# White lesions in the oral cavity: clinical presentation, diagnosis, and treatment

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■ **Abstract**

White lesions in the oral cavity are common and have multiple etiologies, some of which are also associated with dermatological disease. While most intraoral white lesions are benign, some are premalignant and/or malignant at the time of clinical presentation, making it extremely important to accurately identify and appropriately manage these lesions. Due to their similar clinical appearances, it may be difficult sometimes to differentiate benign white lesions from their premalignant/malignant counterparts. This review will discuss many of the most common intraoral white lesions including their clinical presentation, how to make an accurate diagnosis, and effective treatment and management strategies.

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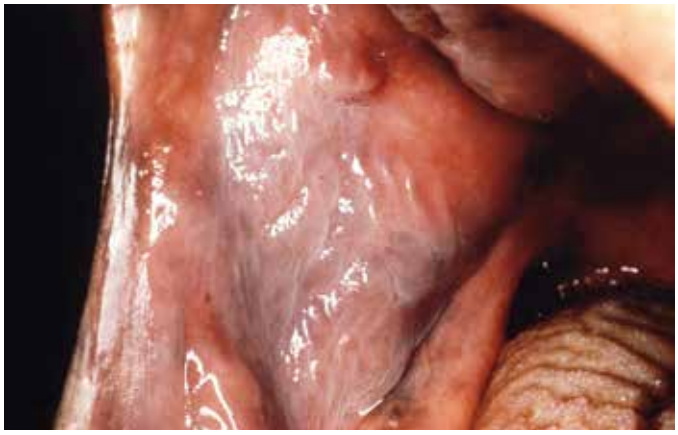

■ **FIGURE 1.** Leukoedema on the right buccal mucosa. When affected areas are physically stretched, the lesions often disappear.

White lesions of the oral cavity are common and may have multiple etiologies. Often, due to their similar clinical appearances, a biopsy is necessary to establish the diagnosis. This review will focus on some of the more common intraoral white lesions with emphasis placed on clinical presentation, how to establish the diagnosis, treatment, and long-term management.

## Hereditary lesions

### Leukoedema

Leukoedema is a common, benign, asymptomatic intraoral condition found within several populations such as those of Indian, Caucasian, Mexican, and African American descent (Figure 1).[1-3] Clinically, it appears as a thin, grey-white, wrinkled film that cannot be wiped off and usually appears bilaterally on the buccal mucosa; however, other sites may be affected including the floor of mouth, larynx, labial, and vaginal mucosa. Presentation can occur at any age and its severity may increase with time.[4] Leukoedema often disappears upon stretching of the affected area, a helpful sign that can be used to distinguish it from other white lesions. Factors such as smoking, poor oral hygiene, and the use of highly spiced foods have been suggested as potential etiologic factors; however, no definitive cause-and-effect relationships have been established.[1] Given the high prevalence of leukoedema in several demographic groups, it is now accepted as a variation of normal. No treatment is necessary because it is not associated with any other disease process and has no potential for malignant transformation or patient morbidity.

### White sponge nevus

Inherited in an autosomal dominant fashion, white sponge nevus (WSN) is characterized by the presence of asymptomatic, thick, spongy, white plaques located primarily within the oral cavity (Figure 2). Rarely, other mucous membrane sites may be affected including those of the nose, penis, anus, vagina, and esophagus.[5-7] Within the mouth, WSN is most common on the buccal mucosa followed by the labial mucosa, alveolar ridges, and floor of mouth.[5] The severity and extent of the plaques vary and may wax and wane over time within each affected patient. In a majority of cases, lesions are first noted during childhood and appear to affect males and females equally.[5]

WSN is caused by mutations in either the keratin 4 (KRT4) or keratin 13 (KRT13) genes.[8,9] These mutations lead to an abnormal perinuclear accumulation of keratin tonofilaments, intracellular edema, acanthosis, and hyperparakeratosis of the epithelium. In general, WSN has not been linked to any long-term diseases such as dysplasia or cancer. The vast majority of patients require no management; however, for rare symptomatic cases (ie, pain, sensitivity) several empirical approaches have been suggested. These include bland, warm-water mouth rinses of baking soda, tetracycline, penicillin, or chlorhexidine with the goal of reducing local microbial overgrowth that occasionally occurs on WSN plaques and can cause local irritation.[5,10-14]

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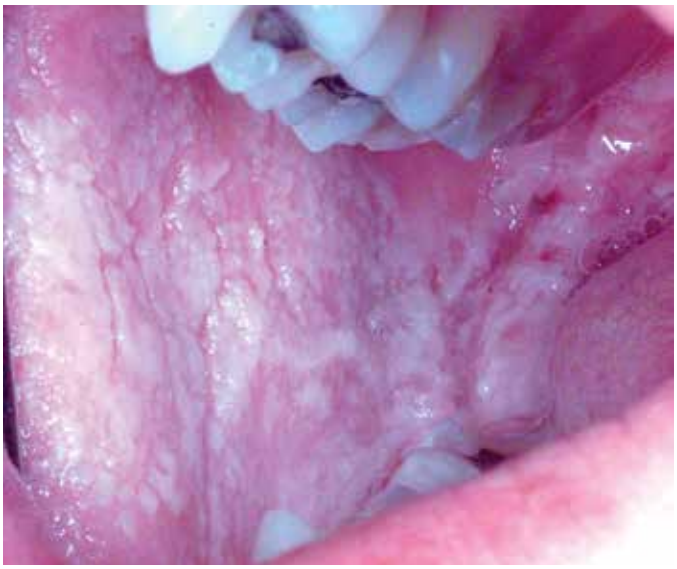

**FIGURE 2.** White sponge nevus on the right buccal mucosa. The characteristic thick, spongy, white plaques seen here are typically asymptomatic.

## Reactive lesions

### Frictional hyperkeratosis

As the name implies, frictional hyperkeratosis (FH) on intraoral surfaces is caused by chronic trauma such as an ill-fitting denture, excessive tooth brushing, food impaction, or via a factitial injury (Figure 3). The term morsicatio mucosae oris is also sometimes used to describe FH.[15,16] Regardless of the source of irritation, the oral epithelium reacts to chronic trauma via increased cellular turnover and keratin production, often with accompanying acanthosis and little to no inflammatory response of the underlying connective tissue.[15,17]

FH lesions may be found on any intraoral surface, but most commonly affect the retromolar pad (area posterior to the last mandibular molar), the edentulous alveolar ridge, and the lateral tongue. FH lesions are discrete, nonulcerated, nonerythematous, white papules or plaques with a rough-to-corrugated surface that cannot be wiped off.[18] Histologically, a majority of cases are associated with benign epithelial hyperplasia along with significant surface bacterial colonization without any appreciable underlying inflammation.[15] The location and clinical appearance of these lesions usually make their identification relatively straightforward.

