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RECURRENT APHTHOUS STOMATITIS: ETIOLOGY, SERUM AUTOANTIBODIES, ANEMIA, HEMATINIC DEFICIENCIES, AND MANAGEMENT

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Abstract: Recurrent aphthous stomatitis (RAS) is one of the most common chronic inflammatory disorders of the oral mucosa and is characterized by repeated episodes of painful, shallow ulceration on non-keratinized mucosal surfaces. Although its exact cause remains unresolved, current evidence supports a multifactorial pathogenesis involving genetic susceptibility, T-cell-mediated immune dysregulation, local trauma, psychological stress, systemic disease, and nutritional deficiency. Increasing attention has been directed toward serum autoantibodies and hematologic abnormalities in patients with RAS. Studies have shown elevated frequencies of antigastric parietal cell and antithyroid autoantibodies in subsets of patients, suggesting that autoimmune mechanisms or autoimmune comorbidity may contribute to disease expression in selected cases. In parallel, anemia and hematinic deficiencies, particularly iron, vitamin B12, and folate deficiency, are repeatedly associated with RAS and may impair epithelial integrity, oxygen delivery, and mucosal repair. Management is therefore not limited to symptomatic ulcer control; it also requires identification and correction of predisposing systemic abnormalities. First-line treatment remains topical corticosteroid therapy, while severe or refractory disease may require systemic corticosteroids, immunomodulatory therapy, and specialist referral. This article reviews the current understanding of RAS etiology, the clinical significance of serum autoantibodies, the role of anemia and hematinic deficiency, and contemporary management strategies.

Keywords: recurrent aphthous stomatitis, oral ulcers, serum autoantibodies, anemia, iron deficiency, vitamin B12 deficiency, folate deficiency, topical corticosteroids, oral medicine

Introduction

Recurrent aphthous stomatitis is a common oral mucosal disease marked by recurrent, painful ulcers that usually arise on movable, non-keratinized mucosa such as the labial and buccal mucosa, ventral tongue, floor of mouth, and soft palate. Clinically, RAS is classified into minor, major, and herpetiform forms. Minor aphthae account for most cases, are usually less than 1 cm in diameter, and heal without scarring. Major aphthae are larger, deeper, more painful, and may heal with scar formation, whereas herpetiform lesions present as multiple small clustered ulcers that can coalesce.

RAS has major clinical relevance because it causes pain, interferes with eating, swallowing, speaking, and oral hygiene, and substantially reduces quality of life. Despite its frequency, diagnosis remains essentially clinical. There is no single pathognomonic laboratory test for idiopathic RAS, so clinicians must exclude other causes of recurrent oral ulceration, including Behçet disease, inflammatory bowel disease, celiac disease, immunodeficiency, and other vesiculobullous or ulcerative disorders. Persistent ulcers, atypical lesions, systemic symptoms, genital or ocular lesions, or severe adult-onset disease should prompt broader evaluation.

Etiology and Pathogenesis

The etiology of RAS is multifactorial rather than monocausal. Current evidence supports a central role for immune dysregulation, especially a T-cell-mediated inflammatory response targeting the oral epithelium. Histopathologic and immunologic observations indicate that lymphocytic infiltration precedes ulcer formation, and cytokines such as tumor necrosis factor-alpha, interleukin-2, interleukin-6, interleukin-1β, and others participate in mucosal injury and ulcer evolution. Cytotoxic immune activity, amplified by proinflammatory cytokine release, appears to promote epithelial destruction in genetically predisposed individuals.

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Genetic susceptibility is strongly suspected because a positive family history is frequently reported. Environmental and behavioral factors may trigger episodes in susceptible patients, especially minor trauma from sharp teeth, dental appliances, vigorous brushing, or accidental biting. Emotional stress is another common precipitating factor. Smoking cessation has also been associated with the appearance or exacerbation of RAS, possibly because tobacco-related keratinization may reduce mucosal vulnerability in some individuals.

Systemic associations are equally important. RAS-like ulceration may accompany celiac disease, Crohn disease, ulcerative colitis, Behçet disease, HIV infection, and other immunologic or inflammatory conditions. Therefore, RAS should be approached not only as a local oral lesion but also as a potential mucosal marker of broader systemic disturbance. This is especially true in patients with severe, persistent, late-onset, or treatment-resistant disease.

Serum Autoantibodies and Autoimmune Associations

The relationship between RAS and autoimmunity has attracted growing interest. Although RAS is not defined by a disease-specific serum autoantibody, several studies have demonstrated increased frequencies of organ-specific autoantibodies in affected patients. In particular, antigastric parietal cell antibody (GPCA), thyroglobulin antibody (TGA), and thyroid microsomal antibody (TMA, commonly corresponding to anti-thyroid peroxidase activity) have been reported in meaningful subsets of patients. In the review by Chiang et al., prior data from 355 RAS patients showed positivity rates of 13.0% for GPCA, 19.4% for TGA, and 19.7% for TMA. These findings suggest that autoimmune comorbidity is not rare in RAS populations.

The clinical significance of these antibodies is not that they diagnose RAS directly, but rather that they may uncover associated autoimmune disorders with consequences for oral disease expression. GPCA positivity is especially relevant because it may indicate autoimmune gastritis and a predisposition to pernicious anemia and vitamin B12 deficiency. Similarly, thyroid autoantibodies may reveal autoimmune thyroid disease, which has also been linked to a higher frequency of RAS in more recent observational work. A 2023 BMC Oral Health study reported that RAS frequency was significantly higher in patients with autoimmune thyroid disease, reinforcing the concept that autoimmune background may contribute to susceptibility in a subset of patients.

