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Tracking the Trail Of Oral Epithelial Dysplasia; The History of Classifications

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ABSTRACT:- Oral epithelial dysplasia (OED) is the histological terminology for various premalignant lesions of the oral cavity. These premalignant or precancerous lesions and are clinically named as the leukoplakia, erythroplakia, oral lichen planus, and oral submucous fibrosis. The severity of such lesions is indicated by the grade of dysplasia present within the lesion. On extensive literature search various classifications regarding the grading of oral epithelial dysplasia can be enumerated. The aim of this review is to streamline the origin and concepts of grading of dysplasia from history to the present. The ultimate aim of review is to bring about the best grading system which can aid in proper diagnosis and treatment of these premalignant lesions and is only possible with a proper knowledge of their clinical and histopathological features.

KEYWORDS: Oral epithelial dysplasia, grading of dysplasia

I. INTRODUCTION

Dysplasia as a term has been used for many years and has been implemented again in the latest version of WHO Classification of Tumor in the Oral Cavity and Oropharynx. Dysplastic features of a stratified squamous epithelium are characterized by cellular atypia and loss of normal maturation and stratification; a combination of architectural and cytological changes that are associated with an increased risk of malignant transformation compared to normal mucosa.[1]

Epithelial dysplasia represents a spectrum of changes and does not refer to a precise diagnostic category.[2] No existing criteria can precisely divide this spectrum definitively into mild, moderate or severe dysplasia (Fig 1). Therefore, pathologists frequently face difficulties in the accurate assessment of dysplasia grade, mainly due to a lack of specific classification criteria, limited objectivity for evaluation of the diagnostic criteria and insufficient information about the important criteria that may be used to predict malignant transformation.[3]

Since Oral Epithelial Dysplasia (OED) is considered a precursor for malignant transformation, pathologists need to evaluate accurately the dysplastic changes of the potentially malignant disorders for accurate prediction and effective management. It is well-recognized that the classification system is not perfect, however it is highly recommended for the selection of treatment options to help and improve clinical outcomes.[3]

GRADING SYSTEMS OF ORAL EPITHELIAL DYSPLASIA

There are a variety of elaborative histological grading systems put forth by different authors [4]

1. Smith and Pindborg system (1969)
2. Banoczy and Sciba (1976)
3. W.H.O. (1978)
4. Kramer (1980)
5. Burkhardt and Maerkar (1981)
6. Lumermann H. et al. (1995)
7. Neville et al. (1995)
8. Speight P M et al. (1996)
9. Kuffer and Lombardi (2002)
10. Brothwell D J et al. (2003)
11. Ljubljana (2003)
12. WHO (2005)
13. Binary system (2005) proposed by Omar Kujan et al.
14. WHO (2017)

1. Smith and Pindborg system (1969)

The first attempt to standardize the grading of epithelial dysplasia was done by Smith and Pindborg in the year 1969. This system was based on the means of the photographic method along with various different histological changes. It was subjective and it involves comparisons of the histologic section with a series of the standardized photographs. They allocated 13 histologic features and graded OED as absent, slightly or marked and gave a score. A grading of absent was scored as zero, whereas grading of slight or marked was allocated a score between 1 and 10. Score range from 0 to 75.[5]

Epithelial Atypia Index (EAI)	Interpretation
0-10	Non-dysplastic
11-25	Mild
26-45	Moderate
46-75	Severe

1) Drop shaped rete pegs
2) Irregular epithelial stratification
3) Keratinization of cells below keratinized layer
4) Basal cell hyperplasia
5) Loss of intercellular adherence
6) Loss of polarity
7) Hyperchromatic nuclei
8) Increased nuclear-cytoplasmic ratio in basal and prickle cell layers
9) Anisocytosis and anisonucleosis
10) Pleomorphic cells and nuclei
11) Mitotic activity
12) Level of mitotic activity
13) Presence of bizarre mitoses

2. Banoczy and Sciba (1976)

They studied 500 leukoplakia patients and analyzed them for the characteristics of the epithelial dysplasia. Nine characteristic features for grading are:[6]

1. Irregular epithelial stratification.
2. Increased density of the basal cell layer or prickle cell layer or both.
3. Increased number of mitotic figures (a new abnormal mitoses may be present).
4. Increased nuclear-cytoplasmic ratio.
5. Loss of polarity of cells.
6. Nuclear pleomorphism.
7. Nuclear hyperchromatism.
8. Keratinization of single cells or cell groups in the prickle cell layer.
9. Loss of intercellular adherence.

