

Diagnosis of Oral Ulcers

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Abstract

Ulcers commonly occur in the mouth. Their causes 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. The most common causes of rapid-onset oral ulcers include acute necrotizing ulcerative gingivitis, allergies and erythema multiforme. The two common forms of acute (short-term) recurrent oral ulcers, "cold sores" or "fever blisters," which are caused by the herpes simplex virus, and recurrent aphthous ulcers ("canker sores"), may be distinguished largely on the basis of their location. Most types of multiple chronic oral ulcers are associated with disturbances of the immune system. They include erosive lichen planus, mucous membrane pemphigoid and pemphigus vulgaris. Clinical criteria which are most useful in identifying the cause of oral ulcers are vesicles or bullae, which may not be seen because they rupture rapidly in the oral environment; constitutional signs and symptoms; and lesions on the skin and/or other mucosa. In some cases, diagnosis depends upon culture or biopsy, particularly with the application of immunofluorescence to the surgical specimen.

Key Words: Oral ulcers, vesiculobullous oral lesions, gingival ulcers, mucosal ulcerations.

Diagnosis of Oral Ulcers

Ulcers occur in the mouth with considerable frequency. Traumatic lesions usually resolve rapidly and are not seen by clinicians. For relatively common conditions such as recurrent herpetic vesiculoulcers and aphthous ulcers, presumptive diagnoses are often made without recourse to laboratory tests. While the diagnosis of some types of oral ulcers is facilitated by their association with constitutional signs and symptoms or lesions on the skin and/or other mucous membranes, ulcers which are localized to the oral cavity may be more difficult to identify (Table). Several diseases are

TABLE
Oral Ulcers

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

* Vesicles or bullae may occur in these conditions

The table categorizes oral ulcers according to their number and chronology. Those are two features which are useful in their recognition.

vesiculobullous; this feature is useful in narrowing the differential diagnosis, but lesions rupture so rapidly in the oral environment that the vesicular aspect of the ulcers is easily missed. There are, therefore, a wide variety of oral ulcers which are biopsied because they are less readily recognizable on the basis of their clinical features.

Most traumatic oral ulcers can be identified by their association with an identifiable mechanical, chemical, thermal or radiotherapeutic cause. They may be single or multiple, symmetrical or irregular in shape, and are usually painful. Most are of recent onset, but some are chronic. Acute traumatic ulcers have a removable, yellow-white base and erythematous borders. Chronic traumatic ulcers may be non-painful with an indurated base and raised borders; consequently, they may be indistinguishable from squamous cell carcinomas on the basis of their clinical features.

Multiple painful oral ulcers often occur as a result of radiotherapy for head and neck cancer and as a side effect of chemotherapy for many malignancies. Radiation mucositis often appears after the first week of treatment and focal ulcerations may develop within affected areas. The mucositis persists for several weeks beyond the end of therapy and the mucosa remains atrophic. Anticancer

Diagnosis of Oral Ulcers—Schneider

drugs cause multiple oral ulcers by bone marrow suppression or by reducing replication of the oral epithelium. Both types of ulcers heal within a few weeks following the end of therapy.

Two forms of acute (short-term) recurrent oral ulcers are extremely common. Recurrent herpetic ulcers (“cold sores” or “fever blisters”) may be distinguished from recurrent aphthous ulcers (“canker sores”) primarily on the basis of their location. The recurrent lesions caused by the type I herpes simplex virus occur as a cluster of small vesicles which ulcerate on the vermilion of the lips or on adjacent skin (1). Each vesiculo-ulcer is only 1 mm or less in diameter. Recurrent herpetic lesions are uncommon inside the mouth in otherwise healthy people and occur as a cluster on keratinized mucosa which is bound to underlying bone, on the hard palate near the teeth or on the gingiva. Recurrent aphthous ulcers occur on areas of the mouth where the mucosa is non-keratinized and loosely attached, particularly the buccal mucosa, labial mucosa, floor of the mouth, ventral surface of the tongue, and soft palate. In contrast to the viral lesions, aphthous ulcers do not have a vesicular stage, and they are larger than the individual viral ulcers.

