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Oral Ulcer

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ABSTRACT

Oral ulceration is the loss or erosion of part of the delicate tissue that lines the inside of the mouth (mucous membrane).In most cases, oral ulcers are harmless and resolve by themselves within 10 days without the need for any treatment. Aphthous ulcers are recurring ulcers with no known cause. They affect around 20 to 30 percent of the population. The ulcer is a break in the continuity of the epithelium brought about by molecular necrosis. Ulcers are most common in the oral region, for which the patient takes help from their physician/dental surgeon. The presenting complaints are usually redness, burning sensation, and/or pain. They can present in any part of the oral cavity but may be painful if it occurs in the movable area.

INTRODUCTION:

Oral ulcers are a very common disorder of the oral mucosa. Several predisposing factors have been suggested and oral ulcers can be a feature of various systemic disorders including inflammatory bowel disease. The nature, site, duration, and frequency of oral ulcers are determined by underlying systemic conditions [1]. Oral ulcers are common, with an estimated point prevalence of 4% worldwide. Aphthous ulcers may affect as many as 25% of the population worldwide. Patients with an oral ulcer may present initially to a general practitioner or dental practitioner. Most ulcers are benign and resolve spontaneously but a small proportion of them are malignant. The incidence and prevalence of oral cancers are varied across the world. Some of the highest incidences are seen in the Indian subcontinent, southern France, South America. Importantly, the incidence of oral cancer is rising in most populations, particularly in young women[2]. Mouthy ulcers are sores on the inside lining of the mouth. Blisters or sores on the lips or around the outside of the mouth are usually cold sores, not mouth ulcers[3]. Oral sores can be painful, annoying, and unsightly. Some appear inside the oral on the gums, lips, tongue, cheeks. Others, like cold sores, can appear outside the mouth, such as on and around the lips, under the nose, and on the chin. Mouth sores can be caused by oral cancer or bacterial, viral, or fungal infections. Although there are many types of mouth sores, the most common are canker sores, cold sores, leukoplakia (a thick white or gray patch), and candidiasis or thrush (a fungal infection)[4]. The aim of this review is to provide a clinically oriented overview of the classification of oral ulcers based on pathogenesis, type of oral ulcers, and diagnosis and treatment of oral ulcers.

Classification of oral ulcer :[5]

Table No. 1: Classification of oral ulcers based on clinical

Types	Surrounding skin	Ulcer features	Other features
Spreading is seen	Inflamed	No granulation tissue	
Healing	Not inflamed	Granulation tissue is present in floor	Slight serous discharge is seen
Callous	Induratons	pale granulation tissue is seen at floor and indurations are seen at base and edge	No tendency towards healing

Table No. 2: Classification of oral ulcers based on pathogenesis

1. Malignant ulcers
    a) Carcinoma in situ
    b) Ulcerating squamous cell carcinoma
    c) Basal cell carcinoma
    d) Malignant melanoma
    e) Mucoepidermoid carcinoma
2. Ulcers due to infection and inflammation
    a) Viral
        i. Intraoral herpes simplex infection
        ii. Herpes zoster
        iii. Infectious mononucleosis
        iv. Hand foot and mouth disease
        v. Herpangina
        vi. Primary HIV infection
    b) Bacterial
        i. Acute necrotizing ulcerative gingivitis
        ii. Noma
        iii. Syphilitic ulcers
        iv. Gonorrhoeal ulcers
        v. Tuberculous ulcers
    c) Fungal
        i. Histoplasmosis
        ii. Candidiasis
3. Ulcers due to allergy and immunological dysfunction
    a. Recurrent aphthous ulcers
    b. Behcet's syndrome
    c. Reiters's syndrome

d. Erythema multiforme and stevens-johnson syndrome

e. Lupus erythematosus

f. Mucous membrane pemphigoid

g. Erosive lichen planus

h. Pemphigus vulgaris

i. Wegener's granulomatosis

j. Drug-related ulcers

4. Ulcers caused by hormonal changes

5. Metabolism , nutrition and storage related ulcers

   a. Langerhans call histiocytosis

   b. Vitamin C deficiency

   c. Glycogen storage disease

6. Traumatic ulcers

7. Iatrogenic ulcers

8. Idiopathic ulcers

9. Ulcers associated with systemic disorders

   a. Anemia (pernicious anemia , iron deficiency anemia)

   b. Agranulocytosis

   c. Cyclic neutropenia

   d. Leukemia

   e. Myelic aplasia

   f. Myelodysplastic syndrome

   g. Ulcerative colitis

   h. Crohn's disease

i. GERD

10. Miscellaneous

a. Necrotizing sialometaplasia

GERD: Gastroesophageal reflux disease

❖ **PATHOGENESIS OF ULCERS :**

➢ **Ulcers due to malignancy :**

Oral cancer, like other malignancies, arises from the accumulation of several discrete genetic mutations in genes that control cell cycle, survival, and motility ultimately leading to a malignant phenotype. The invasion of carcinomas through penetration of the basement membrane, connective tissue, and vascular system results from alterations in adhesion molecules and is associated with enzymatic degradation of the extracellular matrix.[5]. Further, neoplastic proliferation exhausts the blood supply, eventually leading to ulcer formation. Malignant ulcers are usually painless early in their course due to the destruction of peripheral sensory nerve endings. Enlarged metastatic lymph nodes also are characteristically painless and firm.[6].

