Clinical features and presentation of oral potentially malignant disorders

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Oral potentially malignant disorders (OPMDs) are conditions that precede the onset of invasive cancers of the oral cavity. The term embraces precancerous lesions and conditions referred to in earlier World Health Organization (WHO) definitions. Leukoplakia is the most common OPMD; erythroplakia, although rare, is more serious. Several variants of leukoplakia are recognized, and clinical subtyping may help determine the prognosis to a limited extent. Biopsy is essential to confirm the provisional clinical diagnosis, and timely referral to a specialist is indicated. Certain OPMDs, such as oral submucous fibrosis, are encountered particularly in population groups from Asia with specific lifestyle habits. This review provides clinical descriptions of the wide range of potentially malignant disorders encountered in the oral cavity as a prelude to the topics discussed in this focus issue. (Oral Surg Oral Med Oral Pathol Oral Radiol 2018;125:582–590)

A range of oral mucosal disorders with an increased risk of malignancy has been described in the literature, and these disorders are listed under the umbrella term oral potentially malignant disorders (OPMDs). The spectrum of OPMDs include oral leukoplakia, erythroplakia, erythroleukoplakia, oral submucous fibrosis (OSF), palatal lesions in reverse smokers, oral lichen planus, oral lichenoid reactions, graft-versus-host disease (GvHD), oral lupus erythematosus, and some hereditary conditions, such as dyskeratosis congenita and epidermolysis bullosa. Actinic cheilitis of the lower lip is also associated with an increased risk of lip cancer. The majority of these disorders may be asymptomatic in the early stages of their evolution and may be detected by dental practitioners on routine oral examination. It is essential, therefore, that health professionals are knowledgeable about the clinical features and diagnostic aspects of OPMDs to further investigate and, where appropriate, make referrals to specialists for treatment.

It has been known for over a century that oral cancer may develop in areas of pre-existing mucosal pathology in the oral cavity. In the literature, these lesions have been referred to by such terms as “pre-cancer,” “precancerous/ premalignant lesions,” and “intraepithelial neoplasia.” A more precise term, “potentially malignant disorders,” was adopted by the WHO Collaborating Center because there is no certainty that all precancerous lesions will eventually develop into oral cancer. The term also embraces precancerous lesions and conditions that were included in the previous WHO classifications.3 In this focus issue, it is proposed to introduce a new term “potentially premalignant oral epithelial lesions [PPOELs]” (see Editorial). The underlying concept is that these lesions have the potential to become malignant, so in their current state, that is, before malignant transformation, they are still (potentially) premalignant.

Since the 2007 publication characterizing OPMDs,1 new evidence has emerged to support the inclusion of oral lichenoid lesions and oral lesions of GvHD as potentially malignant disorders. Brief descriptions of these conditions are also included here.

LEUKOPLAKIA

To precisely diagnose oral leukoplakia, it is important to consider its definition.3 Historically, the term leukoplakia was used clinically to denote any adherent white patch or plaque (keratosis). Over several decades, clinicians realized that all white patches arising in the oral cavity should not be labeled oral leukoplakia. Several definitions of oral leukoplakia have been put forth in the past few decades. The most recent definition in use refers to leukoplakia as “predominantly white plaques of questionable risk, having excluded (other) known diseases or disorders that carry no increased risk for cancer.” Examples of other benign white lesions that should be excluded to arrive at the diagnosis of oral leukoplakia are frictional keratosis (cheek biting), alveolar ridge keratosis, leukoedema, white sponge nevus, and Fordyce granules, which are usually buff colored.

Oral leukoplakia may be asymptomatic or display a benign clinical appearance making it difficult for the
clinician to sometimes differentiate it from common reactive or inflammatory (benign) disorders of the oral mucosa.

Leukoplakias are usually diagnosed after the fourth decade of life. They are more common in males and are 6 times more common among smokers than among non-smokers. Alcohol consumption is an independent risk factor. Leukoplakia is not associated with any chemical or physical causative agents except tobacco, alcohol, or betel quid. In a minority of leukoplakias, human papillomavirus may have a potential role. Some leukoplakias are idiopathic and may not have a known risk factor. The risk factors for oral leukoplakia are considered in detail in a later article in this focus issue.

