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Diseases of the Oral Mucosa

SUMMARY

This article provides a clinical approach to the more common oral mucosal lesions. Histologic diagnoses are not included, apart from their use in diagnosis and management. In a small number of oral mucosal lesions, clinical appearance is sufficiently distinctive to permit accurate diagnosis, but a biopsy is usually necessary. Clinical appearance is important in directing further investigations such as culture and serologic testing. (*Can Fam Physician* 1988; 34:1443–1451.)

RÉSUMÉ

Cet article veut offrir une approche clinique concernant les lésions les plus fréquentes de la muqueuse buccale. Il ne traite pas des diagnostics histologiques sauf lorsqu'ils sont utiles pour préciser le diagnostic et faciliter le traitement. Il faut habituellement procéder à une biopsie sauf dans un faible nombre de lésions de la muqueuse buccale où l'aspect clinique est suffisamment caractéristique pour poser un diagnostic précis. La visualisation est importante pour mieux orienter les investigations supplémentaires telles la culture et les tests sérologiques.

Key words: oral mucosa, mucocutaneous diseases, acquired immunodeficiency syndrome

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THE ORAL MUCOSA is affected by a variety of diseases that span a wide spectrum in their clinical significance. There are entirely benign conditions, such as geographic tongue, which produce an abnormal appearance of the oral mucosa but are rarely symptomatic and do not require treatment. Oral mucosal lesions are frequently the result of dental or periodontal disease or irritation by dentures, and they indicate the need for restorative or prosthetic dental care. Extensive, desquamative, oral lesions may occur in a number of mucocutaneous diseases. They cause considerable discomfort and interfere with eating and speaking so that protracted treatment and follow-up are required for control of symptoms. In some cases, oral lesions represent the initial manifestation of a serious mucocutaneous disease, such as pemphigus vulgaris, and accurate diagnosis of the lesions will facilitate management of the disease. Viral infections often produce characteristic oral lesions; although treatment is often unnecessary or only alleviates the symptoms, their early recognition is important to limit the spread of infection to others. Squamous cell carcinoma presents as a mucosal abnormality in its earliest stage, and routine examination of the oral mucosa for suspicious oral lesions is important for early diagnosis and treatment of these malignant lesions.

Because the oral mucosa has a limited repertoire of responses, diverse diseases may produce similar manifestations. Thus, oral mucosal diseases usually present as one or more of five broad categories:

- white lesions (thickening of the oral epithelium and/or the keratinized layer);
- red lesions (desquamation or atrophy of the oral epithelium);
- ulcerations (discrete areas of loss of the entire thickness of oral epithelium);

• pigmented lesions varying from brown to bluish-black; and
• surface irregularities (papillary or nodular areas).

In contrast to lesions of the skin, vesicles and bullae of the oral mucosa rarely persist for more than a day or two, because of constant trauma from biting, chewing, and speaking. Thus intraoral vesiculo-bullous diseases typically present as erosions and ulcerations, with the occasional bulla that is easily missed unless a careful examination is made. As a practical aid to diagnosis, the more common diseases affecting the oral mucosa that are the subject of this article are listed in Table 1 according to their clinical appearance. The interested reader may consult a recent publication on differential diagnosis of oral lesions based on this approach.[1] For more exhaustive information on oral mucosal diseases, standard oral pathology textbooks may be used.[2,3]

Any discussion of lesions of the oral mucosa is necessarily closely related to a discussion of oral tumours.[4] For example, lesions of epithelial dysplasia and early squamous cell carcinoma are pertinent to both discussions. Similarly, melanocytic nevi and melanoma may be considered in both contexts. The topics of leucoplakia, erythroplakia, epithelial dysplasia, and squamous cell carcinoma, as well as melanocytic nevi and melanoma have been covered, in this issue, in the article on oral tumours.[4] Although they will not be discussed in this article, under the appropriate circumstances they obviously should be considered in the evaluation of oral mucosal lesions.

Lesions of Dental and Periodontal Origin

Dental and periodontal diseases primarily affect the gingiva and adjacent alveolar mucosa. Dental abscess originating from a necrotic tooth often appears as a painless swelling that partly obliterates the labial or buccal sulcus. A more subtle manifestation is a parulis, a papule in the alveolar mucosa near the junction with the gingiva, which represents the opening of a sinus tract that drains from an intra-alveolar abscess. Definitive treatment of a dental abscess is either endodontic treatment (root-canal filling) or dental extraction. Antibiotic therapy or incision and drainage will only remove the signs and symptoms temporarily, as the source of the abscess remains untreated; these procedures are often useful as adjunctive measures, however, in combination with treatment of the offending tooth.

