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Review Article

A brief review on classification of oral ulcerative lesions

Hina Handa[1], Pooja Khere[1], Kriti Shrivastava[2,*]

[1]*Dept. of Oral Medicine and Radiology, Peoples Dental Academy, Bhopal, Madhya Pradesh, India*
[2]*Dept. of Oral Medicine and Radiology, Rishiraj Dental College, Bhopal, Madhya Pradesh, India*

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ABSTRACT

Oral cavity is considered as a mirror of systemic diseases. The oral cavity consists of the lips, teeth, gums, oral mucous membranes, palate, tongue and oral lymphoid system. Various diseases affect the oral cavity of which ulcers are one of the most common disease. While most diseases of the oral cavity can be diagnosed by visual inspection, some disorders can be perplexing and their diagnoses may be elusive. They can be represented as manifestation of systemic disease or can have a specific etiology behind the disease. This article highlights the causes of oral ulcers and various classification added to it.

1. Introduction

Ulcers are among the most common mouth lesions. The epidemiology varies, depending upon the cause of the ulceration. Ulcers and erosions are the final common manifestation of a spectrum of conditions ranging from autoimmune diseases to neoplastic, traumatic, infectious lesions, nutritional deficiencies and drug reactions, and they represent a diagnostic challenge for dental practitioners.[1]

The various types of oral ulcers may appear clinically to be very similar. Features which are helpful in identifying the cause of ulcers are the associated constitutional signs and symptoms, presence of lesions on the skin and/or other mucosa, and the presence of bullae and vesicles.

The list of possible diseases that may present as an ulcerative lesion in the oral cavity is quite extensive. The focus here will be on the most common causes of these lesions. Included are acute and chronic processes, benign and malignant diseases, generalized and systemic manifestations of ulcerative lesions in the oral cavity.

2. History of Oral Ulcers

In 1857, William Brinton was one of the first doctors to describe the stomach ulcer. But without diagnostic tools such as endoscopy and X-rays, ulcer detection remained difficult. Ulcers were absent from the 1899 first edition of the Merck Manual, the bible of diagnosis and therapy.

Throughout the beginning of the twentieth century, doctors began to recognize ulcers as an infection, treating the condition with antacids or surgery. But, because scientists could find no causative agent, this "focal infection" theory became passé. As with cancer, stroke, and heart disease, the three most common killers there was no single associated germ. Therefore, the tide turned to the study of psychic and environmental factors.[1] Eventually, theories about infection and dyspepsia gave way for a theory that diet, smoking, and stress cause ulcers. Oral ulcer or ulceration is characterized by the complete loss of epithelium accompanied by a variable loss of the underlying connective tissue, resulting in a crateriform appearance, which may be augmented by oedema and/or a proliferation of the surrounding tissue.[2]

Ulcers are the final common manifestation of a spectrum of conditions ranging from autoimmune diseases to neoplasia, traumatic, infectious lesions, nutritional

* *Corresponding author*.
E-mail address: kriti_s2007@yahoo.co.in (K. Shrivastava).

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deficiencies and drug reactions and they represent a diagnostic challenge for dental practitioners.[3]

3. Classifications of Oral Ulcers

Ulcers which commonly occur in the mouth have causes that may range from minor irritation to malignancies and systemic diseases. Innocent solitary ulcerations, which result from trauma and infections, must be distinguished from squamous cell carcinomas, which also typically present as solitary ulcers. Multiple oral ulcers may be classified as acute, recurrent and/or chronic. Various classification system that has been given under which ulcers were classified.

Bascones-Martínez A et al. (2005) stated that ulcers commonly occur in the oral cavity, their main symptom being pain. There are different ways to classify oral ulcers. The most widely accepted form divides them into[5] -

1. Acute ulcers-Sudden onset and short lasting and
2. Chronic ulcers-Insidious onset and long lasting. Commonest acute oral ulcers include traumatic ulcer, recurrent aphthous stomatitis, viral and bacterial infections and necrotizing sialometaplasia. On the other hand, oral lichen planus, oral cancer, benign mucous membrane pemphigoid, pemphigus and drug-induced ulcers belong to the group of chronic oral ulcers.

Another classification given was[5]

3.1. Reactive lesion

Traumatic ulceration.

