ABSTRACT: Chronic irritation from smoking is the most common cause of white mucosal lesions. Because benign leukoplakic growths are virtually impossible to distinguish from carcinoma, biopsy is essential. Obtain a specimen at a nonulcerated area, using a scalpel or biting forceps and an injected or topical anesthetic. Squamous cell carcinoma is generally hyperkeratotic, but it may resemble erythroplakia, be granular, or be ulcerative with a zone of central necrosis. Lichen planus in the oral cavity is usually asymptomatic and requires no treatment, except for the erosive form, which causes pain and burning and warrants prednisone therapy (20 mg/d). Reexamine all patients with lichen planus periodically, since there is risk of transformation to squamous cell carcinoma. Several hereditary syndromes are characterized by white oral lesions; they are generally not precancerous, except for dyskeratosis congenita, which has a strong tendency to malignant transformation. Candidal infection usually presents as a thick white plaque produced by a matted collection of mycelia and desquamated epithelium. Treatment may be local (oral rinsing with nystatin suspension) or systemic (fluconazole, 100 mg/d for 7 to 10 days).

Key words: leukokeratosis, hyperkeratosis, hairy leukoplakia, verrucous carcinoma, squamous cell carcinoma, lichen planus, stomatitis nicotina, white sponge nevus, leukoedema, Darier-White disease

V arious mucosal abnormalities as well as proliferative and destructive lesions can occur in the oral cavity. Their causes include infectious agents, metabolic disorders, endocrinopathies, injuries, neoplasms, developmental abnormalities, genetic syndromes, and immunologic disturbances.

Authors of textbooks and atlases on oral medicine classify these lesions according to their appearance or to the responsible agent. I find that classification based on a lesion’s appearance facilitates diagnosis, since the list of possibilities to consider is more finite.

In a series of articles, I will offer practical advice on how to differentiate between oral lesions that require treatment—and those that may be safely left alone. I focus on white lesions (Table 1). In future articles, I will address erythematous, pigmented, and erosive (punctate and bullous) oral lesions.

OVERVIEW OF CAUSES

White mucosal lesions may result from thickening of one or several layers of the oral epithelium. They vary in size and depth, generally have an irregular outline, and may be solitary or multifocal. Common sites are the buccal mucosa, lateral border of the tongue, floor of the mouth, and hard palate. The remainder of the tongue, soft palate, lips, and gingiva are less often involved.

Chronic irritation from all forms of smoking represents the most common cause of white mucosal lesions. Less often, the direct contact of tobacco with the oral mucosa is responsible. Snuff dipping is a potent irritant and carcinogen. Ill-fitting dentures, rough teeth, and dental restorations are also irritants.

Chronic inflammation heads the list of many possible causes, but genetic disorders, infectious agents, and chemical substances may also be operative. Accordingly, a complete physical examination and thorough history taking are indicated. Ask particularly about the use of prescription and over-the-counter medications. Since few lesions can be diagnosed from physical appearance alone, a biopsy is generally necessary.

The term “leukokeratosis” is often used generically to describe any white, plaquelike lesion of the oral cavity. “Leukoplakia” is similarly applied by some authors. Others reserve the term “leukoplakia” for lesions that show dyskeratosis on histologic examination; they designate the remaining lesions “pachyderma orale.”
Leukokeratosis, which can arise at any site in the oral cavity, occurs most often on the buccal mucosa and least often on the soft palate and gingiva (Figure 1). Peak incidence is in midlife, and men are more frequently affected. The lesions are generally asymptomatic, although patients may occasionally complain of burning or an area of roughness. In most cases, the lesion is discovered during a routine physical or dental examination.

Because it is virtually impossible to distinguish between these benign entities and carcinoma, biopsy is essential. If dysplasia is demonstrated, consider such lesions premalignant. They have the propensity to transform into carcinoma in situ or invasive squamous cell carcinoma. Thus, such leukoplakic growths must be excised completely and the region observed closely for recurrence.

Always attempt to identify and eliminate the irritant that caused the lesion. Many lesions involute when this is done, but new ones may appear. Periodic follow-up examination and repeated biopsy are essential. If oral disease is widespread, sample multiple areas.

