



Disease in a Nutshell

Aphthous stomatitis

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ARTICLE INFO

Article history:

Received for publication May 17, 2016.

Received in revised form June 29, 2016.

Accepted for publication July 5, 2016.

Introduction

Recurrent aphthous stomatitis (RAS) is the most common inflammatory and ulcerative condition of the oral cavity. The term *aphthous* is derived from a Greek word *aphtha*, which means ulceration. It is estimated that at least 1 in 5 individuals have been affected by aphthous stomatitis. The disorder most commonly affects young adults (with some studies reporting a prevalence as high as 60% in students), decreasing in frequency and severity after 50 years of age. The cause is unknown in most patients, although in some the disease manifests secondary to an underlying infectious, inflammatory, immunologic, or nutritional disorder.

Classification

RAS has been classified based on the size and evolution of lesions into 3 forms: minor aphthae (Mikulicz aphthae), major aphthae (Sutton disease, also referred to as peradenitis mucosa necrotica recurrens), and herpetiform ulcerations.¹ Table 1 describes the 3 types. Complex aphthosis refers to the persistent presence of 3 or more ulcers, associated genital lesions, and resultant serious disability, in the absence of Behçet disease (BD),² because orogenital ulceration reminiscent of complex aphthosis is a diagnostic feature of BD. Ocular lesions, erythema nodosum, pustular lesions, cutaneous pathergy (nodule formation after intra-dermal injection of saline), and bizarre neurologic findings also occur in BD, setting this condition apart.³ Table 2 describes conditions associated with complex aphthae that may be seen by an allergist/immunologist.

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Disclosures: Authors have nothing to declare.

<http://dx.doi.org/10.1016/j.janai.2016.07.005>

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Immunopathogenesis

The pathogenesis of aphthous stomatitis is largely unknown, although an abnormal T-cell-mediated immune reaction appears to be involved in patients with RAS. In some studies, lymphocytes infiltrating RAS lesions expressed cytokine transcripts, such as interferon γ (IFN- γ), tumor necrosis factor α (TNF- α) and interleukin 15 (IL-15), and signaling/transcription factors, such as interferon regulatory factor 1 (IRF1), signal transducer and activator of transcription (STAT-1), and STAT-4, representing a T_H1 pattern.^{4,5} T_H2-related genes were not overexpressed in RAS tissues, with the exception of CCR3. Although further studies of lesional T cells are required, published studies do not suggest the presence of T_H3 or T_H17 cell types.⁵ Serum levels of IL-17 and IL-18 were elevated in patients with RAS in one study.⁶ Buno and coworkers⁴ used lesional polymerase chain reaction and found transcripts for IL-2, IL-4, IL-5, and IFN- γ but not for IL-10, suggesting defective tissue healing responses. The presence of TNF- α in the lesions lends some credence to the use of biological anti-TNF- α agents in refractory disease. A role for oral microbiota in disease pathogenesis has also been proposed.⁷

Etiology

Although most patients with RAS have a primary form of the disease, certain inflammatory, nutritional, toxic, and metabolic factors (Table 2) may contribute to disease pathogenesis.^{1,2,8} Predisposing factors for aphthous stomatitis include trauma; tobacco use; use of certain medications; deficiencies of vitamin B12 and folic acid; gluten sensitivity (and enteropathy); chemical irritants, including sodium lauryl sulfate (found in certain brands of toothpaste); hormonal changes; and microbial factors. The actual role of vitamin deficiencies is uncertain, and in 1 published trial, multi-vitamin supplementation did not reduce the number or duration of RAS episodes. RAS may be a marker of an underlying systemic illness, notably, celiac disease; Behçet syndrome; mouth and genital ulcers with inflamed cartilage (MAGIC) syndrome; periodic

Table 1
Classification of Recurrent Aphthous Stomatitis (RAS)

Feature	Minor RAS	Major RAS	Herpetiform RAS
Frequency, %	75	10–15	5–10
Size	<1.0 cm	>1.0 cm	1–3 mm
Time to healing, wk	1–2	4–6	1–4
Scarring	No	Yes	No
Systemic features	None	Fever, odynophagia	None
Location	Buccal/labial	Labial/soft palate or tongue/pharynx	Any location orally
Onset	Early	Early/puberty	Late/females

fever; aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome; and sweet syndrome/acute neutrophilic dermatosis or cyclic neutropenia (Table 2).^{1,2,8} Infections with human immunodeficiency virus, *Yersinia*, tuberculosis, and salmonella have been associated with RAS by some investigators. Several studies have addressed the prevalence of recurrent aphthous ulcerations in celiac disease, placing this number between 4% and 40%.⁸ Oral ulcers may be the first sign of celiac disease in some patients.⁸ Challenge with small amounts of gluten has led to recurrence of oral ulcerations in celiac disease.⁹ In children, the association of symmetric enamel defects with recurrent oral ulcerations has been considered a presentation of silent celiac disease.¹⁰

