Premalignant and malignant oral mucosal lesions: Clinical and pathological findings

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Learning objectives
After completing this learning activity, participants should be able to recognize key clinical features of common premalignant and malignant oral mucosal neoplasms; identify clinically suspicious oral mucosal lesions; and choose the most appropriate next step in management and follow up.

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The second article in this continuing medical education series discusses the clinical and histopathologic features of common premalignant and malignant lesions of the oral cavity. It is imperative for dermatologists to be able to appropriately recognize suspicious lesions, determine the need to obtain a biopsy specimen, counsel, and refer patients presenting with premalignant or malignant conditions. Given the higher rates of mortality and morbidity of oral mucosal malignancies because of late diagnosis, appropriate treatment with multidisciplinary care in a timely manner is essential to patients with these neoplasms. (J Am Acad Dermatol 2019;81:59-71.)

Key words: adenoid cystic carcinoma; erythroplakia; mucoepidermoid carcinoma; mucosal melanoma; oral leukoplakia; oral lichen planus; oral mucosal squamous cell carcinoma; proliferative verrucous leukoplakia; verrucous carcinoma.

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Abbreviations used:

ACC:	adenoid cystic carcinoma
MEC:	mucoepidermoid carcinoma
OL:	oral leukoplakia
OLP:	oral lichen planus
OMM:	oral mucosal melanoma
OmSCC:	oral mucosal squamous cell carcinoma
OVC:	oral verrucous carcinoma
PVL:	proliferative verrucous leukoplakia

PREMALIGNANT LESIONS

Oral leukoplakia

Key points

- **Oral leukoplakia is a potential malignancy of the oral mucosa**
- **Oral leukoplakia can be homogeneous or nonhomogeneous, with nonhomogenous lesions having a higher risk for malignant transformation**
- **Treatment and prevention include tobacco cessation, chemoprevention, and surgical excision**

Background

Oral leukoplakia (OL) is a common and potentially malignant condition of the oral mucosa[1] that is characterized by a white, irreversible, nonscrapable lesion (Table I). A flow chart on the management of potentially malignant oral cavity lesions can be found in Figure 1. OL can be associated with consumption of tobacco, betel quid, and alcohol but can also be idiopathic in nature.[2,3] Causal association with human papillomavirus (HPV) has also been identified.[4,5] In the general population, the OL prevalence is approximately 2%, with increasing prevalence rates for older populations. OL is more commonly found in men ≥40 years of age.[6-8] The diagnosis of OL involves histologic evaluation of a biopsy specimen, although other less definitive methods, such as toluidine blue dye assessment, salivary diagnostics, and obtaining a brush biopsy specimen, are also used for early detection.[9]

Clinical features

OL may present as either homogeneous or nonhomogeneous. Homogenous lesions appear as white, superficial, and flat with clearly evident borders (Fig 2), whereas nonhomogeneous OL lesions may be characterized by an erythroleukoplakia, formerly known as a speckled red and white irregular lesion, be verrucous or exophytic with a corrugated and wrinkled surface, or have a nodular presentation characterized by polypoid outgrowths.[3,10] OL can develop anywhere on the oral mucosa, although the location may correlate directly with the type and placement of tobacco product.[11] Nonhomogenous OL presents a higher risk for malignant transformation; however, the reported rate of malignant transformation is still contested, ranging between 0.1% to 36.4% with an annual rate of transformation of 2% to 3%.[10,12]

Proliferative verrucous leucoplakia (PVL) is an uncommon type of multifocal OL that demonstrates an aggressive behavior. It more commonly affects women after the sixth decade of life.[13,14] PVL presents as an asymptomatic, nonhomogenous white plaque often with a verrucous, keratotic surface (Fig 3, *A*). Lesions can begin as single growths that spread and become multifocal. The sites most often involved are the gingiva, buccal mucosa, alveolar ridges and, less frequently, the tongue. Modified criteria for the diagnosis of PVL include the presence of leukoplakia showing verrucous areas involving >2 subsites, a minimum size of 3 cm, a documented period of disease evolution of ≥5 years, and ≥1 supportive biopsy specimen that has ruled out the presence of carcinoma.[15] Histologic features vary upon the disease stage, ranging from single hyperkeratosis to verrucous hyperplasia and varying degrees of dysplasia (Fig 3, *B*).[16] Because 60% to 100% of PVLs progress to oral carcinoma,[16] close 6-month follow-up is recommended.