Gingivitis is most commonly the inflammatory response to irritation from dental plaque. It is well recognized that individual responses to plaque irritation vary greatly, and that there is some correlation with hormonal status. Clinically marked gingivitis is more common in adolescence, when pubertal hormonal changes are thought to contribute to a heightened inflammatory response to plaque. Other factors that predispose to gingivitis are mouth-breathing, orthodontic brackets and appliances, and irregular alignment of

Table 1
Oral Mucosal Diseases Listed According to Clinical Appearance

White Lesions	Red Lesions	Ulcerated Lesions	Vesiculobullous Lesions	Pigmented Lesions	Papillary/ Nodular Lesions
Frictional keratosis	Gingivitis	Traumatic ulcer	Benign mucous membrane pemphigoid	Amalgam tattoo	Papillary hyperplasia of the palate
Lichen planus (reticular and plaque forms)	Geographic tongue	Aphthous ulcer	Pemphigus vulgaris	Black hairy tongue	Fibroepithelial hyperplasia
Oral hairy leukoplakia	Median rhomboid glossitis	Syphilis (primary chancre)	Erythema multiforme	Oral Kaposi's sarcoma	Mucocele
Candidiasis (pseudo-membranous and hyperplastic forms)	Lichen planus (erosive form)		Epidermolysis bullosa	Oral melanotic macule	Verruca vulgaris
Syphilis (mucous patches)	Benign mucous membrane pemphigoid Pemphigus vulgaris Erythema multiforme Epidermolysis bullosa Acute herpetic gingivostomatitis Candidiasis (atrophic form) Syphilis (mucous patches)		Acute herpetic gingivostomatitis Recurrent herpetic labialis Herpes zoster Herpangina		Condyloma acuminatum Focal epithelial hyperplasia

teeth. Gingivitis is also more common during the second and third trimester of pregnancy (pregnancy gingivitis), when red edematous gingiva that bleeds readily may cause some concern. Since the primary cause of gingivitis is dental plaque, gingivitis is both prevented and treated by maintaining good oral hygiene.

Dental restorative and surgical procedures may result in implantation of small particles of dental amalgam within the oral mucosa, usually in the vicinity of teeth or extraction sockets. The result will be a bluish-black area of discoloration known as an "amalgam tattoo". There is usually little associated inflammation, and the lesion is asymptomatic. The diagnosis can often be confirmed by means of an intra-oral radiograph that shows radio-opaque amalgam particles within the soft tissues. When the clinical diagnosis is uncertain, the discolored area may be excised and submitted for microscopic examination, primarily to rule out an early lesion of malignant melanoma (see below).

Lesions Caused by Denture Irritation

Irritation from ill-fitting dentures affects the edentulous alveolar ridges and the palate. Acute and severe irritation, as from new dentures, causes traumatic ulceration. More commonly, chronic irritation leads to a proliferative response that conforms in its distribution to the shape of the denture. A denture flange that is overextended into the labial or buccal sulcus characteristically produces a ridge of hyperplastic mucosa along the denture flange; this lesion is called "epulis fissuratum". As continuous resorption of the edentulous ridge results in the denture settling more deeply into the sulcus, additional ridges of hyperplastic tissue are formed and are often separated by shallow elongated ulcers.

A maxillary denture which adapts poorly to the palate causes papillary hyperplasia that is typically confined to the mucosa beneath the denture. The mucosa is red and velvety, and careful examination reveals innumerable, closely packed, minute, mucosal polyps. Treatment for all forms of denture irritation consists of denture adjustment or fabrication of new, properly fitted dentures. Well-developed masses of hyperplastic tissue must usually be excised and normal tissue contours restored before corrections to the dentures are made. Elderly patients with ill-fitting dentures are prone to develop candidiasis (see below), and therefore require topical antifungal therapy in addition to improvement of the dentures.

True allergy to properly polymerized denture acrylic is relatively rare as compared to irritation from poor denture hygiene and lack of fit. The clinical features of true acrylic allergy are nonspecific; they are those of generalized inflammation of the mucosa beneath the denture. Diagnosis of allergy to denture acrylic is made on the basis of a positive patch test, in which a piece of denture acrylic is applied to the skin of the forearm for 48 hours. Allergy to cast-alloy partial denture framework has also been reported occasionally; nickel is the most common component of the alloy that is responsible. When it is strongly suspected that the mucosal reaction is allergic in nature, substitution of alternative denture materials is necessary. If the suspected allergy is to acrylic and the patient is completely edentulous, replacement of acrylic with other polymers for denture fabrication is often quite unsatisfactory, and so, to avoid unnecessary hardship to the patient, it is important to be certain of the diagnosis of allergy to denture acrylic.

Traumatic Lesions

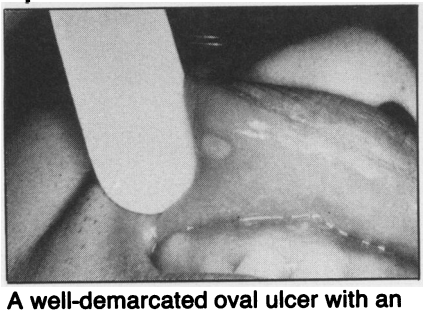
Traumatic ulcers may result from biting of the lip, cheek, or tongue, or from the rubbing of these mucosae on sharp edges of teeth and dental restorations. These ulcers are sometimes difficult to differentiate clinically from malignant ulcers, especially when the ulcer persists for weeks and is associated with induration of surrounding tissues. Moreover, carcinomatous ulcers often appear at sites that are chronically irritated. When there is any uncertainty about the nature of a mucosal ulcer, a biopsy should be made to rule out malignancy.

Milder forms of chronic trauma may produce an area of hyperkeratinization (frictional keratosis) or of fibroepithelial hyperplasia, usually as a fibroepithelial polyp. Once the diagnosis is established, these traumatic lesions are simply treated by removing the source of irritation.

