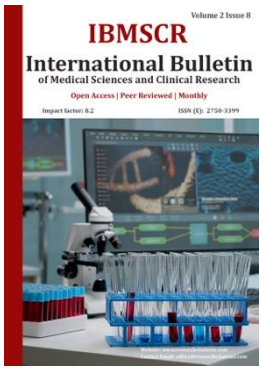

ORAL MANIFESTATIONS OF CHRONIC APHTHOUS STOMATITIS

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Abstract. Chronic aphthous stomatitis (CAS), commonly known as recurrent aphthous ulceration, is one of the most frequent inflammatory diseases affecting the oral mucosa. It is characterized by recurrent, painful, and shallow ulcerations that significantly impact the patient's quality of life, nutrition, and speech. The etiology of CAS remains multifactorial, involving genetic predisposition, immune dysregulation, nutritional deficiencies, local trauma, hormonal factors, and stress. This article aims to provide a comprehensive overview of the clinical features, etiopathogenesis, and diagnostic aspects of chronic aphthous stomatitis, emphasizing the diverse oral manifestations and their correlation with systemic factors.

Keywords: chronic aphthous stomatitis, recurrent aphthous ulcer, oral mucosa, immune response, etiology, clinical manifestation, oral health.

Introduction

Chronic aphthous stomatitis (CAS) represents one of the most prevalent recurrent oral mucosal disorders, affecting approximately 15–25% of the global population. It is a condition marked by repeated episodes of ulceration that occur on non-keratinized mucosal surfaces of the mouth, such as the buccal and labial mucosa, the floor of the mouth, and the lateral borders of the tongue. The disease is not life-threatening but often leads to chronic discomfort, difficulties in eating, and decreased quality of life due to pain and recurrence.

Despite being recognized for centuries, the exact etiology of CAS remains incompletely understood. Numerous studies have indicated that this disorder is multifactorial, involving a complex interplay between immune dysfunction, genetic susceptibility, local trauma, hormonal influences, and even psychological stress. Additionally, deficiencies in certain nutrients, particularly vitamin B12, folate, and iron, have been linked to the increased occurrence of aphthous ulcers. The clinical importance of CAS lies not only in its recurrence but also in its potential to signal underlying systemic conditions such as celiac disease, inflammatory bowel disease, or immunodeficiency states.

Materials and methods

The pathogenesis of chronic aphthous stomatitis involves a combination of immune-mediated mucosal damage and abnormal host responses to local or systemic triggers. Several studies have demonstrated that the lesions result from a T-cell–mediated immune reaction, in which cytotoxic T lymphocytes attack the epithelial cells of the oral mucosa, leading to localized ulceration. Elevated levels of cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-2 (IL-2), and interferon-gamma (IFN-γ) have been observed in patients with active ulcers, suggesting an exaggerated inflammatory response [1].

Genetic predisposition is another critical factor in CAS. Research indicates a familial tendency, with a higher prevalence among first-degree relatives. Associations with certain human leukocyte antigen (HLA) types—particularly HLA-B12, HLA-B51, and HLA-Cw7—have

been reported, indicating that specific genetic profiles may increase susceptibility. Environmental factors such as emotional stress, smoking cessation, food hypersensitivity (e.g., to chocolate, nuts, gluten, or citrus fruits), and local trauma (from dental appliances or sharp teeth) can precipitate or exacerbate the lesions.

Nutritional deficiencies, especially of vitamin B12, folate, iron, and zinc, impair epithelial integrity and immune regulation, further promoting mucosal vulnerability. Hormonal fluctuations—particularly in women during menstruation—have also been linked to flare-ups, likely due to changes in mucosal vascularization and immune modulation.

Results and discussion

Although chronic aphthous stomatitis is primarily localized to the oral cavity, its occurrence may reflect systemic immune or gastrointestinal disorders. Numerous studies have documented associations between CAS and celiac disease, Crohn's disease, ulcerative colitis, HIV infection, and Behçet's disease. In such cases, aphthous-like lesions may serve as the first clinical manifestation of systemic pathology.

Differential diagnosis is crucial to exclude other ulcerative oral conditions. Herpetic stomatitis can mimic minor aphthae but typically involves keratinized mucosa and presents with vesicles before ulceration. Traumatic ulcers usually have a single lesion with a clear mechanical cause. Erythema multiforme, lichen planus erosivus, and pemphigus vulgaris may also resemble aphthous lesions but can be differentiated through biopsy and histopathological examination.

Diagnosis of chronic aphthous stomatitis is primarily clinical, based on the history of recurrent, self-healing ulcers and the absence of systemic illness. However, laboratory investigations may assist in identifying underlying causes. Blood tests for hemoglobin, ferritin, folate, vitamin B12 levels, and autoimmune markers are recommended. In recurrent or atypical cases, biopsy and histopathology can help rule out malignancy or autoimmune vesiculobullous diseases [2].

