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MOUTH ULCER: PATHOPHYSIOLOGY, CLINICAL ASPECTS AND MEDICAL TREATMENT

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ABSTRACT

An excruciating inflammatory process of the mouth mucosa is known as oral aphthosis. Oral aphthous can develop on its own or as a side effect of several different medical conditions. Recurrent aphthous stomatitis is the term used when recurrence happens frequently. Although the pathogenesis of oral aphthous ulcers is yet unknown, the microbiology of these lesions includes a variety of microorganisms. In literature, three morphological kinds are highly significant since they aid in the appropriate management of the sickness. The pertinent data and information were obtained by searching the PubMed and Google Scholar databases. Various terms, such as "Aphthous ulcer causes," "Aphthous ulcer AND Microbiota," "Canker sores," "Aphthous stomatitis," and "Aphthous ulcer AND treatment." Oral aphthous ulcerations can have a wide range of causes, including malignant disease processes, uncommon syndromes, underlying intestinal diseases, and localized trauma. The doctor or dermatologist can help determine whether the condition is genuinely idiopathic or connected to a systemic illness process by obtaining a complete history and performing a thorough examination of the systems. Oral aphthous ulcers are difficult to treat. Topical medicines are preferred for treating oral aphthous ulcers or recurrent aphthous ulcers resulting from underlying diseases since they have fewer negative effects. In the event that the illness worsens, systemic drugs become required. It is safe to state that topical corticosteroids are the first line of treatment, given the limitations of the research and literature supplied. The pathophysiology, kinds, causes, diagnosis, and recommended treatment ladder of oral aphthous stomatitis as reported in the literature are discussed by the author here.

Keywords: Oral Aphthosis, Oral Aphthous, Microbiota, Corticosteroids, Recurrent Aphthous Ulcer, Diagnosis.

I. INTRODUCTION

1. Context

This page discusses the most recent developments in oral aphthosis, a common ailment that is characterized by a large number of small, spherical, or oval ulcers with limited edges. The condition usually manifests itself in adolescence as an erythematous lesion with a yellowish-grey floor (1). Hippocrates initially used the term "aphthae" to refer to illnesses of the mouth; canker sores are another name for ulcers or aphthae (1,2). Humanity has suffered from aphathous ulcers throughout the entirety of recorded history (3). The patient has mouth ulcers due to this ailment. These ulcers may manifest on their own or in conjunction with an underlying medical condition (4). Oral ulcers are typically excruciating sores that are linked to a number of disorders that arise in the oral cavity. Oral aphthous is a well-known condition that significantly impairs a patient's quality of life by producing excruciating pain and making it difficult for them to speak and chew food. There is much study on this sickness, and it is one of the most prevalent oral ulcerative conditions observed in clinical studies (4). The largest frequency of aphthous ulceration is found in developed nations, with women slightly more likely than males to get it. Usually, men and women are equally afflicted but in a unique variety called herpetiform ulcers, women are at a slightly larger prevalence, cause of this remains unexplained. One of the most prevalent oral lesions in the general population, phathous ulcers afflict 20–25% of the population (3). Recurrence rates can reach 50%, and it can happen at any moment during life with a frequency that varies up to three months. These ulcers, which most frequently develop on the non-keratinized oral mucosa, can be extremely painful and make it difficult to chew, consume, and speak. Oral aphthous is a global condition, however it seems to be more prevalent in wealthier nations. A small number of ulcers are cancerous, although the majority are benign and self-resolving. Worldwide variations exist in the incidence and frequency of mouth cancer. A sizable portion of mouth ulcers are cancerous. Patients who have an ulcer that lasts longer than three weeks should be sent to a specialist right once because they may have malignancy (5). It is important to keep an eye out for the

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emergence of any new skin lesions in patients with oral aphthosis, especially in cases of complex aphthosis. This will help rule out other systemic illnesses and simplify the diagnosingprocess.