FH has no known malignant potential and thus can be managed by treating the source of tissue irritation. Many patients may not be consciously aware of a causative oral habit, making it challenging to identify and modify the behavior. Occasionally, lesions may also be secondarily infected with opportunistic fungal organisms necessitating the use of antifungal medications. Once the source of irritation has been removed along with any underlying infection, these lesions often completely resolve.[16]

### Smokeless tobacco changes

Smokeless tobacco (ST) is used predominantly in one of three forms in the United States: a coarsely cut type known as chewing tobacco, a finely ground dry form known as snuff, and a finely ground moist form known as dipping tobacco. Placing the ST between the lip/cheek and the gingiva, typically in the lower vestibule, is seen in all three types. The use of ST has historically predominated in specific geographic regions of the US such as in the South and Midwest and within certain groups such as professional baseball players.[19,20] From 2000 to 2010, the rate of ST use, specifically snuff, was on the rise in young, non-Hispanic white males.[21]

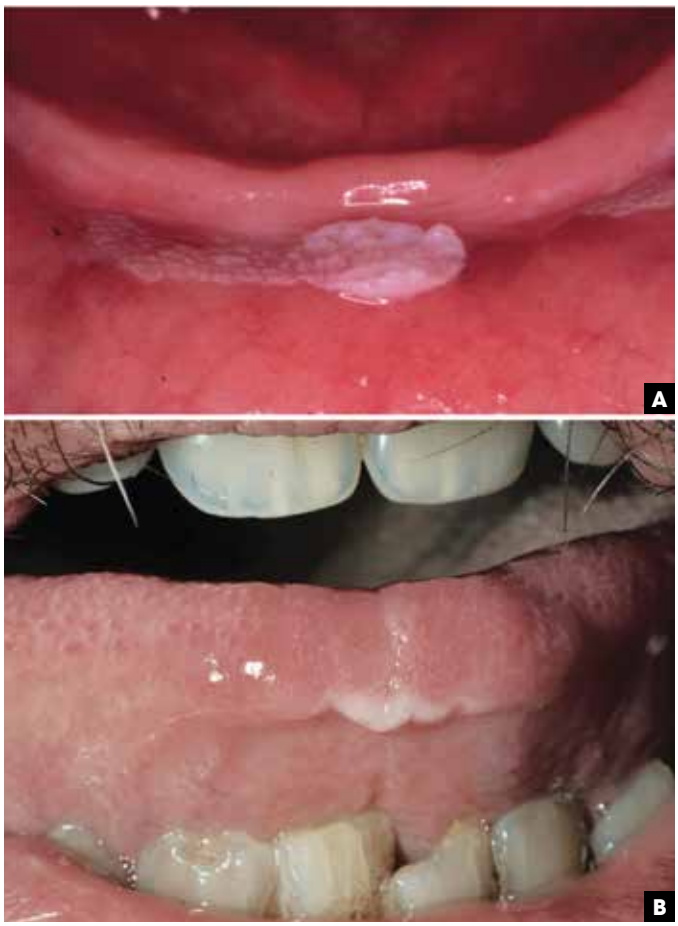


**FIGURE 3. A)** Frictional hyperkeratosis on the mandibular gingiva underneath an ill-fitting denture. **B)** Frictional hyperkeratosis on the anterior tip of the tongue, likely due to chronic rubbing of the fractured lower incisor directly below the lesion.

In addition to smokeless tobacco, the use of electronic cigarettes (eg, e-cigarettes) has been on the rise since 2006. These devices contain a metal heating element that vaporizes a solution containing nicotine and other chemicals, which is then inhaled/exhaled by the user. Little is known about the long-term effects of e-cigarette use on the oral mucosa or any associations it may have with the development of oral cancer and periodontal disease. Further studies are needed to determine the role that e-cigarettes play, if any, in the development of oral mucosal lesions.

ST products have been known for decades to cause white changes in the oral mucosa adjacent to the area in which the tobacco is held. These mucosal changes are known as snuff dipper's lesion, tobacco pouch keratosis, or smokeless tobacco keratosis.[22] The lesional mucosa is painless and may show a white and wrinkled, almost leathery appearance with or without erythema (Figure 4). The lesion cannot be wiped away nor does it disappear upon stretching of the surrounding tissue. Up to 60% of individuals that use ST

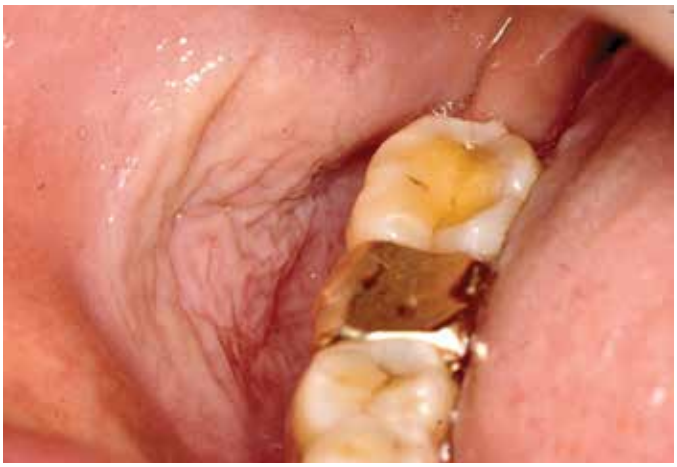

**FIGURE 4.** Soft tissue changes of the right mandibular buccal vestibule where the patient habitually placed his smokeless tobacco. Note the significant occlusal wear of the last molar, which is often seen in conjunction with smokeless tobacco soft tissue lesions.

