



White lesions of the oral cavity

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White lesions are frequently found during the examination of the oral cavity. Although some benign physiologic entities may present as white lesions, systemic conditions, infections, and malignancies may also present as white oral lesions. An appreciation of the many clinical entities that white lesions may represent is necessary if a differential diagnosis of white lesions is to be elucidated. The appreciation of subtle clinical findings associated with white lesions of the oral cavity permits clinicians better to care for their patients.

Leukoedema

Leukoedema is a common oral condition of unknown cause. The oral mucosa appears to have an asymptomatic, symmetric, opalescent milky-white film with accentuation of edematous folds or streaks (Fig. 1). Leukoedema most commonly occurs bilaterally on the buccal mucosa; it may also be noted on the floor of the mouth and palatopharyngeal tissues. The white opaque character of the lesion diminishes or disappears with the stretching and eversion of the oral mucosa. Leukoedema has a greater prevalence in the black population; its prevalence has been reported to be as high as 90% in black adults. This high preva-

lence indicates that it is a variant of normal versus a pathologic process. Some reports have suggested, however, that leukoedema is more severe in smokers and lessens with cessation.

Histopathology

Oral lesions of leukoedema show parakeratosis and an increase in thickness of the oral mucosa epithelium with intracellular edema of the spinous layer. The cells of the spinous layer are large with pyknotic nuclei. Rete ridges may be elongated. No dysplasia or hypergranulosis is evident.

Diagnostic tests

The white lesions of leukoedema do not rub off. Stretching of the oral mucosa and the resultant disappearance of the opalescence in the mucosa is diagnostic. Any diffuse white lesions of the oral mucosa should always be stretched out to rule out any other underlying lesions.

Treatment

No treatment is necessary. Leukoedema has no malignant potential.

Linea alba

Linea alba (horizontal bite line) is a very common benign alteration of the buccal mucosa. Linea alba

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Fig. 1. Leukoedema. Opalescent, whitish gray, ill-defined patches on buccal mucosa. They are usually bilateral and present in dark-skinned individuals. Lesions disappear when mucosa is stretched.

presents as a distinct white line that is usually bilateral on the buccal mucosa at the level of the occlusal plane of the adjacent teeth. The line varies in prominence from barely visible to highly prominent. The horizontal line becomes more pronounced distally toward the posterior teeth.

Pathophysiology

The horizontal alignment of this finding, and its presence only in patients who are dentulous, suggests that the linea alba is caused by a combination of frictional irritation and mild sucking trauma along the facial surfaces of the teeth and along the opposing occlusal surfaces.

Histologic picture

Hyperkeratosis overlying normal mucosa is demonstrated. Sometimes a mild chronic inflammatory cells infiltrate may be seen.

Diagnostic tests

The clinical picture is pathognomonic to establish a diagnosis. No biopsy is required.

Treatment

Bite splints worn at night may protect the cheek mucosa from involuntary biting.

Morsicatio buccarum et labiorum

Morsicatio buccarum (chronic cheek and lip biting) is a physical reaction to chronic trauma to the oral mucosa caused by chronic nibbling. Morsicatio buccarum is frequently found bilaterally on the buccal mucosa, or combined with labial and tongue lesions. Clinically morsicatio presents as thickened, shredded white areas that can be peeled off by the patient [1]. Intervening zones of erythema, erosions, or focal traumatic ulcerations can be seen. The affected areas are more pronounced along the occlusal plane and in the anterior one third of the buccal mucosa. When the lips are affected, it is the lower lip that is typically more severely affected than the upper lip. Most patients are aware of their habit but many deny the self-inflicted injury or perform the act subconsciously. It occurs more often in women and over the age of 35.

Pathophysiology

Morsicatio comes from the Latin word *morsus*, meaning bite. Chronic nibbling of the cheek produces lesions that are located more frequently on the buccal mucosa but sometimes the lingual mucosa (morsicatio labiorum) and lateral border of tongue (morsicatio linguarum) can also be affected.

Histopathology

Hyperparakeratosis with numerous keratin projections lined by and colonization by bacterial organisms are characteristic of morsicatio. Clusters of vacuolated keratinocytes may be present in the superficial layers of the spinous cell layer. Similar findings in linea alba and leukoedema also may be noted.

The clinical findings on the lateral border of the tongue and the histologic findings may resemble oral hairy leukoplakia, a lesion most frequently found in HIV patients. The bacterial colonization, however, is diagnostic.

Diagnostic tests

The clinical presentation and location are characteristic.

Treatment

Instructing the patient to avoid cheek biting is important. If the habit is uncontrollable, an acrylic shield that covers the facial surfaces of the teeth may be beneficial. Medications to control the habit may be used as adjunct therapy.

White sponge nevus

White sponge nevus (WSN) is an autosomal-dominant disorder characterized by asymptomatic white, thickened, and folded spongy plaques occurring symmetrically on the buccal mucosa. The tongue, labial mucosa, alveolar ridges, and floor of the mouth are also commonly affected. WSN presents at birth or early in childhood; rarely, the condition may appear during adulthood. Once they appear, they remain unchanged throughout the patient's life, except sometimes they become more pronounced during pregnancy. Extraoral mucous sites are less commonly affected; 15% to 30% can be found on the nose, esophagus, vagina, anus, and penis.

Pathophysiology

Recent genetic linkage analysis demonstrated a novel mutation in a vital domain of the K13 protein caused WSN in a large Scottish family, confirming a mutation hotspot in the mucosal keratins [2]. It seems that mutations in both keratin 4 and 13 may be present in WSN [3]. Some authors suggest that oral microflora could contribute to the stimulation of the lesion, because it has been demonstrated that WSN improved after tetracycline treatment.