Epithelial dysplasia was graded into:

1. Mild dysplasia: Presence of 2 histological changes
2. Moderate dysplasia: Presence of 2-4 histological changes
3. Severe dysplasia: Presence of more than 5 histological changes

3. W.H.O. (1978)

A collaborating reference center was established by WHO in year 1967, with an aim to characterize and define those lesions that should be considered as oral precancer and to determine their relative risk of becoming malignant. In year 1997, the WHO published the "histopathological typing of cancer and precancer of the oral mucosa," by listing 12 characteristics of the epithelial dysplasia and graded epithelial dysplasia as mild, moderate and severe in the area where the characters are present. Characteristic features of WHO grading system 1-9 relate to disturbed cell proliferation and 10-12 relate to disorderly maturation seen in epithelial dysplasia.

They graded epithelial dysplasia as:

- Mild
- Moderate
- Severe

Mild dysplasia
Basal third of epithelium exhibits slight nuclear abnormality and the upper layer exhibits minimal nuclear abnormality with cell showing maturation. Few abnormal mitosis may be seen accompanied by chronic inflammation.
Moderate dysplasia
Basal 2/3rd of the epithelium exhibits marked amount of nucleoli and nuclear abnormalities persisting up to the surface. Cell maturation and stratification are evident in the upper layer. Parabasal and Intermediate layer exhibit mitosis.
Severe dysplasia
More than 2/3rd of the epithelium show marked nuclear abnormalities and loss of maturation. Superficial layers exhibit some stratification. Abnormal mitosis may be present in the upper layer. Carcinoma in situ was merged into severe dysplasia.

4. Kramer (1980)
Listed 14 dysplastic features. Epithelium was called dysplastic if it showed presence of 2 or more of the dysplastic features. Dysplasia was graded as present or absent. Grading was based on the same criteria as that of WHO (1978). Following new dysplastic features were added [7,8]

- Cell crowding
- Abnormal mitosis

5. Burkhardt and Maerkar (1981)
They included both cytological and histological parameters for diagnosing and classifying epithelial dysplasia. Additional dysplasia indicators were increase in sub-epithelial lymphocytes, interepithelial cells and plasma cells and Presence of Candida organisms.[9]

6. Lumermann H. et al. (1995)
In the year 1995, Lumerman et al. listed 3 characteristics as a "minimal criteria" to diagnose OED. The characteristics are:
1. Basal cell hyperplasia
2. Drop shaped rete pegs
3. Nuclear enlargement and hyperchromocity
They graded epithelial dysplasia as:

- Mild dysplasia: Dysplastic features seen in the lower third of the epithelium
- Moderate dysplasia: Dysplastic features seen till the 2/3rd of the epithelial thickness
- Severe dysplasia: Dysplastic features are seen in more than 2/3rd of the epithelial thickness but still the entire thickness is not involved
- Carcinoma in situ: It involves the entire thickness of the epithelium. It shows the presence of the epithelial cells showing hyperchromatic nuclei, enlarged cell with a variable number of atypical mitotic figures without invading into the submucosa
- Verrucous hyperplasia with dysplasia: Epithelium exhibits thickening along with surface papillations, parakeratin plugging, and hyperkeratosis seen in lower third of the epithelium.[8]

7. Neville et al. (1995)
They considered that the alterations in the epithelial cells are same as that seen in squamous cell carcinoma. This system grades OED into:
1. Mild dysplasia: Pleomorphic and hyperchromatic nuclei seen in basal and suprabasal layer.
2. Moderate dysplasia: Dysplasia extends up to the middle of the spinous layer characterized by nuclear pleomorphism, hyperchromatism along with cellular crowding.
3. Severe dysplasia: Disordered arrangement along with cellular crowding seen throughout the epithelial thickness. Slight maturation and cell flattening seen at the epithelial surface.
4. Carcinoma in situ: whole of the epithelial thickness in involved dysplasia extend from the basal layer till the overlying mucosa without invasion into the underlying connective tissue.[9,10]