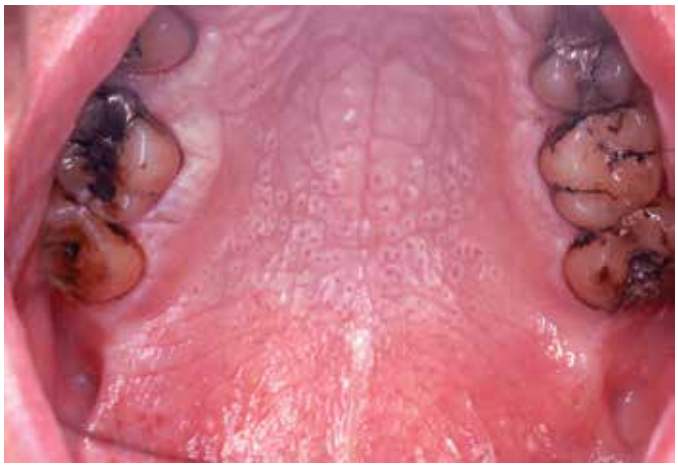

**FIGURE 5.** Nicotine stomatitis in a habitual pipe/cigar smoker. Note the white cobblestone appearance of the hard palate and numerous red puncta representing inflamed minor salivary gland ducts.

will develop some type of mucosal tissue change, especially those who use dipping tobacco and snuff.[22-26] There is a direct correlation between the amount and type of ST used and the degree of white changes seen clinically.[25] If ST use is discontinued, these changes normally resolve completely within a matter of weeks, regardless of the length of time that ST was used. Interestingly, when ST lesions are biopsied, the vast majority typically only show hyperkeratosis and acanthosis of the epithelium, with minimal dysplasia.[22-27] If cell atypia is present, it rarely rises above the level of mild dysplasia. More clinically problematic are the extensive periodontal defects found adjacent to areas of ST use, such as severe gingival recession and/or tooth abrasion.[22,26,28] Given that ST lesions rarely display dysplasia histologically, there has been considerable debate as to the role that ST plays in the development of oral cancer. Several studies using large longitudinal cohorts have shown that the progression to cancer from ST induced white lesions is negligible, leading many to now conclude that ST use, in the absence of other concurrent tobacco habits, contributes only minimally to the risk of developing oral cancer.[23,27,29]

After cessation of ST, any red and/or white changes that do not resolve within several weeks should be biopsied. For those who continue using ST, it is recommended that any suspicious red changes or ulcerations be biopsied immediately. Otherwise, ongoing clinical follow-up of ST lesions is recommended.

### Nicotine stomatitis (smoker's palate)

Nicotine stomatitis (NS), also known as smoker's palate, presents initially as erythema of the hard palate followed by the development of diffuse white papules and plaques, whose clinical appearance has been likened to that of a "dry riverbed" (Figure 5). Punctuating the white plaques are red dots representing inflamed minor salivary gland ducts. NS is generally observed in those who smoke pipes/cigars, which is prevalent in men over the age of 45, or in those who engage in reverse smoking (smoking with the lit end of the cigarette inside the oral cavity).[22,30] It is believed that the combination of intense heat and carcinogens in the smoke irritates the tissue, resulting in NS. This hypothesis is supported by the observation that pipe/cigar smokers who wear a complete upper denture covering the hard palate while they smoke do not present with signs of NS.[31] Histologically, there is hyperkeratosis, epithelial hyperplasia, and squamous metaplasia of the minor salivary gland ducts along with some inflammation of the glands themselves. These reactive changes usually resolve upon cessation of smoking.[22,30]

Nicotine stomatitis palatal lesions in pipe/cigar smokers only occasionally exhibit mild dysplasia, thus they are not at high risk for malignant transformation. NS is, however, an indication of a heavy smoking habit and for this reason patients with NS should be thoroughly examined for other preneoplastic/neoplastic lesions elsewhere within the oral cavity.[30] Unlike pipe/cigar smokers, reverse smokers are much more likely to have substantial cellular atypia in NS lesions and have a significantly higher risk of developing squamous cell carcinoma of the hard palate.[31] Like smokeless tobacco users, patients should be advised to discontinue using all tobacco products and any lesions that do not resolve after two to three weeks should be biopsied. For those who continue smoking, routine clinical follow-up is advised along with biopsies of any ulcerated or other suspicious areas. Special attention should be given to known reverse smokers since they are at a much higher risk of developing malignant neoplasms of the hard palate than pipe/cigar smokers.

### Hairy tongue

Hairy tongue (HT) normally occurs on the posterior third to two-thirds of the dorsal tongue. It is caused by an abnormal increase in the length of the filiform papillae along with a simultaneous decrease in their rate of desquamation. This leads to an accumulation of chromogenic bacteria, fungi, and debris that impart a variety of colors including black, green, yellow, tan, and white (Figure 6).[32,33] There are many proposed causes including tobacco, alcohol, xerostomia, poor oral hygiene, oxidizing mouthwashes, antibiotics, and xerostomia-inducing drugs.[33,34] In one review, antibiotics were the causative agents in 18 (82%) of the 22 HT cases. Xerostomia inducing drugs, such as antipsychotics, were also strongly associated with HT.[33] The lesion can present at any age, but is typically found in men over the age of 40, especially in those who smoke.[33-35] It is

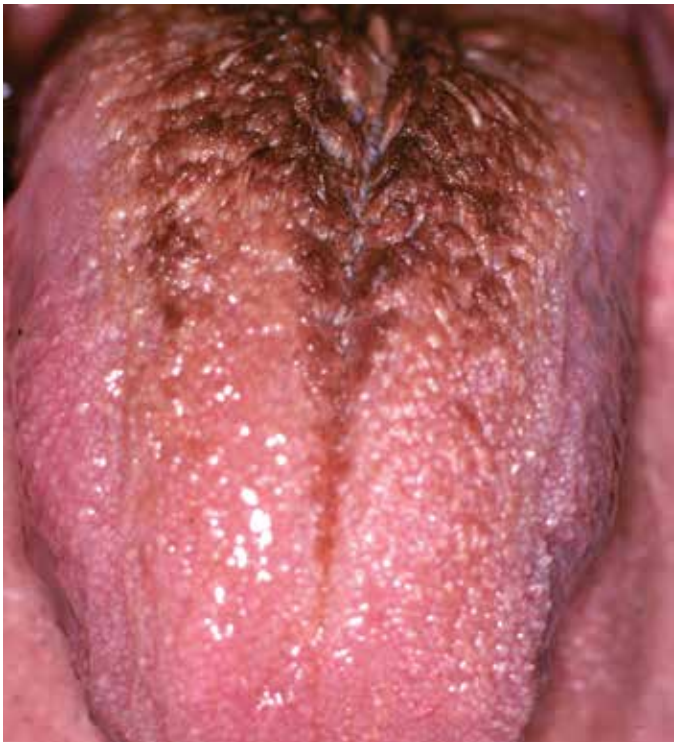

**FIGURE 6.** Hairy tongue on the posterior two-thirds of the dorsal tongue. Elongated filiform papillae with brown discoloration associated with a buildup of chromogenic bacteria, fungi, and/or debris can be seen.

normally asymptomatic; however, for some patients, the increased numbers of papillae can cause halitosis, dysgeusia, gagging, and nausea.[34]

Patients with HT should be reassured that the changes are part of a completely benign process. Conservative treatments include abstention from smoking, alcohol, and drugs that may cause or exacerbate HT. An emphasis on excellent oral hygiene and gentle scraping of the dorsum of the tongue with a tongue scraper can also help aid in reducing the film on the tongue. While mechanical debridement remains the most widely used and effective therapy, several pharmacologic approaches have been reported, such as the use of gentian violet (an antifungal), topical triamcinolone acetonide, topical 40% urea solution, salicylic acid, podophyllin, and topical oral retinoids.[32,33] While good oral hygiene is important in all patients, treatment is not necessary unless patients are symptomatic or find the condition cosmetically objectionable.

