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ORAL ULCERS –A REVIEW

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ABSTRACT: Oral ulcers have been a source of diagnostic difficulty. This has been due to the overlap in their clinical appearances. The problem is complicated because a number of oral ulcers may be superimposed by infections due to their easy access to the oral cavity and the thin nature of the oral mucous membrane is an additional challenge to their diagnosis. While the diagnosis of some types of oral ulcers is done by their association with constitutional signs and symptoms or lesions on the skin and/or mucous membranes in other regions, ulcers that are localized only to the oral cavity may be more difficult to identify. Most oral ulcers are, biopsied because they are less readily recognizable on the basis of their clinical features. The similarity in histologic features due to contamination by the oral liquids and microflora also, on occasion, makes it difficult to distinguish by masking the basic pathology. Proper history taking, including the personal history and a thorough clinical examination, is a must to rule out malignancy. The diagnosis and treatment of oral lesions are often challenging due to the clinician's limited exposure to the conditions that may cause the lesions and their similar appearances. This review aims at a systematic approach towards the diagnosis of oral ulcers based on their clinical and histopathological features while eliminating unrelated factors.

INTRODUCTION: Ulcer is a break in continuity of the epithelium by molecular necrosis. Ulcers are most common in the oral region, for which the patient consults physician/dental surgeon. The chief complaints are usually redness, burning sensation and pain. They can be found in any part of the oral cavity but painful if it occurs in the movable area [1].

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Based on the duration ulcers are classified into acute (short term) or chronic (long term). Acute ulcers such as traumatic ulcers, aphthous ulcers, herpetic ulcers and chancres persist not more than three weeks and regress spontaneously.

Chronic ulcers stay for a longer period of time, weeks and months, such as major aphthous ulcers, ulcers from odontogenic infection, malignant ulcers, gumma, ulcers secondary to systemic disease, and some traumatic ulcers [2]. An oral mucosal ulcer is a common clinical complaint. This article gives a wide classification of common mucosal ulcerative lesions to reach a diagnosis and to provide a treatment plan [3].

Classification of Oral Ulcerative Lesions:

1. Traumatic Ulcers: The most common ulcer is a traumatic ulcer, and it is acute in nature. The ulcers are usually caused by physical, thermal, or chemical trauma to the oral mucosa. Physical trauma can be caused during regular activities like tooth brushing or flossing and even the sharp edges of denture or tooth and sometimes it can be self-inflicted by the patient when he/she is under local anesthesia during a dental procedure [4]. The commonly encountered thermal burns are from hot food substances or beverages like pizza, coffee or tea or from a heated dental instrument during a dental procedure.

Oral mucosal damage can be from the unintentional use of therapeutic agents during dental procedures such as eugenol, formocresol, sodium hypochlorite, and monomer. Chemical burns due to aspirin are seen in patients who keep the aspirin tablet sublingual to relieve pain [5]. Mucosal alterations can also be from mouthwashes or oral hygiene products with high alcohol content. Lips are the common site for electrical burns. Burn injuries from food are small and localized to the hard palate and lips. These present with pain and an area of erythema that develop into ulcers which may take several days to heal depending on the extent of trauma. The ulcers have a yellowish-white necrotic pseudo-membrane with raised and erythematous borders. Ulcers in the lip are usually crusted [6].

The traumatic ulcers usually heal within 7-10 days if the cause is removed. It is important to distinguish traumatic ulcers from squamous cell carcinoma. If the ulcer does not heal within two weeks, a biopsy is recommended to rule out a deep fungal infection or malignancy [4]. These ulcers are usually single, but syphilis may present as single ulcers in primary and tertiary stages.

2. Necrotizing Sialometaplasia: Necrotizing Sialometaplasia (NS) is acute and also chronic in nature. It is a self-limiting, benign, non-neoplastic, inflammatory disease of the salivary glands mimicking a malignancy both clinically and histopathologically [7]. It is more commonly seen in men of middle-age. The most common location of involvement is the palate, followed by the lower lip, retromolar area, sublingual region, tongue and larynx.

The lesion initially starts as a non-ulcerated swelling presenting with pain, and later the necrotic tissue sloughs leave a crater-like ulcer. The ulcer is indurated with well-delineated borders. Lesion ranges from 1 cm to 5cm in size [6] and the ulcer regresses on its own within 5 to 7 weeks [8].

