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# Pathology of Malignant and Premalignant Oral Epithelial Lesions

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## Histologic and taxonomic parameters

Oral mucous membranes and the surrounding structures are largely composed of stratified squamous epithelium that is supported by a fibrous connective tissue lamina propria and a submucosa of fibroadipose tissue. Minor salivary glands, nerves, and capillaries course abundantly throughout the supporting collagen and fibrofatty submucosa. Premalignant and malignant lesions arise most frequently from epithelium, and these epithelial lesions ultimately account for 95% of all cancers of the oral cavity. Malignant neoplasia of bone, cartilage, salivary glands, and connective tissue and those of lymphoproliferative derivatives are far less common occurrences in the oral cavity. Malignant neoplasms can and do arise from the tooth germ apparatus, but neoplasms of odontogenic elements are rare and are not included in this discussion.

## Premalignant and malignant lesions of the oral mucous membrane

### *Erythroplakia and leukoplakia*

#### *Erythroplakia*

Erythroplakia is characteristically defined as a velvety red patch that cannot be clinically or pathologically ascribed to any specific disease entity (Figs. 1 and 2). Many investigators consider erythroplakia to be the first sign of asymptomatic squamous cell carcinoma of the oral cavity [1].

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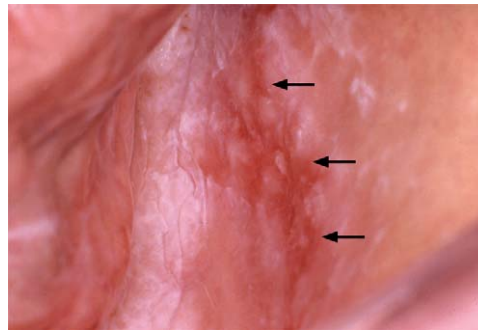

Fig. 1. Erythroplakia of the posterior buccal mucosa (*arrows*), rimmed posteriorally and superiorly by a margin of leukoplakia (Photograph courtesy of Dr. John McDowell.)

Erythroplakic and leukoplakic lesions can be considered as a continuum, because both can transition to malignant lesions. Fig. 3 shows a schematic presentation of an erythroplakic/leukoplakic continuum that defines the microscopic findings that can be seen in association with potential neoplastic change of the oral mucous membrane as the tissue progresses from benign hyperkeratosis through various stages of erythroleukoplakia.

Many systemic diseases can appear as red plaques (erythroplakic plaques), but most of these disorders have a distinctive histopathologic appearance, and they therefore are not classified as erythroplakia or leukoplakia [2]. Erythroplakic and leukoplakic lesions are sometimes categorized together as either speckled leukoplakia or speckled erythroleukoplakia; in many instances it is not possible to separate the two entities definitively.

*Leukoplakia*

Leukoplakia is best defined as a white patch or plaque of the oral mucous membrane that cannot be removed by vigorous scraping and cannot be classified on the basis of clinical findings or microscopic features as any specific

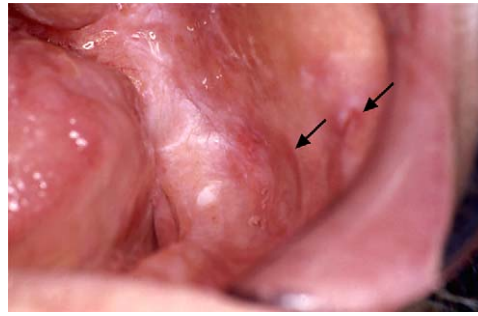

Fig. 2. Erythroplakia, (*arrows*) with a margin of leukoplakia in the buccal mucosa and retromolar trigone region. Lesions seen in Figs 1 and 2 are sometimes referred to as "speckled" erythroleukoplakia. (Photograph courtesy of Dr. John McDowell.)

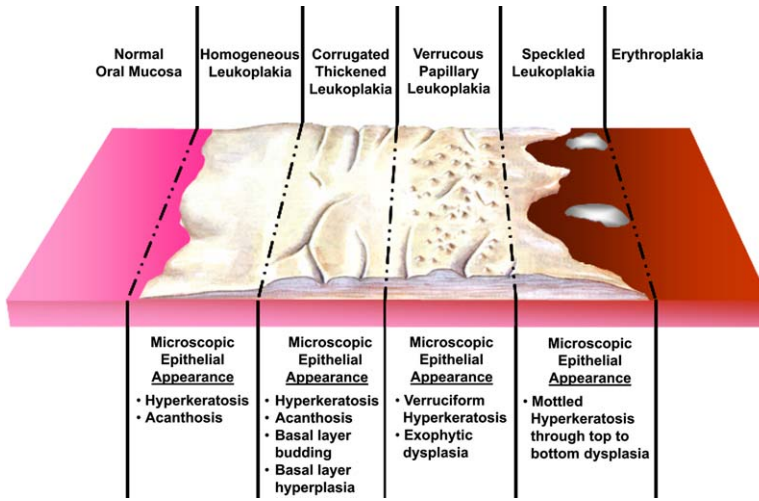


Fig. 3. Leukoplakia/erythroplakia continuum from hyperkeratosis to carcinoma in situ showing graded clinical and pathologic alterations.

disease entity [2,3]. Leukoplakia can occur at any age but seems to develop most often before the age of 40 years and with a distinct male predilection. Leukoplakia has been classified by Pindborg and colleagues [4] and by Sugar and Banocyz [5] into several different subtypes (Table 1). Pindborg and colleagues [4] have further suggested that approximately 6% of all oral leukoplakias become malignant, and Sugar and Banocyz [5] in an evaluation of 670 leukoplakic patients followed for 3 years showed that 31% of the lesions disappeared, 25% remained unchanged, and 30% improved. Burkhardt [6] has attempted to codify leukoplakia into three microscopic forms: (1) papillomatous and exophytic, (2) papillary and endocytic, and (3) plane. Most authorities, however, suggest that leukoplakia is better used as a clinical term with no distinctive histologic features that define it as a unique histologic process. Figs. 4 and 5 show examples of oral leukoplakia, with Fig. 5 demonstrating a pinpoint zone of associated erythroplakia.

Table 1
Clinical subtypes of oral leukoplakia

| Authors | Leukoplakia subtype |
|---|---|
| Pindborg et al [4]. | Homogeneous; white patch with a variable appearance, smooth or wrinkled; smooth areas may have small cracks or fissures, speckled or nodular: erythematous base with white patches or nodular excrescences. |
| Sugar and Banocyz [5] | Leukoplakia simplex: white, homogeneous keratinized lesion, slightly elevated Leukoplakia verrucosa: white, verrucous lesion with wrinkled surface Leukoplakia erosive: white lesion with erythematous areas, erosions, fissures. |

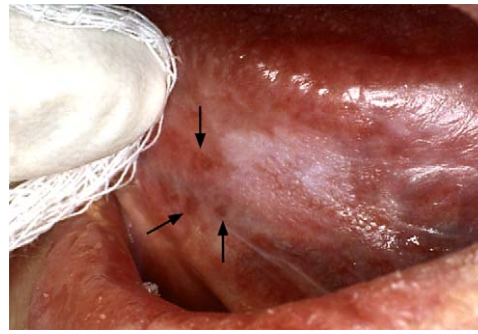

Fig. 4. Leukoplakia, ventral surface of tongue (*arrows*). (Photograph courtesy of Dr. John McDowell.)