### Hairy leukoplakia

Hairy leukoplakia (HL) was first described in 1984 as a white lesion seen in young HIV positive homosexual men, who subsequently went on to develop AIDS.[36] Although it can be found on any intraoral site, HL predominantly presents on the lateral borders of the tongue, often bilaterally, and has slightly raised, ill-defined borders with a shaggy or corrugated surface (Figure 7A).[37,38] The Epstein Barr Virus (EBV) can be detected within affected cells of HL lesions and is now recognized as the causative etiologic factor.[37-39]

Histologically, HL shows hyperparakeratosis, acanthosis, and usually no dysplasia. Suprabasal, edematous, balloon cells show EBV cytopathic changes such as a perinuclear halo and intranuclear peripheral condensation of chromatin (Figure 7B-D). About half of these lesions are also secondarily infected with Candida species of fungi.[39,40] It is not well understood why HL occurs predominantly on the lateral border of the tongue. Some studies have shown that Langerhans cells, a type of antigen presenting cell, are essentially absent in the epithelium of HL lesions.[41] Moreover, parts of the dorsal and lateral tongue naturally contain lower levels of Langerhans cells, which could predispose these areas to EBV infection or latent EBV reactivation in immunocompromised patients.[41,42]

HIV infection along with other causes of local or systemic immunosuppression should be assessed in all cases of HL.[43,44] Treatment of HL should focus first on restoring a normal functioning immune system, when possible, since local treatments offer only a temporary resolution. In one study, bone mar-

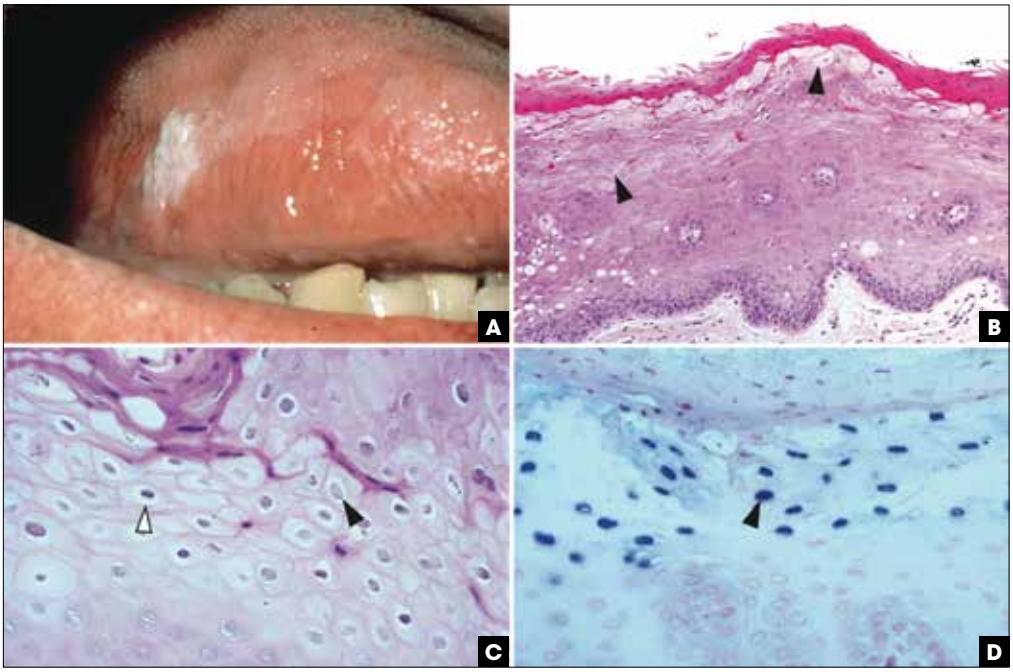


**FIGURE 7. A)** Hairy leukoplakia on the right lateral surface of the tongue. **B)** Biopsy shows normal basal layer cells, acanthosis, hyperkeratosis, and cellular ballooning in the suprabasal layers (black arrowheads). **C)** At higher magnification Epstein Barr Virus (EBV) cytopathic effects such as perinuclear halos (white arrowhead) and intranuclear peripheral condensation of chromatin (black arrowhead) can be seen. **D)** In-situ hybridization with an anti-EBV probe (EBER) shows positive cells in dark blue (black arrowhead).

row transplant patients with HL-like lesions following bone marrow ablation had no clinical signs of HL six months after bone marrow transplantation, suggesting that reconstitution of the immune system was sufficient to clear these lesions.[45] Systemic treatments with acyclovir as well as the topical use of gentian violet, retinoids, podophyllin, and acyclovir have been reported.[38,39] Good, but temporary, results have been reported with the use of combined acyclovir and podophyllin topical therapy.[38] Because fungal infections of HL lesions are present in about 50% of cases, it may be advisable to also treat these lesions concurrently with antifungal therapy.