3. Primary Herpetic Gingivostomatitis: Primary herpetic gingivostomatitis is the frequent oral manifestation of symptomatic herpes simplex virus (HSV) infection. More than 90% of the cases are caused by HSV-1, which occurs above the waist. HSV-2 occurs below the waist. With the fluctuating sexual practices, it is not unusual to culture HSV-2 from oral lesions [9]. Usually, the age of occurrence is between 6 months to 5 years, with a peak incidence of occurrence between 2 and 3 years. Prodromal symptoms include fever, nausea, anorexia, and irritability [10].

The initial contact with the virus is acquired by inoculating infected secretions into the mucosa, skin, and eye resulting in primary infection. The virus then establishes a chronic latent infection in the sensory ganglion, such as the trigeminal ganglion migrating along the sensory nerve axons [4]. Clusters of vesicles and/or ulcers appear on both the hard and soft palate. Other sites are attached gingival, tongue, buccal and labial mucosa. The vesicles break down to ulcers that range from 1 to 5 mm and coalesce to form large ulcers. The borders are erythematous and scalloped. The mouth is tender, red and often causes difficulty in swallowing and eating. Reactivation of HSV may cause asymptomatic shedding of HSV in the saliva, and oral secretions, which may cause ulcers at the site of innervations, usually in the vermillion border of lips and perioral skin, and they are called as herpes labialis/cold sores/fever blisters [11]. Recrudescent HSV in immune-compromised patients occurs mainly on the keratinized mucosa with oral ulcers similar to primary HSV infection [12]. Recurrent HSV ulcers may also look like traumatic ulcers seen on the palate. Primary herpetic gingivostomatitis might show ulcers similar to coxsackievirus infections, but the latter does not present ulceration on the gingiva and are not clustered. Viral culture or a cytology smear distinguishes the two. A cytological smear or viral culture is necessary to eliminate aphthous ulcers, necrotizing ulcerative gingivitis, and ulcers

secondary to cytomegalovirus infection from recurrent intraoral herpes in immune-compromised patients.

4. Varicella-Zoster Virus Infection: Primary VZV infection or chickenpox occurs in the first two decades of life. The disease started with a low-grade fever, malaise, and the development of an intensely pruritic, maculopapular rash [13] and is followed by "dewdrop-like" vesicles.

Some patients present with involvement of the trigeminal nerve, and the condition is painful if the maxillary branch is involved. Some patients have tenderness and burning sensation [1]. After the prodromal symptoms, clusters of ulcers are seen unilaterally on the gingiva or hard palate. These ulcerations coalesce to form larger ulcers with a scalloped border.

These ulcers heal within 10 to 14 days [14]. The pain that is experienced before the onset of vesicles and ulcerations may mislead to the diagnosis of pulpitis, leading to unnecessary dental treatment. HSV and herpes zoster infection can be differentiated by culture. Autoimmune diseases like pemphigus and pemphigoid also present with skin and oral ulcerations, but these lesions are chronic and are not unilateral. If the patient is immune-compromised, acute necrotizing ulcerative periodontitis should be considered, which can be eliminated with appropriate tests.

5. Erythema Multiforme: Clinically, erythema multiforme can be classified into major, minor, and persistent variations. The condition can be present with typical or atypical skin lesions. Target lesions located on the extensor surfaces of the acral extremities are the pathognomic presentation for this disorder. These lesions consist of a dusky central blister, a dark red inflammatory zone surrounded by a pale ring of edema, and an erythematous halo on the periphery of the lesion. Lesions may also manifest in the mucous membranes of the oral, ocular, or genital mucosa and can occur with or without cutaneous lesions [15]. Oral involvement occurs with 25%-60% of patients with erythema multiforme. It is of forms major and minor [16].

Lesions associated with erythema multiforme typically appear over the course of three to five days and resolve within 1 to 2 weeks. However, the more severe cases of erythema multiforme with the involvement of the mucous membranes may take up to 6 weeks to regress [15]. These episodes may recur on an average of six times per year, which may last up to six to 10 years.