Trauma to the ducts of minor salivary glands can cause their severance or occlusion, leading, respectively, to formation of a mucus extravasation cyst or a mucus retention cyst. These are often collectively known as mucoceles and present as small, bluish, dome-shaped lesions, most commonly on the lower labial mucosa. The patient may report that the lesion has gradually enlarged, ruptured, and then recurred. Treatment consists of excision of the lesion, along with adjacent lobules of minor salivary gland, which ensures that the damaged salivary gland tissue has been removed. Oral mucoceles may recur, particularly if the injured salivary glands have not been excised, but unlike the antral mucocele, they rarely become large or behave aggressively.

Thermal and chemical burns are occasionally the source of a patient's complaints. Thermal burns from hot food are most common on the palate. Chemical burns are often caused by excessive or incorrect use of mouthwashes or medications. An example is aspirin burn, which results from placement of aspirin tablets in the buccal sulcus in an attempt to alleviate a toothache. Aspirin burn is usually seen as an area of whitish-grey, sloughed tissue. These lesions should heal once the source of trauma is removed.

Figure 1
Aphthous Ulcer



A well-demarcated oval ulcer with an erythematous halo is present on the labial mucosa.

Aphthous Ulcer

Recurrent aphthous stomatitis (RAS) is a common condition affecting the oral mucosa, as it has been estimated that 20% of the general population suffers from it at some time in life. It is characterized by sharply demarcated, round to oval ulcers with an erythematous halo (Figure 1). The ulcers heal without treatment after one to several weeks, depending on the subtype of RAS (see below). In some individuals, the ulcers are preceded by a recognizable prodromal stage that has been described variously as a tingling sensation, mucosal edema, or the appear-

ance of small nodules. The ulcers are typically painful, and during severe attacks of RAS, eating and speaking become greatly impaired.

Three forms of RAS have been described: major, minor, and herpetiform. Minor RAS is the most common form; ulcers do not exceed 1 cm in diameter and heal without scarring in seven to 10 days. The ulcers of major RAS are larger, deeper, and more numerous. They heal with scarring. In herpetiform RAS, crops of pinhead-size ulcers appear, and each crop of ulcers lasts seven to 10 days. As the name implies, these ulcers bear some clinical resemblance to herpetic lesions, but herpes virus cannot be cultured or demonstrated in them, and they are generally thought to represent a variant of RAS.

The etiology of RAS remains unknown, although several hypotheses have been proposed, including hypersensitivity to an L-form streptococcus and a local immune response to antigenically altered mucosa. Aphthous ulcers are usually diagnosed without much difficulty on the basis of their characteristic clinical appearance and history of previous self-limited ulcers. Many forms of treatment have been tried to alleviate pain and promote healing of the ulcers, but none has been completely effective. Tetracycline mouthrinses are often helpful, especially if used during the early phase of ulceration. Occlusive ointments such as Orabase, used alone or with topical steroids, have also been reported to reduce symptoms.

In most patients suffering from RAS, the ulcers are not accompanied by extra-oral manifestations. Recurrent self-limited ulcers that are clinically indistinguishable from aphthous ulcers may occur in patients with inflammatory bowel disease; in these patients, the course of the oral ulcers closely parallels that of exacerbations of the bowel disease. Aphthous ulcers may also be seen as part of Behçet's syndrome, a systemic inflammatory disease of unknown etiology that most commonly affects young male adults. Behçet's disease is characterized by the triad of oral ulcers, genital ulcers, and ocular inflammation. In addition, the inflammatory changes of this disease are now known to affect multiple tissues and organs, including skin, joints, blood vessels, heart, lungs, and the central nervous system.

Lesions of the Tongue

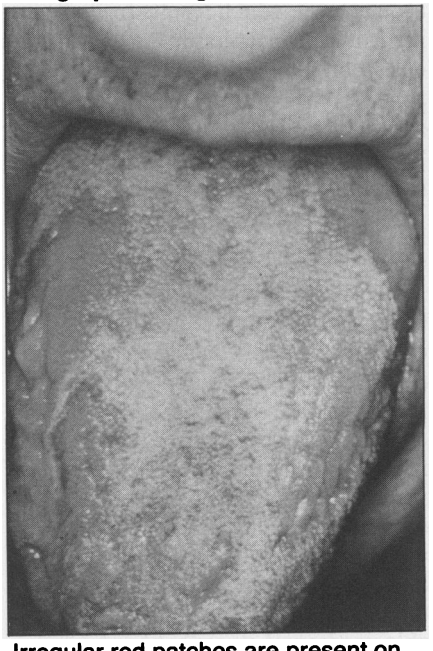
The tongue, a highly mobile organ with important functions in taste, mastication, and speech, is covered by a specialized mucosa. It is scarcely surprising that in addition to the oral mucosal diseases described in other sections of this article, the tongue mucosa is also affected by several conditions that primarily involve that organ.

Geographic tongue is a benign condition of unknown etiology, with a clinical appearance that is often pathognomonic. There are irregularly shaped, smooth, red patches on the dorsum and lateral borders of the tongue that are caused by loss of the filiform papillae (Figure 2). These are often surrounded by a yellowish-white or greyish-white border, resulting in a map-like appearance of the tongue mucosa. The filiform papillae regenerate in the denuded areas, while adjacent tongue mucosa undergoes loss of filiform papillae in turn, so that the red patches appear to migrate, giving rise to the alternative name for this condition: benign migratory glossitis. Geographic tongue occurs in persons of all ages, and lesions may appear, disappear, and recur over several years. Despite the abnormal appearance of the tongue, which is easily noticed by the patient, this condition is asymptomatic or causes only mild complaints of discomfort, and so treatment is unnecessary.

