Review Article

Various Grading Systems of the Oral Epithelial Dysplasia: A Review

Heena Sadiq[1], Priti Gupta[2], Nisha Singh[3], Sahil Singh Thakar[4], Ishan Prabhakar[4], Jyotsana Thakral[5]

[1]Post Graduate Student, Department of Oral Pathology, Microbiology and Forensic Odontology, I.T.S Dental College Hospital & Research Centre, Greater Noida, Uttar Pradesh, India, [2]Post Graduate Student, Department of Oral Medicine and Radiology, I.T.S Dental College Hospital & Research Centre, Greater Noida, Uttar Pradesh, India, [3]Post Graduate Student, Department of Oral Pathology, Microbiology and Forensic Odontology, Sudha Rastogi College of Dental Sciences and Research, Faridabad, Haryana, India, [4]Post Graduate Student, Department of Community Dentistry I.T.S Dental College Hospital & Research Centre, Greater Noida, Uttar Pradesh, India, [5]Private Practitioner, Faridabad, Haryana, India

ABSTRACT

From every diagnostically active pathologist grading of dysplasia is demanded almost daily. Every pathologist while assessing oral precancerous lesions with dysplastic features knows that evaluation grading of oral epithelial dysplasia (OED) is one of the greatest problems as it is based on subjective impression. Often the pathologist confers the diagnosis with their colleagues realizing that it is not standardized. The problem in evaluating precancerous lesion arises from two factors (1) lack of sufficient knowledge about the various important criteria for predicting future development of cancer. (2) Lack of objectivity in evaluating the criteria which is already established. Thus, this article attempts to provide a detailed review of all the grading systems put forth till date for the classifications of OED.

Keywords: atypia, carcinoma in situ, Epithelial dysplasia, epithelium, grading

Corresponding Author: Dr. Heena Sadiq, I.T.S Dental College Hospital & Research Centre, Greater Noida, Uttar Pradesh, India.
E-mail: heenasadiqpg@gmail.com

INTRODUCTION

The oral epithelial dysplastic lesion also called as a pre-cancer lesion is among the most intricate topics of head and neck pathology.[1] The concept of a stepwise development of cancer in the oral mucosa, i.e., the initial presence of a precursor (pre-malignant/precancerous) lesion subsequently developing into cancer is well established. The presence of epithelial dysplasia may be even more important in predicting malignant development than the clinical characteristics.[2,3] In standard medical terminology, dysplasia means an abnormality of development, while in histomorphology, it expresses cellular and structural changes in the epithelium.[1] The presence of dysplasia is more important in predicting malignant development than its clinical presentation such as leukoplakia, erythroplakia or leuko-erythroplakia. It may also be seen in cases of verrucous or papillary leukoplakia and in the margins of chronic mucosal ulcer.[2] The term dysplasia, principally encountered in epithelium, was introduced by Reagon in year 1958 which means atypical, abnormal proliferation. In the past, epithelial atypia, dyskeratosis, and epithelial dysplasia were used synonymously.[3] The development of cancer as a continuum from mild dysplasia is well established. The transformation rate of dysplasia to cancer is 36.4% and this represents a relatively late phase in the multistage process of oral carcinogenesis.[4] Assessment and prognosis of transformation potential depends on the histologic grading, which is done by quantifying the degree of architectural and cellular abnormality above the epithelial basement membrane by H and E stained section. As outlined before, a histological dysplasia system ideally should meet two basic requirements. At first, it should be easily applicable in daily routine practice with low inter and intra-observer variability. Second, it should allow a clear separation between patients, who need treatment to prevent progression towards malignancy and those for whom no treatment is needed. 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 epithelial dysplasia have been proposed in order to standardize the severity of dysplastic features. Any grading system is said to be clinically useful if

they are reproducible between separate observers. In addition, the parameters considered in the histological assessment should be biologically meaningful, reflecting the malignant potential of the lesion.[5] Grading dysplasia is not an exact science and pathologists are doing their best to reach optimal results. Improvement in the standard of the histopathology reporting of oral epithelial dysplasia (OED) lesions could be achieved by consideration of several issues. Of these, there is a need for a universal definition of the architectural and cytological features that are the basis of any OED grading process. A minimum data set for reporting OED lesions should be set up along with its consensus in scoring.

EPITHELIAL DYSPLASIA AND VARIOUS GRADING SYSTEMS

Grading is not an exact science and the pathologists are doing their best to reach optimal results. Histological grading system ideally should meet two basic requirements. First, it should be easily applicable in daily routine practice with low inter and intra-observer variability. Second, it should allow a clear separation between the patients, who need treatment to prevent progression towards malignancy and those who need no treatment. There are a variety of elaborative histological grading systems put forth by different authors.