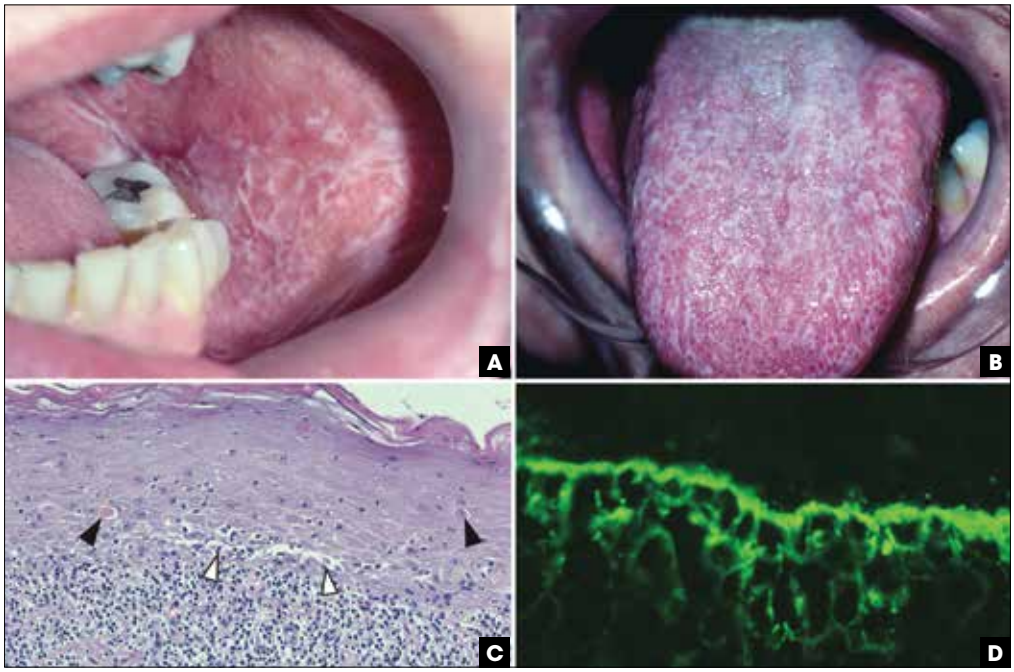


**FIGURE 8. A)** Reticular form of oral lichen planus (OLP) on the left buccal mucosa. **B)** Reticular form of OLP on the dorsal tongue. **C)** Lesional biopsy showing a band-like infiltrate of lymphocytes at the epithelial-connective tissue junction, hyperkeratosis, and basal layer keratinocyte destruction in the form of vacuolar degeneration (white arrowheads) and dying keratinocytes (black arrowheads). **D)** Direct immunofluorescence showing deposits of fibrinogen at the basement membrane.

## Inflammatory-mediated lesions

### Oral lichen planus

Lichen planus is a well-known mucocutaneous disorder of presumptive autoimmune origin that may affect numerous sites including the skin, oral cavity, genitals, esophagus, nails, and scalp.[46] In contrast to the cutaneous form, oral lichen planus (OLP) tends to persist over time with less spontaneous remission.[47] OLP is polymorphous with six main patterns: reticular, erosive (ulcerative), papular, plaque-like, atrophic (erythematous), and bullous. Multiple forms may be present simultaneously and may change over time within the same patient, a finding that can aid in distinguishing OLP from pemphigus vulgaris and mucous membrane pemphigoid since mixed lesions are usually exclusive to OLP.[48] The reticular and erosive forms of OLP are the most common.[48-50] The reticular type is usually asymptomatic and is characterized by numerous white anastomosing lace-like lesions, known as Wickham's striae. In contrast, the erosive form tends to be painful and is usually comprised of both ulcerated and reticular areas.

OLP lesions may be present on any intraoral surface; however, they are most commonly found bilaterally on the buccal mucosa followed by the gingiva, dorsal tongue, lateral tongue, labial mucosa, and floor of mouth (Figure 8A-B).[49] Depending on the population studied, OLP has a prevalence of 0.11% to 1.9% and affects middle-aged women more often than men in an approximately 2:1 to 3:1 ratio.[2,46,49,50] The histology of OLP is similar to cutaneous forms with a band-like infiltrate of lymphocytes at the junction of the epithelium and connective tissue, hyperparakeratosis, basal keratinocyte vacuolar changes, and apoptotic cells (Civatte bodies). Unlike cutaneous forms of lichen planus, OLP lesions show deposition of fibrinogen along the basement membrane, which can be detected using direct immunofluorescence and is often helpful in establishing the diagnosis (Figure 8C-D). The microscopic findings should always be correlated with the patient's clinical presentation, as the histologic features of OLP are not always pathognomonic and may mimic other conditions such as hypersensitivity reaction.

Prior to treatment, presumptive OLP lesions should be biopsied to confirm the diagnosis. In contrast to cutaneous lichen planus, the generally accepted practice is to biopsy oral lesions with emphasis on atypical or unusual appearing forms. Biopsy also permits microscopic examination to rule out dysplasia and OSCC, both of which can arise in the setting of OLP and can clinically mimic atypical forms of OLP. Oral lesions may precede cutaneous or genital involvement and patients should be assessed for this possibility.[46] OLP is often initially treated with systemic and topical corticosteroids, although the use of other immune modulating drugs, such as cyclosporine and tacrolimus, have been reported.[47,48] For maintenance therapy, topical corticosteroids such as fluocinonide (0.05%) and clobetasol propionate (0.05%), applied to affected areas between one and five times per day depending on disease severity, are effective. Several delivery methods are available and include ointments and mouth rinses; but clinicians should be aware that a significant challenge is the short contact time between steroid and lesion for many oral preparations. Corticosteroids in ointment form may be applied topically via a vehicle (modified dental trays or gauze) in order to improve contact time with tissues.[51] Additionally, corticosteroids can be compounded with orabase-b, a sticky dental paste containing benzocaine, in a 1:1 ratio that can be very helpful in achieving adequate contact time with oral mucous membranes. If corticosteroids in liquid form are used, such as dexamethasone elixir (0.1mg/ml), rinsing for one minute one to two times daily and abstaining from eating or drinking for 60 minutes afterwards can also be helpful in treating widespread OLP lesions.

