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Review Article

Oral Aphthous: Pathophysiology, Clinical Aspects and Medical Treatment

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Abstract

Oral aphthosis is a painful inflammatory process of the oral mucosa. Oral aphthous can appear alone or secondary to numerous distinct disease processes. If recurrence occurs frequently, it is called recurrent aphthous stomatitis. The pathophysiology of oral aphthous ulcers remains unclear but various bacteria are part of its microbiology. Three morphological types hold great importance in literature because these types help manage the illness properly. Google Scholar and PubMed databases were used to retrieve the relevant data and information. Different keywords including “Aphthous”, “Aphthosis”, “Canker sores”, “Aphthous stomatitis”, “Aphthous ulcer causes”, “Aphthous ulcer AND Microbiota” and “Aphthous ulcer AND treatment”. The causes for oral aphthous ulcerations are widespread and ranges from localized trauma to rare syndromes, underlying intestinal disease, or even malignant disease processes. A detailed history and thorough examination of systems can assist the physician or dermatologist in defining whether it is related to a systemic disease process or truly idiopathic. Management of oral aphthous ulcers is challenging. For oral aphthous or recurrent aphthous ulcers from an underlying disease, topical medications are preferred due to their minimum side effects. Systemic medications are necessary if the disease progresses. Within the limitation of research and literature provided, it is safe to say that topical corticosteroids are the first line of treatment. Herein, the author discusses the pathophysiology, types, causes, diagnosis, and appropriate treatment ladder of oral aphthous stomatitis as described in the literature.

Keywords: Oral aphthosis, Oral aphthous, Microbiota, Corticosteroids, Recurrent aphthous ulcer, Diagnosis

1. Context

This article reviews current aspects of oral aphthosis that is a typical condition characterized by numerous tiny, spherical, or oval ulcers with confined margins, it typically presents first in adolescence in form of an erythematous lesion with the yellowish-grey floor (1). Canker sores are another name for aphthae or ulcers, these were first stated by Hippocrates who used the term aphthae’ to describe diseases related to the mouth (1, 2). Aphthous ulcers have afflicted mankind throughout documented history (3). In this condition, the patient suffers from mouth ulcers. These ulcers can appear alone or can be associated with some underlying disease (4). Oral ulcers are usually painful lesions that are related to numerous conditions developing within the oral cavity. Oral aphthous is a known disorder that has an important effect on the patients’ excellence of life, causing much pain and difficulty with mastication and speech. It is among the most common oral ulcerative condition seen in

clinical trials and there is enough research about this illness (4). Developed countries have the highest prevalence of aphthous ulceration, and women are at a slightly greater risk than men. Usually, men and women are equally affected but in a special type called herpetiform ulcers, women are at a slightly high incidence, etiology of this remains unknown. Aphthous ulcers affect between 20-25% of the population and are one of the most common oral lesions in the overall population (3). It can reoccur any time in life with a frequency that varies up to 3 months and the recurrence rates are as high as 50%. These ulcers, most commonly appear on the non-keratinized oral mucosa, they can cause substantial pain, and may cause difficulty with chewing, eating, and speaking. Oral aphthous occurs worldwide although it appears most common in the developed countries. Most ulcers are benign and self-resolving but a small percentage of them are malignant. The incidence and prevalence of oral cancers vary across the world. A significant minority of oral ulcers are malignant. Patients with an ulcer that persists for more than three weeks should be suspected of malignancy and it requires urgent referral to a specialist (5). Patients with oral aphthosis especially complex aphthosis must be monitored for the development of any other skin lesions, this will help rule out other systemic conditions and make the diagnosis quite easy.

This review aims to provide a clinically oriented overview of pathophysiology, clinical aspects, causes, diagnosis, and treatment of aphthous ulcers in the light of scientific knowledge.