Median rhomboid glossitis, which has a characteristic clinical appearance, is also a benign condition of the tongue of unknown etiology. There is a rhomboid or oval-shaped red patch at the midline of the dorsum of the tongue, just anterior to the line of circumvallate papillae. This patch may be flat or nodular and may be elevated or depressed from the surrounding tongue, but is clearly demarcated because filiform papillae are absent (Figure 3). This condition is usually seen in adults and may be associated with a burning sensation. The two best-known hypotheses relating to its etiology are that it is a developmental anomaly, or that it represents chronic atrophic candidiasis of the tongue dorsum. Candidal hyphae can often be demonstrated in smears or biopsies of this lesion, and some relief of the burning sensation can often be obtained from topical antifungal therapy. Although there may be a superficial resemblance to squamous cell carcinoma, the characteristic location and appearance of this disorder usually indicate the correct clinical diagnosis.

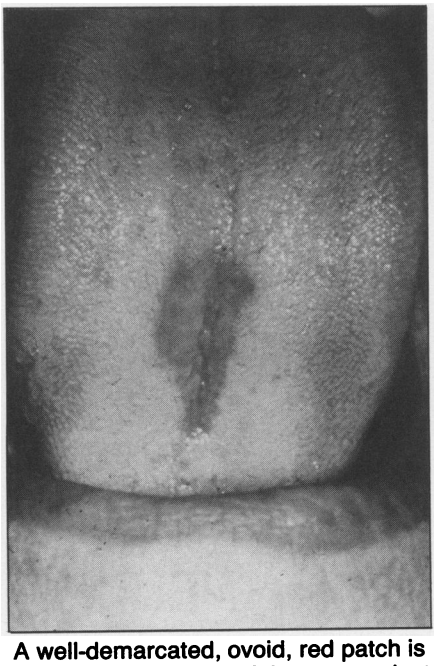
Hairy tongue is caused by hypertrophy and/or lack of normal desquamation of the filiform papillae.

Figure 2
Geographic Tongue



Irregular red patches are present on the dorsum of the tongue because of loss of filiform papillae.

Figure 3
Median Rhomboid Glossitis



A well-demarcated, ovoid, red patch is seen on the dorsum of the tongue, just anterior to the circumvallate papillae.

The altered surface texture predisposes to staining by tobacco, dietary constituents, or chromogenic bacteria, and the tongue dorsum may be stained brownish-black in colour. The etiology is unknown, although some cases are associated with protracted use of antibiotics, such as tetracyclines, or of antiseptic mouthwashes, such as hydrogen peroxide and sodium perborate, perhaps through alteration in the normal balance of oral microflora by these agents. In such cases, the abnormality usually disappears when the antibiotic or mouthwash is discontinued. Brushing of the tongue sometimes helps to promote desquamation and reduce accumulation of debris.

Burning tongue primarily affects women in their sixth and seventh decades, and can cause considerable distress. In most cases, there is no detectable abnormality in the appearance of the tongue, nor is there a demonstrable metabolic disturbance. The condition is discussed, in this issue, in the article on Oral and Facial Pain.[5] In a small number of cases, burning tongue is a manifestation of deficiency in an essential nutrient, usually iron, folic acid, or vitamin B_{12}. The tongue is smooth, red, and sensitive to touch, while the remainder of the oral mucosa may also appear red and atrophic, but to a less marked degree. Such cases of burning tongue usually respond well to correction of the mineral or vitamin deficiency. Atrophy of the tongue mucosa resulting in a smooth, red, burning tongue occurs as part of the Plummer-Vinson syndrome. This is a syndrome that occurs chiefly in women in the fourth and fifth decades of their life. It is characterized by iron-deficiency anemia, atrophy of the oral mucosa, particularly the tongue mucosa, dysphagia caused by esophageal strictures, and a predisposition for development of oral and esophageal carcinoma.

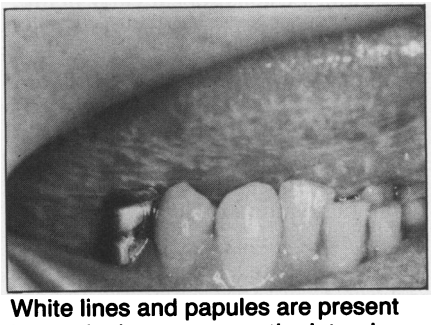
Mucocutaneous Diseases

Oral lesions are a prominent component of a number of mucocutaneous diseases: lichen planus, benign mucous membrane pemphigoid (cicatricial pemphigoid), pemphigus vulgaris, erythema multiforme, and epidermolysis bullosa. These disorders produce erosive and ulcerative oral lesions that are painful and often extensive, and that cause difficulties with eating and maintenance of oral hygiene. Oral and extra-oral lesions may be synchronous or metachronous. When oral lesions are the initial manifestation of disease, their accurate diagnosis will facilitate diagnosis and management of subsequent lesions on the skin or other mucous membranes. This is particularly true of pemphigus vulgaris and of benign mucous membrane pemphigoid.