8. Speight P M et al. (1996)
They considered height of the epithelium which exhibited cellular and tissue changes:
1. Mild dysplasia: Dysplastic changes seen in parabasal layer.
2. Moderate dysplasia: Dysplastic changes extending to the middle one-third.
3. Severe dysplasia: Dysplastic changes extending to the upper layer.[11]

9. Kuffer and Lombardi (2002)
In the year 2002, they proposed a unified classification and based on gynecological model. They considered that the clinical criteria for the diagnosis and terminology of precancer due to the disordered mixture of dysplastic

and non-dysplastic lesions. They recommended to give emphasis on histological criteria to diagnose precancer. They proposed that all the lesions which histologically do not show dysplasia should be categorized as "risk lesions" and to place lesions with dysplasia into the category of precursor of Squamous cell carcinoma.[12]

10. Brothwell D J et al. (2003)

In an attempt to determine the extent of observer agreement in diagnosing OED, they graded 64 histological sections on 5 characters.[13]

The criteria are

0 = No dysplasia

1 = Mild dysplasia: Increase in the number of cells in the basal and parabasal epithelial regions showing nuclear hyperchromatism and pleomorphism.

2 = Moderate dysplasia: Presence of bulbous rete pegs showing increased number of cells nuclear pleomorphism and hyperchromatism including the basal, parabasal, and prickle cell layer.

3 = Severe dysplasia: Presence of bulbous rete pegs showing increased number of cells having nuclear pleomorphism and hyperchromatism through the entire thickness of the epithelium.

4= Carcinoma in situ: Exhibiting atypical changes like nuclear pleomorphism and hyperchromatism, which encompass the entire thickness of the epithelium leading to a suggestion of early connective tissue invasion without any convincing evidence.

11. Ljubljana Classification-Squamous Intraepithelial Lesions (SIL)

The Ljubljana classification was developed to be used for special clinical and histological laryngeal abnormalities. This system is more complicated even for the experience pathologist to use when compared to the WHO concept of dysplasia.

The Ljubljana grading system identifies four categories: simple and abnormal hyperplasia both of which are regarded as benign, atypical hyperplasia which is pre-malignant, and carcinoma in situ (CIS) which is malignant without detectable invasion.[14]

1) Simple hyperplasia is characterized by increased thickness of the spinosum (prickle) cells layer without cellular atypia.

2) Abnormal hyperplasia shows hyperplasia of basal and parabasal cell layers which constitutes up to one-half of full epithelial thickness.

3) Atypical hyperplasia or risky hyperplasia is characterized by recognizable changes toward malignancy but epithelial stratification is unchanged.

4) Carcinoma in situ shows marked cellular atypia, abnormal mitotic figures and complete loss of epithelial stratification.

Although this system is quite difficult even for well-trained pathologists, it focuses on clinical decision though its scores. Simple and abnormal hyperplasia does not require close follow-up, while close follow-up is required for risky hyperplasia, and CIS needs intervention.[14]

A classification system with an easy routine daily application is required for an accurate diagnosis and subsequent successful management, with a universal grading system requires a high level of agreement between pathologists.[15]

12. WHO Classification System (2005)

The WHO Consensus Group made great efforts to establish a universal classification of OED by updating and improving the grading system used for OED. The WHO classification system is mainly based on two main characteristic features: cellular atypia and architectural deregulation of epithelial tissue as well as the dysplastic layer thickness in relation to full epithelial thickness.[16]

The 5-score grading system has been proposed in the latest WHO Working Group. This classification system recognizes five-point ordinal scale grading system depending on nine-cellular and seven-architectural criteria, listed in table. Architectural and cytological features used in grading of OED in 2005 WHO classification system are given in table 1.[16]

The 5 grades of the 2005 classification system include:

- Hyperplasia,
- Mild Dysplasia,
- Moderate Dysplasia,
- Severe Dysplasia and
- Carcinoma in situ.