Histopathology

The histologic findings are characteristic but not pathognomonic. These findings include prominent hyperparakeratosis and acanthosis with clearing of the cytoplasm in the spinous layer. Sometimes eosinophilic condensation, presented as aggregates of keratin intermediate filaments, is seen in the superficial layers of the epithelium.

Diagnostic tests

Exfoliative cytology of the epithelial cells stained with Papanicolaou's method show the characteristic eosinophilic perinuclear condensation better than histopathologic sections.

Treatment

No treatment is necessary.

Keratosis follicularis

Keratosis follicularis (Darier's disease or Darier-White disease) is a condition characterized by sym-

metric waxy, dirty keratotic papules involving the scalp, face, trunk, and flexures of the extremities (seborrheic distribution). As the disease progresses, the neck, shoulders, extremities, trunk, buttocks, genitals, and oral cavity may be affected. The lips may ulcerate or crust, fissure, and become edematous. Intraoral involvement occurs on the dorsal surface of the tongue. Small pebbly keratotic white papules are present on keratinized mucosa of the gingiva and hard palate.

Pathophysiology

Keratosis follicularis is an autosomal-dominant genodermatosis [4]. Defects in the tonofilament-desmosomal complex are reported. In some families, a linkage to the Duffy blood group locus at 1q21-q22 [5] has been made. Others have demonstrated linkage to markers in the 12q23-q24.1 region [6,7]. The site on chromosome 12 of this disorder of keratinization is distal to that of the type II keratin gene cluster at 12q11-q13 [8]. A defect in the gene encoding the SERCA2 (Ca²⁺)-ATPase (ATP2A2) has been found as the causative mutation in keratosis follicularis.

Histopathology

Perivascular infiltration in the dermis and submucosa is typically seen on histologic evaluation. Dermal villi protrude into the epidermis, with suprabasal detachment of the spinous layer forming lacunae and containing acantholytic cells. Dyskeratotic round epidermal cells and grains of parakeratotic cells are seen within a hyperkeratotic horny layer of the stratum corneum.

Diagnostic tests

A complete physical evaluation permits differentiation from other syndromes. The palmar surface may also have punctate keratoses, raising the differential diagnostic possibility of nevoid basal cell carcinoma syndrome (Gorlin's syndrome). Nail involvement shows subungual hyperkeratosis, fragility, and red streaks. The free edge may show triangular nicking. Involvement of the oropharynx, esophagus, hypopharynx, larynx, and the anorectal mucosa in keratosis follicularis has been reported.

Dyskeratosis congenita

Dyskeratosis congenita is an inherited disorder with x-linked, autosomal-recessive and autosomal-



Fig. 2. Dyskeratosis congenita. Diffuse white striae along the buccal mucosa. These areas are premalignant. (Courtesy of R.S. Rogers III, MD, Rochester, MN.)

dominant pedigrees. Dyskeratosis congenita is characterized by skin pigmentation, leukoplakia, and nail dystrophy associated with a progressive bone marrow failure (Fig. 2). Clinical manifestations in dyskeratosis congenita often appear during childhood. The skin pigmentation and nail changes typically appear first, usually by the age of 10 years [9–11]. Mucosal leukoplakia and epiphora appear later and by the mid-teens the serious complications of bone marrow failure and malignancy begin to develop. Rarely, marrow abnormalities may appear before the skin manifestations.

Pathophysiology

An RNA component of telomerase is mutated [12].

Treatment

Treatment for this fatal disease remains unsatisfactory.

Pachyonychia congenita

Pachyonychia congenita (Jackson-Lawler syndrome or Jadassohn-Lewandowsky syndrome) are a group of ectodermal dysplasias. The autosomal-dominantly inherited disorder is characterized by onychogryphosis; hyperkeratosis of the palms, soles, knees, and elbows; extensive tiny cutaneous horns; and leukokeratosis of the oral mucous membranes (Fig. 3). Hyperhidrosis of the hands and feet is present frequently. Autosomal-recessive and late-onset pedigrees have been described.

Oral leukokeratosis is similar in its appearance to that observed in dyskeratosis congenita. Dysplasia, however, does not develop.

Pathophysiology

The genetic defect associated with pachyonychia congenita is localized to chromosome 17q12-q21 and chromosome 12q13. Both of these result in keratin defects.

Treatment

Topical retinoids and topical podophyllin, although not approved by the Food and Drug Administration, have been used.

Focal epithelial hyperplasia

Focal epithelial hyperplasia (Heck's disease) is a benign, proliferative, wart-like disease of the oral mucosa that shows an unusual racial and geographic distribution. The lesions predominantly affect children and young adults, with girls more than boys. The lesions are asymptomatic, soft, fleshy papules and plaques ranging in color from pink to white, most frequently occurring on the lips, buccal mucosa, and lateral borders of the tongue. The anal-genital mucosa may be affected, whereas skin involvement is rare. The lesions range from 2 to 4 mm and mostly appear multiple and confluent. A cobblestone or fissured



Fig. 3. Pachyonychia congenita. Diffuse white plaques along the lingual aspect of the palate. (Courtesy of R.S. Rogers III, MD, Rochester, MN.)

pattern is observed with coalescing sheets of the lesions. The surface may be smooth or papillary [13].