*Proliferative verrucous leukoplakia*

Proliferative verrucous leukoplakia (PVL), a form of leukoplakia defined by Hansen and colleagues [7] in 1985 and more clearly defined in the past 20 years, is a series of proliferative, generally irregular white patches or plaques that progress slowly and multifocally on oral mucous membranes and in nearly 100% of cases develop into either squamous cell carcinoma or verrucous carcinoma (Fig. 6). Even when these clinical lesions are removed periodically, with apparent clear surgical margins, the lesions seem to progress. PVL is a clinically descriptive term that should not be used as a microscopic descriptor. The histopathologic corollary to PVL is the microscopic entity verrucous hyperplasia. Verrucous hyperplasia is characterized histologically by the presence of a corrugated epithelial surface that shows church-spire hyperkeratosis or so-called ''toadstool'' hyperkeratosis with parakeratin plugging between papillary fronds (Figs. 7 and 8) [8]. Verrucous hyperplasia can, on a microscopic level, show atypical cytologic features ranging from bland spiking hyperkeratosis to features consistent with marked severe dysplasia.

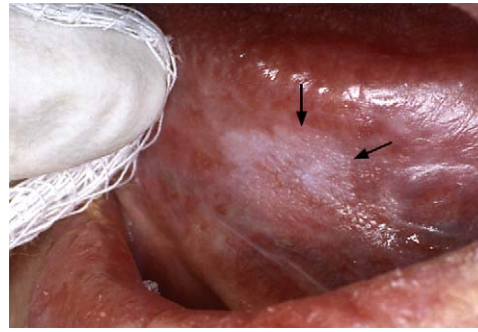

Fig. 5. Pinpoint zones of erythroplakia (*arrows*) distal to a leukoplakic plaque. (Photograph courtesy of Dr. John McDowell.)

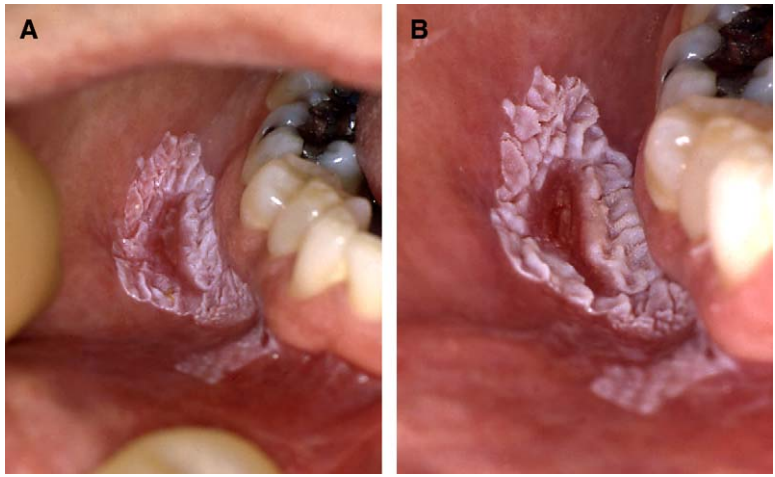


Fig. 6. (*A* and *B*) The exophytic white corrugated/papillary pattern of proliferative leukoplakia. (Photograph courtesy of Dr. John McDowell.)

The overarching clinical disease process is characterized by recurrence, persistence, and a multifocal proliferation. The progression of this process from simple hyperkeratosis to verrucous carcinoma or squamous cell carcinoma has been well documented using polymerase chain reaction (PCR) techniques. Greer and Shroyer [9,10] have also documented the presence of human papillomavirus (HPV), most frequently high-risk HPV16, -18, and occasionally -6 and −11, in PVL.

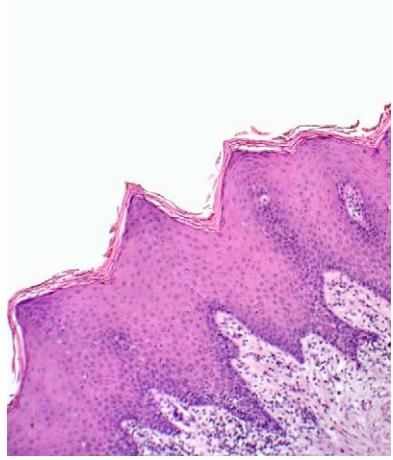

Fig. 7. Classic histologic pattern of verrucous hyperplasia with its corrugated epithelial surface and church-spire or chevron type of hyperkeratosis.

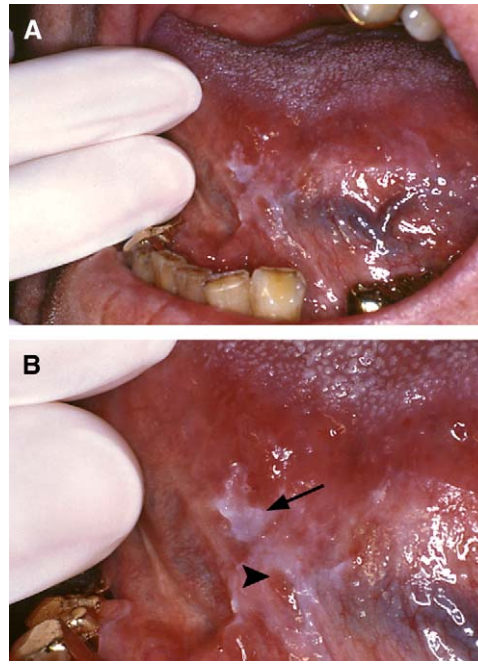


Fig. 8. (*A* and *B*) Epithelial dysplasia of the ventral surface of the tongue. Arrows in B demonstrate zones of (*long arrow*) leukoplakia and (*short arrow*) erythroplakia, which on microscopic examination were histologically consistent with moderate epithelial dysplasia. (Photograph courtesy of Dr. John McDowell.)

PVL is in fact a form of field cancerization in which tissue that appears clinically normal progresses through advanced stages of dysplasia to culminate in some form of epithelial cancer. PVL is more common in women than in men, with a peak incidence at 60 to 70 years of age. Most patients who have PVL are nonsmokers, and Marks [11] has reported that in 92% of cases he studied, the lesions harbored *Candida albicans* species at the time of microscopic tissue examination [11]. Marks suggests that it is possible that *Candida* colonization and the *Candida* organisms act as topical carcinogens in the PVL process because of their ability to produce nitrosamines, thus transforming normal oral mucosa into dysplastic tissue and ultimately malignant tissue. Typically periodic acid–Schiff stains are used to identify *Candida* organisms in PVL. This procedure is mandatory because treatment often involves surgery in association with an antifungal regimen.

Greer and colleagues [12] have reported the overexpression of telomerase, an enzyme that regulates cell longevity in cases of verrucous hyperplasia, the histologic counterpart of PVL. Some investigators have reported PVL to be an end-stage form of hypertrophic lichen planus. There is considerable debate as to whether this transition actually occurs.

*Oral epithelial dysplasia*

Epithelial dysplasia is premalignant condition characterized clinically by an alteration in the oral epithelium that may cause the oral mucosa to turn red, white, or some other color variation (Fig. 8). Epithelial dysplasia is characterized by atypical microscopic changes in the epithelium that can include but are not limited to prominent nucleoli, hyperchromatic nuclei, nuclear pleomorphism, altered nuclear/cytoplasmic ratios, increased atypical mitotic activity, increased individual cell characterization, basal cell hyperplasia, and basal layer budding.

Dysplasia is generally classified, microscopically, as mild, moderate, or severe (Figs. 9–11). Box 1 lists some of the atypical cytologic features diagnostic of dysplasia. Dysplastic atypia extending from the basal layer of the epithelium to include the superficial keratin layer of the epithelium is termed ''carcinoma in situ'' (Fig. 12). Epithelial dysplasia can become progressive over time, or, in some instances, mild forms of dysplasia may be reversible. It is unlikely that carcinoma in situ is a reversible lesion, and there is an increasing consensus among pathologists that lesions that have been classified as severe dysplasias in the past for the most part in fact represent carcinoma in situ.