Several other dermatologic diseases have also been reported to produce oral mucosal lesions, but the oral lesions are a less prominent component of the disease, and diagnosis is usually based on the skin lesions. These include psoriasis, bullous pemphigoid, dermatitis herpetiformis, and chronic discoid lupus erythematosus. Oral lesions of the first group of mucocutaneous diseases will be described below. The interested reader may consult oral pathology textbooks about oral lesions of the second group of diseases listed above.[1,2]

Lichen Planus is a chronic inflammatory mucocutaneous disease of unknown etiology. It is primarily a disease of adults, with a peak incidence in the fifth and sixth decades, and a predilection for women. Oral lesions of lichen planus appear in three forms. The reticular form consists of white, papular, and linear lesions arranged in a network. It appears most commonly on the posterior buccal mucosa and lateral borders of the tongue (Figure 4). The plaque form presents as fairly homogeneous white plaques, often seen on the tongue. The erosive form produces large, irregular, eroded, and ulcerated areas, most commonly on the tongue and buccal mucosa. Reticular lesions are often present at the periphery of the ulcerated areas. While reticular and plaque lesions are usually asymptomatic and are often incidental findings, erosive lesions are painful and require treatment. A clinical diagnosis of lichen planus can frequently be made on the basis of the characteristic appearance of the reticular lesions, but the plaque and erosive forms are less specific in their appearance and require biopsy for diagnosis. Most persons experience symptomatic relief of erosive lesions from topical steroid therapy such as 0.1% betamethasone ointment or intralesional steroid injections.

Figure 4
Oral Lichen Planus



White lines and papules are present in a reticular pattern on the lateral border of the tongue. This patient has bilateral lesions on both sides of the tongue and on the buccal mucosa.

Patients with oral lichen planus should be followed and examined periodically. There have been numerous case reports of oral squamous cell carcinoma developing in lesions of lichen planus. Since oral lichen planus and oral cancer are both relatively common diseases, some of these cases may represent fortuitous development of the two diseases in the same site of oral mucosa. Other cases appear to be misdiagnoses of a lesion of epithelial dysplasia for lichen planus, since there are clinical and histologic similarities between these two lesions. Nevertheless, it is generally recognized that a small probability exists for development of squamous cell carcinoma in a lesion of oral lichen planus, and so continued observation of these lesions is warranted.

Benign mucous membrane pemphigoid is a chronic vesiculo-bullous disease of the oral mucosa and other mucous membranes, such as those of the nasal cavity, pharynx, larynx, esophagus, vagina, and anus. It occurs most commonly in the fifth and sixth decades of life, and women are more frequently affected than men. Palpebral and bulbar conjunctivitis is a highly significant feature of the disease because the scarring and adhesions it causes may lead to blindness. Bullae of the oral mucosa are relatively thick-walled; they may persist for a day or two before rupturing to form painful, eroded, and ulcerated areas. Careful examination may reveal one or two intact bullae, in addition to areas of ulceration. The oral lesions usually heal without scarring. The gingiva is almost always affected, while the palate, buccal mucosa, and tongue are less often involved. Thus the most common mode of presentation in the oral cavity is that of "desquamative gingivitis". Diagnosis is based on clinical examination and biopsy. Because the histologic appearance is not very specific, direct immunofluorescence to demonstrate deposits of immunoglobulins and complement along the basement membrane

may be helpful, since these deposits are reported to be present in about 90% of cases.[6] Severe oral lesions are best controlled by intramuscular injections of myochrysine (gold sodium thiomalate). Patients who are treated with gold salts should be monitored with complete blood count and urinalysis because of possible side-effects of aplastic anemia and nephritis. Treatment with topical or systemic steroids appears to be less effective. Patients diagnosed as having oral lesions of benign mucous membrane pemphigoid should have an ophthalmic examination for eye lesions.

Pemphigus vulgaris is characterized by loss of adhesion among squamous epithelial cells (acantholysis) and formation of thin-walled intraepithelial bullae on the skin and mucous membranes. These rupture quickly to leave extensive areas of denuded skin and mucosa. The disease is progressive and, if untreated, has a high mortality rate. Pemphigus vulgaris is primarily a disease of adulthood and is rare in persons under 30 years of age, although a variant form of pemphigus has been reported in children (juvenile pemphigus vulgaris). It is well recognized that the disease is more common in Jewish persons. Oral lesions are common and may precede skin lesions, thus providing the initial signs and symptoms of this serious disease. Typical oral lesions consist of superficial, irregular, painful ulcerations and detachment of the superficial epithelium can be extended at the margins of the ulcers by exerting a sliding pressure on the mucosa (Nikolsky's sign). The oral lesions become secondarily infected, and frequently show candidal overgrowth. Diagnosis is based on clinical examination and cytologic smear and biopsy to demonstrate acantholysis and formation of suprabasal bullae. Antibodies (predominantly IgG) against intercellular substance of stratified squamous epithelium can be demonstrated in virtually all cases by direct immunofluorescence. Circulating antibodies against intercellular substance can be detected in about 90% of cases by indirect immunofluorescent examination of the patient's serum, although this test tends to be negative in patients who have only oral lesions without generalized disease elsewhere.[7] Treatment of pemphigus vulgaris is with systemic steroids, and the dose is adjusted for the individual patient to control lesions without incurring unwarranted side-effects.

