



MINI-SYMPOSIUM: HEAD AND NECK PATHOLOGY

Epithelial dysplasia of the oral mucosa—Diagnostic problems and prognostic features

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KEYWORDS

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Summary Many oral cancers are preceded by potentially malignant lesions, which may appear as white or red patches on the oral mucosa. In the absence of validated molecular markers, the histological grading of oral epithelial dysplasia remains the only determinant of potential malignant change. Grading is notoriously unreliable, with wide intra- and inter-observer variability. However, conformity may be achieved between pathologists using similar standards and some objective criteria can be used for diagnosing and grading dysplasia. Oral dysplasia is graded simply as mild, moderate or severe, by an evaluation of a combination of cytological and architectural changes in the oral epithelium. Mild epithelial dysplasia, shows relatively few cytological aberrations involving only the lower third of the epithelium, while at the other end of the scale, severe dysplasia may show significant cytological atypia extending into the involved upper third of the epithelium. At its worst, dysplasia involves the full thickness of the epithelium and may be designated carcinoma in situ. This review describes the clinical and histopathological features of oral epithelial dysplasia and guides the pathologist on diagnosis and key prognostic factors.

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Introduction

Alterations of the head and neck (H&N) mucosa have, for centuries, been intimately involved in the advancement of our understanding of precancers or potentially malignant lesions. Baillie¹ and his Royal Society committee in Edinburgh first proposed the

concept of premalignancy in 1806, but the first to actually apply the concept, Sir James Paget,² gave it a decidedly maxillofacial focus by speculating, in 1851, that pipe smokers with 'leukokeratosis' or 'smoker's patch,' i.e. nicotine palatinus, carried an increased risk of oral cancer. Shortly thereafter Gibb³ applied this meaning to an erythematous patch of the vocal cords and Schwimmer⁴ applied it to the dorsal tongue 'leukoplakia' or white patch of syphilitic glossitis.

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In addition, shortly after the first microscopical analysis of preinvasive or 'incipient carcinoma' of the uterine cervix,⁵ Darier et al.⁶ published the histopathology of the first oral example of 'erythroplasia of Queyrat,' a macular lesion of the buccal mucosa. The popular diagnostic term, carcinoma in situ (CIS), was coined by Broders⁷ in 1932 using a laryngeal example. Today a variety of H&N precancers are known (Table 1), but the prognostic significance of an individual lesion still eludes us and is still based primarily on a rather primitive classification of the clinical appearance, refined somewhat by the microscopical assessment of cytological atypia or dysplasia.^{8–11}

Thus far, none of a number of promising molecular markers have proven to be prognostically significant and none have been assessed through a long-term follow-up investigation.^{12–14} Until such studies are published, investigators are forced to compare marker intensity with severity of epithelial dysplasia for prognostic significance. This strongly emphasizes the need for a uniform understanding and application of the principles of dysplasia grading for oral mucosal lesions. While that is the main focus of the present paper, a short review of the clinical features of pertinent lesions is in order, especially since these features are still strongly considered in prognostic and treatment decisions.

Clinical features of potentially malignant oral lesions—prognostic significance

The clinical features and prognosis of oral precancers will necessarily depend on the exact premalignancy involved (Table 1). As a general rule

they present as white macules with excess surface keratin, or as red, non-blanching macules with minimal surface keratin. Since white and red macules are relatively common on the H&N mucosa, potentially malignant lesions are often included in a clinician's differential diagnosis.

Leukoplakia

This lesion represents 80% of potentially malignant oral lesions and is defined as a 'white patch or plaque that cannot be characterized clinically or pathologically as any other disease and is not associated with any physical or chemical causative agent except the use of tobacco.'¹⁵ This is a diagnosis by exclusion for a lesion that cannot be given another specific diagnostic name and does not typically disappear with removal of known aetiological factors, excepting smoked tobacco.^{10,11,15,16} Leukoplakia has had more than 75 names applied to it and the term was used, until recently, for similar lesions of the larynx, vagina, uterine cervix and bladder. Oral leukoplakia occurs most frequently on the lip vermilion, buccal mucosa, lateral border of tongue, floor of mouth and gingival mucosa (Fig. 1).¹⁶

It should be emphasized that oral leukoplakia is a diagnosis of exclusion that requires the clinician to be so well acquainted with all other white oral lesions as to be able to rule them out prior to using the term leukoplakia for a particular keratosis in a particular patient. It must also be emphasized that leukoplakia is a clinical term. The presence or absence of dysplastic cells does not alter the *clinical* diagnosis, although a recent World Health Organization (WHO) *Workshop on Potentially Malignant Oral Mucosal Lesions and Conditions* has suggested that the term leukoplakia be redefined

