RED AND WHITE LESIONS OF THE ORAL MUCOSA

INDRANEEL BHATTACHARYYA, DDS, MSD
DONALD M. COHEN, DMD, MS, MBA
SOL SILVERMAN JR., DDS, MS

HEREDITARY WHITE LESIONS
Leukoedema
White Sponge Nevus
Hereditary Benign Intraepithelial Dyskeratosis
Dyskeratosis Congenita

REACTIVE/INFLAMMATORY WHITE LESIONS
Linea Alba (White Line)
Frictional (Traumatic) Keratosis
Cheek Chewing
Chemical Injuries of the Oral Mucosa
Actinic Keratosis (Cheilitis)
Smokeless Tobacco–Induced Keratosis
Nicotine Stomatitis
Sanguinaria-Induced Leukoplakia

INFECTIOUS WHITE LESIONS AND WHITE AND RED LESIONS
Oral Hairy Leukoplakia
Candidiasis
Mucous Patches
Parulis

IDIOPATHIC “TRUE” LEUKOPLAKIA
Etiology
Clinical Features
Varieties
Histopathologic Features
Diagnosis and Management
Prognosis

BOWEN’S DISEASE

ERYTHROPLAKIA
Clinical Features
Histopathologic Features
Differential Diagnosis
Treatment and Prognosis

ORAL LICHEN PLANUS
Etiology and Diagnosis
Clinical Features
Histopathologic Features
Immunofluorescent Studies
Differential Diagnosis
Clinical Course and Prognosis
Treatment

LICHENOID REACTIONS
Drug-Induced Lichenoid Reactions
Graft-versus-Host Disease

LUPUS ERYTHEMATOSUS (SYSTEMIC AND DISCOID)
Clinical Features, Diagnosis, and Treatment
Histopathologic Features
Malignant Potential, Importance, and Scope of Oral Lesions

DEVELOPMENTAL WHITE LESIONS: ECTOPIC LYMPHOID TISSUE

FORDYCE’S GRANULES
Features
Treatment

GINGIVAL AND PALATAL CYSTS OF THE NEWBORN AND ADULT
Features in the Newborn
Features in the Adult

MISCELLANEOUS LESIONS
Geographic Tongue
Hairy Tongue (Black Hairy Tongue)
Oral Submucous Fibrosis
Any condition that increases the thickness of the epithelium causes it to appear white by increasing the distance to the vascular bed. Lesions most often appear white because of a thickening of the keratin layer, or hyperkeratosis. Other common causes of a white appearance include acanthosis (a thickening of the spinous cell layer), an increase in the amount of edema fluid in the epithelium (ie, leukoedema), and reduced vascularity in the underlying lamina propria. Surface ulcerations covered by a fibrin cap can also appear white, as would collapsed bullae. (These latter two types of lesions are covered in Chapter 4, “Ulcerative, Vesicular, and Bullous Lesions.”)

**HEREDITARY WHITE LESIONS**

**Leukoedema**

Leukoedema is a common mucosal alteration that represents a variation of the normal condition rather than a true pathologic change. It has been reported in up to 90% of black adults and up to 50% of black teenagers. The incidence in white persons in different studies is highly variable (10 to 90%). This difference can be attributed to the darker coloration of the mucosa in black persons, rendering the alteration more visible. Similar edematous changes have been reported in other mucosal surfaces, such as the vagina and larynx.

**FEATURES**

The most frequent site of leukoedema is the buccal mucosa bilaterally, and it may be seen rarely on the labial mucosa, soft palate, and floor of the mouth. It usually has a faint, white, diffuse, and filmy appearance, with numerous surface folds resulting in wrinkling of the mucosa (Figure 5-1). It cannot be scraped off, and it disappears or fades upon stretching the mucosa. Microscopic examination reveals thickening of the epithelium, with significant intracellular edema of the stratum spinosum. The surface of the epithelium may demonstrate a thickened layer of parakeratin.

**TREATMENT**

No treatment is indicated for leukoedema since it is a variation of the normal condition. No malignant change has been reported.

**White Sponge Nevus**

White sponge nevus (WSN) is a rare autosomal dominant disorder with a high degree of penetrance and variable expressivity; it predominantly affects noncornified stratified squamous epithelium. The disease usually involves the oral mucosa and (less frequently) the mucous membranes of the nose, esophagus, genitalia, and rectum. The lesions of WSN may be present at birth or may first manifest or become more intense at puberty. Genetic analyses of families with WSN have identified a missense mutation in one allele of keratin 13 that leads to proline substitution for leucine within the keratin gene cluster on chromosome 17. A new study, using sequence analysis, has reported a glutamine insertion localized in the helix initiation motif of the 1A alpha helical domain of Keratin 4 gene.

**DIFFERENTIAL DIAGNOSIS**

The lesions of WSN may be grossly similar to those of other hereditary mucosal syndromes such as hereditary benign intraepithelial dyskeratosis or pachyonychia congenita, infections such as candidiasis, traumatic lesions seen in cheek chewing, and chemical burns or preneoplastic/neoplastic processes. This differential diagnosis is best resolved in many cases by incisional biopsy specimens interpreted in the context of the clinical history and physical findings.

**TREATMENT**

No treatment is indicated for this benign and asymptomatic condition. Patients may require palliative treatment if the condition is symptomatic. One study has reported some relief of symptoms with a tetracycline rinse.

**Hereditary Benign Intraepithelial Dyskeratosis**

Hereditary benign intraepithelial dyskeratosis (HBID), also known as Witkop’s disease, is a rare autosomal dominant disorder characterized by oral lesions and bilateral limbal conjunctival plaques. This condition is noted specifically in a triracial isolate of white, Native American, and African American people and their descendants in Halifax county, North Carolina. It exhibits a high degree of penetrance.
Red and White Lesions of the Oral Mucosa

FEATURES

The oral lesions are similar to those of WSN, with thick, corrugated, asymptomatic, white “spongy” plaques involving the buccal and labial mucosa. Other intraoral sites include the floor of the mouth, the lateral tongue, the gingiva, and the palate. The oral lesions are generally detected in the first year of life and gradually increase in intensity until the teens. The most significant aspect of HBID involves the bulbar conjunctiva, where thick, gelatinous, foamy, and opaque plaques form adjacent to the cornea. The ocular lesions manifest very early in life (usually within the first year). Some patients exhibit chronic relapsing ocular irritation and photophobia. The plaques may exhibit seasonal prominence, with many patients reporting more pronounced lesions in the spring and regression during the summer months. A few cases of blindness due to corneal vascularization following HBID have been reported. The histopathologic features of HBID are characteristic, and the epithelium exhibits marked parakeratin production with thickening of the stratum spinosum and the presence of numerous dyskeratotic cells. Ultrastructural findings in patients with HBID reveal the presence of numerous vesicular bodies in immature dyskeratotic cells, densely packed tonofilaments within the cytoplasm of these cells, and the disappearance of cellular bridging in mature dyskeratotic cells.

TREATMENT

Since HBID is a benign condition, no treatment is required for the oral lesions. For evaluation and treatment of the ocular lesions, the patient should be referred to an ophthalmologist.

Dyskeratosis Congenita

Dyskeratosis congenita, a recessively inherited genodermatosis, is unusual due to the high incidence of oral cancer in young affected adults. It is a rare X-linked disorder characterized by a series of oral changes that lead eventually to an atrophic leukoplakic oral mucosa, with the tongue and cheek most severely affected. The oral changes occur in association with severely dystrophic nails and a prominent reticulated hyperpigmentation of the skin of the face, neck, and chest. Many cases also exhibit hematologic changes including pancytopenia, hypersplenism, and an aplastic or Fanconi’s anemia (ie, an anemia associated with an inherited inability to repair deoxyribonucleic acid [DNA] defects, leading to a high frequency of leukemia and lymphoma). The oral lesions commence before the age of 10 years as crops of vesicles with associated patches of white ulcerated necrotic mucosa often infected with Candida. Erythroplakic changes and nail dystrophy follow, with leukoplakic lesions and carcinoma supervening on the oral lesions in early adulthood.

▼ REACTIVE AND INFLAMMATORY WHITE LESIONS

Linea Alba (White Line)

As the name implies, linea alba is a horizontal streak on the buccal mucosa at the level of the occlusal plane extending from the commissure to the posterior teeth. It is a very common finding and is most likely associated with pressure, frictional irritation, or sucking trauma from the facial surfaces of the teeth. This alteration was present in about 13% of the population in one study.

CLINICAL FEATURES

Linea alba is usually present bilaterally and may be pronounced in some individuals. It is more prominent in individuals with reduced overjet of the posterior teeth. It is often scalloped and restricted to dentulous areas.

TREATMENT

No treatment is indicated for patients with linea alba. The white streak may disappear spontaneously in some people.

Frictional (Traumatic) Keratosis

CLINICAL FEATURES

Frictional (traumatic) keratosis is defined as a white plaque with a rough and frayed surface that is clearly related to an identifiable source of mechanical irritation and that will usually resolve on elimination of the irritant. These lesions may occasionally mimic dysplastic leukoplakia; therefore, careful examination and sometimes a biopsy are required to rule out any atypical changes. Histologically, such lesions show varying degrees of hyperkeratosis and acanthosis. Prevalence rates as high as 5.5% have been reported. Such lesions are similar to calluses on the skin. Traumatic keratosis has never been shown to undergo malignant transformation. Lesions belonging to this category of keratosis include linea alba and cheek, lip, and tongue chewing. Frictional keratosis is frequently associated with rough or maladjusted dentures (Figure 5-2) and with sharp cusps and edges of broken teeth.

TREATMENT

Upon removal of the offending agent, the lesion should resolve within 2 weeks. Biopsies should be performed on lesions that do not heal to rule out a dysplastic lesion.

![Figure 5-2](image-url) Leukoplakic-appearing area of frictional keratosis from an ill-fitting denture.
**Cheek Chewing**

White lesions of the oral tissues may result from chronic irritation due to repeated sucking, nibbling, or chewing.\(^{24–29}\) These insults result in the traumatized area becoming thickened, scarred, and paler than the surrounding tissues. Cheek chewing is most commonly seen in people who are under stress or in psychological situations in which cheek and lip biting become habitual. Most patients with this condition are somewhat aware of their habit but do not associate it with their lesions. The white lesions of cheek chewing may sometimes be confused with other dermatologic disorders involving the oral mucosa, which can lead to misdiagnosis.\(^{30}\) Chronic chewing of the labial mucosa (morsicatio labiorum) and the lateral border of the tongue (morsicatio linguarum) may be seen with cheek chewing or may cause isolated lesions. Prevalence rates ranging from 0.12 to 0.5% have been reported in Scandinavian populations, compared with a prevalence rate of 4.6% for South African school children in mental health treatment facilities; these rates support the role of stress and anxiety in the etiology of this condition.\(^{26–28}\)

**Typical Features**

The lesions are most frequently found bilaterally on the posterior buccal mucosa along the plane of occlusion. They may be seen in combination with traumatic lesions on the lips or tongue. Patients often complain of roughness or small tags of tissue that they actually tear free from the surface. This produces a distinctive frayed clinical presentation (Figure 5-3). The lesions are poorly outlined whitish patches that may be intermixed with areas of erythema or ulceration. The occurrence is twice as prevalent in females and three times more common after the age of 35 years.

The histopathologic picture is distinctive and includes hyperparakeratosis and acanthosis. The keratin surface is usually shaggy and ragged with numerous projections of keratin that demonstrate adherent bacterial colonies. When the lesion is seen on the lateral tongue, the clinical and histomorphologic features mimic those of oral hairy leukoplakia.\(^{29}\)

**TREATMENT AND PROGNOSIS**

Since the lesions result from an unconscious and/or nervous habit, no treatment is indicated. However, for those desiring treatment and unable to stop the chewing habit, a plastic occlusal night guard may be fabricated. Isolated tongue involvement requires further investigation to rule out oral hairy leukoplakia especially when appropriate risk factors for infection with human immunodeficiency virus (HIV) are present. Differential diagnosis also includes WSN, chemical burns, and candidiasis.

**Chemical Injuries of the Oral Mucosa**

Transient nonkeratotic white lesions of the oral mucosa are often a result of chemical injuries caused by a variety of agents that are caustic when retained in the mouth for long periods of time, such as aspirin, silver nitrate, formocresol, sodium hypochlorite, paraformaldehyde, dental cavity varnishes, acid-etching materials, and hydrogen peroxide.\(^{31–42}\) The white lesions are attributable to the formation of a superficial pseudomembrane composed of a necrotic surface tissue and an inflammatory exudate.

**Specific Caustive Agents**

**Aspirin Burn.** Acetylsalicylic acid (aspirin) is a common source of burns of the oral cavity.\(^{43–45}\) Usually, the tissue is damaged when aspirin is held in the mucobuccal fold area for prolonged periods of time for the relief of common dental pain (Figure 5-4).

**Silver Nitrate.** Silver nitrate is commonly used by health care practitioners as a chemical cautery agent for the treatment of aphthous ulcers.\(^{46}\) It brings about almost instantaneous relief of symptoms by burning the nerve endings at the site of the ulcer. However, silver nitrate often destroys tissue around the immediate area of application and may result in delayed healing or (rarely) severe necrosis at the application site (Figure 5-5).\(^{46}\) Its use should be discouraged.
Red and White Lesions of the Oral Mucosa

Hydrogen Peroxide. Hydrogen peroxide is often used as an intraoral rinse for the prevention of periodontal disease. At concentrations of $\geq 3\%$, hydrogen peroxide is associated with epithelial necrosis.\(^{40}\)

Sodium Hypochlorite. Sodium hypochlorite, or dental bleach, is commonly used as a root canal irrigant and may cause serious ulcerations due to accidental contact with oral soft tissues.\(^{32}\)

Dentifrices and Mouthwashes. Several cases of oral injuries and ulcerations due to the misuse of commercially available mouthwashes and dentifrices have been reported (Figure 5-6).\(^{31,33,42,47}\) An unusual sensitivity reaction with severe ulcerations and sloughing of the mucosa has been reported to have been caused by a cinnamon-flavored dentifrice (Figure 5-7). However, these lesions probably represent a sensitivity or allergic reaction to the cinnamon aldehyde in the toothpaste.\(^{47}\) This reaction can appear to be very similar to the reactions caused by other chemical agents such as aspirin and hydrogen peroxide. Caustic burns of the lips, mouth, and tongue have been seen in patients who use mouthwashes containing alcohol and chlorhexidine.\(^{33,42}\) A case of an unusual chemical burn, confined to the masticatory mucosa and produced by abusive ingestion of fresh fruit and by the concomitant excessive use of mouthwash, has also been reported.\(^{42}\)

TYPICAL FEATURES

The lesions are usually located on the mucobuccal fold area and gingiva. The injured area is irregular in shape, white, covered with a pseudomembrane, and very painful. The area of involvement may be extensive. When contact with the tissue is brief, a superficial white and wrinkled appearance without resultant necrosis is usually seen. Long-term contact (usually with aspirin, sodium hypochlorite, phenol, paraformaldehyde, etc) can cause severer damage and sloughing of the necrotic mucosa. The unattached nonkeratinized tissue is more commonly affected than the attached mucosa.