Dysplasia of the oral epithelium has not undergone the close diagnostic scrutiny or extensive subclassification that dysplasia of the uterine cervix has, and the histologic classifications are still best categorized as mild, moderate, or severe. With mild dysplasia, the severity of the atypical cytologic changes is minimal. These atypical cytologic patterns become more pronounced in cases of moderate dysplasia and severe dysplasia to include altered nuclear/cytoplasmic ratios, dyskeratosis, basal layer hyperchromatism, and significant atypical mitotic forms. It has been proposed that the term ''oral intraepithelial neoplasia'' (OIN) be used in synchrony with the classification of the cervix and the vaginal intraepithelial neoplasia (VIN) system that is used for vaginal wall dysplasia. To date, however, pathologists have not generally accepted this proposal.

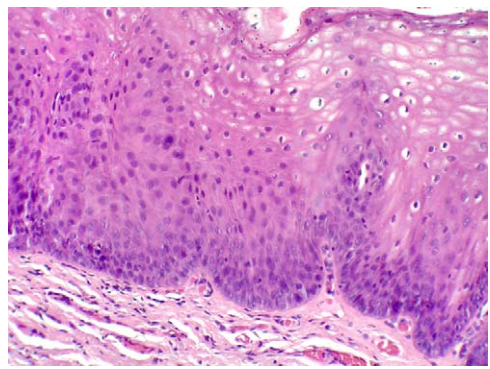

Fig. 9. Mild epithelial dysplasia demonstrating focal basal layer hyperplasia, loss of cellular polarity, and a solitary dyskeratotic cell.

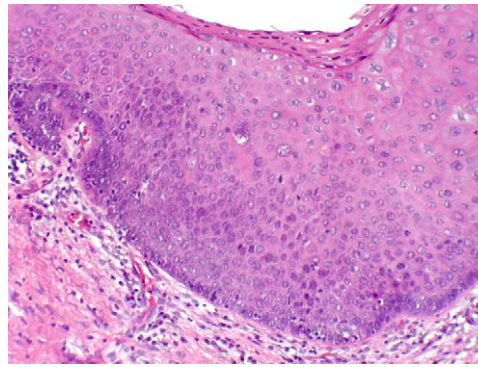

Fig. 10. Moderate epithelial dysplasia demonstrating an intact epithelial basement membrane with zones of dyskeratosis, altered nuclear cytoplasmic ratios, atypical mitoses, enlarged nuclei, and increased number of mitotic figures.

There has been significant debate as to whether dysplastic lesions of the oral mucous membrane that are in continuity with the skin surface are better characterized as actinic keratosis or as mild, moderate, or severe dysplasia. This author believes that, regardless of contiguous skin surface association, these lesions should be classified using dysplastic criteria and not simply lumped into the category of actinic change or actinic keratosis, largely because the basic biologic behavior of dysplastic lesions of the oral mucosa is significantly more aggressive than that of corresponding skin.

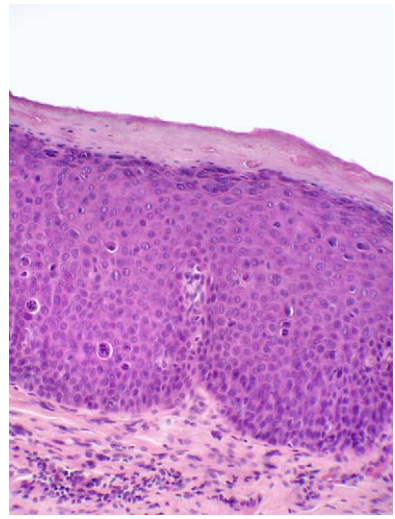

Fig. 11. Severe epithelial dysplasia with an abundance of atypical mitoses that extend high into the epithelium, zones of dyskeratosis, focal loss of cellular polarity, basal layer hyperplasia, and considerable nuclear pleomorphism.

**Box 1. Common microscopic features associated with oral epithelial dysplasia**

Increased nuclear/cytoplasmic ratio
Sharply angled rete processes
Loss of cellular polarity
Cellular pleomorphism
Nuclear pleomorphism
Enlarged nucleoli
Reduction of cellular cohesion
Individual spinous layer cell keratinization
Increased number of mitotic figures
Presence of mitotic figures in the superficial half of the epithelium
Basal cell layer hyperplasia
Loss of polarity of the basal cells

The risk of transformation of oral epithelial dysplasia to squamous cell cancer has been reported to be as high as 23.4%, a much higher transformation rate than the 6.5% reported for homogenous leukoplakias [1]. The anatomic location of oral epithelial dysplasia is a significant factor in assessing the risk of that dysplasia undergoing malignant transformation. Lesions of the tongue and floor of the mouth have a much greater risk of transformation than lesions at other sites in the oral cavity.

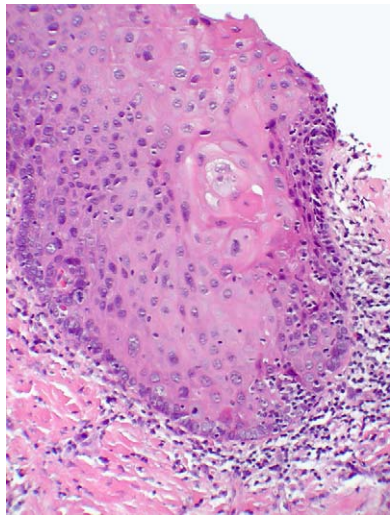

Fig. 12. Carcinoma in situ demonstrating epithelial dysplasia with marked zones of dyskeratosis. The dysplastic change extends from the basal layer of the epithelium to the fragmented surface keratin layer.

Oral epithelial dysplasia has been reported to arise in association with the vesicular bullous disease lichen planus. Greer and colleagues [13] report that 2% of 588 lichen planus cases they studied over a 20-year period underwent malignant transformation. This preneoplastic transformation is sometimes referred to as "lichenoid dysplasia," but lichenoid dysplasia is a controversial term: some authorities suggest that lichen planus does not in fact transform to dysplasia or squamous cell carcinoma over time. It has been suggested that such lesions are probably improperly diagnosed squamous cell carcinoma or dysplasia from their start. The bulk of the information in the literature, however, indicates that a small percentage of lichen planus cases do undergo dysplastic and malignant transformation.

*Carcinoma in situ*

Carcinoma in situ can present in the oral cavity as a red or white lesion, as some other mucosal discoloration, or as a distinct tumor mass. Mashberg and Meyers [1] suggest that suspicious red lesions in high-risk individuals have the highest propensity to develop into carcinoma in situ. The microscopic diagnosis of carcinoma in situ requires rigid histologic criteria, and the distinction between carcinoma in situ and severe epithelial dysplasia is often difficult and sometimes arbitrary. Lesions representing carcinoma in situ show a host of dysplastic changes with the key histologic feature required for the diagnosis being the presence of an intact basement membrane and top-to-bottom dysplastic epithelial dysplasia from the basal layer to the keratinized layer of the oral epithelium (Fig. 12). The characteristic features required for this diagnosis are the same as for carcinoma in situ for of the cervix.

*Smokeless tobacco keratosis*

In 1983 Greer and associates [14] reported a classification scheme for tissue changes associated with the use of smokeless tobacco products by teenagers and described a special form of leukoplakia, which they termed smokeless tobacco leukoplakia or smokeless tobacco hyperkeratosis. These investigators ultimately were able to identify HPV DNA in 15% of the smokeless tobacco hyperkeratoses they studied, suggesting that HPV may play a synergistic role in the development of lesions that are defined clinically as smokeless tobacco leukoplakias. In a longitudinal study in which more than 10,000 persons enrolled as high school students have been evaluated over a 20-year period, smokeless tobacco dysplasia has been a rare finding.