Management

Many methods exist to prevent and treat OL, but there is no uniform management modality.[17] Clinical surveillance and risk factor cessation are initial strategies, and chemoprevention using vitamin A, bleomycin, beta-carotene, or retinoids have been used.[6,10] Conventional scalpel excision, photodynamic therapy, cryosurgery, and laser ablation have also been used to treat OL. One recent study demonstrated a statistically significant improved outcome using an erbium:yttrium aluminum garnet laser compared with traditional cold scalpel excision[10] (level of evidence, IV). There is a lack of literature indicating a standard method of prevention and treatment.[17,18]

ERYTHROPLAKIA

Key points

- **Erythroplakia is an erythematous patch or plaque of the oral mucosal lesion**
- **It carries a high rate of malignant transformation**
- **Tobacco, alcohol use, and high-risk HPV are risk factors for the condition**

Background

Erythroplakia classically presents as a solitary, erythematous lesion of the oral mucosa,[19,20] and tobacco, alcohol use, and high risk HPV are risk

Table I. Clinical and histopathologic characteristics of premalignant oral neoplasms

Premalignant	Common oral sites	Clinical appearance	Histopathology
Leukoplakia	Any mucosal site	Homogenous type: white, superficial, and flat with clearly evident borders (Fig 2) Nonhomogeneous type: erythroleukoplakia, verrucous/exophytic, or nodular presentation[3,10]	Recommended to differentiate between nondysplastic and dysplastic lesions; histopathologic stages vary from squamous hyperplasia, mild, moderate, or severe dysplasia, and carcinoma in situ[98]
Proliferative verrucous leukoplakia	Gingiva, buccal mucosa, alveolar ridges, and tongue[13]	Single, large spreading or multifocal lesions that demonstrate a homogenous white plaque with a verrucous, keratotic surface	Often series of biopsy procedures are required; there is no single histopathologic feature; verrucous hyperplasia with different degrees of dysplasia are common features[99]
Erythroplakia	Buccal mucosa, palate, ventral tongue, and the floor of the mouth[20,22,25]	Asymptomatic, erythematous oral mucosal lesion with a smooth or velvety in appearance (Fig 4)[19,20]	Epithelium is nonkeratinized, thin, and atrophic, allowing for visualization of underlying microvasculature[22,25]; squamous hyperplasia may be seen without concomitant dysplasia (benign), varying degrees of dysplasia, or carcinoma in situ[22]
Lichen planus	Buccal mucosa, followed by the gingiva (desquamative) and the tongue[37]	The forms of oral lichen planus include reticular, papular, plaque, erythematous or atrophic, erosive, or bullous forms[33]; a combination of characteristics of different subtypes may coexist (Fig 5)[33,36]	Band-like lymphocytic infiltration and liquefaction degeneration of the basal cell layer[39]; other features include hyperkeratosis, the presence of civatte bodies, and hydropic degeneration of basal cells[38]

factors for the condition.[21] The prevalence is between 0.02% and 0.83%.[22] Adults >45 years of age are most commonly affected. After PVL, erythroplakia has the highest malignant transformation rate—as many as 50% of high-risk cases lead to dysplasia, carcinoma in situ, or invasive carcinoma.[22,23] Aside from PVL, 85% to 90% of early oral squamous cell carcinomas initially present as erythroplakia.[19,22] Patients with oral high-risk HPV infection have a 3 to 4 times higher risk for developing erythroplakia.[24]

Clinical features

Erythroplakia is characterized by an erythematous oral mucosal lesion that is smooth and velvety in appearance (Fig 4).[19,20] Lesions can be flat or depressed below the mucosal surface and typically have a solitary presentation within the oral cavity.[19,20] The epithelium will be thin and atrophic with visualization of the underlying microvasculature.[22,25] The lesion itself may be either soft or hard to palpation[20] and may range in size from <1 cm to >4 cm in diameter.[26]

Erythroplakia most frequently involves the soft palate, the ventral surface of the tongue, and the floor of the mouth.[20,22,25] There are usually no other associated symptoms.[25] Diagnosis is one of exclusion.[21] The differential diagnosis includes erythematous candidiasis, inflamed or erosive oral lichen planus (LP), and lupus erythematosus.[25,27] However, the solitary presentation of erythroplakia can distinguish it from these other conditions, which tend to present multifocally.[20,27]

Management

Because of the high malignant transformation rate of erythroplakia, early treatment is recommended.[21] Treatment involves obtaining either an excisional or incisional biopsy specimen, with follow-up complete excision of lesions that exhibit severe epithelial dysplasia on microscopic examination.[22,28] Continuous monitoring is recommended for lesions that show moderate to no dysplasia. A larger initial lesion size has been associated with postoperative recurrence. A lesion size ≥80 mm^2 has been reported to be the greatest predictor of recurrence.[22] Other