2. Evidence Acquisition

For the retrieval of the relevant review articles and information databases such as Google Scholar, Scopus and PubMed were used. Different keywords including “Aphthous”, “Aphthosis”, “Canker sores”, “Aphthous stomatitis”, “Aphthous ulcer causes”, “Oral Aphthous Pathophysiology”, “Aphthous ulcer AND Microbiota” and “Aphthous ulcer AND treatment” were used.

3. Results

3.1. Pathophysiology of Oral Aphthous

The pathogenesis of recurrent aphthosis stomatitis (RAS) remains poorly defined. It likely involves a predominantly cell-mediated inflammation involving T-cells and TNF-α (tumor necrosis factor-alpha) production. Light and electron-microscope examination of oral aphthous ulcers showed a penetrating, early, lympho-monocyte infiltration of the epithelium. According to a study by Lehner (6), under light microscopy, oral ulcer epithelium showed considerable intercellular edema and degenerative changes. There was epithelial hyperplasia and only the basement membrane adjacent to the ulcer was affected, the rest of the basement membrane appeared intact. 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. According to Lehner (6), the Intra-nuclear inclusion bodies were found in 3 out of the 25 biopsies examined by electron microscopy. The affected nuclei were slightly larger and the nucleoli were uneven in shape. Inclusion bodies were not seen in the cytoplasm. Herpetiform ulcers differ from recurrent aphthous ulcers in that they showed epithelial vesicles and intra-nuclear inclusion bodies, suggesting a virus etiology. The immuno-fluorescent studies showed predominantly IgG and IgM binding only in autologous tissues from patients with aphthous ulcers (7). This reaction could indicate blood group antigens, trapped globulins due to the inflammatory reaction, non-immunological physicochemical binding of the fluorescent conjugate, or normal immunoglobulin transport through the oral mucosa. An immunofluorescent examination couldn’t detect specific globulin binding to salivary gland tissue in the oral aphthous lesion. Major aphthous ulcers do not differ much from minor aphthous ulcers, but they have an increase in the degree of severity of the pathological changes. There were no vascular abnormalities and fibrinous necrosis noticed in recurrent oral ulcers. A

three-fold rise in mast cells was found in recurrent oral aphthous, in contrast to a decreased count in non-specific ulcers. Mast cell count was present in all three groups of oral ulcers when it was compared with that in other oral lesions and normal tissue. Leukocytes have a normal chemotactic function in oral aphthosis but in Behcet's disease, they showed hyperactive function (6). There's a chance that a few immunologically arbitrated mechanisms are playing an important role in the pathogenesis of oral aphthosis. It may be due to an unopposed or excessive production of IL (interleukin)-1 or IL-6, which is essential for its development, a concept that may explain why ulceration worsens after local injury, or cessation of smoking, or both (8).

3.2. Microbiota of Aphthous Ulcers

Several different bacterial species have been associated with an aphthous ulcer. There have been a few studies to know about the association of bacteria with these ulcers (9-11). These studies aimed to estimate the bacterial diversity in oral lesions using a culture-independent molecular approach. These studies have supported a possible relationship between *Streptococcus sanguinis* (*S. sanguinis*) and this condition. Amongst the bacterial infections, the role of a Streptococcus strain which was first identified as *S. sanguinis* but now reclassified as *S. oralis* has been extensively studied since its isolation from a recurrent aphthous stomatitis lesion (12). Other streptococcal species, such as *S. mitis* and *S. oralis*, have also been suspected to provoke the development of a recurrent aphthous ulcer (9).

Pyrosequencing analysis can be successfully employed to compare the oral microbiota of RAS patients with healthy controls. The mucosal microbiota of RAS lesions is characterized as a decrease in the members of healthy core microbiota (normal oral flora) but an increase of rare species, also a decrease in *S. salivarius,* and an increase in *Acinetobacter johnsonii* are related with RAS. Two of the ulcers containing Cytomegalovirus (CMV) DNA were found on the mucosa of the lips and one on the posterior palatal mucosa, whereas all Helicobacter pylori DNA-positive ulcers were present on the buccal mucosa. The results indicated that Cytomegalovirus and Helicobacter pylori (HP) DNA can be found in isolated oral mucosal ulcers in normal healthy adults with a competent immune system. The possible causal role of CMV or HP remains unclear. However, further studies are now in progress regarding the presence of CMV and HP in oral mucosal lesions (13, 14).