➢ **Ulcers due to virus :**

Viruses are a unique group of infectious agents that induce host metabolism to synthesize genetic components for their sustenance. Following its fusion with the host epithelial cell the viral genome is uncoated and transported to the nucleus where the replicating viral genome is incorporated in the host DNA forming virion components that are then released extracellularly[7]. The virion then infects the adjacent host cells resulting in profound changes in cell structure and function leading to a break in the epithelium, and thus forming an ulcer.

➢ **Ulcers due to immunological dysfunction including drug allergy**

Low molecular weight antigens, through various sources including drug molecules, combine with endogenous proteins and form “haptens,” which results in a hyperimmune response, or drug allergy[8].In contact stomatitis, Langerhans’ cells bound to haptens in the mucosal

epithelium, migrate to the regional lymph nodes and present the antigen to T-lymphocytes, which become sensitized and undergo clonal expansion[9].

(i) presence saliva which causes dilution of the potential antigen preventing their penetration into the oral mucosa

(ii) richer vascularity of the oral mucosa which rapidly removes potential antigens that have penetrated it before an allergic reaction can occur, and

(iii) lesser keratin in the oral mucosa which decreases the possibility for hapten formation[9].

- **Ulcers due to defect in metabolism, nutrition, and storage**

Vitamin C is a cofactor in various enzymatic reactions, and when dysfunctional, leads to the development of scurvy, characterized by healing defects including oral ulcers. This is attributed to the inadequate hydroxylation of procollagen which requires vitamin C, the defective formation of collagen, which is vulnerable to enzyme degradation or their poor secretion from fibroblasts. The diminished antioxidant effect of vitamin C further plays an important role in ulcer aggravation[10]. Glycogen storage diseases are a rare group of genetic disorders involving the metabolic pathways of glycogen caused by a defect in the microsomal translocate for glucose 6-phosphate,[11] .inability of the lysosomes of macrophages to hydrolyze the phagocytozed storage material, and ultimately rupture of the lysosomal membranes. The oral ulcers that result are of neutropenic origin [12]. Langerhans cell histiocytosis, a clonal proliferative disease of Langerhans of probable metabolic etiology may occur as any of the three forms, of which eosinophilic granuloma appears as localized solitary or multiple oral ulcerations[13].

- **Ulcers caused by hormonal changes :**

Hormonal imbalances manifest as local physical changes including in the oral cavity. Oral ulcers seen in females during normal menstrual cycle and pregnancy occur due to the increase in salivary estrogen which causes an increase in the proliferation and desquamation of the oral mucosa[14]. Corticosteroids that damp down inflammatory reaction of body tissue are known to become ulcerogenic to the gastrointestinal system with prolonged use[15].

- **Traumatic ulcers**

The traumatic ulcer is by far the most common oral mucosal ulcer[6] the source of which ranges from mechanical, chemical, electrical, or thermal and may be accidental, self-inflicted, or iatrogenic and accordingly vary in size. A cause-and-effect relationship helps in making a definitive diagnosis and in identifying the traumatizing agent. Healing usually occurs within 2 weeks of removal of the traumatic influence. Persistent ulcers not responding to local treatment might be a sign of the malignant transformation of the ulcer[6].

- **Iatrogenic ulcer:**

Oral ulcers can occur due to procedural errors in dentistry from improper use of chemicals or therapy [16] Detection requires a thorough clinical and radiographic examination of teeth and supporting structures.

- **Idiopathic ulcers**

Ulcers of unknown etiology are considered idiopathic and provide no clinical or microscopic sign specific to the causative factor. Investigations such as serum tests and radiography may be done to arrive at a diagnosis.

- **Ulcers associated with systemic disorders**

Ulcers form a common oral manifestation of systemic disorders especially those of the hematopoietic system. These may be confused with the shallow persistent ulcers such as traumatic ulcers, early SCC, chancre, early MEC, ANUG, cyclic neutropenia, and leukemia.[17] .The gastroesophageal reflux disease may lead to oral ulceration by the disruption of the oral mucosal barrier by the backflow of acidic contents. Endoscopy and laboratory investigations like acid perfusion test or 24-h esophageal pH monitoring are useful diagnostic aids.[18].

