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Premalignant Lesions of the Upper Aerodigestive Tract: Pathologic Classification

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Abstract Intraepithelial neoplasia of the upper aerodigestive tract (UADT), including both histologically defined dysplasia and carcinoma *in situ* (CIS), appears to fall into two broad groups similar to intraepithelial neoplasia of other squamous mucosae, keratinizing and non-keratinizing. Keratinizing dysplasia/CIS is common in the UADT and uncommon in other sites such as the cervix. In general, keratinizing epithelial proliferation results in thick epithelium, usually with prominent superficial keratin expression with a whitish or "leukoplakic" clinical appearance. Although most clinical leukoplakic changes in the UADT mucosa do not represent neoplastic transformation and do not progress to invasive carcinoma, keratinizing dysplasia, defined by nuclear atypism and maturation alterations, has an appreciable progression to invasive carcinoma. Non-keratinizing dysplasia/CIS, common in the cervix, is less common in the UADT mucosa. In general, non-keratinizing epithelial alterations consist of a proliferation of incompletely differentiated cells as measured by a spectrum of maturation markers. These changes result in a thin epithelium which commonly has a red, or clinically "erythroplakic," appearance. Non-keratinizing dysplasias are less common, but are more likely to harbor high grade dysplasia or early invasive carcinoma.

Key words: leukoplakia, dysplasia, intraepithelial neoplasia

Pathologists recognize alterations of epithelial proliferation and differentiation as generic responses to a variety of insults involving the squamous mucosa of the upper aerodigestive tract (UADT). In some cases, these changes are self-limiting and reversible; in others they persist, or progress, toward squamous cell carcinoma (SCC). The neoplastic potential of mucosal proliferation and differentiation abnormalities may be viewed as a function of their location and histology. Our objective in this presentation is to define and summarize the clinical and histopathologic factors used to predict the biologic behavior of UADT mucosal lesions.

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Unfortunately, the terminology applied to this subject is confusing, due primarily to overlap between clinical and pathologic nomenclature. For this reason, we provide a glossary of relevant definitions (Table I). In it, leukoplakia, erythroplakia, and keratosis are defined clinically. As will be seen, these entities have strong but imperfect correlations to their pathologic counterparts—hyperplasia, dysplasia, and hyperkeratosis. Dysplasia connotes a purely histopathologic entity, in contrast to squamous intraepithelial neoplasia (SIN), used for a combination of histologic dysplasia and the molecular and genetic level alterations characterizing neoplastic transformation.

The presence of dysplasia is the single most important factor predicting risk for the subsequent development of invasive neoplasia. As in other anatomic sites, dysplasia is characterized

morphologically by inappropriate intercellular relationships, loss of normal, orderly maturation, and nuclear anaplasia. Normally, squamous mucosal cells display incremental organized maturation (differentiation) during migration from the basal layer to the surface. Additional cytoplasm is acquired at a rate similar to that of upward migration. The nuclei remain equidistant and maturation of cells at a given level is similar. In dysplasia, uneven and incomplete differentiation accompany increased nuclear size, pleomorphism, and hyperchromatism, resulting in a disorganized architecture where most cells have increased nuclear/cytoplasmic (N/C) ratios. Cells may also mature prematurely before approaching the surface. This is recognized as cytoplasmic keratin in otherwise immature cells (dyskeratosis), or as formation of intraepithelial keratin pearls.

Individual cell abnormalities in dysplasia provide important insights into the genetic and functional aberrations underlying intraepithelial neoplasia. Cytoplasmic keratinization is a physiological protective adaptation near the mucosal surface. When it occurs within the epithelium in dysplasia, it signifies disordered, inappropriate maturation and reflects abnormal gene expression. Distribution of mitotic figures is also useful to assess dysplasia. Normally, mitoses are found only in or near the basal layer. Identification of mitoses in the upper layers of the mucosa indicates a loss of normal proliferation controls or deregulated growth. Finally, increased nuclear size, shape and density of staining in dysplasia represent abnormal DNA (chromosomal) content. It is unclear whether these changes are the cause or consequence of genetic alterations that induce neoplastic transformation. Although nuclear atypism is the hallmark, dysplasia may otherwise be characterized by excessive, irregular, or even an absence of stainable keratin production. It is this aspect of dysplasia which accounts for its pathologic heterogeneity and clinical overlap with the hyperplasia that results from purely inflammatory or physical injuries.