Pure cultures of a transitional L form of bacteria were isolated from numerous lesions in RAS patients, their examination suggested that an association exists between the L form of bacteria and the pathogenesis of RAS (15). By DNA sequencing, plasmid DNA purification, and by sequencing the 16S ribosomal RNA gene, the presence of many previously unidentified bacteria was revealed in the gingival sulcus. Prevotella is a genus that consistently appears only in RAS samples and corresponds to 16% of all lesion-derived clones (9). There has been a vast diversity of bacteria in oral aphthous, it is confirmed that the healthy oral flora is replaced by rare species of bacteria. There's no association of the herpes simplex virus with oral aphthous. The only virus that has been found in the patient of oral aphthous is cytomegalovirus.

3.3. Types of Oral Aphthosis and Clinical Aspects

Aphthous ulcer is one or several rounded, superficial, painful ulcers that remain between a few days to a few months. Before the actual ulcer appears, patients will infrequently have on and off symptoms of an itchy or burning sensation (4). Oral aphthous most often begin after 10 years of life and may be caused by minor strain, menstruation or stress, or contact with certain hot or spicy foods. During this initial phase, erythema develops, and it is localized to a specific part. Within hours, small white papules form which later ulcerates, and slowly enlarges over the next 48–72 hours (2). There are three morphological types of aphthous ulcers.

3.3.1. Minor Aphthous Ulcer

It affects about 70-80% of patients. Ulcers are tiny less than 4 mm in diameter, spherical, usually with a

yellowish or grey-white false membrane and erythema is also present. It usually occurs on non-keratinized surfaces particularly the mucosa of lips and mucosa of the mouth, and floor of the mouth (8). If we talk about the sex ratio, we can safely say men and women are equally affected. The age of onset for minor aphthae is approximately between 10-19 years. The number of ulcers is usually 1-5 and the size is less than 10 mm. Scarring does not occur, and the ulcer heals within 10-14 days. If recurrence occurs, it will occur between 4-14 months (16).

3.3.2. Major Aphthous Ulcer

Major RAS is a severe form of RAS also known as peri adenitis mucosa necrotica recurrent in the USA. 10% of the affected patients present with this complaint. These ulcers usually occur on the lips, cheeks. tongue, palate, and pharynx. Just like a minor aphthous ulcer, the sex ratio in men and women is equal. The age of onset for major aphthae is approximately between 10-19 years. The number of ulcers is usually 1-10 and the size is greater than 10 mm. If recurrence occurs, it will occur in less than a month. They persist for up to 6 weeks and scarring may or may not occur. Large ulcers may take a longer time to resolve and mostly heal without scarring. The major ulcer will rarely leave a scar. They can be mistaken as malignant lesions due to their clinical appearance (17). The major aphthous ulcer usually appears after puberty, it is chronic, and persists for up to 30 years (18).

3.3.3. Herpetiform Aphthous Ulcer

Herpetiform ulceration (HU), is a rare form of aphthous ulcer, only 1-10% of patients are affected. It is characterized by multiple recurrent picks of extensive, minor, painful ulcers (8). This ulcer usually occurs on the lips, cheeks, tongue. pharynx, palate. gingiva, the floor of the mouth. In herpetiform aphthous ulcers, females are more affected than males, cause and reason for this are maybe it is stress associated. During stress situations and menses, some women might develop these ulcerative lesions. The age of onset for herpetiform ulcers is almost mid-twenties. The number of ulcers is usually 10-100 and the size is greater than 10 mm. Scarring can occur following the fusion of ulcers. If recurrence occurs, it will occur in less than a month. Despite the name, there is no association with herpes viruses (9).

