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Understanding Oral Epithelial Dysplasia

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ABSTRACT
Oral dysplasia, a histologically diagnosed lesion, poses a potential risk of progressing to cancer. Despite the association between histological grade and progression risk, accurately predicting which lesions will advance remains a challenge. While most oral pathologists adhere to established criteria for grading epithelial dysplasia based on architectural and cytological changes, significant variability exists in both inter- and intra-examiner assessments of dysplasia presence, absence, and grade. This article aims to review the alterations observed in oral epithelial dysplasia, the criteria utilized for grading, the various grading systems employed, and the markers utilized to assess the malignant transformation potential of epithelial dysplasia.

I. INTRODUCTION

The term "Dysplasia" was first introduced by Reagon in 1958 in the context of cells exfoliated from uterine cervix lesions. Dysplasia represents a concerning premalignant change. In the past, terms such as epithelial dysplasia, epithelial atypia, and dyskeratosis were used interchangeably. Dysplasia, indicating the first signs of malignant transformation, is defined as "A precancerous lesion of stratified squamous epithelium characterized by cellular atypia and loss of normal maturation and stratification short of carcinoma in situ." Pindborg (1977) defined epithelial dysplasia as a lesion where part of the epithelial thickness is replaced by cells exhibiting varying degrees of cellular atypia.[1]

Lumermann et al. (1995) defined epithelial dysplasia as a diagnostic term used to describe histopathological changes observed in chronic progressive and premalignant disorders of oral mucosa. The presence of dysplastic areas in the upper aerodigestive tract epithelium is associated with a probable progression to cancer. Dysplastic features in stratified squamous epithelium are characterized by cellular atypia and loss of normal maturation and stratification.[2]

There is evidence supporting the notion that the severity of dysplasia correlates with the likelihood of progression to malignancy. Accumulation of genetic and epigenetic alterations occurs during malignant development, reflected in well-defined clinical and histological changes indicative of dysplasia in the oral mucosa. However, the histological findings of dysplasia only suggest a statistically increased risk of malignant transformation and cannot reliably predict malignant change in individual cases. Thus, there is a need for studies on potential biomarkers to introduce more objectivity into prediction.[3, 4, 5]

ALTERATIONS IN DYSPLASIA

Dysplasia encompasses a series of subtle cellular changes indicating an impending development of anaplasia. It's considered theoretically reversible and thus not yet malignant, representing a premalignant alteration at the tissue level, distinct from atypia, which occurs at the cellular level. Dysplasia denotes controlled cellular alteration, potentially reverting to normal when the underlying stimulus is removed. The alterations in dysplasia involve genetic and epigenetic changes, as well as surface alterations. These physical and morphological changes hold diagnostic and prognostic relevance, collectively termed precancerous changes. Genetic changes involve complex interactions between host genetic factors and environmental carcinogens, including activation of proto-oncogenes, inactivation of tumor suppressor genes, and destabilization of genomic stability genes. Epigenetic changes refer to heritable alterations in gene expression without changes in DNA sequence. They involve modifications in gene activation without altering DNA structure, including activation or silencing of chromatin proteins associated with DNA. These changes can be preserved during cell division and may be inherited across generations. Two primary epigenetic mechanisms are DNA methylation and histone modification, with RNA playing a crucial role in forming repressive chromatin states. Surface alterations include reversible and irreversible changes. Reversible changes may regress if causative factors are eliminated but can progress to irreversible changes if they persist. Irreversible changes are characterized by accelerated cell division, leading to genetic damage accumulation and further driving transformation towards neoplasia or cell death. [6,7]

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CRITERIA FOR DYSPLASIA

When architectural disruption coincides with cytological atypia, characterized by variations in the size and shape of keratinocytes, the term dysplasia is warranted. The criteria utilized for diagnosing oral epithelial dysplasia, encompass features broadly classified into alterations in the epithelial architecture (strata) and manifestations of cellular atypia.[3]

GRADING OF DYSPLASIA

Numerous dysplastic characteristics, presented in various combinations, have been employed for grading purposes. Yet, challenges persist in evaluating and establishing standardization across different degrees of epithelial dysplasia. To address this, several grading systems for epithelial dysplasia have been suggested to standardize the severity of dysplastic features. Furthermore, it's essential that the parameters considered in histological assessment hold biological significance, accurately reflecting the malignant potential of the lesion.[8] The various grading systems put forth by different authors are as follows:

1. Smith and Pindborg photograhic method (1969)
2. Mehta et al (1971)
3. Bancozy and Csiba (1976)
4. WHO (1978)
5. Kramer (1980)
6. Burkhardt and Maerkar (1981)
7. Shafer (1983)
8. Lumermann H et al (1995)
9. Neville et al (1995)
10. Speight PM et al (1996)
11. Kuffer and Lombardi (2002)
12. Ljubljana (2003)
13. Brothwell DJ (2003)
14. WHO system (2005)
15. Binary system (2005)

Smith and Pindborg Method [9,10]

The Smith-Pindborg criteria, proposed in the late 1960s, introduced a scoring system based on a set of photographic standards. This system aimed to assess epithelial dysplasia in a standardized manner, reducing observer bias. The criteria included 13 histological features, each graded as "absent," "slight," or "marked." This approach provided a numerical score or epithelial atypia index. Katz et al. (1985) confirmed the system's utility for standardization, emphasizing the importance of eliminating observer bias through the use of standardized photographs. Each feature was graded ‘absent’, ‘slight’ and ‘marked’ as follows:

Grading

Epithelial dysplasia index is the sum of 13 scores. Each feature carries a weighted score like basal cell hyperplasia = 4 and marked pleomorphism of cells and nuclei = 6. A grading of ‘none’ was scored 0 (zero). Grading of ‘slight’ or ‘marked’ was scored from 1 to 10.

The grading finally was done as follows:

Total score (EDI)	Grade
0-10	Not dysplastic
11-25	Mild dysplasia
26-45	Moderate dysplasia
46-75	Severe dysplasia

While the epithelial dysplasia index provides a structured approach to grading dysplasia, it still has limitations. One drawback is its reliance on the weighting assigned to individual criteria by the original authors, which doesn't fully address the issue of subjectivity in assessment. Additionally, the system can be laborious to use and hasn't seen widespread adoption for routine diagnostic purposes.

Warnakulasuriya (2001) noted further challenges with the system, highlighting those even inflammatory or reactive lesions, which are non-neoplastic, may exhibit some features of dysplasia. This observation underscores the complexity of accurately diagnosing dysplastic changes and emphasizes the need for more refined and universally applicable grading systems in clinical practice.

Mehta et al (1971)

Mehta et al diagnosed epithelial dysplasia when two or more features of Smith–Pindborg criteria were present

Bancozy and Csiba (1976)[12]

They diagnosed epithelial dysplasia using the following criteria:

- Irregular epithelial stratification
- Increased density of the basal cell layer or prickle cell layer or both
- Increased number of mitotic figures
- Increased nuclear cytoplasmic ratio
- Loss of polarity of cells
- Nuclear pleomorphism
- Hyperchromatism
- Keratinization of single cells or cell groups in the prickle cell layer
- Loss of intercellular adherence.

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Grading
They graded epithelial dysplasia as:

- Mild: When two of the above listed histological changes were present.
- Moderate: When two to four changes were present.
- Severe: When five or more of the changes were present.

The drawback is that the grading was based on subjective interpretation of the features and did not take into account which factor was important in determining the malignant potential.

WHO System (1978)

The 12 histological characteristics that characterized the epithelial dysplasia are:

- Loss of polarity of basal cells
- The presence of more than one layer of cells having basaloid appearance
- An increased nuclear-cytoplasmic ratio
- Drop-shaped rete pegs ï Irregular epithelial stratification
- Increased number of mitotic figures
- The presence of mitotic figures in the superficial half of the epithelium
- Cellular polymorphism
- Nuclear hyperchromatism ï Enlarged nucleoli
- Reduction of cellular cohesion
- Keratinization of single cells or cell groups in the prickle cell layer (Kramer IRH et al 1978).[13]

Grading of Epithelial Dysplasia

- Mild dysplasia: Slight nuclear abnormalities, most marked in the basal third of the epithelial thickness and minimal in the upper layers, where the cell show maturation and stratification. A few, but no abnormal mitoses may be present, usually accompanied by keratosis and chronic inflammation.
- Moderate dysplasia: More marked nuclear abnormalities and nucleoli tend to be present, with changes most marked in the basal two-third of the epithelium, nuclear abnormalities may persist upto the surface, but cell maturation and stratification are evident in the upper layers. Mitoses are present in the parabasal and intermediate layers, but none is abnormal.
- Severe dysplasia: Marked nuclear abnormalities and loss of maturation involve more than two-third of the epithelium, with some stratification of the most superficial layers. Mitoses some of which are abnormal may be present in the upper layers.