This subset of the disorder is recurrent erythema multiforme and may be associated with a herpes simplex virus infection [16]. In rare cases, there is a continuous appearance of lesions without interruption that may continue for longer than 1 year. This variant is known to be persistent erythema multiforme and may be associated with viral infection.

6. Acute Necrotizing Ulcerative Gingivitis (Anug) and Acute Necrotizing Ulcerative Periodontitis (Nup): ANUG is also called 'Trench Mouth' since it was common in the soldiers in trenches during World War I. NUG and NUP are mostly associated with immune suppression, smoking, poor oral hygiene, and debilitation [17]. Punched out ulcer with a crater-like depression which is covered by pseudomembranous slough, is seen in the gingival at the crest of the interdental papilla [18]. Marginal and attached gingival are affected. The early symptoms are excessive salivation, a metallic taste, gingival sensitivity, and bleeding along with halitosis. NUG and NUP may progress to Noma (Cancrumoris) in immune-suppressed or malnutrition patients [19].

7. Recurrent Aphthous Stomatitis: The term aphthae comes from the Greek word aphthi, which means "to set on fire" or "to inflame," and is thought to have been first used by the philosopher Hippocrates to describe the pain associated with a common disorder of the mouth during his time (likely, aphthous stomatitis) [20]. Local injury, genetical factors, nutritional deficiencies, viral and bacterial infections, and immune or endocrine disturbances have been known to as etiological factors of frequent oral ulcers. In some patients, where the etiology is unknown such cases are known as recurrent aphthous stomatitis (RAS) [21]. Three types of RAS exist minor (>70% of cases), major (10%), and herpetiform (10%). These subtypes differ in morphology, distribution, severity, and prognosis **Table 1**. All types of RAS have an impact on quality of life [22].

TABLE 1: CLINICAL FEATURES OF MINOR, MAJOR, AND HERPETIFORM RECURRENT APHTHOUS STOMATITIS (RAS)

	Minor Ras	Major Ras	Herpetiform Ras
Gender predilection	Equal	Equal	Female
Morphology	Round or oval lesions Gray-white psuedomembrane. Erythematous halo.	Round or oval lesions Gray-white psuedomembrane. Erythematous halo.	Small, deep ulcers that commonly converge. Irregular contour.
Distribution	Lips, cheeks, tongue, floor of mouth	Lips, soft palate, pharynx	Lips, cheeks, tongue, floor of mouth, gingival
Number of ulcers	1–5	1–10	10–100
Size of ulcers	<10mm	>10mm	2–3mm
Prognosis	Lesions resolve in 4–14 days. No scarring.	Lesions persist >6 weeks. High risk of scarring.	Lesions resolve in <30 days. Scarring uncommon.

8. Behçet Disease [Bd] (Behçet Syndrome): Behcet's disease (BD) is a multisystem inflammatory disease characterized by recurring episodes of oral aphthous ulceration, genital ulceration, other skin lesions, and ocular lesions [23]. The pathogenesis of BD is unknown but mostly due to autoimmunity. It can affect all age groups, but it is rarely seen before puberty and after 60years of life. The most common are the oral ulcerations, which are recurrent and tender in most of cases and cannot be distinguished clinically or histologically from RAS. Some are mild and recurrent, and others have deep, large, and scarring lesions.

A diagnosis of Behcet's is made when recurrent aphthous ulcerations are seen along with two of the following lesions, namely oral, genital ulceration, ocular lesions, and skin lesions [24].

9. Chronic Ulcers:

Sustained Traumatic Ulcers: They are most commonly seen on the tongue, lips, buccal mucosa, and floor of the mouth at the lingual sulcus. Traumatic ulcers heal within 7 to 10 days, but some lesions persist for weeks to months due to constant injury and irritation or secondary infection [25].