3.4. Causes of Oral Aphthous

Oral ulcers may have a lot of causes, although in some patients no cause is identified. If oral ulcers persist for less than three weeks' duration, they are called 'acute' and if they persist for longer than three weeks, they are called chronic. Oral ulcers may be recurrent. The majority of patients with a complaint of aphthous ulcers do not have a related underlying systemic disease, but aphthous-like ulcers may occur in association with systemic diseases such as Crohn's disease or MAGIC (mouth and genital ulcers with inflamed cartilage**)** syndrome, or they can occur due to the use of medication such as non-steroidal anti-inflammatory drugs (5).

3.4.1. Local Causes

One of the most common causes of oral ulceration is local trauma (19). It is most frequently caused by tooth procedures, braces, or sharp/broken teeth. It can also be due to accidental tongue or cheek biting, scratching of the tongue with fingernails, or eating rough/hot foods. These ulcers generally start to heal within 10 days after removal of the cause. Persistence after the presumed cause has been removed should lead to urgent further investigation (19). Dr. Harding stated that ulcers can arise due to chemical injury from direct contact of oral mucosa with aspirin or Bisphosphonates (20).

3.4.2. Malignant Causes

Malignant causes of oral ulcers include oral squamous cell carcinoma (most common) lymphoma, minor salivary gland tumors, tumor extension from the maxillary sinus, Odontogenic tumors, metastatic neoplasms, neoplasms of bone, neoplasms of connective tissue, neoplasms of melanocytes, and vascular neoplasms (20). Unusually, smoking may be protective of oral aphthous, even though smoking makes many oral ulcers and skin conditions worse. It

has been recommended that cigarette smoking improves keratinization of the oral mucosa thus it stops aphthous ulcers to grow in the oral cavity (21, 22).

3.4.3. Systemic Causes

There are a few systemic diseases that also contain oral ulcers and can be a leading cause of oral aphthous ulcers. One of these systemic illnesses is MAGIC syndrome (23), the other one is Sweet Syndrome also known as acute febrile neutrophilic dermatosis (8).

Oral ulceration is the most common indicator of Behcet's disease and can occur in up to 99% to 100% of patients with the disease that is why Behcet's disease is a major cause of RAS. Inflammatory bowel diseases (IBDs) affect the intestinal tract, but it has been recently suggested that it also has extra-intestinal involvement within the oral cavity (24). Oral ulcers are seen along with intestinal symptoms of Crohn's disease in about 60% of these patients (25, 26).

3.5. Diagnosis of Oral Aphthous

The diagnosis of oral aphthous is pretty critical because there is no specific diagnostic test currently available. And in this situation diagnosis is based on history and clinical findings. There is a need to exclude other possible causes of recurrent oral ulceration, such as Behcet's disease, PFAPA (Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis) syndrome, and possible infection by HIV. It is necessary to differentiate between the lesions in Behcet's disease and those in oral aphthosis to make a proper diagnosis (8). Also, special attention should be focused on detailed history. Medical specialists should ask about dental procedures before the emergence of the ulcer, and any recent local or chemical injury. Also, ask about the current use of drugs and the history of tobacco and alcohol use. As it is discussed above the causes of oral aphthous so, there is a need to prevent all those causes. Information about any other systemic illnesses or the use of drugs like NSAIDS or bisphosphonates should also be questioned. After the history, the next important step is the examination of the oral cavity. According to Paleri, Staines (5), a complete intraoral examination should be performed to examine the mucosa of the oral cavity. This process requires a good light source and preferably two dental mirrors. Tissues of the oral cavity can be held back with tongue depressors, and it will help with a clear visualization of the whole cavity. There are seven regions in the oral cavity, these must be examined thoroughly to avoid missing a lesion, these sites include lips, cheek mucosa, the floor of the mouth (mainly the posterior floor of the mouth between the tongue and the mandible), teeth and gums, hard palate, oral tongue, and the retro-molar trigone (27, 28). If an ulcer is present assess whether it is localized or inflamed. The shape and margins of the ulcer should be noted. Induration of the ulcer should be felt along with the surrounding tissue and ensure that there is no fixation of moveable tissues such as the tongue. Note the relation of any prosthesis, sharp or broken teeth, or dental repairs to an ulcer if present. An extra-oral examination to look for swelling or lymphadenopathy should always be performed (27).