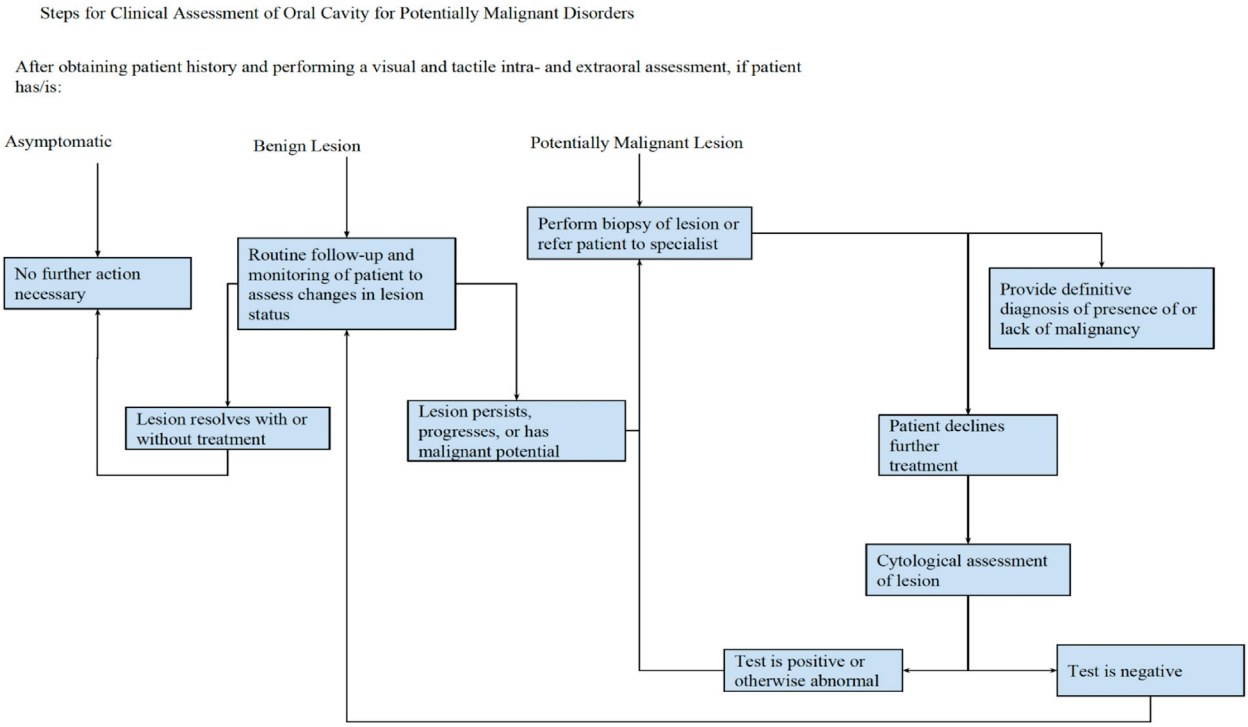

Fig 1. Flow chart for managing potentially malignant lesions of the oral cavity, based on Journal of the American Dental Association guidelines.[97] *Asymptomatic*, Absence of clinical lesion or symptoms.

recommended therapy is laser surgery (level of evidence, IV).[27] Ablation by CO_2 laser has been shown to be effective for erythroplakia with low associated morbidity.[22]

LICHEN PLANUS

Key points

- **Oral LP is a chronic, immunologically driven inflammatory disease that affects both the skin and mucous membranes**
- **The most common presentation is a lacy white reticular mucosal lesion**
- **Topical corticosteroids are considered first-line treatment**

Background

LP is a chronic, immunologically driven inflammatory mucocutaneous disease that affects 1% to 2% of the general population.[29,30] The etiology of the disease is not fully understood, but it is thought to be an autocytotoxic T cell–mediated immune response to basal keratinocytes.[30,31] Oral LP (OLP) is a subtype that affects the oral mucosa.[31] Compared with cutaneous LP, which may remit within 6 to 12 months, OLP is by nature a chronic disorder.[32,33] The prevalence is estimated to be 0.5% to 2.2%.[30] Of patients diagnosed with cutaneous LP, ≤65% may also present with oral lesions, and 15% to 35% may only have

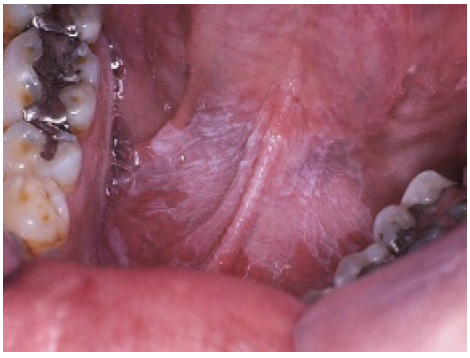

Fig 2. Leukoplakia. The homogenous, white plaque–like lesion with striations can be identified on the ventral surface of the tongue. (Courtesy of John McDowell, DDS.)

oral involvement.[34] Women between 30 and 60 years of age are most frequently affected.[35] Malignant transformation rates of OLP range from 0.07% to 5.8%.[31] The most common clinical subtype associated with malignant transformation is erosive OLP (1.7%), followed by erythematous or atrophic OLP (1.3%) and finally reticular OLP (0.1%). Overall, 1.1% of patients with OLP have been shown to develop oral squamous cell carcinoma (OSCC).[31]

Clinical features and diagnosis

OLP most often presents as a proliferation of white, fine, lacy lines on the mucosa known as Wickham