Erythema multiforme is probably best described as a symptom complex that is triggered by a variety of factors, including viral infections such as herpes simplex and influenza, and ingestion of drugs such as barbiturates, sulfonamides, penicillin, and salicylates. In many cases a triggering factor cannot be identified. The disease is acute and self-limited, but may be recurrent. It is most commonly seen in young adults, and males are affected more frequently than females. Macular, papular, and vesicular lesions of rapid onset are seen on the skin and mucous membranes. In some cases, oral lesions occur without skin involvement. Recurrent attacks typically affect the same areas of skin or mucosa. Oral lesions become ulcerated soon after their appearance and are typically extensive, painful, and hemorrhagic. All areas of oral mucosa may be involved, but the labial mucosa and vermilion border are almost invariably affected. Diagnosis is based on clinical examination and biopsy. A history of recent viral infection or use of the drugs mentioned above is helpful for diagnosis. The histologic appearance of oral lesions is not very specific, but biopsy is often useful for excluding other diseases such as pemphigus vulgaris. Erythema multiforme has been reported to respond well to systemic steroid therapy, but the current opinion is that the disease is a self-limited one, and lesions will regress in seven to 10 days without treatment.

Epidermolysis bullosa is an inherited mucocutaneous disease that may occur in several forms: simplex, dystrophic dominant, dystrophic recessive, and lethalis. Oral lesions are most common and significant in the dystrophic recessive form. Lesions appear early in life, at birth or during childhood. Bullae develop after minor trauma such as that caused by chewing or swallowing or by an oral examination. These bullae rupture to form painful extensive ulcerations which heal with scarring, resulting in obliteration of sulci and restriction of movement. Dysphagia is common as a result of lesions of the pharynx and esophagus. The oral mucosal lesions are accompanied by missing, deformed, or hypoplastic teeth. There is no satisfactory treatment, except to avoid trauma as much as possible and to use antibiotics to control secondary infection.

An acquired form of epidermolysis bullosa has been described. Its oral mucosal lesions are similar to those of the dystrophic recessive form, except that onset occurs in adult life.

Viral Diseases

A large variety of viral diseases may affect the oral mucosa. Viral infections such as varicella (chickenpox), measles, and infectious mononucleosis may produce oral mucosal lesions, but these are rarely a prominent feature of the disease. (The reader is referred to oral pathology textbooks for further information.) Herpes simplex, herpes zoster (affecting the trigeminal nerve), and herpangina have prominent oral manifestations. Human papilloma virus is thought to cause a number of proliferative lesions of the oral mucosa, including verruca vulgaris, condyloma acuminatum, and focal epithelial hyperplasia. Among systemic viral diseases, the acquired immunodeficiency syndrome (AIDS) often produces oral lesions that may be among the earliest manifestations of this disease.

Primary infection with herpes simplex virus usually occurs early in life and does not produce clinical manifestations. In a minority of cases, clinical signs and symptoms result from such infection, and the condition is known as "acute herpetic gingivostomatitis". The gingiva becomes red and edematous, and multiple crops of vesicles appear on the oral mucosa. The vesicles rupture to form coalescent painful ulcers. The oral lesions are often accompanied by fever and cervical lymphadenopathy; lesions subside after 10 to 14 days. Treatment during the acute disease phase consists of bedrest, soft diet, and antipyretic and analgesic medications as required.

Recurrent herpetic lesions are caused by reactivation of latent herpes simplex virus and commonly present as vesiculo-ulcerative lesions on the vermilion border that are covered by a brownish crust (recurrent herpetic labialis). Such lesions often appear to be triggered by respiratory tract infections (hence "cold sore"), excessive exposure to sunlight, menstruation, or other forms of stress; they last for seven to 10 days. In individuals who are otherwise healthy, treatment of these self-limited lesions with currently

available systemic antiviral agents is probably not warranted, although topical forms of antiviral agents (for example, acyclovir) are being investigated and are potentially useful.

Recurrent herpetic stomatitis has been described as vesiculo-ulcerative lesions of the oral mucosa primarily on the gingiva and palate; however, the cause of such lesions is uncertain because herpes simplex virus is rarely demonstrated in them by culture or biopsy, and many probably represent herpetiform aphthous ulcers (see above).

Herpes zoster is caused by reactivation of latent infection by the varicella-zoster virus. It is predominantly seen in adults and tends to be more severe in elderly individuals. It may occur in individuals who are otherwise healthy, but is more common and more severe in immunocompromised patients and in patients with malignant disease, particularly Hodgkin's and non-Hodgkin's lymphoma. Herpes zoster is characterized by a vesicular eruption of the skin and mucous membrane that is strictly limited to the area of distribution of a sensory nerve. Oral mucosal lesions, usually accompanied by a vesicular eruption of the face, occur when the affected nerve is the second or third division of the trigeminal nerve. The first manifestation of oral herpes zoster is fever, malaise, and pain along the course of the trigeminal nerve. This is followed in a few days by a unilateral, painful, vesiculo-ulcerative eruption that characteristically stops abruptly at the midline. Lesions usually heal in 10 to 14 days unless they become secondarily infected. In rare cases, pain may persist for weeks following healing of the mucosal lesions (post-herpetic neuralgia). Mild attacks of herpes zoster are treated with bedrest and analgesics. Severe cases require systemic antiviral therapy such as intravenous acyclovir.

Herpangina results from infection by Coxsackie group A viruses. Most cases are seen as sporadic outbreaks of infection among children. The disease begins with low-grade fever, malaise, and sore throat. The mucosa of the pharynx and posterior part of the oral cavity is inflamed, and numerous small vesicles appear and quickly rupture to form small ulcers. Lesions heal in seven to 10 days. Clinical symptoms from herpangina are usually mild, and patients are adequately treated with bedrest and soft diet.