In the context of scientific understanding, this review attempts to offer a clinically focused summary of the pathophysiology, clinical features, etiology, diagnosis, and management of aphthous ulcers.

II. EVIDENCE ACQUISITION

In order to get pertinent review papers, databases like Google Scholar, Scopus, and PubMed were consulted. Various terms were used, such as "Aphthous ulcer causes", "Oral Aphthous Pathophysiology", "Aphthous ulcer AND Microbiota", "Canker sores", "Aphthous stomatitis", "Aphthous ulcer AND treatment".

III. RESULTS

3.1. Pathophysiology of Oral Aphthous

It is still unclear what causes recurrent aphthosis stomatitis (RAS). It probably involves T-cells and the production of TNF-α (tumor necrosis factor-alpha), which is mostly a cell-mediated inflammatory response. Oral aphthous ulcers examined under a light and electron microscope revealed a penetrating, early infiltration of lympho-monocytes into the epithelium. Lehner (6) reported that oral ulcer epithelium exhibited significant intercellular edema and degenerative alterations when examined under light microscopy. Only the basement membrane next to the ulcer was impacted by epithelial hyperplasia; the remainder of the membrane seemed to be unaffected. Normally located in the basal-cell and prickle-cell layers of the epidermis, mononuclear cells are primarily lymphocytes and monocytes; however, neutrophil polymorphs have also been identified superficially and directly adjacent to ulcers. As stated by Lehner (6), Of the twenty-five biopsies that were analyzed using electron microscopy, three contained intra-nuclear inclusion bodies. The nucleoli had irregular shapes and the impacted nuclei were somewhat bigger. There were no inclusion bodies observed in the cytoplasm. Herpetiform ulcers have intra-nuclear inclusion bodies and epithelial vesicles, indicating a viral etiology, which sets them apart from recurrent aphthous ulcers. Only autologous tissues from patients with aphthous ulcers exhibited primarily IgG and IgM binding, according to immunofluorescence investigations (7). Blood group antigens, globulins trapped by the inflammatory response, non-immunological physicochemical binding of the fluorescent conjugate, or regular immunoglobulin transit over the oral mucosa are all possible causes of this reaction. The oral aphthous lesion did not exhibit particular globulin binding to salivary gland tissue, according to an immunofluorescent study. Principal

The histological alterations in major aphthous ulcers are more severe than in mild aphthous ulcers, but otherwise they are similar. Recurrent oral ulcers did not exhibit fibrinous necrosis or vascular abnormalities. In contrast to a lower count in non-specific ulcers, recurring oral aphthous was associated with a three-fold increase in mast cells. When the mast cell count was compared to that of other oral lesions and normal tissue, it was found in all three groups of mouth ulcers. In oral aphthosis, leukocytes exhibit a normal chemotactic function; however, in Behcet's illness, they exhibit a hyperactive function (6). It is possible that a small number of immunologically arbitrated processes are key players in the development of oral aphthosis.

It could be the result of smoking cessation, unchecked or overproduction of IL (interleukin)-1 or IL-6, which is necessary for its development and could explain why ulceration gets worse after a local damage (8).

3.2. MICROBIOTA OF APHTHOUS ULCERS

Aphthous ulcers have been linked to a variety of bacterial species. A few studies have been conducted to learn more about the connection between bacteria and these ulcers (9–11). These investigations used a molecular technique that is independent of culture to evaluate the bacterial diversity in oral lesions. These investigations have provided evidence for a potential connection between this illness and Streptococcus sanguinis (S. sanguinis). Since its isolation from a recurrent aphthous stomatitis lesion, a Streptococcus strain that was initially designated as S. sanguinis but is now reclassified as S. oralis has been the subject of substantial research in the field of bacterial infections (12). There is also a possibility that other streptococcal species, like S. mitis and S. oralis, can cause recurring aphthous ulcers (9).