### Table 1 – White oral lesions

<table>
<thead>
<tr>
<th>Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukokeratosis, hyperkeratosis, and leukoplakia</td>
</tr>
<tr>
<td>Hairy leukoplakia</td>
</tr>
<tr>
<td>Verrucous carcinoma</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>Lichen planus</td>
</tr>
<tr>
<td>Lichenoid reactions</td>
</tr>
<tr>
<td>Stomatitis nicotina</td>
</tr>
<tr>
<td>Genetic lesions</td>
</tr>
<tr>
<td>Benign intraepithelial dyskeratosis</td>
</tr>
<tr>
<td>White sponge nevus</td>
</tr>
<tr>
<td>Leukoedema</td>
</tr>
<tr>
<td>Darier-White disease</td>
</tr>
<tr>
<td>Pachyonychia congenita</td>
</tr>
<tr>
<td>Dyskeratosis congenita</td>
</tr>
<tr>
<td>Viral lesions (eg, focal epithelial hyperplasia)</td>
</tr>
<tr>
<td>Candidiasis</td>
</tr>
<tr>
<td>Aspirin burn</td>
</tr>
<tr>
<td>Contact allergy reaction</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
</tr>
</tbody>
</table>

### Microscopic characteristics.

Hyperkeratosis (thickening of the outer keratin layers), parakeratosis (persistance of pyknotic nuclei in the outer epithelial layer), acanthosis (enlargement or edema of the spinous layer of the skin), and dyskeratosis may be seen. The presence of dyskeratosis implies disordered maturation of the various epithelial layers; loss of polarity of the basal cells; and such cytologic features as hyperchromatism, pleomorphism, enlarged nuclei, increased mitoses, and an increased nuclear-cytoplasmic ratio. Studies of biopsy specimens of white lesions of the oral cavity revealed a 2% to 4% incidence of dyskeratosis; in 2% to 11% of these cases of dyskeratosis, invasive carcinoma was present.4,6

### Treatment.

After biopsy, residual lesions may be destroyed with a carbon dioxide laser. To decrease keratinization, oral retinoid therapy has been tried, but no clinical benefit was demonstrated.8

### HAIRY LEUKOPLAKIA

This lesion requires special consideration because it occurs only in patients with HIV infection. Hairy leukoplakia (so called because of the filamentous nature of the plaques) arises principally on the lateral border of the tongue, but it may also involve the buccal and labial mucosa. It is a classic example of virally induced epithelial hyperplasia.

Histologic examination reveals hyperkeratosis, parakeratosis, and koilocytes. A koilocyte shows ballooning degeneration and has an inclusion body that is believed to represent opportunistic Epstein-Barr virus infection.9 Biopsy establishes the diagnosis, but no treatment is necessary. Hairy leukoplakia is asymptomatic and benign.

### VERRUCOUS CARCINOMA

As its name implies, this slow-growing tumor is an exophytic papillary lesion that has well-defined borders and does not metastasize. It...
arises principally on the buccal mucosa and gingiva in the oral cavity and is associated with the use of chewing tobacco and snuff.

Microscopic examination shows that verrucous carcinoma is extremely keratotic, with a pushing rather than an infiltrative pattern of growth into the deeper tissues. Consequently, limited biopsy specimens often lead to a misdiagnosis of hyperkeratosis. Wide local excision is generally curative.

**SQUAMOUS CELL CARCINOMA**

Carcinoma within the oral cavity grows insidiously; pain eventually results from ulcerative lesions. Otalgia often develops with advanced tumors of the posterior oral cavity and oropharynx. The peak incidence is during the sixth and seventh decades, predominantly among men. A history of smoking and alcohol use is common, and syphilitic glossitis is a strong predisposing factor. The most frequently involved sites are (in descending order):

- Lateral border of the tongue.
- Floor of the mouth.
- Gingiva.
- Buccal mucosa.
- Palate.

Routinely examine the oral cavity to detect malignant lesions in the early stage; the prognosis for oral carcinoma is directly related to its extent. The lesions primarily consist of squamous cell carcinomas, the majority of which are invasive.

**Appearance.** The mucosal abnormality is generally hyperkeratotic, but it may resemble erythroplakia, be granular, or be ulcerative with a zone of central necrosis (Figure 2). Always palpate to assess its true extent, since an area of induration may underlie the apparent mucosal portion. This finding represents infiltrative spread of the carcinoma into the deeper tissues. It is especially characteristic of squamous cell carcinoma of the tongue, where the tumor can spread along the muscle bundles.