TREATMENT AND PROGNOSIS

The best treatment of chemical burns of the oral cavity is prevention. Children especially should be supervised while taking aspirin tablets, to prevent prolonged retention of the agent in the oral cavity.\(^{31,41,45}\) The proper use of a rubber dam during endodontic procedures reduces the risk of iatrogenic chemical burns. Most superficial burns heal within 1 or 2 weeks. A protective emollient agent such as a film of methyl cellulose may provide relief.\(^{37,45}\) However, deep-tissue burns and necrosis may require careful debridement of the surface, followed by antibiotic coverage. In case of ingestion of caustic chemicals or accidental exposure to severely corrosive agents, extensive scarring that may require surgery and/or prosthetic rehabilitation may occur.\(^{48}\)

Actinic Keratosis (Cheilitis)

Actinic (or solar) keratosis is a premalignant epithelial lesion that is directly related to long-term sun exposure.\(^{39}\) These lesions are classically found on the vermilion border of the
lower lip as well as on other sun-exposed areas of the skin. A small percentage of these lesions will transform into squamous cell carcinoma.\textsuperscript{50} Biopsies should be performed on lesions that repeatedly ulcerate, crust over, or show a thickened white area. These lesions are commonly found in individuals with extensive sun exposure, such as those with outdoor occupations and/or fair complexions.\textsuperscript{49}

**TYPICAL FEATURES**

Actinic keratosis may be seen on the skin of the forehead, cheeks, ears, and forearms. On the lip, it appears as a white plaque, oval to linear in shape, usually measuring < 1 cm in size (Figure 5-8). The surface may be crusted and rough to the touch. Histopathologically, the surface epithelium appears atrophic, with a basophilic homogenous amorphous alteration of the collagen (solar elastosis) in the lamina propria. Varying degrees of atypical features such as increased nucleocytoplasmic ratios, loss of cellular polarity and orientation, and nuclear and cellular atypia are found within the epithelium. A mild lymphocytic infiltrate may also be noted in the lamina propria.\textsuperscript{49}

**TREATMENT AND PROGNOSIS**

The mainstay of treatment of actinic keratosis is surgery. Chemotherapeutic agents such as topical 5-fluorouracil have been used with some success.\textsuperscript{50} However, follow-up biopsies in individuals who were treated with 5-fluorouracil showed that the dysplastic changes persist in clinically healthy-appearing epithelium. Patients treated with nonsurgical methods therefore require long-term follow-up. About 10% of these lesions will undergo malignant transformation.\textsuperscript{51}

**Smokeless Tobacco–Induced Keratosis**

Chewing tobacco is an important established risk factor for the development of oral carcinoma in the United States.\textsuperscript{52} Habitually chewing tobacco leaves or dipping snuff results in the development of a well-recognized white mucosal lesion in the area of tobacco contact, called smokeless tobacco keratosis, snuff dipper’s keratosis, or tobacco pouch keratosis.\textsuperscript{53} While these lesions are accepted as precancerous, they are significantly different from true leukoplakia and have a much lower risk of malignant transformation.\textsuperscript{54}

This habit was once almost universal in the United States and is very common among certain other populations, most notably in Sweden, India, and Southeast Asia.\textsuperscript{52,53–60} Smokeless tobacco use among white males in the United States has shown a recent resurgence.\textsuperscript{60–62} The estimated proportion of adult men in the United States who regularly use “spit” tobacco ranges from 6 to 20%.\textsuperscript{38,63} This range is attributed to significant geographic, cultural, and gender variations in chewing habits.\textsuperscript{54} The cumulative incidence for smokeless tobacco use was highest for non-Hispanic white males.\textsuperscript{54} Unfortunately, the habit starts relatively early in life, usually between the ages of 9 and 15 years, and is rarely begun after 20 years of age. Recent epidemiologic data indicate that over five million Americans use smokeless tobacco and that more than 750,000 of these users are adolescents. It is estimated that each year in the United States, approximately 800,000 young people between the ages of 11 and 19 years experiment with smokeless tobacco and that about 300,000 become regular users.\textsuperscript{55–59,63}

Smokeless tobacco contains several known carcinogens, including N-nitrosornornicotine (NNN), and these have been proven to cause mucosal alterations.\textsuperscript{64} In addition to its established role as a carcinogen, chewing tobacco may be a risk factor in the development of root surface caries and, to a lesser extent, coronal caries. This may be due to its high sugar content and its association with increased amounts of gingival recession.\textsuperscript{35} The duration of exposure is very important in the production of mucosal damage. Leukoplakia has been reported to develop with the habitual use of as little as three cans of snuff per week for longer than 3 years.\textsuperscript{53} Although all forms of smokeless tobacco may result in mucosal alterations, snuff (a finely powdered tobacco) appears to be much more likely to cause such changes than is chewing tobacco.\textsuperscript{53,59}

Smokeless tobacco is not consistently associated with increased rates of oral cancer.\textsuperscript{54} Approximately 20% of all adult Swedish males use moist snuff, yet it has not been possible to detect any significant increase in the incidence of cancer of the oral cavity or pharynx in Sweden. By international standards, the prevalence of oral cancer is low in Sweden.\textsuperscript{52} This has been attributed to variations in the composition of snuff, in particular, the amount of fermented or cured tobacco in the mixture. The carcinogen NNN is present in much lower concentrations in Swedish snuff, probably because of a lack of fermentation of the tobacco. Also, the high level of snuff use might decrease the amount of cigarette smoking and therefore lead to a lesser prevalence of oral cancer.\textsuperscript{52,54}

**TYPICAL FEATURES**

Numerous alterations are found in habitual users of smokeless tobacco. Most changes associated with the use of smokeless tobacco are seen in the area contacting the tobacco. The most common area of involvement is the anterior mandibular vestibule, followed by the posterior vestibule.\textsuperscript{53} The surface of the mucosa

![FIGURE 5-8](image) Distinctive raised white plaque, representing actinic cheilitis.
Red and White Lesions of the Oral Mucosa

appears white and is granular or wrinkled (Figure 5-9); in some cases, a folded character may be seen (tobacco pouch keratosis). Commonly noted is a characteristic area of gingival recession with periodontal-tissue destruction in the immediate area of contact (Figure 5-10). This recession involves the facial aspect of the tooth or teeth and is related to the amount and duration of tobacco use. The mucosa appears gray or gray-white and almost translucent. Since the tobacco is not in the mouth during examination, the usually stretched mucosa appears fissured or rippled, and a “pouch” is usually present. This white tobacco pouch may become leathery or nodular in long-term heavy users (Figure 5-11). Rarely, an erythroplakic component may be seen. The lesion is usually asymptomatic and is discovered on routine examination. Microscopically, the epithelium is hyperkeratotic and thickened. A characteristic vacuolization or edema may be seen in the keratin layer and in the superficial epithelium. Frank dysplasia is uncommon in tobacco pouch keratosis.62

TREATMENT AND PROGNOSIS

Cessation of use almost always leads to a normal mucosal appearance within 1 to 2 weeks.54,64,65 Biopsy specimens should be obtained from lesions that remain after 1 month. Biopsy is particularly indicated for those lesions that appear clinically atypical and that include such features as surface ulceration, erythroplakia, intense whiteness, or a verrucoid or papillary surface.53, 62, 64 The risk of malignant transformation is increased fourfold for chronic smokeless tobacco users.66

Nicotine Stomatitis

Nicotine stomatitis (stomatitis nicotina palati, smoker’s palate) refers to a specific white lesion that develops on the hard and soft palate in heavy cigarette, pipe, and cigar smokers. The lesions are restricted to areas that are exposed to a relatively concentrated amount of hot smoke during inhalation. Areas covered by a denture are usually not involved. The lesion has become less common since pipe smoking has lost popularity. Although it is associated closely with tobacco smoking, the lesion is not considered to be premalignant.57–69 Interestingly, nicotine stomatitis also develops in individuals with a long history of drinking extremely hot beverages.70 This suggests that heat, rather than toxic chemicals in tobacco smoke, is the primary cause. Prevalence rates as high as 1.0 to 2.5% have been reported in populations of different cultures.69–72 “Reverse smoking” (ie, placing the burning end of the cigarette in the oral cavity), seen in South American and Asian populations, produces significantly more pronounced palatal alterations that may be erythroleukoplakic and that are definitely considered premalignant.73

TYPICAL FEATURES

This condition is most often found in older males with a history of heavy long-term cigar, pipe, or cigarette smoking. Due to the chronic insult, the palatal mucosa becomes diffusely gray or white (Figure 5-12, A). Numerous slightly elevated papules with punctate red centers that represent inflamed and metaplastically altered minor salivary gland ducts are noted.
Microscopically, the surface epithelium exhibits hyperkeratosis and acanthosis with squamous metaplasia and hyperplasia of the salivary ducts as they approach the surface (see Figure 5-12, B). The subjacent connective tissue and minor salivary glands exhibit a mild to moderate scattered chronic inflammation. No atypical or dysplastic changes are usually identified.72

TREATMENT AND PROGNOSIS

Nicotine stomatitis is completely reversible once the habit is discontinued. The severity of inflammation is proportional to the duration and amount of smoking.72 The lesions usually resolve within 2 weeks of cessation of smoking. Biopsy of nicotine stomatitis is rarely indicated except to reassure the patient. However, a biopsy should be performed on any white lesion of the palatal mucosa that persists after 1 month of discontinuation of smoking habit.

Sanguinaria-Induced Leukoplakia

Sanguinaria extract, a mixture of benzophenanthridine alkaloids derived from the common bloodroot plant (Sanguinaria canadensis), has been used in oral rinses and toothpaste products since 1982. The most widely used product with Sanguinaria, Viadent, has been shown, through extensive clinical trials, to be effective against plaque buildup and gingivitis.74,75 Importantly, sanguinaria extract has also been shown to be carcinogenic in many studies.76,77 In 1999, Damm and associates78 reported an increased prevalence of leukoplakia of the maxillary vestibule in patients who used sanguinaria-based products on a routine basis. They conducted a retrospective review of 88 patients with leukoplakia of the maxillary vestibule and found that 84.1% of the patients reported having used Viadent. The prevalence of Viadent use was only 3% among randomly selected adults in their study. Eversole and colleagues79 compared and contrasted biomarkers and ploidy data from maxillary gingival leukoplakias associated with dentifrices and mouth rinses containing sanguinaria with those from other forms of benign and premalignant mucosal keratosis. They used computerized image analysis and biomarker immunohistochemical assays to assess ploidy, DNA content, and p53 and proliferating cell nuclear antigen immunoreactivity of nuclei in tissue from these groups. A significantly higher (four-fold) DNA content and higher numbers of cells with hyperploid nuclei were found in the group with sanguinaria-associated keratoses. Although this group did not harbor significant numbers of p53-expressing nuclei, a significant elevation in nuclei labeled with proliferating cell nuclear antigen was noted. The authors concluded that sanguinaria-associated keratoses show marker and image analysis profiles similar to those of non-sanguinaria-induced dysplastic lesions of the lip and mucosa.79 Hence, preparations containing sanguinaria should be avoided until the risk for malignant transformation is determined.80 This recommendation is further supported by the lack of regression in some Viadent-induced leukoplakias months after the cessation of Viadent use.

TYPICAL FEATURES

Most patients are adults in the fourth to ninth decades of life. In the study by Damm and colleagues, the range of Viadent use before the development of lesions was 6 months to 12 years, with a mean of 4.4 years.78 Typically, patients present with a white, velvety, wrinkled or corrugated patch of leukoplakia in the maxillary vestibule, involving both the attached gingiva and vestibular mucosa (Figure 5-13, A). The lesions may also be seen in the anterior mandibular vestibule (see Figure 5-13, B). The area is usually very distinct and sharply demarcated from the surrounding tissue. The lesions are localized to these areas since the anterior portions of the maxillary and mandibular
vestibule exhibit prolonged retention of the product due to the greater distance from the major salivary ducts. Histopathologically, all biopsy specimens demonstrate significant surface keratosis with a verrucoid pattern. Minimal atypical changes (including basilar hyperplasia, nuclear hyperchromatism, and increased nucleocytoplasmic ratios) limited to the lower one-third of the epithelium are noted in most specimens. More significant atypical changes have also been reported.78

**TREATMENT**

No appropriate treatment has been established for sanguinaria-induced leukoplakia. However, an initial biopsy is mandatory. If a histopathologic diagnosis of dysplasia is rendered, the condition should be treated in a fashion similar to the treatment of other potentially premalignant processes. The less severe changes should be managed according to clinical judgment, depending on the extent and duration of the lesion. In all cases, complete discontinuation of Sanguinaria-containing products and cessation of any other harmful habits such as tobacco or alcohol use is mandatory. All patients should be given careful clinical follow-up, with a biopsy of any recurrent or worsening lesion(s).

**\VISUAL{FIGURE 5-13} A, Typical white corrugated leukoplakia in the maxillary vestibule, associated with sanguinaria use. B, Mandibular vestibular lesion in the same patient.**

Infectious White Lesions and White and Red Lesions

**Oral Hairy Leukoplakia**

Oral hairy leukoplakia is a corrugated white lesion that usually occurs on the lateral or ventral surfaces of the tongue in patients with severe immunodeficiency.81,82 The most common disease associated with oral hairy leukoplakia is HIV infection.82 Oral hairy leukoplakia is reported in about 25% of adults with HIV infection but is not as common in HIV-infected children. Its prevalence reaches as high as 80% in patients with acquired immunodeficiency syndrome (AIDS).83 Epstein-Barr virus (EBV) is implicated as the causative agent in oral hairy leukoplakia.84–86 A positive correlation with decreasing cluster designation 4 (CD4) cell counts has been established in HIV-positive patients. The presence of this lesion has been associated with the subsequent development of AIDS in a large percentage of HIV positive patients.83 Hairy leukoplakia has also occasionally been reported in patients with other immunosuppressive conditions, such as patients undergoing organ transplantation and patients undergoing prolonged steroid therapy.87–89 Rare cases may occur in immunocompetent persons after topical steroid therapy.90,91

**TYPICAL FEATURES**

Oral hairy leukoplakia most commonly involves the lateral border of the tongue but may extend to the ventral or dorsal surfaces. Lesions on the tongue are usually corrugated and may have a shaggy or frayed appearance, mimicking lesions caused by tongue chewing (Figure 5-14). Oral hairy leukoplakia may also present as a plaquelike lesion and is often bilateral. Histopathologic examination of the epithelium reveals severe hyperparakeratosis with an irregular surface, acanthosis with superficial edema, and numerous koilocytic cells (virally affected

**\VISUAL{FIGURE 5-14} Bilateral linear leukoplakic lesions on the dorsolateral tongue, suggestive of oral hairy leukoplakia. (Courtesy of Dr. Parnell Taylor, Riverton, Wyoming)**
“balloon” cells) in the spinous layer. The characteristic microscopic feature is the presence of homogeneous viral nuclear inclusions with a residual rim of normal chromatin. The definitive diagnosis can be established by demonstrating the presence of EBV through in situ hybridization, electron microscopy, or polymerase chain reaction (PCR).

**DIFFERENTIAL DIAGNOSIS**

It is important to differentiate this lesion from other clinically similar entities such as hyperplastic candidiasis, idiopathic leukoplakia, leukoplakia induced by tongue chewing, tobacco-associated leukoplakia, lichen planus, lupus erythematosus, WSN, and verrucous leukoplakia. Since oral hairy leukoplakia is considered to be highly predictive of the development of AIDS, differentiation from other lesions is critical.