It is possible to compare the oral microbiota of RAS patients with that of healthy controls using pyrosequencing analysis. The healthy core microbiota, or normal oral flora, is represented in the mucosal microbiota of RAS lesions by a decrease in members, but an increase in rare species, a decrease in S. salivarius, and an increase in Acinetobacter johnsonii are all associated with RAS. All of the ulcers with Helicobacter pylori DNA-positive were on the buccal mucosa, however two of the ulcers with Cytomegalovirus (CMV) DNA were on the mucosa

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of the lips and one on the posterior palatal mucosa. The findings showed that in healthy, normal persons with functioning immune systems, isolated oral mucosal ulcers can contain DNA from Helicobacter pylori (HP) and Cytomegalovirus. The potential cause It's unclear how CMV or HP function. On the other hand, more research on the existence of CMV and HP in oral mucosal diseases is now underway (13,14).

Following the isolation of pure cultures of a transitional L form of bacteria from several lesions in RAS patients, an analysis revealed a possible correlation between the pathophysiology of RAS and the L form of bacteria (15).

3.3. TYPES OF ORAL APHTHOSIS AND CLINICAL ASPECTS

An aphthous ulcer is any one or more spherical, painful, superficial ulcers that last for a few days to a few months. Patients may occasionally have intermittent symptoms of an itching or burning sensation before the ulcer actually forms (4). Most cases of oral aphthous start after the age of ten. It might be brought on by mild strain, stress or menstruation, or exposure to certain hot or spicy meals. Erythema appears during this early stage and is restricted to a particular area. Little white papules appear within hours, become ulcerative later, and gradually get larger over the following 48 to 72 hours (2). Phthous ulcers can be classified into three morphological forms.

3.4. CAUSES OF ORAL APHTHOUS

Many factors can contribute to oral ulcers, yet in certain instances there may be no known reason. Oral ulcers are classified as "acute" if they last for less than three weeks and as "chronic" if they last more than three weeks. Recurrent oral ulcers are possible. Phthous-like ulcers can occur in conjunction with systemic diseases like Crohn's disease or MAGIC (mouth and genital ulcers with inflamed cartilage) syndrome, or they can occur as a result of medication like non-steroidal anti-inflammatory drugs. However, most patients complaining of aphthous ulcers do not have a related underlying systemic disease (5).

3.4.1. LOCAL CAUSES

Local trauma is one of the most frequent causes of mouth ulcers (19). The most common causes include dental operations, braces, and broken or sharp teeth. Inadvertent tongue or cheek biting, fingernail scratching, and consuming harsh or spicy foods can all be causes. After the cause is eliminated, these ulcers usually begin to heal in ten days. Urgent additional research should be conducted if the suspected reason is still present after it has been eliminated (19). According to Dr. Harding, ulcers may result from chemical damage caused by aspirin or bisphosphonates coming into direct touch with the oral mucosa (20).

3.4.2. MALIGNANT CAUSES

Oral squamous cell carcinoma, the most common type, lymphoma, minor salivary gland tumors, tumor extension from the maxillary sinus, odorogenic tumors, metastatic neoplasms, neoplasms of bone, neoplasms of connective tissue, neoplasms of melanocytes, and vascular neoplasms are among the malignant causes of oral ulcers (20). Surprisingly, despite the fact that smoking exacerbates numerous skin problems and oral ulcers, it may protect against oral phathous. It has been suggested that smoking cigarettes enhances the keratinization of the oral mucosa, preventing the development of phathous ulcers in the mouth cavity (21,22).

3.4.3. SYSTEMIC CAUSES

Oral aphthous ulcers can be caused by a number of systemic disorders, which can also induce oral ulcers. Acute febrile neutrophilic dermatosis, or Sweet Syndrome, is another name for one of these systemic disorders, which is MAGIC syndrome (23).