Histologically, aphthous ulcers show ulcerated epithelium with fibrin deposition, infiltration of neutrophils and lymphocytes, and subepithelial edema. Immunohistochemical studies often reveal upregulated expression of TNF-α and adhesion molecules, confirming the immune-mediated nature of the disease.

Treatment of CAS focuses on symptom relief, reducing recurrence, and managing underlying causes. Topical corticosteroids (such as triamcinolone acetonide 0.1% or clobetasol propionate) are first-line therapies for reducing inflammation and pain. Topical anesthetics (benzocaine, lidocaine) provide symptomatic relief. Antimicrobial mouth rinses, such as chlorhexidine gluconate 0.12%, may reduce secondary infection [3].

In severe or recurrent cases, systemic therapies are indicated, including oral corticosteroids, colchicine, dapsone, or thalidomide — though the latter requires careful monitoring due to its teratogenic potential. Nutritional supplementation (vitamin B12, folic acid, iron) is effective when deficiencies are identified. Psychological stress management and avoidance of known dietary triggers also help minimize recurrence.

The prognosis for CAS is generally favorable. Although complete remission is rare, proper management can significantly decrease the frequency and severity of ulcers. Long-term follow-up is essential to monitor for potential systemic associations.

Recent research has demonstrated that chronic aphthous stomatitis (CAS) represents not merely a localized oral condition but also a reflection of systemic immunologic imbalance. The chronic inflammatory process underlying CAS involves an abnormal response of the mucosal immune system, particularly within the lamina propria. Immunohistochemical analyses reveal a marked predominance of CD8+ cytotoxic T-lymphocytes and Th1-type cytokines in perilesional tissue, supporting the theory that mucosal epithelial cells are damaged by cell-mediated immune reactions. This chronic inflammatory microenvironment leads to epithelial necrosis, microvascular damage, and the characteristic ulcer formation [4].

Additionally, the microbiological aspect of CAS has gained increasing attention. Although the condition is not infectious, recent molecular studies have identified possible bacterial and viral triggers that modulate immune activity in susceptible individuals. For instance, *Streptococcus sanguinis* antigens have been shown to elicit cross-reactive immune responses with mucosal keratinocytes, suggesting a possible role in disease activation. Moreover, the detection of cytomegalovirus DNA and human herpesvirus 6 in some lesions implies that latent viral infections may contribute to episodic exacerbations in genetically predisposed hosts.

From a clinical standpoint, the morphological diversity of lesions can provide diagnostic clues to the severity and chronicity of the disease. In long-standing cases, patients often develop ulcers in successive phases, with old lesions healing as new ones emerge, resulting in continuous discomfort. The ulcers are frequently surrounded by an erythematous ring, and in severe recurrent forms, adjacent ulcers may merge to form extensive necrotic patches covering large mucosal areas. These lesions can lead to secondary bacterial infections, halitosis, and even mild regional lymphadenopathy.

Patients with chronic aphthous stomatitis often experience extraoral manifestations as well, including fatigue, low-grade fever, or gastrointestinal discomfort, particularly when the condition is associated with nutritional deficiencies or systemic inflammatory diseases. In pediatric populations, CAS may coincide with conditions such as celiac disease or selective IgA deficiency, while in adults, it can appear as an early indicator of inflammatory bowel disease or HIV-related immunosuppression. Recognizing these associations is crucial for clinicians to conduct comprehensive diagnostic evaluations and to detect underlying systemic disorders early.

Diagnostic innovation has also evolved in recent years. Non-invasive methods such as salivary cytokine analysis and optical coherence tomography (OCT) have been employed to monitor disease activity. Elevated salivary levels of TNF-α, IL-6, and IL-10 have been reported during active ulceration phases, indicating the potential use of salivary biomarkers as diagnostic or prognostic tools. OCT imaging, on the other hand, provides real-time visualization of mucosal integrity and inflammatory depth, aiding in differential diagnosis between CAS and other ulcerative mucosal diseases such as erosive lichen planus or pemphigoid.

Furthermore, emerging evidence suggests a strong psychoneuroimmunological component in CAS pathogenesis. Chronic psychological stress and anxiety are linked to increased production of cortisol and catecholamines, which suppress mucosal immunity and delay epithelial healing. Studies conducted in dental clinics at King's College London (2018) and the University of Helsinki (2021) demonstrated that stress-management programs and behavioral therapy significantly reduced recurrence frequency among patients with chronic

aphthous ulcers. This highlights the importance of integrating psychological assessment and stress control into treatment protocols [5].

Conclusion

Chronic aphthous stomatitis remains a complex, multifactorial disorder of the oral mucosa that reflects both local and systemic disturbances. Its hallmark feature — recurrent painful ulceration — significantly affects the patient's daily functioning and quality of life. The condition's oral manifestations, ranging from minor recurrent ulcers to severe, persistent lesions, provide crucial diagnostic insight into the body's immune and nutritional status. Understanding the interplay of immune, genetic, and environmental factors is key to effective diagnosis and treatment. Early identification and appropriate management can prevent complications, reduce recurrence, and improve the patient's overall oral health and well-being.

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