3.2. Bacterial infection

1. Syphilis
2. Gonorrhea
3. Tuberculosis
4. Leprosy
5. Actinomycosis
6. Noma

3.3. Fungal infection

1. Deep fungal infection
2. Subcutaneous
3. Sporotrichosis
4. Opportunistic –Phycomycosis

3.4. Immunological disease

1. Aphthous ulcer
2. Behcets syndrome
3. Reiters Syndrome
4. Erythema multiforme
5. Drug Reactions
6. Contact allergies
7. Wegeners Granulomatosis
8. Midline Granuloma
9. Chronic Granulomatous disease
10. Cyclic neutropenia

3.5. Neoplasm

1. Squamous cell carcinoma
2. Carcinoma of maxillary sinus.

Van Heerden et al. (2007) modified the classification system and gave a new classification of oral ulcers based on etiology and appearance.

3.6. Solitary ulcers

1. Traumatic ulcerations
2. Malignant neoplasms
   a. Squamous cell carcinoma
   b. Extranodal non-Hodgkins lymphoma
   c. Metastatic tumours
3. Infections
   a. Tuberculosis
   b. Syphilis
   c. Deep fungal infections

3.7. Recurrent ulcers that heal spontaneously

1. Recurrent aphthous stomatitis
2. Beçhet's syndrome
3. Reiter's syndrome
4. Erythema

3.8. Persistent ulcers without vesicle formation

1. Gastrointestinal disease
   a. Crohn's disease
   b. Ulcerative colitis
2. Haematological disorders
   a. Leukaemia
   b. Neutropaenia
3. Rheumatoid diseases
   a. DLE
4. Cutaneous disease
   a. Ulcerative lichen planusd
5. Drug reactions (may be preceded by vesicles)

3.9. Ulcers with preceding vesicle formation

1. Cutaneous disease
   a. Mucous membrane pemphigoid
   b. Pemphigus vulgaris
2. Viral disease
   a. Herpes simplex infections
   b. Varicella zoster infections

Table 1: Schneider et al (1998) classified oral ulcers according to their number and chronology.[4]

Acute	Multiple Ulcers Recurrent	Chronic	Solitary Ulcers
Acute necrotizing ulcerative gingivitis	Aphthae	Allergies* Bullous pemphigoid*	Aphthae Chancre
Allergies*	Herpes simplex virus, secondary*	Epidermolysis bullosa*	Fungi (deep) Gumma
Chemotherapy		Lupus erythematosus	Necrotizing Herpangina
Erythema multiforme*		Mucous membrane pemphigoid*	Necrotizing sialometaplasia
Herpangina*			
Herpes simplex virus, primary* Herpes zoster virus*		Lichen planus*	Tuberculosis
Mucous patches		Pemphigus vulgaris*	Squamous cell carcinoma
Radiotherapy		Paraneoplastic pemphigus*	Trauma

* Vesicles or bullae may occur in these conditions

c. Herpangina
d. Hand foot-and-mouth disease
e. Measles

Second most accepted classification of oral ulcers given was based on number and morphology.[6]

3.10. The patient with acute multiple lesions

1. Herpesvirus Infections
2. Primary Herpes Simplex Virus Infections
3. Coxsackievirus Infections
4. Varicella-Zoster Virus Infection
5. Erythema Multiforme
6. Contact Allergic Stomatitis
7. Oral Ulcers Secondary to Cancer Chemotherapy
8. Acute Necrotizing Ulcerative Gingivitis

3.11. The patient with recurring oral ulcers

1. Recurrent sphthous stomatitis
2. Behçet's syndrome
3. Recurrent herpes simplex virus infection

3.12. The patient with chronic multiple lesions

1. Pemphigus
2. Subepithelial bullous dermatoses
3. Herpes simplex virus infection in immunosuppressed patients

3.13. The patient with single ulcers

1. Histoplasmosis
2. Blastomycosis
3. Mucormycosis
4. Other Principal causes of oral ulceration

*3.14. Solitary ulcer**

1. Trauma
2. Squamous cell carcinoma
3. Infections (e.g. syphilis, tuberculosis)

3.15. Recurrent bouts of one or more ulcers healing spontaneously

1. Recurrent aphthous stomatitis (RAS)
2. Behc¸et's disease
3. 'Aphthous-like' ulcers due to systemic disease or drug therapy.
4. Recurrent erythema multiforme

3.16. Single bout of ulceration, preceded by vesicles and affecting multiple oral sites

1. Viral infections (e.g. herpangina and primary herpetic stomatitis
2. Erythema multiforme
3. Persistent oral ulceration affecting different sites_
4. Mucocutaneous disease (e.g. oral lichen planus)
5. Immunobullous disease (e.g. oral pemphigus)
6. Gastrointestinal disease (e.g. Crohn's disease)
7. Haematological (e.g. leukaemia)
8. Drug therapy (e.g. nicorandil)

If a single persistent oral ulcer shows no sign of healing 10–14 days after any putative trauma is removed, then it must be considered as malignant, unless proven otherwise.