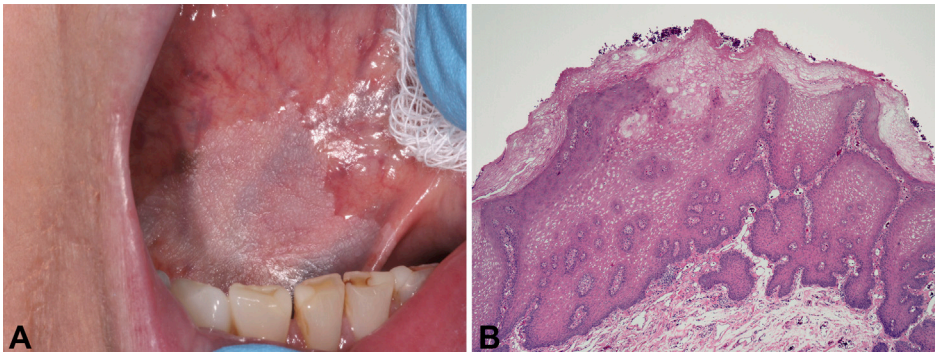

Fig 3. Proliferative verrucous leukoplakia. **A**, A well-circumscribed plaque-like corrugated area of leukoplakia involving the mucosa of the ventral surface of the tongue. **B**, Progressive verrucous leukoplakia is characterized by markedly hyperkeratinized papillary acanthotic squamous epithelium with chevron keratinization—an exophytic spiking form of keratinization that involves the oral epithelium. (*A*, Courtesy of John McDowell, DDS.)

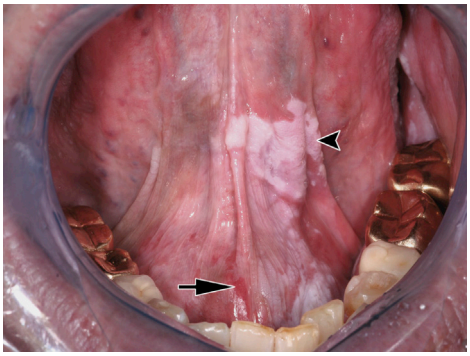

Fig 4. Erythroplakia/leukoplakia. A diffuse white and focally erythematous plaque-like lesion can be seen involving the ventral surface of the tongue. The arrow shows the erythroplakic area. The arrowhead shows the leukoplakic area. (Courtesy of John McDowell, DDS.)

striae (Fig 5).[36] The most commonly affected sites are the buccal mucosa, followed by the gingiva and tongue.[37] Lesion distribution is usually bilateral, although disease affecting the gingiva may be localized.[32,38] Approximately 10% of patients have gingival OLP, which typically is desquamative.[33]

Clinical forms of OLP include reticular, papular, plaque, erythematous or atrophic, erosive, and bullous.[33] Lesions may have a combination of characteristics, and different subtypes may coexist.[33,36] Reticular OLP is the most common, characterized by Wickham striae and hyperkeratotic plaques or papules.[33,37] Erosive OLP has an atrophic appearance, with areas of ulceration and associated keratotic white striae.[36] Erythematous OLP is characterized by mucosal atrophy and commonly occurs alongside reticular OLP.[33] Bullous OLP is rare, with bullae that can rupture and lead to erosive OLP.[36] Plaque-like OLP often occurs on the tongue and is defined by white lesions that are similar in appearance to oral leukoplakia.[36] Plaque-like lesions are more commonly seen in smokers.[38] Erosive and erythematous OLP may cause significant pain, and lesions can interfere with speech, swallowing, and chewing.[38]

OLP is clinically similar to a lichenoid drug reaction, lichenoid mucositis, and lichenoid dermatitis.[36] The diagnosis of OLP is typically made clinically and confirmed histologically.[38,39] Histopathologic diagnostic criteria are included in Table II.[38,39] Direct immunofluorescence may be used to support a diagnosis of OLP and to distinguish it from other conditions.[38]

Management

Treatment of OLP is generally palliative and not curative. The principal goal of management is to reduce inflammation and alleviate symtomatology.[38,40] Asymptomatic reticular lesions generally do not require treatment, but continued observation is recommended.[40] Initial treatment of symptomatic OLP is usually done with topical steroids. Intralesional corticosteroids have been used in the treatment of erosive OLP.[41] Systematic steroids are used in more severe or refractory cases.[33] Topical calcineurin inhibitors may be used if patients do not respond to corticosteroid treatment.[33,40] Topical cyclosporine and systemic immunosuppressants have also been used to treat OLP (level of evidence, IIC).[33,39]

MALIGNANT LESIONS

Mucoepidermoid carcinoma

Key points

- **Mucoepidermoid carcinoma is the most common malignant salivary tumor to arise in children and young adults**
- **Tumors occur most commonly in the parotid, submandibular, and minor salivary glands**

Table II. Clinical and histopathologic characteristics of Malignant oral neoplasms