Behcet's disease is a prominent cause of RAS since oral ulceration is the most common symptom of the illness and can occur in 99% to 100% of patients. In addition to affecting the digestive system, inflammatory bowel disorders (IBDs) may also have extra-intestinal involvement in the oral cavity, according to recent research (24). About 60% of these patients have oral ulcers in addition to the intestinal Crohn's disease symptoms (25,26).

3.5. DIAGNOSIS OF ORAL APHTHOUS

The lack of a precise diagnostic test makes the diagnosis of oral aphthous extremely important. Furthermore, the history and clinical findings are the basis for the diagnosis in this case. Other potential causes of recurring mouth ulcers, such as Behcet's disease, PFAPA syndrome (Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis), and potential HIV infection, must be ruled out. Making the correct diagnosis requires distinguishing between the lesions in oral aphthosis and those in Behcet's illness (8).

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Tongue depressors can be used to hold back oral cavity tissues, which will facilitate a clear view of the whole cavity. The oral cavity consists of seven regions that need to be thoroughly examined in order to miss any lesions: the lips, cheek mucosa, floor of the mouth (primarily the posterior floor between the tongue and the mandible), teeth and gums, oral tongue, hard palate, and retro-molar trigone (27,28). Determine whether an ulcer is localized or inflammatory if one is present. It is important to record the ulcer's shape and edges. Feel the ulcer's indentations along with the surrounding tissue to make sure that any movable tissues have not been fixed, such as like the tongue. If an ulcer is present, take note of how any prosthesis, damaged or sharp teeth, or dental repairs relate to it. Always undertake an extra-oral examination to check for lymphadenopathy or edema (27).

Immune dysfunction is evident in RAS patients. Mucosal ulcerations with a broad inflammatory infiltration and big granular lymphocytes are known as oral aphthous ulcers. Keeping in mind that these cells and inflammatory infiltrate are more prevalent throughout the pre-ulcerative and healing phases, histology can be used to determine a diagnosis. In addition to another serological test, a normal complete blood count (CBC) and hematinic can be performed (29)

3.6. TREATMENT OF ORAL APHTHOUS

3.6.1. Applications on the Skin

3.6.1.1. Hormone-based

The cornerstone of treatment for oral aphthous ulcers is topical corticosteroids. Triamcinolone acetonide is administered to the ulcer site four times a day as an ointment or emollient paste. It might require several applications to ensure its permanence. It is possible to achieve better adherence of triamcinolone in ointment or emollient paste by first drying the ulcer before applying the medication. Prior to using ointment, one should refrain from eating or drinking for at least thirty minutes (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

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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 but due to the increased risk of serious side effects, it should be used carefully and only in severe conditions (48).

IV. CONCLUSION

To sum up, oral aphthosis is a quite frequent mucosal ailment of the mouth. Its exact pathophysiology is yet unknown, but T-cells and TNF-α-mediated inflammation are probably the primary players. Numerous conditions, such as microbiota, vitamin deficiencies, Behcet's illness, HIV infection, Sweet syndrome, IBD, and IgA deficiency, may be linked to oral aphthosis. Skin lesions or systemic disease manifestations are possible presentations of oral aphthosis. The classification of oral aphthosis is not clear. As a result, a thorough history and physical examination should be performed on all patients with oral aphthous while keeping these disorders in mind. Serologic and hematologic tests can be used to make a diagnosis. After the diagnosis, treating the underlying medical condition generally results in the ulcers going away. An additional Treatment outcomes and patient outcomes may be enhanced by standardizing the assessment of oral aphthosis, which includes accurately characterizing the ulcers, following a planned management strategy, and providing adequate follow-up time. Dermatologists are well-suited to provide primary care for patients who may need different systemic medications. Mouthwash rinses and systemic medications are among the effective and symptomatic treatments available. Topical corticosteroids, in particular, are crucial for treating ulcers. Thalidomide is helpful for people with co-occurring HIV infection. Aphthous ulcers have also been successfully treated with a number of anti-TNF medications.

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