Smokeless tobacco is sold as either leaf tobacco or snuff, which is ground tobacco. The product, which is placed into the oral cavity, generally between the cheek and gum, contains potential carcinogens. This form of noncombustible tobacco does not result in the formation of benzopyridine epoxides seen with tobacco that is burned, and therefore the incidence of invasive squamous cell carcinoma or verrucous carcinoma does not seem to be as high in persons who use smokeless tobacco as in cigarette smokers. Smokeless tobacco

products do produce a clinically identifiable form of hyperkeratosis that affects the oral mucous membrane, a hyperkeratotic plaque that is frequently referred to as a "snuff dippers patch" or "snuff dippers pouch" (Fig. 13). The lesions tend to develop directly at the site of application of the tobacco product. A similar form of hyperkeratosis has been reported in India, China, Sri Lanka, and other Asian countries in association with the use of betel nut or slake lime products. A lengthy neoplastic induction time that can range from 15 to 50 years is associated with the use of these all these products.

The histopathology of a smokeless tobacco lesion is shown in Fig. 14. A host of histologic changes can be seen in association with smokeless tobacco use, but most such lesions demonstrate hyperparakeratosis and epithelial hyperplasia. There may also be hyperplasia of the basal epithelial layer and characteristic chevron or church spire keratinization and fibrosis or scarification of an underlying collagen as well as chronic sialadenitis.

Hyperkeratoses induced by smokeless tobacco are generally reversible when the product is discontinued, but certain lesions, specifically those that have a corrugated, papillary, or velvety surface, are considered to be high-risk lesions. Shroyer and Greer [9] and Greer and Eversole [15,16] have reported that such lesions show a greater degree of epithelial atypia than lesions that have a homogeneous white surface. These investigators have also reported that more than 40% of smokeless tobacco lesions harbor HPV-specific antigens. Overexpression of the enzyme telomerase has also been reported to occur in smokeless tobacco lesions [12].

*Oral submucous fibrosis*

Oral submucous fibrosis is a disorder that has been reported predominately in East India, Sri Lanka, and Southeast Asian cultures. The causative agent for this precancerous lesion is thought to be related to *Areca catecha*, a component of betel nut products that is thought to affect collagen synthesis pathologically. This product, along with slake lime, is used recreationally in these geographic regions. The most common clinical presentation is thickened

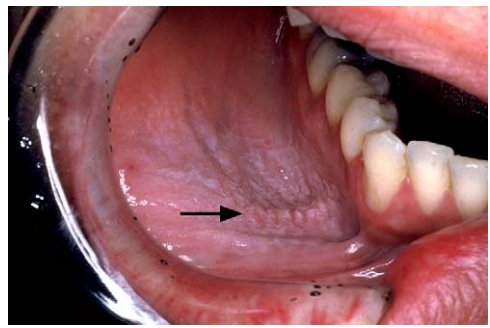

Fig. 13. Grade III smokeless tobacco keratosis (*arrow*) demonstrating a corrugated leukoplakic surface with red furrows and marked diffuseness as it extends into the buccal vestibular mucosa.

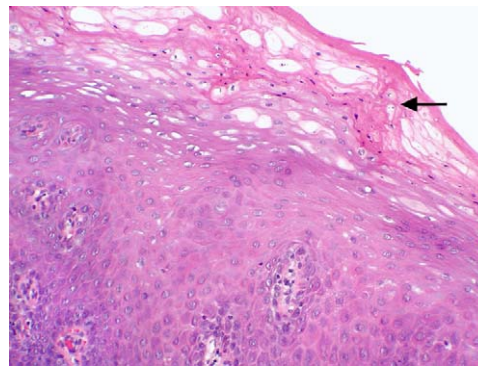

Fig. 14. Smokeless tobacco hyperkeratosis, Grade II, demonstrating chevron keratinization (*arrow*).

white mucosa lacking elasticity. Histopathologically, submucous fibrosis is characterized by connective tissue alterations in which the collagen becomes avascular and adjacent skeletal muscles atrophy. Chronic inflammatory cells may or may not be present within the collagen, and the epithelium typically shows changes that range from atrophy to hyperkeratosis. Neoplastic transformation of the overlying oral epithelium to squamous cell carcinoma occurs in some instances, as does progressive fibrosis and trismus.

*Nicotine stomatitis*

Nicotine stomatitis is a form of leukoplakia that occurs most commonly in the palate in patients who have been long-term smokers, most frequently pipe and cigar users. The condition seems to be proportional to the degree and frequency of the tobacco habit. In this disorder the mucosa appear white and thickened, with acanthosis and hyperkeratosis seen microscopically. Clinically, pinpoint, thin, red zones of normal oral mucosa are surrounded by circinate zones of hyperkeratosis (Fig. 15). Nicotine stomatitis

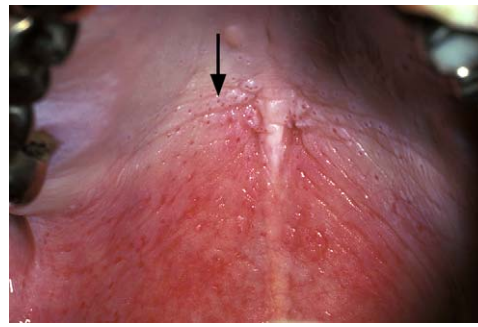

Fig. 15. Nicotine stomatitis. Note pinpoint, red, plugged minor salivary gland ducts (*arrow*) and rough textured leathery surrounding hyperkeratosis.

is easily identifiable clinically and can usually be diagnosed on the basis of a through examination and evaluation of the patient's history. Histologically, in addition to epithelial acanthosis, the lesions of nicotine stomatitis show inflammation of minor salivary glands. Salivary gland ducts may show hyperplasia and squamous metaplasia, but dysplasia is not a feature of this disorder. These red mucosal zones represent focal areas of inflammation at the point of minor salivary gland duct openings. No specific treatment is required for this condition other than to counsel patients to modify or discontinue their tobacco habit.

## Malignant epithelial neoplasms

### *Squamous cell carcinoma of the oral cavity—clinicopathologic perspectives*

A range of histologic features can be identified in squamous cell carcinoma of the oral cavity, but all show a commonality. Clinically, squamous cell carcinoma can present as a red lesion, a white lesion, an ulcer or tumor mass, or some other variation or color. Fig. 16 shows examples of oral squamous cell carcinoma.

The basement membrane of the oral epithelium is violated in all cases of squamous cell carcinoma, and the neoplastic process extends beyond the basement membrane into the connective tissue lamina propria as broad sheets, nests, cords, and islands neoplastic cells of epithelial origin. The

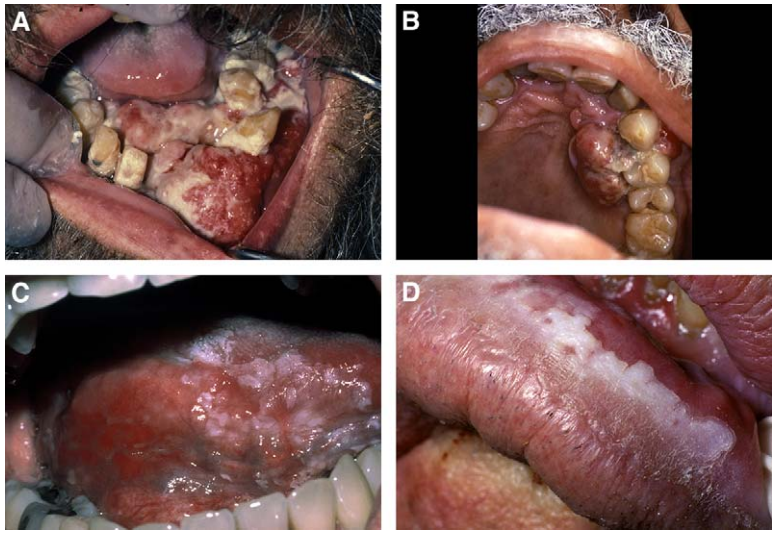


Fig. 16. (*A*) Exophytic squamous cell carcinoma of the mandibular alveolus. (*B*) Nodular hemorrhagic squamous cell carcinoma of the lingual gingival. (*C*) Corrugated and plaque-like squamous cell carcinoma of the ventral and lateral surface of the tongue. (*D*) Squamous cell carcinoma at the vermillion border of the lip.

