence of lesions (4). One cross-sectional study that evaluated the clinical and demographic factors of RAS found that the condition was related to anxiety but not depression (11). Conversely, by evaluating the relationship between salivary cortisol levels and anxiety and depression in patients with RAS, other researchers found RAS to be related to depression but not anxiety (17). In another study, no correlation was found between RAS and stress, anxiety, and depression (14). Thus, the conclusions of these studies are contradictory, and the relationship between RAS, anxiety, and depression deserves further exploration.

Conclusion

In conclusion, recurrent aphthous stomatitis (RAS) remains a complex and incompletely understood condition with no single identifiable cause. Current evidence supports a multifactorial etiopathogenesis involving a dynamic interplay between genetic predisposition, immune dysregulation, environmental triggers, and systemic factors. Genetic susceptibility—particularly involving HLA variants and cytokine gene polymorphisms—appears to influence both disease onset and severity, while immune mechanisms, including heightened pro-inflammatory cytokine activity and abnormal T-cell responses, play a central role in mucosal damage.

Additionally, oxidative stress and impaired antioxidant defenses contribute to tissue injury, and nutritional deficiencies may further compromise mucosal integrity and repair. Although microbial agents and psychological factors have been implicated, their roles remain inconclusive due to conflicting evidence.

Overall, RAS should be viewed as a multifaceted disorder in which various internal and external factors converge to trigger and perpetuate ulcer formation in susceptible individuals. Further research is needed to clarify the initiating mechanisms and to develop more targeted and effective therapeutic strategies.

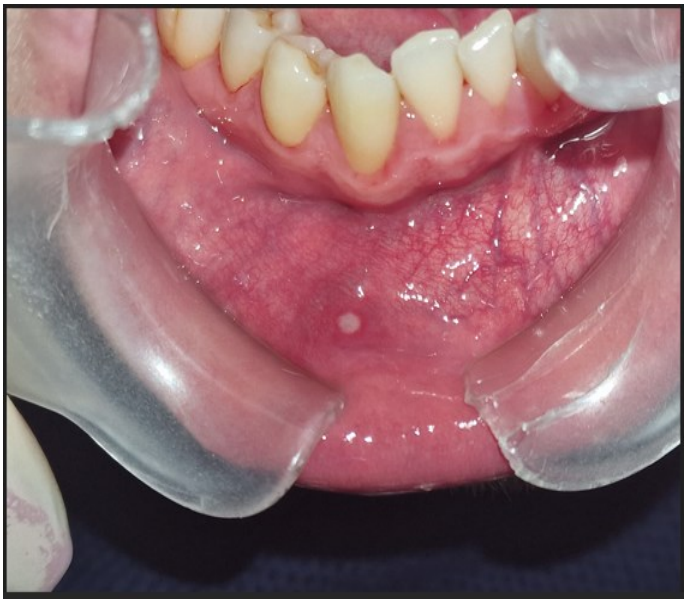

Figure 1. Minor aphthous ulcer on the lower lip mucosa. The picture depicts an ulcer with a yellow fibrinous membrane and surrounded by an erythematosus halo.

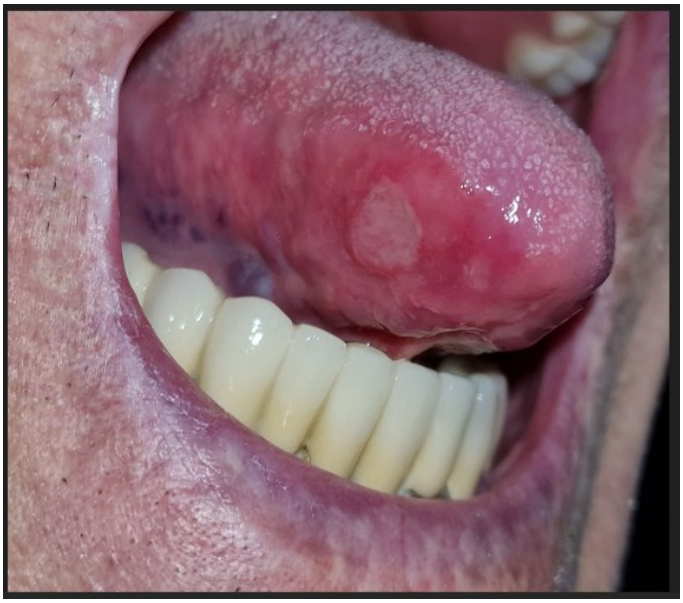

Figure 2. Major aphthous ulcer on the ventral surface of the tongue. When the lateral or ventral surfaces of the tongue are affected, pain tends to be out of proportion to the size of the lesion.

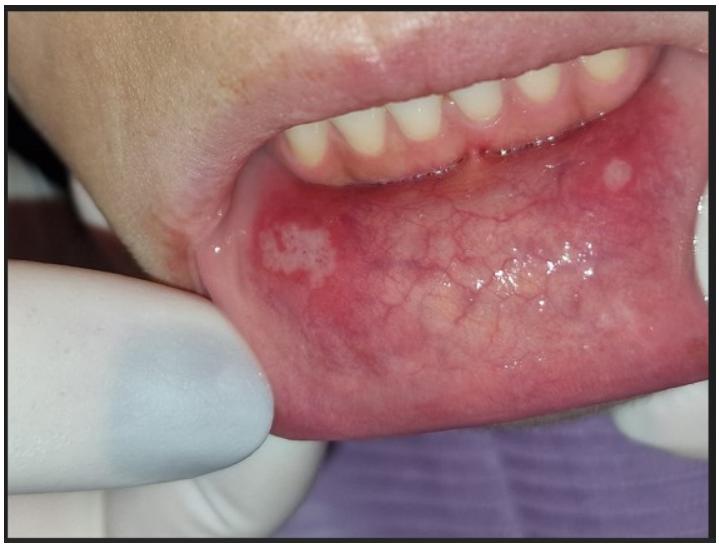

Figure 3. Herpetiform aphthous ulcer on the lower lip mucosa. The picture depicts multiple pinpoint ulcers coalescing into each other.

Table 1. Clinical features of recurrent aphthous stomatitis.

	Minor aphthae	Major aphthae	Herpetiform aphthae
Size	< 5 mm	> 5 mm	< 5 mm
Shape	Oval	Crateriform	Oval
Number	1-5	1-10	10-100
Location	Non-keratinized mucosa	Non-keratinized mucosa	Any intraoral site

Table 2. Comparison of recurrent aphthous stomatitis and Secondary Herpes Simplex Virus

	Aphthous ulcers	Herpes simplex virus
Cause	Immune dysfunction	HSV1
Triggers	Stress, trauma, diet, hormones, depressed immunity	Stress, trauma, ultraviolet light, depressed immunity
Prodrome	Little prodrome	Prodromal symptoms
Appearance	Nonspecific microscopy, no vesicles	Viral cytopathic changes, vesicles precede ulcers
Sites	Nonkeratinized mucosa	Keratinized mucosa
Treatment	Corticosteroids	Antiviral treatment

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