Pathophysiology

Focal epithelial hyperplasia is frequently seen in Inuits and Indians from North, Central, and South America [14,15]. Focal epithelial hyperplasia was first described by Archard et al [16] in 1965 in 15 Navajo children suffering from verruciform papules and nodules in the oral cavity. The causative organism is human papilloma virus (HPV) types 13 and 32; additional HPV types 6, 11, and 26 have also been identified.

Histopathology

Acanthosis and elongation with prominent clubbing and lateral anastomosing of the rete pegs is characteristic. Keratinocytes show typical HPV transformed cells characterized by pyknotic nuclei and perinuclear vacuoles [13].

Treatment

Usually therapy includes surgery, cryosurgery, and laser excision. Recently, Steinhoff et al [17] showed successful elimination of these lesions using a topical interferon- β gel after 12 weeks of daily application.

Discoid lupus erythematosus

Lupus erythematosus (LE) is an autoimmune condition with a broad spectrum of disease manifestations. LE may present in chronic form or it may present acutely. Occasionally, subacute lesions can be seen. Skin and oral lesions characterize chronic mucocutaneous LE. Subacute cutaneous LE is characterized by recurring superficial non-scarring annular skin lesions that are more disseminated and present more acute features both clinically and histologically than those seen in the chronic discoid type. Acute systemic LE lesions present as erythematous edematous plaques on the skin and erosions of the mucous membranes.

Chronic cutaneous LE primarily affects the skin but the oral mucosa can also be affected [18]. Patients with discoid lupus erythematosus (DLE) lesions typically have cutaneous findings and, rarely, they may also present with oral findings. DLE is used to describe both the skin and oral findings. Cutaneous DLE lesions are common on the scalp, face, and in the ears. In the skin, central atrophic hypopigmented and

peripheral hyperpigmented plaques are common. Overlying scale forming “carpet tack” follicular plugs is noted. Less commonly, other sites may be affected. Distinctive oral plaques of DLE appear as “sunburst” with erythematous plaques surrounded by white, radiating striations. Telangiectasias at the peripheral border may be noted (Fig. 4). Scale is not found in the oral cavity [19].

Although any mucosal surface may be involved, the buccal mucosa, the vermilion borders, the gingiva, and the labial mucosa are affected in decreasing order of frequency. The oral lesions may become secondarily infected with *Candida*. Discoid LE lesions may be painful, particularly when acidic or salty foods are ingested. Oral DLE plaques may resemble erosive lichen planus or a lichenoid mucositis. Oral DLE plaques, however, are less likely to be symmetric and more frequently are associated with lesions on the vermilion or facial skin. A small subset of patients may have only oral DLE lesions.

Histopathology

Oral DLE lesions reveal hyperkeratosis, vacuolar degeneration of the basal cell layer, and a thickened basement membrane. An interface mucositis with a mild to moderate perivascular infiltrate can be seen.

Diagnostic tests

Patchy deposits of periodic acid–Schiff–positive material in the basement membrane are noted. Direct immunofluorescence testing of oral tissue may reveal a granular band of immunoreactants (IgG, IgM, and IgA), complement (C3), and fibrinogen along the basement membrane of long-standing lesions (Fig. 5). The



Fig. 4. Discoid lupus. Erythematous and white plaques on the buccal mucosa with a rim or erythema secondary to telangiectasias

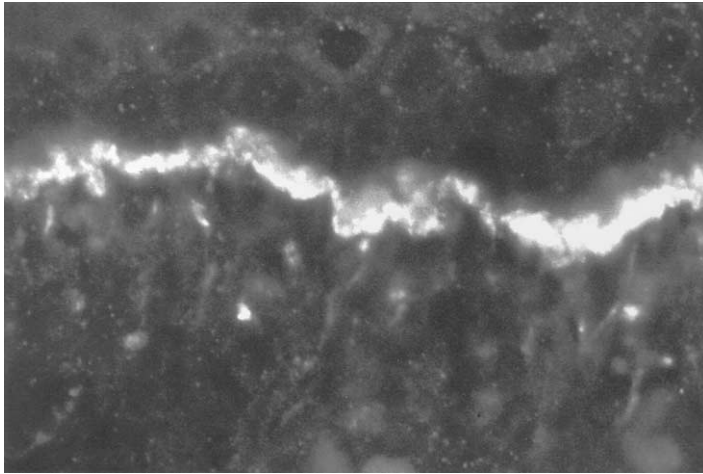


Fig. 5. Discoid lupus. Granular deposition of IgG along the basement membrane zone confirming the diagnosis of lupus erythematosus. (Courtesy of R.S. Rogers III, MD, Rochester, MN.)

finding of granular C3 deposits along the basement membrane zone or fibrinogen is not diagnostic. The presence of anti-ssDNA occurs with widespread active disease.

Treatment

Topical corticosteroids may expedite the resolution of oral LE lesions. If patients have painful discoid lesions, intralesional corticosteroids are recommended and, if these treatments are unsuccessful, patients may require systemic medications.

Pyostomatitis vegetans

Pyostomatitis vegetans is a rare inflammatory pustular disorder of the oral mucosa. This rare finding is a specific marker of inflammatory bowel disease [50]. Most patients have ulcerative colitis. Pyostomatitis vegetans has also been reported, however, in Crohn's disease, sclerosing cholangitis, and other liver diseases. Clinically, yellowish, elevated pustules are found on an erythematous mucosa. These pustules quickly rupture leading to erosions and ulcerations. The ruptured pustules form a "snail track" (Fig. 6).