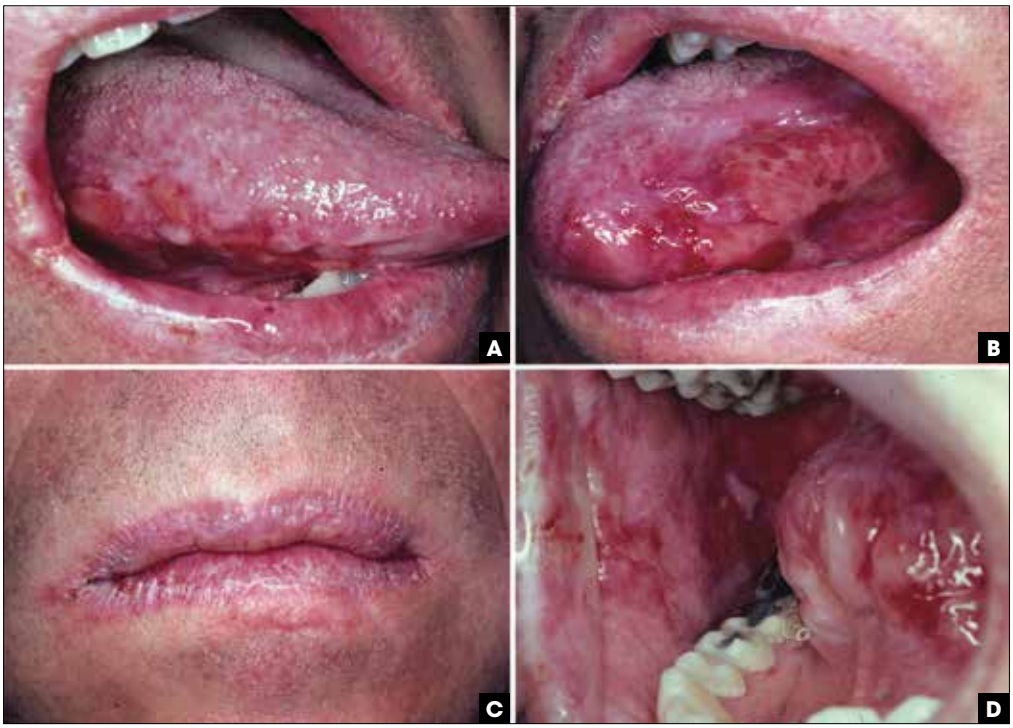


**FIGURE 9.** Drug-induced oral lichenoid reaction on the **A)** right lateral tongue; **B)** left lateral tongue; **C)** lips; **D)** right buccal mucosa from the same patient. The reticular and erosive patterns seen here are clinically similar to changes seen in oral lichen planus.

The risk of OLP transforming into oral cancer is controversial and not fully understood.[49,52-54] Current studies estimate the incidence of oral squamous cell carcinoma (OSCC) in OLP patients to be between 0.36% and 1% over five years.[47,53] Since patients with OLP may have a slightly increased risk of developing OSCC, they should be routinely clinically screened, often every six months to once a year, to ensure that their OLP is well controlled and to monitor for the development of dysplasia and OSCC.[55] Routine biopsies of OLP lesions are usually not indicated unless clinically observable changes have occurred, such as either changes in color, texture, pain, etc or the presence of nonhealing, treatment refractory ulcers. Biopsies in these instances are warranted in order to ensure that any such changes are not preneoplastic or malignant.

### Oral lichenoid reactions

Oral lichenoid reactions (OLR) are nearly identical clinically and histologically to OLP (Figure 9). OLR occur less frequently intraorally than they do in the skin and tend to present unilaterally, occasionally with ulcerations.[56] Although the pathogenesis of these reactions is not well understood, various medications have been implicated and the list of possible offenders is legion. The most commonly reported drugs associated with OLR are nonsteroidal anti-inflammatory medications, antihypertensives, and HIV antiretrovirals.[48] Treatment of these lesions involves removal of the offending drug, if possible, or management with topical corticosteroids. Other lichenoid reactions can be caused by dental restorative materials and certain food flavorings. Amalgam fillings containing mercury are one of the most common causes of OLR, although similar reactions to many other dental restorative materials, such as nickel and composite resins, have been documented.[48,57] Flavoring agents like cinnamaldehyde and peppermint oil used in chewing gum or dental hygiene products are also known to cause OLR.[58,59] OLR lesions are normally in close proximity to the source of irritation and often present with reticular or erosive lesions nearly identical to those seen in OLP. Treating lesions can be challenging, as it is sometimes difficult to identify the source of irritation. Once the irritant is removed, oral lesions normally completely resolve. Lichenoid lesions that do not resolve should be biopsied to rule out dysplasia and OSCC. If the irritant cannot be identified, treatment with topical corticosteroids should be initiated.

Distinguishing OLP from OLR is nearly impossible by microscopy alone. Four features that have been suggested to differentiate OLR from OLP are: 1) an inflammatory infiltrate located deep to the superficial infiltrate in some or all areas, 2) a focal perivascular inflammatory infiltrate, 3) plasma cells in the connective tissue, and 4) neutrophils in the connective tissue. Clinically, OLRs tend to present unilaterally whereas OLP has a symmetric distribution. Ultimately, a final diagnosis is made based on a synthesis of both clinical and pathological information.[60]

## Preneoplastic/neoplastic

### Oral leukoplakia

The usage and application of the term 'oral leukoplakia' (OL) has generated confusion and controversy. In its simplest form, OL simply means a white patch found within the oral cavity. This broad definition encompasses all pathologic processes of the oral mucosa that culminate in the formation of an intraoral white patch. Since some benign intraoral white lesions can be diagnosed clinically, several groups have advocated a narrower definition of OL. Although the exact terminology continues to evolve, OL in this context is generally defined as an idiopathic white lesion that cannot be wiped off, cannot be characterized as any other definable lesion, and has malignant potential.[61] This definition implies that a biopsy has yet to be performed, making the preliminary clinical diagnosis of OL a placeholder until a histologic diagnosis can be made. When biopsied, OL lesions often show hyperkeratosis or grades of epithelial dysplasia microscopically; once a microscopic diagnosis has been rendered, this diagnosis then becomes the correct clinical diagnostic term (Figure 10).

Four clinical patterns of OL have been described: homogeneous, nodular, speckled (ie, contains red and white changes), and proliferative verrucous leukoplakia.[62] These lesions occur within a wide age range, although the majority develop during the 5th and 6th decades of life.[17,18,63] The male-to-female ratio varies depending

on geographic location, although in two retrospective studies conducted within the United States, the ratios were 1.3:1 and 3.7:1.[17,18,64] Several risk factors associated with developing OL have been identified. These include certain genetic disorders such as dyskeratosis congenita and fanconi anemia, the use of tobacco or areca/betel nut, and alcohol consumption.[65-68] In one retrospective review of 1,676 clinically diagnosed OLs, most lesions originated from the tongue (28%) followed by the buccal mucosa (19%), mandibular sulcus (15%), palate (13%), maxillary sulcus (11%), floor of mouth (11%), and labial mucosa (2%). The vast majority of these lesions were diagnosed as idiopathic hyperkeratosis without dysplasia (75%), mild-to-moderate dysplasia (19%), severe dysplasia to carcinoma in-situ (5%), and OSCC (1%).[17] In general, any intraoral white lesion fitting the clinical criteria of OL should be biopsied, especially if it has any associated red changes, as these mixed red and white lesions (known as erythroleukoplakias) have a significantly higher risk of presenting with, or progressing to, OSCC.[63,66]

