International Journal Dental and Medical Sciences Research
Volume 6, Issue 2, Mar - Apr 2024 pp 635-639 www.ijdmsrjournal.com ISSN: 2582-6018

Challenges Encountered In Grading Oral EpithelialDysplasia; A Review

Dr Ajish M Saji

Submitted: 15-04-2024 Accepted: 25-04-2024

ABSTRACT
Being vigilant about oral health is crucial, especially when it comes to identifying and monitoring oral potentially malignant disorders, as they pose a significant risk of progressing into malignant lesions. Assessing the degree of malignancy in precancerous lesions can be challenging, given the various classification and grading systems available, which exhibit considerable variability and are subject to inter-observer bias. This review is valuable as it comprehensively examines the different grading systems for oral potentially malignant disorders, highlighting their strengths andlimitations.

I. INTRODUCTION

A disease can disrupt the dynamic activity within a living cell, resulting in dysfunction. It is noted that cells typically maintain a relatively normal structure and function within a designated range until significant cellular stresses occur. Pathology, as a field, starts by investigating diseases at the cellular level, where changes in structure and function occur in response to evolving demands and advancements. The mortality rate of oral cancer has surged sevenfold over the past 50 years. India, in particular, grapples with one of the highest incidences of oral cancer globally, partly due to the widespread habit of tobacco chewing. Various forms of tobacco chewing prevalent in India include pan (consisting of betel leaf, sliced areca nut, lime, catechu, and other spices, sometimes with or without tobacco), pan masala[1]

Leukoplakia is the most commonly encountered potentially malignant disorders. 2% of leukoplakia may undergo malignant transformation per year. In lesions with epithelial dysplasia this rate could vary between 1.1% -17.5%.[9] Longitudinal studies of rural populations in India revealed 80.6% of oral cancers being preceded by precancerous lesions or conditions. [2]

Though erythroplakia is uncommon, it often presents with dysplasia or intra epithelial carcinoma when compared to leukoplakia which generally show no dysplasia or may just present with mild to moderate dysplasia. Similarly the malignant transformation potential for smokeless tobacco keratosis has been questionable. It is known that the tobacco habit itself is said to carry a risk fourtimes greater than normal mucosa. About 16% of biopsied lesion showed mild dysplasia, and a few chewers showed severe dysplasia.[3]

The customary grading system of oral epithelial dysplasia into mild, moderate and severe does not allow accurate prediction of which cases may eventually transform into malignancy. Many studies have remarked that precancers with epithelial dysplasia have shown to develop into cancer more readily than lesions without. Nevertheless all precancer or epithelial dysplasia do not develop into cancer, whereas, some have even shown to regress with time.[4]

This review seeks to explore various classifications of oral epithelial dysplasia (OED), examining their constraints and significance in assessing the likelihood of malignant progression. Grasping the connection between the clinical identification of potentially malignant oral potentially malignant disorders (OPMD) and the histopathological diagnosis of OED is crucial for prompt detection and effective clinical intervention.

II. DISCUSSION

The term "dysplasia" was first introduced by Reagon in 1958 in reference to cells exfolliates from lesions of the uterine cervix. Dysplasia denotes abnormal, atypical cell proliferation primarily observed in epithelial tissues.[5] Historically, terms such as epithelial dysplasia, epithelial atypia, and dyskeratosis were often used interchangeably. Dysplastic changes have the potential to return to a normal state once the underlying stimulus is eliminated. In stratified squamous epithelium, dysplastic features manifest as cellular atypia and a disruption of typical maturation and layering. The World Health Organization (WHO) monograph on head and neck tumors (2005) employs the term "epithelial precursor lesions," defining it as "altered epithelium with an elevated risk of progressing to squamous cell carcinoma."[6]

Pindborg (1977) defined epithelial

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dysplasia as lesions wherein a portion of the epithelialthickness is substituted by cells exhibiting varying degrees of cellular atypia. The terms "intraepithelial neoplasia" and "atypical epithelial hyperplasia" were used interchangeably.