Commonly Used Grading Systems

1. Smith and Pindborg's classification[6]
2. 1978 WHO classification[7]
3. Ljubljana classification squamous intraepithelial lesions (SIL)[8,9]
4. 2005 WHO classification[10]
5. New Binary system[11]

Other Less Common Grading Systems

1. Bánóczy and Csiba classification[12]
2. Lumerman *et al*. classification[5]
3. Burkhardt and Maerkar classification[13]
4. Neville *et al*. grading system[14]
5. Speight *et al*. grading system[15,16]
6. Kuffer and Lombardi grading system[17]
7. Brothwell *et al*. grading system[18]

Smith and Pindborg Classification[6]

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 (Table 1).

Score range from 0 to 75. Sections with a score of 0-10 are regarded as a non-dysplastic and 11-25 was regarded as mild; score between 26 and 45 as moderate, and severe (Table 2).

1978 WHO Classification[7]

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 histologic features are:
1. Loss of polarity of basal cells
2. The presence of more than one layer of cells having the basaloid appearance
3. An increased nuclear-cytoplasmic ratio
4. Drop shaped rete pegs
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

Table 1: Smith and Pindborg grading system

Type of change	Severity of dysplasia		
Drop shaped rete pegs	None	Slight	Marked
Irregular epithelial stratification	None	Slight	Marked
Keratinization of cells below keratinized layer	None	Slight	Marked
Basal cell hyperplasia	None	Slight	Marked
Loss of intercellular adherence	None	Slight	Marked
Loss of polarity	None	Slight	Marked
Hyperchromatic nuclei	None	Slight	Marked
Increased nuclear-cytoplasmic ratio in basal and prickle cell layers	None	Slight increase	Marked increase
Anisocytosis and anisonucleosis	None	Slight	Marked
Pleomorphic cells and nuclei	None	Slight	Marked
Mitotic activity	Normal	Slight increase	Marked increase
Level of mitotic activity	None	Slight	Marked
Presence of bizarre mitoses	None	Slight	Marked

Table 2: Scoring (0-75)

0-10	No dysplastic
11-25	Mild dysplasia
26-45	Moderate dysplasia
Above 45	Severe dysplasia

9. Nuclear hyperchromatism
10. Enlarged nucleoli
11. Reduction of cellular cohesion
12. Keratinization of single cells or cell groups in the prickle cell layer (Kramer *et al*., 1978).

Characteristic features of WHO grading system 1-9 relate to disturbed cell proliferation and 10-12 relate to disorderly maturation seen in epithelial dysplasia.[8,19]

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.

Ljubljana Classification SIL

Zeodner in year 2003 proposed the use of Ljubljana classification of laryngeal precancer for grading hyperplastic epithelial lesions of the oral cavity and they categorized it to be.

Simple hyperplasia
It is a benign hyperplastic process where basal and parabasal layer remains unchanged without cellular atypia. Prickle cell layer exhibits thickening.

Abnormal hyperplasia
It shows augmentation of the basal layer up to half of the epithelial thickness. Stratification is retained to the fullest. Nuclei are moderately enlarged. Mitosis if present is seen near the basal cell layer. Less than 5% of the epithelial cells exhibit dyskeratosis.

Atypical hyperplasia "risky epithelium."
Exhibit alterations of the epithelial cells toward malignancy are still not to an extent of carcinomatous cells. Epithelial stratification is still preserved. Enlarged nuclei with an irregular contour are seen with marked staining intensity. 2/3rd of the epithelium exhibit increased number of mitotic figures along with increased nuclear-cytoplasmic ratio. Dyskeratotic cells along with civatte bodies may be present.

Carcinoma in situ
It exhibits complete loss of stratification and the presence of the mitotic figures throughout the epithelium.[9]

2005 WHO Classification[10]

WHO in year 2003 classified OED as Mild, moderate, severe, carcinoma *in situ* or hyperplasia according to the presence and severity of cellular atypia and the architectural features. This was published in the new book by WHO "classification of tumors of the head and neck."[10]

Architectural characteristics
- Irregular epithelial stratification
- Loss of polarity of basal cells
- Drop-shaped rete ridge
- Increased number of mitotic figures
- Abnormally superficial mitoses
- Keratin pearls within rete pegs