Table 1 Potentially malignant lesions of the oral, pharyngeal and laryngeal mucosa, clinical terms only (modified from Speight et al., 1996).⁹

Disease name	Malignant transformation potential
Proliferative verrucous leukoplakia	*****
Erythroplakia	*****
Nicotine palatinus in reverse smokers [†]	*****
Oral submucous fibrosis	****
Speckled, granular (non-homogeneous) leukoplakia	****
Laryngeal keratosis/leukoplakia	***
Actinic cheilitis	***
Smooth, thick (homogeneous) leukoplakia	**
Smokeless tobacco keratosis	*
Lichen planus	*

[†]Reverse smoking: smoking with the lit end of the cigarette in one's mouth.



Figure 1 Non-homogeneous leukoplakia of the floor of the mouth. The lesion has erythroleukoplakic (speckled) and granular areas and showed areas of dysplasia on biopsy. Photo credited to: Dr. N. Vigneswaran, University of Texas at Houston, Houston, Texas, USA.

to become a combined clinical/histological term.¹⁷ With the new terminology the diagnosis 'leukoplakia' is never used without the histopathological qualifiers 'with dysplasia' or 'without dysplasia'. Unfortunately, this begs the question of what to do with leukoplakic lesions that are never biopsied. Be that as it may, experience has shown that 5–25% of oral leukoplakias have dysplasia when biopsied.^{9,10,16,18}

Numerous follow-up studies have established malignant transformation rates for oral leukoplakia, ranging from 1–28% (excluding clinical subtypes), with an average of about 4% overall.^{10,19,20} Schepman et al.¹⁹ suggested an annual transformation rate of 2.9% per year, while in a global systematic review, Petti calculated a rate of 1.36% per year.²¹ These figures generally exclude cases in which a small carcinoma is found at initial biopsy, which represent approximately 7% of oral leukoplakias, but various studies have reported figures ranging from 0.1–40%.^{10,18} The typical cancer arising from a leukoplakic lesion is diagnosed 2–4 years after the leukoplakia is clinically noted, but transformation may occur within months or after several decades.^{18–21}

Leukoplakia is more often associated with progression to cancer when the lesion is non-homogeneous.¹⁵ The surface becomes thickened and rough or granular (Fig. 1) and may be nodular or verruciform, or when red areas of minimal keratin production are interspersed amongst the background of thickened keratin (erythroleukoplakia, speckled leukoplakia). The increased risk of transformation for each of these clinical appearances is reflected in the rankings seen in Table 1.

Proliferative verrucous leukoplakia

A special case, proliferative verrucous leukoplakia (PVL) is considered by some to be a different clinical entity entirely and by others to be simply an extreme variant of leukoplakia. The previously mentioned WHO Workshop preferred the latter interpretation.¹⁷ First described in 1985, PVL is a progression of white mucosal plaques which virtually always develop nodular, papillary or verruciform surface projections and which gradually, sometimes rapidly, spread laterally to encompass large regions of the oral mucosa.^{10,22,23} On average, 2.6 mucosal sites are affected and, unlike other leukoplakias, four out of every five affected patients are females.

At initial diagnosis, almost half of all PVL samples demonstrate epithelial dysplasia and few cases are spared this change eventually. More than 70% of affected patients will develop an oral carcinoma during the decade following PVL diagnosis. Thus far no better treatment has been identified than aggressive and frequent surgical interventions and very close follow-up.

Palatal leukoplakia in reverse smoking

Certain rural populations in the Indian subcontinent, New Guinea and the Amazon basin place the lighted end of homemade cigarettes and cigars inside the mouth. This leads to a unique form of leukoplakia, with very thick keratin buildup on the surface of the hard palate, often stained dark brown by the tobacco. This 'reverse smoking' is linked to a very high rate of malignant transformation of the affected palatal mucosa, a site that seldom develops carcinoma otherwise.²⁴ In populations with more routine smoking habits, very heavy cigarette smoking, cigar smoking or pipe smoking may produce a mild version of this lesion. Called nicotine palatinus (nicotine stomatitis), this is considered to have no malignant transformation potential and is, moreover, thought to result from the heat of the smoke rather than its carcinogens.^{8,10}

Erythroplakia

Erythroplakia is the clinical term for a chronic red mucosal macule which, like leukoplakia, cannot be given another specific diagnostic name and cannot be attributed to traumatic, vascular or inflammatory causes (Fig. 2).^{10,11,15,25} Such lesions are less common than white precancers but very careful observation will reveal erythroplakia in association

with many early invasive oral carcinomas.²⁶ Erythroplakia may also be associated with leukoplakia (erythroleukoplakia) and in mixed red and white lesions it is the red portion that is more worrisome than the white. Most cases of erythroplakia are found on the mucosa of the lateral and ventral tongue, the oral floor and the soft palate.