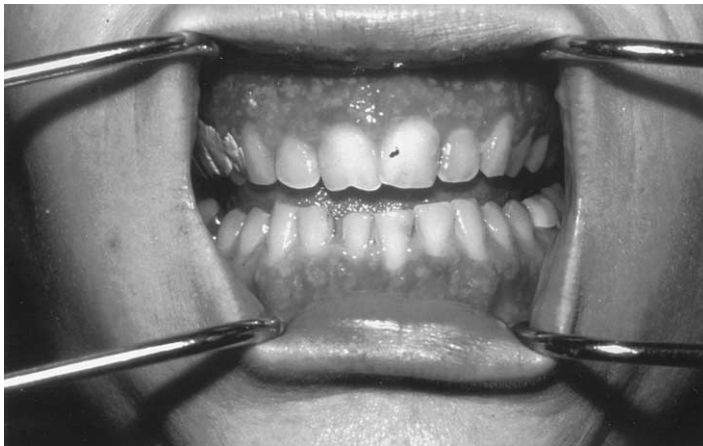


Fig. 6. Pyostomatitis vegetans. Extensive discrete superficial pustules along the gingivae and vestibule. (Courtesy of R.S. Rogers III, MD, Rochester, MN.)

Vegetative plaques may also be found on the buccal mucosa. Patients may have mild to moderate pain particularly when the erosions and ulcers appear. The most commonly affected areas of the oral cavity include the buccal mucosa, labial mucosa, and attached gingivae. The oral lesions may either precede or be concurrent with intestinal findings [17,20,21].

Histopathology

Microscopically pyostomatitis vegetans shows marked edema that may have a hyperkeratotic and acantholytic appearance. In the spinous layer an accumulation of eosinophils and neutrophils forms intraepithelial abscesses. An infiltrate of eosinophils, neutrophils, and lymphocytes is noted in the submucosa. Perivascular inflammation has also been reported.

Diagnostic tests

Direct immunofluorescence testing is usually negative. This helps differentiate pyostomatitis vegetans from other autoimmune disorders, such as pemphigus and pemphigoid. A peripheral eosinophilia may be found in up to 90% of patients.

Treatment

Topical and systemic corticosteroids may be effective to treat oral lesions. When oral disease activity correlates with the gastrointestinal disease, management of the underlying inflammatory bowel disease with systemic corticosteroids, sulfasalazine, dapsone, diet, or surgery may clear the oral lesions. Recurrences are frequent if therapy is stopped. Pyostomatitis vegetans may be refractory to therapy [22].

Proliferative verrucous leukoplakia

Proliferative verrucous leukoplakia (PVL) was first described by Hansen et al in 1985 [23]. PVL is characterized by progressive expanding exophytic- verrucous white plaques. Early lesions appear as a solitary, homogeneous leukoplakia. Women are affected four times as frequently as men. The most common sites for women are the buccal mucosa and gingiva, and for men, the tongue. Early biopsies show only hyperkeratosis without dysplasia [24]. These innocuous lesions recur and spread to involve several sites resulting in a diffuse, multifocal, exophytic, or warty-type presentation. Hansen et al [23] reported that 86.7% of the patients developed carcinoma at the

lesion site in a follow-up time of up to 20 years. When compared with other oral sites, the tongue and gingiva have a higher tendency for malignant transformation. The authors suggest that if mortality data from both reports were combined, the PVL-associated deaths would be 50%.

Pathophysiology

Smoking [25] has not been associated in most individuals. Ultimately, PVL is associated with considerable morbidity and a strong potential for malignant transformation. HPV seems to be a possible etiologic factor for PVL. Palefsky et al [26] found that 89% of their patients were HPV positive.

Histopathology

Individual lesions progress from benign-appearing hyperkeratosis to verrucous hyperplasia, to different degrees of dysplasia to verrucous or squamous cell carcinoma. The inflammatory cell infiltrate in the connective tissue is quite variable ranging from mild and diffuse to dense subepithelial clustering [25,27].

Diagnostic tests

Polymerase chain reaction testing for HPV 16 on DNA samples from tissue samples can be performed to confirm the presence of HPV in these specimens [26].

Treatment

The treatment for PVL continues to be unsatisfactory with a very high rate of recurrence after surgical excision. Still, the treatment of choice is surgical or laser excision.

Florid oral papillomatosis

Florid oral papillomatosis is a rare condition considered to be premalignant by some authors and is usually associated with a marked capacity for progression and recurrence [28]. Florid oral papillomatosis is characterized by multiple papillomas involving the whole oral mucosal including the palate, tongue, and lips (Fig. 7).

Pathophysiology

Some authors suggested a viral etiology but the role of HPV in these lesions remains unclear [28].



Fig. 7. Florid oral papillomatosis. Diffuse confluent and adherent papillated white hyperkeratosis along the attached and free gingivae. (Courtesy of R.S. Rogers III, MD, Rochester, MN.)

Histopathology

Hyperplasia with parakeratosis and acanthosis is observed. Dysplastic changes are rare.

Treatment

Various modes of therapy have been proposed including surgery, bleomycin chemotherapy, radiotherapy, interferon alfa-2a injections, and laser surgery [28].

Syphilis mucous patches

Mucous patches are an oral manifestation of secondary syphilis. The plaques are usually oval and covered with white or gray membrane that is removed easily to reveal underlying raw connective tissue. Roughly 30% of patients with secondary syphilis present with superficial painless oral lesions with irregular, grayish mucosal necrosis. These patches are found on the tongue, lips, buccal mucosa, and palate. Mucous patches may heal spontaneously, but have a high incidence of recurrence (Fig. 8).