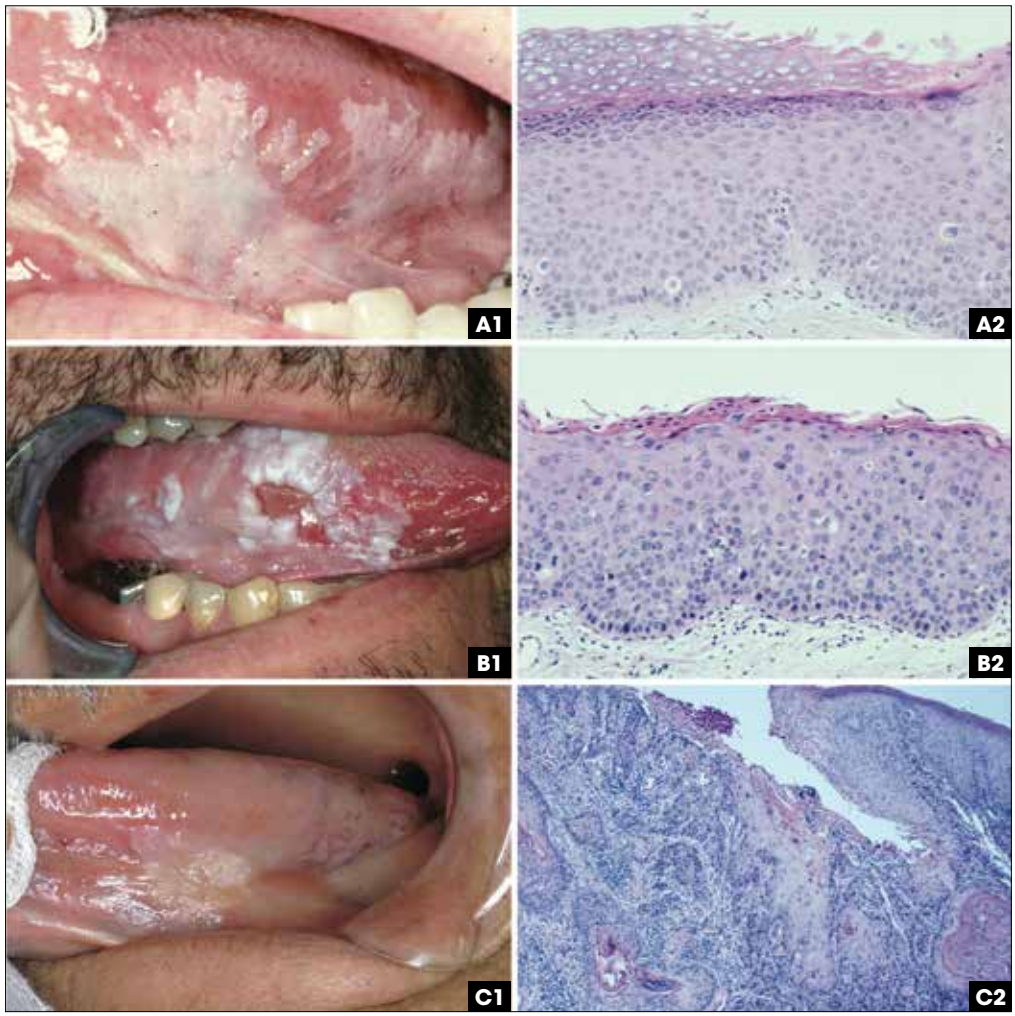


**FIGURE 10. A1, B1, C1)** Intraoral white lesions preliminarily described clinically as oral leukoplakia prior to biopsy. The corresponding microscopic diagnosis of each lesion was **A2)** moderate dysplasia; **B2)** severe dysplasia; **C2)** squamous cell carcinoma. Prior to biopsy, oral leukoplakias can look similar clinically, underscoring the need for biopsy in order to properly diagnose and treat these lesions.

Any OL, as defined in this review, has premalignant potential, but those that contain epithelial dysplasia microscopically have a higher risk of transforming into OSCC than those without dysplasia.[69-71] A recent meta-analysis analyzing the overall malignant transformation rate of OLs reported ranges of 0.0% to 36.4%, with an overall pooled average of 12.3%. When accounting for the histologic grade of dysplasia present (mild to moderate vs severe to carcinoma in-situ), the rates were 10.3% and 24.1%, respectively.[71] In another study, the pooled malignant transformation rate of OLs with severe dysplasia or carcinoma in-situ was 15.6%.[72] In contrast, some studies report that for the individual patient the grade of dysplasia does not predict the risk of transformation to OSCC.[73] Several risk factors for malignant transformation of OL have been assessed and include a history of never smoking (presumably due to underlying genetic aberrations), a history of heavy smoking, female gender, intraoral site where the lesion is located (eg, the floor of mouth and lateral borders of the tongue are at higher risk of malignant transformation than other intraoral sites such as the buccal mucosa and gingiva), size of the lesion, homogeneity vs heterogeneity of the lesion, presence of dysplasia, and altered p53, p16INK4a, and Ki-67 expression patterns; none, however, are reliably predictive.[69,74-76]

Clinical management of OL lesions has proven difficult. Various treatment options such as surgical excision, laser ablation, photodynamic therapy, cryotherapy, and topical/systemic therapies have been used; however, strong evidence in the form of randomized, controlled trials evaluating their effectiveness in preventing recurrence and/or transformation to OSCC is lacking.[77,78] Currently, idiopathic hyperkeratotic and mildly dysplastic lesions are usually carefully monitored, whereas lesions with moderate-to-severe dysplasia or carcinoma in-situ are removed along with normal marginal tissue. Surgical excision is preferred because unlike laser ablation that destroys lesional tissue, surgical excision allows for histologic study of the specimen in order to assess for variations in the grade of dysplasia and the presence of OSCC. Although some smaller studies do not show a decrease in OSCC transformation rates for patients who have had their dysplastic lesions removed surgically, a meta-analysis of 14 studies comprising over 900 patients showed that these rates actually do decrease by more than half from 14.6% to 5.4% after surgical excision.[71,78]

Recurrence is a common problem following excision of any OL.