1. Squamous hyperplasia is characterized by increased cell numbers in the spinous layer without cellular atypia and with a regular stratification. The hyperplasia may also be seen in the basal or parabasal cell layers.
2. Mild dysplasia: the architectural disturbances are limited to the lower third of the epithelium associated with minimum cellular atypia.

3. Moderate dysplasia shows a considerable degree of atypia with architectural disturbances extending to the middle third of the epithelium.
4. Severe dysplasia shows a significant degree of atypia with architectural disturbances affecting more than two-thirds of the epithelium.
5. Carcinoma in situ: the architectural disturbances involve the full or almost the full epithelial thickness, with marked cytological atypia.

13. Binary Grading System

It should be emphasized that using five point system is found to be associated with inter- and intra-examiner variability in the assessment of OED and a better agreement may be achieved by reducing this number into a two-point classification system.[2]

Kujan and co-workers (2006) evaluated the scheme of a "high-risk" and "low-risk" binary grading system based on the same architecture and cytology criteria used by the WHO classification 2005 for grading epithelial dysplasia.

- The high-risk grade which has the potential for malignant transformation is assigned using a minimum of four architectural changes and five cellular alterations, whilst
- The low-risk grade which has low tendency for malignant transformation was assessed using less than four architectural changes and less than five cellular alterations.

According to this system all hyperplasias and mild dysplasias are classified as low-risk, whereas, all cases with severe dysplasia and carcinoma in situ are considered as high-risk. With respect to moderate dysplasia, the binary grading system can classify moderate dysplasia cases into either low-risk or high-risk grade. The evaluation of this system suggested that a binary scoring system reduced observer variability and increased agreement between pathologists, compared with the five-point system and that it may be easier to use, less subjective and have better discriminatory powers. Kujan et al.'s (2006) study demonstrated reasonable values of sensitivity and specificity (85% and 80%, respectively) with a test accuracy of 82% for predicting malignant transformation.[3]

14. WHO (2017)

The main change between the 2017 and 2005 WHO classifications is the simplification into a 2-tier system from a 4-tier system by the unification into high-grade dysplasia of former moderate dysplasia, severe dysplasia, and carcinoma in situ.

WHO 2017 classification of OED remains unclear, similar to the 2005 version. The list of diagnostic criteria has been modified to 8 architectural and 8 cytologic criteria from the 2005 version of 7 architectural and 9 cytologic criteria. Moreover, the text in the 2017 WHO chapter states that ''there is no good evidence to indicate how the presence of individual features could be translated into a grade of dysplasia and that dysplasia grading is poorly reproducible between observers.

II. OBSERVER'S VARIABILITY IN GRADING ORAL EPITHELIAL DYSPLASIA

The histopathological grading of epithelial dysplasia remains the most clinically applicable predictor of potential MT.[17] According to Guillaud et al. (2008), the significance of dysplasia phenotypes as cancer risk prognosticators is well documented and the strong association of higher grade dysplasia with increased risk of cancer progression has been observed and confirmed in multiple body sites; this is why histopathologic diagnosis of dysplasia remains the current gold standard.[18] However, this standard is subjective with low intra-and inter-observer agreement in grading epithelial dysplasia, lack of knowledge of the weight characteristics used to assess histopathologic grades and the problem of reactive changes in oral epithelial term which can cause changes similar to low-grade dysplasia, making differential diagnosis in early disease problematic.

So, assessment of epithelial dysplasia by histological examination remains subjective and is greatly dependent upon individual pathologist's experience. Therefore, disagreement on grading between pathologists is not uncommon. The degree of agreement between pathologists is measured by kappa statistics (weighted and un-weighted) which takes the value zero when there is no agreement or the value one for perfect agreement. A kappa value lower than 0.4 represents fair agreement, between 0.4 and 0.6 moderate agreement, between 0.6-0.8 substantial agreement and between 0.8-1.0 almost perfect or excellent agreements.[19] Kujan et al. (2006) showed better agreement in the histological assessment of the presence or absence and the degree of OED between inter-and intra-observer variation of a novel binary grading system compared with the 2005 WHO system. This improvement was mainly due to the reduction in the number of grading points from five grades in the WHO to two grades in the binary system making decisions simpler.[3,20]

III. CONCLUSION

Several studies on inter-and intra-observer variability have demonstrated considerable variations in the assessment of the presence, absence and degree of OED using different scoring systems. These variations may be due to the lack of objectivity in the evaluation of established criteria and lack of sufficient knowledge which are important for the prediction of malignant transformation. Although reducing the points for a grading system may improve the agreement among pathologists, the subjectivity in evaluation the histopathological criteria remains the main cause of observer variability.