Common sites of involvement in Western industrialized populations include the lateral margin of the tongue and the floor of mouth. However, among Asian populations, the buccal mucosa and the lower buccal grooves are commonly affected because of placement of betel quid at these locations. Gingival leukoplakia (affecting gums) is uncommon but has been reported to affect predominantly the Japanese population.

A patch of oral leukoplakia may vary in size from a quite small and circumscribed area to an extensive lesion involving a large area of the oral mucosa.

Two main clinical types of leukoplakia are encountered in clinical practice: homogeneous and nonhomogeneous leukoplakia. The distinction is based on surface color and morphologic (thickness and texture) characteristics. Homogeneous leukoplakias are uniformly flat and thin, have a smooth surface, and may exhibit shallow cracks. Nonhomogeneous varieties comprise 3 clinical types and are usually symptomatic:

1. Speckled—mixed, white and red in color (also termed erythroleukoplakia), but retaining predominantly white coloration
2. Nodular—small polypoid outgrowths, rounded, red or white excrescences
3. Verrucous or exophytic—wrinkled or corrugated surface appearance

Generally, most leukoplakias are asymptomatic and are found during a routine visual examination by a practitioner. Symptoms, if present, are associated with the nonhomogeneous speckled variety and, in our experience, include discomfort, tingling, and sensitivity to touch, hot beverages, or spicy foods. A red component in the leukoplakia (erythroleukoplakia) indicates possible colonization by Candida species and an increased risk for dysplasia and/or malignancy.

When widespread or multiple patches of leukoplakia are noted, the term proliferative verrucous leukoplakia (PVL) is used. Other criteria for a diagnosis of PVL are given in a later section. This is a distinct entity that carries a higher risk for malignant transformation and is, fortunately, rare.

A provisional clinical diagnosis of leukoplakia is made for a white patch after excluding any local trauma as a cause and confirming that it cannot be scrapped off and that the color does not disappear after stretching the tissue. Due consideration must also be given to excluding other conditions that clinically appear white in color.

Figures 1 through 3 illustrate clinical presentations of both homogeneous and nonhomogeneous leukoplakias. Figure 4 illustrates a carcinoma arising in a mixed, white-and-red lesion (erythroleukoplakia).

Several tobacco-induced lesions, such as smoker’s palate (leukokeratosis nicotina palati), palatal keratosis of reverse smokers, and snuff [or snus] dipper’s lesions are traditionally separated from leukoplakia, although they are white in appearance and are also associated with tobacco use.

As leukoplakia is a provisional clinical diagnosis, tissue biopsy should be performed on the observed white patch.
and a representative sample of the specimen sent for histopathologic analysis. The reasons for biopsy are (1) to exclude other pathologies (including carcinoma) that might be responsible for the white patch, and (2) to evaluate the presence and degree of epithelial dysplasia within the patch. An additional reason is to assess for any candidial colonization within the epithelium. The grade of dysplasia as reported by a pathologist, in spite of controversies regarding interpretation, remains our best aid for assessment of the risk for malignant transformation of OPMDs.

PROLIFERATIVE VERRUCOUS LEUKOPLAKIA

Any leukoplakic lesion that becomes warty, exophytic, and widespread over a period and that has recurred after treatment should arouse clinical suspicion of PVL. The widespread nature of the condition may involve multiple sites of the oral cavity, primarily the gingiva, alveolar mucosa, tongue, and buccal mucosa. Figure 5 illustrates a case of PVL with extensive keratosis affecting the gingiva and the alveolar and buccal mucosa. A set of criteria for the diagnosis of PVL was presented by Cerero-Lapiédra et al. The major clinical criteria they proposed include (1) leukoplakic lesion with greater than 2 oral sites, most frequently the gingiva, alveolar processes, and palate, (2) existence of a verrucous area, (3) lesions that have spread or engrossed during development of the disease, and (4) recurrence in a previously treated area.

All PVLs do not have a verrucoid appearance, especially in the initial stages, and a group of US experts have recently ascribed a clinical diagnosis of PVL to patients presenting with multifocal lesions that are devoid of a verrucous appearance. On the basis of the argument that involvement of multiple sites is a more important criterion than a verrucous appearance, Aguirre-Urizar has proposed an alternative term “proliferative multifocal leukoplakia” for this condition.