Patients may report intermittent oral ulceration if these conditions undergo periods of remission.[7]

3.17. Systemic causes

Blood (haematological) disease

1. Anaemias
2. Leukaemias and myelodysplastic syndromes
3. Neutropenias
4. Hypereosinophilic syndrome
5. Hypoplasminogenaemia

Infections

1. Viral
2. HSV
3. VZV
4. EBV
5. CMV
6. HIV
7. Coxsackie viruses
8. ECHO viruses
9. Bacterial
10. Mycobacteria
11. Treponema pallidum
12. Mycotic (candidosis, histoplasmosis, paracoccidioidomycosis)

Parasitic

1. Leishmania
2. Others

Gastrointestinal disease

1. Coeliac disease
2. Crohn's disease
3. Ulcerative colitis
4. Others

Skin disease

1. Lichen planus
2. Pemphigus
3. Pemphigoid
4. Erythema multiforme
5. Dermatitis herpetiforme
6. Linear IgA disease
7. Epidermolysis bullosa
8. Others

Vasculitides

1. Lupus erythematosus
2. Behçet's disease
3. Wegener's granulomatosis
4. Sweet's syndrome
5. Reiter's syndrome
6. Periarteritis nodosa
7. Others

Malignant disease

1. Oral carcinoma
2. Antral carcinoma
3. Lymphomas
4. Kaposi's sarcoma
5. Salivary neoplasms
6. Others

Local causes

1. Trauma
2. Burns
3. Necrotising sialometaplasia
4. Others

Aphthae and aphthous-like ulcers

1. PFAPA (periodic fever, aphthae, pharyngitis, adenitis)
2. Other periodic syndromes.

Drugs

1. Cytotoxic agents
2. Alendronate
3. Nicorandil
4. Phenytoin
5. NSAIDs
6. Lamotrigine
7. Mycophenolate
8. Sirolimus
9. Tiotropium
10. Others (many)

4. Definitions of Ulcer

There are numerous definitions proposed till date-

JD Spouge et al. (1973) defined an ulcer as "deep crater that extends through the entire thickness of surface epithelium and involves underlying connective tissue.[8]

Fregall F et al. (1983) said that an ulcer is a "break in the surface continuity of skin or mucous membrane.[9]

Zain (1999) discussed that the term "ulcer" is used usually where there is damage to both epithelium and lamina propria and a crater sometimes made more obvious clinically by swelling caused by odema or proliferation in surrounding tissue.[8]

Das S(2006) defined an ulcer is a "break in the continuity of the overlying epithelium skin or mucosa. It may be either follow molecular death of the surface of epithelium or its traumatic removal.[9]"

Leao (2007) opined that the term ulcer is used where "there is damage to both epithelium and lamina propria.[10]"

"Ulcers are well circumscribed often depressed lesion with epithelial defect that is covered by a fibrin clot, causing a yellowish white appearance.[11]"

RP Langlais et al (2009) defined the term ulcer as an "open sore inside the mouth caused by a break in the mucous membrane or the epithelium on the lips or surrounding the mouth.[12]"

The ulcer has also been described as a "breach in the continuity of the surface epithelium of skin or mucous membrane to involve the underlying connective tissue as a result of micro molecular cell death of the surface epithelium or its traumatic removal.[13]

5. Examination of Oral Ulcers

To diagnose a mucosal disorders thorough examination including a brief history and clinical examination should be done-

The history taking is frequently underemphasized, but, when correctly performed, it gives as much information as does the clinical examination.