- **Necrotizing sialometaplasia**

Necrotizing sialometaplasia is a benign, chronic, self-limiting inflammatory process hypothesized to be caused by ischemic necrosis of minor salivary glands following vascular infarction.[19].

❖ TYPES OF ULCERS :

Based on the duration ulcers can be broadly classified into acute (short term) or chronic (long term). Acute ulcers persist no more than three weeks and regress spontaneously such as traumatic ulcers, aphthous ulcers. Chronic ulcers persist for weeks and months such as major aphthous ulcers**.**

A) Types of acute ulcer :

➢ **Traumatic ulcers**:

Traumatic ulcers are quite common and acute. The ulcers are caused usually by physical, thermal, or chemical trauma to the oral mucosa causing tissue damage and resultant ulceration.

Physical trauma can be caused during regular activities like tooth brushing (Figure 1a) or flossing, sharp edges of denture or tooth (Figure 1b), oral piercings, and sometimes can be self-inflicted by the patient when he/she is under local anesthesia during a dental procedure [20]. The commonly encountered thermal burns occur when ingesting hot food substances or beverages like pizza, coffee, or tea or from a heated dental instrument during a dental procedure.

Among the dental materials, liquids are likely to cause chemical oral burns because they can be difficult to manipulate. Chemical burns due to aspirin are seen in patients who keep the aspirin tablet to relieve pain (Figure 2) [21].

The traumatic ulcers usually heal within 7-10 days when the cause is removed. It is important to distinguish traumatic lesions from squamous cell carcinoma. If the ulcer does not heal within two weeks, a biopsy should be taken to rule out a deep fungal infection or malignancy [20].

Figure No. 1: a) Traumatic ulcer in the gingvia in brush injury.

b) Traumatic ulcer due to sharp teeth.

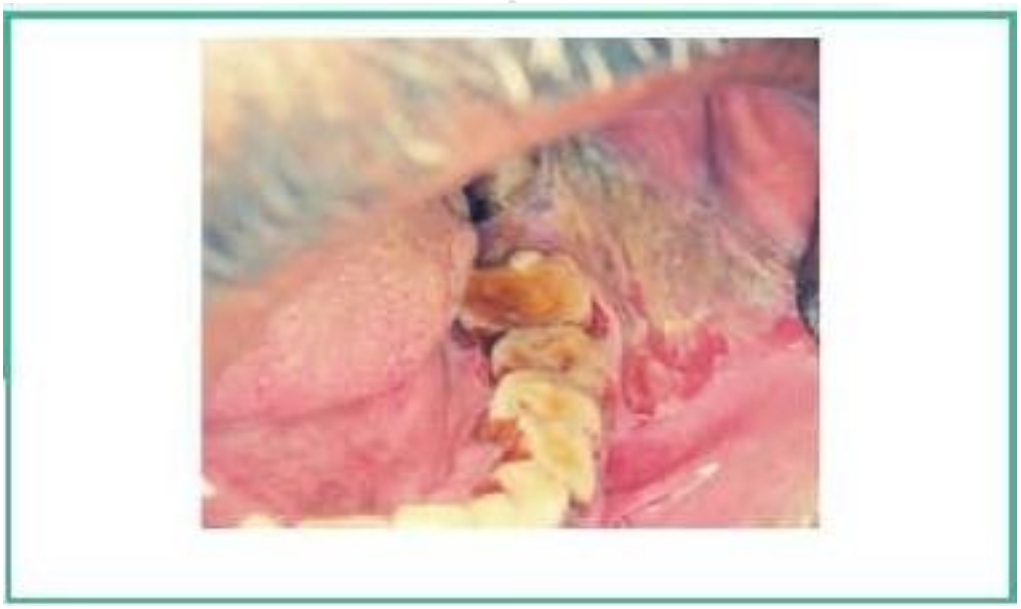

Figure No. 2: Chemical burn produced by the placement of tablet aspirin.

- **Necrotizing Sialometaplasia:**

Necrotizing Sialometaplasia (NS) is both acute and chronic. It is a self-limiting, benign, non-neoplastic, inflammatory disease of the salivary glands mimicking a malignancy both clinically and histopathologically. Most common site of involvement is the palate, followed by lower lip, retromolar area, sublingual region, tongue and larynx. The lesion initially starts

as a nonulcerated swelling associated with pain and later the necrotic tissue sloughs leaving a crater like ulcer.

The size of the lesion usually ranges from 1cm to more than 5cm [23]. The ulcer resolves on its own within 5 to 7 weeks [24].