Recurrent aphthous ulcers (2) may affect 20% of the population. Immunologic, hereditary, and nutritional pathogenetic factors have their advocates, but none of the numerous theories is widely accepted. The ulcers may be single or multiple and are very painful. Minor aphthae are less than 1 cm in size, and symmetrical in shape, with a yellow base surrounded by a red halo. They heal spontaneously in less than 2 weeks, with ulcer-free periods varying from individual to individual. Major aphthae are much less common. They are larger, deeper, irregular in shape, may persist for several weeks, and may thus be mistaken for a malignant lesion. Major aphthae often heal with scarring, which distinguishes them from minor aphthae. Numerous forms of treatment have been recommended but topical corticosteroids still appear to be the most effective.

In most cases, recurrent aphthous ulcers are limited to the mouth, without a definitive correlation with any other disease. The lesions are occasionally the result of a systemic condition. Deficiencies of iron, folate and vitamin B-12 have been linked to the ulcers. Lesions resembling aphthae also occur in patients suffering from chronic inflammatory bowel disease, cyclic neutropenia, Behçet’s syndrome and Reiter’s syndrome. Particularly severe aphthous-type ulcers occur in HIV-positive individuals.

While the multiple acute vesiculo-ulcers in recurrent herpes simplex virus infection are limited to the lips and, rarely, to the keratinized areas of the oral cavity, a more widespread distribution of multiple acute vesiculo-ulcers occurs in primary herpetic gingivostomatitis, other viral infections and allergic conditions. Primary herpetic gingivostomatitis usually occurs in children who lack previous exposure and immunity to the virus. Vesicles develop throughout the mouth and perioral skin. Marked gingival involvement, in the form of edema and erythema, is a major feature of the disease. Constitutional manifestations are common, with the disease subsiding within two weeks, but localized recurrences, particularly herpes labialis, may occur. Although diagnosis is usually made clinically, it can be confirmed by various techniques. Viral isolation with immunotyping of the isolates is the most sensitive diagnostic test for herpes simplex virus, but results cannot be obtained for 2–4 days. Cytological smears obtained from a recently opened vesicle reveal acantholytic epithelial cells, some

Diagnosis of Oral Ulcers—Schneider

of which may be multinucleate and exhibit nuclear viral inclusions. This test is rapid but does not distinguish between the herpes simplex and zoster viruses. HSV-1 may be identified in a few hours if cytological specimens are subjected to direct immunofluorescence using kits which are commercially available (3). Serology for immunoglobulins is positive in primary herpes simplex infections in 1 week, reaching a peak in 3 weeks. A fourfold or greater elevation of circulating serum HSV-1 antibody levels in the convalescent sera is considered diagnostic of recent HSV-1 infection (4). Acyclovir is more effective in treating immunocompromised patients than people who are otherwise healthy.

Oral vesiculo-ulcers occur in varicella. Unilateral, clustered vesicles characterize herpes zoster. Although lesions are similar in appearance to those caused by the herpes simplex virus, they may be recognized by their distribution pattern and severe pain along the affected branch of the trigeminal nerve.

Herpangina is caused by the *Coxsackie* virus and is clinically manifested by vesicles limited to the pharynx and posterior region of the mouth. This disease occurs in epidemics, most often affecting children, usually in summer. Constitutional symptoms are mild, with resolution within 10 days.

Acute hypersensitivity reactions to systemically administered drugs or foods include erythema, vesicles and ulcers of the oral mucosa, which are often associated with concurrent skin lesions. Similar oral lesions occur as a result of contact allergies but are less common. Cinnamon is a well-documented example of an offending agent.

Erythema multiforme (5) is an ulcerative mucocutaneous disease, some cases of which appear to be an acute hypersensitivity reaction to systemically administered drugs, to foods, or to the herpes simplex virus. Intact vesicles or bullae rupture rapidly. Although there is widespread mucosal involvement with severe crusting of the lips, the gingiva are characteristically spared. The oral condition is usually accompanied by skin lesions. The combination of oral, ocular and genital lesions is known as Stevens-Johnson syndrome.

Erythema multiforme is sometimes confused with primary herpetic gingivostomatitis. Both are vesiculo-ulcerative conditions with sudden onset, most often affecting young people. They may be distinguished, however, by the shape and distribution pattern of the oral lesions. Herpetic ulcers are small, round and shallow, and are accompanied by gingival edema, whereas the lesions of erythema multiforme are larger and more irregular in shape. Erythema multiforme is also characterized by severe ulceration and crusting of the lips, with little gingival involvement. That diagnosis is, of course, much more obvious if typical skin lesions are present.