LEUKOPLAKIA AND ERYTHROPLAKIA

Squamous mucosal hyperplasia includes epithelial thickening due to increased cell layers (acanthosis) and varying degrees of accumulation of surface keratin (hyperkeratosis), resulting in clinical leukoplakia. Leukoplakic changes are usually found on normally thick mucosal surfaces such as buccal mucosa, dorsal tongue, and alveolar ridge sites, where invasive carcinomas are relatively infrequent. Historically, there are numerous references to leukoplakia as "premalignant," a precursor to the development of SCC. However, follow-up of patients with oral leukoplakia documents a relatively low frequency of progression to invasive squamous cell carcinomas [1] (Table II). This is probably due to the low incidence of dysplasia occurring in such leukoplakias [5]. Less than 10% of nondysplastic leukoplakias progress to cancer (Table III); however, in dysplastic leukoplakias, 13%–36% of patients ultimately progress to carcinoma (Table IV). Leukoplakic changes occurring on normally thin mucosa, including the floor of the mouth, ventral tongue, and soft palate, should be viewed with suspicion; these anatomic sites are more commonly associated with dysplastic changes that signal risk for progression to invasive carcinoma [2].

In contrast to leukoplakia, erythroplakic mucosa is thin (fewer cell layers) and composed of undifferentiated, basal-layer type cells without keratinization. This is the morphologic hallmark of "classic" carcinoma *in situ* (CIS) recognized in the cervix. Abnormal vascular patterns and inflammation in the submucosa contribute to the red appearance on clinical examination. Erythroplakia is often encountered in the floor of the mouth, ventral tongue, soft palate-tonsil complex, pyriform sinus, and hypopharynx; sites where squamous cell carcinomas are common and the mucosa is normally thin. Erythroplakic mucosal changes are commonly associated with invasive carcinoma and CIS [1,3] (Table II) which reflects their high incidence of dysplasia. Erythroplakia is a common clinical manifestation of early, asymptomatic SCC.

Confusion regarding the clinical significance of erythroplakia and leukoplakia occurs because of their indeterminate transition forms, or speckled patterns. Speckled mucosal changes should be considered a variant of erythroplakia, not leukoplakia, due to the high association of erythroplakia with underlying dysplasia (Table II).

Table I. Glossary

Hyperplasia. Hyperplasia is an increased number of cells in the epithelium resulting in thicker mucosa. Hyperplasia can develop in reaction to a number of injuries, usually has an orderly normal maturation, and is reversible. Neoplastic forms of hyperplasia can occur, and are diagnosed when disordered maturation or atypical cells are present. Neoplastic hyperplasias are referred to as dysplasia or intraepithelial neoplasia. These neoplastic forms usually persist or progress to more severe lesions. The difference between reversible (benign) hyperplasia and neoplastic forms of hyperplasia is based on the presence (or absence) of epithelial maturation abnormalities, or cytologic alterations, associated with dysplasia and/or intraepithelial neoplasia.

Leukoplakia. Leukoplakia is a mucosal thickening with a whitish appearance on gross inspection. There is no defined histopathologic counterpart for leukoplakia; it represents a clinical description and should not be used as a pathologic diagnosis. The appearance of leukoplakia is usually associated with mucosal thickening and only rarely contains cellular and/or epithelial maturation abnormalities.

Erythroplakia. Erythroplakia is a mucosal alteration with a reddish appearance. Like leukoplakia, erythroplakia has no specific histopathologic definition. Erythroplakic mucosa is usually thin with prominent submucosal inflammation and hyperemia providing the red appearance. Erythroplakia has significant maturation abnormalities and cellular alterations, and often has morphologic changes of severe dysplasia or CIS.