Malignant	Common oral sites	Clinical appearance	Histopathology
Mucoepidermoid carcinoma	Major salivary glands: parotid gland, submandibular gland, and sublingual gland[44,45,47,48] Minor salivary glands: palate Other sites: retromolar trigone of the mandible, buccal mucosa, tongue, lips, and floor of the mouth	Painless, fixed, rubbery or soft mass[42,45] Superficial intraoral tumors: may present as bluish red swelling similar to a vascular lesion or mucocele[45]	Composed of mucous, intermediate, and epidermoid cells, with columnar, clear cells, and oncocytoid features[45]
Adenoid cystic carcinoma	Adenoid cystic carcinoma affects both major and minor salivary glands; intraoral tumors occur most commonly in the palate, followed by parotid and submandibular glands[57]	Painful and slow growing, can invade surrounding bone, and nerves causing significant local destruction and facial nerve palsies[53,57]	*Cribriform:* Swiss cheese appearance, numerous cylindrical cyst-like spaces within islands of basaloid epithelial cells *Tubular:* similar to the cribriform variant, with tubules or small ducts within the hyalinized stroma *Solid:* sheets or large islands of tumor cells that typically do not shown a tendency toward duct or cyst formation[44]
Oral squamous cell carcinoma	Posterior lateral border of the tongue, followed by the floor of the mouth, soft palate, gingiva, buccal mucosa, and hard palate[44]	White to erythematous lesions that are painless unless ulcerated, to exophytic tumor masses[44]	*Low grade/well differentiated:* resemble their native tissue, slower growing with later metastasis. *Moderately differentiated:* recognizable native cells, less differentiation. *High grade or poorly differentiated:* unable to distinguished from their native, epidermoid forms with little to no keratin production, rapidly growing, high propensity for early metastasis[44,69]
Oral verrucous carcinoma	Exophytic lesions appearing gray or white in color with a pebbly or cauliflower-like textured surface texture[77,78]	Buccal mucosa, mandibular vestibule, gingiva, tongue, and hard palate[70,74,75]	Epithelium hyperplasia with broad and bulbous rete pegs "pushing margins" into the underlying connective tissue but no invasion of the basement membrane[100]
Mucosal melanoma	Asymptomatic, irregular, single or multiple lesions, varying in color from black-brown tones to a red-purple color[83]	Hard palate and maxillary gingival are the most commonly affected sites; less frequent sites are the labial and buccal mucosa[85]	In situ, invasive, or nodular; combined pattern can be seen

Background

Mucoepidermoid carcinoma (MEC) is the most common salivary gland malignancy in adults and the most common tumor to arise in children and young adults <20 years of age.[42,43] MEC accounts for about 10% of all major salivary gland neoplasms and approximately 15% to 23% of all minor salivary gland neoplasms.[44] MEC has a broad age range of

occurrence, from the second to seventh decades of life, and has a female predilection.[44-46]

Clinical features and diagnosis

MEC usually presents as a painless, fixed, rubbery soft tissue nodule or mass.[42,45] Intraoral tumors may appear bluish red.[45] MEC affects the parotid gland most often (84%), followed by submandibular and minor salivary glands.[44,45,47,48] When the minor salivary glands are involved, MEC most commonly affects the palate (Table II). Other less common sites include the retromolar trigone of the mandible, buccal mucosa, tongue, lips, and floor of the mouth.[45] Tumors can be graded histologically as low, intermediate, and high-grade lesions. Histologically, tumors will be composed of mucous, intermediate and epidermoid cells, with columnar, clear cells, and oncocytoid features set in a collagenous matrix.[45] Lesion grading is typically based on the amount of cyst formation, degree of cytologic atypia, and the comparative number of mucous, intermediate, and epidermoid cells.[43-45] High-grade lesions have few cystic spaces and mucous secretory cells, whereas low-grade lesions have many cystic spaces and no mucous secretory cells.

Management

A biopsy specimen obtained with fine needle aspiration is typically included as a preoperative assessment of parotid or submandibular tumors. Biopsy specimens are typically obtained from minor salivary tumors.[45] Tumor management is based on histopathologic grade, tumor location, the degree of tumor invasion, and evidence of metastatic disease. The overall 5-year survival rate is approximately 81.8%.[49] Low-grade tumors are typically treated with surgical excision with modest margins. High-grade tumors require a larger surgical excision, possible neck dissection, and postoperative radiation therapy (level of evidence, IV).[44,50] Low-grade lesions treated with surgical excision have a >90% cure rate. High-grade tumors have a poor prognosis, with only 30% to 54% of patients surviving 5 years.[44]

ADENOID CYSTIC CARCINOMA

Key points

- **Adenoid cystic carcinoma is an aggressive tumor with a high recurrence rate, and is prone to distant metastasis**
- **Overall, ACC has a poor prognosis**

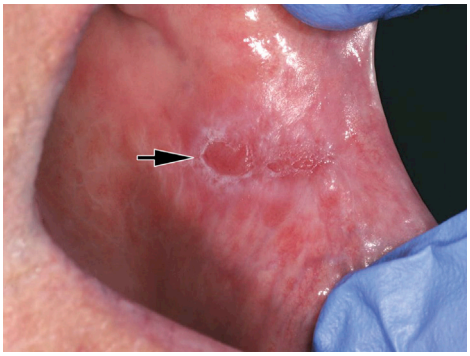

Fig 5. Ulcerative lichen planus. Note the focal area of ulceration (arrow) surrounded by areas of white reticular focally lacy leukoplakia. The lesion extends superiorly and inferiorly in a striated fashion. (Courtesy of John McDowell, DDS.)