ERYTHROPLAKIA

The term erythroplakia is used analogously to leukoplakia and has been defined as “a fiery red patch that cannot be characterized clinically or pathologically as any other definable disease.” The lesions of erythroplakia are usually irregular in outline, although well defined, and have a bright red velvety surface. Occasionally, the surface is granular. The most commonly involved subsite is the soft palate (Figure 6). Just as there are many oral lesions that present clinically as white patches on the mucosa, there are a number of conditions that appear as red areas. Examples of other red patches that need to be differentiated from erythroplakia have been outlined by Reichart and Philipsen. Two common examples of entities often mistaken by practitioners as erythroplakia are erythematous candidiasis (denture-associated somatitis) and erythema migrans. Other conditions to include in the differential diagnosis are erosive disorders, desquamative...
gingivitis, discoid lupus, erosive lichen planus, pemphigoid, and other inflammatory/infectious conditions. Well-demarcated, solitary presentation of erythroplakia helps clinically distinguish it from the other more widespread disorders listed above.

A diagnostic biopsy is essential to obtain a pathologist’s opinion to distinguish erythroplakia from the above-mentioned specific and nonspecific inflammatory oral lesions. This should be undertaken urgently because in many cases, the erythroplakia is dysplastic or may harbor carcinoma in situ or even frank carcinomas.

**ERYTHROLEUKOPLAKIA**

Mixed white-and-red lesions, previously referred to as *speckled leukoplakia*, are now termed *erythroleukoplakia*. The red component (see Figure 2) shows either atrophy (thinning) or sometimes speckling. Erythroleukoplakia, unlike leukoplakia or erythroplakia, may have an irregular margin. The patient may experience some soreness, often as a result of colonization by candidal hyphae.

**ORAL LICHEN PLANUS**

The oral manifestations of lichen planus (OLP) vary from patient to patient. Oral mucosal lesions are usually multiple and have a symmetric distribution. The clinical presentation of OLP can be divided into several clinical subtypes: linear, reticular, annular, papular, plaque, atrophic, and ulcerative OLP. Bullous lichen planus is rare. In dark-skinned people, the affected area shows signs of pigmentation. Patients often display features of more than one subtype simultaneously.

Lichen planus lesions usually present as a bilateral keratotic lace-like network of white striae on the buccal mucosa and the lateral margins of the tongue. The reticular type is the most frequent type encountered in clinical practice, and most patients are asymptomatic. The reticular lesions appear as interlaced, raised lines forming a latticework (Figure 7). Sometimes, the striae may have a linear or annular presentation. Reticular OLP can also be found on the mucobuccal fold, gingiva, floor of mouth, labial mucosa, lips, and, rarely, palate. The papular type presents as small, white, raised papules that the clinician must differentiate from Fordyce granules. The plaque type commonly found on the dorsum of the tongue closely resembles leukoplakia; however, keratotic white striae are found at the lesion periphery. Atrophic erosive and ulcerative types may present as erythematous areas or with frank ulceration. Often, keratotic white striae are seen at the margins. When the lesion is ulcerated, patients typically complain of soreness or a burning sensation while eating hot or spicy food.

Atrophic OLP presenting on the gingiva, can be seen as desquamative gingivitis. The bullous type is rare, tends to recur, and is important to be differentiated from pemphigus or mucous membrane pemphigoid.

Some patients may exhibit cutaneous lichen planus, and medical history may help identify OLP cases. Other extraoral mucosal sites, such as the genitalia, may also be affected. Genital examination may help to identify persons with the vulvovaginal gingival variant of lichen planus.

Lichen planus is usually diagnosed clinically. Its bilateral distribution and the presence of the classic reticular forms with keratotic white striae are helpful for chairside diagnosis. The differential diagnosis for OLP, when it presents with a reticular/erythematous appearance, includes lichenoid lesions, lichen sclerosus, discoid lupus erythematosus (DLE), when ulcerative, chronic ulcerative stomatitis, and, when plaque-like, oral leukoplakia. Biopsy and histopathologic examination are recommended to make a definitive diagnosis. The essential histologic findings are comparable, regardless of the areas involved or the subtype of clinical presentation.
Microscopy also aids in identifying the presence of epithelial dysplasia and, on rare occasions, malignancy. Direct immunofluorescence studies do not aid in the diagnosis of lichen planus but could help rule out DLE or mucous membrane pemphigoid.