Dysplasia. Dysplasia is an abnormal epithelial maturation or "disordered growth". This general term is applied to mucosal maturation abnormalities in a wide variety of tissues. Dysplasia is a morphologic term. The more severe forms represent intraepithelial neoplasia. Dysplasias are graded mild, moderate, and severe, according to the degree of epithelial alteration present. The grading scheme represents an estimation or prediction of the probability for persistence or progression of the dysplasia.

Carcinoma* in situ *(CIS). CIS is the most severe intraepithelial change. It invariably represents neoplastic transformation and has a high likelihood of being associated with, or progressing to, invasive cancer. CIS, like dysplasia, is defined by morphologic change. Severe dysplasia and CIS are often combined because their biologic behavior is similar.

Squamous Intraepithelial Neoplasia (SIN). SIN is applied to the spectrum of epithelial alterations that may precede invasive carcinoma and that are currently categorized by morphologic criteria such as dysplasia/CIS. The major objective in classifying these epithelial alterations is to identify neoplastic transformation within the epithelium. The concept of SIN is broader than the pure morphologic criteria for diagnosis of dysplasia/CIS and potentially could incorporate other markers indicative of neoplastic transformation.

(Hyper)Keratosis. Keratosis is an increase in surface keratin (hyperkeratosis) usually in a thickened epithelium, commonly resulting in a leukoplakic clinical appearance. The term "keratosis" traditionally has been used to describe a variety of laryngeal mucosal alterations. The historical rationale for this term is that keratinizing forms of dysplasia are poorly defined both from a morphologic and clinical perspective. Independent criteria for the diagnosis of keratosis were described to avoid the controversial criteria for diagnosing keratinizing dysplasia.

Dyskeratosis. Dyskeratosis is the "switching" of intracellular production of low molecular weight keratins to high molecular weight keratins. This results in single cell expression and accumulation of keratin, similar to that normally found on the surface of reactive squamous mucosa. An accumulation of dyskeratotic cells can result in extracellular keratin "pearls" developing in the epithelium.

MORPHOLOGIC INTERPRETATION OF SQUAMOUS INTRAEPITHELIAL NEOPLASIA (SIN)

A morphologic diagnosis of intraepithelial neoplasia is readily established in biopsy specimens from normally thin mucosa (such as the pharynx). This is because dysplastic lesions from these sites are characterized by hyperproliferation of "immature" nonkeratinizing cells with minimal cytoplasm (*i.e.*, erythroplakia). This histologic appearance provides insight into the pathology of intraepithelial neoplasia, a loss of normal control over the intimately linked

TABLE II. Histopathologic Changes Associated With Mucosal Appearance

Histopathologic Changes		Reference
Leukoplakia		
Dysplasia	Carcinoma	
3/43 (7%)	4/43 (7%)	[3]
153/3256 (5%)	104/3256 (3%)	[1]
0/117	12/117 (10%)*	[4]
Speckled		
Leukoplakia	Erythroplakia	
6/58 (10%)	33/58 (57%)**	[3]
Erythroplakia		
Dysplasia	Carcinoma	
1/44 (2%)	28/44 (64%)	[3]
26/65 (40%)***	33/65 (51%)	[1]

*Ten invasive cancer; two CIS.
**Includes both CIS and invasive cancer.
***65 biopsies in 58 patients from a series of 65,354 biopsy specimens.

TABLE III. Malignant Transformation of Clinical Oral Leukoplakia

No. Patients	No. Subsequent Carcinomas	Reference
248	11 (4.4%)*	[6]
117	7 (5.9%)**	[4]
782	31 (4%)***	[7]

*3.7years to development of cancer; seven patients had speckled appearance.
**3–4years to development of cancer; two patients had speckled appearance.
***Cumulative frequency for patients observed 10 years.