This lesion has been called 'dangerous oral mucosa' because it, typically, is found to be CIS, severe epithelial dysplasia or superficially invasive carcinoma when biopsied.^{10,26,27} In very high risk settings, such as oral floor lesions in heavy smokers



Figure 2 Erythroplakia of the right soft palate demonstrated severe dysplasia and carcinoma in situ on biopsy, with one area of superficially invasive squamous cell carcinoma.

and alcohol abusers, 80% of these red patches may already contain focal areas of microinvasive cancer at the time of initial biopsy. Follow-up studies are not available for erythroplakia, but its usual microscopic counterpart, CIS, has been shown to recur and transform into invasive carcinoma in approximately 25% of treated cases (Table 2).

Smokeless tobacco keratosis

Smokeless tobacco keratosis (snuff pouch, snuff dipper's lesion, tobacco pouch) is a chronic white or grey/translucent mucosal macule localized in areas of direct contact with smokeless tobacco.^{10,36,37} The lesion cannot be scraped off, disappears with cessation of the tobacco habit and is poorly demarcated from surrounding mucosa. Typically there is a soft, velvety feel to the altered mucosa and further palpation of a tobacco chewer's cheek will usually reveal a distinct 'pouch' caused by flaccidity in the chronically stretched muscles in the area of tobacco placement. As tobacco is not in the mouth during a clinical examination the usually stretched mucosa appears folded or fissured. Occasional inflammatory erythema may be noted.

It usually takes 5–10 years of tobacco habit for smokeless tobacco keratosis to become apparent, but it may be present after less than a year. Once present, it typically remains unchanged unless the

Table 2 Malignant transformation rates (%) for microscopically diagnosed oral carcinoma in situ and/or severe epithelial dysplasia, ranked by cumulative years of follow-up.

Reference	Country	No. patients	Cumulative follow-up (years)	Mean follow-up (years)	Malignant transformation rate (%)
Gupta et al. ²⁴	India	90	945	10.5	7.0
Schepman et al. ¹⁹	Netherlands	166	415	2.5	12.0
Bouquot et al. ²⁸	USA	32*	346	10.8	15.6
Silverman et al. ²⁰	USA	22	162	7.4	36.0
Banoczy and Csiba ²⁹	Hungary	23	145	6.3	21.8
Amagasa et al. ³⁰	Japan	12	120	10.0	50.0
Vedtofte et al. ³¹	Denmark	14	55	3.9	35.7
Mincer et al. ³²	USA	16*	48	3.0	18.8
Pindborg et al. ³³	India	21	63	3.0	14.3
Lumerman et al. ³⁴	USA	7	11	1.5	14.3
Jaber et al. ^{35,†}	England	480	?	?	3.2
Total/weighted mean		883	2310	5.9	15.6‡

Cancers not arising from the site of the precancer are excluded (expanded from Bouquot and Ephros).²⁵ Follow-up times in two examples are estimated from comments in the published report.

*Includes only carcinoma in situ cases.

†Excludes severe dysplasia.

‡Statistically weighted for different follow-up time periods and sample sizes, excludes Jaber et al.³⁵ which was a study of mild and moderate dysplasias only.

daily smokeless tobacco contact time increases, in which case it will gradually become thickened to the point of appearing as a distinctly white, leathery or nodular plaque, clinically indistinguishable from leukoplakia.

The development of smokeless tobacco keratosis in users is very much dependent on the type of habit popular in a society. Snuff appears to produce more keratoses, for example, than chewing tobacco and persons who keep their quid in one site are more prone to keratoses than those using multiple sites. Other factors leading to a high risk of keratosis include the specific brand of tobacco used, an extended duration of the habit, excessive daily contact-hours of tobacco on oral mucous membranes, an increased amount of tobacco consumed daily and a deficiency of beta-keratin or vitamin A.