Iatrogenic causes have to be entertained in RAS. Antibiotics, β -blockers, angiotensin-converting enzyme inhibitors, and certain antiarrhythmic drugs and nonsteroidal anti-inflammatory agents have been associated with oral ulceration.¹¹ Multivariate paired analysis has revealed a significant association between nonsteroidal anti-inflammatory agent and β -blocker use and aphthous stomatitis.¹² Drug-induced ulcers are located usually on the side of the tongue, are solitary, and are resistant to usual treatments until use of the medication is discontinued.¹¹ One specific medication linked to recurrent oral ulceration is nicorandil, used for management of coronary artery disease.¹³ This drug is associated with a delayed appearance of oral and gastrointestinal ulcers, sometimes taking as long as 74 weeks to develop, although patients on a high-dose regimen developed the ulcers earlier. The RAS may be disabling enough that use of this medication needs to be discontinued.

Clinical Features

Aphthous stomatitis presents as shallow, round to oval, clearly defined, painful ulcers in the oral mucosa. There are 3 different clinical variants of RAS: minor aphthous stomatitis (Mikulicz aphthae), major aphthous stomatitis (Sutton disease or periaadenitis mucosa necrotica recurrens), or herpetiform ulceration. These are summarized in Table 1. Figure 1 shows select clinical findings in patients with major aphthous stomatitis. A thorough evaluation for iatrogenic causes, presence of orogenital disease, hematologic dyscrasias, or underlying systemic disorders, including inflammatory bowel disease and gluten sensitivity, is essential.

Diagnosis

Diagnosis of aphthous stomatitis can be made by history, clinical examination, and histopathologic analysis. Diagnostic testing is suggested in Table 2 and should be based on history and clinical findings. Biopsy of the ulcer is rarely necessary but may be helpful when infection, vasculitis, or neoplasia cannot be excluded by other means. Histopathologic analysis of an aphthous ulcer reveals superficial tissue necrosis, infiltration by neutrophils, and the presence of cellular debris. There is fibrinopurulent exudate, and numerous red blood cells may coalesce to form hemorrhagic foci. The epithelium is infiltrated with variable numbers of

Table 2
Evaluation of Complex Aphthous Stomatitis

Underlying condition	Features	Diagnostic test
Nutritional deficiency	Stomatitis, oral ulcers, neuropathy	Serum B1, B2, B6, B12, folate, zinc
Behçet syndrome	Orogenital ulcers, ocular disease, neurologic disease	Pathergy test, epidemiology, biopsy
MAGIC syndrome	Mouth and genital ulcers, inflamed cartilage	Elevated inflammatory markers
PFAPA syndrome	Periodic fever, aphthous stomatitis, pharyngitis, adenopathy	High ESR/CRP; no ELA2 mutation
Sweet syndrome	Fever, erythematous skin papules, plaque, or nodule, stomatitis; underlying malignant tumor, pregnancy, or infection	High ESR; biopsy-dense neutrophilic infiltrate; no vasculitis
Cyclical neutropenia	Fever every 18–24 days, oral ulcers, neutropenia (neutrophil count, <500/mm ³); diagnosed in infancy	ELANE mutation; CBC weekly $\times 5$; promyelocyte maturation arrest; in bone marrow

Abbreviations: CBC, complete blood cell count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MAGIC, Mouth and genital ulcers, inflamed cartilage; PFAPA, periodic fever, aphthous stomatitis, pharyngitis, adenopathy.

intraepithelial lymphocytes and some neutrophils. None of these findings are specific to any disease entity but may help exclude vasculitis or infection.

Management

There is no definite treatment for RAS. Systemic disorders that underlie RAS need to be evaluated for and managed effectively. Deficiencies of zinc, red cell folate, iron, and/or vitamins B1, B6, and B12 may need to be corrected. Underlying inflammatory bowel disease, celiac disease, MAGIC syndrome, PFAPA syndrome, cyclical neutropenia, BD, Sweet syndrome, Reiter syndrome, and reactive arthritides or infection may require targeted therapy, including immunosuppression or the use of biological agents.^{1,2,8,14}

Specific Management of RAS

Treatment is directed toward symptomatic relief (of pain), prevention of recurrences, and accelerating healing.

Education

Educational and preventive aspects are essential to successful management of RAS. Avoidance of food triggers, especially alcohol, carbonated beverages, spicy foods (pepper, curry), and acidic fruits (citrus fruits, tomatoes, and strawberries), may be important.¹⁵ Avoidance of oral hygiene products that contain sodium lauryl sulfate may also be helpful in some patients. Oral hygiene is essential and needs to be stressed because poor oral hygiene might introduce a microbial and infectious component to recurrence or persistence.