Kramer (1980)[14-16]

This grading system suggests that an epithelium shows dysplasia if it has any two or more of the following features:

- Drop shaped rete pegs: Rete pegs that are wider in the deeper portions than they are more superficially.
- Loss of polarity of the basal cells: Where the basal cells are not perpendicular to the epithelial connective tissue junction, but are at an angle to the junctions.
- Basal cell hyperplasia: The development of basal layer that is several layers thick.
- Loss of epithelial stratification or loss of polarization: Is due to an apparent inability to properly differentiate and mature from basal cells to prickle cells to flattened keratinocytes, thus affecting the regular stratification pattern.
- Cellular pleomorphism or anisocytosis: Variation in the size and shape of the cells.
- Nuclear hyperchromatism: The nuclei in the cells are darkly stained due to increased DNA synthesis.
- Prominent nucleoli: Enlarged, often eosinophilic nucleoli. May stand out like a golf ball.
- Increase in nuclear cytoplasmic ratio: The nucleus enlarges and occupies a greater part of the cell as compared to the cytoplasm (normal ratio is 1:4 to 1:6).
- Cell crowding: Cells appear to be crowded more closely than normal keratinocytes. There is an increase in the number of cells per unit area brought about by basal cell hyperplasia.
- Increased mitosis: Is the increase in frequency of mitotic figures.
- Mitosis in upper layers: Is the spread of mitotic activity to the higher levels of the epithelium.
- Abnormal mitosis: May be defined as mitotic figures found in unusual locations above the basal cell layer, e.g.: Tripolar or star-shaped mitotic figures.
- Loss of cellular adhesion or cohesion: The cells lose their attachment to the neighboring cells, because of faulty or reduced attachment of their desmosomes.
- Intraepithelial keratinization and individual cell keratinization: Is premature production of keratin within the cytoplasm of individual cells or group of cells.

Burkhardt and Maerkar (1981)[17-19]

They used the following characteristics:

- Basal cell hyperplasia
- Loss of basal cell polarity
- Cellular pleomorphism

- An increase in mitotic figures
- Dyskeratosis
- Abnormal and absent epithelial stratification.

Additional indicators for dysplasia were as follows:

- An increase in subepithelial lymphocytes, plasma cells and interepithelial cells (stroma reaction)
- Presence of Candida organisms.

Grading

They graded dysplastic criteria for classification according to the degree of dysplasia and characteristics of carcinoma in situ

Shafer (1983)[14]

Shafer listed the criteria for epithelial dysplasia:

- Increased and particularly abnormal mitosis ï Individual cell keratinization
- Epithelial pearls within spinous layer
- Alteration in the nuclear cytoplasmic ratio
- Loss of polarity ï Large prominent nucleoli
- Dyskaryosis
- Poikilokaryosis
- Basilar hyperplasia.

Grading

Based on the number of individual histological features and extension of the cytological changes from the basal cell layer and upward epithelial dysplasia has been subdivided into:

- Mild (Grade I): Demonstrates proliferation of atypical or immature basal cells above the parabasal region but not extending beyond the lower third of the epithelium.
- Moderate (Grade II dysplasia): Similar proliferation as in grade I into the middle one-third of the epithelium.
- Severe grades (Grade III): Reserved for abnormal proliferation from the basal layer into the upper third of the epithelium.

Lumermann H et al (1995)[2]

They considered the following features as 'minimal' criteria for the diagnosis of oral epithelial dysplasia. The features are:

- Basal cell hyperplasia
- Nuclear enlargement and hyperchromicity
- Drop-shaped rete pegs.

Grading

The dysplastic changes were graded as:

- Mild epithelial dysplasia: 'Minimal' dysplastic alterations confined to the lower third of the epithelium.
- Moderate epithelial dysplasia: Dysplastic changes seen in upto two-thirds of the thickness of the epithelium.
- Severe epithelial dysplasia: Dysplastic cells fill more than two-thirds but less than the entire thickness of the epithelium.
- Carcinoma in situ: The entire thickness of the epithelium contains less differentiated basaloid or squamous epithelial cell with enlarged, hyperchromatic nuclei and a variable number of typical and atypical mitotic figures with no invasion into the submucosa.
- Verrucous hyperplasia with dysplasia: The epithelium exhibits considerable thickening with surface papillations, hyperparakeratosis and parakeratin plugging and occasional dysplastic cells confined to the lower one-third of the epithelium.[16,19]

Neville et al (1995)[20]

Neville et al graded dysplasia as:

- Mild: Hyperchromatic and slightly pleomorphic nuclei are noted in the basal and suprabasal cell layers of stratified squamous epithelium.
- Moderate: Dysplastic changes extend from the basal layer to the midportion of the spinous layer and are characterized by nuclear hyperchromatism, pleomorphism and cellular crowding. Hyperkeratosis on the epithelial cell layer with prominent granular cell layer.
- Severe: Cellular crowding and disordered arrangement throughout most of the epithelial thickness, although slight maturation and flattening of the cells appears to be present at the epithelial surface. Epithelial cells are seen to mature very little as they progress toward the hyperparakeratotic surface.
- Carcinoma in situ: When the entire thickness of the epithelium is involved, the term carcinoma in situ is used. Dysplastic cells extend from the basal layer to the surface of the mucosa (top to bottom change) with no invasion into the underlying connective tissue.