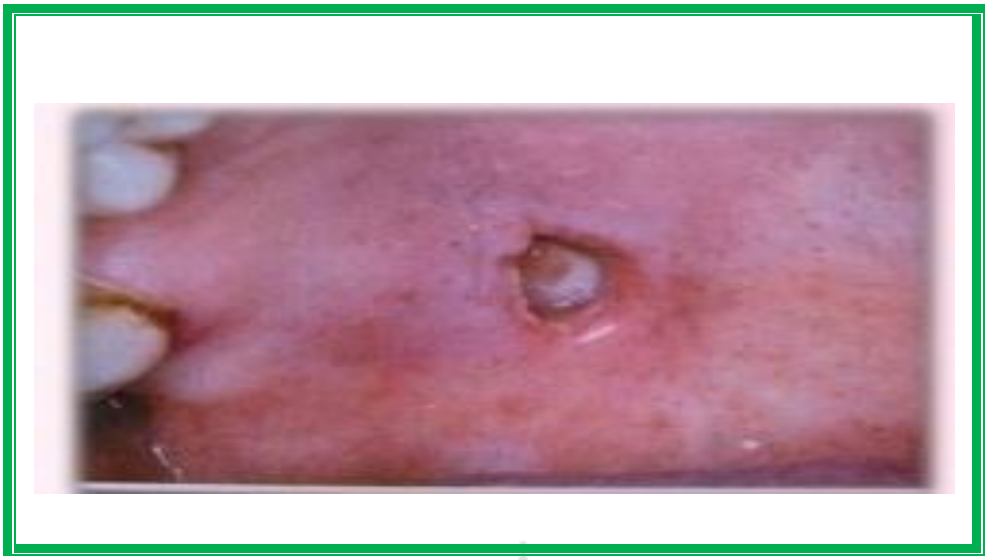

Figure No. 3: Necrotizing sialometaplasia.

- **Primary herpetic gingivostomatitis:**

Primary herpetic gingivostomatitis is the most common 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, whereas HSV-2 occurs below the waist.[25]. Usually, the age of occurrence is between 6 months to 5 years with a peak incidence between 2 and 3 years. Prodromal symptoms include fever, nausea, anorexia, and irritability[26].

Figure No. 4: Primary Herpetic Gingivostomatitis

- **Recurrent aphthous stomatitis**

Recurrent Aphthous Stomatitis (RAS) is characterized by recurring ulcers confined to the oral mucosa in the absence of other signs of disease. They are classified as minor ulcers, major ulcers and herpetiform ulcers.[27].

Classification:

- **Minor RAS**:

This is the most common presentation of the disease, representing 70%-85% of all cases. It manifests as small rounded or oval lesions covered by a grayish-white pseudomembrane and surrounded by an erythematous halo. Each episode involves the appearance of one-to-five ulcers measuring less than1 cm in diameter, which are self-limiting and resolve within 14 days without scarring.

Figure No. 5: Minor Aphthae

- **Major RAS**:

This is the most severe presentation of the disease, representing 10% of all cases. The ulcer measure over 1 cm in size and tend to appear on the lips, soft palate, and pharynx. The lesions can persist for over 6 weeks and can leave scars.

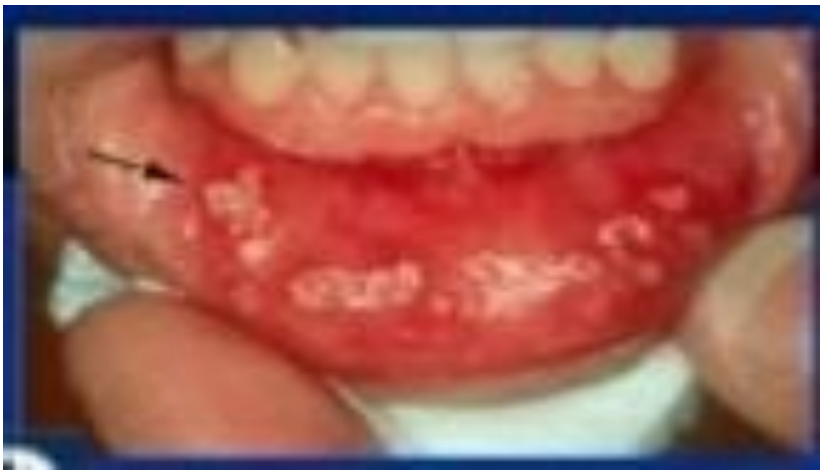

Figure No. 6: Major Aphthae

- **Herpetiform RAS**:

This subtype accounts for 1%-10%of all cases and is characterized by recurrent outbreaks of small, deep, and painful ulcers. Up to 100 aphthae can develop simultaneously, measuring 2-3 mm in size, although they tend to merge to form larger ulcerations with an irregular contour. In contrast to the minor and major RAS subtypes, this presentation is more often seen in female patients and patients of older age. Lesions resolve within 15 days.[28].