When cancer manifests following a preceding epithelial lesion, that lesion may display cellular alterations indicative of potential subsequent malignancy. These individual cellular changes are termed "atypia," while the broader disturbance in the epithelium is termed "dysplasia." Certain features of epithelial dysplasia also mirror aspects of normal cellular growth, proliferation, maturation, and organization.[5]

GRADING SYSTEMS FOR ORAL EPITHELIAL DYSPLASIA

The severity of dysplastic characteristics is categorized as the Grade of epithelial dysplasia. Numerous dysplastic features, in various combinations, have been employed for grading purposes. However, challenges arise in evaluating and standardizing the diverse degrees of epithelial dysplasia. To address this, numerous grading systems for epithelial dysplasia have been proposed to establish a standardized approach to assessing severity. A grading system is deemed clinically valuable if it demonstrates reproducibility among different observers.[7]

The primary objective of a classification and grading system is to facilitate consistent reporting and management while also enabling the assessment of lesions in epidemiological studies. Over the past two decades, more than 20 classification systems have been introduced in an effort to standardize grading systems for oral epithelial dysplasia (OED). For a grading system to be clinically effective, it must demonstrate reproducibility, and the histological evaluation should accurately reflect the malignant potential of the lesion.[7]

The severity of dysplastic features is designated as grade of epithelial dysplasia. Many dysplastic features in varying combinations have been used for grading. However, difficulties have been encountered in assessing and standardizing the different degrees of epithelial dysplasia. Many systems of grading oral epithelial dysplasia have been proposed in order to standardize the severity of dysplastic features and the relationship of epithelial dysplasia in its varying grades to the subsequent development of cancers has still to be worked out.[8]

Any grading system is said to be clinically useful if they are reproducible between different observers. In addition, the parameters considered in the histological assessment should be biologically meaningful, reflecting the malignant potential of the lesion.[9]

The various grading systems put forth by different authors are as follows:- 1. Smith and Pindborgs Photographic method (1969) 2. Banoczy and Csiba (1976) 3.WHO (1978) , Burkhardt and Maerkar (1981) , Lumermann H et al (1995), Neville et al (1995), Speight P M et al (1996), Bouquot JE (1997) ,Soames JV (1998), Kuffer and Lombardi (2002), Brothwell DJ (2003) ,. WHO (2005), Binary System by Kujan O (2006) and World Health Organization (WHO) 2017 classification

Smith and Pindborg (1969)attempted to standardize the grading of dysplasia by photographic method. They placed the diagnosis of epithelial dysplasia on an objective and semi quantitative level by: (i) Concentrating the observer's attention on one photographically standardized microscopic feature at a time and (ii) Enabling the observer to assess each feature individually and allocate a weighed score to each one.[10]

The system was subjective involving the comparison of histological sections with a series of standardized photographs. They used 13 histologic features which were standardized by a set of photographs. Each feature was graded Absent, Slight and Marked as follows:

Histologic features for Smith & Pindborg (1969) classification of oral epithelial dysplasia.[10]

	Type of change	**Severity of dysplasia**		
1.	Drop shaped retepegs	None	Slight	Marked
2.	Irregular epithelial stratification	None	Slight	Marked
3.	Keratinization of cells below keratinized layer	None	Slight	Marked

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4.	Basal cell hyperplasia	None	Slight	Marked
5.	Loss of intercellular adherence	None	Slight	Marked
6.	Loss of polarity	None	Slight	Marked
7.	Hyperchromatic nuclei	None	Slight	Marked
8.	Increased nucleo-cytoplasmic ratio in basal and prickle cell layers	None	Slight Increase	Marked Increase
9.	Anisocytosis and anisonucleosis	None	Slight	Marked
10	Pleomorphic cells and nuclei	None	Slight	Marked
11	Mitotic activity	Normal	Slight Increase	Marked Increase
12	Level of mitotic activity	Normal	Slight	Marked
13	Presence of bizarre mitoses	None	Slight	Marked

Scoring**:** A grading of 'none' was scored – 0 (zero). Grading of 'slight' or 'marked' was scored – 1to 10. The total score of all the features was taken as epithelial dysplasia index (EDI) which was asemi objective score. It could vary from 0-75. The grading finally was done as follows: Total score (EDI) 0-10 : Not dysplastic, 11-25 : Mild dysplasia, 26-45 : Moderate dysplasia and 46-75 - Severedysplasia.[10]