The malignant transformation potential of smokeless tobacco keratosis has not been determined, but the tobacco habit itself is said to carry a risk four times greater than normal, based on a case-control study of female American oral cancer patients.³⁸ Investigations using large numbers of tobacco chewers have found few, if any, keratotic lesions with serious dysplasias, although older and smaller investigations have concluded that as many as 16% of biopsied cases show at least mildly dysplastic cells.^{36,37}

Some authorities have attempted to provide a clinical grading scale for smokeless tobacco keratoses according to the intensity of whiteness, erythema and fissuring. Unfortunately, none of these grading systems has successfully correlated clinically severe or high-grade lesions with an increased risk of malignancy.

Oral submucous fibrosis

This irreversible precancerous condition is strongly associated with the habit of chewing areca nuts ('betel quid', 'gutka'). Affected users experience a burning sensation of the oral mucosa, occasional mucosal ulceration, a peculiar marble-like blanching of the mucosa and palpable fibrous bands of the buccal mucosa, soft palate and lips. Leukoplakic lesions are commonly seen and oral carcinoma development has been shown to occur in 5% of users during a 15 year period of follow-up.^{39,40} Whether or not these cancers develop more from the leukoplakias than from the non-leukoplakic mucosa is as yet unknown, but presumably the leukoplakias behave in the same potentially malignant fashion as leukoplakias in persons without submucous fibrosis. It should be emphasized that the increased risk of

oral cancer in betel quid chewers is greater for those who include tobacco in the quid; without the addition of tobacco the relative risk is less, although all other features of the disease remain the same.

Lichen planus

This autoimmune disorder typically presents as intertwining, thin strands or streaks of white keratosis (Wickham's striae) of the bilateral buccal mucosa.^{10,41,42} Lesions tend to vary in intensity and similar clinical features may be induced by a variety of medications and other antigens, including betel quid. Purple or brownish, pruritic papules are also seen on the skin of some patients, but only the oral lesions are considered to be precancerous. The more severe oral involvement demonstrates an erythematous background (erosive lichen planus) and may present with bullae or ulcers (bullous lichen planus, ulcerative lichen planus).

The malignant transformation rate for lichen planus is less than 1%, according to follow-up studies.^{10,11,41,42} Some question the precancerous nature of lichen planus and presume that the disease is so common that, of course, occasional patients will get oral cancers, but not at a rate higher than persons without lichen planus.^{11,17}

This issue is considerably clouded by the concept of lichenoid dysplasia, which presumes that lichenoid microscopic changes associated with dysplastic cells are simply an immune-mediated response to a conventional epithelial dysplasia. According to this theory then, such lesions are not true lichen planus at all. Many now believe that a number of the previous reports of malignant progression are due to misdiagnosis and that lichenoid lesions resembling lichen planus represent a subset of lesions which may be potentially malignant.⁴³ These lesions probably represent leukoplakia resembling lichen planus clinically and with an interface mucositis (lichenoid reaction) on histological examination.

Histopathological grading of dysplasia

Most pathologists grade oral epithelial dysplasia according to a combination of architectural and cytological changes (Table 3), but evaluation of these features is subjective and considerable inter- and intra-observer variations in the scoring of oral epithelial dysplasia have been reported.^{44,45} This has led some to question the continued use of a dysplasia grading system. One recent report,

however, has indicated 'substantial intra- and inter-observer consistency and almost perfect conformity' between pathologists trained in the same institution.⁴⁶ This is corroborated by a blinded review of 568 H&N leukoplakic lesions in which one reviewer's grade of dysplasia differed from the original histopathological grade in only four instances.¹⁸ The reviewer was trained in the same institution. In our experience, moreover, oral dysplasia grades are typically one grade higher than the cervical dysplasia grade for similar epithelial changes. Regardless of individual emphasis, the final grading or diagnosis should be based on the most severely involved area of change, even if that area represents only a small portion of the tissue.

Table 3 Microscopic features associated with oral epithelial dysplasia.⁴⁷

Cellular changes:

Abnormal variation in nuclear size (anisonucleosis)
Abnormal variation in cell size (anisocytosis)
Increased nuclear/cytoplasmic ratio
Enlarged nuclei and cells
Hyperchromatic nuclei
Increased mitotic figures
Abnormal mitotic figures (abnormal in shape or location)
Nuclear and cellular pleomorphism
Increased number and size of nucleoli

Architectural (tissue) changes:

Loss of polarity
Disordered maturation from basal to squamous cells
Includes top-to-bottom change of carcinoma in situ
Increased cellular density
Basal cell hyperplasia
Dyskeratosis (premature keratinisation and keratin pearls deep in epithelium)
Bulbous drop-shaped rete pegs
Secondary extensions (nodules) on rete tips

Recently the latest WHO classification of head and neck tumours has attempted to further clarify the grading criteria (Table 4).⁴⁷ Although they have recommended continued use of the classic oral system,⁴⁸ rather than adopting systems used at other sites, they have attempted to encourage the use of a combination of architectural and cytological changes with more explicit consideration of levels of change within the epithelium.