TABLE IV. Malignant Transformation of Clinical Oral Leukoplakia with Dysplasia

Dysplasia	Subsequent Cancers	References
68	9 (13.2%)	[8]
21	3 (14%)	[9]
22	8 (36%)	[2]

processes of proliferation and differentiation. When partial cytoplasmic "maturation" occurs at or near the surface, dysplasia is termed mild or moderate, indicating less profound growth control derangements and a generally less advanced, or aggressive, clinical disease. Therefore, the degree of loss in growth control and maturation in dysplasia (*i.e.*, level of neoplastic transformation) may be defined by the degree and extent of proliferation among pre-differentiated (stem cell) populations before maturation, or differentiation, occurs. Theoretically, this relationship is morphologically straightforward in nonkeratinizing lesions. Admittedly, morphologic subdivision of dysplasias into four diagnostic categories may be subjective. However, clinical studies have validated the utility of "grading" dysplasia/SIN of the UADT similar to those of the cervix.

"Classic" non-keratinizing forms of dysplasia/CIS associated with an erythroplakic mucosal appearance are uncommon in the UADT. Epithelial maturation and cytologic abnormalities for keratinizing forms of dysplasia or SIN are less well defined, though they are more common in UADT sites. This may be the reason for much of the confusion regarding the definition of dysplasia/CIS, and/or SIN, in the UADT mucosa [10,11].

KERATINIZING DYSPLASIA/SIN

An anatomic site commonly involved by keratinizing forms of hyperplasia, dysplasia/CIS, and SIN is the laryngeal glottis. Although hyperplasia and keratin production are stereotyped reactions to injury throughout the UADT, the glottis represents a special type of squamous mucosa that possesses a remarkable propensity to develop surface keratin. Both mechanical and carcinogenic injuries to the glottic mucosa result in proliferation of the epithelium, leading to acanthosis and some accumulation of surface keratin, which may appear leukoplakic on clinical examination. Erythroplakic changes are seldom encountered in the glottis, but they occur at other sites in the laryngeal mucosa, especially the supraglottic area. In several series of carefully studied laryngeal keratosis, 3.26%–4.31% of patients developed subsequent invasive carcinomas [12–14]) (see Table V). The observed progression of laryngeal glottic epithelial alterations is summarized in Table VI [15]. Most epithelial proliferations of the laryngeal glottis do not demonstrate appreciable cytologic atypia, accounting for the observed low progression to invasive cancer, similar to leukoplakia in the oral cavity and other sites in the UADT. Because of the keratinizing nature of laryngeal glottic dysplasia, it may be overlooked or undergraded in biopsy material. This occurs because dyskeratosis, or prominent surface keratin, may be misinterpreted as appropriate cytoplasmic differentiation. Keratinizing forms of SIN cannot, by definition, fulfill criteria for "classic" CIS (*i.e.*, lack of any appreciable differentiation).

VERRUCOUS CARCINOMA

Verrucous carcinoma is a rare but distinctive, well-differentiated, cytologically bland form of squamous neoplasia with excessive surface keratin. Despite an apparent lack of anaplasia, the tumor is invasive. However, these neoplasms exhibit a smooth, "pushing" interface with the submucosa in contrast to the ragged "small

TABLE V. Frequency of Subsequent Carcinoma in Laryngeal Keratosis

No. SCC/No. Patients	Percentage	Reference
3/84	3.57	[13]
4/116	4.31	[14]
3/92	3.26	[12]

SCC: Squamous cell carcinoma

TABLE VI. Progressions of Laryngeal Glottic Epithelial Alterations [15]

Mucosal Change	Total	To atypia (%)	To CIS (%)	To CA (%)
Keratosis without atypia	362	7 (1.9)	2 (0.5)	5 (1.4)
Keratosis with atypia	230	—	10 (4.3)	31 (13.5)
CIS/severe dysplasia	367	—	—	42 (12.5)

CA: Cancer
CIS: Carcinoma *in situ*

TABLE VII. Associated Mucosal Pathology Oral Cavity Verrucous Carcinoma

	Total Patients	Number with Leukoplakia	Separate* Foci of VC	Separate Foci of SCC in Oral Cavity	Separate Foci of SCC in UADT	Reference
	57	32	17	9	—	[17]
	77	17	3	8	6	[18]
	37	14	4	11	1	[19]
	104	NA	NA	25	6	[16]
Total	275	63/171 (37%)	24/171 (14%)	53/274 (19%)	13/218 (6%)	