WHO System (1978): In an attempt to standardize the criteria for oral precancer, established a collaborating reference center in 1967. The center aimed to characterize and define those lesionsthat should be considered as oral precancer and to determine, if possible their relative risk of becoming malignant. In its report in 1978**,** WHO defined and listed the 12 histologic characteristics of epithelial dysplasia as follows :- 1) Loss of polarity of basal cells. 2) The presence of more than one layer of cells having basaloid appearance-Basal cell hyperplasia. 3) An increased nuclear-cytoplasmic ratio. 4) Drop shaped retepegs. 5) Irregular epithelial stratification. 6) Increased number of mitotic figures. 7) The presence of mitotic figures in the superficial half of the epithelium. 8) Cellular polymorphism. 9) Nuclear hyperchromatism. 10) Enlarged nucleoli. 11) Reduction of cellular cohesion. 12) Keratinization of single cells or cell groups in the prickle cell layer.[11]

Neville BW et al (1995) 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 mid portion of the spinous layer and are characterized by nuclear hyperchromatism, pleomorphism, cellular crowding and hyperkeratosisof the epithelial cell layer along with prominent granular cell layer. Severe: Cellular crowding and disordered arrangement throughout most of the epithelial thickness, although slight maturationand flattening of the cells appears to be present at the epithelial surface. Epithelial cells are

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less matured 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.[12]

WHO Classification (2005) A working group that convened for an editorial and consensus conference in Lyon, France in July 16-19-2005 put forward criteria for grading epithelial dysplasia which is published as WHO classification(2005).They have used a combination of architectural & cytological changes with more explicit consideration of levels of changes within the epithelium. Criteria used were in two groups Architecture Criteria **:** 1. Irregular epithelial stratification, 2. Loss of polarity of basal cells, 3. Drop-shaped rete ridges, 4. Increased number of mitotic figures, 5. Abnormal superficial mitoses, 6. Premature keratinisation in single cells (dyskeratosis), 7. Keratin pearls within rete ridges, Cytology Criteria **:** 1. Abnormal variation in nuclear size (Anisonucleosis), 2. Abnormal variation in nuclear shape (nuclear pleomorphism), 3. Abnormal variation in cell size (anisocytosis), 4. Abnormal variation in cell shape (cellular pleomorphism), 5. Increased nuclear cytoplasmic ratio, 6. Increased nuclear size, 7. Atypical mitotic figures, 8. Increased number and size of nucleoli, 9. Hyperchromatism.[11]

Binary System of Grading Dysplasia - Omar Kujan (2006): Proposed a new binary system of grading oral epithelial dysplasia for prediction of malignant transformation. They used same morphological criteria used by the WHO classification (2005) and graded the lesion into low-risk or high-risk based on scoring the features. High-risk lesion (with potential susceptibility for malignant transformation) was based on observing at least four architectural changes and five cytological changes. Low-risk lesion (does not have the potential susceptibility for malignant transformation) was based on observing less then four architectural changes or less than five cytological changes.[13]

World Health Organization (WHO) 2017 classification In the recently published 2017 WHO grading system, features of "squamous hyperplasia (acanthosis and basal cell hyperplasia)" and "carcinoma in situ (CIS)" present in the2005 WHO 26 classification has been dropped from the OED grading . The term CIS is removed from the 2017WHO classification and used synonymously with severe dysplasia. The cytological/cellular feature, "increase in nuclear size" in the 2005 WHO classification has also been dropped from 2017 WHO diagnostic criteria of OED. The architectural feature "loss of epithelial cell cohesion" has been included in 2017 WHO diagnostic criteria[11]

III. CONCLUTION

The grading of dysplasia remains a contentious issue, characterized by subjectivity and a lack of consistency in both intra- and interobserver assessments. This inconsistency stems from the absence of validated morphological criteria and the inherent biological complexity of dysplasia. Additionally, the absence of a consensus has led to the use of multiple grading systems. . Many systems of grading oral epithelial dysplasia have been proposed in order to standardize the severity of dysplastic features and the relationship of epithelial dysplasia in its varying grades to the subsequent development of cancers has still to be worked out.

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