Other findings associated with secondary syphilis include a papulosquamous eruption with prominent copper-colored scaly plaques involving the palms and soles; a moth-eaten alopecia; and genital condylomata lata lesions, which may be associated with a mild lymphadenopathy, hepatosplenomegaly, and a residual chancre.

Pathophysiology

Syphilis is caused by the spirochete *Treponema pallidum*.

Histopathology

Histologic evaluation of syphilis mucous patches is nonspecific. The epithelium may be either ulcerated or hyperplastic. The lamina propria may have increased vascular channels and chronic inflammatory reaction. This inflammatory perivascular infiltrate is principally comprised of lymphocytes and plasma cells.

Diagnostic tests

Special stains, such as Warthin-Starry or Steiner, may be used and often show the spirochetes. The most specific tests are the demonstration of the spirochete in skin biopsy or darkfield examination. False-positive results are possible in the oral cavity because of morphologically similar bacteria *T. microdentium*, *T. macrodentium*, and *T. mucosum*.

Confirmation of syphilis should be performed with serology following biopsy or darkfield examination. The serologic tests in secondary syphilis are usually positive. Serologic tests, which are nonspecific and highly sensitive, include the Venereal Disease Research Laboratory and the rapid plasma reagin. Specific and highly sensitive serologic tests for syphilis include the fluorescent treponemal antibody absorption test. This test becomes positive at the development of the initial lesion and is positive for life. It is less effective in diagnosis of second infection of syphilis.

Treatment

The treatment of choice for syphilis is benzathine penicillin G, 2.4 million units in a single intramuscular dose. Patients should have follow-up serologic titers at 3 and 6 months to ensure a fourfold decline in titers. In addition, patient reporting to proper public health



Fig. 8. Syphilis mucous patch. Well-demarcated erythroleukoplakia on the palate of a patient with secondary syphilis. (Courtesy of R.S. Rogers III, MD, Rochester, MN.)

agencies ensures tracking and management of known sexual partners.

Candidosis (candidiasis)

Candidosis, synonymously called candidiasis, is caused by *Candida* organisms, fungi that inhabit the oral cavity, gastrointestinal tract, other mucous membranes, and the skin [29]. Moniliasis is an old and inaccurate term that should be abandoned. Candidosis is the most common infection of the oral cavity with the exception of dental caries and periodontal diseases.

Oral candidosis manifests in six specific clinical forms [30]:

1. Pseudomembranous candidiasis
2. Acute atrophic-erythematous candidiasis
3. Chronic atrophic candidiasis
4. Angular cheilitis (perlèche)
5. Chronic hypertrophic-hyperplastic candidiasis (*Candida* leukoplakia)
6. Median rhomboid glossitis

Pseudomembranous candidiasis presents with superficial curdlike white patches that wipe off, leaving an erythematous base (Fig. 9). Any mucosal surface may be affected. The elderly, infants, and AIDS patients are frequently affected, as are patients with a history of broad-spectrum antibiotics or corticosteroid treatment, nutritional deficiency, and diabetes mellitus. Patients may complain of stomatodynia and dysgeusia.



Fig. 9. Pseudomembranous candidiasis. Localized removable white plaques on the dorsal aspect of the tongue. (Courtesy of R.S. Rogers III, MD, Rochester, MN.)

Erythematous candidiasis is a generalized category of candidiasis that appears as focal or diffuse areas of erythema with variable causes and symptoms. These include items 2 through 6 on the previous list, as discussed next.

Acute atrophic candidiasis is most often seen on the tongue and palate, and is a frequent complication of broad-spectrum antibiotic, corticosteroid, and corticosteroid aerosol therapy. These lesions present as small or generalized large red patches of inflammation and edema of the surrounding tissues.

Chronic atrophic candidiasis presents as red diffuse areas with a slightly pebbly or velvet surface located on the palate and upper and lower edentulous ridges. This entity is frequently found under ill-fitting dentures or poorly cleaned dentures (denture stomatitis).

Angular cheilitis presents as fissures, erosions, and crusting with underlying erythema developing at the commissures (corners of the mouth). Predisposing factors include ill-fitting dentures with overclosure, drooling at the corners of the mouth, lip-licking habits, and thumb sucking habits.

Chronic hyperplastic candidiasis (candidal leukoplakia) appears as well-demarcated, white, thick, or verrucous white plaques that cannot rub off. These develop most frequently on the anterior buccal mucosa and palate.

Median rhomboid glossitis was previously thought to be a congenital anomaly from faulty involution of the tuberculum impar at the junction of the anterior two thirds and posterior one third of the tongue. It appears as a diamond- or oval-shaped erythematous depapillated area of the posterior dorsum of the tongue (Fig. 10). The surface could be smooth or lobulated, and it is asymptomatic. It occurs more frequently in AIDS patients.

There is a generalized mucocutaneous form of candidosis that presents as chronic infection of the oral mucosa, nails, skin, and vaginal mucosa. It usually starts as pseudomembranous candidiasis, and then proceeds to become chronic hyperplastic candidiasis. Several types are familial and can present during early childhood. Another familial form exists in association with endocrinopathy, such as hypoparathyroidism, Addison's disease, hypothyroidism, or diabetes mellitus.

When changes occur in the host environment that results in an imbalance of the flora or a decrease in resistance, *Candida* becomes an opportunistic pathogen. Most cases of oral candidiasis are caused by *Candida albicans*, although a large number of other yeast species may be found intraorally. These include *C. tropicalis*, *C. krusei*, *C. parapsilosis*, and *C. guilliermondii*. These different species can be differenti-



Fig. 10. Median rhomboid glossitis. In chronic candidiasis, localized asymptomatic erythematous patch on the mid-dorsal surface of the tongue. Long-standing lesions may become nodular.

ated from one another by polymerase chain reaction techniques that are being developed to aid in the diagnosis [31].