**TREATMENT AND PROGNOSIS**

No treatment is indicated. The condition usually disappears when antiviral medications such as zidovudine, acyclovir, or gancyclovir are used in the treatment of the HIV infection and its complicating viral infections. Topical application of podophyllin resin or tretinoin has led to short-term resolution of the lesions, but relapse is often seen. The probability of patients developing AIDS was found to be 48% at 16 months and as high as 83% at 31 months after the initial diagnosis of oral hairy leukoplakia.

<table>
<thead>
<tr>
<th>TABLE 5-1 Classification of Oral Candidiasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
</tr>
<tr>
<td>Pseudomembranous</td>
</tr>
<tr>
<td>Atrophic (erythematous)</td>
</tr>
<tr>
<td>Antibiotic stomatitis</td>
</tr>
<tr>
<td>Chronic</td>
</tr>
<tr>
<td>Atrophic</td>
</tr>
<tr>
<td>Denture sore mouth</td>
</tr>
<tr>
<td>Angular cheilitis</td>
</tr>
<tr>
<td>Median rhomboid glossitis</td>
</tr>
<tr>
<td>Hypertrophic/hyperplastic</td>
</tr>
<tr>
<td>Candidal leukoplakia</td>
</tr>
<tr>
<td>Papillary hyperplasia of the palate (see denture sore mouth)</td>
</tr>
<tr>
<td>Median rhomboid glossitis (nodular)</td>
</tr>
<tr>
<td>Multifocal</td>
</tr>
<tr>
<td>Mucocutaneous</td>
</tr>
<tr>
<td>Syndrome associated</td>
</tr>
<tr>
<td>Familial +/- endocrine candidiasis syndrome</td>
</tr>
<tr>
<td>Myositis (thymoma associated)</td>
</tr>
<tr>
<td>Localized</td>
</tr>
<tr>
<td>Generalized (diffuse)</td>
</tr>
<tr>
<td>Immunocompromise (HIV) associated</td>
</tr>
</tbody>
</table>

**Candidiasis**

“Candidiasis” refers to a multiplicity of diseases caused by a yeastlike fungus, Candida, and is the most common oral fungal infection in humans. The various diseases are classified in Table 5-1 according to onset and duration (acute or chronic); clinical features, including color (erythematous/atrophic); location (median rhomboid glossitis, denture stomatitis, multifocal candidiasis, and angular cheilitis); the presence of skin lesions as well as oral lesions (mucocutaneous); and association with an immunocompromised host (HIV associated). Other clinical features include a hyperplastic or hypertrophic appearance (papillary hyperplasia of the palate, candidal leukoplakia, and hyperplastic median rhomboid glossitis). Candida is predominantly an opportunistic infectious agent that is poorly equipped to invade and destroy tissue. The role of Candida as opportunistic invader versus etiologic agent in patients with oral white lesions has not been clearly established. However, the demonstration of the catalytic role of some Candida strains in endogenous cellular nitrosamine production, the statistically significant association of certain strains with dysplastic red and white lesions (speckled leukoplakia), and the hyperplastic effects on epithelium of Candida in vitro indicate that Candida may be a carcinogen or promoting agent, rather than only an innocuous opportunistic infectious entity.

**ACUTE PSEUDOMEMBRANOUS CANDIDIASIS (THRUSH)**

**Clinical Features.** Thrush is the prototype of the oral infections caused by Candida. It is a superficial infection of the outer layers of the epithelium, and it results in the formation of patchy white plaques or flecks on the mucosal surface (Figure 5-15, A). Removal of the plaques by gentle rubbing or scraping usually reveals an area of erythema or even shallow ulceration. Because of their prevalence, characteristic appearance, and ease of removal, the lesions of thrush are easily recognized, and a diagnosis of thrush is frequently made on the basis of the appearance of the lesion. A smear demonstrating a yeast or myelin is helpful when the diagnosis is uncertain.

Thrush is seen in children and in adults of all ages whenever the number of Candida organisms in the oral cavity increases significantly. When Candida is reduced or eliminated by the administration of antifungal agents, the lesions of thrush rapidly disappear. Transient episodes of thrush may occur as isolated phenomena, with lesions that disappear spontaneously with minimal or no treatment. These episodes are usually unrelated to any recognized predisposing factor and are common in neonates and young children. Alternatively, the lesions may promptly recur following treatment, suggesting the persistence of a predisposing factor, as is often seen in adult patients with candidiasis.

The typical lesions in infants are described as soft white adherent patches on the oral mucosa. The intraoral lesions are generally painless and can be removed with little difficulty. In the adult, inflammation, erythema, and painful eroded areas are more often associated with this disease, and the typical
Red and White Lesions of the Oral Mucosa

Pearly white plaquelike lesions are relatively inconspicuous at times. Any mucosal surface may be involved, and erythematous or white areas often develop beneath partial or complete dentures. The lesions may involve the entire oral mucosa (see Figure 5-15, B) or may involve relatively localized areas where normal cleansing mechanisms are poor.

A prodromal symptom of a rapid onset of a bad taste and the loss of taste discrimination is described by some adults. A burning sensation of the mouth and throat may also precede the appearance of the white pseudomembranous lesions. Symptoms of this type in a patient receiving broad-spectrum antibiotics are strongly suggestive of thrush or other forms of oral candidiasis. Patients with immunodeficiencies, such as those suffering from AIDS or hematologic malignancies, are also especially susceptible to this form of candidiasis.

The differential diagnosis of thrush includes food debris, habitual cheek biting, and rarely, a genetically determined epithelial abnormality such as white sponge nevus.

**Causative Organism and Frequency.** The yeastlike fungus that causes thrush and other manifestations of candidiasis occurs in both yeast and mycelial forms in the oral cavity. The organism grows by a budding of the yeast cells to form germ tubes and individual hyphal elements, which undergo limited peripheral branching to form a pseudomycelium. These phenomena can be demonstrated in smears and tissue sections and form the basis for confirmatory laboratory diagnostic tests for candidiasis.

*Candida* species are normal inhabitants of the oral flora of many individuals, but are present in the mouth of the healthy carrier in a low concentration of 200 to 500 cells per milliliter of saliva. At this concentration, the organism cannot usually be identified by direct microscopic examination of smears from the oral mucosa, and its presence can be demonstrated only by inoculation onto a selective medium such as Sabouraud agar. Saliva samples give a carrier rate of 20 to 30% for healthy young adults whereas imprint cultures, which sample colonized sites rather than detached cells and organisms in the mixed saliva, give a figure as high as 44%. Imprint cultures suggest that the papillae of the posterior oral surface of the tongue are the primary colonization site in the oral cavity of healthy dentate carriers and that other areas are contaminated or secondarily colonized from this site.

The asymptomatic carrier state is affected by a number of known factors, including the immune status of the host, the strain of *Candida*, the local oral environment, smoking, prior use of antibiotics, and the general health of the host. The carrier state is more prevalent in diabetic individuals, and the density of *Candida* at various oral sites is also increased in persons with diabetes. As reported by Guggenheimer and colleagues, diabetic patients with clinical features of candidiasis were more likely to have a longer duration of insulin-dependent diabetes mellitus (IDDM), to have poorer glycemic control, and to experience the complications of nephropathy and retinopathy. The wearing of removable prosthetic appliances is also associated with higher asymptomatic carrier prevalence rates. Importantly, simple measures to improve the oral health of the patient will reduce the rate of *Candida* colonization of the oral mucosa and denture.

Because *Candida* spp are normal oral inhabitants, thrush and other forms of oral candidiasis may be classified as specific endogenous infections. A variety of species of *Candida* have been isolated from carriers and from patients with candidiasis. *Candida albicans*, *Candida tropicalis*, and *Candida glabrata* account for over 80% of medical isolates; *Candida parapsilosis*, *Candida guilliermondii*, *Candida krusei*, and *Candida pseudotropicalis* are also recognized as pathogens. Candidiasis in HIV-positive patients is often associated with a shift in species, from *Candida albicans* to *Candida glabrata* and *Candida krusei*. The particular species involved with a given oral infection is generally not thought to be of any significance, but *Candida albicans* is most commonly found in thrush, and several subtypes of this species have been implicated as cocarcinogens in speckled leukoplakia. Severity and refractoriness of *Candida* infection to treatment possibly depend more on the site of involvement and on predisposing factors.
factors than on properties of the infecting species. While certain phenotypic characteristics such as tissue invasion may give strains of *Candida* a competitive advantage in the oral cavity, it is the host's immunocompetence that ultimately determines whether clearance, colonization, or candidiasis occurs. Like other microorganisms involved in endogenous infections, *Candida* spp are of low virulence, are not usually considered contagious, and are involved in mucosal infection only where there is a definite local or systemic predisposition to their enhanced reproduction and invasion.

**Predisposing Factors.** The following predisposing factors for oral candidiasis have been defined by clinical observation:

1. Marked changes in oral microbial flora (due to the use of antibiotics [especially broad-spectrum antibiotics], excessive use of antibacterial mouth rinses, or xerostomia).
2. Chronic local irritants (dentures and orthodontic appliances)
3. Administration of corticosteroids (aerosolized inhalant and topical agents are more likely to cause candidiasis than systemic administration)
4. Poor oral hygiene
5. Pregnancy
6. Immunologic deficiency
   — congenital or childhood (chronic familial mucocutaneous candidiasis ± endocrine candidiasis syndrome [hypoparathyroidism, hypoadrenocorticism], and immunologic immaturity of infancy)
   — acquired or adult (diabetes, leukemia, lymphomas, and AIDS)
   — iatrogenic (from cancer chemotherapy, bone marrow transplantation, and head and neck radiation)
7. Malabsorption and malnutrition

So important are these predisposing factors in the etiology of this infection that it is extremely rare to find a case of oral candidiasis in which one or more of these factors cannot be identified. A diagnosis of thrush should always be followed by a search for a possible undiagnosed medical disorder, a review of the patient's medications, and a search for some locally acting predisposing factor such as a denture.

Xerostomia and chronic local irritants may alter the oral mucous membranes, predisposing them to colonization and invasion. Shifts in the bacterial flora often accompany these situations and provide an opportunity for *Candida* spp to increase. Radiation to the head and neck also affects the oral mucous membranes and produces xerostomia. In Sjögren's syndrome, sarcoidosis, and other diseases of the salivary glands, xerostomia often develops gradually and is tolerated by the patient until superinfection with *Candida* develops. The mucosal lesions, pain, and associated symptoms of thrush then cause the patient to seek medical or dental care.

Knowledge of the ecology and epidemiology of *Candida* in the human mouth has increased substantially in recent years, particularly in regard to the attachment of the organism to oral mucosal surfaces. *Candida* colonization and infection depend on the initial ability of the organism to adhere to host surfaces. In immunocompromised hosts, adhesion varies significantly among species of *Candida*. Also, the quality of the epithelial cells in immunocompromised (HIV-positive) patients, including the cells' receptivity to *Candida*, may play a role in increasing the oral concentration of yeast.

**Histologic Features.** Microscopic examination of the lesions of thrush reveals a localized superficial inflammatory reaction, with hyperparakeratosis and ulceration of the surface. The ulcer is covered with a fibrinoid exudate, in which are found large numbers of yeast and pseudohyphae. The fungi rarely penetrate below this superficial layer. This pseudomembrane imparts the characteristic white-flecked appearance to the mucosal lesions. Thrush is correctly described as an acute pseudomembranous candidiasis.

**ACUTE ATROPHIC CANDIDIASIS**

Acute atrophic candidiasis presents as a red patch of atrophic or erythematous raw and painful mucosa, with minimal evidence of the white pseudomembranous lesions observed in thrush. Antibiotic sore mouth, a common form of atrophic candidiasis, should be suspected in a patient who develops symptoms of oral burning, bad taste, or sore throat during or after therapy with broad-spectrum antibiotics. Patients with chronic iron deficiency anemia may also develop atrophic candidiasis (Figure 5-16).

**CHRONIC ATROPHIC CANDIDIASIS**

Chronic atrophic candidiasis includes denture stomatitis (denture sore mouth), angular cheilitis, and median rhomboid glossitis.

**Denture Stomatitis (Denture Sore Mouth).** Denture stomatitis is a common form of oral candidiasis that manifests as a diffuse inflammation of the maxillary denture-bearing areas and that is often (15 to 65% of cases) associated with angular cheilitis.

**FIGURE 5-16** A patient with a history of chronic iron deficiency anemia developed red, raw, and painful areas of the mucosa, diagnosed as acute atrophic candidiasis.
At least 70% of individuals with clinical signs of denture stomatitis exhibit fungal growth, and this condition most likely results from yeast colonization of the oral mucosa, combined with bacterial colonization.\textsuperscript{112} Candida spp act as an endogenous infecting agent on tissue predisposed by chronic trauma to microbial invasion.\textsuperscript{113} Lesions of chronic atrophic candidiasis have also been frequently reported in HIV-positive and AIDS patients.\textsuperscript{113}

Three progressive clinical stages of denture sore mouth have been described.\textsuperscript{114,115} The first stage consists of numerous palatal petechiae (Figure 5-17, A). The second stage displays a more diffuse erythema involving most (if not all) of the denture-covered mucosa (see Figure 5-17, B and C). The third stage includes the development of tissue granulation or nodularity (papillary hyperplasia) (see Figure 5-17, D), commonly involving the central areas of the hard palate and alveolar ridges.

Antifungal treatment will modify the bright red appearance of denture sore mouth and papillary hyperplasia specifically but will not resolve the basic papillomatous lesion, especially if the lesions have been present for more than 1 year. Antifungal therapy and cessation of denture wearing usually is advisable before surgical excision since elimination of the mucosal inflammation often reduces the amount of tissue that needs to be excised.

Yeast attached to the denture plays an important etiologic role in chronic atrophic candidiasis.\textsuperscript{116} The attachment of yeast to the patient’s appliances is increased by mucus and serum and decreased by the presence of salivary pellicle, suggesting an explanation for the severity of candidiasis in xerostomic patients. Rinsing the appliance with a dilute (10%) solution of household bleach, soaking it in boric acid, or applying nystatin cream before inserting the denture will eliminate the yeast. Disinfection of the appliance is an important part of the treatment of denture sore mouth. Soft liners in dentures provide a porous surface and an opportunity for additional mechanical locking of plaque and yeast to the appliance. In general, soft liners are considered to be an additional hazard for patients who are susceptible to oral candidiasis.

Denture sore mouth is rarely found under a mandibular denture. One possible explanation for this is that the negative pressure that forms under the maxillary denture excludes salivary antibody from this region, and yeast may reproduce, undisturbed, in the space between the denture and mucosa. The closer adaptation of the maxillary denture and palate may also bring the large number of yeasts adhering to the denture surface into contact with the mucosa.