Conflict of interest

All authors have indicated they have no potential conflicts of interest and no financial relationships relevant to this article to disclose. **"Declarations of Interest: none"**

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FIGURE CAPTIONS:

Figure 1: Photomicrograph showing as histopathological presentation of various grades of dysplasia
A) Mild dysplasia B) Moderate dysplasia C) Severe dysplasia

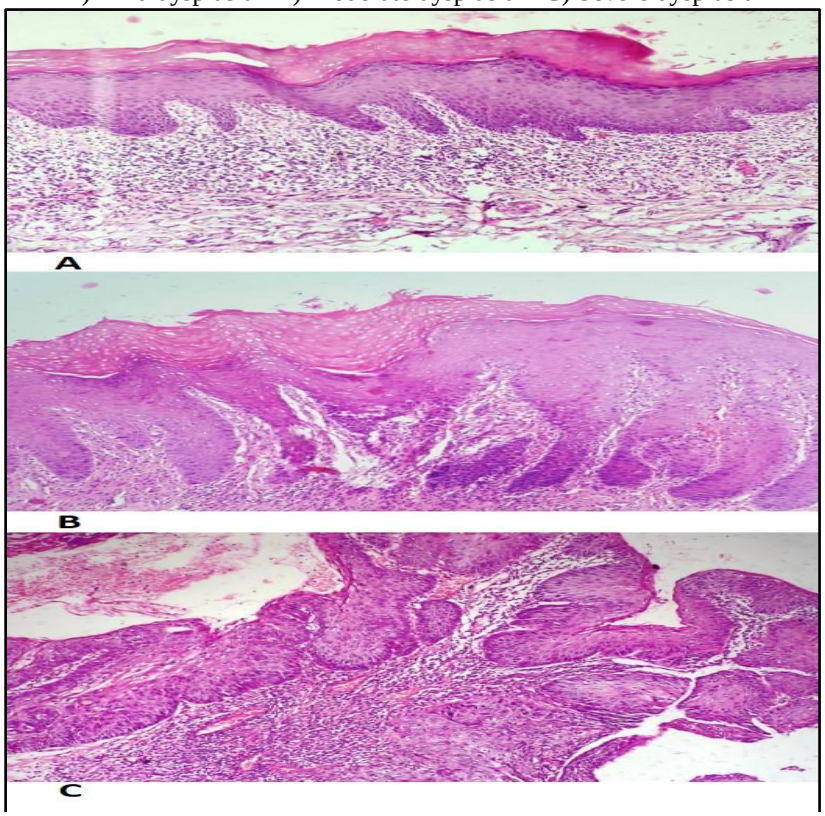

Table 1: Architectural and cytological features used in grading of OED in 2005 WHO classification system

Architecture	Cytology
1. Irregular Epithelial Stratification	1. Abnormal Variation In Nuclear Size (Anisonucleosis)
2. Loss Of Polarity Of Basal Cells	2. Abnormal Variation In Nuclear Shape (Nuclear Pleomorphism)
3. Drop- Shaped Rete Ridges	3. Abnormal Variation In Cell Size (Anisocytosis)
4. Increased Number Of Mitotic Figures	4. Abnormal Variation In Cell Shape (Cellular Pleomorphism)
5. Abnormal Superficial Mitoses	5. Increased Nuclear- Cytoplasm Ratio
6. Premature Keratinisation In Single Cell(Dyskeratosis)	6. Increased Nuclear Size
7. Keratin Pearls Within Rete Pegs	7. Atypical Mitotic Figures
	8. Increased Number And Size Of Nucleoli
	9. Hyperchromasia

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