Candida albicans exists in several forms from yeast to hyphae. The yeast form is commensal and harmless; the hyphae form is invasive, pathogenic, and causes clinical candidiasis. Recently, it has been shown [32] that adherence of hyphae to the oral keratinocyte may be caused by a protein called Hwp1. This protein forms a covalent bond to epithelial cells with the aid of the enzyme transglutaminase. The authors state that without Hwp1, adherence of the hyphae to human oral mucosal cells is reduced 80%.

There are several predisposing factors to *Candida* infection, such as diabetes; congenital or acquired immunodeficiency, such as AIDS; xerostomia or decreased salivary flow; and patients undergoing radiotherapy or chemotherapy for cancer treatments. Patients on long-term therapy with antibiotics or corticosteroids are all susceptible to develop candidosis. Leukemia, organ, or bone marrow transplant patients and denture-wearing patients are all prone to candidal infection.

Diagnostic tests

The most common laboratory test is the digestion of an exfoliative cytology smear of the oral sites affected with 10% potassium hydroxide, demonstrating the pseudohyphae or budding cells that are consistent with the *Candida* morphology. A cytologic smear or biopsy can be stained with periodic acid–Schiff. This method stains the abundant carbohydrates in the fungal cell walls. The organisms are identified easily by their bright magenta color. Definitive identification of the fungi is performed by culture growing on Sabouraud's dextrose agar.

Treatment

Several antifungal medications have been developed for managing oral candidiasis. There are three main categories [29]. The polyenes, which include amphotericin B and nystatin, destroy the protein gradient in the cell because of leakage of cellular components. Amphotericin B is highly effective when given intravenously, but could cause toxicity and renal dysfunction. The second group is the azoles, including clotrimazole, ketoconazole, fluconazole, and itraconazole. These inhibit ergosterol biosynthesis. The third category is 5-flucytosine. This drug disrupts the DNA and protein synthesis of the cell. It is usually used in combination with amphotericin B, fluconazole, or itraconazole (Table 1).

Warts

There are two main categories of warts: common warts (*verruca vulgaris*) and venereal warts (*condyloma acuminatum*).

Verruca vulgaris (common warts) are the result of epithelial hyperplasia, which appear as solitary or multiple, asymptomatic, exophytic growths with roughened or verrucous surface identical to cutaneous

Table 1
Most common antifungal drugs for treatment of oral candidiasis

Drugs	Route	Dosage
Nystatin	Oral (suspension, troches), topical	200,000–400,000 U, 4–5 times/d
Amphotericin B	IV, oral suspension	IV: 1–3 mg/kg/d, oral: 100 mg, 4–6 times/d
Clotrimazole	Oral (troches), topical	10 mg, 5 times/d
Ketoconazole (Nizoral)	Oral, topical	200–400 mg/d
Fluconazole (Diflucan)	Oral (tablet, suspension)	100–200 mg/d
Itraconazole (Sporanox)	Oral (capsules, suspension)	200–400 mg/d

warts. Lesions are either pedunculated or sessile and range in color from pink to white. Individual lesions usually achieve an average size of about 0.5 to 1 cm. Oral verruca vulgaris arise more frequently in children than in adults. The lesions develop in sites of inoculation, mainly the labial mucosa, tongue, and gingiva. Although warts are more common in the skin, they are present in the oral mucosa mostly because of auto-inoculation from hands and fingers. Common warts are caused by viral infection with HPV types 2, 4, 40, and 57 [13].

Condyloma acuminatum (venereal warts or genital warts) is the most common sexually transmitted disease and arises in the oral mucosa because of auto-inoculation or more commonly by orogenital sexual transmission. The incubation period for a condyloma is 1 to 3 months from the time of sexual contact. It is associated more frequently with HPV types 6, 11, 16, and 18. It is also very common in HIV patients. Recently, Greenspan et al [33] demonstrated that in AIDS patients using the highly active antiretroviral therapy, there is a striking increase in oral warts.

Lesions are frequently present in the labial mucosa, followed by lingual frenum, soft palate, and gingiva. They present as asymptomatic, pink, sessile, less frequently pedunculated, exophytic cauliflower-like growths. They are multiple rather than single. They are usually larger than verruca vulgaris, ranging from 1 to 3 cm.

Histopathology

Warts are characterized by a proliferation of hyperkeratotic stratified squamous epithelium arranged into finger-like projections with connective tissue cores [34]. The converging or “cupping” arrangement of the peripheral rete ridges and a prominent granular cell layer demonstrate coarse, clumped keratohyaline granules. Numerous koilocytes that are virally transformed cells characterized by pyknotic nuclei and perinuclear vacuoles are present.

Diagnostic tests

Electron microscopy, immunoperoxidase staining, or in situ hybridization can detect HPV viral particles in the biopsy samples.

Treatment

Both oral and cutaneous lesions are treated by surgical excision, cryosurgery, electrosurgery, and laser. Recently, the use of podophyllin as a 20% solution of tincture of benzoin has been used with

some success. Because the agent is teratogenic and toxic to the kidneys, brain, and myocardium it has to be applied to the areas by the dentist or physician.