Thus, serum autoantibody testing is not necessary for every patient with occasional minor aphthae, but it is reasonable in recurrent, severe, unexplained, or hematologically abnormal cases, particularly when there are signs of thyroid disease, glossitis, fatigue, pallor, paresthesia, or gastrointestinal symptoms suggestive of autoimmune gastritis or malabsorption. In this context, autoantibodies help identify a clinically relevant systemic substrate rather than merely labeling the oral lesions.

Anemia and Hematinic Deficiencies

Among systemic factors linked to RAS, hematologic abnormalities are among the most practical and clinically actionable. Iron, folate, and vitamin B12 are essential for erythropoiesis, epithelial maturation, DNA synthesis, and mucosal repair. Deficiency in any of these can weaken mucosal integrity, reduce resistance to trauma, impair healing, and alter local immune responses. This provides a biologically plausible explanation for why hematinic deficiency can predispose to recurrent oral ulceration.

The association has been documented repeatedly. Chiang et al. reported that, among 273 RAS patients, anemia was present in 20.9%, iron deficiency in 20.1%, vitamin B12 deficiency in 4.8%, folic acid deficiency in 2.6%, and hyperhomocysteinemia in 7.7%. These abnormalities were significantly more frequent than in healthy controls. Such findings support routine hematologic screening, especially in patients with frequent recurrences, major aphthae, associated glossodynia or atrophic glossitis, fatigue, or poor response to empirical local therapy.

Iron deficiency deserves special emphasis because it is often the most common abnormality in RAS cohorts. Reduced iron stores may impair oxygen transport and epithelial turnover, increasing mucosal fragility and delaying re-epithelialization. Vitamin B12 and folate deficiency

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similarly interfere with DNA synthesis in rapidly dividing epithelial cells and may contribute to atrophic oral mucosa, glossitis, burning sensations, and recurrent ulceration. In some patients, these deficiencies are nutritional; in others, they arise from malabsorption, autoimmune gastritis, or gastrointestinal disease.

For this reason, the diagnostic work-up of recurrent or severe RAS should include complete blood count and targeted hematinic studies, typically serum ferritin or iron studies, vitamin B12, and folate. In selected patients, homocysteine, thyroid studies, celiac-related testing, or gastrointestinal referral may also be justified. Importantly, correction of the deficiency may reduce recurrence frequency and improve treatment response, even when the ulcers are not caused by deficiency alone.

Management

Management of RAS should follow a combined symptomatic and etiologic strategy. The first goal is pain control and acceleration of healing; the second is identification and correction of modifiable triggers and systemic abnormalities. For most patients with mild-to-moderate disease, topical therapy is sufficient. Topical corticosteroids remain the mainstay of treatment and are widely considered first-line therapy. They reduce inflammation, shorten ulcer duration, and improve oral function. Commonly used forms include corticosteroid adhesive preparations, mouth rinses, sprays, and soluble tablets, chosen according to lesion site and severity.

Adjunctive symptomatic measures include topical anesthetics, protective barrier preparations, non-irritating oral hygiene, and avoidance of sharp, acidic, or spicy foods during active episodes. Patients should also be advised to eliminate local traumatic factors such as defective restorations, ill-fitting appliances, or hard-bristled toothbrushes. In individuals with frequent attacks, early treatment during the prodromal burning stage may reduce lesion severity.

When ulcers are large, numerous, continuous, or associated with major impairment in nutrition and speech, systemic treatment may be needed. A short course of systemic corticosteroids is commonly reserved for severe episodes. Refractory or continuous RAS should be managed by an oral medicine specialist because more advanced therapy may include immunomodulatory agents such as azathioprine, pentoxifylline, or thalidomide in selected cases, with careful monitoring for adverse effects. Intralesional corticosteroid injection may be useful for isolated, deep, very painful major ulcers.

Equally important is correction of hematinic deficiency when present. Iron, folate, vitamin B12, and related vitamin supplementation can lessen disease activity in some patients, particularly when laboratory-confirmed deficiency exists. This step is often overlooked when treatment is limited to topical agents alone. In patients with evidence of autoimmune thyroid disease, autoimmune gastritis, malabsorption, or inflammatory bowel disease, appropriate medical referral and management of the underlying disorder are essential parts of oral care.

Conclusions

Recurrent aphthous stomatitis is a common but biologically complex oral mucosal disorder with a multifactorial basis. Current evidence supports a model in which genetic susceptibility, immune dysregulation, local triggers, systemic disease, and nutritional deficiency interact to produce recurrent ulceration. Serum autoantibodies are not diagnostic of RAS itself, but they may identify clinically significant autoimmune comorbidity, especially autoimmune gastritis and autoimmune thyroid disease. Anemia and hematinic deficiencies, particularly iron, vitamin B12, and folate deficiency, are among the most important reversible factors and should be actively investigated in recurrent or severe cases. Effective management therefore requires more than symptomatic ulcer suppression: it demands a structured diagnostic approach, topical corticosteroid-based local therapy, and correction of underlying systemic abnormalities. A personalized, multidisciplinary strategy offers the best chance of reducing pain, shortening healing time, preventing recurrence, and improving patient quality of life.

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