OLP may last for several years, with periods of symptom flare-ups and remission. In patients with the ulcerative type of OLP, sclerotic fibrous bands may appear. A systematic review has confirmed malignant transformation of OLP lesions, but there are no specific criteria to assess this risk.

**ORAL LICHENOID LESIONS**

Oral lichenoid lesions (OLLs) are intraoral white-and-red lesions with a reticular, striated appearance and clinical features similar to those of OLP; however, OLLs have an underlying causative agent. Another term used analogously is oral lichenoid reactions (OLRs). OLLs/OLRs can be classified into 3 types: (1) in topographic relationship to a dental restoration, often amalgam, also named oral lichenoid contact lesions (OLCRs), (2) drug-related, and (3) in association to chronic graft-versus-host disease (cGvHD).

OLLs/OLRs present as white or mixed white-and-red lesions, sometimes with additional ulceration. Associated clinical signs are white reticular, linear, or annular striae and/or white plaque-like patches. In the erosive type of OLLs/OLRs, red and mixed lesions appear as erythematous atrophic patches, often with some ulceration of the oral mucosa. The differentiation from OLP may be clinically difficult in some cases.

OLLs/OLRs caused by hypersensitivity to dental restorations are, however, often localized to the site that is in contact with the allergenic material (Figure 8), whereas OLP has a bilateral and widespread presentation. OLLs/OLRs that are induced by a reaction to drugs show various clinical features, with a certain tendency toward being unilateral and erosive. OLRs also occur in betel-quid chewers at the site of placement of betel quid (Figure 9).

The diagnosis of OLPs/OLLs/OLRs is mostly based on the combined findings from history; clinical examination; a skin patch test, when indicated; and microscopy. In cases of OLLs/OLRs suspected to be drug induced, the history of any correlation between the start of medication intake and first symptoms may also be informative, even though reactions can occur several weeks or months after the prescription. However, the distinction between OLLs/OLRs and OLP is often difficult microscopically, and there is no universal agreement among pathologists to distinguish these 2 entities. Possible malignant transformation in OLL was first described in a case series from The Netherlands.

**GRAFT-VERSUS-HOST DISEASE**

GvHD is a complication arising in recipients of allogenic hematopoietic stem cell or bone marrow transplants. cGvHD is a systemic condition with a wide variety of signs and symptoms and affects many organ sites. The oral cavity is one of the most frequently affected sites. GvHD can be widespread in the mouth. The primary symptom relates to soreness at mealtimes. The disease presents with keratotic striations, white plaques, or erosive and ulcerative areas of the oral cavity. There is typically involvement of the buccal mucosa and the lateral tongue. The dorsum of the tongue may show papillary atrophy. Other clinical features include xerostomia (oral dryness), and patients may develop recurrent mucoceles on the labial and buccal mucosae, tongue, or soft palate. Malignant transformation has been reported in follow-up studies.

**DISCOID LUPUS ERYTHEMATOSUS**

Lupus erythematosus is a chronic autoimmune disease, which can be subdivided into 3 forms: (1) systemic, (2) drug-induced, and (3) discoid. It is the last benign variant that commonly affects skin and may involve the mucosal
surface of lips and the oral cavity. Oral lesions may also manifest in approximately 20% patients with systemic lupus. The disease is driven by an immune complex deposition in the affected sites, leading to vasculitis.