Acute ulcerative necrotizing gingivitis (“trench mouth”) is another ulcerative disease of sudden onset. It primarily affects the gingiva, but other parts of the mouth may also be involved. Gingiva are bright red and hemorrhagic. Painful non-vesicular ulcerations first appear on the interdental papillae (the small triangular areas of mucosa between the crowns of adjacent teeth). The

Diagnosis of Oral Ulcers—Schneider

ulcers extend along the marginal gingiva and are covered by a gray necrotic pseudomembrane. Fever, malaise, and lymphadenopathy may be present. Anaerobic organisms are involved. The number of the fusospirochetal organisms correlates with the course of the disease, but impaired local and systemic host resistance is of major importance in this condition. Local treatment consists of debridement and irrigation. Antibiotics may be required.

Rapidly progressive periodontal disease with soft tissue necrosis and exposure of underlying bone occurs in HIV patients (6). The condition is characterized by deep, aching pain in the jaws and a lack of response to conventional treatment. In severely debilitated individuals, acute ulcerative necrotizing gingivitis can spread to other parts of the mouth by direct extension or by contact with adjacent mucosa. In the condition known as necrotizing stomatitis, noma or cancrum oris, extensive soft tissue loss and bone sequestration can occur with large areas of discolored necrotic tissue (7).

Mucous patches are the most common oral manifestation of secondary syphilis. The ulcerations are irregular in outline, covered by a gray-white necrotic membrane and surrounded by erythema. They may be multiple and are sometimes painful. “Snail-track” ulcers are confluent mucous patches which heal in a few weeks. Less common oral lesions include roseolas, which are small red-brown macules, papules and condyloma lata. If these oral lesions, constitutional symptoms, and the typical macular-papular skin rash are absent, mucous patches may be confused with other types of multiple oral ulcers.

Squamous cell carcinoma is one condition which presents as a solitary, chronic ulcer of the oral mucosa. While advanced lesions are readily recognized by their cratered appearance, with an indurated base and rolled borders, early lesions may easily be missed. Small, painless indurations, erosions, or red macules which fail to heal when any possible source of irritation is removed should be considered to be malignant until proven otherwise. This approach is particularly valid when there is a history of smoking and alcohol consumption, and when lesions occur in the high risk sites, which are the lateral and ventral surfaces of the tongue, the floor of the mouth, and the soft palate. Incisional biopsy is the only dependable way to distinguish squamous cell carcinoma from benign chronic solitary ulcerations, which include traumatic lesions, major aphthous ulcers, and infectious ulcers.

Necrotizing sialometaplasia (8) is a dramatic and benign condition which may be mistaken both clinically and histologically for a malignancy. Most cases occur unilaterally on the posterior hard palate, but the lesions may be bilateral or may occur on the soft palate and in other parts of the mouth. It most often presents as a deep ulceration of up to several centimeters in diameter and has irregular, well-defined borders which are neither indurated nor raised. The ulcer base is uneven and yellow or gray in color, and may be painful. Patients report that the lesion had developed very rapidly (sometimes in a few days) and that the roofs of their mouths suddenly fell out, with spontaneous healing occurring in a period of several weeks to months. However, only those clinicians with the highest level of intestinal fortitude rely on its clinical features for their diagnosis. Pathologists who are familiar with the condition have no difficulty making the diagnosis on an incisional biopsy specimen.

Diagnosis of Oral Ulcers—Schneider

Multiple chronic oral vesiculo-ulcers occur in mucous membrane pemphigoid, pemphigus vulgaris, paraneoplastic pemphigus, epidermolysis bullosa and occasionally in lichen planus. Mucous membrane pemphigoid (5, 9) is an auto-immune disease which most often occurs in women over the age of forty. Lesions are often hemorrhagic and may heal with scarring. They are often Nikolsky positive: a superficial layer of apparently healthy mucosa detaches from underlying tissue when gentle pressure or an air-jet is applied. Other mucous membranes may be affected. Scarring may occur, hence the synonymous term “cicatricial pemphigoid.” Conjunctival involvement may result in blindness due to scarring. Mucous membrane pemphigoid is a major cause of desquamative gingivitis, which is described below. Cleavage occurs in the subepithelial zone. In the subtypes of mucous membrane pemphigoid, autoantibodies are produced against various antigens in this region, including BPAG1, an intracellular, hemidesmosomal desmoplakin, BPAG2, a transmembrane protein in the basal plasmalemma of basal keratinocytes, and epiligrin (laminin 5), a matrix protein in the lamina lucida of the basal lamina.