One retrospective study of 52 patients that underwent surgical excision of OL lesions reported a recurrence rate of around 15%, although recurrence rates ranging from 5% to 39.5% have also been reported.[79,80] Interestingly, the grade of dysplasia in these studies did not predict the risk of recurrence.[79,80] Significant risks for recurrence included age over 59 years, lesions on the gingiva, positive surgical margins, and surgical margins less than 3mm. The median time between surgery and recurrence was 17 months (range 2 to 40 months).[79] Smoking cessation has been shown to reduce the rate of recurrence as well as lower the risk of transformation into OSCCs.[63,81] Some studies have even shown that smoking cessation may cause a reduction or complete regression of OL lesions over time.[63,66]

Clinicians should be particularly cautious of OLs on the floor of the mouth, gingiva, and lateral/ventral tongue since conversion rates to OSCC are higher at these sites. Some groups report that the majority of OLs that will transform into OSCCs do so during the first two to five years of follow-up after biopsy, with lower transformation rates in subsequent years.[63,66,73] For this reason, we believe it is critical to closely monitor patients every three to four months following a diagnosis of idiopathic hyperkeratosis/dysplasia, even though some question whether this practice actually improves survival rates of patients that eventually convert to OSCC.[64] Any change in the color and texture of OL or the development of discomfort/pain in the vicinity of these lesions warrants a new biopsy. More research is needed to identify and validate molecular markers that can predict which OL lesions will progress to OSCC as well as which treatment modalities offer patients the best long-term outcomes.

### Squamous cell carcinoma

Squamous cell carcinoma (SCC) of the head and neck, which includes various anatomic sites such as the nasal/paranasal sinuses, oral cavity, oropharynx, hypopharynx, and larynx, is the sixth most common cancer worldwide and affects between 35,000 and 45,000 people annually within the United States.[82-84] The overall 5-year survival rate is approximately 57%; however, those diagnosed at earlier stages may have improved 5-year survival rates of up to 75% to 90%.[83,85,86] Indeed, the stage of the disease at the time of diagnosis, which takes into account tumor size, involvement of regional lymph nodes, and distant metastases, is one of the strongest prognostic factors for patient survival.[86] Unfortunately, about two-thirds of patients will present with advanced disease upon initial diagnosis.[86]

Although SCC diagnosed in the mouth and throat are often collectively known simply as 'oral cancer,' the oral cavity and oropharynx have distinct anatomic boundaries as well as risk factors associated with SCC development and overall prognosis. By convention, the oral cavity includes the anterior two-thirds of the tongue and all intraoral soft tissues anterior to the first tonsillar pillar (the palatoglossal arch). In turn, the oropharynx comprises the posterior third of the tongue (base of tongue) and is bordered superiorly by the soft palate, laterally by the tonsillar pillars and palatine tonsils, and inferiorly by the epiglottis. Known risk factors associated with both oral and oropharyngeal SCC include the use of cigarettes, alcohol, and betel quid/paan.[82,86] Conversely, high risk human papilloma virus subtypes (usually HPV 16) are a significant risk factor for developing oropharyngeal SCCs, but not oral SCCs, since the virus is found in up to 72% of oropharyngeal SCCs compared to only 7% of oral SCCs.[84]

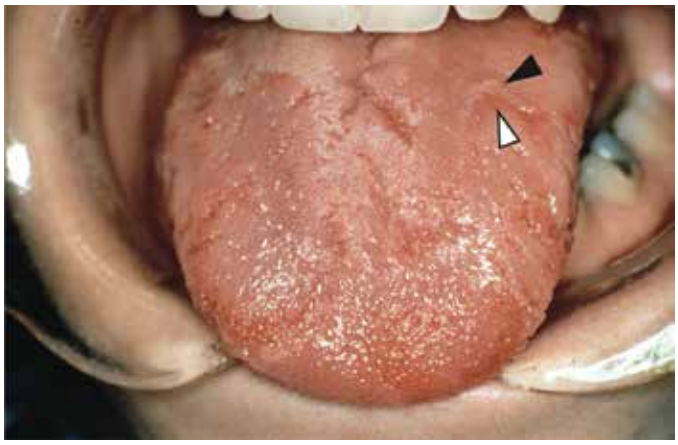

**FIGURE 11.** Geographic tongue. Multiple circinate areas of erythema due to depappillation (ie, loss of filiform papillae, white arrowhead) surrounded by white borders (black arrowhead) can be seen. These lesions are usually asymptomatic.

Oral SCC can present clinically in a number of ways. The classical presentation is that of a nonhealing ulcer with indurated borders. However, it can also commonly appear as a white and/or red patch or as an exophytic/verrucous mass (Figure 10).[86,87] Although SCC can occur anywhere in the oral cavity, favored high risk sites include the lateral/ventral tongue and floor of mouth.[85,86] Because of its ability to clinically mimic other benign and preneoplastic intraoral white lesions, a biopsy and microscopic examination are crucial in determining the correct diagnosis. Once diagnosed, patients are typically treated surgically along with radiotherapy and/or chemotherapy, all of which have significant side effects.

## Other

### Geographic tongue (benign migratory glossitis)

Geographic tongue, also known as benign migratory glossitis (BMG), is a benign condition of the tongue whose etiology is currently unknown and that affects approximately 2% of the United States population.[30] Single or multiple well-defined circinate areas of erythema due to depapillation (loss of filiform papillae) can be seen on the dorsal tongue surrounded by white borders (Figure 11). These lesions may resemble a topographical map (hence the name geographic tongue) and often change shape and location within hours to days.[88] Although predominantly located on the dorsal tongue, BMG lesions may also rarely occur on other intraoral surfaces, such as the buccal mucosa and gingiva, and in this context is known as erythema migrans.[89] Lesions often wax and wane over time and are normally asymptomatic; however, occasionally patients with BMG lesions will complain of burning, dysgeusia (altered taste sensation), or discomfort in response to acidic and/or spicy foods.

Histologically, BMG resembles psoriasis, especially pustular psoriasis.[89] Sterile spongiotic pustules and subcorneal pustules composed of neutrophils can be identified in areas of depapillation on the tongue along with psoriasiform hyperplasia of the epithelium. These pustular areas are bordered microscopically by hyperkeratotic epithelium that corresponds clinically with the

white borders of BMG lesions. Despite the microscopic similarities shared with psoriasis, there is no convincing evidence of a relationship between the two diseases.[90-92]

Patients with symptomatic BMG can be managed in a number of ways. First, it is often helpful to rule out any fungal infection, as this can mimic or exacerbate BMG-related signs and symptoms. The avoidance of acidic and/or spicy foods may also prove helpful in relieving symptoms. Pharmacologic treatments include the use of systemic and/or topical corticosteroids.[88] In cases refractory to corticosteroids, some groups have reported success using systemic cyclosporine and topical tacrolimus.[93,94] BMG lesions do not need to be biopsied since they are usually straightforward to identify clinically and are completely benign.

## Conclusion

Intraoral white lesions have numerous etiologies and include a range of benign and malignant disorders. Most cases require biopsy to establish the diagnosis and to select/initiate the appropriate therapy.

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