1. A detailed history of the present illness is of particular importance when attempting to diagnose oral mucosal lesions. Three pieces of information that should be obtained early in the history will help the clinician rapidly categorize a patient's disease and length of time the lesions have been present (acute or chronic lesions), past history of similar lesions (primary or recurrent disease), and number of lesions present (single or multiple).
2. A complete review of systems should be obtained for each patient, including.
3. Questions regarding the presence of skin, eye, genital, and rectal lesions.
4. Questions should also be included regarding symptoms of diseases associated with oral lesions; that is, each patient should be asked about the presence of symptoms such as joint pains, muscle weakness, dyspnea, diplopia, and chest pains.
5. The clinical examination should include a thorough inspection of the exposed skin surfaces; check for number, size, shape, edge, margins, surrounding area, discharge tenderness bleeding etc.[13]

Vinidh Paleri et al. (2010) proposed clinical evaluation of oral ulcers.

History - A detailed history is vital. For example, a patient could perceive recurrent spontaneously healing ulcers in different sites as a single chronic ulcer.

Inquire about dental procedures such as tooth restorations before the emergence of the ulcer, and about problems with dental prosthesis.[13]

Ask patient about current use of drugs and history of tobacco and alcohol use. NSAIDS and antihypertensives are examples of drugs that have been associated with oral ulceration. Bisphosphonates may cause oral ulceration directly or through osteonecrosis of the jaw; oral ulceration may develop in mucosa directly overlying an area of necrosis, or in an adjacent area such as the tongue after frictional trauma from exposed bone. Nicorandil can cause one or more large (0.5-3 cm) chronic painful ulcers that are usually localized on the inner aspect of the cheeks or on the tongue. Healing should occur with dose reduction or complete cessation of the drug.[8] Inquiry about any possible coexisting diseases, such as those listed below, may help to differentiate between malignant and non-malignant cases.

1. Autoimmune diseases: Systemic lupus erythematosus and Behçet's syndrome.
2. Dermatological diseases: Lichen planus, erythema multiforme, and mucous membrane pemphigoid can involve oral mucosa without any extraoral involvement or may be associated with skin and extraoral involvement.
3. They can be difficult to distinguish intraorally because they can all cause widespread erosions, blisters, and full thickness gingivitis (desquamative gingivitis).
4. Gastrointestinal disease: Inflammatory bowel disease (Crohn's disease and ulcerative colitis) may be associated with aphthous like ulcers or with snail track ulceration involving the oral mucosa and gingival tissue or pustular patches (pyostomatitis vegetans). Coeliac disease is associated with recurrent aphthous like ulcers.
5. Haematological disease: History of anaemia or myeloproliferative disorder may be associated with ulceration. Chemotherapy can cause mucositis and oral ulceration.
6. Psychosocial factors: Repeated intended or inadvertent self inflicted trauma.

A thorough intraoral examination to assess the mucosa of the oral cavity should be done. If an ulcer is present, assess whether it is localized or part of widespread ulceration and whether the surrounding areas seem inflamed. Note the shape and margins of the ulcer. Feel for induration of the ulcer and surrounding tissue and ensure that there is no fixation of mobile tissues such as the tongue. Note the relation of any prosthesis, sharp teeth, or dental restorations to an ulcer if present. Extraoral examination to look for swelling or lymphadenopathy in the head and neck region should always be performed.[13]

Following history should be noted in examining an ulcer.[9]

1. Mode of onset-How has ulcer developed? Following trauma or spontaneously?
2. Duration of ulcer-Acute for shorter duration and chronic for longer duration.
3. Pain-Ulcer associated with inflammation will be painful. Ulcer from malignant disease such as epithelioma or basal cell carcinoma are painless.
4. Discharge-Does the ulcer discharge or not ?
5. Associated disease-If present.

6. Physical Examination

1. **General survey-** Ulcer will be sequel of malnutrition general artherosclerosis syphilis etc.
2. **Local examination**

6.1. Inspection

Size and shape- Tuberculous ulcer are oval, Syphilitic ulcer are similarly circular.

Number- Tuberculous and gummatous ulcer.

Position –Malignant ulcers occur on tongue, lip.

Edge- In spreading ulcer edge is inflamed and oedamatous, whereas in a healing ulcer the edge if traced from the red granulation tissue in the centre towards periphery, will show a blue zone and a white zone. [9]

Rolled out everted edge- squamous cell carcinoma

Everted ulcer - is a characteristics features of squamous cell carcinoma or an ulcerated adenocarcinoma.

Punched out edge –is seen in gummatous ulcer.