The human papilloma virus (HPV) has been shown to cause verruca vulgaris of the skin. Lesions with a similar clinical and histologic appearance occur on the vermilion border of the lips. They are rare within the oral cavity, but have been reported on the labial mucosa, palate, and gingiva as small sessile lesions with a papillary keratotic surface. Children and young adults are most often affected. Viral particles have been demonstrated in some of these lesions by electron microscopy. In some cases, there are concurrent lesions on the fingers and the oral mucosa, suggesting that the oral lesions may have resulted from transmission of infection through sucking or biting the fingers.

The most common proliferative lesion of the oral stratified squamous epithelium is the squamous papilloma. The characteristic lesion is a pedunculated, arborescent lesion with a cauliflower-like appearance. The surface may be pink or white, depending on the degree of keratinization. Viral particles are not demonstrable by electron microscopy. These lesions are generally considered to be of benign neoplastic or reactive nature and not viral in origin. However, recent studies of oral epithelial lesions using immunohistochemical staining and DNA hybridization have shown the presence of papilloma viral antigen and DNA in some oral papillomas.[8,9] The findings suggest that at least some papillomas of the oral mucosa are also caused by HPV and so indicate that they are closely related to verruca vulgaris.

Oral lesions of condyloma acuminatum are also thought to be caused by HPV. Viral particles have been found in these lesions by electron microscopy. These are relatively uncommon lesions compared to papillomas and are most frequently found on the palate, gingiva, and tongue of young adults. A history of contact of the oral mucosa with genital warts has been obtained in some cases. These lesions present as sessile, white-pink, cauliflower-like masses that are usually more extensive than papillomas.

Small lesions of condyloma acuminatum may be difficult to distinguish clinically and histologically from papillomas. These benign proliferative lesions of the oral epithelium are treated by simple excision and are not known to have any malignant potential. Those that are caused by HPV may be difficult to eliminate, because of repeated re-infection of the oral mucosa.

Focal epithelial hyperplasia (Heck's disease) is a condition of the oral mucosa often observed among Inuit and American Indians; it is rare among other populations. The disease presents as multiple, asymptomatic, nodular lesions of the labial and buccal mucosa and the tongue. The nodules are of the same colour as the adjacent mucosa and tend to disappear when the mucosa is stretched. Viral particles with the appearance of HPV have been seen in these lesions by electron microscopy, and both antigen and DNA of specific types of HPV have been demonstrated.[9] This is a benign condition that regresses spontaneously after several months or years, and treatment is unnecessary.

The oral manifestations of Acquired Immunodeficiency Syndrome (AIDS) are important because they may be the first overt indication of disease.[10] Oral candidiasis is frequently found in patients with AIDS, either as white pseudomembranous lesions or as painful, red, atrophic lesions (see below). The lesions respond to topical antifungal therapy, but recurrences are common. In more than half of the individuals at risk for AIDS, unexplained oral candidiasis is followed, within several months, by development of a major opportunistic infection or Kaposi's sarcoma. Oral hairy leucoplakia (condyloma planus) is a white lesion predominantly found on the lateral borders of the tongue, and its presence is always associated with infection by the human immunodeficiency virus (HIV). This lesion is an asymptomatic white patch with a fairly characteristic, striated, corrugated, or "hairy" appearance. A clinical impression of oral hairy leucoplakia should be confirmed by histologic examination, since this diagnosis is significant for predicting the development of AIDS within 30 months in a high percentage of cases. Replicating Epstein-Barr virus has been demonstrated in these lesions, but the exact role of this virus in their etiology is not clear at present.

In contrast to Kaposi's sarcoma that develops in individuals who do not have AIDS, that in AIDS patients often produces oral lesions, most commonly in the form of asymptomatic purplish-red patches or plaques in the palate. Biopsy should be made of such lesions to distinguish Kaposi's sarcoma from other

causes of discoloration of the oral mucosa.

A variety of other oral lesions have been reported in persons with AIDS and are presumed to reflect the immunodeficient state of these individuals. These include ulcerative and granulomatous fungal infections, increased frequency and severity of recurrent herpes simplex infections and herpes zoster, severe and refractory periodontal disease, and an increased incidence of non-Hodgkin's lymphoma and squamous cell carcinoma. The management of oral lesions of opportunistic infections and Kaposi's sarcoma is part of the treatment of this serious systemic disease.

Candidiasis

Candida albicans is present on the oral mucosa of many individuals who are apparently healthy. Opportunistic overgrowth by candida to produce signs and symptoms of disease occurs as the result of local or systemic abnormalities. Thus, an important aspect of the treatment of oral candidiasis is to control the factors that predispose to candidal overgrowth. Local factors include prolonged topical steroid treatment, poor denture hygiene, and the presence of another mucosal disease, such as pemphigus vulgaris or radiation mucositis. Candidal hyphae can be demonstrated in some lesions of oral epithelial dysplasia and squamous cell carcinoma, but the function of candida in the etiology of these lesions is controversial, as it is possible that the candidal infection is a secondary event. Systemic factors predisposing to oral candidiasis include endocrine diseases, uremia, immunosuppressive therapy, chemotherapy for malignant disease, and disseminated malignancies. The association between oral candidiasis and AIDS has been described in the preceding section.

From a clinical perspective, oral candidiasis presents in three major forms. In all cases, candida can be demonstrated morphologically in smears and biopsies stained with periodic acid-Schiff stain (PAS) or by culture in a variety of media.