The discoid variety typically affects the sun-exposed areas of the face and neck and may present with the typical butterfly rash across the nasal bridge. The oral lesions consist of central zones of ulceration or erythema (representing vasculitis) surrounded by white striations, bearing a close resemblance to OLP (Figure 10). Immunofluorescence studies demonstrate subepithelial immunoglobulin and complement deposition (the lupus band), which assist in distinguishing DLE from lichen planus. During resolution, erosive areas of DLE may lead to postinflammatory pigmentation. Oral lesions typically affect the buccal mucosa, palate, and lips. The lower lip is the most commonly affected site in DLE-related malignant transformation. DLE has been recognized by the Collaborating Center of the WHO as a potentially malignant disorder, but malignant transformation is known to be exceedingly rare. In a recent review of the literature, Arvanitidou et al. documented 21 reported cases of carcinoma of the vermilion border of the lip arising in DLE lesions and added a further case of their own. DLE-related squamous cell carcinoma (SCCs) has been observed to be more aggressive than conventional lip cancers.

**ORAL SUBMUCOUS FIBROSIS**

OSF is a chronic, insidious disease that affects the lamina propria of the oral mucosa, and as the disease advances, it involves tissues deeper in the submucosa of the oral cavity, with resulting loss of fibroelasticity. History of chewing betel quid and areca nut in an Asian patient who has limited mouth opening should arouse suspicion of this condition.

The disease is characterized by the presence leathery mucosal texture and palpable fibrous bands in the oral mucosa, ultimately leading to limitation of mouth opening and rigidity of the tongue. Early features include blanching of mucosa (Figure 11), loss of normal pigmentation, and a burning sensation in the mucosa when spicy food is eaten. On clinical examination, sunken cheeks and limitation of mouth opening may be obvious. In addition, the tongue may be small, exhibit limited mobility, and show marked loss of papillae. The palate may appear pale, with horizontal bands across the soft palate (Figure 12), and the uvula may be shrunken or deformed. The severity and permutations of the signs and symptoms of OSF are highly variable. The severity of the disease is generally measured objectively by assessing mouth opening and by the presence of leukoplakia or erythroplakia as multiple lesions. Progressive limitation of mouth opening is a hallmark feature of OSF,
and this disease has a significant impact on quality of life of affected individuals.\textsuperscript{38} Among betel quid users, a new lesion with malignant potential, particularly in association with OSF, has been described as “oral verrucous hyperplasia.”\textsuperscript{39} In a consensus report by a panel of South Asian pathologists,\textsuperscript{40} this “mass type” novel lesion, which has both exophytic and verrucous phenotypes that has been observed betel quid chewers in South Asia, has been termed \textit{exophytic oral verrucous hyperplasia}. Data from other studies have complemented these findings.\textsuperscript{39}

\textbf{PALATAL CHANGES IN REVERSE SMOKERS}

Reverse smoking, which is an unusual form of smoking, the lighted end of a cigar, \textit{chutta} (an Indian smoking product), or cigarette, is placed inside the mouth. The habit is prevalent in parts of India, the Caribbean Islands, Colombia, Panama, Venezuela, Jamaica, Sardinia, and the Philippines. The observed mucosal changes associated with reverse smoking were comprehensively described in a 10-year follow-up study of Indian villagers by Gupta et al.\textsuperscript{34} The mucosal changes that were described in reverse \textit{chutta} smokers included thickened leukoplakic plaques of the palate, mucosal nodularity, excrences around the orifices of the palatal (minor) mucosal glands, yellowish brown staining, erythema, and ulceration. The changes noted involved most of the palatal surface exposed to direct heat and smoke. Comparable palatal lesions were noted among Filipino women\textsuperscript{39} and from a territory in Colombia among persons with similar habits.\textsuperscript{39} Follow-up studies reported from India\textsuperscript{35} clearly demonstrated the potentially malignant nature of this condition as 6 persons in a cohort of almost 3000 patients studied over 6 years developed palatal cancer. Reverse smokers’ palatal lesions are more persistent than leukokeratosis nicotina palati lesions found in regular cigarette smokers (referred to earlier) and, compared with leukoplakia, have a higher risk of developing into malignancies.