Cellular characteristics
- Anisonucleosis
- Nuclear pleomorphism
- Anisocytosis
- Cellular pleomorphism
- Increased nuclear-cytoplasmic ratio
- Dyskeratosis
- Atypical mitotic figures
- Increased number and size of nucleoli

Graded OED Into

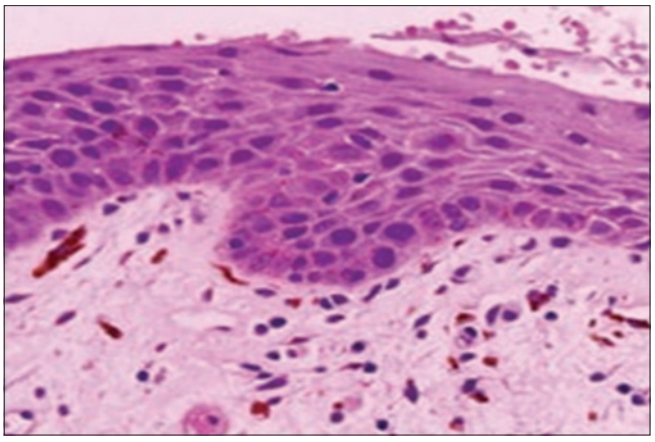

Figure 1: Mild dysplasia: Architectural changes are noted in the lower third of the epithelium. Mild cellular atypia is present

1. Mild dysplasia: Architectural changes limited to the lower third of the epithelium along with the cytological atypia (Figure 1).
2. Moderate dysplasia: Architectural changes extending to the middle third of the epithelium. Degree of cytologic atypia requires upgradation (Figures 2 and 3).
3. Severe dysplasia: Greater than 2/3rd of the epithelium exhibits architectural disturbances and the increased number of the cytologic atypia (Figure 4).
4. Carcinoma *in situ*: Full thickness of the epithelium exhibits architectural disturbances. Abnormal superficial mitosis and atypical figures are seen commonly.

NEW BINARY SYSTEM[11]

All the grading systems published so far had the shortcomings like intra-observer variability and low reproducibility, thus Kujan *et al*. in the year 2005 proposed a new classification based on the morphological criteria used by WHO 2005, into high risk and low risk on scoring the features. In the year 2006, the binary system was proposed as a reliable and feasible tool for grading epithelial dysplasia in oral leukoplakia.[11] They divided OED into:

1. High-risk lesions: Presence of five cytological changes and four architectural changes. They have a potential for malignant transformation.
2. Low-risk lesions: It does not show potential transformation. It exhibits <4 cytological changes and architectural changes.[10,11]

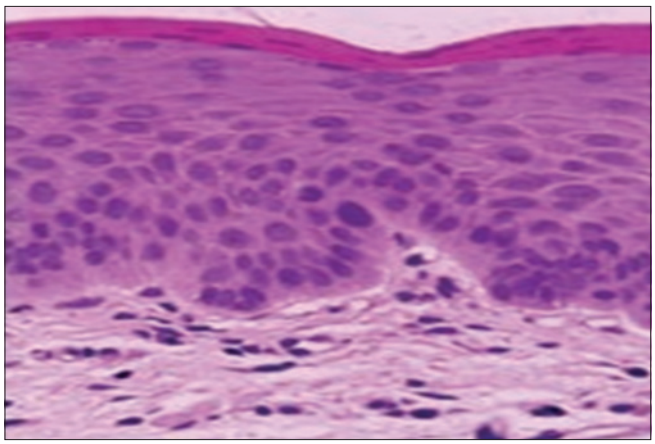

Figure 2: Moderate dysplasia: Architectural changes extend to the middle third. Cellular atypia is moderate dysplasia

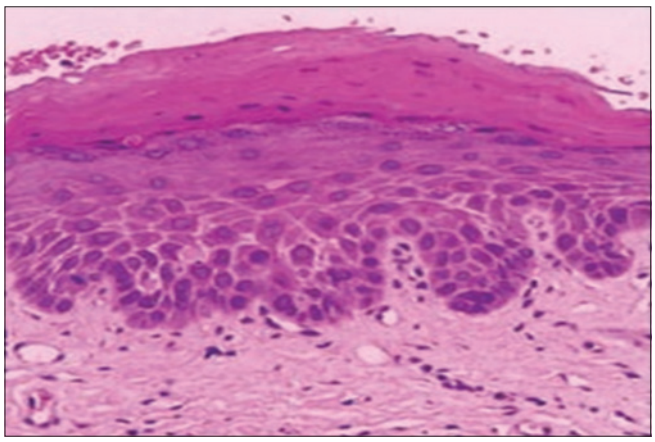

Figure 3: Moderate dysplasia: Architectural changes extend to the middle third. Cellular atypia is moderate