Oral epithelial dysplasia has traditionally been divided into three categories: mild, moderate and severe. Mild dysplasia (grade I) demonstrates proliferation of atypical or immature basal cells above the parabasal region but not extending beyond the lower third of the epithelium (Fig. 3). Moderate dysplasia (grade II) demonstrates a similar proliferation of atypical cells extending into the middle one-third of the epithelium (Fig. 4). The term severe dysplasia (grade III) is reserved for abnormal proliferation from the basal layer into the upper third of the epithelium (Fig. 5). CIS, thought by some to be a premalignancy and by others to be

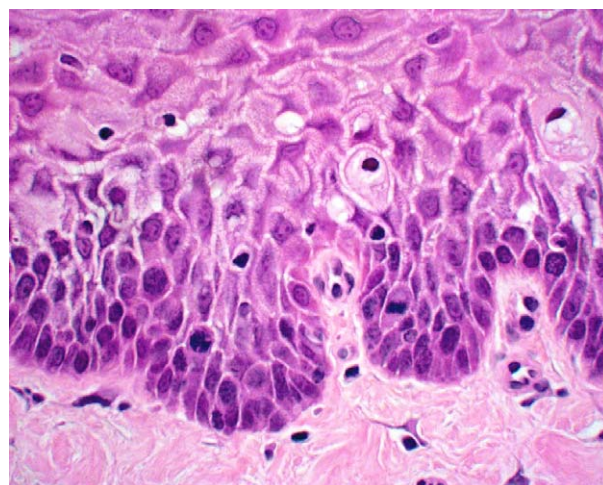


Figure 3 Mild (grade I) epithelial dysplasia. There is pleomorphism, hyperchromatism and basal cell crowding, but the changes are limited to the lower third of the epithelium.

Table 4 Classification schemes for histopathological levels of H&N epithelial dysplasia.^{47–49}

Classic oral system (WHO, 2005) ⁴⁷	Oral intraepithelial neoplasia (OIN) System	Ljubljana system (for laryngeal keratosis)	Classic laryngeal system
No dysplasia	n/a	Simple hyperplasia	Laryngeal keratosis
Mild dysplasia	OIN 1	Basal/parabasal hyperplasia	Hyperplasia
Moderate dysplasia	OIN 2	Atypical hyperplasia	Keratosis with dysplasia
Severe dysplasia	OIN 3		
Carcinoma in situ		Carcinoma in situ	Carcinoma in situ

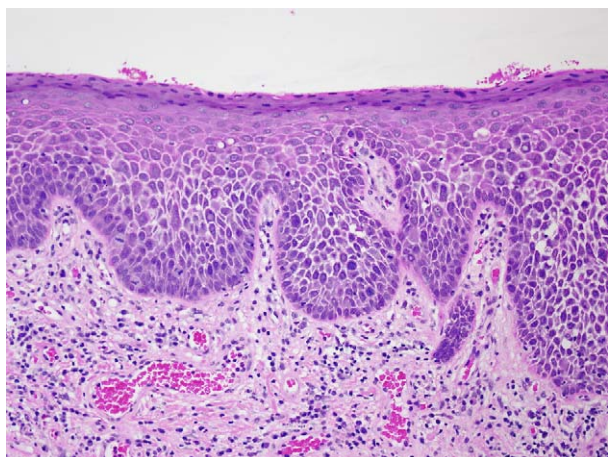


Figure 4 Moderate (grade II) epithelial dysplasia. Cytological changes are similar to those in Fig. 3 but extend into the middle third of the epithelium. Centrally there is an enlarged bulbous rete peg.