Diagnosis of some multiple-ulcerative conditions, including mucous membrane pemphigoid, depends upon recognition of the tissue level at which clefting and/or necrosis occurs and the application of the direct immunofluorescent technique (10). The biopsy specimen should include perilesional (clinically normal) tissue. (Some laboratories request two biopsies, one from the edge of a fresh lesion and the other from normal-appearing mucosa, at least 3 mm from the lesion.) The specimen is divided into halves. One piece is placed in 10% formalin for routine staining with hematoxylin and eosin. If the other cannot be frozen immediately, it is placed in Michel’s solution until direct immunofluorescence can be performed. Because of the expense, this is not carried out routinely. The specimen is incubated with fluorescein-labeled antibody against the autoantibody (which is bound to antigen in the tissue). The bound fluorescein emits a bright yellow-green light when the tissue is exposed to ultraviolet light.

Multiple oral vesiculo-ulcers occur less commonly in several other auto-immune, subepithelial cleavage diseases, including bullous pemphigoid, linear IgA bullous dermatoses, dermatitis herpetiformis and epidermolysis bullosa acquisita, each of which is characterized by different antigens (10). Severe oral vesiculo-ulcers also occur in some of the inherited (non-autoimmune) types of epidermolysis bullosa, particularly the recessive, dystrophic form (11).

Pemphigus vulgaris (5, 9) is an autoimmune, mucocutaneous, potentially fatal disease in which the oral mucosa is usually affected. Cleavage occurs within the stratified squamous epithelium due to autoantibodies against the desmosomal component, desmoglein 3. In the mouth, thin-walled vesicles and bullae rupture quickly and the lesions continue to increase in size, producing large, irregular, shallow ulcerations. It may be distinguished from other chronic, vesiculo-ulcerative diseases by the identifying rounded, acantholytic epithelial cells in exfoliative cytology specimens obtained by opening an intact vesicle, but biopsy is more reliable for definitive diagnosis. Direct immunofluorescence is usually unnecessary for diagnosis, but indirect immunofluorescence, which detects circulating antibodies, is valuable in monitoring progress of the disease while it is treated with steroids. Paraneoplastic pemphigus (12) is an extremely severe form of pemphigus which occurs in association with malignancies, particularly non-Hodgkin’s lymphomas and certain leukemias.

Diagnosis of Oral Ulcers—Schneider

Cleavage occurs both within the epithelium and in the basement membrane zone. There are circulating autoantibodies against both desmosomal and hemidesmosomal antigens.

Lichen planus (13) is a chronic autoimmune condition which occurs in middle age, slightly more often in women than in men. Oral lesions may occur in the absence of skin lesions. They tend to have a bilateral and symmetrical distribution in the mouth. In the erosive form, the ulcers cause a burning sensation and may be accompanied by more typical, white reticular lesions. There are rare cases in which bullae are seen. Cleavage is due to destruction of basal epithelial cells associated with an infiltration of T-lymphocytes into this layer. It is one of the more common causes of desquamative gingivitis. Treatment is steroid administration, preferably topical.

Desquamative gingivitis (14) is the term applied to red, edematous, and glazed gingiva. There may be areas of superficial ulceration or desquamation which may exhibit Nikolsky's sign. This gingival condition is seen in mucous membrane pemphigoid, erosive lichen planus, pemphigus vulgaris, drug and food reactions, as well as epidermolysis bullosa acquisita, linear IgA dermatosis, and systemic lupus erythematosus. Some cases affect only the gingiva, and in some of these no antigens or antibodies are detected.

Conclusion

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. In some cases, however, laboratory procedures are required to make the diagnosis. Biopsy is necessary in the management of several of these conditions, especially in multiple ulcers due to autoimmune diseases, necessitating the application of immunofluorescence to the surgical specimen for definitive diagnosis.

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Diagnosis of Oral Ulcers—Schneider

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