Background

Adenoid cystic carcinoma (ACC) is a rare salivary gland malignancy that accounts for approximately 5% to 10% of all salivary gland tumors and 1% to 4% of all head and neck malignancies.[51-55] ACC is the second most common salivary gland tumor.[51,52] ACC can occur in other glandular tissues, including the lung, cervix, skin, breast, prostrate, and lacrimal glands.[52,54,56] They most frequently affect middle-aged adults between the fifth and sixth decades of life and have a slight female predilection.[44,53]

Clinical features and diagnosis

ACC affects both major and minor salivary glands, with the parotid gland most frequently affected followed by the minor salivary glands of the palate and then the submandibular gland (Fig 6, *A*). Tumors are slow growing, and when pain is present, it is typically described as dull, with intensity increasing with tumor growth.[57] ACC can invade surrounding bone and nerves causing significant bony destruction along with nerve palsies.[53,57]

The diagnosis can be made via incisional or fine needle aspiration biopsy procedures. ACCs are composed of ductal and myoepithelial cells and have a propensity for perineural invasion.[44] There are 3 major ACC histopathologic patterns: cribriform, tubular, and solid (Fig 6, *B*). All 3 histologic patterns can be found in 1 tumor (Table II). Immunohistochemical assessment can help distinguish ACC from polymorphous low-grade adenocarcinoma, canalicular adenoma, and basal cell carcinoma.[44]

Management

ACC is an aggressive tumor with a high recurrence rate.[44,56,58] The tumor is classically treated with

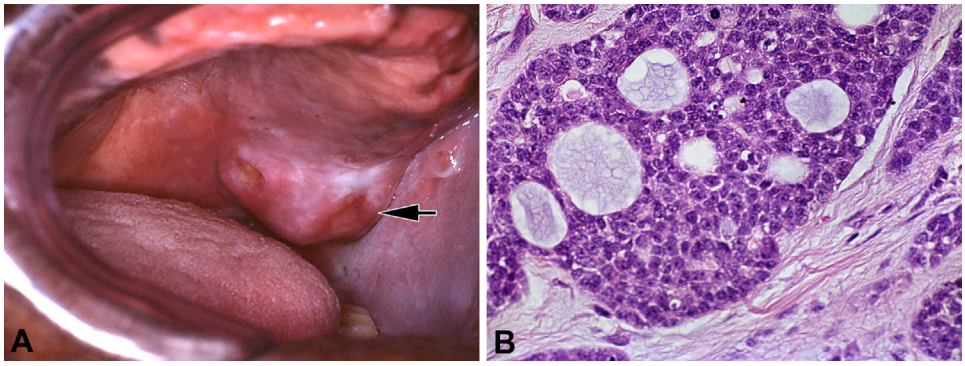

Fig 6. Adenoid cystic carcinoma. **A**, Ulcerated polypoid nodular mass involving the maxillary mucosa. **B**, Neoplastic islands composed of tumor cells with angular nuclei and eosinophilic cytoplasm. The tumor cells are arranged in a cribriform pattern and set in a matrix of loose reticular connective tissue. (*A*, Courtesy of John McDowell, DDS.)

surgical excision and adjunctive radiation therapy (level of evidence, IIIA).[44,53,59] The National Cancer Care Network recommends postoperative radiation therapy for patients with T3-T4 disease and consideration of postoperative radiation therapy for patients with T1-T2 disease.[60] Metastasis to regional lymph nodes is extremely rare, but late metastasis to the lungs and cranial extension in the case of minor salivary gland tumors of the palate is common.[61] Patient prognosis is based on tumor size and staging of the initial lesion.[54,57] The 5-, 10-, and 15-year survival rates are approximately 85%, 71%, and 34%, respectively.[51,57] The solid variant of ACC has the worst prognosis.[44,52]

ORAL MUCOSAL SQUAMOUS CELL CARCINOMA

Key points

- **Oral mucosal squamous cell carcinoma accounts for >90% of all oral malignancies**
- **Treatment commonly involves wide surgical excision, neck dissection, radiation therapy, chemotherapy, or more commonly combination therapy**

Background

Oral mucosal squamous cell carcinoma (omSCC) accounts for the majority (>90%) of all oral malignancies.[62] The annual incidence of oral SCC varies from 5 to 15 per 100,000 persons in the United States. Oral mucosal SCC affects males more than females (3:1), with middle age to older males being most often affected.[63] The etiology of omSCC is multifactorial and is associated with tobacco use, alcohol use, sun exposure, radiation, systemic diseases, metabolic deficiencies, premalignant oral lesions, viruses (HPV), and sexually transmitted diseases.[44,63-65]

Clinical features and diagnosis

OmSCC can present clinically as leukoplakia, erythroplakia, erythroleukoplakia, or a nodular mass (Fig 7, *A*). OmSCC is commonly separated from SCC of the lip vermilion, because omSCC has a more aggressive course and poorer prognosis when compared with SCC of lip, and SCC of lip has a worse prognosis when compared with cutaneous SCC of head and neck.[66] OSCC is most often found on the posterior lateral border of the tongue, followed by the floor of the mouth, soft palate, gingiva, buccal mucosa, and hard palate (Table II).[44] OmSCC of the tongue represents approximately 50% of oral SCCs.[67]

Metastasis of omSCC is primarily via lymphatic drainage through ipsilateral cervical lymph nodes, although tumors may invade contralateral or bilateral lymph nodes. Distant metastasis most commonly occurs to the lungs, bones, and liver.