10. Traumatic Ulcerative Granuloma (Eosinophilic Ulcer of the Tongue): Traumatic Ulcerative Granuloma with Stromal Eosinophilia (TUGSE) is a chronic solitary ulcer of oral mucosa seen often in patients over 40 years of age but sometimes seen in children and young patients. The tongue is the most common site, followed by the buccal mucosa, retromolar region, the floor of the mouth, and lips. These are traumatic ulcers, but due to the penetration of inflammation, it results in myositis. Similar ulcers can be seen on the ventral tongue in infants when the tongue rasps against newly erupted primary incisors, leading Riga-Fede disease [26]. Buccal mucosa, labial mucosa, the floor of the mouth and vestibule, and sites with more underlying skeletal muscle can also be involved. In some cases, the lesions present as an ulcerated, mushroom-shaped, polypoid mass on the lateral side of the tongue [27]. The presence of induration leads the practitioner to suspect for squamous cell carcinoma (especially if it is on the tongue) or other malignancy of salivary gland or lymphoid origin.

Pemphigus and Pemphigoid: These lesions are a group of autoimmune, life-threatening that present with blisters and eroded skin and mucous membranes.

11. Pemphigus: Very common type is Pemphigus vulgaris. The antibodies are targeted against DSG3. When the lesion is confined to the mucosa and antibodies are targeted against DSG1 and DSG3 [28]. The oral lesions may start as a bulla which ruptures to form shallow ulcers. A thin layer of epithelium peels away, leaving behind a denuded base referred to as Nikolsky's sign named after Pyotr Nikolsky (1858-1940), a Russian physician [29]. The lesions are most commonly seen along the occlusal plane on the buccal mucosa. Palate and gingiva are also other sites involved. The oral lesions last for months before the skin lesions. However, the duration of the lesion is important to distinguish from viral ulcers. If the lesion is treated early, there is a chance for it to remit and control. It is also important to distinguish these lesions from RAS. The lesions in the RAS may be severe but heal and recur. The lesions in the pemphigus last for weeks to months.

12. Pemphigoid: Pemphigoid are classified as mucous membrane and bullous pemphigoid.

The auto antibodies are targeted against BP180 and BP230 present at the basement membrane. Oral lesions of bullous type occur in 30 to 50% of patients. The oral lesions are smaller, slow in rate of progression, and are less painful than pemphigus. Early remission is seen in such type of pemphigoid. The lesions of the mucous membrane pemphigoid present as desquamative gingivitis and the gingiva appears to be bright red which mimics erosive lichen planus and pemphigus. The lesions may be in the form of vesicles on the gingiva or other mucosal surfaces [29] but rate of progression of these lesions is slower than pemphigus and are self-limiting.

13. Mucormycosis: Mucormycosis is an opportunistic infection caused by a saprophytic fungus normally occurring in soil or mold over decaying food. Infection occurs in patients with compromised host resistance, such as patients with uncontrolled diabetes, hematological malignancies, those undergoing chemotherapy or immune-suppressive drug therapy. The fungus invades arteries leading to damage secondary to thrombosis and ischemia. The oral lesions present as ulcers on the palate, which result from necrosis caused due to invasion of palatal vessels. The ulcer is large and deep enough, causing denudation of underlying bone structure. The other intraoral sites involved are the gingiva, lip, and alveolar ridge [30].

14. Tuberculous Ulcers: Granulomatous diseases can lead to ulcers in the oral mucosa. Oral manifestations of tuberculosis and leprosy can be secondary to systemic conditions but are however rare. Tuberculosis can be pulmonary or extrapulmonary. Pulmonary TB can be classified as primary, secondary or miliary. Primary TB is generally seen in children. It is mostly asymptomatic sometimes, it can present with febrile illness and dry or productive cough. Oral lesions are usually uncommon and are secondary to the primary disease. It is likely the organisms are carried away in the sputum and enter into the mucosal tissue via a small break in the surface. Oral manifestations of secondary tuberculosis may present at any intraoral site, the tongue being the most commonly affected site. The other sites generally involved are the gingiva, floor of the mouth, palate, lips, and buccal mucosa. The oral ulcers are chronic, show induration with irregular undermined edge and thick mucous material in its base. Tuberculous ulcers are usually painless, chronic, and typically angular with over-hanging or undermined edges and a pale floor, but can be ragged and irregular, often present with tenderness [31]. The infection can be confirmed with special microbial stains and a culture of infected tissue or sputum. The presence of acid-fast bacilli in the sputum is usually demonstrated for the diagnosis of tuberculosis. Chest radiographs and tuberculin tests are supplemental aids in TB diagnosis.