Angular Cheilitis. Angular cheilitis is the term used for an infection involving the lip commissures (Figure 5-18). The majority of cases are Candida associated and respond to the patient’s appliances is increased by mucus and serum and decreased by the presence of salivary pellicle, suggesting an explanation for the severity of candidiasis in xerostomic patients. Rinsing the appliance with a dilute (10%) solution of household bleach, soaking it in boric acid, or applying nystatin cream before inserting the denture will eliminate the yeast. Disinfection of the appliance is an important part of the treatment of denture sore mouth. Soft liners in dentures provide a porous surface and an opportunity for additional mechanical locking of plaque and yeast to the appliance. In general, soft liners are considered to be an additional hazard for patients who are susceptible to oral candidiasis.

Denture sore mouth is rarely found under a mandibular denture. One possible explanation for this is that the negative pressure that forms under the maxillary denture excludes salivary antibody from this region, and yeast may reproduce, undisturbed, in the space between the denture and mucosa. The closer adaptation of the maxillary denture and palate may also bring the large number of yeasts adhering to the denture surface into contact with the mucosa.

Angular Cheilitis. Angular cheilitis is the term used for an infection involving the lip commissures (Figure 5-18). The majority of cases are Candida associated and respond

\[ \text{Angular Cheilitis. Angular cheilitis is the term used for an infection involving the lip commissures (Figure 5-18). The majority of cases are Candida associated and respond} \]
promptly to antifungal therapy. There is frequently a coex-istent denture stomatitis, and angular cheilitis is uncom-mon in patients with a natural dentition. Other possible eti-ologic cofactors include reduced vertical dimension; a nutritional deficiency (iron deficiency anemia and vitamin B or folic acid deficiency) sometimes referred to as perlèche; and (more rarely) diabetes, neutropenia, and AIDS, as well as co-infection with *Staphylococcus* and beta-hemolytic *Streptococcus*. More-extensive desquamative lesions affecting the full width of the lip and sometimes extending to the adjacent skin are associated with habitual lip sucking and chronic *Candida* infection.

**Median Rhomboid Glossitis.** Erythematous patches of atrophic papillae located in the central area of the dorsum of the tongue are considered a form of chronic atrophic candidiasis (Figure 5-19). When these lesions become more nodular, the condition is referred to as hyperplastic median rhomboid glossitis. These lesions were originally thought to be developmental in nature but are now considered to be a manifestation of chronic candidiasis.

**CHRONIC HYPERPLASTIC CANDIDIASIS**

Chronic hyperplastic candidiasis (CHC) includes a variety of clinically recognized conditions in which mycelial invasion of the deeper layers of the mucosa and skin occurs, causing a proliferative response of host tissue (Figure 5-20).117

*Candidal leukoplakia* is considered a chronic form of oral candidiasis in which firm white leathery plaques are detected on the cheeks, lips, palate, and tongue (Figure 5-21). The differ-entiation of candidal leukoplakia from other forms of leukoplakia is based on finding periodic acid–Schiff (PAS)–positive hyphae in leukoplakic lesions. CHC also occurs as part of chronic mucocutaneous candidiasis, often with identifiable predisposing immunologic or endocrine abnormalities. These patients develop similar lesions around the nails and other skin sites or alternatively develop only isolated oral lesions. CHC also occurs on the dorsum of the tongue and may resemble median rhomboid glossitis (Figure 5-22).

Approximately 10% of oral leukoplakias satisfy the clinical and histologic criteria for CHC.118 Epithelial dysplasia occurs four to five times more frequently in candidal (speckled) leukoplakia than in leukoplakia in general119 and has been reported in as many as 50% of cases of candidal (speckled) leukoplakia in some series.120 *Candida* is known to cause epithelial proliferation, and this high number of cases of dys-plasia may be exaggerated because of the induction of inflam-matory or atypical (reactive) changes in the epithelium (ie, changes that do not constitute actual dysplasia). However, dys-plastic and carcinomatous changes are more common in speckled leukoplakia than in homogeneous leukoplakia.121

**CHRONIC MULTIFOCAL CANDIDIASIS**

Patients may present with multiple areas of chronic atrophic candidiasis. These are most often seen in immunocompro-mised individuals or in patients with predisposing factors such as ill-fitting dentures. The changes frequently affect the dor-
Red and White Lesions of the Oral Mucosa

Persistent infection with 
Candida usually occurs as a result of a defect in cell-mediated immunity or may be associated with iron deficiency. Hyperplastic mucocutaneous lesions, localized granulomas, and adherent white plaques on affected mucous membranes are the prominent lesions that identify chronic mucocutaneous candidiasis (CMC) (Figure 5-24). In many cases, persistent and significant predisposing factors can be identified. Two categories of CMC have been described: (1) syndrome-associated CMC and (2) localized and diffuse CMC. Syndrome-associated CMC is further categorized as either familial or chronic. The familial form, candidiasis endocrinopathy syndrome (CES), is a rare autosomal recessive disorder characterized by an onset of CMC during infancy or early childhood, associated with the appearance of hypoparathyroidism, hypoadrenocorticism, and other endocrine anomalies. Patients develop persistent oral candidiasis and hyperplastic infections of the nail folds at an early age. Some patients also have low serum iron and iron-binding capacity. The other syndrome-associated form is chronic candidiasis associated with thymoma, which appears with other autoimmune abnormalities such as myasthenia gravis, polymyositis, bullous lichen planus, and hypogammaglobulinemia.

Localized CMC is a variant associated with chronic oral candidiasis and lesions of the skin and nails. Lesions usually begin within the first two decades of life. The diffuse variant is characterized by randomly occurring cases of severe mucocutaneous candidiasis with widespread skin involvement and development of Candida granulomas. It is often associated with other opportunistic fungal and bacterial infections. A majority of patients are iron deficient.

Both oral and cutaneous lesions of CMC can be controlled by the continuous use of systemic antifungal drugs; once treatment is discontinued, however, the lesions rapidly reappear.

IMMUNOCOMPROMISED (HIV)-ASSOCIATED CANDIDIASIS

Oral candidiasis is the most frequent opportunistic infection associated with immunocompromised individuals. The role of weakened specific immune defense mechanisms is apparent from the fact that patients who are on immunosuppressive drug regimens or who have HIV infection, cancer, or hematologic malignancies have an increased susceptibility to oral candidiasis. This supports an important role for T lymphocytes in immunity to Candida, especially in regard to chronic candidiasis. Host factors affecting the adherence of Candida to mucosal cells (such as salivary ABO antigens), as well as variation in the virulence and invasiveness of the fungal organism, also play a role.

The possible importance of local immunoglobulin A (IgA) as a first line of protection against acute candidiasis has been emphasized. Salivary IgA (but not immunoglobulin G [IgG]) affects the adherence of Candida to buccal epithelial cells, and levels of Candida-specific IgA are elevated in the saliva of healthy patients with chronic oral candidiasis. In HIV-infected patients who develop oral candidiasis, the level of salivary anti-Candida IgG is increased while serum and

**FIGURE 5-21** A, Candidal leukoplakia, a chronic form of candidiasis in which firm red white plaques form, most often in the cheeks. B, Occasionally, the plaques develop in the palate opposite a tongue lesion (kissing lesions). (Courtesy of Dr. Robert Howell, West Virginia University, School of Dentistry)

**FIGURE 5-22** Chronic hyperplastic candidiasis occurs on the dorsum of the tongue as a mammilated form of median rhomboid glossitis.
FIGURE 5-23  A, B, and C, Chronic multifocal candidiasis presents with multiple areas of chronic atrophic candidiasis, usually involving the palate (midline and under a denture) (A), the commissures (B), and the dorsum of the tongue (C). The tongue lesion is almost healed after 14 days of nystatin therapy. The patient had poor oral hygiene and was a heavy smoker but was not immunocompromised.

FIGURE 5-24  Chronic mucocutaneous candidiasis manifests as hyperplastic mucocutaneous lesions including granulomas and nodules. A, Localized granulomas and nodules on the tongue. B, The same condition, affecting the skin. C, Adherent white plaques that represent speckled leukoplakia.
IDIOPATHIC “TRUE” LEUKOPLAKIA

This helps explain the strong association between candidiasis and HIV positivity, especially in those who are about to develop full-blown AIDS.

TREATMENT OF ORAL CANDIDIASIS

A variety of topical and systemically administered medications are now available to supplement the older polyene antifungal antibiotics nystatin and amphotericin B. An imidazole derivative ( clotrimazole) is available for topical use. Systemic therapy includes the use of any one of these three: ketoconazole, itraconazole, and fluconazole. Fluconazole and amphotericin B may be used intravenously for the treatment of the resistant lesions of CMC and systemic candidiasis.

The majority of acute oral Candida infections respond rapidly to topical nystatin and will not recur, provided that the predisposing factors have also been eliminated. Seven to 21 days’ use of a nystatin rinse three to four times daily is usually adequate although some resistant cases may require a second course of treatment. Nystatin in cream form may also be applied directly to the denture or to the corners of the mouth. Patients for whom predisposing factors such as xerostomia and immunodeficiency cannot be eliminated may need either continuous or repeated treatment to prevent recurrences. Clotrimazole troches can also be used for treatment of oral lesions. The consumption of yogurt two to three times per week and improved oral hygiene can also help, especially if underlying predisposing factors cannot be eliminated.

Better patient compliance and more effective treatment of both acute and chronic candidiasis can usually be attained by a once-daily dose of 200 mg of ketoconazole, 100 mg of fluconazole, or itraconazole oral suspension (100 to 200 mg/d) for 2 weeks. When these medications are used for this short period, side effects such as increased liver enzymes, abdominal pain, and pruritus are rare. Vaginal candidiasis responds to ketoconazole and fluconazole even more rapidly than does oral candidiasis, and the likelihood of re-infection is reduced by the control of Candida at various sites. Fluconazole is more effective than ketoconazole, but its frequent use can lead to the development of resistance to the drug. Fluconazole therapy for oral candidiasis associated with HIV infection often results in the development of resistance to fluconazole. Itraconazole can be substituted for fluconazole in resistant patients, but fluconazole is still the mainstay of therapy for HIV-associated candidiasis.

Fluconazole interacts with a number of other medications and must be prescribed with care for patients who are using anticoagulants, phenytoin, cyclosporine, and oral hypoglycemic agents. The simultaneous administration of ketoconazole (or the related antifungal itraconazole) and cisapride or antihistamines (terfenadine and astemizole) is associated occasionally with ventricular arrhythmias and other serious cardiovascular events.

Mucous Patches

A superficial grayish area of mucosal necrosis is seen in secondary syphilis; this lesion is termed a “mucous patch.” Secondary syphilis usually develops within 6 weeks after the primary lesion and is characterized by diffuse maculopapular eruptions of the skin and mucous membranes. On the skin, these lesions may present as macules or papules. In the oral cavity, the lesions are usually multiple painless grayish-white plaques overlying an ulcerated necrotic surface. The lesions occur on the tongue, gingiva, palate, and buccal mucosa. Associated systemic signs and symptoms (including fever, sore throat, general malaise, and headache) may also be present. The mucous patches of the secondary stage of syphilis resolve within a few weeks but are highly infective because they contain large numbers of spirochetes.

Parulis

A parulis, or gumboil, is a localized accumulation of pus located with the gingival tissues (Figure 5-25). It originates from either an acute periapical abscess or an occluded periodontal pocket. The cortical bone is destroyed by the inflammatory process, and the gumboil often appears as a yellowish white bump on the gingiva. The lesion is usually painful, and pain relief occurs when the “boil” ruptures or drains spontaneously. To permanently resolve this problem, the nonvital tooth or periodontal abscess must be treated.

IDIOPATHIC “TRUE” LEUKOPLAKIA

Leukoplakia is a white oral precancerous lesion with a recognizable risk for malignant transformation. In 1972, the World Health Organization (WHO) defined a precancerous lesion as a “morphologically altered tissue in which cancer is more likely to occur than in its apparently normal counterpart.” The most commonly encountered and accepted precancerous lesions in the oral cavity are leukoplakia and erythroplakia.

Leukoplakia is currently defined as “a white patch or plaque that cannot be characterized clinically or pathologically as any other disease” (WHO, 1978). This definition has no histologic connotation and is used strictly as a clinical description. The risk of malignant transformation varies according to the histologic and clinical presentation, but the total lifetime risk of malignant transformation is estimated to be 4 to 6%.

FIGURE 5-25 The elevated white nodule above the maxillary right canine is a parulis, or gumboil.
Etiology

A number of locally acting etiologic agents, including tobacco, alcohol, candidiasis, electrogalvanic reactions, and (possibly) herpes simplex and papillomaviruses, have been implicated as causative factors for leukoplakia. True leukoplakia is most often related to tobacco usage; more than 80% of patients with leukoplakia are smokers. The development of leukoplakia in smokers also depends on dose and on duration of use, as shown by heavier smokers having a more frequent incidence of lesions than light smokers. Cessation of smoking often results in partial to total resolution of leukoplakic lesions.

Smokeless tobacco is also a well-established etiologic factor for the development of leukoplakia; however, the malignant transformation potential of smokeless tobacco–induced lesions is much lower than that of smoking-induced lesions.

Alcohol consumption alone is not associated with an increased risk of developing leukoplakia, but alcohol is thought to serve as a promoter that exhibits a strong synergistic effect with tobacco, relative to the development of leukoplakia and oral cancer.

In addition to tobacco, several other etiologic agents are associated with leukoplakia. Sunlight (specifically, ultraviolet radiation) is well known to be an etiologic factor for the formation of leukoplakia of the vermilion border of the lower lip. Candida albicans is frequently found in histologic sections of leukoplakia and is consistently (60% of cases) identified in nodular leukoplakias but rarely (3%) in homogeneous leukoplakias. The terms “candidal leukoplakia” and “hyperplastic candidiasis” have been used to describe such lesions.

Whether Candida constitutes a cofactor either for excess production of keratin or for dysplastic or malignant transformation is unknown (see previous section on candidiasis). Human papillomavirus (HPV), particularly subtypes HPV-16 and HPV-18, have been identified in some oral leukoplakias. The role of this virus remains questionable, but there is evidence that HPV-16 may be associated with an increased risk of malignant transformation. Of interest, there is some evidence that oral leukoplakia in nonsmokers has a greater risk for malignant transformation than oral leukoplakia in smokers.

Clinical Features

The incidence of leukoplakia varies by geographic location and patients’ associated habits. For example, in locations where smokeless tobacco is frequently used, leukoplakia appears with a higher prevalence. Leukoplakia is more frequently found in men, can occur on any mucosal surface, and infrequently causes discomfort or pain (Figure 5-26). Leukoplakia usually occurs in adults older than 50 years of age. Prevalence increases rapidly with age, especially for males, and 8% of men older than 70 years of age are affected. Approximately 70% of oral leukoplakia lesions are found on the buccal mucosa, vermilion border of the lower lip, and gingiva. They are less common on the palate, maxillary mucosa, retromolar area, floor of the mouth, and tongue. However, lesions of the tongue and the floor of the mouth account for more than 90% of cases that show dysplasia or carcinoma.

Subtypes

Many varieties of leukoplakia have been identified.

“Homogeneous leukoplakia” (or “thick leukoplakia”) refers to a usually well-defined white patch, localized or extensive, that is slightly elevated and that has a fissured, wrinkled, or corrugated surface (Figure 5-27). On palpation, these lesions may feel leathery to “dry, or cracked mud-like.”