Leukoplakia

Leukoplakia is a nonspecific clinical descriptive term for a white patch or plaque in the oral cavity that cannot be characterized clinically or pathologically as any other disease. Although leukoplakia may be a premalignant lesion, it does not imply that dysplasia is always present. Leukoplakia usually occurs after the age of 40 and the incidence increases with age, with the highest incidence in men. The main predisposing factors for the development of oral leukoplakia are smoking and alcohol consumption. Physical irritants, chronic trauma, and poor oral hygiene have also been implicated.

Leukoplakia can appear in several clinical forms. Leukoplakia may range in size from a few millimeters to several centimeters; the surface can be smooth or verrucous and range from slightly elevated white, hyperkeratotic plaque to thick corrugated lesions. Long-term clinical studies suggest that 5% to 50% of the lesions turn malignant; this depends on the histologic grading, length of follow-up, and the presence of risk factors [35,36].

Histopathology

The microscopic picture consists of a wide spectrum of findings ranging from hyperkeratosis to dysplasia, carcinoma in situ, and squamous cell carcinoma.

Treatment

The standard treatment is surgical resection or laser ablation.

Frictional keratosis

Chronic irritation to the oral mucosa causes morphologic changes that appear as white areas called frictional keratoses. Trauma is the most common etiologic factor in the development of these lesions; examples are chronic cheek or lip biting, poor-fitting dentures, sharp teeth cusps, and broken dental restorations [37].

These white plaques vary in size, shape, and thickness depending on the degree and duration of trauma. The tongue is frequently affected followed by

the labial mucosa, alveolar ridge, and buccal mucosa. Single or multiple areas may be involved.

Histopathology

The most common histopathologic features are hyperkeratosis and acanthosis. No dysplasia is observed.

Treatment

Elimination of the primary cause of trauma is the first line of treatment. If lesions do not resolve, then a biopsy is mandatory.

Viadent-associated leukoplakia

Viadent refers to a toothpaste and oral rinse that contain extracts of the bloodroot plant *Sanguinaria canadensis*, which are known to have anti-inflammatory, antibacterial, and antifungal activity [38]. The active ingredient in this extract is the benzophenanthridine alkaloids. The toothpaste has been shown in several clinical trials [39–41] to be effective against plaque build-up and gingivitis. The role of Viadent in the development of oral leukoplakia is controversial. Damm et al [42] showed that in a review of 74 patients with leukoplakia of the maxillary vestibule, 84.1% of them used Viadent toothpaste. All 74 patients were whites. The ages ranged from 38 to 89 years with a higher predilection in women or proportion of patients who were women.

The maxillary leukoplakia was located in the anterior vestibule, sometime extending to the alveolar mucosa (Fig. 11). Lesions varied in size and consistency from a smooth to a corrugated texture.

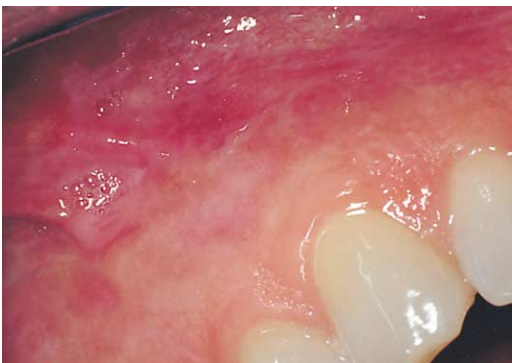


Fig. 11. Viadent-associated leukoplakia. Ill-defined white plaques on the maxillary vestibule not associated with any risk factors other than with the use of Viadent rinse.

A recent review article by Munro et al [43] concludes that the available clinical and animal data do not support the hypothesis that the use of Viadent toothpaste products may be associated with development of leukoplakia of the maxillary vestibule.

Histopathology

All cases demonstrated hyperorthokeratosis mixed with hyperparakeratosis. The dysplastic changes were minimal but included increased cellularity and hyperchromatism of the basilar one third of the epidermis.

Treatment

Discontinuation of the Viadent toothpaste and close follow-up of the lesions followed by surgical removal of lesions is recommended.

Tylosis

Tylosis is an autosomal-dominant disorder associated with defective keratinization of the palms and soles. In addition to palmoplantar keratoderma, a growing number of kindreds have been identified who have had both tylosis and esophageal carcinoma. In some of the families oral leukoplakia is a prominent feature.

Pathophysiology

The causative gene, the tylosis esophageal cancer gene, is located on chromosome 17q25. This tumor-suppressor gene is also found in sporadic cancers of the esophagus. Numerous studies suggest that the loss of envoplakin function could be responsible for the formation of palmoplantar keratoderma [44].

Histopathology

Recognizable dysplasia is noted in older individuals. Dysplasia was characterized by abnormal maturation with prominent basophilic inclusions and clear cell acanthosis. Parakeratinization and orthokeratinization were also noted. Inflammation and individual cell keratinization are noted in young affected individuals. The individual cell keratinization was significantly more common in affected younger individuals and was found to be a morphologic marker of increased risk [45].

Treatment

Early diagnosis and frequent clinical evaluations are necessary if late sequelae of esophageal cancer is to be avoided.

Nicotinic stomatitis

Nicotinic stomatitis (smoker's palate) is a benign process with no malignant potential. Nicotinic stomatitis is always confined to the hard palate and begins as erythema of the palate. Later the palate assumes a grayish white and nodular appearance (Fig. 12). A characteristic finding is the appearance of multiple red dots, which represent the dilated and inflamed duct openings of the minor salivary glands. The lesions are asymptomatic and discovered during an oral examination.