15. Syphilitic Ulcers: Primary syphilitic ulceration most commonly occurs as a result of oro-genital or oro-anal contact with an infectious lesion. The involvement of the oral cavity is very rare, and it seldom diagnosed due to its shorter duration. Deep ulcer with ragged border and is seen [1]. The differential diagnosis includes chronic traumatic ulcer and squamous cell carcinomas. A brief history of sexual and social life helps in the proper diagnosis of such lesions. Tertiary syphilis presents as punched out ulcers on the tongue. Tertiary syphilis develops as a swelling, sometimes with a yellowish centre which undergoes necrosis, leaving a deep painless ulcer. The ulcer is rounded, soft, punched-out edges. The floor appears pale and depressed [1]. Serological tests are found out to be highly sensitive and are specific such as fluorescent treponemal antibody absorption and T.pallidum haem-agglutination assays.

Management: Traumatic ulcers are treated initially by eliminating the causative agent and observed for signs of remission. In painful ulcers, the surface is treated with fluocinonide or triamcinolone in an emollient base after meals and before going to bed. This relieves pain and reduces duration of healing. Any ulcer devoid of signs of healing for 2 weeks need biopsy to rule out malignancy by biopsy.

For mild aphthous ulcers, anesthetic gel is given for applying topically. In more severe cases, the use of a highly potent topical steroid preparation is recommended, such as 1.5% cortisone acetate, hydrocortisone acetate, triamcinolone, clobetasol cream, beclomethasone spray applied directly over the lesion reduces healing time and reduces the size of the ulcers, intralesional injection of triamcinolone actinide for aphthous major ulcers. Other agents tried with various levels of success

include tetracycline mouth wash 250 mg / 5ml four times daily for 5 to 10 days, chemical cauterizing agents reduces the tenderness but no other beneficial effect. For severe lesions several systemic drugs have been used for treatment, including systemic corticosteroids like prednisone 20-40 mg/day for a week, half the dose for next week and then taper the dose gradual, dapsone (Tap Daps one 25/50/100 mg), colchicine, thalidomide, pentoxifylline [32, 33]. Levamisole, (Tab Dewormis, Vermisol, Diceris, 50/150 mg), an anti-helminthic drug that can modulate immune responses, has been used successfully as a monotherapy and as an adjunct to treatment in a variety of diseases. Because of its modulating effects on immune responses, levamisole has been used in a wide range of diseases with varying degrees of success [34].

For primary HSV Infection, aspirin or acetaminophen is administered for fever, IV fluids to maintain proper hydration and electrolyte balance, topical anesthetics preferred before meals to reduce the difficulty during eating and drinking.

Recurrent herpetic lesions are self-limiting and the use of topical anti-viral reduces shedding, infectivity, pain, and the size and duration of lesions. The recommended systemic acyclovir for adults is 200 mg five times a day for five days, and for children below 2 years, 100 mg 5 times a day for 5 days. Prednisone 40-60 mg/daily for one week to prevent postherpetic neuralgia in old patient. (ACIVIR 200 mg, 400 mg, 500 mg DT – Dispersible tablet). In mucormycosis, the ulcers are treated with a combination of surgical debridement of the infected area with systemic amphotericin B. other antifungal agents used are posaconazole and isavuconazole. The underlying etiological factor must be addressed, which may affect the outcome of the treatment. The mild erythema multiform can be managed with topical analgesics for pain, corticosteroids, antiseptic mouthwashes, soft or liquid diet, intravenous rehydration, and anti pyretic and supportive care. Severe cases are treated with systemic corticosteroid prednisone 30-50 mg/day for one week, and the dose should be tapered and stopped.

Vesiculo-bullous lesions such as pemphigus and pemphigoid are best treated with topical and systemic corticosteroids depending on the severity of symptoms or site and extent of involvement. If the treatment is begun when the lesion is confined to the oral mucosa, the prognosis is good [35].

CONCLUSION: Ulcers are usually common in the oral cavity, and patients overlook the lesions if it does not cause discomfort. However, it is the utmost responsibility of the dental practitioner to look into such lesions even during regular visits, give counseling to the patients and plan the treatment accordingly. Proper history taking, including the personal history and a thorough clinical examination, is a must to rule out malignancy.

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