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Review article

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The Articulate Canker-Aphthous Ulcer

Anubha Bajaji[1*]

[1]*Histopathologist in A.B. Diagnostics, New Delhi, India.*

[*]**Corresponding author**
Anubha Bajaji, Histopathologist in A.B. Diagnostics, New Delhi, India.

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Abstract

Aphthous ulcer occurs as a frequent, idiopathic, painful, singular, multiple or reoccurring oral ulceration. Of obscure aetiology, oral trauma, stress, anxiety, diverse systemic diseases as coeliac disease, Crohn's disease, Behçet's syndrome, reactive arthritis or infection with human immune deficiency virus (HIV), drugs such NSAIDs, β-blockers, angiotensin converting enzyme (ACE) inhibitors, deficiencies of vitamins and trace elements as zinc, iron, B12, folate or sensitivity to food and chemicals may engender the ulcer. Contingent to magnitude, aphthous ulcer is subcategorized into minor ulcer, major ulcer or herpetiform ulcer. Aphthous ulcer manifests upon non-keratinized oral mucosa as a well circumscribed, centric, necrotic ulcer circumscribed by a grey, fibrinous exudate and an erythematous halo. The ulcer requires a segregation from contact dermatitis, lichen planus, oral carcinoma, infection with herpes simplex virus (HSV), various drug induced lesions or autoimmune diseases. Aphthous ulcer can be evaluated with clinical examination, complete blood count with nutritional deficiencies of iron, folate or vitamin B12, neutropenia, serum anti-endomysial antibodies and transglutaminase (tTg-IgA) for coeliac disease and investigations for HIV. Cogent therapeutic options are local anaesthetics, coating or occlusive agents as bismuth subsalicylate, sucralfate, 2-octyl cyanoacrylate, bio-adherent emollient pastes, oral antiseptics as chlorhexidine gluconate, hydrogen peroxide, anti-inflammatory agents as glucocorticoids, metalloprotease inhibitors, antimicrobials as tetracycline, doxycycline, minocycline, honey, immunomodulatory agents as amlexanox, colchicine, cyclosporine, cyclophosphamide, dapsone, methotrexate, montelukast, thalidomide or retinoids.

Key Words: Idiopathic, Oral Ulcer, Recurrent.

Introduction

Aphthous ulcer is denominated as a painful, singular, multiple or reoccurring oral ulceration which obstructs speech, mastication or may engender dysphagia. The frequent, idiopathic condition may demonstrate repetitive, painful aphthous ulcers confined to non-keratinized mucous membranes of the oral cavity. Aphthous ulcer may occur as a familial condition or may be discerned occasionally. The consistently painful ulcer may be miniature or enlarged. The condition is additionally designated as canker sore, recurrent aphthous ulcer (RAU), aphthous stomatitis or recurrent aphthous stomatitis (RAS).

Disease Characteristics

Aphthous stomatitis may be discerned in around one fifth (20%) of population whereas recurrent aphthous ulcer exhibits an incidence of nearly 1.5% in children and adolescents. The condition demonstrates a female preponderance and is commonly discerned in Caucasians although a definitive racial predilection is absent. Although disease onset is within childhood, lesions are generally discerned within second decade to third decade [1, 2]. Non-smokers, ex-smokers and affluent individuals of enhanced socio-economic status below <40 years are commonly implicated. Advancing age is associated with declining disease incidence [1, 2]. Of obscure aetiology, oral trauma, stress, anxiety, diverse systemic diseases as coeliac disease, Crohn's disease, Behçet's syndrome, reactive arthritis or infection with human immune deficiency virus (HIV), drugs such NSAIDs, β-blockers, angiotensin converting enzyme (ACE) inhibitors, deficiencies of vitamins and trace elements as zinc, iron, B12, folate or sensitivity to food and chemicals may contribute to disease emergence [1, 2]. Besides, aphthous stomatitis may emerge as a manifestation of Behcet's syndrome, systemic lupus erythematosus (SLE), reactive arthritis or inflammatory bowel disease, especially Crohn's disease [1, 2]. The idiopathic, multifactorial aphthous stomatitis possibly demonstrates activation of cell mediated immunity in the emergence of ulceration [1, 2]. Acute infection is non-contributory to occurrence