Patients with RAS show signs of immune dysregulation. Oral aphthous ulcers are mucosal ulcerations with a varied inflammatory infiltrate and large granular lymphocytes. These cells and inflammatory infiltrate predominate in the pre ulcerative and healing phases, keeping this in mind histology can be performed to make a diagnosis. Normal CBC (complete blood count) and hematinic can be done along with another serological testing (29).

3.6. Treatment of Oral Aphthous

Treatment of oral aphthous consists of both topical and systemic agents. There is a multitude of therapies for oral aphthous ulcers. The goals of therapy include analgesia which means control of the pain of an ulcer, ulcer healing, and prevention of recurrence.

3.6.1. Topical Treatments

3.6.1.1. Corticosteroids

Topical corticosteroids are the mainstay of therapy in the case of oral aphthous ulcers. Triamcinolone acetonide is used as an ointment or emollient paste and it is applied to the ulcer site 4 times a day. To make

sure it stays in place, additional applications may be necessary. Improved adhesion of triamcinolone in ointment or emollient paste can be obtained by drying the ulcer before drug application. Food and fluid intake should be restricted for at least 30 minutes before the use of ointment (30, 31).

3.6.1.2. Amlexanox

Amlexanox has already been used in Japan for the treatment of asthma but according to recent clinical trials 5%, Amlexanox paste is effective in the treatment of a type of aphthous ulcer. An overall excellent safety profile for 5% Amlexanox paste is supported by the following very low reported incidence of side effects in subjects treated for aphthous ulcers (32-34).

3.6.1.3. Triclosan

Tricoslan is an antibacterial agent used in toothpaste and mouth rinses. A cross-over study was performed to examine the effect of triclosan on the incidence of oral aphthous when administered in mouth rinses. The results showed that the patients experienced a significant decrease in the number of oral ulcers during the experimental period when the mouth rinses contained triclosan (30, 35).

3.6.1.4. Levamisole

A double-blinded study was performed by De Cree, Verhaegen (36) to check the effectiveness of levamisole in the treatment of aphthous ulcers. According to the results and statistical evaluation of this study, patients who were treated with levamisole showed a reduction in the number of lesions and reduced pain of lesions. These results have been confirmed by subsequent follow-up in an open trial (37).

3.6.1.5. Benzydamine

Benzydamine mouthwash has been found to have a transient local anesthetic effect, which gave pain relief for oral ulcers (38), but it doesn't aid healing (39).

3.6.1.6. Tetracycline

A double-blind trial of a tetracycline suspension was carried out in patients with aphthous oral ulcerations, the tetracycline group showed significant reductions in ulcer duration, size, and pain. In the UK according to a clinical trial, doxycycline 100 mg in 10 ml water used for 2–3 minutes, 4 times daily for 3 days as a mouthwash has provided some good results for the treatment of ulcers (8, 40).

3.6.2. Systemic Treatment

Recurrent aphthous ulceration is often known as an "orphan" disease. Patients are often seen by a range of medical specialties including dermatologists, dental surgeons, and otolaryngologists, with no certain medical specialty assuming particular interest in the management of these patients. Dermatologists are often faced with referrals of patients suffering from oral aphthosis, many of these patients are transferred from dentists or Orthodontists**.** It is therefore important that we can treat such patients with the specialized care that they require. No doubt that topical treatment is effective in such patients but in severe cases, systemic treatment is important as well.