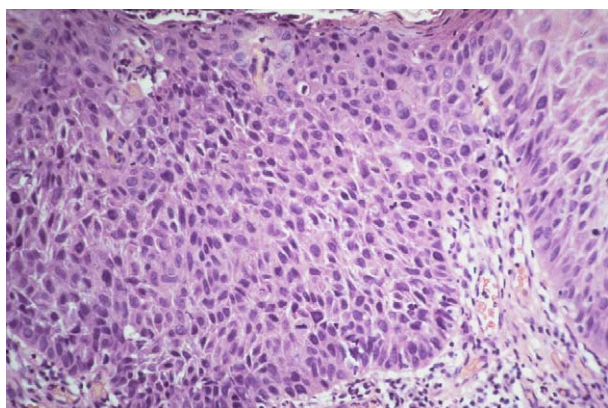


Figure 5 Severe (grade III) epithelial dysplasia. Atypical cytological changes extend the full thickness of the epithelium. Some may regard this lesion as carcinoma in situ, but a thin layer of keratin may still be seen at the surface.

an actual preinvasive malignancy, requires top-to-bottom change with undifferentiated, primitive cells from the basal layer to the topmost layer. In the oral mucosa, however, most authorities accept a thin layer of surface keratin with abrupt transition into the underlying atypical cells.^{10,47,49}

Variations of this classical scheme are outlined in Table 4. These variations are sometimes based on a simple change of nomenclature and sometimes on a combination of two separate disease categories into one. The oral intraepithelial neoplasia (OIN) system uses terminology to emphasize that all levels of dysplasia are actually different levels of true neoplasia, albeit prior to invasion.^{47,49} It does not consider simple epithelial hyperplasia to be part of the dysplasia process, since it can be seen in

so many other disorders of the mucosa. The two laryngeal classification schemes include hyperplasia as part of the dysplastic process and they both combine moderate and severe dysplasias into one category, called either keratosis with dysplasia or atypical hyperplasia.⁵⁰ Some authorities advocate the application of the laryngeal systems to oral lesions, but the new WHO book does not support this and even advocates the use of the mild, moderate and severe terminology for laryngeal lesions.⁴⁷

Cellular changes in dysplasia

Specific alterations of individual epithelial cells are important in the determination of epithelial dysplasia (Table 3, Figs. 3–6). Cells and nuclei take on a more primitive appearance, similar to those of basal cells, and often show nuclear enlargement, dark-staining nuclei (hyperchromatism), and an *increased nuclear-to-cytoplasmic ratio* as well as variation in the shape of the cells and nuclei. This *pleomorphism* is unusual outside cancers and precancers. In addition, cells and nuclei show marked variation in size (anisonucleosis and anisocytosis, respectively) and may have enlarged, often eosinophilic nucleoli (prominent nucleoli). Epithelial cells also appear to be crowded more closely together than normal keratinocytes (increased cellular density) as a result of basal cell proliferation and their normal orderly arrangement is lost. This is sometimes referred to as a loss of basal cell polarity.

There is often an increase in mitotic activity in dysplastic epithelium, but this is also seen in many reactive lesions. Enlarged, tripolar or star-shaped mitotic figures (abnormal mitoses), however, are much more indicative of precancerous changes. Abnormal mitosis may also be defined as mitotic

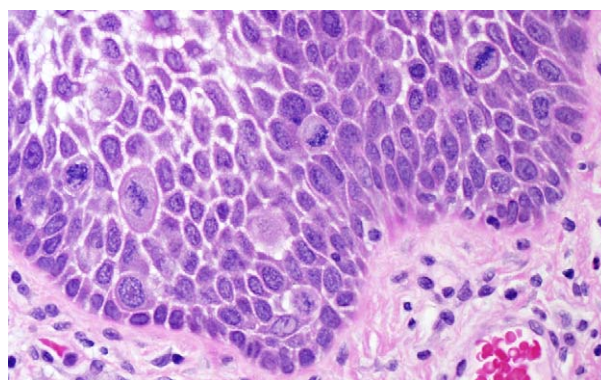


Figure 6 Cellular changes in dysplasia. There is basal cell crowding with pleomorphism and abnormal mitoses.

figures found in unusual locations above the basal cell layer (Fig. 6).

Premature production of keratin below the surface layer is another important alteration, but it is much more commonly seen in oral carcinomas than in oral premalignancies. This dyskeratosis may be represented by individually keratinized cells or by tight concentric rings of flattened keratinocytes (epithelial pearls). The pathologist must be careful not to misinterpret a keratin-filled surface indentation cut tangentially as true intraepithelial keratosis.

Cellular necrosis and loss of cellular cohesiveness (acantholysis) are major signs of poorly differentiated carcinoma but are unusual in oral epithelial dysplasia. When present, these features must be distinguished from intercellular oedema, intraepithelial inflammatory cells and apoptotic cells with pyknotic nuclei and vacuolated cytoplasm.