Floor- Pale and granulation tissue indicates a slow healing ulcer.

Discharge- A healing ulcer scanty serous discharge.

Surrounding area- If surrounding area of an ulcer is glossy red and odematous, the ulcer is acutely inflamed.

6.2. Palpation

1. Tenderness- Acutely inflamed ulcer is always tender. Chronic tuberculosis and syphilitic ulcer are slightly tender.
2. Margin – is a junction between normal epithelium and ulcer, so it is boundary of ulcer.
3. Edge- is the area between margin of floor of ulcer.
4. Base- On which the ulcer rest.
5. Depth
6. Bleeding- Common in malignant ulcer.
7. Relation with deeper structure- Malignant ulcer will be fixed to deeper structure.
8. Surrounding skin- Increased temperature and tenderness of the surrounding skin indicates that the ulcer is of acute inflammatory region.

7. Investigations for Oral Ulcer

Oral ulcers are unique: They have diverse causes but frequently show similar histological changes; therefore they cannot be differentiated by routine microscopy. The following changes are inferred when the clinician encounters a microscopic diagnosis of "nonspecific" ulcer.

1. The complete thickness of the surface epithelium is missing, and the exposed connective tissue often is necrotic on the surface and covered by a fibrinous exudates.
2. Depending on its age and the circumstances relating to its development, the ulcer has acute inflammation with polymorph nuclear leukocytes in the connective tissue at its borders.
3. A less acute phase of the ulcer shows a greater concentration of chronic inflammatory cells, such as lymphocytes, plasma cells, and possibly macrophages with some fibroblastic proliferation.

Some ulcers can be diagnosed when they are stained with hematoxylin and eosin or special stains. For example, histological changes in squamous cell carcinoma and ulcerative mesenchymal minor salivary gland tumors are diagnostic as long as the biopsy includes a section of tumor underlying the ulcer.

Lesions such as chancres, herpetic ulcers, and tuberculous, sarcoid, and fungal lesionsmay produce tissue changes that indicate a definitive diagnosis, but usually, special staining procedures must be used to assist in making a definitive microscopic identification in over 80% of case. Other advanced methods of investigations include immunofloursence Fluorescent-antibody stained smears using fluorescent conjugated monoclonal antibodies is more reliable than is routine cytology and is positive. Cytology is a rapid method of evaluation that can be used in cases in which the diagnosis is uncertain. The most accurate method of diagnosis is viral isolation in tissue culture, but this test is more expensive and the results take days rather than hours.

Demonstration of a rising antibody titer is rarely necessary for diagnosis except in cases of zoster sine eruption when it is the only means of confirming suspected cases.

8. Conclusion

Oral ulcerations are common lesions encountered in day to day life. Oral ulcers can have a localized etiology or be a manifestation of a variety of systemic conditions or disorders. Accurate diagnosis of the cause of oral ulceration depends on an understanding and knowledge of the various patterns of oral ulcers as reviewed. There are several important features to be determined based on history. These include knowing the exact etiology of the ulcers, differentiating acute from chronic oral ulcers based on the time frame and length of affliction. If an ulcer is acute in presentation, the clinician needs to determine whether this is an isolated episode or recurrent phenomenon. Determination of this allows differentiation into two differing subsets of etiology. Appropriate management depends on the correct diagnosis, which at times can be difficult due to similar clinical features. The presence of systemic features must be sought on direct inquiry. These include constitutional symptoms, such as fever, malaise, and weight loss, symptoms of gastrointestinal disturbance; genital or ocular involvement; or other features suggestive of systemic disease. A dietary history must be obtained and a detailed review of other medical illnesses and a thorough drug history.

In the absence of associated systemic features, further evaluation of patients with oral ulcers includes a full blood count and differential, screen for hematinic deficiencies, routine serum chemistry, thyroid screen, and an endomysial antibody. The medical history should exclude relevant systemic disorders (haematological, infections, gastrointestinal, or skin diseases) or causal drug use. The

possibility of trauma from local factors including sharp and/or broken teeth, the wearing of dentures and other appliances, and biting during chewing should be checked.

For further investigations cytology and biopsy are performed. Other advanced investigations include viral culture, immunofluorescence etc.

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10. Conflict of Interest

The authors declare that there is no conflict of interest.

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Author biography

Hina Handa, Reader

Pooja Khere, Reader

Kriti Shrivastava, Reader

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