appearance of these tumor cell nests is quite variable, depending on the degree of tumor differentiation. In some lesions, the tumor islands may show tumor cells of epithelial origin, with large amounts of keratin, mimicking the overlying epithelium. These well-differentiated neoplasms generally have minimal cellular atypia and mitotic atypia (Fig. 17). Poorly differentiated lesions, on the other hand, demonstrate little evidence of keratin formation, and atypical mitoses are prominent, as is cellular pleomorphism and nuclear atypia (Fig. 18). Th histologic appearance of moderately differentiated lesions falls somewhere between that of poorly differentiated squamous cell carcinoma and moderately differentiated tumors (Fig. 19).

*Pathogenesis of oral squamous cell carcinoma*

The pathogenesis of oral squamous cell carcinoma, like that of other malignancies, is related to an accumulation of multiple genetic insults that ultimately program epithelial precursor cells to develop invasive neoplastic properties. The changes that initiate oral cancer on a genetic level are related to alterations in genes that are responsible for encoding proteins that control a host of features in the development of cells, including cell motility, cell cycle regulation, cell survival, and angiogenesis. The process of clonal evolution, in which genetic mutations confer selective growth advantages on cell precursors, ultimately causing the expansion of mutant cells, seems to be the key to the multistep genetic progression toward oral epithelial cancer. Few genetic changes are required for the acquisition of a malignant phenotype, and oral epithelial cancers seem to transition through the process of aberrant cell cycle control and increased cell motility quite easily. Both of these events occur as a result of the increased expression of oncogenes and the decreased expression of so-called ''tumor suppressor genes'' [17]. Alterations of the groups of genes that control the cell cycle are of immense importance in the development of oral squamous cell carcinoma, and the overexpression of oncogenic proteins or lack of expression of tumor

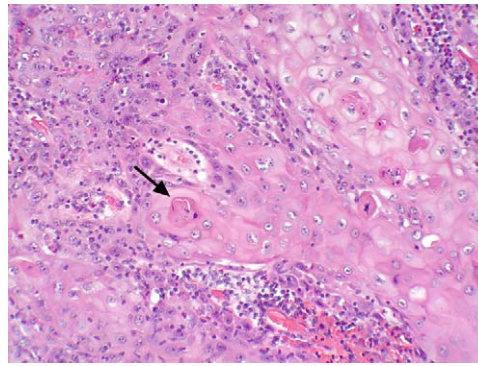

Fig. 17. Well-differentiated squamous cell carcinoma. Arrow notes keratin pearl formation.

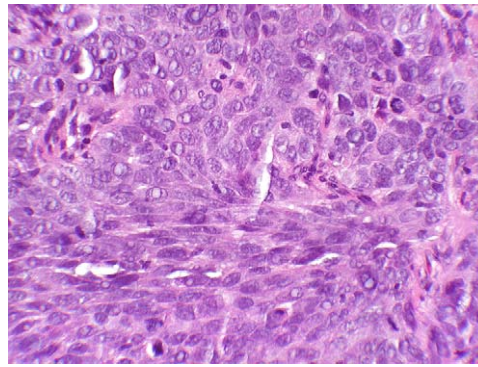

Fig. 18. Poorly differentiated squamous cell carcinoma displaying lack of keratin formation and focal spindle cell aggregation of tumor cells.

suppressor anti-oncogenic proteins can be enough to trigger neoplastic transformation. Figs. 20, 21, and 22 show schematic examples of how squamous epithelial cells also can transform to neoplastic cells through minute alterations in protein expression, cell cycle regulation, and angiogenesis.

Finally, for neoplasms to grow, they must have an adequate blood supply. Angiogenesis, the method by which this increased blood supply develops, requires the overexpression of certain tumor-induction proteins. Vascular epidermal growth factor controls tumor-mediated induction or overexpression of anti-oncogenic proteins, whereas fibroblastic growth factor and interleukin 8, a proinflammatory cytokine, are believed to be responsible in part for the promotional angiogenesis associated with oral squamous cell cancers [17].

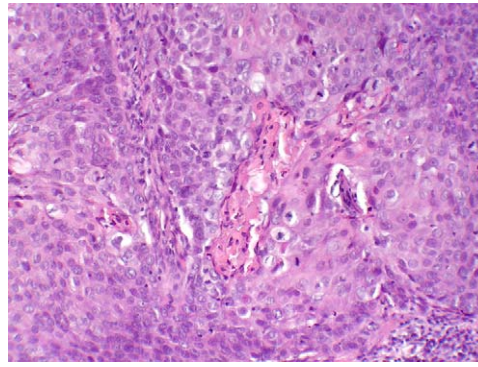

Fig. 19. Moderately differentiated squamous cell carcinoma. This moderately differentiated squamous cell carcinoma shows an accumulation of atypical cells of squamous origin with occasional nests resembling differentiated squamous epithelium and end zones of keratin formation.

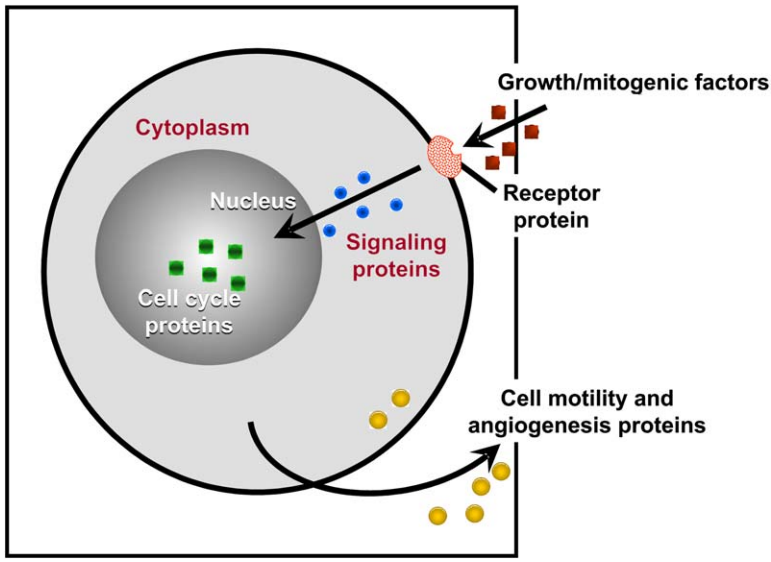


Fig. 20. Alterations in gene expression in a model of oral cancer.