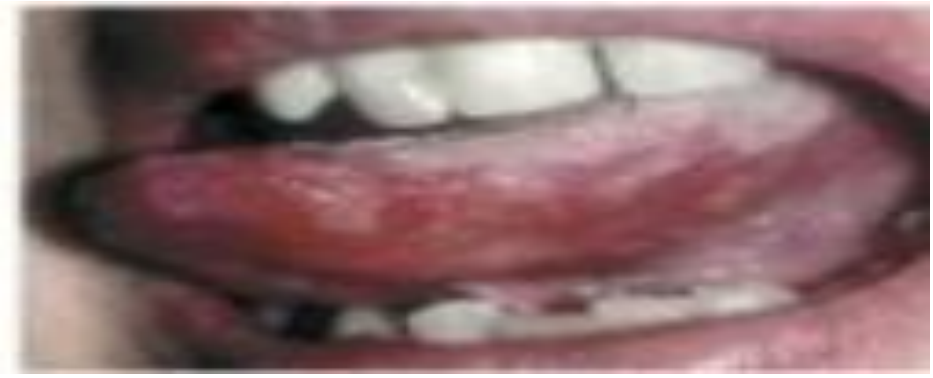

Figure No. 7: Herpetiform Ulcerations

B) Types of chronic ulcer:

- **Sustained traumatic ulcers (Decubitus ulcer) :**

Chronic injury to the oral mucosa may lead to long standing traumatic ulcers characterized by fibrosis surrounded by ulcerations. They are mostly seen on the tongue, lips, buccal mucosa and floor of the mouth at the lingual sulcus (Figure 6). Traumatic ulcers heal within 7 to 10 days but some persist for weeks to months due to constant traumatic insults and irritation or secondary infections[29].

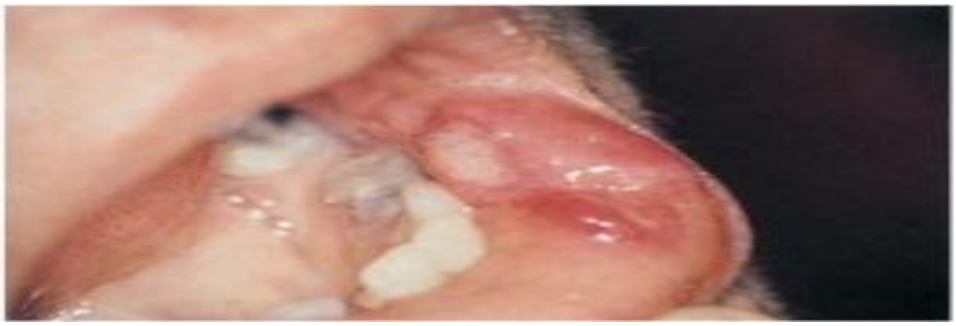

Figure No. 8: Traumatic Ulcer.

Squamous cell carcinoma:

Squamous cell carcinoma is the most common oral malignancy and accounts for more than 90% of oral cancers. It can present as an exophytic, ulcerative, red, and white, or a mixed lesion. The ulcerative SCC presents as a crater-like lesion with rolled out margins and an indurated border (Figure 7). Lips, the floor of the mouth, lateral, and ventral borders of the tongue are commonly involved. The lesion is usually solitary. The lesion is destructive and timely diagnosis and treatment are crucial in determining the prognosis of the patient.

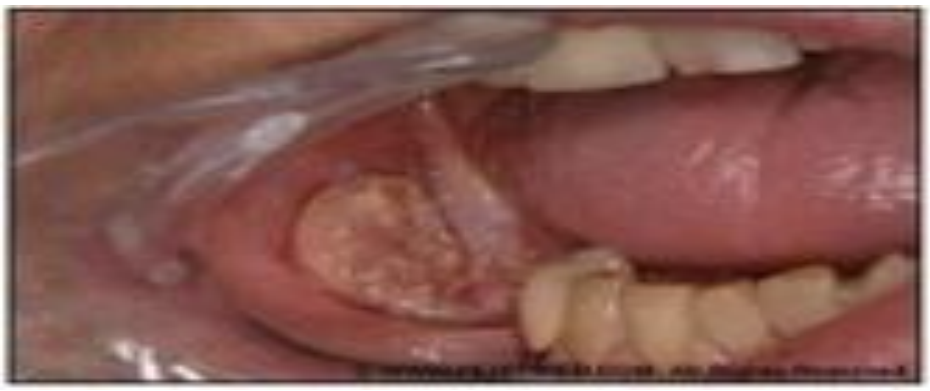

Figure No. 9: Sqamous cell carcinoma

➢ **Syphilitic ulcers :**

Primary syphilitic ulceration usually occurs as a result of orogenital or oroanal contact with an infectious lesion. It develops on the lips, tongue, pharynx, or tonsils as a solitary ulcer. The upper lip is more commonly affected in males and the lower lip in females. The ulceration is usually deep, with a red-purple or brown base ragged rolled border and accompanied by cervical lymphadenopathy[30].