of the non-contagious aphthous ulcer [1, 2]. Aphthous stomatitis may be triggered by localized trauma, psychological or physiological stress, allergic reaction to specific agents such as sodium lauryl sulphate, a constituent of toothpaste or various oral hygiene products, cinnamon, cheese, citrus, figs or pineapple, toxins as nitrates in drinking water, hormonal imbalance as menstruation or alterations within the oral microbiome [1, 2]. Disorders such as malabsorption, enteropathy or coeliac disease may concur. Haematinic deficiencies of iron, folate, vitamins B6, B12, vitamin D, zinc or thiamine may appear [1, 2]. Aphthous ulcer is infrequent in individuals with adequate oral hygiene. Of obscure pathogenesis, diverse host and environmental factors are implicated in disease emergence as •a definitive family history which may be elucidated in around one third of subjects with recurrent aphthous stomatitis. Genetic predisposition is associated with frequent emergence of human leukocyte antigen (HLA) subtypes A2, A11, B12 and DR2(3,4). •activation of T helper subtype 1 (Th1) is intense. Enhanced incidence of recurrent aphthous stomatitis is associated with psychological stress, Crohn's disease, celiac disease and administration of non-steroidal anti-inflammatory drugs (NSAIDs), factors which augment a Th1 immune response [3, 4]. In contrast, disorders which prohibit Th1 immune response such as pregnancy and ingestion of thalidomide, glucocorticoids or tetracycline decimate the incidence of aphthous ulcers. An interplay of active immune mechanisms is observed in disease emergence [3, 4]. •a significantly elevated serum level of tumour necrosis factor alpha (TNF-α) is observed in up to ~40% individuals within ulcerative stage of recurrent aphthous stomatitis. Medications exhibiting anti-tumour necrosis factor alpha (TNF-α) effect such as pentoxifylline, levamisole, and thalidomide may be suitable for treating recurrent aphthous ulcers [3, 4]. Pre-eminently and predominantly, aphthous ulcer emerges as a consequence of T cell mediated immune dysfunction. Besides, neutrophil and mast cell mediated disintegration of mucosal epithelium is exemplified [3, 4]. Diverse intercellular mediators such as interferon gamma (IFN-ϰ), tumour necrosis factor alpha (TNF-α) and interleukins 2, 4, 5 (IL-2), (IL-4) and (IL-5) may be elevated. Also, various adhesion molecules integrating cellular communication and epithelial integrity may be altered. Thus, the inflammatory process engenders a pseudo-membrane comprised of fibrinous exudate, bacteria, inflammatory cells and necrotic mucosal cells [3, 4].

Clinical Elucidation

Aphthous stomatitis exemplifies clinical symptoms as a burning sensation, pain upon consumption of acidic foods or exacerbating pain within mobile, ulcerated area. Ulceration with ingestion of certain medications, HIV infection, joint pain, ulcer reoccurrence and association with genital ulcer may be discerned. Aphthous ulcer exhibits diverse variations contingent to ulcer magnitude as •minor ulcer with dimension between 4 millimetres to 9 millimetres •major ulcer exceeding > 1-centimetre magnitude and •herpetiform ulcer below <3-millimetre diameter (3,4). Minor ulcer is a commonly discerned variant and occurs as a spherical or elliptical, well demarcated, singular or multiple ulcers beneath <1-centimetre diameter which heal in the absence of scarring within 2 weeks [3, 4]. Singular or multiple minor ulcers appear encased within a yellowish white or grey pseudo-membrane circumscribed by an inflamed, erythematous zone [5, 6]. Major aphthous ulcer is deep seated, enlarged up to 3-centimetre dimension with an irregular, raised perimeter and heals with scarring within several weeks to months [5, 6]. Herpetiform recurrent aphthous ulcers appear in clusters of around 100 ulcers throughout the oral cavity, are up to 2-millimetre magnitude and heal within few weeks [5, 6]. A characteristic history of preceding ulceration is exemplified. Generally, mucosal burning may appear a day or two prior to onset of oral mucosal ulceration. Typically, pyrexia, rash, headache or lymphadenopathy are absent [5, 6]. The afebrile, apparently well individuals displaying aphthous stomatitis require a comprehensive physical assessment with investigations for uveitis or genital ulceration in order to exclude conditions such as Behçet's syndrome or MAGIC syndrome comprised of mouth and genital ulcers with inflamed cartilage [5, 6]. Upon examination, ulcer of aphthous stomatitis emerges upon non-keratinized oral mucosa and exhibits a well circumscribed, centric, necrotic ulcer circumscribed by a grey, fibrinous exudate and an erythematous halo [5, 6]. The ulcer is infiltrated by a mononuclear cell inflammatory infiltrate followed by secondary bacterial infection which initiates a neutrophilic invasion [6, 7]. Aphthous ulcer occurs upon non-keratinized oral mucosal surfaces such as the labial or buccal surface, soft palate, floor of the mouth, ventral or lateral margin of the tongue, tonsillar region, unattached, marginal gingiva adjacent to teeth and alveolar gingiva confined to maxillary and mandibular sulci. Characteristically, ulcers appear upon buccal mucosa, labial mucosa, floor of the mouth, ventral surface of tongue and soft palate [6, 7].

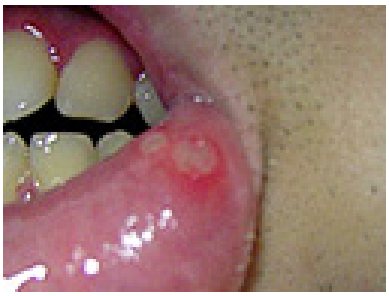

Figure 1: Aphthous ulcer demonstrating a centric, necrotic ulcer with a grey, fibrinous exudate and an erythematous halo (13).

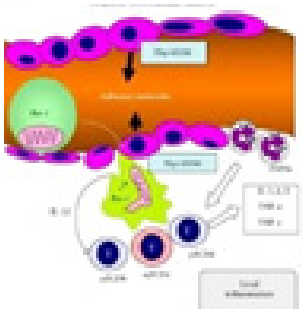

Figure 2: Aphthous stomatitis exemplifying the interplay of various inflammatory cytokines and interleukins which generate the ulcer (14).