Nodular (speckled) leukoplakia is granular or nonhomogeneous. The name refers to a mixed red-and-white lesion in which keratotic white nodules or patches are distributed over an atrophic erythematous background (Figure 5-28). This type of leukoplakia is associated with a higher malignant transformation rate, with up to two-thirds of the cases in some series showing epithelial dysplasia or carcinoma.

“Verrucous leukoplakia” or “verruciform leukoplakia” is a term used to describe the presence of thick white lesions with papillary surfaces in the oral cavity (Figure 5-29). These lesions are usually heavily keratinized and are most often seen in older adults in the sixth to eighth decades of life. Some of these lesions may exhibit an exophytic growth pattern.

Proliferative verrucous leukoplakia (PVL) was first described in 1985. The lesions of this special type of leukoplakia have been described as extensive papillary or verrucoid white plaques that tend to slowly involve multiple mucosal sites in the oral cavity and to inexorably transform into squamous cell carcinomas over a period of many years (Figure 5-30).

Histopathologic Features

The most important and conclusive method of diagnosing leukoplakic lesions is microscopic examination of an adequate biopsy specimen. Benign forms of leukoplakia are characterized by variable patterns of hyperkeratosis and chronic inflammation. The association between the biochemical process of hyperkeratosis and malignant transformation remains an enigma.
However, the increased risk for malignant transformation and thus “premalignant designation” is documented in Table 5–2.143 Waldron and Shafer, in a landmark study of over 3,000 cases of leukoplakia, found that 80% of the lesions represented benign hyperkeratosis (ortho- or parakeratin) with or without a thickened spinous layer (acanthosis).140 About 17% of the cases were epithelial dysplasias or carcinomas in situ. The dysplastic changes typically begin in the basal and parabasal zones of the epithelium. The higher the extent of epithelial involvement, the higher the grade of dysplasia. Dysplastic alterations of the epithelium are characterized by enlarged and hyperchromatic nuclei, cellular and nuclear pleomorphism, premature keratinization of individual cells, an increased nucleocytoplasmic ratio, increased and abnormal mitotic activity, and a generalized loss of cellular polarity and orientation (Figure 5-32). When the entire thickness of the epithelium is involved (“top-to-bottom” change), the term “carcinoma in situ” (CIS) is used. There is no invasion seen in CIS. Only 3% of the leukoplakic lesions examined had evolved into invasive squamous cell carcinomas.140

**Diagnosis and Management**

A diagnosis of leukoplakia is made when adequate clinical and histologic examination fails to reveal an alternative diagnosis and when characteristic histopathologic findings for leukoplakia are present. Important clinical criteria include location, appearance, known irritants, and clinical course. Many white lesions can mimic leukoplakia clinically and should be ruled out before a diagnosis of leukoplakia is made. These include lichen planus, lesions caused by cheek biting, frictional keratosis, smokeless tobacco–induced keratosis, nicotinic stomatitis, leukoedema, and white sponge nevus.140,141

**FIGURE 5-27** Homogeneous leukoplakia as it appears at different sites: A, the lower lip; B, the floor of mouth; and C, the gingiva.

**FIGURE 5-28** Nodular or speckled leukoplakia appears as a red velvety plaque with associated white spots or papules on the lateral border of the tongue. The nodular ulcerated area anterior to the red plaque is a spindle cell squamous cell carcinoma.
If a leukoplakic lesion disappears spontaneously or through the elimination of an irritant, no further testing is indicated. For the persistent lesion, however, the definitive diagnosis is established by tissue biopsy. Adjunctive methods such as vital staining with toluidine blue and cytobrush techniques are helpful in accelerating the biopsy and/or selecting the most appropriate spot at which to perform the biopsy.

Toluidine blue staining uses a 1% aqueous solution of the dye that is decolorized with 1% acetic acid. The dye binds to dysplastic and malignant epithelial cells with a high degree of accuracy. The cytobrush technique uses a brush with firm bristles that obtain individual cells from the full thickness of the stratified squamous epithelium; this technique is significantly more accurate than other cytologic techniques used in the oral cavity. It must be remembered that staining and cytobrush techniques are adjuncts and not substitutes for an incisional biopsy. When a biopsy has been performed and the lesion has not been subsequently removed, another biopsy is recommended if and when changes in signs or symptoms occur.

### TABLE 5–2 Malignant Transformation in Oral Leukoplakia

<table>
<thead>
<tr>
<th>Investigator (Country)</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Malignancies (%)</th>
<th>Yr Observed (Avg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silverman (India)</td>
<td>1976</td>
<td>4,762</td>
<td>0.13</td>
<td>2</td>
</tr>
<tr>
<td>Gupta (India [Bhavnagar])</td>
<td>1980</td>
<td>360</td>
<td>0.30</td>
<td>1–10 (7)</td>
</tr>
<tr>
<td>Gupta (India [Ernakulam])</td>
<td>1980</td>
<td>410</td>
<td>2.20</td>
<td>1–10 (7)</td>
</tr>
<tr>
<td>Roed-Petersen (Denmark)</td>
<td>1971</td>
<td>331</td>
<td>3.60</td>
<td>&gt;1</td>
</tr>
<tr>
<td>Einhorn (Sweden)</td>
<td>1967</td>
<td>782</td>
<td>4.00</td>
<td>1–20</td>
</tr>
<tr>
<td>Pindborg (Denmark)</td>
<td>1968</td>
<td>248</td>
<td>4.40</td>
<td>1–9</td>
</tr>
<tr>
<td>Kramer (England)</td>
<td>1969</td>
<td>187</td>
<td>4.80</td>
<td>1–16</td>
</tr>
<tr>
<td>Baroczy (Hungary)</td>
<td>1977</td>
<td>670</td>
<td>5.90</td>
<td>1–30 (8.8)</td>
</tr>
<tr>
<td>Silverman (USA)</td>
<td>1968</td>
<td>117</td>
<td>6.00</td>
<td>1–11 (3.5)</td>
</tr>
<tr>
<td>Schepman (Netherlands)</td>
<td>1998</td>
<td>166</td>
<td>12.00</td>
<td>5–17 (2.7)</td>
</tr>
<tr>
<td>Silverman (USA)</td>
<td>1984</td>
<td>257</td>
<td>17.50</td>
<td>1–39 (7.2)</td>
</tr>
</tbody>
</table>

Reproduced with permission from Schepman KP et al.143

Avg = average.
Definitive treatment involves surgical excision although cryosurgery and laser ablation are often preferred because of their precision and rapid healing. Total excision is aggressively recommended when microscopic dysplasia is identified, particularly if the dysplasia is classified as severe or moderate. Most leukoplakias incur a low risk for malignant transformation. Following attempts at removal, recurrences appear when either the margins of excision are inadequate or the causative factor or habit is continued. In any event, such patients must be observed periodically because of the risk of eventual malignancy.

The use of antioxidant nutrients and vitamins have not been reproducibly effective in management. Programs have included single and combination dosages of vitamins A, C, and E; beta carotene; analogues of vitamin A; and diets that are high in antioxidants and cell growth suppressor proteins (fruits and vegetables).

### Prognosis

After surgical removal, long-term monitoring of the lesion site is important since recurrences are frequent and because additional leukoplakias may develop. In one recent series of these lesions, the recurrence rate after 3.9 years was 20%. Smaller benign lesions that do not demonstrate dysplasia should be excised since the chance of malignant transformation is 4 to 6%. For larger lesions with no evidence of dysplasia on biopsy, there is a choice between removal of the remaining lesion and follow-up evaluation, with or without local medication.

Repeated follow-up visits and biopsies are essential, particularly when the complete elimination of irritants is not likely to be achieved. In such cases, total removal is strongly advisable. Follow-up studies have demonstrated that carcinomatous transformation usually occurs 2 to 4 years after the onset of leukoplakia but that it may occur within months or after decades.

Each clinical appearance or phase of leukoplakia has a different potential for malignant transformation. Speckled leukoplakia carries the highest average transformation potential, followed by verrucous leukoplakia; homogeneous leukoplakia carries the lowest risk. For dysplastic leukoplakia, the clinician must consider the histologic grade when planning treatment and follow-up. In general, the greater the degree of dysplasia, the greater the potential for malignant change. In addition, multiple factors play a role in determining the optimum management procedure. These factors include the persistence of the lesion over many years, the development of leukoplakia in a nonsmoker, and the lesion’s occurrence on high-risk areas such as the floor of the mouth, the soft palate, the oropharynx, or the ventral surface of the tongue.

### BOWEN’S DISEASE

Bowen’s disease is a localized intraepidermal squamous cell carcinoma of the skin that may progress into invasive carcinoma over many years. Bowen’s disease also occurs on the male and female genital mucosae and (rarely) in the oral mucosa as an erythroplakic, leukoplakic, or papillomatous lesion. Bowen’s disease occurs most commonly on the skin, as a result of arsenic ingestion. It grows slowly as an enlarging erythematous patch, with little to suggest a malignant process. The histologic picture is very characteristic, with the epithelium exhibiting a significant loss of cellular polarity and orientation, increased and abnormal mitoses, multiple highly atypical hyperchromatic nuclei, and cellular pleomorphism. Individual cell keratinization at different levels of the epithelium is seen. Lesions of this type are often associated with visceral cancer.

Because of the clinical and histologic similarity between Bowen’s disease and erythroplakia (both of which can be characterized as red patches of the mucous membrane that histologically contain severely dysplastic epithelium or intraepithelial carcinoma), the question has been raised as to whether they are the same disorder. Current opinion, based on the comparison of oral erythroplakias with the oral lesions of Bowen’s disease, holds that they are separate disorders.

A nodular, benign, and virus-associated epithelial dysplasia with a histologic picture resembling Bowen’s disease (bowenoid papulosis) occurs on the genital mucosa of sexually active young adults and has been reported on multiple oral mucosal surfaces on rare occasions.

### ERYTHROPLAKIA

Erythroplakia has been defined as a “bright red velvety plaque or patch which cannot be characterized clinically or pathologically as being due to any other condition.” The word
is an adaptation of the French term “erythroplasie de Querat,” which describes a similar-appearing lesion of the glans penis with a comparable premalignant tendency. Although red lesions of the oral mucosa have been noted for many years, the use of the term “erythroplakia” in this context has been common for only about 25 years. Erythoplastic lesions are easily overlooked, and the true prevalence of the condition is unknown. Erythroplakia is far less common than leukoplakia in most histopathologic series, but this reflects the fact that leukoplakias are more likely to have biopsies performed on them and emphasizes the lack of appreciation of the clinical significance of erythroplakia since it has been proposed that most erythoplastic lesions are precursors of oral squamous cell carcinoma. A number of studies have shown that the majority of erythroplakias (particularly those located under the tongue, on the floor of the mouth, and on the soft palate and anterior tonsillar pillars) exhibit a high frequency of premalignant and malignant changes since it has been proposed that most erythoplastic lesions are precursors of oral squamous cell carcinoma. 

Although the etiology of erythroplakia is uncertain, most cases of erythroplakia are associated with heavy smoking, with or without concomitant alcohol abuse.

Clinical Features

Several clinical variants of erythroplakia have been described, but there is no generally accepted classification. Shear described “homogeneous erythroplakia, erythroplakia interspersed with patches of leukoplakia, and granular or speckled erythroplakia”; most authors consider this last category to be identical to speckled leukoplakia (Figure 5-33). Many of these lesions are irregular in outline, and some contain islands of normal mucosa within areas of erythroplakia, a phenomenon that has been attributed to the coalescence of a number of precancerous foci.

Erythroplakia occurs predominantly in older men, in the sixth and seventh decades of life. Erythroplakias are more commonly seen on the floor of the mouth, the ventral tongue, the soft palate, and the tonsillar fauces, all prime areas for the development of carcinoma. Multiple lesions may be present. These lesions are commonly described as erythematous plaques with a soft velvety texture. Almost all of the lesions are asymptomatic and therefore unlikely to be drawn to the dentist’s attention by the patient.

Histopathologic Features

Different studies have demonstrated that 80 to 90% of cases of erythroplakia are histopathologically severe epithelial dysplasia, carcinoma in situ, or invasive carcinoma. In one study, none of the cases of erythroplakia was histologically found to represent benign keratosis.

Differential Diagnosis

In view of the clinical significance of erythroplakia, its differentiation from other red inflammatory lesions of the oral mucosa is critical. Clinically similar lesions may include erythematous candidiasis, areas of mechanical irritation, denture stomatitis, vascular lesions, and a variety of nonspecific inflammatory lesions. Because localized areas of redness are not uncommon in the oral cavity, areas of erythroplakia are likely to be disregarded by the examiner, and they are often falsely determined to be a transient inflammatory response to local irritation. Differentiation of erythroplakia from benign inflammatory lesions of the oral mucosa can be enhanced by the use of a 1% solution of toluidine blue, applied topically with a swab or as an oral rinse. Although this technique was previously found to have limited usefulness in the evaluation of keratotic lesions, prospective studies of the specificity of toluidine blue staining of areas of early carcinoma contained in erythroplakic and mixed leukoplakic-erythroplakic lesions reported excellent results, with false-negative (underdiagnosis) and false-positive (overdiagnosis) rates of well below 10%.

Treatment and Prognosis

The treatment of erythroplakia should follow the same principles outlined for that of leukoplakia (see section on management of leukoplakia, above). Observation for 1 to 2 weeks
following the elimination of suspected irritants is acceptable, but prompt biopsy at that time is mandatory for lesions that persist. The toluidine blue vital staining procedure may be redone following the period of elimination of suspected irritants. Lesions that stain on this second application frequently show extensive dysplasia or early carcinoma. Epithelial dysplasia or carcinoma in situ warrants complete removal of the lesion. Actual invasive carcinoma must be treated promptly according to guidelines for the treatment of cancer. Most asymptomatic malignant erythroplakic lesions are small; 84% are ≤ 2 cm in diameter, and 42% are ≤ 1 cm.165–167 However, since recurrence and multifocal involvement is common, long-term follow-up is mandatory.

▼ ORAL LICHEN PLANUS

Oral lichen planus (OLP) is a common chronic immunologic inflammatory mucocutaneous disorder that varies in appearance from keratotic (reticular or plaquelike) to erythematous and ulcerative. About 28% of patients who have OLP also have skin lesions.173–175 The skin lesions are flat violaceous papules with a fine scaling on the surface. Unlike oral lesions, skin lesions are usually self-limiting, lasting only 1 year or less. The lack of sound epidemiologic studies and the variations in signs as well as symptoms make estimates of prevalence difficult.

Etiology and Diagnosis

The etiology of lichen planus involves a cell-mediated immunologically induced degeneration of the basal cell layer of the epithelium. Lichen planus is one variety of a broader range of disorders of which an immunologically induced degeneration of the basal cell layer of the epithelium. Lichen planus is one variety of a broader range of disorders in which both clinical and histologic similarities between lichen planus and lichenoid dermatoses and stomatitis are associated with drugs, some autoimmune disorders, and graft-versus-host reactions.179,180 Although lichen planus may manifest as a particularly well-defined and characteristic lesion, the differential diagnosis for less specific lesions is extensive. Speculated cofactors in causation, such as stress, diabetes, hepatitis C, trauma, and hypersensitivity to drugs and metals, have varying degrees of support, with the last three having the most convincing evidence.174,175,181,182 At the very least, some of these factors may add to the risk of developing OLP in susceptible patients.