Another significant factor related to development of oral epithelial cancer, especially as it relates to the replicate lifespan of tumor cells, is the overexpression or neo-expression of the enzyme telomerase. This intranuclear enzyme, present in cancer cells but absent in normal cells, seems to confer

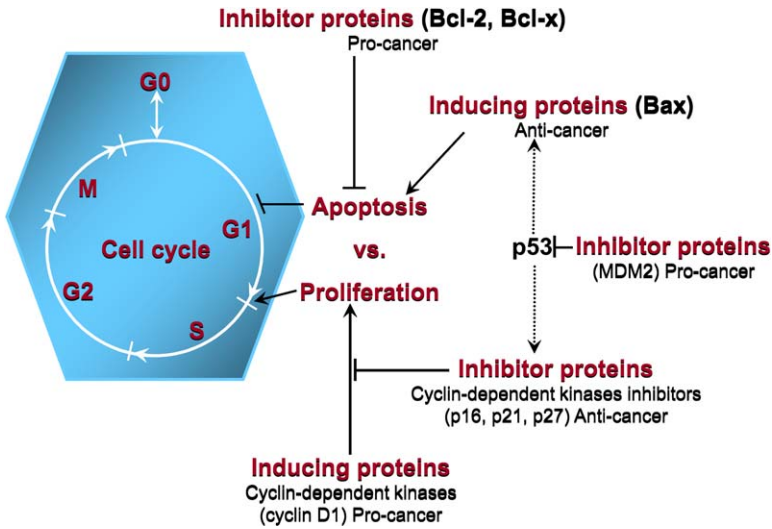


Fig. 21. Alteration in cell cycle regulation (G1-S) phase in a model of oral cancer.

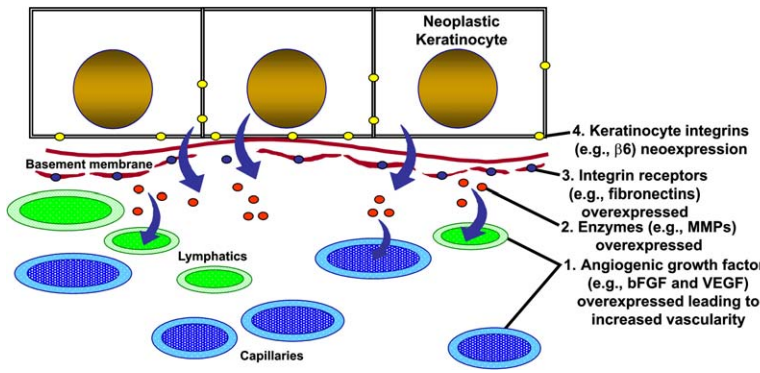


Fig. 22. Transformation of normal squamous epithelial cells to neoplastic cells through angiogenesis. bFGF, basic fibroblast growth factor; MMP, matrix metalloproteinase; VEGF, vascular endothelial growth factor.

increased longevity on tumor cells by allowing life span–controlling telomeres to retain their length at the ends of chromosomes. These telomerase–DNA protein complexes at the ends of chromosomes are responsible for cell degradation. When allowed to maintain their length indefinitely, they allow tumor cells to remain viable. Greer and colleagues [12,18] have reported the overexpression of telomerase in precancerous oral lesions.

### *Histopathology of oral squamous cell carcinoma*

Histologically, oral squamous cell carcinomas are typically categorized as well differentiated, moderately differentiated, poorly differentiated, or undifferentiated. Undifferentiated neoplasms are often referred to as ''nonkeratinizing squamous cell carcinomas.'' Tumors also have been classified as grades I through IV [19]. Grade I tumors greatly mimic the tissue from which they have arisen histopathologically and readily resemble their epithelial tissue of origin, where as grade IV tumors have little resemblance to oral squamous epithelium.

Well-differentiated squamous cell carcinomas are composed of neoplastic cells that have a marked similarity to the normal cells of squamous epithelium and thus demonstrate round to oval nuclei with eosinophilic cytoplasm and intracellular bridging. There may be variable degrees of nuclear hyperchromatism and mitotic activity, ranging from minimal atypia to bizarre mitoses. Keratin formation is a common feature associated with well-differentiated squamous cell carcinomas, as is individual cell keratinization. These two features are rarely seen in poorly differentiated neoplasms, and cytokeratin staining may be necessary to demonstrate these features in undifferentiated neoplasms.

The defining hallmark of squamous cell carcinoma is its invasion into the connective tissue lamina propria of the oral cavity. Thus, the classic pattern

that must be identified microscopically is the infiltration of neoplastic squamous epithelial cells into the supporting connective tissue stroma. This stroma may be chronically inflamed with an abundance of plasma cells and lymphocytes.

Moderately differentiated squamous cell carcinoma displays a more varied histologic pattern in which the tumor cells may resemble normal squamous epithelial cells but with a greater degree of hyperchromatism, pleomorphism, and anisocytosis and a loss of attachment between cells. There also may be an increased frequency of atypical mitoses and decreased frequency of keratin formation. In tumors that are poorly differentiated, there is little evidence that the tumors are of squamous origin, and individual cell keratinization often is lacking. Nuclear cytoplasm ratios can be dramatically altered, and there may be significant pleomorphism among cells and considerable atypical mitoses.

Undifferentiated squamous cell carcinomas, those tumors that are commonly referred to as ''nonkeratinizing squamous cell carcinoma,'' bear little resemblance to the tissue from which they have arisen, and defining tumor cells as epithelial in origin may be difficult. On occasion, electron microscopic evaluation may be helpful, but the more common method of identifying such undifferentiated neoplasms is immunohistochemical staining for cytokeratin using a pancytokeratin panel. Stromal changes in these undifferentiated tumors may include desmoplastic fibrosis, vascular hyperplasia, and a diffuse infiltrate of chronic inflammatory cells. The histologic grading of oral squamous cell carcinoma is subjective, and clinical staging may prove to correlate more accurately with prognosis than the grading of tumors histopathologically.

### *Histologic features of prognostic significance in squamous cell carcinoma*

For many years pathologists have attempted to define histologic features that are of predictive value in accessing patient outcome for squamous cell carcinoma. Yamamoto and colleagues [20], and more recently Crissman and colleagues [21], have documented two significant histologic patterns for squamous cell carcinoma that may be predictive of patient outcome. These potential histologic findings include (1) the pattern of tumor invasion within the supporting collagenous stroma, and (2) the depth of tumor invasion into that supporting collagenous stroma. Yamamoto's group [20] and Crisman's team [21] reported a greater frequency of lymph node metastasis when the neoplasm's infiltrative pattern was associated with noncohesive areas of tumor cells or with the spread of individual tumor cells within the collagenous stroma.

Shingaki and colleagues [22] have reported that the depth of invasion of a squamous epithelial neoplasm into the collagenous stroma is of great prognostic significance. These authors reviewed a series of squamous cell carcinomas of the oral cavity and pharynx and were able to demonstrate that tumors that invaded the connective tissue stroma to a depth of less than 4 mm had an 8.3% rate of metastasis. Tumors that showed a 4- to

8-mm depth of invasion demonstrated metastatic rates of 35%. In tumors where the invasion of neoplastic nests was greater than 8 mm into the connective tissue stroma, the metastatic rate was 83%. These studies indicate that the depth of invasion of a squamous epithelial neoplasm into the connective tissue lamina propria of the oral cavity can be a significant factor in indicating whether metastasis will be problematic in a patient's course of therapy.

The anatomic site of presentation of a tumor can be of considerable significance in patient prognosis, and certain site-specific considerations account for variations in the behavior patterns of squamous cell carcinoma of the oral cavity. In a study of 898 squamous cell carcinomas of the oral cavity and pharynx, Shear and colleagues [23] demonstrated that tumors of equal size that involved the lip, buccal mucosa, hard palate, and the gingiva had a similar risk of metastatic spread to regional lymph nodes. The prognosis for squamous cell carcinoma arising in certain other anatomic sites, including the posterior lateral border of the tongue and the floor of the mouth, is much worse than that associated with the four aforementioned sites. Cervical lymph node metastasis, extracapsular lymph node extension, angiolymphatic invasion by the neoplasm, and perineurial invasion reflect a worse prognosis.

Investigators have made many attempts to determine the significance of positive tumor margins when there has been frozen section control of a squamous cell carcinoma at the time of surgery. Byers and colleagues [24] reviewed a series of cases of head and neck invasive squamous cell carcinomas and carcinoma in situ in which there were positive tissue margins with frozen section control and demonstrated a recurrence rate of 80% when a surgical margin was involved by tumor. Conversely, these authors found that tumors that had margins free of neoplasia had recurrence rates of 12% and 18%, respectively, for squamous cell carcinoma or carcinoma in situ.