Topical Therapy

Topical therapies are usually safe, well tolerated, and effective. Topical agents can be administered using vehicles such as oral pain reliever anesthetic paste (Orabase). Triamcinolone acetonide, flucaninonide, and topical anesthetic agents can be applied using anesthetic paste, up to 4 times a day until healing occurs. Patients can be educated to self-treat themselves when a flare occurs because early treatment might lessen the duration and severity of the illness. Topical tetracycline or minocycline has been used with varying success¹⁶ and might work by antibacterial effects and

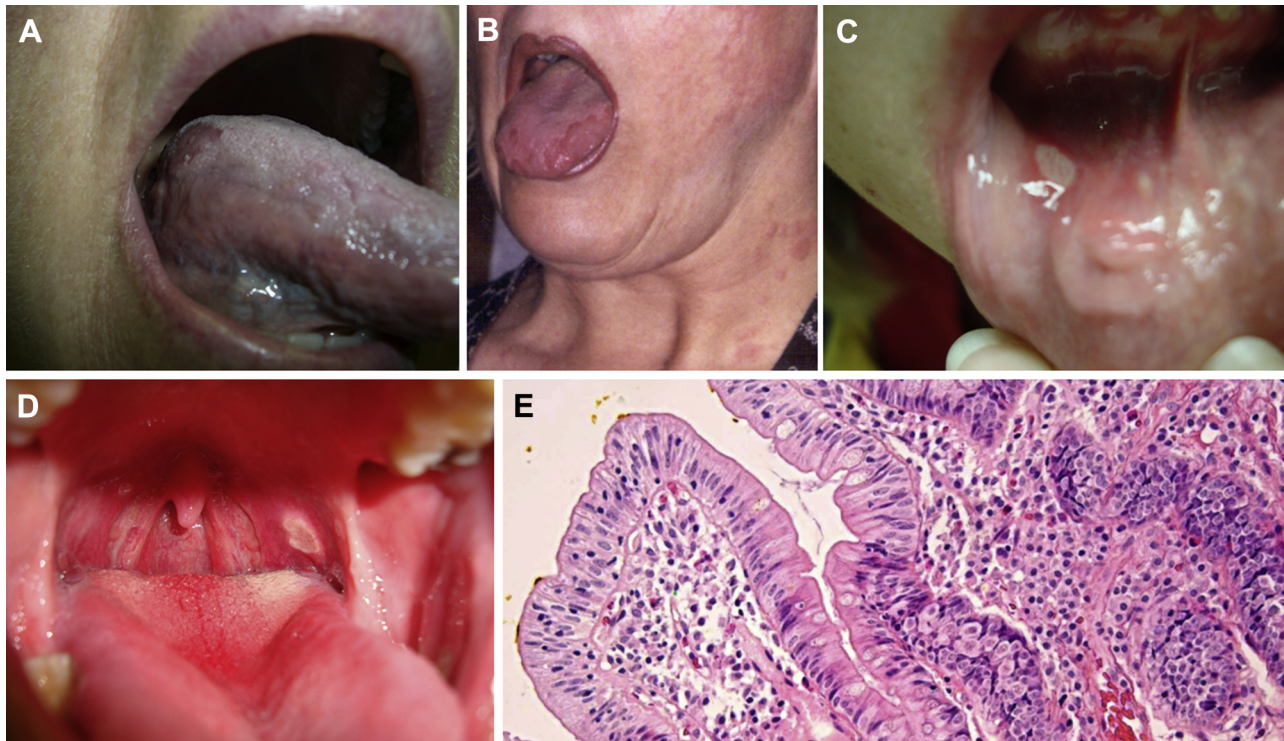


Figure 1. (A) Major aphthous ulcer on dorsal aspect of the tongue. (B) Multiple ulcers on the lateral aspect of the tongue, including several coalescent ulcers. (C) Major aphthous ulcer on buccal mucosa of a patient with celiac disease. (D) A solitary large soft palatal ulcer in a patient with celiac disease. (E) Duodenal biopsy in a patient with celiac disease demonstrating typical findings including loss of villi and intense inflammatory cell infiltration.

broader effects on inflammation and expression of collagenases. Other interventions have been attempted and have had sporadic success. These interventions include surgical or laser ablation, ultrasonography, and chemical cautery with silver nitrate and can lead to rapid improvement in pain, although these modalities have not convincingly accelerated healing. Medicated toothpaste that contains the enzymes amyloglucosidase and glucose oxidase have also been used as adjuncts to chemical cautery. The application of topical local anesthetics before cautery may decrease pain and discomfort.

Immune Modulation

Oral and intravenous steroids can be used in acute exacerbation in combination with other immunosuppressants, especially for complex aphthae or severe disease that results in odynophagia or intractable pain. Thalidomide has significant benefit, especially in patients with human immunodeficiency virus. It acts by reducing activity of TNF- α by degrading messenger RNA. Pentoxifylline has benefit and probably works by inhibiting TNF- α production. Colchicine, levamisole, dapsone, antimetabolites (azathioprine and methotrexate), biologics (infliximab and etanercept), alkylating agents (chlorambucil and cyclophosphamide), and interferon alfa have some benefit in patients with RAS.^{1,2,8,17,18} These options can be considered in refractory or disabling RAS, realizing that the data supporting their use are limited to case studies. Opportunistic infections and/or late neoplastic complications limit the use of these medications for minor aphthae.

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