As stated above, in “true” OLP a specific causative factor cannot be identified. However, clinical and microscopic changes that are consistent with OLP will often occur in response to a variety of agents (eg, drugs, chemicals, metals, and foods).174,183,184 When these manifestations take place, they are referred to as “lichenoid” reactions. When the offending agent or antigen is removed, the signs and symptoms are reversed; examples in reported cases include reactions to dental restorations, mouth rinses, antibiotics, gold injections for arthritis, and immunocompromised status such as graft-versus-host disease.174,176,183 These reactions are not to be confused with other hypersensitivity reactions such as urticaria or erythema multiforme, which differ both clinically and microscopically.

These often confusing clinical variations (Figure 5-34) mandate a thorough clinical work-up and histologic examination to rule out possible dysplasia and carcinoma. This requires not only an initial biopsy but also follow-up biopsies when changes in signs and symptoms occur.

(Because some lesions of oral lichen planus are erosive and others are bullous, this disorder is also discussed in Chapter 4. The emphasis in this chapter is on the white non-erosive non-bullous forms of lichen planus.)

Clinical Features

In general, studies of patients with OLP reveal that there is no evident genetic bias or uniform etiologic factor. The mean age of onset is the fifth decade of life, and there is clearly a female predominance. Although OLP may occur at any oral mucosal site, the buccal mucosa is the most common site. OLP may be associated with pain or discomfort, which interferes with function and with quality of life. Approximately 1% of the population may have cutaneous lichen planus. The prevalence rate of OLP ranges between 0.1 and 2.2%.27,30,173,174 The skin lesions of lichen planus have been classically described as purple, pruritic, and polygonal papules.

OLP is classified as reticular (lace-like keratotic mucosal configurations), atrophic (keratotic changes combined with mucosal erythema), or erosive (pseudomembrane-covered ulcerations combined with keratosis and erythema) and bullous (vesiculobullous presentation combined with reticular or erosive patterns).181,185 Apart from the erosive and bullous forms of the disorder, reticular OLP is quite frequently an indolent and painless lesion that is usually asymptomatic before it is identified during a routine oral examination. The clinical features of the lesions in a given patient often vary with time, as does their extent and the area of erosion of the atrophic mucosa.181

The reticular form consists of (a) slightly elevated fine whitish lines (Wickham’s striae) that produce either a lace-like pattern or a patern of fine radiating lines or (b) annular lesions. This is the most common and most readily recognized form of lichen planus. Most patients with lichen planus at some time exhibit some reticular areas. The most common sites include the buccal mucosa (often bilaterally), followed by the tongue; lips, gingivae, the floor of the mouth, and the palate are less frequently involved. Whitish elevated lesions, or papules, usually measuring 0.5 to 1.0 mm in diameter, may be seen on the well-keratinized areas of the oral mucosa. However, even large plaquelike lesions may occur on the cheek, tongue, and gingivae, and these are difficult to distinguish from leukoplakia.

Bullous lichen planus (see Chapter 4) is rare and may sometimes resemble a form of linear IgA disease.186 Atrophic lichen planus presents as inflamed areas of the oral mucosa covered by thinned red-appearing epithelium. Erosive lesions probably develop as a complication of the atrophic process when the thin epithelium is abraded or ulcerated. These lesions are invariably symptomatic, with symptoms that range from mild burning to severe pain.
Papular, plaquelike, atrophic, and erosive lesions are very frequently accompanied by reticular lesions, a search for which is an essential part of the clinical evaluation in suspected cases of lichen planus. Characteristically, the affected areas of the oral mucosa are not bound down or rendered inelastic by lichen planus, and the keratotic white lines cannot be eliminated by either stretching the mucosa or rubbing its surface. Reticular papular lesions are generally asymptomatic; atrophic, erosive, and bullous forms are generally associated with pain.

Atrophic or erosive lichen planus involving the gingivae results in desquamative gingivitis (see Figure 5-34, B), a condition characterized by bright red edematous patches that involve the full width of the attached gingivae. Lichen planus must be distinguished histologically from other diseases that cause desquamative gingivitis, such as mucous membrane pemphigoid and pemphigus. Lichen planus has occasionally been described in association with autoimmune diseases.174,177,187

**Histopathologic Features**

Three features are considered essential for the histopathologic diagnosis of lichen planus: (1) areas of hyperparakeratosis or hyperorthokeratosis, often with a thickening of the granular cell layer and a saw-toothed appearance to the rete pegs; (2) “liquefaction degeneration,” or necrosis of the basal cell layer, which is often replaced by an eosinophilic band; and (3) a dense subepithelial band of lymphocytes (Figure 5-35). Isolated epithelial cells, shrunken with eosinophilic cytoplasm and one or more pyknotic nuclear fragments (Civatte bodies), are often scattered within the epithelium and superficial lamina propria. These represent cells that have undergone apoptosis. The linear sub-basilar lymphocytic infiltration is composed largely of T cells. Immunohistochemical studies have confirmed that the T4/T8 ratio of the lymphocytes in the epithelium and lamina propria in lichenoid lesions is higher than in either normal or leukoplakic mucosa, thus providing an additional feature for distinguishing leukoplakia from a lichenoid reaction.177

**Immunofluorescent Studies**

Immunofluorescent studies of biopsy specimens from lesions of lichen planus reveal a number of features that are not seen in hematoxylin-eosin (H&E)–stained sections and that both reflect the mode of development of these lesions and aid in distinguishing lichen planus from a number of other dermatoses. Direct immunofluorescence demonstrates a shaggy band of fibrinogen in the basement membrane zone in 90 to 100% of cases.187–189 Patients also may have multiple mainly IgM-staining cytoid bodies, usually located in the dermal papilla or in the peribasalar area. These cytoid bodies are considered to be highly suggestive of lichen planus if they are present in large numbers or grouped in clusters.189

**Figure 5-34** Forms of lichen planus. A, Reticular lichen planus of the buccal mucosa. B, Atrophic lichen planus of the gingiva. C, Erosive lichen planus of the tongue.
### Differential Diagnosis

Differential diagnosis of lichen planus must consider the range of other lichenoid lesions (e.g., drug-induced lesions, contact mercury hypersensitivity, erythema multiforme, lupus erythematosus, and graft-versus-host reaction), as well as leukoplakia, squamous cell carcinoma, mucous membrane pemphigoid, and candidiasis. 

Although it does not always provide an unequivocal diagnosis, a biopsy should be carried out before treatment of the lesions, because of the tendency for corticosteroids to confuse the diagnosis. Asymptomatic reticular lichen planus is often left untreated, and biopsy is not usually performed. Biopsy of papular and plaquelike OLP should be performed to rule out dysplastic changes and leukoplakia. Biopsy is usually performed on the erosive and bullous forms, partly because they are symptomatic (and thus brought to the clinician’s attention) and partly to differentiate them from other vesiculobullous disorders.

### Clinical Course and Prognosis

The lesions of OLP appear, regress, and re-appear in a somewhat unpredictable fashion. Andreasen calculated that 41% of reticular lesions healed spontaneously whereas 12% of atrophic lesions, 7% of plaquelike lesions, and 0% of erosive lesions healed without treatment. Silverman and Griffith reported that when observed longer than 1 year, approximately 10% of a group of patients with predominantly erosive lesions had remissions. In a more recent, larger, and prospective study, Thorn and associates reported that papular and ulcerative (erosive) changes were short-term lesions whereas atrophic and plaquelike changes were characterized by many remissions and newly developing lesions. Thorn and co-workers demonstrated that long-term topical steroid and antifungal therapy had no apparent effect on the course of the disease. Numerous reports have related lichenoid lesions to a contact sensitivity to mercury and, less often, gold and food flavorings.

Removal of amalgam fillings in mercury-sensitive individuals who have contact-related lesions has almost always led to the complete resolution of the disease or at least to significant improvement.

It must be stressed that lichenoid lesions that are caused by a contact allergy to dental materials such as amalgam occur only directly opposite the restoration. In patients with lichen planus, the general removal of amalgam fillings that are not directly opposite a lesion is not justified.

The status of OLP as a premalignant condition has been debated for many years. Numerous publications have described the clinical and histopathologic follow-up of lesions (in some cases, over many decades). The occurrence of squamous cell carcinoma in most series ranges from 0.4 to 2.0% per 5-year observation period. The most recent and extensive study reported a rate of 1.5% for patients observed over 7.5 years. These rates are similar to those quoted for malignant change in leukoplakia and represent some 50 times the rate for the general population. OLP fulfills the criteria for a “premalignant” condition and was so designated at the 1984 International Seminar on Oral Leukoplakia and Associated Lesions Related to Tobacco Habits. Although malignant transformation is reported to be more likely in erosive lesions, possibly due to the exposure of deeper layers of the epithelium to oral environmental carcinogens, there appears to be no consistent clue to the identity of those lesions that are likely to become malignant. Several investigators have described a lesion (referred to as oral lichenoid dysplasia) on the basis of a defined histopathologic picture and have postulated that this lesion is an independent precancerous lesion that mimics lichen planus and represents the true precursor of malignant change in lichen planus.

There is no general agreement on the grading of lichen planus, either clinically or histopathologically. Therefore, continued surveillance, repeated biopsy, and (where possible) eradication of erosive lesions and those lesions demonstrating dysplastic changes remain the safest course. Most cases of squamous cell
candida retinoic diagnosis and management of oral and salivary gland diseases

Treatment

There is no known cure for OLP; therefore, the management of symptoms guides therapeutic approaches. Corticosteroids have been the most predictable and successful medications for controlling signs and symptoms. Topical and/or systemic corticosteroids are prescribed electively for each patient after orientation to OLP and by patient choice.178,179,185,201–203

Topical medications include high-potency corticosteroids, the most commonly used of which are 0.05% fluocinonide (Lidex) and 0.05% clobetasol (Temovate).202,203 These are frequently prescribed as pastes or as gels. The topical forms are applied daily to meet each patient’s needs. Topical steroids can be applied to the lesions with cotton swabs or (especially on the buccal mucosa) with gauze pads impregnated with steroid. In addition, extensive erosive lesions of OLP on the gingiva (desquamative gingivitis) may be treated effectively by using occlusive splints as carriers for the topical steroid. Long-term studies show no adverse systemic side effects with topical steroids, but occlusive therapy with high-potency steroids does cause systemic absorption, and patients should be carefully monitored and treated with the minimal amount of medication required to manage each individual.204 Candida overgrowth with clinical thrush may develop, requiring concomitant topical or systemic antifungal therapy. Some studies have shown that the use of an antibacterial rinse such as chlorhexidine before steroid application helps prevent fungal overgrowth.

Systemic steroids are rarely indicated for brief treatment of severe exacerbations or for short periods of treatment of recalcitrant cases that fail to respond to topical steroids.201 Systemic administration of prednisone tablets may be done with dosages varying between 40 and 80 mg daily for less than 10 days without tapering. The time and dosage regimens are determined individually, based on the patient’s medical status, severity of disease, and previous treatment responses. End points and stabilization of treatment are determined by each patient since symptoms are managed only to individual satisfaction or acceptance. Consultation with the patient’s primary care physician is important when underlying medical problems are present.204

Retinoids are also useful, usually in conjunction with topical corticosteroids as adjunctive therapy for OLP.205,206 Systemic and topically administered beta all-trans retinoic acid, vitamin A acid, systemic etretinate, and systemic and topical isotretinoin are all effective, and topical application of a retinoid cream or gel will eliminate reticular and plaquelike lesions in many patients. However, following withdrawal of the medication, the majority of lesions recur. Topical retinoids are usually favored over systemic retinoids since the latter may be associated with adverse effects such as liver dysfunction, chelitis, and teratogenicity.205,206 A new systemically administered retinoid, temarotene, is reported to be an effective therapy for OLP and to be free of side effects other than a slight increase in liver enzymes.207 Other topical and systemic therapies reported to be useful, such as dapsone, doxycycline, and antimalarials, require additional research.185

Topical application of cyclosporine appears to be helpful in managing recalcitrant cases of OLP. Although this has been confirmed in double-blind trials, the cost of cyclosporine solution, its hydrophobicity and unpleasant taste, and the yet unanswered questions regarding the drug’s ability to promote viral reproduction and malignant change in epithelial cells have limited its use except for patients with extensive and otherwise intractable oral lesions.184,208–210

When lesions have been confined to the mucosa just opposite amalgam restorations and when patients have been positive for patch tests to mercury or other metals, complete removal of the amalgam restorations has been curative in most patients.211–213 Surgical excision is usually not indicated for the treatment of OLP except in cases where concomitant dysplasia has been identified.199

Lichenoid Reactions

Lichenoid reactions and lichen planus exhibit similar histopathologic features.174 Lichenoid reactions were differentiated from lichen planus on the basis of (1) their association with the administration of a drug, contact with a metal, the use of a food flavoring, or systemic disease and (2) their resolution when the drug or other factor was eliminated or when the disease was treated.174,212 Clinically, lichenoid lesions may exhibit the classic appearance of lichen planus, but atypical presentations are seen, and some of the dermatologic lesions included in this category show little clinical lichenification.174

Table 5-3 lists some of the disorders that are currently proposed as lichenoid reactions.214

Drug-Induced Lichenoid Reactions

Drug-induced lichenoid eruptions include those lesions that are usually described in the dental literature under the topic of lichenoid reactions (ie, oral mucosal lesions that have the clinical and histopathologic characteristics of lichen planus, that are associated with the administration of a drug, and that resolve following the withdrawal of the drug).174,216

A drug history can be one of the most important aspects of the assessment of a patient with an oral or oral-and-skin

<table>
<thead>
<tr>
<th>Site of Reaction</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and oral mucosa</td>
<td>Lichen planus, lupus erythematosus, erythema multiforme, lichenoid and fixed drug eruptions, secondary syphilis, graft-versus-host disease</td>
</tr>
</tbody>
</table>

Reproduced with permission from Weedon D.214
lichenoid reaction. Clinically, there is often little to distinguish drug-induced lichenoid reactions from lichen planus. However, lichenoid lesions that include the lip and lichenoid lesions that are symmetric in distribution and that also involve the skin are more likely to be drug related.\(^{214}\) Histopathologically, lichenoid drug eruptions may show a deep as well as superficial perivascular lymphocytic infiltrate rather than the classic bandlike infiltrate of lichen planus, and eosinophils, plasma cells, and neutrophils may also be present in the infiltrate.

Drug-induced lichenoid reactions may resolve promptly when the offending drug is eliminated. However, many lesions take months to clear; in the case of a reaction to gold salts, 1 or 2 years may be required before complete resolution. Gold therapy, nonsteroidal anti-inflammatory drugs (NSAIDs), diuretics, other antihypertensives, and oral hypoglycemic agents of the sulfonylurea type are all important causes of lichenoid reactions (Table 5-4; Figure 5-36).\(^{216–224}\) (Because more drugs are being added to it on a continual basis, this list should by no means be considered complete.)