Tissue (architectural) changes

Many oral precancers, particularly leukoplakias, show excess surface keratin (hyperkeratosis, hyperparakeratosis, hyperorthokeratosis) and most show hyperplasia of the prickly cell layer (acanthosis), but both changes are common to a number of mucosal lesions without an increased malignant potential and neither is necessary to the diagnosis of dysplasia. Smokeless tobacco keratosis is characterized by a somewhat unique intracellular vacuolization or 'oedema' of the superficial layers (Fig. 7), perhaps interspersed with streaks of parakeratinized cells. This change most probably results from a low-grade chemical burn from the alkaline tobacco.^{10,36,37} It has been referred to as surface etching and has no implications relative to the risk of malignant transformation.

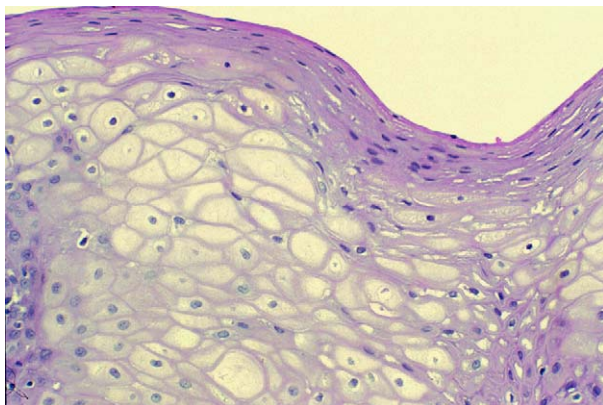


Figure 7 Smokeless tobacco keratosis may be characterized by superficial Intracellular oedema.

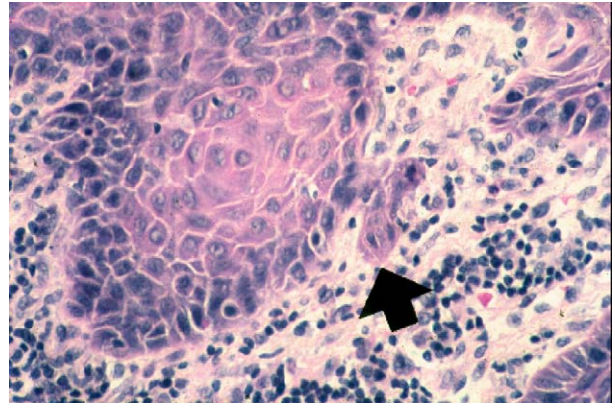


Figure 8 Irregular bulbous rete processes with irregular nodular budding of the basal layers.

One of the most important changes in tissue architecture is alteration of the rete processes. Rete processes with a bulbous enlargement of the lowermost region (drop-shaped rete processes) are worrisome, regardless of their size, and result from excessive basal cell proliferation (Fig. 4). An additionally worrisome feature is the presence of secondary projections or nodules that arise from the basal layer and branch at indifferent angles into the lamina propria and connective tissue papillae (Fig. 8). There is no physiological explanation for secondary nodules extending laterally from a rete peg of the oral mucosa. To some these alterations are ominous enough to justify upgrading the histopathological grading of a lesion to a higher level. It should be noted that extremely elongated rete processes with minimal cellular atypia are of little concern, as they are characteristic of a variety of hyperplastic conditions, including papillomavirus infections, frictional keratosis, psoriasis and pseudoepitheliomatous hyperplasia.

Dysplastic epithelium may be atrophic as well as acanthotic and some experts believe that atrophic forms have a higher risk of malignant transformation. Atrophic epithelium often lacks rete processes and may be ulcerated, thereby mimicking a traumatic or inflammatory lesion with thin, regenerating epithelium creeping in from the margins. Regenerating epithelium, fortunately, often has granulation tissue beneath it to distinguish it from precancerous dysplasia in atrophic epithelium. The very nature of thin, atrophic epithelium presents a diagnostic grading dilemma because basal cell hyperplasia very quickly extends to the surface (Fig. 9). There are no standards for this situation, but Speight et al.⁹ have recommended that these be regarded as severe dysplasia. Leukoplakias of the vermilion border of the lower lip in actinic cheilitis (actinic cheilosis, farmer's lip, sailor's lip) are especially prone to these difficulties.^{10,51}