*Both synchronous and metachronous

SCC: Squamous cell carcinoma
UADT: Upper aerodigestive tract
VC: Verrucous carcinoma

group" invasion which characterize the usual squamous carcinoma. We view verrucous carcinomas as malignant tumors which, despite having acquired an ability to invade host tissue, nonetheless display a strong tendency to "mature", or differentiate. This accounts for the absence of regional metastatic spread in these patients compared to those with conventional squamous carcinomas. The relevance of verrucous carcinoma to premalignant UADT alterations has to do with its possible histopathologic confusion with non-invasive, or even self-limiting, reactive conditions. Verrucous carcinoma also illustrates a dichotomy between invasion and differentiation as more or less mutually exclusive processes. In dysplasia, proliferation and differentiation exhibit a similar, reciprocal relationship. Not uncommonly (19.2%), less well-differentiated foci develop within these tumors, which invade host stroma with the ability to metastasize [16]. Verrucous carcinoma is strongly associated with the use of smokeless tobacco products and other forms of UADT mucosal pathology (Table VII) [16–19]. Thirty-seven percent of these patients have multicentric leukoplakia, 19% have foci of conventional invasive squamous carcinoma, and 14% have second verrucous carcinomas [16–19]. This is believed to reflect a carcinogenic "field effect" of tobacco on the oral and UADT mucosa.

MULTICENTRIC SCC OF THE UADT

Numerous studies document the occurrence of multiple cancers involving the UADT and lower respiratory tract mucosa. In 1980, we reported a 10.4% incidence of synchronously diagnosed cancers, identified by panendoscopy, during evaluation of the UADT for SCC [20]. In the same study, 11.7% of patients developed second cancers. Recent, larger studies found second synchronous cancers in 10.7% of patients. Most of the second cancers were in the UADT (61.3%) or lower respiratory tract (27.3%) [21]. Other studies show higher frequencies of second cancers. In a comprehensive review, Licciardello *et al.* [22] concluded that 9–14% of patients with SCC of the UADT would have synchronous cancers. The majority would be in the UADT, followed by esophagus and lung. The Radiation Therapy Oncology Group (RTOG) reviewed its experience in diagnosing metachronous cancers in a series of 928 patients with SCC of the UADT [23]. These radiotherapy-treated patients developed second cancers; 10% at three years, 15% at five years, and 23% at eight years.

The clinical importance of multicentricity extends to UADT SIN. We have quoted literature describing progression of SIN lesions to invasive neoplasia. It is often not clear, and it should not be inferred, that carcinomas arose from the lesion initially biopsied. Both histologic heterogeneity (*i.e.*, sampling artifact) and/or multicentricity may account for development of invasive cancer in low grade SIN lesions.

SUMMARY

The histologic manifestation of squamous intraepithelial neoplasia/dysplasia is an informative and direct reflection of the deregulated growth and differentiation controls which define neoplastic transformation. Due largely to a propensity for abnormal keratin production, low grade UADT dysplasias are clinically and pathologically heterogeneous and sometimes confused with reactive, self-limiting lesions. Although inappropriate differentiation, including hyperkeratosis and dyskeratosis, are important features of dysplasia/SIN, we have emphasized the critical nature of nuclear cytology in diagnosis.

Correlations between pathology and clinical behavior are strong but imperfect in UADT SIN. Verrucous carcinoma, for example, is an invasive tumor despite its strong tendency to "differentiate" and mild cytologic alterations. Further, conventional histopathology is unable to distinguish the earliest stages of neoplastic transformation from reactive/inflammatory conditions. Pathologists are similarly unable to discern the point at which host invasion is imminent or inevitable. Genetic and molecular analyses of all pathologies represent more specific but not necessarily more sophisticated ways to measure the neoplastic state. It is our hope and expectation these studies will provide solutions to our unanswered questions.

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