Acute pseudomembranous candidiasis has a characteristic appearance of soft white lesions that can be scraped off to reveal an eroded mucosa. The white pseudomembrane contains large numbers of candidal hyphae. Chronic atrophic candidiasis has a less specific appearance of smooth red lesions that are often sensitive and painful. Chronic hyperplastic candidiasis consists of elevated, firm, white lesions that cannot be removed easily. These lesions should be examined histologically for the presence of dysplastic changes in the epithelium. Oral candidiasis is treated with topical antifungal agents, of which the most effective one is nystatin. In refractory cases, antifungal therapy has to be maintained over many weeks.

Syphilis

Among the various bacterial infections that may cause oral mucosal lesions, primary and secondary syphilis deserve special attention because of the non-specific clinical appearance and the highly contagious nature of the oral lesions. Primary syphilis of the oral mucosa presents as an indurated painless ulcer that is associated with cervical lymphadenopathy. The lesion lasts for three weeks to two months and disappears without scarring. Secondary syphilis of the oral mucosa occurs as part of the generalized, asymptomatic, mucocutaneous rash. Oral lesions (mucous patches) may be the initial abnormality discovered, and diagnosis may be missed because of the non-specific appearance and lack of symptoms. These consist of irregular, whitish-grey patches associated with areas of erythema and ulceration. There are often multiple lesions throughout the oral mucosa. Lesions persist for a few weeks and regress spontaneously but may recur over several years. Diagnosis is primarily by serology; individuals with secondary syphilis are always positive in serologic tests for syphilis, but those with primary syphilis may be negative. Dark-field examinaton of smears for spirochetes is not reliable for oral lesions because treponema microdentium, a common and non-pathogenic oral organism present in non-syphilitic individuals, may be confused with treponema pallidum, the causative organism for syphilis.

Melanotic Lesions

Increase in melanin content of the oral epithelium occurs in several conditions. Racial pigmentation of the oral mucosa represents a variation of normal appearance and is typically seen as bilateral, diffuse, tan to dark-brown areas of pigmentation on the gingiva, as well as other areas of oral mucosa. The pigmented areas appear early in life, during childhood or adolescence. They are asymptomatic and require no treatment. Diffuse pigmentation of the skin and oral mucosa may develop in Addison's disease as a result of overproduction of adrenocorticotropic hormone (ACTH). The oral mucosal pigmentary changes may be more noticeable than those of the skin, and thus they may occasionally be the earliest sign of Addison's disease.

The oral melanotic macule is a small, discrete, brownish-black, flat lesion of the oral mucosa. The lesion is benign and asymptomatic, and may appear at any age. Its clinical appearance may be similar to that of an amalgam tattoo. Pigmentation is caused by an increase in melanin in the basal epithelial cells. There is no known malignant potential. Since pigmented lesions of the oral mucosa are rare compared to those of the skin, it is recommended that all such lesions be excised for microscopic examination to differentiate benign lesions from early malignant melanoma; exceptions are cases where a definite diagnosis can be made from the clinical appearance: for example, racial pigmentation and most cases of amalgam tattoo. Multiple, small, melanotic macules are seen on the face, oral mucosa, and hands and feet in Peutz-Jeghers syndrome, a hereditary disease characterized by melanin pigmentation and multiple intestinal polyps. The distinctive distribution of numerous, small, melanotic macules over the lips, buccal mucosa, gingiva, and palate usually allows a clinical diagnosis of the cause of pigmentation. Areas of melanin pigmentation have also been

reported to occur on the oral mucosa, chiefly the palate, as a result of the use of chloroquin or related drugs.

Overview

This article provides a clinical overview of the more common oral mucosal lesions. For a small number of oral mucosal lesions, the clinical appearance is sufficiently distinctive to permit accurate diagnosis on the basis of clinical features alone. In most cases, biopsy is necessary to establish a diagnosis. Careful evaluation of the clinical features of an oral mucosal lesion is important to direct further investigations such as biopsy, culture, and serologic testing. ■

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References

1. Eversole LR. *Clinical outline of oral pathology: diagnosis and treatment.* Philadelphia: Lea and Febiger, 1984.

2. Shafer WG, Hine MK, Levy BM. *A textbook of oral pathology.* Philadelphia: W. B. Saunders, 1983.

3. McCarthy PL, Shklar G. *Diseases of the oral mucosa.* Philadelphia: Lea and Febiger, 1980.

4. Lecavalier DR, Main JHP. Oral tumours. *Can Fam Physician* 1988; 34:1377–82.

5. Mock D. Oral and facial pain. *Can Fam Physician* 1988; 34:1351–3.

6. Laskaris G, Angelopoulos A. Cicatricial pemphigoid: direct and indirect immunofluorescent studies. *Oral Surg* 1981; 51:48–54.

7. Laskaris G. Oral pemphigus vulgaris: an immunofluorescent study of fifty-eight cases. *Oral Surg* 1981: 51:626–31.

8. Loning T, Ikenberg H, Becker J, et al. Analysis of oral papillomas, leucoplakias and invasive carcinomas for human papillomavirus type related DNA. *J Invest Dermatol* 1985; 84:417–20.

9. Beaudenon S, Praetorius F, Kremsdorf D, et al. A new type of human papillomavirus associated with oral focal epithelial hyperplasia. *J Invest Dermatol* 1987; 88:130–5.

10. Silverman S. AIDS update, oral findings, diagnosis and precautions. *JADA* 1987; 115:559–63.