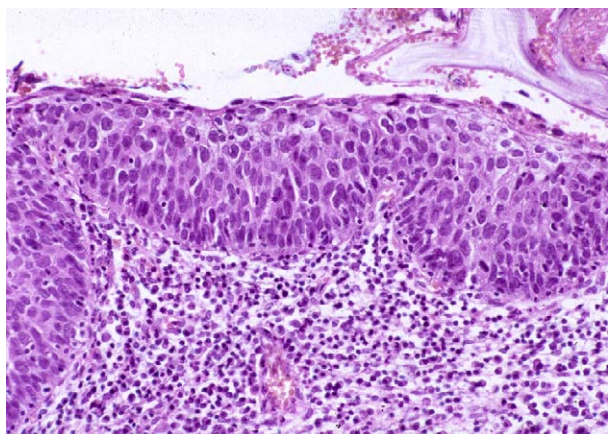


Figure 9 Dysplasia in atrophic epithelium. In thinned epithelium, the abnormal cytological features quickly extend to the surface, and should be regarded as severe epithelial dysplasias or carcinoma in situ.

An alarming morphological alteration of dysplastic epithelium is loss of stratification due to an apparent inability to properly differentiate and mature from basal cells to prickle cells to flattened keratinocytes. Cells high in the epithelium have the same immature appearance as those in the basal layers. This feature is especially pronounced in severe epithelial dysplasia and CIS (Figs. 5 and 9).

The pathologist must pay particular attention to the appearance of the epithelial cells at the lateral surgical margins and the presence or absence of dysplasia should be mentioned in the histopathological description of the lesion. The presence of squamous metaplasia of the excretory ducts of the minor salivary glands should also be mentioned, especially when cellular atypia is evident. Many treatments for oral precancers remove or destroy only the most superficial portions of the submucosal tissues, thus leaving behind the salivary glands and their ducts.

The grading of dysplastic oral epithelium must take into consideration the degree of cellular atypia, in addition to the extent of tissue change as described above. Those lesions with marked cytological alterations should be elevated to a higher grade level, regardless of how extensively the atypical cells fill the epithelium,⁴⁷ but this is not a universal practice among pathologists. Similarly, lesions that show marked architectural abnormalities with grossly bulbous rete pegs extending deeply into the underlying connective tissue but little atypia should also be upgraded. It is difficult to determine the amount of basal cell hyperplasia in mucosal precancers because of transverse sectioning of tissue samples and because of the natural undulation of the inferior margin of

squamous epithelium. It may be helpful to make this determination from the top of the connective tissue papillae because of the great variability of rete process length in acanthomatous epithelium, but there is no established standard for this practice and, in many cases, the basal hyperplasia is confined to the rete processes themselves, not to the epithelium above the papillae. Care must also be taken to interpret dysplasia in the correct clinical context. For example, dysplasia, particularly if mild, occurring immediately adjacent to ulceration may not be significant and, in these circumstances, it is advisable to examine the epithelium as far away from the ulcer as possible.

Correlation of dysplasia grades with malignant transformation

Cancers from dysplastic lesions usually develop within 2–5 years of the dysplasia diagnosis, but can occur much later.^{10,11,14,18–20,28–35} Moreover, one in three dysplasias will recur after complete removal. Table 2 demonstrates an overall malignant transformation rate of approximately 16% for oral CIS or combined CIS and severe dysplasia, with a wide range of 7–50%. As a general rule, the biological behaviour of severe epithelial dysplasia and CIS appears to be identical, or so similar as to make the distinction moot.^{10,48} This is the reasoning, for example, behind the combining of severe dysplasia and CIS under the single OIN 3 category in one of the classification schemes (Table 4).

The few investigations that have followed up moderate dysplasias have determined malignant transformation potentials of 3–15%.^{11,35} At the opposite end of the spectrum, mild epithelial dysplasia so seldom eventuates in carcinoma (less than 5% of cases) and is so similar to reactive epithelial change, that few pathologists consider it a serious threat or recommend complete removal of the associated white lesion.^{11,14,35} It is always assumed, however, that the more severe dysplasias must have begun life as less severe lesions and that a certain proportion of mild dysplasias will progress to a more severe stage.

There is, at the present time, considerable debate as to the efficacy of grading dysplasias, but so far no other suitable or appropriate method has been developed for routine clinical use. While the debate continues, it is likely that grades will still influence treatment and prognostic decisions, but methods such as aneuploidy or loss of heterozygosity are under active evaluation and may be developed for clinical use in the near future.^{13–15}

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