OTHER LESS COMMONLY USED GRADING SYSTEMS

Bancozy Sciba[12]

They studied 500 leukoplakia patients and analyzed them for the characteristics of the epithelial dysplasia on the criteria suggested by Mehta *et al*. (1971). Nine characteristic features for grading are:[12]

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

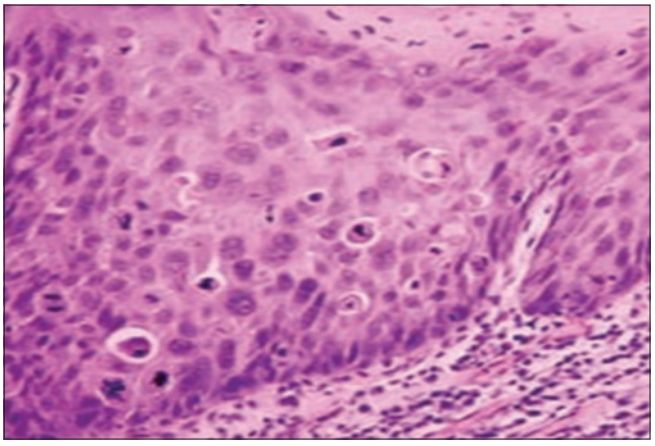

Figure 4: Severe dysplasia: Architectural changes extend to the upper third of the epithelium. Cellular atypia is marked

Lumerman *et al*.[5,13]

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:
1. Mild dysplasia: Dysplastic features seen in the lower third of the epithelium
2. Moderate dysplasia: Dysplastic features seen till the 2/3rd of the epithelial thickness
3. Severe dysplasia: Dysplastic features are seen in more than 2/3rd of the epithelial thickness but still the entire thickness is not involved
4. 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
5. Verrucous hyperplasia with dysplasia: Epithelium exhibits thickening along with surface papillations, parakeratin plugging, and hyperkeratosis seen in lower third of the epithelium.

Burkhardt and Maerker (1981)[13]

They included both cytological and histological parameters for diagnosing and classifying epithelial dysplasia:
1. Basal cell hyperplasia
2. Loss of basal cell polarity
3. Cellular pleomorphism
4. An increase in mitotic figures
5. Dyskeratosis
6. Abnormal and absent epithelial stratification

Additional dysplasia indicators were:
- Increase in sub-epithelial lymphocytes, inter-epithelial cells and plasma cells (stroma reaction)
- Presence of Candida organisms

Neville *et al*.[14]

They considered that the alterations in the epithelial cells are same as that seen in squamous cell carcinoma and they included the following criteria:[14]
- Enlarged nuclei and cells
- Large and prominent nucleoli
- Increased nuclear-cytoplasmic ratio
- Hyperchromatic (excessively dark-staining) nuclei
- Pleomorphic (abnormally shaped) nuclei and cells
- Dyskeratosis (premature keratinization of individual cells)
- Increased mitotic activity (excessive numbers of mitoses)
- Abnormal mitotic figures (tripolar or star-shaped mitoses or mitotic figures above the basal layer).

Additional histological alterations are seen:
- Tear drop-shaped or bulbous rete ridges
- Loss of polarity (lack of progressive maturation toward the surface)
- Keratin or epithelial pearls (focal, round collections of concentrically layered keratinized cells)
- Loss of epithelial cell cohesiveness.

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. Prominent granular cell layer with hyperkeratosis on epithelial cells.
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.

Speight *et al*.[15-17]

They considered height of the epithelium which exhibited cellular and tissue changes:
1. Mild dysplasia: Dysplastic changes seen in para-basal layer.
2. Moderate dysplasia: Dysplastic changes extending to the middle one-third.
3. Severe dysplasia: Dysplastic changes extending to the upper layer.

Kuffer and Lombardi[17]

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.

Brothwell *et al*.[18]

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

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.

DISCUSSION

Due to the discrepancy of the epithelial maturation patterns in assessing the diagnosis of the epithelial dysplasia is subjective. Accurate grading of OED presents an enormous challenge to the pathologist. Thus, many systems of grading are proposed and reviewed. Smith and Pindborg in year 1969, first scored epithelial dysplasia by a standardized photographic method, which was based on 13 dysplastic features'. Pindborg and Reibel working separately found this grading system to be laborious and cumbersome for daily use. They emphasized on improving the photographic standards in use by including the thickness of the epithelium as an important parameter.[20] Warnakulasurya commented that the scores for these categories show subjectivity leading to interobserver and intraobserver variations which goes in accordance with the statement given by Vinay Hazarey.[21] Difficulty is encountered in obtaining Smith and Pindborg monograph.[22]

WHO in year 1978 defined histological changes which contributed to the diagnosis of OED and classified epithelial changes as mild, moderate, severe, and carcinoma *in situ*. Remarks made in this system were as we increase the degree of dysplasia the considerable risk of developing cancer increases. However, this co-relation is not a very close one, i.e., cases with the slightest degree of dysplasia turned into carcinoma whereas severe dysplasia cases had persisted very little change for years.[23]

Pindborg *et al*. in the year 1985 commented that out of all the grading systems put forward, the criteria laid down in the WHO publications from 1978 can be used for uniform criteria for the diagnosis of OED. In the year 2001 Sudbo *et al*.[22] confirmed poor agreement in an effort in assessing inter-examiner variability. Burkhardt and Maerker in the year 1981 added the presence of Candida organism and Lumerman *et al*. in the year 1995 added Verrucous hyperplasia with dysplasia in the characteristic features of 1978 WHO classification.

The Ljubljana grading system for the laryngeal hyperplastic lesions when applied to the hyperplastic lesions of the oral cavity appears to be a better one as it divides the hyperplastic lesions into benign, risky and carcinoma *in situ,* which requires separate treatment options. Histological criteria are well-illustrated and clearly defined and thus it should discuss the interobserver variation between the pathologies. This also have prognostic value in oral epithelial hyperplasia.[1] Gale and Warnakulasurya in year 2008 stated the Ljubljana classification could not categorize certain oral lesions like oral submucous fibrosis and oral lichen planus, which have atrophic epithelium and are without significant atypia. This system is considered complex time-consuming and is doubtful for oral lesions.[24,25]

WHO in year 2005 classified OED according to the presence and severity of cellular atypia and to the architectural features based on the thickness of the dysplastic layers when compared with the total epithelial height. The current histopathological grading system is notoriously unreliable due to the lack of the validated grading systems. Pindborg and Kujan[26,27] demonstrated poor to moderate agreement on grading OED, but till date this is the most widely accepted and used classification system. It shows various plus points as it is easy to learn and reproduce. The inter and intraobserver reproducibility is high when compared to other given classifications, so this classification is highly recommended.

Kujan in year 2006 stated that all the proposed grading systems to grade epithelial dysplasia have some shortcomings such as low reproducibility and great variability.[27] Calderia 2011 did a study and commented that the use of the binary system would give support to a reliable clinical approach involving removal of high-risk oral leukoplakia. Hellquist confirmed that the binary system have less interobserver variability as compared to WHO classification. Nankivell in year 2013 mentioned sensitivity and specificity for predicting malignant transformation were 85% to 80%, respectively, using this system.[27]

Due to the absence of consensus over single classification system, several systems are currently employed. However, the classification given by WHO (2005) is widely used and highly recommended. Like every other classification, it also has some shortcomings, but the ease to learn it and reproduce it while diagnosing a case of

dysplasia keeps it way ahead of all other classification systems. The research to formulate a concise and precise classification is still going on, which also focuses on the malignant potential of oral dysplastic lesions. For this, the alterations in molecular and genetic characteristics are studied, but no positive results are still generated for the predictive risk markers. Despite many alternative approaches, conventional histopathological evaluation based on light microscopic examination of Hematoxylin and Eosin stained slides is still the gold standard for assessing the malignant potential of preneoplastic head and neck lesions containing epithelial dysplasia.

CONCLUSION

Grading is an attempt to impose discrete categorization. Any grading effort is therefore by definition artificial. Pathologist needs to provide information, which is useful to clinicians and this is done by creating discrete sub-entities in biological continuum. Unless clear criteria are decided upon, it will remain a hotly debatable subject which lacks subjectivity lacking inter and intra-observer reproducibility. Due to the absence of consensus, several systems are employed. It is unlikely that relatively straightforward molecular parameters will result in unambiguously defined, discrete sub-entities that our clinician asks for.

Some reports indicate a potential for immunohistochemistry and quantitative pathology, but there is no consensus on this type of approach. Then there is the problem of validation of "new" criteria that can be done by comparing these new criteria against some "gold standards." There is no question that the dysplasia classification can best be improved upon by understanding the fundamental biology of the process. This calls for basic research in pathology and put research pathology and applied pathology in a juxtaposition that is essential for future of both.

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