Speight PM et al (1996)[21]

They considered the thickness (height) to which the cellular and tissue changes may extend as important in grading dysplasia.5,19,22 Grading According to them:

- Mild forms of dysplasia: Represented recognizable changes limited to the parabasal layers (lower third).
- Moderate dysplasia: Represented recognizable changes extending to middle third.

- Severe dysplasia: Represented as recognizable changes extending to the upper layers. Drawback:

Warnakulasuriya 200111 commented that there was wide variation in the thickness of the covering epithelium in the oral cavity, which leads to practical difficulties in using this grading system.

Kuffer and Lombardi (2002)[23]

The proposal to reclassify oral precancerous lesions reflects an attempt to address the challenges posed by the current diagnostic terminology. By distinguishing between lesions with and without histological dysplasia, the aim is to create a more refined classification system that accurately reflects the risk of malignant transformation.

Lesions lacking dysplasia would be categorized as "risk lesions," such as simple tobacco keratosis, indicating a potential risk for transformation but not yet engaged in the process of malignant change. Conversely, lesions exhibiting dysplasia would be classified as "precursors" of squamous cell carcinoma, signifying the presence of intraepithelial alterations already involved in the progression to invasive carcinoma.

However, a significant drawback arises from the potential variation in transformation risk among lesions without dysplasia or with mild to moderate dysplasia compared to those with severe dysplasia. Applying the term "risk lesion" to all lesions without dysplasia, including those with minimal transformation potential (e.g., frictional keratosis), may not accurately reflect the true risk profile of these lesions.

Richard26 demonstrated that dysplasia and carcinoma in situ were different aspects of the same disease 'cervical intraepithelial neoplasm (CIN)' and treatment should be same for both. This concept of CIN has now replaced almost completely that of cervical dysplasia. It has been extended with some modification to oral mucosa as 'oral intraepithelial neoplasm (OIN)' and in general as 'squamous intraepithelial neoplasm (SIN)'.[19]

As for CIN, there are three grades of OIN:

- OIN 1: Mild dysplasia less than one-third involvement of the epithelium
- OIN 2: Moderate dysplasia one-third to two-third involvement of the epithelium
- OIN 3: Severe dysplasia–full involvement or equivalent to carcinoma in situ.

The 'Bethesda classification'18 for cervical pathology includes only two grades:

- Low grade SIN corresponds to CIN 2
- High grade SIN corresponds to CIN2, CIN 3

Based on this Bethesda classification, the former system with three grades was replaced by a 2-grade system, which helped in better stratifying patients for clinical protocols. Accordingly they chose to report the diagnosis of oral dysplastic lesions as: – Low grade OIN–including OIN 1 (mild dysplasia) or as – High grade OIN–including OIN 2 (moderate dysplasia) and OIN 3 (severe dysplasia).

Ljubljana Grading System [3]

This classification was developed to cater for the special clinical and histological problems of laryngeal abnormalities.[3] The classification was proposed for grading of epithelial hyperplastic lesions of the larynx, to hyperplastic epithelial lesions arising in the oral cavity.

Grading

- Simple hyperplasia: A benign hyperplastic process with retention of the normal pattern of the epithelium which is thickened because of an increase prickle cell layer. The cellular components of the basal and parabasal region remain unchanged. There is no cellular atypia.
- Abnormal hyperplasia: A benign augmentation of basal and parabasal layers. This is seen upto 1½ of the total epithelial thickness. Stratification is fully retained. Nuclei in the cells of the basal and parabasal layers may be moderately enlarged but still maintain a uniform distribution of nuclear chromatin. Small numbers of epithelial cells, less than 5% are dyskeratotic.
- Atypical hyperplasia or 'risky' epithelium: It demonstrates a recognizable alteration of epithelial cells toward malignancy, but not to such a degree as seen in carcinomatous cells. Stratification is still preserved in the general epithelial structure. The nuclei are enlarged and nuclear contour may be irregular with marked variations in staining intensity. The nuclear cytoplasmic ratio is increased. Mitotic figures are increased and are found within two-third of the epithelium. Civatte bodies (apoptotic cells) may be present.
- Carcinoma in situ: It shows features of carcinoma without invasion. There is loss of stratification throughout the epithelium although 3 to 5 layers of compressed cells may be present on the surface. Marked atypia and mitotic abnormalities are characteristic. Mitotic figures present throughout the epithelium, including its upper one-third and abnormal mitoses are frequently found.