The tumor can be exophytic, with mainly surface spread, or endophytic, with a large submucosal infiltrative component. In rare cases, it is totally submucosal, occurring at such sites as the tonsil and the base of the tongue. This presentation, however, is more typical of neoplasms of minor salivary glands.

Obtain a biopsy specimen at a nonulcerated area using a scalpel or biting forceps and an injected or topical anesthetic. General anesthesia may be required for larger lesions, to assess their true size, and for ulcerated tumors, which are extremely painful.

**Microscopic characteristics.** Examination reveals hyperchromatic and pleomorphic tumor cells that have invaded the basement membrane of the epidermis and show various degrees of mitotic activity. These cells are seen in nests and sheets in the underlying soft tissues. In the more differentiated lesions, keratin pearls are seen.

Carefully palpate the patient’s neck to detect possible lymph node metastases. CT scanning may detect small necrotic lymph nodes that are not clinically apparent as well as mandibular and maxillary erosion. Treatment depends on the site and stage of the tumor; it may involve surgery, radiotherapy, chemotherapy, or some combination of these modalities.

**LICHEN PLANUS**

This common dermatologic disorder of unknown cause generally develops in midlife and occurs more often among women. Although lesions are usually seen on the skin and oral mucosa, there may be no skin involvement. Multiple lesions are generally scattered throughout the oral cavity.

**Pattern variations.** The reticular form of lichen planus is most common and typically appears as a network of white bands (Wickham’s striae) that occur bilaterally on the buccal mucosa (Figure 3). Other patterns include atrophic, erythematous, plaque, papular, bullous, ulcerative, and nummular forms; these may appear on the tongue, palate, gingiva, and lip. The nummular pattern of lichen planus may resemble a thumbprint and may be misdiagnosed as a fungal infection (Figure 4). Keratotic lesions may assume papular and plaquelike forms.

The erosive form of lichen planus must be considered separately. Here areas of erythema and ulcer-
ation develop secondary to vesicle formation within keratotic lesions, and patients complain of pain and burning. Occasionally, the condition may appear as desquamative gingivitis. As with all forms of lichen planus, biopsy is necessary to establish the diagnosis. The differential diagnosis includes the bullous diseases (for example, pemphigus vulgaris and bullous pemphigoid) and ulcerating lesions such as those that are seen in systemic lupus erythematosus (SLE).

**Diagnosis and management.** Biopsy specimens show parakeratosis, elongated rete pegs, and submucosal lymphocytic infiltrates. Except for the erosive form, lichen planus is usually asymptomatic in the oral cavity and requires no treatment. Patients with lichen planus require periodic reexamination, however, since there may be transformation to squamous cell carcinoma in a small number of cases. The incidence has been estimated at 0.5% to 2.8%. 10

Give prednisone to patients with the erosive form of lichen planus to promote reepithelialization of the denuded area. The dosage required to achieve remission (20 mg/d) is lower than that for bullous oral disorders. The white areas remain asymptomatic.

**LICHENOID REACTIONS**

An immune mechanism initiated by systemic drug use may induce oral and skin lesions that resemble lichen planus. The reaction may target the skin, mucosa, or both. Microscopic examination reveals that cells in the basal layer undergo degeneration (apoptosis) with extrusion of the fragments into the dermis to form colloid bodies.

Since the lesions resemble lichen planus, a history of medication use is essential in making the correct diagnosis. While any drug can cause this reaction, it is more common with certain medications, including: 11:

- Antimicrobials (for example, tetracycline and chloroquine).
- Anthypertensives (such as angiotensin-converting enzyme inhibitors and thiazide diuretics).
- Oral hypoglycemics.
- NSAIDs.
- Tranquilizers (lorazepam is one example).
- Iodides.
- Colloidal gold.
- Penicillamine.

The lesions disappear when the medication is discontinued. Oral
prednisone (20 mg/d) may be used for symptomatic relief.

**STOMATITIS NICOTINA**

This lesion occurs in pipe and cigar smokers. Its appearance is virtually diagnostic: the hard and soft palate are covered with keratotic papules that have elevated red centers (inflamed mucous gland orifices). Treatment is smoking cessation. Stomatitis nicotina is self-limited, and carcinomatous transformation does not occur.