Nicotinic stomatitis occurs almost exclusively in heavy pipe smokers and rarely in cigarette or cigar smokers [46]. It is also observed in reverse smokers (lit end placed in the mouth). This observation suggests that a thermal effect is the cause of the clinical changes.

Histopathology

Biopsy specimens from reverse smokers show significant dysplasia and epithelial atypia [37].



Fig. 12. Tobacco-associated keratoses (nicotinic stomatitis). The openings of the minor salivary gland ducts appear as bright red umbilicated papules associated with a rim of white hyperkeratosis. These changes are not premalignant, although they are indicative of extensive exposure to tobacco, tars, and heat. A complete oral examination is indicated to identify other sites more at risk for dysplasia. (Courtesy of R.S. Rogers III, MD, Rochester, MN.)



Fig. 13. Tobacco pouch keratosis (smokeless tobacco pouch). Tobacco pouch of the left mandibular vestibule extending to the buccal mucosa. The lesion is corrugated and wrinkled and is restricted to the area in contact with the snuff.

Treatment

Although nicotinic stomatitis is a benign finding the risk for malignant transformation elsewhere in these patients should not be ignored. Resolution of the changes of nicotinic stomatitis is noted within several months after the cessation of smoking.

Tobacco pouch keratosis (smokeless tobacco pouch)

Lesions induced by smokeless tobacco characteristically have a wrinkled surface that ranges from opaque white to translucent and develop on the mucosal surfaces that contact the tobacco products. These lesions are called *tobacco pouch keratosis*. The mucosal surface has a velvety texture often with a cobblestone appearance and is asymptomatic (Fig. 13). Longstanding lesions in heavy users may become thickened and verrucous [35]. Studies have shown that about 2% to 6% of oral leukoplakia undergoes malignant changes over a period of 5 to 10 years [47].

The use of smokeless tobacco has increased tremendously in the past 25 years, especially among white men aged 15 to 34 years [47]. It is believed that 5% of the population is currently engaged in chewing tobacco or dipping snuff. Many tobacco smokers may see smokeless tobacco as a healthier alternative to smoking cigarettes, but literature has documented the association between smokeless tobacco use and oral and pharyngeal cancer. The use of snuff is associated with lesions that cause an increase in epithelial dysplastic changes greater than those associated with chewing tobacco.

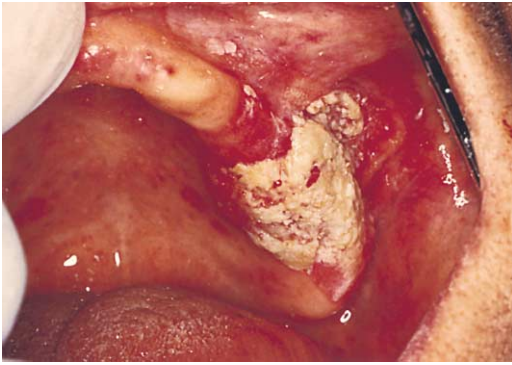


Fig. 14. Squamous cell carcinoma. Discrete plaque with rolled borders extending along the maxillary alveolar ridge onto the hard palate and buccal vestibule. The lesion has features of both erythroplakia and leukoplakia.

Histopathology

The findings are nonspecific acanthosis, orthokeratosis, and marked parakeratosis. Dysplasia is uncommon.

Treatment

Lesions usually resolve within 6 weeks of cessation of tobacco use.

Squamous cell carcinoma

It is beyond the scope of this article to write a detailed overview of oral squamous cell carcinoma (SCC). A brief description is provided.

Oral SCC appears in different clinical forms: leukoplakia, erythroplakia, and nonhealing ulcer. Depending on the amount of keratosis, SCC may vary in color appearing pink, white, or red (Fig. 14). The most common sites for oral SCC are the posterior lateral and ventral surfaces of the tongue; the floor of the mouth is the second most common site. Other sites include the gingival, buccal mucosa, and palate.

The incidence of oral cancer has dramatically increased in the past decade because of an increase in tobacco and alcohol use. Men are affected twice as often as women. There is a higher incidence after the age of 40 years with a peak at 60 years. In the beginning of the twenty-first century, 31,000 new cases of oral cancer will be recognized each year, mostly occurring in the lips, tongue, floor of the mouth, palate, gingiva, alveolar and buccal mucosa, and oropharynx [49]. SCC accounts for 96% of all

oral cancers; sarcomas and salivary gland tumors account for the remainder.

Histopathology

Findings range from well-differentiated (low-grade) lesions, in which the tumors resemble normal epithelium, to poorly differentiated or anaplastic (high-grade) lesions, where the tumor cells lose their resemblance to the epithelial tissues [35].

Despite improvements in therapeutic and reconstructive modalities, oral cancer represents an important cause of cancer morbidity and mortality. The 5-year survival rates for malignancies of the oral cavity and pharynx remain lower than 50%. The head and neck is the only anatomic region in which 5-year survival rates have not improved significantly in the last decade. It is estimated that over 10,000 deaths from oral cancer will occur in the United States this year, which is approximately 2.4% of all cancers. It is the sixth most common type of cancer in whites and the fourth in blacks. The major risk factors are smoking and alcohol consumption. A number of oncogenic viruses may be associated with the development of SCC [35], especially HPV 16. Tumor-suppressor gene p53 has also been implicated in the pathogenesis of SCC [48]. The treatment of choice depends on the stage of the disease and varies from aggressive surgical intervention, sometimes accompanied by postsurgical radiation therapy. Radical neck dissection is performed when evidence of lymph node involvement is given.

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