Brothwell DJ et al (2003) [27]

Brothwell et al27 graded 64 sections of epithelial dysplastic lesions according to 5 point scale routinely utilized at their institution (Faculty of Dentistry, University of Toronto).

Criteria

- 0 = No dysplasia
- 1 = Mild dysplasia: Increased number of cells in the basal and parabasal epithelial regions showing nuclear hyperchromatism and pleomorphism.
- 2 = Moderate dysplasia: Bulbous rete pegs with increased numbers of cells showing nuclear hyperchromatism and pleomorphism, extending to and including the basal, parabasal and prickle cell layer.
- 3 = Severe dysplasia: Bulbous rete pegs with increased numbers of cells showing nuclear hyperchromatism and pleomorphism through the entire thickness of epithelium.
- 4 = Carcinoma in situ: Markedly atypical changes showing nuclear hyperchromatism and pleomorphism in entire thickness of the epithelium, with the suggestion of early superficial connective tissue invasion, but without convincing evidence. The advantage is that using this system, and a different method of statistical analysis, the authors proved that intra- and interobserver agreement in grading the dysplastic lesions were consistent and had almost perfect conformity.

WHO System (2005)

Grading On the basis of architecture and cytology[28]

- Hyperplasia: Describes increased cell numbers. This may be in the spinous layer leading to hyperplasia or acanthosis in the basal/parabasal cell layers (progenitor compartment), termed basal cell hyperplasia. Architecture shows regular stratification and there is no cellular atypia.
- Mild dysplasia: Slight nuclear abnormalities, most marked in the basal third of the epithelial thickness. Cells show normal maturation and stratification. A few, but no abnormal mitoses may be present in the parabasal layers.
- Moderate dysplasia: More marked nuclear abnormalities are seen in the basal two-third of the epithelium. Cell maturation and stratification are evident in the upper layers. Mitoses are present in the parabasal and intermediate layers, but none is abnormal.
- Severe dysplasia: Marked nuclear abnormalities involve more than two-thirds of the epithelium. Mitoses, some of which are abnormal, may be present in the upper layers. Maturation and stratification was still seen in most superficial layers.
- Carcinoma in situ: It is defined as 'a lesion in which the full thickness, or almost the full thickness, of squamous epithelium shows the cellular features of carcinoma without stromal invasion.' Requires top-tobottom change with undifferentiated, primitive cells from the basal layer to the topmost layer.

Binary System (2005) [29]

This system was proposed by Omar Kujan et al29 and considered the lesions under: High risk lesions (with potential susceptibility for malignant transformation): It was based on observing at least four architectural changes and five cytological changes (WHO criteria 2005). Low-risk lesions (does not have the potential susceptibility for malignant transformation): It was associated with observation of less than four architectural changes or less than five cytological changes (WHO criteria 2005).

Biomarkers for Dysplasia

Currently, there is not a substantial body of strong evidence for the use of biomarkers in the progression of oral dysplasia. There is a suggestion from the longitudinal studies that the presence of LOH/A1 at specific loci (3p and 9p), survivin, MMP9 positivity and DNA content (nondiploid) are potential markers for increased risk of progression from oral dysplasia to cancer.30 Other markers identified are p53, p73, MMP1, MMP2 and cathepsin L mRNA, but did not predict progression.

II. CONCLUSION

The grading of dysplasia in oral lesions remains a contentious issue, marked by subjectivity and variability among observers. The lack of a consensus has led to the adoption of multiple grading systems, further complicating the diagnostic process. However, advancements in molecular biology hold promise for enhancing diagnosis and prognostication by identifying genomic aberrations more effectively.

In the future, molecular discoveries and the integration of genomic analysis into routine assessment methods may offer improved tools for diagnosing and predicting the prognosis of oral dysplastic lesions. Despite these advancements, histopathological evaluation remains the current "gold standard" for predicting the malignant transformation of precancerous lesions. Thus, efforts to develop a more refined and standardized system for assessing dysplasia are imperative for

better prognostication and management of oral potentially precancerous lesions.

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