OmSCC classification and prognosis are based on tumor, node, and metastasis staging.[68] Histopathologically, tumors are characterized by the presence of invasive islands and cords of malignant squamous epithelial cells that penetrate through the basement membrane and into the underlying connective tissue, muscle, or bone (Fig 7, *B*). These tumor cells are graded based on the degree to which they resemble their parent cells and function accordingly to produced keratin. Histologic grade correlates to the tumor's behavior (Table II), with high-grade tumors being less differentiated.[44,69]

Oral verrucous carcinoma (OVC) is a low-grade, well-differentiated variant of OSCC that can be locally aggressive but that has a low likelihood of

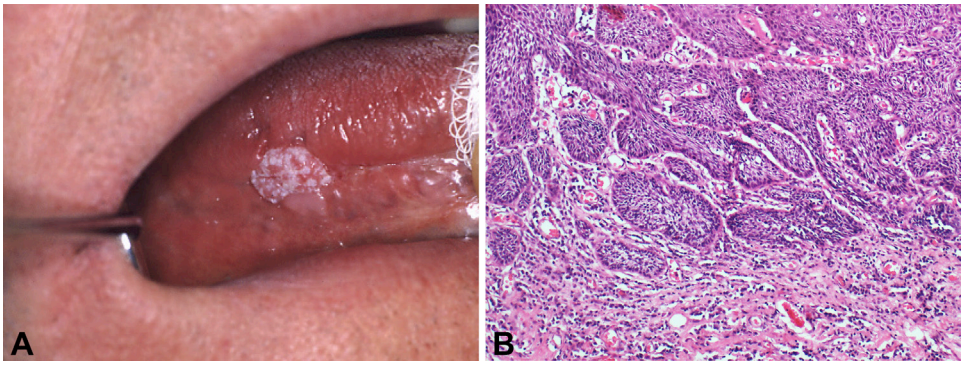

Fig 7. Squamous cell carcinoma. **A**, An exophytic nodular mass involving the maxillary mucosa. **B**, The histologic examination reveals a mucosal ellipse covered by keratinizing squamous epithelium. The epithelium is acanthotic with sheets, nests, and cords of neoplastic cells of squamous origin that penetrates a connective tissue lamina propria that is diffusely chronically inflamed. The neoplastic process is moderately well differentiated. (*A*, Courtesy of John McDowell, DDS.)

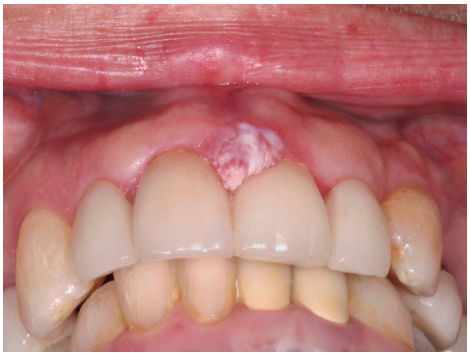

Fig 8. Oral verrucous carcinoma. A corrugated focally erythematous and leukoplakic lesion involving the interdental papilla.

metastasis.[70-72] HPV subtypes 16 and 18 have been found in approximately 40% of patients with OVCs.[63,71] Tobacco and alcohol use are major risk factors in the United States, while betel nut chewing is the main risk factor in Asian countries.[73] The prevalence of OVC ranges from 2% to 12% of all oral carcinomas.[44] It has an 8:2 male:female ratio, and the tumor is seen more often during the sixth and seventh decades of life.[71] Clinically, OVCs are most often exophytic lesions with a pebbly or cauliflower-like textured surface (Fig 8). OVCs most commonly involve the buccal mucosa, mandibular vestibule, gingiva, tongue, and hard palate.[70,74,75] Lesions are typically slow growing, without invasion into the basement membrane and with sporadic local and distal involvement (Table II).[3,35,74,75]

Management

OmSSC of the lip is treated via surgical excision and rarely recurs. The 5-year survival rate is usually >95%. Treatment of omSCC is guided by tumor, node, and metastasis staging and involves wide surgical excision, neck dissection, radiation therapy, chemotherapy or more commonly a combination of surgery and adjunctive therapy.[76] The 5-year survival rate for omSCC is approximately 50% to 59%.[44,77-79]

ORAL MUCOSAL MELANOMA

Key points

- **Oral mucosal melanoma is a rare melanocytic neoplasm, with greater aggressive behavior than cutaneous melanoma**
- **The single most important prognostic factor is early diagnosis**