**GENETIC LESIONS**

Several hereditary syndromes are characterized by white lesions in the oral cavity (Table 2). These have been termed “oral genodermatoses” or “oral genokeratoses.”\(^{12}\) They generally affect the buccal mucosa bilaterally. The conditions are inherited as an autosomal dominant trait, and they have no sexual predilection, except for dyskeratosis congenita.\(^{13,14}\) The latter is also unique in that the oral lesions have a strong tendency toward malignant transformation.

**Benign intraepithelial dyskeratosis.** Large, superficial, soft white plaques appear on the buccal mucosa and oral commissures; they also involve the conjunctiva. Onset is in childhood and occurs only in a limited group of triracial (white, Native American, and black) families in Halifax County, North Carolina.

As its name implies, this condition is characterized by intraepithelial dyskeratotic cells, which are enlarged hyaline eosinophils. When surrounded by adjacent cells, they form a “cell-within-a-cell” pattern. The lesions are not precancerous, and no treatment is required.

**White sponge nevus.** Also referred to as Cannon’s disease, these diffuse, soft, folded white lesions generally appear on the buccal mucosa (Figure 5). They may also arise at other sites in the oral cavity, as well as in the genital and anal regions. Onset is in infancy, and maxi-

<table>
<thead>
<tr>
<th>Condition</th>
<th>Inheritance</th>
<th>Oral sites</th>
<th>Other involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign intraepithelial dyskeratosis</td>
<td>Autosomal dominant</td>
<td>Buccal mucosa, oral commissures</td>
<td>Conjunctiva</td>
</tr>
<tr>
<td>(Witkop’s disease)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White sponge nevus</td>
<td>Autosomal dominant</td>
<td>Buccal mucosa, lateral tongue</td>
<td>Anus, vagina</td>
</tr>
<tr>
<td>(Cannon’s disease)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukoedema</td>
<td>Unknown</td>
<td>Buccal mucosa</td>
<td>—</td>
</tr>
<tr>
<td>Darier-White disease (keratosis follicularis)</td>
<td>Autosomal dominant</td>
<td>Hard palate, gingiva, buccal mucosa</td>
<td>Skin, palmar and plantar hyperkeratosis, nails</td>
</tr>
<tr>
<td>Pachyonychia congenital (Jadassohn-Lewandowsky syndrome)</td>
<td>Autosomal dominant</td>
<td>Tongue dorsum, buccal mucosa</td>
<td>Nails, palmar and plantar hyperkeratosis, nails</td>
</tr>
<tr>
<td>Dyskeratosis congenital (Zinsser-Cole-Engman syndrome)</td>
<td>X-linked recessive</td>
<td>Buccal mucosa, tongue</td>
<td>Nails, skin, blood</td>
</tr>
</tbody>
</table>

Table 2 – Genetic disorders characterized by white oral lesions
mal severity occurs during adolescence. Microscopic examination reveals parakeratosis and acanthosis, and bands of parakeratin are seen in the surface layers of the epithelium. No treatment is indicated.

**Leukoedema.** A condition that occurs principally in blacks, leukoedema presents as a bilateral, diffuse, pearly sheen on the buccal mucosa. It results from an interaction of smoking and racial predisposition in a select population.

Histologic examination shows edema of the spinous layer of the epidermis, but biopsy is not necessary. You can make the diagnosis by stretching the buccal mucosa with two tongue blades; this causes leukoedema to disappear. No treatment is required.

**Darier-White disease (keratosis follicularis).** Often, this is a combined cutaneous and mucosal disorder characterized by broad areas of yellow-to-white papular and keratotic lesions on the skin and oral cavity. The nails show splintering and subungual keratosis. Palmar and plantar hyperkeratosis is often present. The disease can produce large cobblestonelike plaques on both the skin and mucosa (Figure 6). Although it has a predilection for the buccal mucosa, as do other genetic lesions, Darier-White disease can also occur on the palate.

Biopsy is diagnostic. It demonstrates intraepithelial lacunae, hyperkeratosis, acanthosis, and cell-within-a-cell dyskeratosis. Topical vitamin A preparations have been used to decrease keratinization, but success has been limited.