The diagnosis can be made by examining the exudates for spirochetes under a dark field microscope. Serological tests are highly sensitive and are specific such as fluorescent treponemal antibody absorption and T.pallidumhaem agglutination assays.

➢ ***Pemphigus Vulgaris* :**

It is the most common form of pemphigus, accounting for over 80% of cases. The antibodies are targeted against DSG3. When the lesion is confined to the mucosa and targeted against DSG1 and DSG3 when there is the involvement of both the skin and the mucosa [31].

The oral lesions may start as a bulla which breaks to form shallow ulcers [31]. The lesions are mostly seen along the occlusal plane on the buccal mucosa. Palate and gingiva are also other sites of involvement.

❖ **Symptoms of mouth ulcers :**

The symptoms of a mouth ulcer depend on the cause, but may include:

➢ one or more painful sores on part of the skin lining the mouth

➢ swollen skin around the sores

➢ problems with chewing or tooth brushing because of the tenderness

➢ irritation of the sores by salty, spicy, or sour foods

➢ loss of appetite.

❖ **Causes of mouth ulcers :**

Mouth ulcers can be caused by a wide range of factors including:

- accidental biting of the inside of your cheek
- injury from a toothbrush (such as slipping while brushing)
- constant rubbing against misaligned or sharp
- constant rubbing against dentures or braces
- poor oral hygiene
- burns from eating hot food
- irritation from strong antiseptics, such as a mouthwash
- oral thrush infection
- viral infections such as the herpes simplex viral infection (cold sore)
- reaction to certain medications
- skin rashes in the mouth (for example, lichen planus)
- autoimmune diseases
- underlying gastrointestinal disease such as Crohn's disease
- Oral cancer

DIAGNOSIS:

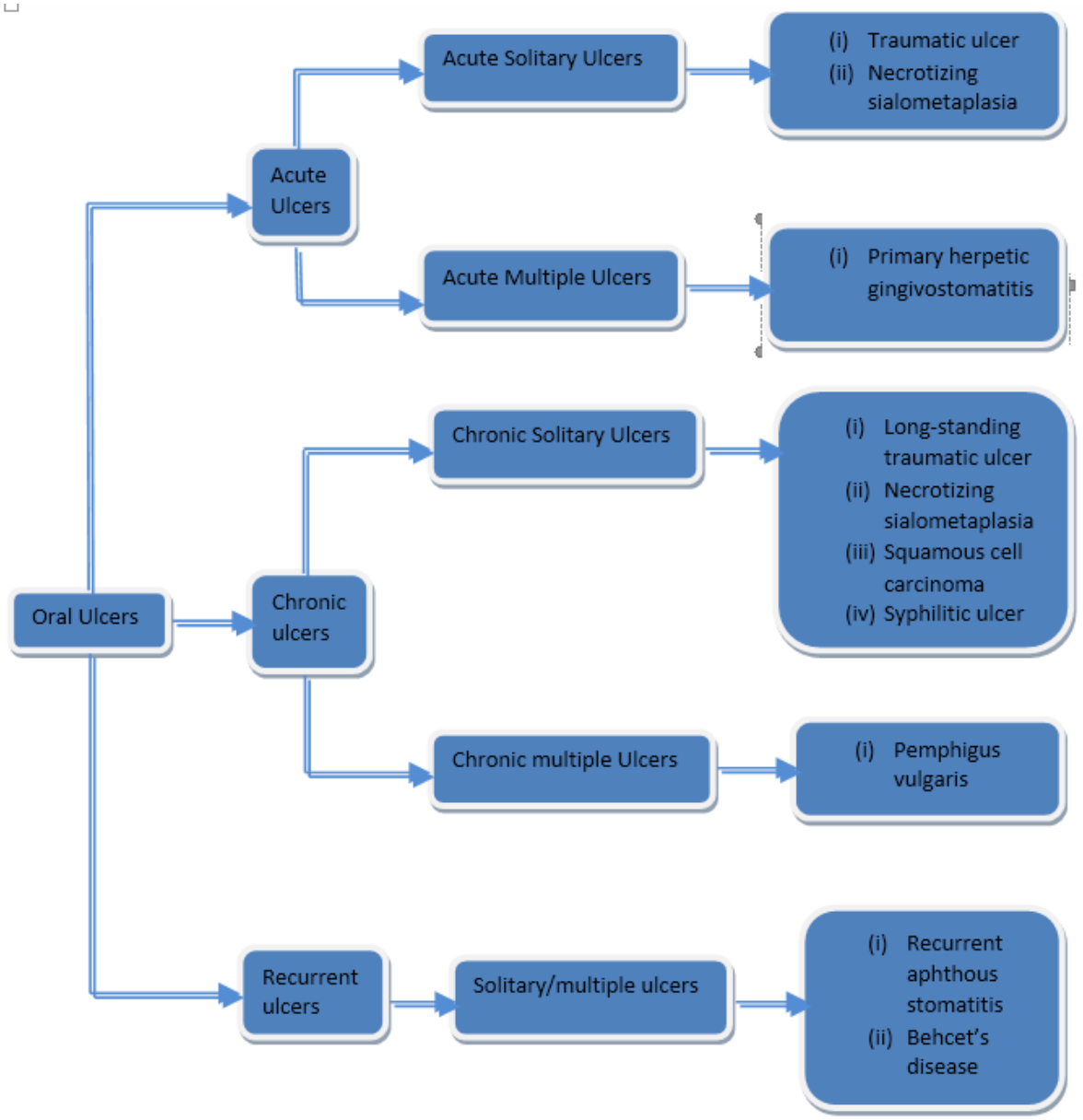

Figure No. 10: The Decision tree of oral ulcerative lesions

❖ **A various diagnostic test is conducted in oral ulcers as follows :**

➢ **Microbiological test:** Darkfield microscopy is used to identify organisms such as treponema that can help in establishing a diagnosis of syphilis. PCR can help in the detection of HSV, CMV, or H.Pylori. Quantiferon gold test is a gold standard test to confirm tuberculosis to rule out false-negative results [32].

➢ **Hematological test:** Cyclic neutropenia can be diagnosed by a reduced count of neutrophils periodically. Blood glucose levels are done to assess anemias, nutritional deficiency, and Diabetes that will help in the diagnosis or corresponding ulcers.

➢ **Bio-assay:** ELISA is used to find the proteins of suspected microorganism, whether the ulcer is healing or nonhealing, or due to certain immunological reasons (immunoglobulins), autoantibodies in Crohn's disease, tissue-specific antibodies, antisalivary duct antibodies, anti-nuclear antibodies as in sjogren syndrome [33].

➢ **Cytological smear:** Cells such as Anitschkow cells are seen in smears taken from ulcers in inflammatory conditions as in RAS. Anda smear is taken from the base of a vesicle (tzank smear) showing the presence Tzank cells (acantholytic cells) can suggest a herpes virus infection or pemphigus.

➢ **Histopathological test:** It is considered the gold standard test to confirm the diagnosis, special stains can be used to confirm microorganism in case of suspicion to ulcer secondary to tuberculosis, syphilis, or mucormycosis. Also, Necrotising sialometaplasia is confirmed by biopsy to rule out a neoplasm.

➢ **Specialized tests:** Immuno-histochemistry can be done to rule out nonhealing ulcers of squamous cell carcinoma.

❖ **Treatment for mouth ulcers :**

➢ Avoid spicy and sour foods until the ulcers heal.

➢ Drink plenty of fluids.

➢ Regularly rinse your mouth out with warm, slightly salted water.

➢ Keep your mouth clean.

➢ Take pain-relieving medication, such as paracetamol.

➢ Apply antiseptic gel to the ulcers.

➢ Use an alcohol-free medicated mouthwash containing chlorhexidine gluconate.

➢ Use a topical steroid mouthwash or ointment generally prescribed by your dentist or oral medicine specialist.

➢ If required, use immunosuppressant medication as prescribed by your oral health professi onal.

CONCLUSION:

Oral ulceration is a common problem in the oral cavity. Mostly it is benign. Some oral ulcers may be associated with systemic disorders. Patients with an ulcer that persists for more than three weeks should be referred; suspected. Chronic ulcer requires urgent referral to a specialist. The diagnosis of oral ulceration is based on patient history and clinical appearance of ulcers. The diagnosis of oral ulcerative lesions might be quite challenging. This narrative review article aims to introduce an updated decision tree of oral ulcerative lesions based on their diagnostic features and also an overview of oral ulcer.

REFERENCES:

1. S. R. PORTER* & J. C. LEAO*Oral Medicine, Division of Maxillofacial Diagnostic, Medical and Surgical Sciences, Eastman Dental Institute for Oral Healthcare Sciences, UCL, Aliment Pharmacol Ther 2005; 21: 295–306.
2. Bangladesh Journal of Plastic Surgery (2010) Vol. 1 (2) © 2010 Society of PlasticSurgeons of Bangladesh
3. Reviewed November 2009, Published February 2011.© Pharmaceutical Society of Australia www.psa.org.au
4. Patient education content ©2013 American Dental Association.
5. Kumar V, Abbas AK, Fausto N, editors. Robbins and Cotran Pathologic Basis of Disease. 7th ed. Philadelphia, PA, Pennsylvania: Elsevier, Saunders; 2005.
6. Wood NK, Goaz PW, editors. Differential Diagnosis of Oral and Maxillofacial Lesions. 5th ed. St. Louis, Missouri: Mosby; 1997.
7. Prescott LM, Harley JP, editors. Microbiology. 5th ed. USA: McGraw Hill; 2002.
8. Ananthanarayan R, Paniker CK, editors. Ananthanarayan and Paniker's Textbook of Microbiology. 7th ed. Hyderabad, India: Orient Longman Private Limited; 2005.
9. Greenberg MS, Glick M, editors. Burket's Oral Medicine: Diagnosis and Treatment. 10th ed. Hamilton, Ontario: BC Decker Inc.; 2003.
10. MacK ay D, Miller AL. Nutritional support for wound healing. Altern Med Rev 2003;8:359-77.
11. Roach PJ, Depaoli-Roach AA, Hurley TD, Tagliabracci VS. Glycogen and its metabolism: Some new developments and old themes. Biochem J 2012;441:763-87.
12. Magoulas PL, El-Hattab AW, Roy A, Bali DS, Finegold MJ, Craigen WJ. Diffuse reticuloendothelial system involvement in Type IV glycogen storage disease with a novel GBE1 mutation: A case report and review. Hum Pathol 2012;43:943-51.
13. Neville BW, Damm DD, Allen CM, Bouquot JE. Oral and Maxillofacial Pathology. 3rd ed. Philadelphia, PA: W. B. Saunders; 2002.
14. Suresh L, Radfar L. Pregnancy and lactation. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004;97:672-82.
15. Guslandi M. Steroid ulcers: Any news? World J Gastrointest Pharmacol Ther 2013;4:39-40.
16. Shah R, Triveni MG, Thomas R, Mehta DS. Management of an iatrogenic ulcer - A case report. J Dent Pract Res 2013;1:1-3.

17. Laskaris G. Pocket Atlas of Oral Diseases. 2nd ed. Stuttgart, New York: Thieme; 2006.
18. Logan R, Harris A, Misiewicz JJ, Baron J, editors. ABC of the Upper Gastrointestinal Tract. 1st ed. London: BMJ Books; 2002.
19. Cardesa A, Slootweg PJ, editors. Pathology of the Head and Neck. 1st ed. Germany: Springer; 2006.
20. Greenberg MS, Glick M, Ship JA. Burket's Oral Medicine. 2008; BC Decker, Hamilton, Canada.
21. Dayakar MM, Pai PG, Madhavan SS. Tetracycline hydrochloride chemical burn" as self-inflicted mucogingival injury: A rare case report. Journal of Indian Society of Periodontology. 2012; 16: 282-285.
22. Suomalainen A, Törnwall J, Hagström J. CT findings of necrotizingsialo metaplasia. Dentomaxillo facial Radiology. 2012; 41: 529-532.
23. Neville BW, Damm DD, Allen CM, Bouquot JE. Oral and Maxillofacial Pathology. 2002; Saunders, St Luis, Mo, USA.
24. Femopase FL, Hernández SL, Gendelman H, Criscuolo MI, López-de-Blanc SA. Necrotizing sialometaplasia: report of five cases. Medicina Oral. 2004; 9: 304-308.
25. Roberts C. Genital herpes in young adults: changing sexual behaviours, epidemiology and management. Herpes. 2005; 12: 10-14.
26. Kolokotronis, S. Doumas. Herpes simplex virus infection, with particular reference to the progression and complications of primary herpetic gingivostomatitis. Clinical Microbiology and Infection. 2006; 12: 202-211.
27. Stoopler ET, Musbah T. Recurrent aphthous stomatitis. CMAJ: Canadian Medical Association Journal. 2013;185: E240-E241.
28. Bagan, J. V., Sanchis, J. M., Milian, M. A., Penarrocha, M., & Silvestre, F. J.(1991). Recurrent aphthous stomatitis: A study of the clinical characteristics of lesions in 93 cases. Journal of Oral Pathology and Medicine, 20,395-397.
29. Ariyawardana Anura. Traumatic Oral Mucosal Lesions: A Mini Review and Clinical Update. OHDM 2014; 13.
30. Mortazavi H, Safi Y, Baharvand M, Rahmani S. Diagnostic features of common oral ulcerative lesions: An updated decision tree. Int J Dent. 2016; 2016: 1-14.
31. Hammers CM, Stanley JR. Mechanisms of Disease: Pemphigus and Bullous Pemphigoid. Annual review of pathology. 2016;11: 175-197.
32. Cağlayan V1, Ak O, Dabak G, Damadoğlu E, Ketenci B, Ozdemir M, et al. Comparison of tuberculin skin testing and Quanti FERON-TB Gold-In Tube test in health care workers. TuberkToraks. 2011; 59: 43-47.
33. Benedict C. Nwomeh, Hui-XiuLiang, KelmanCohen, DorneR. Yager, et al. MMP-8 Is the Predominant Collagenase in Healing Wounds and Nonhealing Ulcers. Journal of surgical research. 1999; 81: 189-195.

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