Numerous evolving methods using an ever-increasing number of genetic and biologic markers attempt to evaluate the significance of positive tumor margins for oral squamous cell carcinoma. There have been attempts to identify the presence of certain gene products and viruses within or at the margins of oral squamous epithelial neoplasms in an effort to correlate their presence with patient outcome [25–27]. Recently investigators have attempted to use the telomerase assay as a molecular marker for identifying positive margins in oral squamous cell carcinoma when microscopic evidence of disease was not evident [28,29]. Chromosomal microsatellite markers at chromosomes 3, 8, 9, 17, and 18 and evidence of *p53* mutations in histologically normal-appearing tissue are also being used to demonstrate that genetically altered tissue which appears normal microscopically may advance to squamous cell carcinoma with certainty, given the presence of these markers [30,31].

The role of HPV in the development of oral cancer has been studied exhaustively in the past 2 decades using a host of molecular biologic

techniques. More than 100 different HPV subtypes have been isolated from both benign and malignant oral mucosal neoplasms, and many investigators have identified HPV antigens and gene products in biopsies of oral cancer and oral pharyngeal cancer as well as precancer [21–23,31–35]. HPV has also been identified in normal metastasis from cancers of the oral cavity and other regions of the head and neck [23]. Recent studies have also shown that the *HPV-16 E-5* gene can induce malignant transformation of epithelial cells by enhancing growth factor–mediated intercellular signal transduction. Finally, Scully [32] has reported that oral carcinogenesis ultimately evolves because oncosuppressor genes act in cyclic association with growth factors and viruses as well as chemical carcinogens and oncogenes to initiate a process that terminates in cancer by way of the process of cyclic interdependence.

Mucosal HPVs are clearly a cause of cervical cancer and probably are the cause of a special subset of oral squamous cell carcinomas. Fourteen high-risk types of HPV have been linked to cervical cancer, and the high-risk types HPV16 and -18 have been detected with increasing frequency in head and neck squamous cell carcinoma [33].

### *Squamous cell carcinoma variants*

#### *Verrucous carcinoma*

Verrucous carcinoma, first described by Friedell and Rosenthal [36], is a variant of squamous cell carcinoma that was fully defined by Ackerman [37] in 1948. The tumor typically appears in the sixth decade of life and accounts for 2% to 8% of all squamous cell carcinomas [37,38]. Verrucous carcinoma is best defined as a clinicopathologic process that begins as part of a histologic spectrum that germinates as a papillary verrucoleukoplakia and terminates as a malignant neoplasm [40]. Some investigators, including Shear and Pindborg [8], suggest that the term ''verrucous hyperplasia'' be applied to early papillary or verrucoid lesions that eventuate to verrucous carcinoma. Batsakis [38], however, has suggested that verrucous hyperplasia simply be considered an early form of verrucous carcinoma, without the necessity of a separate name designation.

Verrucous carcinoma can demonstrate multiple phases of clinical development: it can present as a lesion that can be soft and fleshy, corrugated, fibrotic, red, granular and rough, ulcerative, or papillomatous (Fig. 23) [39]. Invasive squamous cell carcinoma can be identified in verrucous carcinoma in approximately 38% of cases. These so-called ''verrucoid-squamoid'' hybrid lesions can be a difficult diagnostic challenge for pathologists. Therefore it is important for pathologists to section cases thought to be verrucous carcinoma thoroughly to avoid overlooking a possible squamous cell carcinoma.

A body of literature suggests that hyperkeratosis induced by the use of smokeless tobacco products predisposes patients to development of verrucous carcinoma. Shroyer and Greer [9], however, reviewed a large series

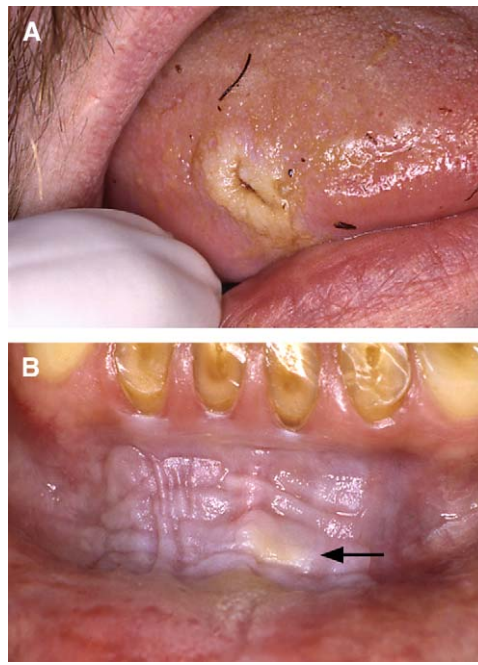


Fig. 23. (*A*) Corrugated elevated and centrally ulcerated verrucous carcinoma of the tongue. (*B*) Verrucous carcinoma of the anterior alveolar vestibular mucosa displaying a leukoplakic area of well delineated mucosal folds. Arrow denotes area of mucosal elevation. (Photographs courtesy of Dr. John McDowell.)

of smokeless tobacco leukoplakias and were unable to demonstrate dysplasia or verrucous carcinoma in any of the cases they reviewed. Their studies support the observation that smokeless tobacco use alone does not seem to initiate verrucous carcinoma in patients who had used the product for less than 7 years. These investigators, however, were able to demonstrate HPV in many of the specimens that they evaluated, and they found that 29% of 14 cases of verrucous hyperplasia that were evaluated for HPV DNA by in situ hybridization and PCR analysis were positive for HPV16. In a follow-up study these same authors reviewed 17 verrucous carcinomas and found, using similar PCR techniques, that 49% of the lesions harbored HPV16 or -11 [40]. These studies suggest that HPV may be an important cofactor in the development of verrucous carcinoma.

Grossly, verrucous carcinoma usually presents as a corrugated mass that is gray, white, or tan and is often rubbery, with finger-like or velvety projections on the surface. Microscopically the tumor is characterized by a proliferation of acanthomatous, papillary squamous epithelium that invaginates superficially as it spreads linearly along the connective tissue lamina propria displaying a broad, pushing front (Fig. 24). The surface epithelium typically shows papillary acanthosis with parakeratin plugging between papillary

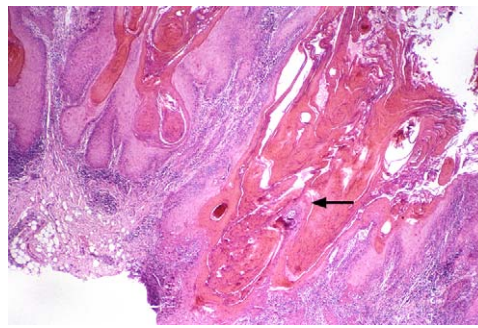

Fig. 24. Verrucous carcinoma displaying broad pushing neoplastic front, papillary acanthosis, lack of cellular atypia, and zones of interpapillary parakeratin plugging (*arrow*).

fronds, and the tumor classically demonstrates little evidence of the cytologic hallmarks of a squamous epithelial malignancy, lacking dyskeratosis, anaplasia, and atypical mitoses. The epithelial basement membrane remains intact as the tumor extends as a blunt proliferation along the connective tissue interface. Ackerman [37] suggests that this blunt proliferation of tumor along a broad, pushing front is a mandatory feature for the diagnosis of the neoplasm. Jacobson and Shear [41] have further suggested that a second highly reproducible histologic feature of verrucous carcinoma is the high incidence of a cupping margin of epithelium at the edge of the tumor that is bent or infolded on itself.