Surveys of medication use among patients with various oral keratoses, including lichen planus, have found the use of antihypertensive drugs to be more common among lichen planus patients.\(^{219}\) The use of NSAIDs was 10 times more frequent among those with erosive lichen planus.\(^{216,218,222}\) Penicillamine is associated with many adverse reactions, including lichenoid reactions, pemphigus-like lesions, lupoid reactions and stomatitis, and altered taste and smell functions.\(^{220,223}\) A number of the drugs that have been associated with lichenoid reactions may also produce lesions of discoid lupus erythematosus (lupoid reactions).\(^ {216}\)

**Graft-versus-Host Disease**

Graft-versus-host disease (GVHD)\(^ {225–240}\) is a complex multisystem immunologic phenomenon characterized by the interaction of immunocompetent cells from one individual (the donor) to a host (the recipient) who is not only immunodeficient but who also possesses transplantation isoantigens foreign to the graft and capable of stimulating it.\(^ {226}\) Reactions of this type occur in up to 70% of patients who undergo allogenic bone marrow transplantation, usually for treatment of refractory acute leukemia. There may be both acute (< 100 days after bone marrow transplantation) and chronic (after day 100, post transplantation) forms of the condition. The pathogenesis is probably related to an antigen-dependent proliferation of transplanted donor T-cell lymphocytes that are genetically disparate from the recipient’s own tissues and that give rise to a generation of effector cells that react with and destroy recipient tissues. Of these, the epidermal (skin and mucous membrane) lesions are often most helpful clinically in establishing a diagnosis.\(^ {227}\)

**CLINICAL FEATURES**

The epidermal lesions of acute GVHD range from a mild rash to diffuse severe sloughing. This may include toxic epidermal necrolysis (Lyell’s disease), a type of erythema multiforme in

**TABLE 5-4 Drugs and Materials Implicated in Oral Lichenoid Reactions**

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs or Materials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobials</td>
<td>Dapsone</td>
</tr>
<tr>
<td></td>
<td>Ketoconazole</td>
</tr>
<tr>
<td></td>
<td>Para-aminosalicylic acid</td>
</tr>
<tr>
<td></td>
<td>Sodium aminosalicylate</td>
</tr>
<tr>
<td></td>
<td>Streptomycin</td>
</tr>
<tr>
<td></td>
<td>Sulfamethoxazole</td>
</tr>
<tr>
<td></td>
<td>Tetracycline</td>
</tr>
<tr>
<td>Antiparasitics</td>
<td>Antimony compounds (stibophen, stibocaptate)</td>
</tr>
<tr>
<td></td>
<td>Organic arsenicals</td>
</tr>
<tr>
<td></td>
<td>Chloroquine</td>
</tr>
<tr>
<td></td>
<td>Pyrimethamine</td>
</tr>
<tr>
<td></td>
<td>Quinacrine</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>ACE inhibitors</td>
</tr>
<tr>
<td></td>
<td>Chlorothiazide</td>
</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide</td>
</tr>
<tr>
<td></td>
<td>Labetalol</td>
</tr>
<tr>
<td></td>
<td>Mercurial diuretics</td>
</tr>
<tr>
<td></td>
<td>Methylthopropionate</td>
</tr>
<tr>
<td></td>
<td>Practolol</td>
</tr>
<tr>
<td>Antiarthritis</td>
<td>Aurothioglucose</td>
</tr>
<tr>
<td></td>
<td>Colloidal gold (Europe only)</td>
</tr>
<tr>
<td></td>
<td>Gold sodium thiomalate, thiosulfate</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>Lorazepam</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Fenclofenac</td>
</tr>
<tr>
<td></td>
<td>Ibuprofen</td>
</tr>
<tr>
<td></td>
<td>Naproxen</td>
</tr>
<tr>
<td></td>
<td>Phenylbutazone</td>
</tr>
<tr>
<td>Oral hypoglycemic agents</td>
<td>Chloropropamide</td>
</tr>
<tr>
<td></td>
<td>Tolazamide</td>
</tr>
<tr>
<td></td>
<td>Tolbutamide</td>
</tr>
<tr>
<td>Uricosuric agents</td>
<td>Allopurinol</td>
</tr>
<tr>
<td>Miscellaneous drugs</td>
<td>Iodides</td>
</tr>
<tr>
<td></td>
<td>Penicillamine</td>
</tr>
<tr>
<td></td>
<td>Quinidine sulfate</td>
</tr>
<tr>
<td>Chemicals; dental restorative materials</td>
<td>Substituted paraphenylenediamines used in color film developers; dental casting alloys and amalgam restorations</td>
</tr>
</tbody>
</table>

Adapted from Firth NA, Reade PD;\(^ {216}\) Hay KD et al;\(^ {217}\) Mason C et al;\(^ {218}\) McCartan BE, McCreary CE;\(^ {219}\) Cohen DM et al;\(^ {220}\) Potts AJC et al;\(^ {221}\) Robertson WD, Wray D;\(^ {222}\) Seeherafer JR et al;\(^ {223}\) Regezi JA, Scuibba JJ;\(^ {224}\) Bez C et al.\(^ {225}\)

ACE = angiotensin-converting enzyme; NSAIDs = nonsteroidal anti-inflammatory drugs.

which large flaccid bullae develop with detachment of the epidermis in large sheets, leaving a scalded skin appearance.\(^ {226,228}\) Oral mucosal lesions occur in only about one-third of cases and are only a minor component of this problem.\(^ {229}\)

Chronic GVHD is associated with lichenoid lesions that affect both skin and mucous membranes. Oral lesions occur in
80% of cases of chronic GVHD; salivary and lacrimal gland epithelium may also be involved. In some cases, the intraoral lichenoid lesions are extensive and involve the cheeks, tongue, lips, and gingivae. In most patients with oral GVHD, a fine reticular network of white striae that resembles OLP is seen. Patients may often complain of a burning sensation of the oral mucosa. Xerostomia is a common complaint due to the involvement of the salivary glands. The development of a pyogenic granuloma on the tongue has been described as a component of chronic GVHD. Because of the potential involvement of salivary glands in chronic GVHD, biopsy of minor salivary glands is a useful diagnostic procedure in some cases. The histopathologic features of chronic GVHD may resemble those of OLP.

**TREATMENT AND PROGNOSIS**

The principle basis for management of GVHD is prevention by careful histocompatibility matching and judicious use of immunosuppressive drugs. In some cases, topical corticosteroids and palliative medications may facilitate the healing of the ulcerations. Ultraviolet A irradiation therapy with oral psoralen has also been shown to be effective in treating resistant lesions.

Topical azathioprine suspension has been used as an oral rinse and then swallowed, thereby maintaining the previously prescribed systemic dose of azathioprine. This resulted in improvement in cases of oral GVHD that was resistant to other approaches to management. Topical azathioprine may provide additional therapy in the management of immunologically-mediated oral mucosal disease.

Clinicians evaluating cases of lichen planus should rule out the possibility of oral lichenoid reactions. Lichenoid drug reactions manifesting in the oral cavity have received some attention, and oral lichenoid GVHD has been well described, but it is likely that oral lichen planus as currently diagnosed also represents a heterogeneous group of lesions that require more specific identification and customized focused treatment.

**LUPUS ERYTHEMATOSUS**

(Systemic and Discoid)

Clinical Features, Diagnosis, and Treatment

Systemic lupus erythematosus (SLE) is a prototypical example of an immunologically mediated inflammatory condition that causes multiorgan damage. (SLE is discussed in more detail in Chapter 18, under “Connective Tissue Diseases”; the brief description here emphasizes its clinical manifestations on the oral mucosa.) The oral lesions of systemic lupus are generally similar to those of discoid lupus (see below) and are most prevalent on the buccal mucosa, followed by the gingival tissues, the vermilion border of the lip, and the palate, in decreasing order of frequency. The lesions are frequently symptomatic, especially if the patient ingests hot or spicy foods, and often consist of one or more of the following components: erythema, surface ulceration, keratotic plaques, and white striae or papules (Figure 5-37). These lesions typically respond well to topical or systemic steroids. Clobetasol (a potent topical steroid) placed under an occlusive tray is very effective for temporary relief of these lesions. Long-term remission of these lesions obviously depends on treatment of the underlying systemic disease.
Discoid lupus erythematosus (DLE) is a relatively common disease and occurs predominantly in females in the third or fourth decade of life.\textsuperscript{242} DLE can present in both localized and disseminated forms and is also called chronic cutaneous lupus (CCL). DLE is confined to the skin and oral mucous membranes and has a better prognosis than SLE.\textsuperscript{20} Typical cutaneous lesions appear as red and somewhat scaly patches that favor sun-exposed areas such as the face, chest, back, and extremities. These lesions characteristically expand by peripheral extension and are usually disk-shaped. The oral lesions can occur in the absence of skin lesions, but there is a strong association between the two. As the lesions expand peripherally, there is central atrophy, scar formation, and occasional loss of surface pigmentation. Lesions often heal in one area only to occur in a different area later.

The oral mucosal lesions of DLE frequently resemble reticular or erosive lichen planus. The primary locations for these lesions include the buccal mucosa, palate, tongue, and vermilion border of the lips. Unlike lichen planus, the distribution of DLE lesions is usually asymmetric, and the peripheral striae are much more subtle (Figure 5-39). The lesions may be atrophic, erythematous, and/or ulcerated and are often painful. Hyperkeratotic lichen planus–like plaques are probably twice as common in patients with CCL as compared to patients with SLE.\textsuperscript{243,244} The oral lesions of DLE are markedly variable and can also simulate leukoplakia. Therefore, the diagnosis must be based not only on the clinical appearance of the lesions but also on the coexistence of skin lesions and on the results of both histologic examination and direct immunofluorescence testing. Despite their similar clinical features, lichen planus and lupus erythematosus yield markedly different immunofluorescent findings. Some authors\textsuperscript{245} believe that the histology of oral lupus erythematosus is characteristic enough to provide a definitive diagnosis at the level of light microscopy, but most feel that the diagnostic standard must involve direct immunofluorescence. Importantly, lesions with clinical and immunofluorescent features of both lichen planus and lupus erythematosus have also been described (overlap syndrome).\textsuperscript{244}

**Histopathologic Features**

The histopathologic changes of oral lupus consist of hyperorthokeratosis with keratotic plugs, atrophy of the rete ridges, and (most especially) liquefactive degeneration of the basal cell layer. Edema of the superficial lamina propria is also quite prominent. Most of the time, lupus patients lack the bandlike leukocytic inflammatory infiltrate seen in patients with lichen planus. Immediately subjacent to the surface epithelium is a band of PAS-positive material, and frequently there is a pronounced vasculitis in both superficial and deep connective tissue. Another important finding in lupus is that direct immunofluorescence testing of lesional tissue shows the deposition of various immunoglobulins and C3 in a granular band.
involving the basement membrane zone. Importantly, direct immunofluorescent testing of uninvolved skin in a case of SLE will show a similar deposition of immunoglobulins and/or complement. This is called the positive lupus band test, and discoid lesions will not show this result.

**Malignant Potential, Importance, and Scope of Oral Lesions**

The precancerous potential of intraoral discoid lupus is controversial. Basal cell and (more commonly) squamous cell carcinomas have been reported to develop in healing scars of discoid lupus. However, this malignant change may have been caused by the radiation and ultraviolet light used in the treatment of lupus in the early twentieth century. The development of squamous cell carcinoma has been described in lesions of discoid lupus involving the vermilion border of the lip, and actinic radiation may play an important adjunct role in this.

Oral ulcers are one of the defining features of lupus erythematosus. The frequency of oral lesions in all forms of lupus combined varies from 5 to >50%. Importantly, oral ulcers are found in SLE patients who have a higher level of disease activity as measured by the system lupus activity measure. One study of 446 SLE patients showed that the extent of oral mucosal involvement was 40 to 54%, with the higher figure occurring in more severely involved patients. The validity of these percentages, however, may be in question. In a recent survey of international centers devoted to the treatment of lupus, there was an extremely low level of agreement on the incidence of oral manifestations of this disease.

An increase in the frequency of generalized periodontal disease has been reported with SLE. However, most studies have found that there is either a decrease in periodontal probing depth in lupus or no change in periodontal status. In fact, recent evidence suggests that the tendency of periodontitis to be more severe or progressive in some patients with collagen vascular diseases is a consequence of xerostomia and not a result of the primary disease.

**▼ DEVELOPMENTAL WHITE LESIONS: ECTOPIC LYMPHOID TISSUE**

Cystic ectopic lymphoid tissue (oral lymphoepithelial cyst) may be found in several locations in the oral cavity. The most common locations are the posterior lateral border of the tongue (where the lymphoid tissue is called the lingual tonsil) and the floor of the mouth and ventral surface of the tongue. These lesions can also occur in the soft palate. Lymphoid tissue is normally present in the oral cavity as a ring of tonsillar tissue located in the pharynx and tongue, called Waldeyer’s ring. This ring of tonsillar tissue includes the lingual, pharyngeal, and palatine tonsils. Connections between the overlying surface epithelium and the tonsillar tissue can often be seen in histologic sections. These so-called crypts can be crypts of Broders and formation of lymphoepithelial cysts. These are keratin-filled cysts within the accessory lymphoid tissue; they usually appear as reddish yellow or white submuco-
atual dome-shaped nodules. In the absence of cystic obstruction, these lymphoid aggregates can become enlarged due to allergy or other inflammatory conditions and can appear as hyperplastic nodules. These are particularly common in the oropharynx, soft palate, and faucial tonsillar area. These lesions can often be diagnosed by clinical features alone. Occasionally, they may become large enough to require a biopsy. Especially in the soft palate area, they can cause some irritation and itching, which will necessitate their removal as well.

**▼ FORDYCE’S GRANULES**

Fordyce’s granules are ectopic sebaceous glands or sebaceous choristomas (normal tissue in an abnormal location) within the oral mucosa. Normally, sebaceous glands are seen within the dermal adnexa, in association with hair follicles; however, Fordyce’s granules do not exhibit any association with hair structures in the oral cavity. This condition is seen in approximately 80 to 90% of the population.

**Features**

Fordyce’s granules present as multiple yellowish white or white papules. They are often seen in aggregates or in confluent collections, most commonly on the buccal mucosa (Figure 5-40, A) and vermilion border of the upper lip. Occasionally, these may be seen on the retromolar pad area and the anterior tonsillar pillars. Men usually exhibit more Fordyce’s granules than women exhibit. The granules tend to appear during puberty and increase in number with age. Fordyce’s granules are completely asymptomatic and are often discovered on routine examination. Histologically, they are identical to normal sebaceous glands found in the dermis (see Figure 5-40, B).

**Treatment**

Usually no treatment is indicated, and since the clinical appearance is virtually diagnostic, no biopsy is usually required. Fordyce’s granules on the vermilion border of the upper lip may require surgical removal for esthetic reasons. Rare cases of pseudocysts and sebaceous cell hyperplasia and adenoma have been reported.