Background

Mucosal melanoma of the head and neck is an uncommon, aggressive melanocytic neoplasm (Fig 9). It accounts for 1% of all melanomas, being the third most common location after cutaneous and ocular melanomas.[80] Oral mucosal melanoma (OMM) represents 0.26% of all primary oral malignancies.[81] Despite a same-cell origin to cutaneous melanoma, oral melanoma has unique epidemiologic characteristics. Unlike cutaneous melanoma, OMM often presents in older individuals, around the fifth decade of life. While the rate of OMM among whites is only twice as high compared with darker skin types, the rate of cutaneous melanoma is 5 to 20 times higher in white populations. Gender predilection varies among studies, with some studies suggesting a 2:1 male preference while others reporting none.[81,82]

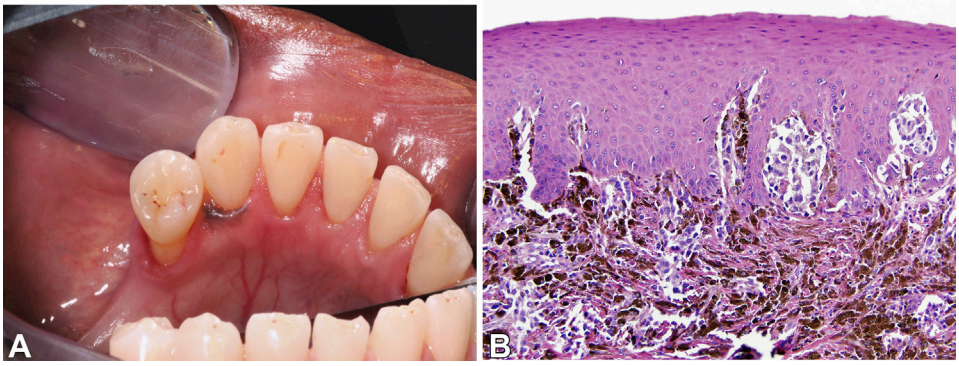

Fig 9. Melanoma. **A**, Circumferential pigmented gingival cuff in a patient with superficial spreading melanoma. **B**, The histologic examination reveals a mucosal ellipse. The ellipse is covered by keratinzing squamous epithelium. Arising from the basal layer of the epithelium, dense aggregates of pigmented malignant cells have dropped off from the epithelium into the superficial connective tissue lamina propria. (*A*, Courtesy of John McDowell, DDS.)

Clinical features and diagnosis

OMM most often manifests as an asymptomatic, irregular, single or multifocal lesion(s), varying in color from black-brown to red-purple (Fig 9, *A*).[83] Hemorrhage and ulceration are often found in late stage disease. Ten percent to 30% of OMMs may be amelanotic.[84] The hard palate and maxillary gingiva are the most commonly affected sites, which are also known as high-risk areas.[85] The etiology and risk factors for OMM are not fully understood. *BRAF* mutations commonly seen in cutaneous melanoma are infrequent in OMM, while c-KIT mutations can be observed in approximately 39% of patients with OMM.[86] Although most cases are thought to arise de novo, about 30% of cases of OMM are found to arise from a preexisting oral pigmented lesion.[87]

Excisional biopsy should be performed for small lesions. Larger lesions can be sampled for thickness, although staging related to depth of invasion is not appropriate for OMM. Similar to its cutaneous counterpart, there is an initial horizontal growth phase to the tumor followed by vertical growth and deeper invasion.[82] Clark level and Breslow thickness assessment are not particularly helpful in predicting tumor behavior because of the absence of a granular layer.[88] Three distinct patterns can be observed on histologic examination (Fig 9, *B*; Table II).[89,90] The reported rate of metastasis is 10% to 50%, and lymph nodes are involved in ≤60% of patients.[91] The use of obtaining a sentinel lymph node biopsy specimen in patients with oral melanomas is not well established.[91-93]

Management

The management of OMM is multidisciplinary, requiring surgical resection followed by adjuvant radiation and chemotherapy. Because of its aggressive behavior, OMM in situ is treated as invasive melanoma.[94] The primary treatment modality is surgical excision with wide margins. Adjuvant postoperative radiotherapy in stage III/IVa disease appears to improve locoregional recurrence (level of evidence, 2C) but without improvement in the rate of distant metastasis.[95] Chemotherapy is palliative and has not been shown to improve survival. The use of immunotherapy in the management of metastatic OMM has not been as well investigated as in cutaneous melanoma; however, case series using PD-1 inhibitor alone or in combination with ipilimumab has demonstrated benefits.[96] Despite evolving treatment modalities, the prognosis of OMM remains poor, with an overall 5-year survival rate of 28% in early stage disease, and 0% in advanced tumors and local tumors with distant metastasis.[82]

In conclusion, clinicians should be aware of the different presentations of oral lesions and maintain vigilance when confronted with premalignant and malignant lesions. Patient history along with clinical features and histopathologic confirmation are the cornerstones for managing suspicious lesions. Early diagnosis and appropriate multidisciplinary care are essential to improve the prognosis.

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Answers to CME examination

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