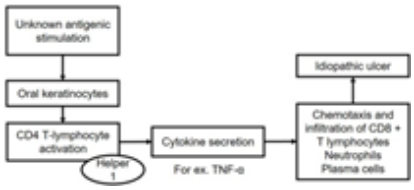

Figure 3: Aphthous ulcer delineating various cytokine stimulants and inflammatory cell exudate engendering the ulcer (15).

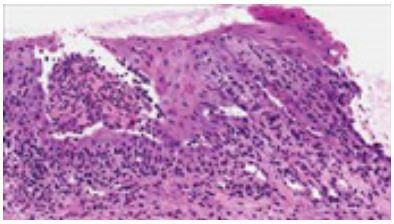

Figure 4: Aphthous ulcer enunciating an ulcerated, non keratinized stratified squamous epithelium with an infiltration of mononuclear cells and polymorphonuclear leukocytes along with a fibrinous exudate (16).

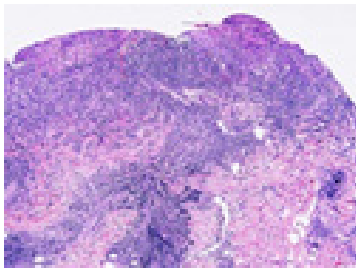

Figure 5: Aphthous ulcer depicting an ulcerated mucosa infiltrated by lymphocytes, macrophages and few neutrophils (17).

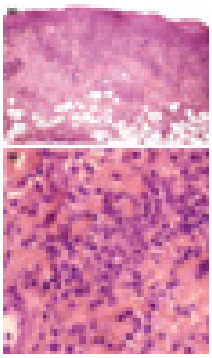

Figure 6: Aphthous ulcer displaying an ulcerated mucosal surface invaded by acute and chronic inflammatory cells (18).

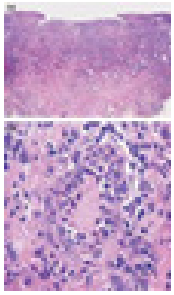

Figure 7: Aphthous ulcer exhibiting a discontinuous superimposed epidermis infiltrated by an acute and chronic inflammatory infiltrate (18).

Differential Diagnosis

Aphthous stomatitis enunciates singular or multiple, shallow, hyperaemic ulcers with circumscribing hyperaemia and a superimposed, subtle, inflammatory exudate. The ulcer requires a segregation from conditions such as contact dermatitis, lichen planus, oral carcinoma, infection with herpes simplex virus (HSV), various drug induced lesions or autoimmune diseases such as lupus [1, 2].

Investigative Assay

Aphthous stomatitis can be adequately discerned upon clinical examination. Biochemical and haematological investigations are superfluous. Nevertheless, persistent, severe or recurrent lesions mandate additional evaluation [6, 7]. A complete blood count may depict nutritional deficiencies of iron, folate or vitamin B12 and neutropenia with accompanying cyclic neutropenia, deficiencies which may engender ulceration [7, 8]. Gluten sensitive enteropathy or coeliac disease is associated with recurrent aphthous stomatitis in roughly <5% instances and can be discerned with determination of serum anti-endomysial antibodies and transglutaminase (tTg-IgA) [7, 8]. Investigations for HIV are required in complex, severe instances, persistent herpetiform or major aphthous stomatitis or ulcers discerned upon keratinized mucosa as the adherent gingival surface, dorsum of tongue and hard palate [7, 8].

Therapeutic Options

Recurrent aphthous stomatitis (RAS) is a problematic condition which mandates appropriate disease circumvention, pain relief and aggressive therapeutic intervention. Generally, pain alleviation, adequate hydration, nutrition, augmented healing and circumventing ulcer reoccurrence are the aims of therapy [9, 10]. Cogent therapeutic options which may be beneficially employed are topical agents as local anaesthetics, coating or occlusive agents as bismuth subsalicylate, sucralfate, 2-octyl cyanoacrylate, bio-adherent emollient pastes, oral antiseptics as chlorhexidine gluconate, hydrogen peroxide, anti-inflammatory agents as glucocorticoids, metalloprotease inhibitors, antimicrobials as tetracycline, doxycycline, minocycline, honey, immunomodulatory agents as amlexanox, colchicine, cyclosporine, cyclophosphamide, dapsone, methotrexate, montelukast, thalidomide or retinoids [9, 10]. Severe, refractory or persistent lesions may be managed with system-

ic steroids, immunomodulatory agents, pentoxifylline or quercetin. Experimental agents such as herbal products, local desiccation with tincture benzoin, cauterization and surgical tissue sampling of the ulcer may be advantageous [9, 10]. Laser therapy appears efficacious in treating severe or reappearing ulcers. Appropriate oral hygiene can circumvent repetitive ulcers. Dietary supplementation with iron, zinc, vitamins B1, B2, B6, B12 and vitamin C may be advantageous. Gluten free diet is recommended in coexistent coeliac disease [9, 10-13].

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