A final important feature that Shafer [42] reports is that in verrucous carcinoma a distinct wedge-like pattern of parakeratin plugging occurs between individual finger-like processes of the neoplasm. This feature is seen infrequently with other papillary lesions, such as papilloma, verruca vulgaris, condyloma acuminatum, or verruciform xanthoma, and the keratohyalin granules that are often a hallmark of verruca vulgaris and other benign papillary lesions are often lacking in verrucous carcinoma.

Differential diagnoses that should be considered when considering a diagnosis of verrucous carcinoma include oral florid papillomatous, pseudoepithelomatous hyperplasia, papillary hyperplasia, papillary squamous cell carcinoma, and keratoacanthoma. Oral florid papillomatosis is characterized clinically by multiple papillary growths as opposed to the solitary neoplastic proliferation seen with verrucous carcinoma. Additionally, oral florid papillomatosis is typically a disorder of children. Pseudoepithelomatous hyperplasia is a disorder in which the epithelial component of this reactive non-neoplastic process tends to proliferate as elongated, knife-like structures that infiltrate the connective tissue lamina propria, in contrast to the broad, pushing front seen with verrucous carcinoma. Papillary hyperplasia is easily defined clinically because of its close association with ill-fitting dentures and its typical confinement to the palate. Finally, the glassy hyalinized appearance of keratoacanthoma and the knife-edged marginal lipping that

are seen with this disorder histologically are rarely seen in verrucous carcinoma.

Verrucous carcinoma can be distinguished from well-differentiated squamous cell carcinoma, with which it can be confused, by a lack of cytologic atypia and the absence of proliferation of the neoplasm beyond the basement membrane zone. Well-differentiated squamous cell carcinoma lacks the broad, pushing front of verrucous carcinoma as it invades the connective tissue and generally has no evidence of parakeratin plugging between papillary fronds.

*Basaloid squamous cell carcinoma*

First described by Wain and coworkers [43] in 1986, basaloid squamous cell carcinoma is an uncommon aggressive neoplasm that typically arises in the larynx. Cases have been described in the oral cavity [44,45] in sites that include the tongue base, hypopharynx, floor of mouth, buccal mucosa, and palate. Most patients who have this tumor have been smokers, and the mean age has been reported to be 62 years. The tumor has two distinct components histopathologically: (1) a component of well- or moderately differentiated squamous cell carcinoma, and (2) infiltrating basaloid-appearing nests of tumor cells. These infiltrative basaloid nests show peripheral palisading and often demonstrate central (comedo) necrosis and a high mitotic rate (Fig. 25). A spindle cell component may also be seen. The stroma between the basal cell nests can show myxoid change or hyalinosis.

The major differential diagnoses for basaloid carcinoma include adenosquamous carcinoma, mucoepidermoid carcinoma, adenoid cystic carcinoma, and small cell carcinoma. The treatment of choice for this neoplasm generally is a combination of radical surgical excision and adjunctive chemotherapy or radiotherapy. This biologically aggressive neoplasm usually demonstrates early regional and distant metastasis.

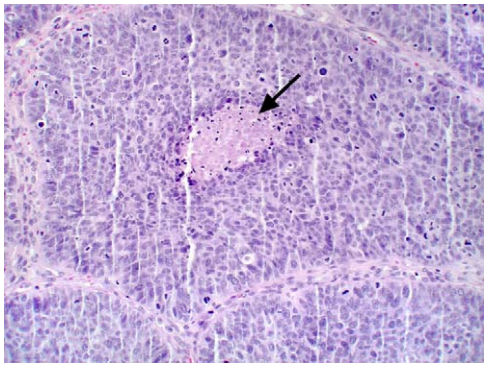

Fig. 25. Basaloid squamous cell carcinoma demonstrating central comedo necrosis (arrow) and a high mitotic rate along the peripheral margin of palisading basaloid cells.

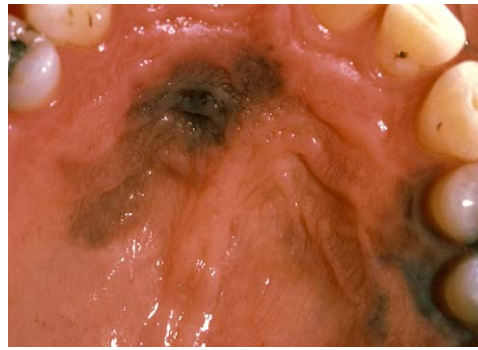

Fig. 26. Melanoma of the oral cavity demonstrating multiple dark black zones of melanoma formation, including one in the central palate and another along the lingual maxillary gingival.

*Spindle cell squamous cell carcinoma*

Spindle cell carcinoma has been reported in the literature under many names, including pleomorphic carcinoma, metaplastic carcinoma, sarcomatoid squamous cell carcinoma, and polypoid squamous cell carcinoma.

Most patients who develop spindle cell carcinoma are men in the sixth or seventh decade of life [46,47], and the most common site is the lip. Spindle cell carcinoma has been etiologically linked to smoking, alcohol abuse, and prior irradiation [48–50]. At present no association with HPV has found. Most spindle cell carcinomas are composed of spindle-shaped cells that are arranged in fasciae, which can be mistaken for sarcoma. When hematoxylin and eosin–stained sections demonstrate equivocal findings, immunohistochemical staining can be used to show keratin antigens.

*Adenosquamous carcinoma*

Adenosquamous carcinoma is a high-grade, aggressive, dimorphic variant of squamous cell carcinoma that shows both squamous carcinoma

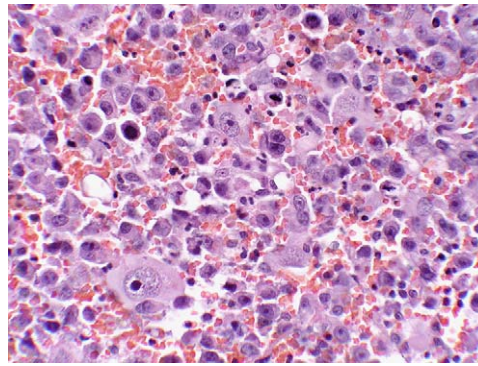

Fig. 27. Markedly anaplastic cells of malignant melanoma.

and adenocarcinoma components. The squamous component is thought to arise from the surface epithelium in the form of dysplasia, in situ carcinoma, or invasive squamous carcinoma. The adenocarcinoma component arises from the minor salivary gland ducts in the form of various grades of malignant gland formation. Gerughty and colleagues [51] first recognized this tumor in 1968. Most cases have been reported in the tongue and floor of mouth [52]. Napier and colleagues [53] have suggested that adenosquamous carcinoma may not be as rare as generally thought. These investigators also report that the volume of the adenocarcinoma component is usually significantly smaller than the squamous counterpart, rendering its recognition as a biphasic tumor difficult in many cases.

*Melanoma*

Malignant melanoma of the oral cavity accounts for about 1% to 8% of all melanomas. It is a rare oral neoplasm with an annual incidence of 1.2 per 10 million people. Rapini and colleagues [54] reviewed a series of 171 cases reported in the English-language literature and reported six new cases. Three of these six patients had tumors with a well-developed radial growth phase. Eighty percent of oral melanomas occur on the hard palate, alveolar mucosa, or gingiva, and the prognosis is poor, with an average survival after diagnosis no longer than 2 years.

The two principal biologic subtypes of oral melanoma are invasive melanoma, which shows a vertical growth pattern with lateral spread, and in situ melanoma, which may feature a relatively long-lasting junctional growth phase before vertical invasion. Fig. 26 shows a palatal melanoma, and Fig. 27 demonstrates the associated histopathology. A third high-risk lesion, termed ''atypical melanocytic hyperplasia,'' although not a true melanoma, requires close long-term scrutiny by the clinician.

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