3.6.2.1. Systemic Corticosteroids

Dexamethasone is an adrenocortical steroid and azathioprine an immunosuppressant if both of these drugs are combined, they're effective in the treatment of oral aphthous ulcers. In a double-blinded, controlled clinical trial, the efficacy and safety of topical dexamethasone and placebo in patients with recurrent aphthous ulcerations were studied. Patients were asked to apply dexamethasone five times a day on ulcers and size, pain level, healing ratio, and safety of dexamethasone were observed. Results of this study revealed the effective healing of ulcers and safety as compared to placebo (41). Studies have also shown that oral prednisolone (31) and tetracycline hydrochloride (42) are also effective in the treatment of severe cases of oral aphthous.

In patients with HIV (human immunodeficiency virus)-positive patients, there are several adverse effects of corticosteroid therapy, and such adverse events place oral corticosteroids among the last treatment options for RAS in HIV-seropositive patients (43).

3.6.2.2. Thalidomide

In patients with immunocompromised systems or those with advanced HIV infection, aphthous ulcers can

become extensive and unbearable. Certain reports advise that thalidomide may promote the recuperation of oral aphthous ulcers. According to a double-blinded, study of thalidomide as therapy oral aphthous ulcers in HIV-infected patients, of the 29 patients in the thalidomide group, 26 (90 percent) had complete or partial responses at the end of week 4 (44, 45). Thalidomide is effective in treating oral aphthous ulcers but, because of its toxicity, side effects, and expensive cost, it should be used only when oral corticosteroids cannot be used (46).

3.6.2.3. Pentoxifylline

This anti-TNF agent (400 mg thrice daily) considerably reduced the amount of RAS when used one month for treatment purposes in a study (47), however concerning 100% of patients developed duct symptoms, and therefore the positive impact wasn't confirmed in an exceedingly newer study. It inhibits TNF-α production and presumably the assembly of another Helper T-cell one and pro-inflammatory cytokines, like IL-1β, that area unit thought to be necessary within the RAS malady method. Those patients who were treated with pentoxifylline had less pain and their ulcers were reduced in size (47).

3.6.2.4. Adalimumab

Adalimumab is an anti-TNF-α monoclonal antibody that has been used to treat severe, recalcitrant, major aphthous ulcers[i] but due to the increased risk of serious side effects, it should be used carefully and only in severe conditions (48).

4. Conclusion

In conclusion, oral aphthosis is a relatively common oral mucosal condition. Although its pathogenesis remains unclear, however, it likely involves a predominantly cell-mediated inflammation involving T-cells and TNF-α. Oral aphthosis may be associated with a lot of factors including Microbiota, vitamin deficiencies, Behcet's disease, HIV infection, Sweet syndrome, IBD, and IgA deficiency. Oral aphthosis may present with skin lesions or as a manifestation of systemic disease. Confusion exists on how oral aphthosis is classified. Therefore, all patients with oral aphthous should be evaluated with these conditions in mind, via careful history-taking and examination. Diagnosis can be made through selective hematologic and serologic testing. Once the diagnosis is made the management of the predisposing medical condition often leads to the resolution of the ulcers. A more standardized assessment of oral aphthosis involving proper characterization of the ulcers together with a structured management algorithm and follow-up duration may improve patient outcomes and treatment results. It may require various systemic therapies; dermatologists are in a good position to offer primary care for these patients. Symptomatic and definitive treatment ranges from mouthwash rinses to systemic agents. In particular, topical corticosteroids are very important in the treatment of ulcers. Thalidomide is beneficial in patients who have associated HIV infection. Several Anti-TNF agents have also been proved efficient in the treatment of aphthous ulcers.

Authors' Contribution

Study concept and design: A. G. B.
Analysis and interpretation of data: A. G. B and S. N.
Drafting of the manuscript: A. G. B., S. N. and A. M
Critical revision of the manuscript for important intellectual content: A. M.
Administrative, technical, and material support: A. G.

Conflict of Interest

The authors declare that they have no conflict of interest.

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