**▼ GINGIVAL AND PALATAL CYSTS OF THE NEWBORN AND ADULT**

**Features in the Newborn**

Gingival cysts of the newborn are often multiple sessile dome-shaped lesions measuring about 2 to 3 mm in diameter. They are chalk white and present predominantly on the maxillary anterior alveolar ridge just lingual to the crest. Those in the posterior region of the jaw are found directly on the crest of the ridge occlusal to the crowns of the molar teeth (Figure 5-41). These lesions are usually seen in newborn or very young infants and disappear shortly after birth; they are thought to originate from remnants of the dental lamina. These cysts tend...
to rupture and disappear spontaneously. The eponyms “Epstein's pearls” and “Bohn's nodules” have both been used to describe odontogenic cysts of dental lamina origin, but these terms are not considered to be accurate. Epstein originally described keratin-filled nodules found along the mid-palatal region, probably derived from entrapped epithelium along the lines of fusion of the palatal processes. These are considered quite rare. Bohn's nodules are thought to be keratin-filled cysts scattered across the palate but most plentiful along the junction of the hard palate and soft palate and are thought to be derived from palatal salivary glands. Bohn's nodules probably relate to what are presently called gingival cysts of the newborn. Krisover reported finding 65 examples of gingival cysts in 17 infants.²⁴² The incidence in Japanese infants was almost 90%, an incidence considered significantly higher than that seen in black or white newborns.²⁶³ Palatal cysts of the newborn occasionally persist into adult life and appear as peripheral odontogenic keratocysts.

**Features in the Adult**

Gingival cysts of the adult are thought to arise from dental lamina rests or from entrapment of surface epithelium.²⁶⁴,²⁶⁵ They are most common in the canine and premolar area of the mandible and maxillary lateral incisor area and usually occur during the fifth and sixth decades of life. They have a very strong resemblance to lateral periodontal cysts, and there is a strong correlation between these two types of lesions. Patients have had lateral periodontal cysts subsequent to the development of a gingival cyst,²⁶⁶ and lateral periodontal cysts are thought to be the intrabony counterpart of the gingival cyst. Gingival cysts usually appear as sessile painless growths involving the interdental area of the attached gingiva. These lesions often appear to be white or yellow white to blue and measure about 0.5 to 1 cm in diameter. They occasionally cause some superficial destruction of the underlying bone. A definite radiolucency is thought to represent a lateral periodontal cyst.²⁶⁷–²⁷²

**VISUALIZATION OF LESIONS**

**FIGURE 5-40 A** Fordyce's granules, appearing as multiple yellowish white papules and often seen as aggregates in the buccal mucosa. **B** Photomicrograph of Fordyce's granules, which microscopically are identical to normal sebaceous glands. (Hematoxylin and eosin, ×20 original magnification)

**FIGURE 5-41** Gingival cysts of the newborn in a 2-year-old with retained teeth. These cysts appear as clusters of pearly white papules on the crest of the ridge in the mandibular molar area.

**VISUALIZATION OF LESIONS**

**FIGURE 5-40** A, Fordyce's granules, appearing as multiple yellowish white papules and often seen as aggregates in the buccal mucosa. B, Photomicrograph of Fordyce's granules, which microscopically are identical to normal sebaceous glands. (Hematoxylin and eosin, ×20 original magnification)

**FIGURE 5-41** Gingival cysts of the newborn in a 2-year-old with retained teeth. These cysts appear as clusters of pearly white papules on the crest of the ridge in the mandibular molar area.

**VISUALIZATION OF LESIONS**

**FIGURE 5-40** A, Fordyce's granules, appearing as multiple yellowish white papules and often seen as aggregates in the buccal mucosa. B, Photomicrograph of Fordyce's granules, which microscopically are identical to normal sebaceous glands. (Hematoxylin and eosin, ×20 original magnification)

**FIGURE 5-41** Gingival cysts of the newborn in a 2-year-old with retained teeth. These cysts appear as clusters of pearly white papules on the crest of the ridge in the mandibular molar area.

**VISUALIZATION OF LESIONS**

**FIGURE 5-40** A, Fordyce's granules, appearing as multiple yellowish white papules and often seen as aggregates in the buccal mucosa. B, Photomicrograph of Fordyce's granules, which microscopically are identical to normal sebaceous glands. (Hematoxylin and eosin, ×20 original magnification)

**FIGURE 5-41** Gingival cysts of the newborn in a 2-year-old with retained teeth. These cysts appear as clusters of pearly white papules on the crest of the ridge in the mandibular molar area.

**VISUALIZATION OF LESIONS**

**FIGURE 5-40** A, Fordyce's granules, appearing as multiple yellowish white papules and often seen as aggregates in the buccal mucosa. B, Photomicrograph of Fordyce's granules, which microscopically are identical to normal sebaceous glands. (Hematoxylin and eosin, ×20 original magnification)

**FIGURE 5-41** Gingival cysts of the newborn in a 2-year-old with retained teeth. These cysts appear as clusters of pearly white papules on the crest of the ridge in the mandibular molar area.

**VISUALIZATION OF LESIONS**

**FIGURE 5-40** A, Fordyce's granules, appearing as multiple yellowish white papules and often seen as aggregates in the buccal mucosa. B, Photomicrograph of Fordyce's granules, which microscopically are identical to normal sebaceous glands. (Hematoxylin and eosin, ×20 original magnification)

**FIGURE 5-41** Gingival cysts of the newborn in a 2-year-old with retained teeth. These cysts appear as clusters of pearly white papules on the crest of the ridge in the mandibular molar area.

**VISUALIZATION OF LESIONS**

**FIGURE 5-40** A, Fordyce's granules, appearing as multiple yellowish white papules and often seen as aggregates in the buccal mucosa. B, Photomicrograph of Fordyce's granules, which microscopically are identical to normal sebaceous glands. (Hematoxylin and eosin, ×20 original magnification)

**FIGURE 5-41** Gingival cysts of the newborn in a 2-year-old with retained teeth. These cysts appear as clusters of pearly white papules on the crest of the ridge in the mandibular molar area.

**VISUALIZATION OF LESIONS**

**FIGURE 5-40** A, Fordyce's granules, appearing as multiple yellowish white papules and often seen as aggregates in the buccal mucosa. B, Photomicrograph of Fordyce's granules, which microscopically are identical to normal sebaceous glands. (Hematoxylin and eosin, ×20 original magnification)

**FIGURE 5-41** Gingival cysts of the newborn in a 2-year-old with retained teeth. These cysts appear as clusters of pearly white papules on the crest of the ridge in the mandibular molar area.

**VISUALIZATION OF LESIONS**

**FIGURE 5-40** A, Fordyce's granules, appearing as multiple yellowish white papules and often seen as aggregates in the buccal mucosa. B, Photomicrograph of Fordyce's granules, which microscopically are identical to normal sebaceous glands. (Hematoxylin and eosin, ×20 original magnification)

**FIGURE 5-41** Gingival cysts of the newborn in a 2-year-old with retained teeth. These cysts appear as clusters of pearly white papules on the crest of the ridge in the mandibular molar area.

**VISUALIZATION OF LESIONS**

**FIGURE 5-40** A, Fordyce's granules, appearing as multiple yellowish white papules and often seen as aggregates in the buccal mucosa. B, Photomicrograph of Fordyce's granules, which microscopically are identical to normal sebaceous glands. (Hematoxylin and eosin, ×20 original magnification)

**FIGURE 5-41** Gingival cysts of the newborn in a 2-year-old with retained teeth. These cysts appear as clusters of pearly white papules on the crest of the ridge in the mandibular molar area.
However, there is controversy over whether the psoriasis patients who manifest geographic tongue actually have intraoral psoriasis. A report of two patients with concurrent pustular psoriasis and mucosal lesions having the characteristic picture of geographic tongue seems to support this hypothesis. Both skin lesions and oral lesions responded positively and in a parallel manner to systemic retinoid treatment, and both had identical histopathologic features. Further support for this association is seen in a report of an unusual case of mucositis with features of psoriasis. In that case, a patient had skin psoriasis including crusted lesions of the upper lip and diffuse erythematous lesions of the labial and buccal mucosa and denture-bearing palatal mucosa. Classic geographic tongue and ectopic geographic tongue were also seen. Importantly, all the lesions had multiple pustules. These references seem to suggest an association between geographic tongue and psoriasis in some cases. Furthermore, both psoriasis and benign migratory glossitis are associated with human leukocyte antigen (HLA)-Cw6 and HLA-DR5. Also, stomatitis areata migrans was found in 5.4% of patients with psoriasis and in 1% of control patients whereas benign migratory glossitis was found in 10.3% of patients with psoriasis and in 2.5% of control patients. This association between these disorders gives supporting evidence that geographic tongue may be a manifestation of psoriasis. However, another study found that 10% of psoriasis patients had oral lesions histologically suggestive of psoriasis but that only 1% had classic geographic tongue.

OTHER ASSOCIATED CONDITIONS

Ectopic geographic tongue is frequently associated with similar tongue lesions. This is especially true in patients with atopy. There is a significant increase in the prevalence of ectopic geographic tongue in atopic patients who have intrinsic asthma and rhinitis versus patients with negative skin test reactions to various antigens. Also, patients with geographic tongue have a significantly greater personal or family history of asthma, eczema, and hay fever, when compared to control populations. Benign migratory glossitis is seen with a fourfold increase in frequency in patients with juvenile diabetes, possibly due to an increased frequency of elevated amounts of the HLA-B15 tissue type. Importantly, this tissue type also has a higher prevalence in atopic individuals.

Geographic tongue has also been seen with increased frequency in patients with pernicious anemia (this often appears as an erythematous form of geographic tongue) (Figure 5-44) and in pregnant patients, in whom it is possibly associated with folic acid deficiency or hormonal fluctuations. Association with the latter condition is supported by one report in which the severity of geographic tongue appeared to vary with hormonal levels. Lesions that are histologically indistinguishable from those of geographic tongue can also be seen in Reiter’s syndrome. The development of geographic tongue has also been associated with the administration of lithium carbonate.

Hairy Tongue (Black Hairy Tongue)

“Hairy tongue” is a clinical term describing an abnormal coating on the dorsal surface of the tongue. The incidence of this condition ranges from 0.5% in the United States to 12.8% among Israeli male geriatric patients and 57% among imprisoned Greek drug addicts. Hairy tongue results from the defective desquamation of cells that make up the secondary filiform papilla. This buildup of keratin results in the formation of highly elongated hairs, which is the hallmark of this entity. The cause of black hairy tongue is unknown; however, there are several initiating or contributing factors. These include tobacco (heavy smoking) and psychotropic agents. Other predisposing factors include broad-spectrum antibiotics such as penicillin and the use of systemic steroids. The use of oxidizing mouthwashes or antacids and the overgrowth of fungal or bacterial organisms have also been associated with this condition. Radiation therapy for head and neck malignancies is
Red and White Lesions of the Oral Mucosa

considered a major factor as well. Importantly, poor oral hygiene can exacerbate this condition. The common etiologic factor for all of these influences may be the alteration of the oral flora by the overgrowth of yeast and chromogenic bacteria.283 (See Chapters 4 and 7 for a more thorough discussion of this entity and its treatment.)

Hairy tongue usually involves the anterior two-thirds of the dorsum of the tongue, with a predilection for the midline just anterior to the circumvallate papillae. The patient presents with elongated filiform papillae and lack of desquamation of the papillae. The tongue therefore appears thickened and matted. Depending on the diet and the type of organisms present, the lesions may appear to range from yellow to brown to black or tan and white. Although the lesions are usually asymptomatic, the papillae may cause a gag reflex or a tickle in the throat if they become especially elongated (Figure 5-45). They may also result in halitosis or an abnormal taste. A biopsy is usually unnecessary. Treatment consists of eliminating the predisposing factors if any are present. Cessation of smoking or discontinuation of oxygenating mouthwashes or antibiotics will often result in resolution. Improvement in oral hygiene is also important, especially brushing or scraping of tongue, in addition to other good oral hygiene practices. Podophyllin resin (a keratolytic agent) has been used in treatment, but there are some questions about its safety. However, a 1% solution of podophyllin resin is available for the treatment of hairy tongue. The efficacy of tooth brushing can be enhanced by a prior application of a 40% solution of urea. Topical tretinoin has recently been tried as treatment of this entity.289,290

Oral Submucous Fibrosis

Oral submucous fibrosis (OSF) is a slowly progressive chronic fibrotic disease of the oral cavity and oropharynx, characterized by fibroelastic change and inflammation of the mucosa, leading to a progressive inability to open the mouth, swallow, or speak.291,292 These reactions may be the result of either direct stimulation from exogenous antigens like Areca alkaloids or changes in tissue antigenicity that may lead to an autoimmune response. It occurs almost exclusively in inhabitants of Southeast Asia, especially the Indian subcontinent.292–295 The inflammatory response releases cytokines and growth factors that promote fibrosis by inducing the proliferation of fibroblasts, up-regulating collagen synthesis and down-regulating collagenase production.292,296

**ETIOLOGY**

Even though the etiopathology is incompletely understood, several factors are believed to contribute to the development of OSF, including general nutritional and vitamin deficiencies and hypersensitivity to certain dietary constituents such as chili peppers, chewing tobacco, etc.293 However, the primary factor is the habitual use of betel and its constituents, which include the nut of the areca palm (Areca catechu), the leaf of the betel pepper (Piper betle), and lime (calcium hydroxide). Approximately 200 million persons chew betel regularly throughout the western
Pacific basin and south Asia. Only three drugs (nicotine, ethanol, and caffeine) are consumed more widely than betel. When betel is chewed, it produces mild psychoactive and cholinergic effects. Betel use is also associated with oral leukoplakia and squamous cell carcinoma. OSF is regarded as a premalignant condition, and many cases of oral cancer have been found coexisting with submucous fibrosis. Cases of submucous fibrosis have been reported in many Western countries, especially in individuals who have immigrated from the Indian subcontinent.

**CLINICAL FEATURES**

The disease first presents with a burning sensation of the mouth, particularly during consumption of spicy foods. It is often accompanied by the formation of vesicles or ulcerations and by excessive salivation or xerostomia and altered taste sensations. Gradually, patients develop a stiffening of the mucosa, with a dramatic reduction in mouth opening and with difficulty in swallowing and speaking. The mucosa appears blanched and opaque with the appearance of fibrotic bands that can easily be palpated. The bands usually involve the buccal mucosa, soft palate, posterior pharynx, lips, and tongue. OSF usually affects young individuals in the second and third decades of life but may occur at any age. Histologic examination reveals severely atrophic epithelium with complete loss ofrete ridges. Varying degrees of epithelial atypia may be present. The underlying lamina propria exhibits severe hyalinization, with homogenization of collagen. Cellular elements and blood vessels are greatly reduced.

**TREATMENT AND PROGNOSIS**

OSF is very resistant to treatment. Many treatment regimens have been proposed to alleviate the signs and symptoms, without much success. Submucosal injected steroids and hyaluronidase, oral iron preparations, and topical vitamin A and steroids are some of the agents that have been used. All of these therapies are essentially palliative. In severe cases, surgical intervention is the only treatment, but the fibrous bands and other symptoms often recur within a few months to a few years. The use of an oral stent as an adjunct to surgery to prevent relapse has also been studied. OSF is considered to be a premalignant condition. In a 17-year follow-up study in India, oral cancer developed in 7.6% of patients with submucous fibrosis. The malignant transformation rate for submucous fibrosis was 4 to 13%.

**REFERENCES**

29. Hjorting-Hansen E, Holst E. Morsicatio mucosae oris and suc-
Red and White Lesions of the Oral Mucosa

119

41. Mucklow ES. Accidental feeding of a dilute antiseptic solution (chlorhexidine 0.05% with cetrimide 1%) to five babies. Hum Toxicol 1988;7(6):567–9.
71. Mani NJ. Preliminary report on prevalence of oral cancer and