\textbf{EPIDERMOLYSIS BULLOSA}

Epidermolysis bullosa (EB) is a skin disease characterized by epithelial fragility that may manifest as blistering and erosions of the oral mucosa. The disease is classified into 32 different subtypes. Intraoral soft tissue manifestations are found in all subtypes and include marked frequency of oral and perioral blistering that leads to ulceration, scaring, and obliteration of the oral vestibule and microstomia.\textsuperscript{37}

Fine et al.\textsuperscript{38} conducted an analysis of a data set on 2745 patients with EB entered on the National EB Registry in the continental United States (1986-2002). At least 1 SCC arose in 2.6% (73 of 2745) of the study population, almost all in sun-exposed areas. Multiple SCCs were found in the group with recessive dystrophic EB (RDEB). On the basis of this analysis, the authors highlighted that in the recessive dystrophic type (i.e., RDEB) the life time risk of developing squamous epidermal cancers is greater than 90%. Only 1 oral SCC was reported on the tongue among noncutaneous cancers.\textsuperscript{38} Others have published case reports or small case series of oral SCCs, particularly among individuals with severe generalized RDEB (reviewed by Wright).\textsuperscript{39} Malignancies in patients with EB can occur in the third decade of life or even earlier. Because of the increased risk of cancer, EB is included as a potentially malignant disorder, although specific oral premalignant lesions associated with EB are not well characterized in the literature. As patients with EB may be at an increased risk of oral SCC, during oral examination, it is prudent to be extra vigilant in monitoring changes of any suspicious features around any oral ulcers, which are frequently observed in this condition.

\textbf{DYSKERATOSIS CONGENITA}

Dyskeratosis congenita (DC) is a rare inherited bone marrow failure syndrome, and patients with DC have significantly increased risk of malignancy. Oral leukoplakia is the most common presentation in this condition, found in 65% to 80% of patients.\textsuperscript{40} Leukoplakic patches of the dorsal tongue and sometimes on the buccal mucosa\textsuperscript{41} are features of the classic triad of signs that include lacy reticular hyperpigmentation of the skin and nail dystrophy. The tongue is affected often from a young age, and most reported cases with oral leukoplakia have occurred in children and adolescents under age 15 years.\textsuperscript{42} One of the early descriptions of oral leukoplakia in DC was in a 10-year-old boy, as reported by Ogden et al. in the journal \textit{Oral Surgery, Oral Medicine, Oral Pathology}.\textsuperscript{43} Oral white lesions are rare in children, and the identification of a white patch on the tongue of a child, in the absence of any other obvious cause (e.g., candidal infection or chronic trauma) must arouse suspicion of this rare condition. The condition is attributed to several mutations of genes that help maintain telomeres, such as the \textit{DKC1} gene, which encodes for the protein dyskerin.\textsuperscript{44} These leukoplakic patches in the mouth of patients with DC have a significantly increased risk of developing to SCC.

\textbf{ACTINIC CHEILITIS}

Actinic cheilitis (AC), a chronic inflammatory condition of the lip, results from excessive exposure to solar ultraviolet radiation and most often affects the lower lip. Those with a fairer skin are at a heightened risk\textsuperscript{45} and may be predisposed to AC, and men show a stronger predisposition for AC compared with females. AC has a wide range of clinical features. Common clinical presentations comprise white lesions, in conjunction with crusting, flaking, dryness, or a mottled appearance indicating the simultaneous presence of erythema.
and white patches.46 During the course of the disease, ulcerative lesions may develop, with inflammation, atrophy, and loss of epithelium.

Sun exposure is the most important risk factor for AC. The development of AC is dose dependent and is associated with the patient’s sun exposure, age, genetic predisposition, geographic latitude of residence, outdoor occupation, leisure activities, and failure to use lip-protective agents.47

SCC of the lip is often found in a background of actinic cheilitis. However, evolution of AC to SCC has not been studied in through careful follow-up, except in a Greek study by Markopoulou et al.,48 who reported 65 cases of AC; on close follow-up, 11 (16.9%) of the 65 developed lip cancer. Progression of AC to SCC can be minimized by use of an appropriate sunscreen when outdoors.

CONCLUSIONS
OPMDs have an increased risk of developing into oral cancer. Several varieties are recognized. Some of them are solitary lesions, whereas others, referred to as conditions, are multifocal or widespread within the oral cavity. Leukoplakia is the most common OPMD encountered in clinical practice. In patients with a clinically evident oral mucosal lesion that is suspected to be an OPMD, clinicians should perform a biopsy of the lesion or provide immediate referral to a specialist.

REFERENCES


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