**Pachyonychia congenita.** In its oral form, this condition is manifested as bilateral buccal lesions that resemble those of white sponge nevus; histologically, the two lesions are similar. With these findings, look for dystrophic nail changes (marked thickening) and palmar and plantar hyperkeratosis to confirm the diagnosis of pachyonychia congenita. Natal teeth often signal the presence of the syndrome. This self-limited disorder requires no treatment.

**Dyskeratosis congenita.** Oral leukoplakia, nail dystrophy, and reticulated skin pigmentation of the face, neck, and chest occur in patients with this rare, sex-linked, recessive disease. About half of the cases are associated with bone marrow failure (anemia, leukopenia, and thrombocytopenia). In the mouth, leukoplakia and atrophic changes occur on the buccal mucosa and tongue in childhood and develop into carcinoma by adolescence and early adulthood. Management includes bone marrow transplantation and treatment of the malignancies that arise.

**VIRAL LESIONS**

Focal epithelial hyperplasia (Heck’s disease) is a virally induced disease that appears in genetically predisposed persons, primarily Native Americans and Eskimos, with limited occurrence in other Americans, Europeans, and Latin Americans. Multiple, small, slightly raised plaques appear on the lips, buccal mucosa, tongue, and gingiva. Microscopic examination reveals acanthotic epithelial nodules with lymphoid hyperplasia. This self-limited condition requires no treatment.

**ORAL CANDIDIASIS**

A candidal infection can appear anywhere in the oral cavity and may take several different forms. It generally presents as a thick white plaque produced by a matted collection of mycelia and desquamated epithelium (Figure 7). This plaque is actually a pseudomembrane; it can be rubbed off readily with a tongue blade, revealing a punctate bleeding base. Occasionally, oral candidiasis is erythematous.

**Hyperplastic candidiasis.** In this variant, a chronic, low-grade fungal infection stimulates keratin formation. The resulting lesion resembles leukoplakia, but it cannot be scraped off. When cells are examined microscopically, pseudohyphae can be seen within the keratin, and these point to the diagnosis.

**Angular cheilosis.** This candidal infection of the oral commissure appears as multiple fissures (Figure 8). You can confirm the diagnosis by culture, which demonstrates the budding yeast cells of *Candida albicans*, and by treating the pellicle with potassium hydroxide to show hyphae.

Long-term antibiotic therapy, diabetes mellitus, and immunodeficiency states (especially AIDS) predispose
patients to this focal fungal overgrowth. In your diagnostic evaluation, keep in mind the common occurrence of oral candidiasis, either the pseudomembranous or angular cheilosis form, in HIV-positive patients. Treatment may be local (oral rinsing with nystatin suspension) or systemic (fluconazole, 100 mg/d for 7 to 10 days).

ASPIRIN BURN
Patients may sometimes place an aspirin tablet in the cheek in an attempt to reduce the regional pain of conditions such as aphthous ulcers, toothache, or thermal burn of the oral mucosa. Aspirin has a causative effect on the oral mucosa, causing coagulation necrosis and formation of a region of white slough. The history provides the diagnosis. Treat these lesions with saline mouthwash and topical application of diphenhydramine syrup.

CONTACT ALLERGY REACTION
Exposure to a variety of substances can produce a lichenoid type of keratotic reaction. For example, it can be induced by allergy to the mercury in amalgam dental restorations. Previously, an electrogalvanic response had been blamed for this effect. The mucosal area involved is directly apposed to the dental filling. Other substances that can produce a lichenoid reaction when applied topically are the essential oils and other flavorings (such as cinnamon) contained in toothpastes and mouthwashes.15

SYSTEMIC LUPUS ERYTHEMATOSUS
Occasionally, SLE presents as a white plaque in the oral cavity, especially on the buccal mucosa. Both discoid and systemic forms of SLE can produce a lesion with central atrophy or ulceration and peripheral, radial, hyperkeratotic striae. Biopsy reveals hyperkeratosis, thickening of the basement membrane, and lymphocytic infiltrates in the submucosa that resemble lichen planus. A high titer of antinuclear antibody and laboratory studies that detect visceral involvement provide the diagnosis. Treatment consists of systemic corticosteroids.

REFERENCES: