REVIEW ARTICLE

An Insight into Various Grading Systems of Oral Epithelial Dysplasia

Snehanjan Sarangi, Sayani Dutta
Department of Oral Pathology, Burdwan Dental College and Hospital, Kolkata, West Bengal, India

Email for correspondence: babi.sarangi@gmail.com

ABSTRACT

Oral potentially malignant disorders, in many cases, are superseded by oral carcinoma. These premalignant lesions usually manifest as erythematous or whitish patches within the oral mucosa. Histopathological grading of these lesions still remains the gold standard in diagnostic pathology; being interpreted as epithelial dysplasia. It refers to a premalignant change in epithelium characterized by a combination of cellular and architectural alterations. Histopathological grading of epithelial dysplasia poses many challenges to oral and diagnostic pathologists, including inter- and intra-observer variability and choice of optimum parameters based on which the grading should be done. Pathologists must resort to using uniform standards and defined criteria for interpretation of dysplasia. Herein, we have briefly discussed various grading systems of epithelial dysplasia.

Key words: Epithelial dysplasia, histopathological grading, oral carcinoma, potentially malignant disorder

INTRODUCTION

The dysplastic epithelial regions, of the upper reaches of aerodigestive tract, are thought to be associated with a probable progression to cancer. Dysplastic characteristics pertaining to stratified squamous epithelium are defined by atypical cellular features, and perturbation of normal maturation and stratification patterns, being represented by architectural changes.[1] The conglomerated effect of cellular and architectural changes observed in the gradual transition to malignancy is termed epithelial dysplasia. Epithelial dysplasia plays a crucial role to ascertain the potential of malignant development in suspicious lesions.[2,3] Performing a proper diagnosis in this respect is the cornerstone for delivering optimum treatment and prognosis; which can be aided by a useful predictive classification system.[4] Reagon first coined the term dysplasia, which refers to atypical, abnormal cellular proliferation. The terms epithelial atypia and dyskeratosis have been used in the past, having similar meanings.[3] The transformation rate of dysplasia to cancer is in the range of 8–10.5%.[4] The histological grading system must be developed in such a way that it can be easily interpreted and possess the low amount of inter and intraobserver variability.[5]

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DEFINING CRITERIA OF EPITHELIAL DYSPLASIA

Epithelial dysplasias encompass two broad ranges of events, i.e., cellular changes and Architectural alteration.[6]

Cellular changes:

1. Prominent nucleoli.
2. Hyperchromatic nuclei.
3. Polarity loss of basal cells.
4. Cellular and nuclear pleomorphisms.
5. Altered nuclear-cytoplasmic ratio.
6. Increased mitotic activity.
7. Abnormal mitotic figures.
8. Multinucleation of cells, i.e., poikilocytosis.

Architectural alteration:

1. Formation of bulbous rete pegs.
2. Basilar hyperplasia.
3. Hypercellularity.
4. Altered keratinocytic maturation pattern.

GRADING SYSTEMS OF EPITHELIAL DYSPLASIA

Histological grading systems should possess two important characteristics. Ease of interpretation in regular clinical practice along with a low degree of interobserver variability is the first criteria. The second criteria are the development of an optimum parameter based on which proper and timely treatment to affected patients, especially those with potentially malignant and malignant disorders, may be delivered.

The aim of this review is to give an insight about routinely employed grading systems of epithelial dysplasia with a special emphasis on developing a logical histopathological grading system, which could be easily employed in day to day clinicopathological aspect. This is of utmost significance; especially from the point of view of optimum diagnosis, prognosis, and future treatment of potentially malignant disorders.

RELEVANCE AND IMPLEMENTATION IN CERVICAL DYSPLASIA GRADING

The concept of a gradual evolution from a normal epithelium through a dysplasia, terminating ultimately in carcinoma, was introduced from studying pathological changes in the uterine cervix.[7] An accumulation of genetic and epigenetic alterations lead to encroachment of progressively more layers of the epithelium until it is replaced by atypical cells in full length. Greater chance of malignant transformation is usually associated with a higher degree of epithelial dysplasia. Despite the limitation of currently available systems, they remain essential, and the proper and thorough diagnosis is a must for delivering optimum prognosis and treatment.[7,8]

The "Bethesda classification," for cervical cytopathology, first introduced in 1988 comprised two grades. The lesions which were termed as low-grade squamous epithelial lesions, corresponded to former cervical intraepithelial neoplasia (CIN) Grade 1, and high-grade squamous epithelial lesions, were similar to Grades 2 and 3. This system has also been implemented for oral lesions.[9]

The College of American Pathology and the American Society of Colonoscopy and Cervical Pathology jointly described a new terminology to delineate human papillomavirus associated squamous lesions of the anogenital tract as low grade squamous intraepithelial lesion (LSIL) or high grade SIL (HSIL) in 2012:[10]

a) CIN 1 is termed as LSIL corresponding to a mild degree of epithelial dysplasia in the oral mucosa
b) CIN 2 is described as LSIL, which are p16-negative, and those that are p16-positive are termed as HSIL akin to moderate degree of oral epithelial dysplasias
c) CIN 3 is referred to as HSIL similar to a severe degree of oral epithelial dysplasia/carcinoma *in situ* (CIS) of the oral mucosa.[10]

COMMONLY USED GRADING SYSTEMS FOR ORAL EPITHELIAL DYSPLASIA

1. Smith and Pindborg classification.[11] Ljubljana classification
2. SIL.[12]
3. 2005 World Health Organization (WHO) classification.[13]
4. New binary system.[14]
5. 2017 WHO classification.[15,16]

Other Less Commonly Employed Classification Systems Include the Following

1. Banoczy and Csiba classification.[17]
2. Lumerman *et al.* classification.[18]
3. Burkhardt and Maerkar classification.[19]
4. Neville *et al.* grading system.[20]
5. Scully *et al.* grading system.[21,22]
6. Kuffer and Lombardi grading system.[9]
7. Brothwell *et al.* grading system.[23]

SMITH AND PINDBORG CLASSIFICATION

Smith and Pindborg devised a monograph in 1969, which tried to interpret dysplasia based on certain specific factors.[11] In this classification, 13 histological features were assessed as essentially present or absent. The feature was assessed as basically slight or marked, if present, in correlation with standard photomicrographs. Each category was assigned a score and the sum of the scores for the 13 categories indicated the epithelial atypia index. An absent grading was scored as zero, wherein grading of slight or marked was assigned a score between 1 and 10. Some of the categories included drop shaped rete pegs, irregular epithelial stratification, and keratinization below keratin layer. The scores were within a domain of 0–75. Scores in the range of 0–10 were interpreted as non-dysplastic and those in the 11–25 range were noted as mild; whereas those between 26 and 45 were regarded as moderate, and more than 45 was categorized as severe.

There were many advantages in this system, but it did suffer from a number of demerits. The

monographs were tough and time consuming to obtain, and the individual scores for features allocated subjectively by the authors and were not evidence-based. Lots of interobserver variation were evident. It did not found much favor among clinicians or researchers for routine clinico-pathological work. However, it did have a particular merit in current research studies in that it could be employed for statistical analysis. The significant criteria regarding the development of malignancy in potentially malignant lesions were studied, and the ones which were given the heaviest weighting were abnormal mitotic figures in spinous and basal layers, mitoses in upper epithelial layers in suprabasal positions and disturbed polarity of epithelial cells.[17]

LJUBLJANA CLASSIFICATION OF SIL

The Ljubljana system was specifically developed to address the clinical and histological problems of laryngeal anomalies. Very thorough criteria for this classification had been published.[24]

The Ljubljana system was somewhat more complicated. The classification used the term simple hyperplasia for indicating an increase in the thickness of stratum spinosum and abnormal hyperplasia for delineating basal cell hyperplasia. In atypical hyperplasia, synonymously called as risky hyperplasia, epithelial stratification was retained, while atypia was evident. In CIS loss of stratification was evident along the entire epithelium, although three to five layers of compressed cells could be found on the surface. Severe degrees of atypia and mitotic abnormalities were characteristic. For both atypical hyperplasia and CIS, two divisions were recognized, namely basal cell type and spinous cell type.[25]

The first two classifications were considered chiefly benign lesions, which possessed a very little risk for malignant transformation. The third degree was considered to be a potentially malignant lesion, and the last one represented a lesion having a high potential for malignant transformation and areas of micro-invasive breach in the basement membrane which should be critically examined. This is how this system can be correlated with commonly employed grading systems for the sake of diagnostic and treatment purposes.

The demerits of the system are as follows:

a) It included a wide spectrum of classifications, and therefore the implementation in real-world clinicopathological scenarios proved very challenging to the pathologists
b) Wide degree of inter- and intra-observer variability was quite evident.[26]

2005 WHO CLASSIFICATION

In the year 2003, the WHO divided epithelial dysplasia in mild, moderate, severe, and CIS categories, based on the extent of cellular atypia and the architectural changes. The WHO book of "classification of tumors of the head and neck" stressed on this fact.[13]

Mild Dysplasia

In general, architectural disturbance limited to the lower third of the epithelium, usually the basal and suprabasal layers of epithelium along with minimal cytological atypia define the mild degree of dysplasia.

Moderate Dysplasia

Architectural disturbance extending up to the middle third of the epithelium was the initial yardstick for understanding moderate dysplasia. Importance was thereafter given to the extent of cytological atypia. A lesion might be categorized as severe dysplasia despite not extending up to the upper third of the epithelium, due to marked cellular atypia. In contrast, lesions possessing mildly atypical features extending up to the middle third of the epithelium might be graded as mild dysplasia.[27]

Severe Dysplasia

The basis of severe dysplasia involved, architectural disturbance with associated cytological atypia, encompassing more than two-third the epithelial thickness. However, architectural disturbance extending up to the middle third of the epithelium with ample cytological atypia necessitated a jump from moderate to severe dysplasia.

CIS

Architectural disturbances were evident through the entire thickness of the epithelium. Abnormal superficial mitosis and atypical mitotic figures were also frequently observed.[27]

These types of dysplasia are pictorially represented in Figures 1-3.[7]

Binary System

Inter- and intra-observer variability and poor reproducibility were the bane of previously

employed epithelial dysplasia grading systems. To address these drawbacks, Kujan *et al.*, in 2005, developed a new dysplasia classification system based on the basic morphological guidelines utilized by the WHO 2005. He categorized the lesions into high-risk and low-risk groups. The binary system finally established itself as an efficient tool for grading epithelial dysplasia in oral leukoplakia.[14] This system classified dysplasia as follows:

1. High-risk lesions: It correlated with no/mild/questionable dysplasia of the WHO classification. They had a high risk for malignant transformation.
2. Low-risk lesions: It did not possess the ability for malignant transformation. It correlated with moderate/severe dysplasia of the erstwhile WHO 2005 classification.[7]

Reducing the degree of the WHO dysplasia classification system from five, i.e., no/mild/moderate/severe/CIS to two parameters, i.e., low risk and high risk would lead to a more usable, accurate, and well-defined grading method. The new binary system augmented the WHO 2005 well and might be a useful adjunct in helping clinicians to make essential clinical decisions especially pertaining to moderate dysplasia.[26]

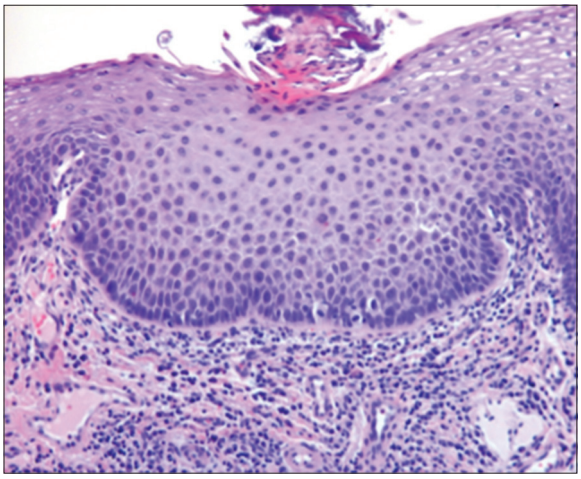

Figure 1: Photomicrograph showing a mild degree of epithelial dysplasia, mild degree of cytological atypia along with increased epithelial thickness along with hyperkeratosis involving basal and suprabasal layers of the epithelium

WHO 2017 System

The WHO in 2017 introduced a biphasic classification, comprising of low-grade and high-grade dysplasia. The terms low- and high-grade SIL can be employed wherever applicable and have similar meanings. This two-phase system might be implemented into a three-phase grading system for optimization of treatment, having a clear contrast between CIS and high-grade dysplasia. The term CIS were used for lesions with marked architectural anomalies, pronounced cellular, and nuclear atypia along with an excessive mitotic count, including atypical mitoses. Proper and timely clinical judgments along with an optimized delivery of treatment, especially in patients having high-grade epithelial

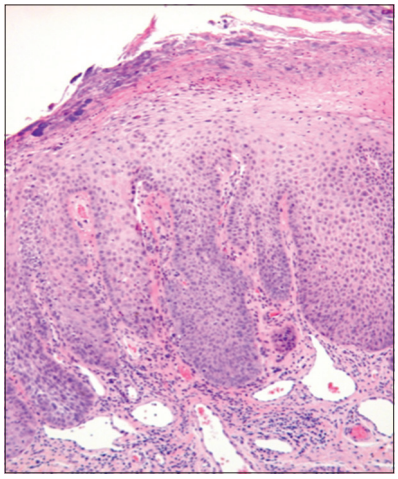

Figure 2: Photomicrograph showing a moderate degree of epithelial dysplasia with blunt and elongated rete pegs along with cytonuclear atypia confined to the middle third of the epithelium

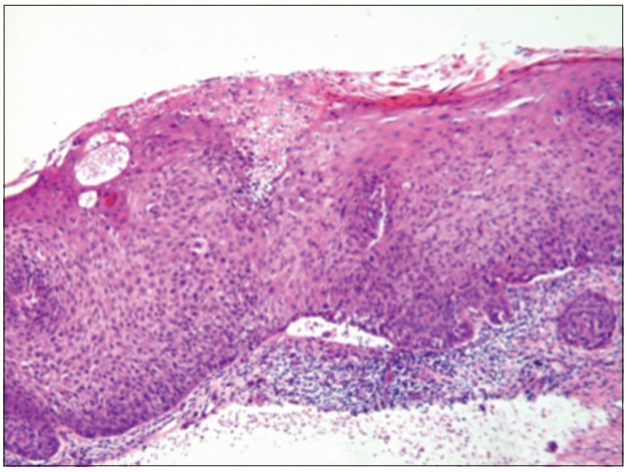

Figure 3: Severe epithelial dysplasia marked cytological atypia extends to the upper third of the epithelium. There is disruption of the normal architecture of the epithelium and bulbous rete pegs are prominent

dysplasia and CIS, should benefit greatly from this system.[28]

PROGNOSTIC AND PRACTICAL ASPECTS OF ROUTINELY EMPLOYED GRADING SYSTEMS

Although a plethora of grading systems for epithelial dysplasia have been in use, there remains a lot of concerning areas. A unified classification, aiming to improve the basic understanding of the epithelial dysplasia concept to both the clinicians as well as the pathologists, must be employed to address the ambiguity caused by a myriad of conflicting concepts and contrasting morphological parameters. Implementation of a lesser number of grades should help a lot in improving the general consensus between pathologists and clinicians. Dividing dysplasia into low grade and high grade should clear up a lot of confusions in this regard along with easy interpretability. This ushers well for the optimum understanding and treatment of the lesions. Furthermore, the usage of unified terminology, along with the proper delineation of the necessary criteria for epithelial dysplasia should be standardized along with all classification systems. These aspects might help us to achieve the goal toward developing a grading system in which the pathologist and clinician should possess a good amount of agreement.[29] This, in turn, helps in delivering optimum diagnosis and treatment without delay.

CONCLUSION

The histopathological assessment of potentially malignant disorders is an area of concern for the associated pathologist. Multiple factors may dictate the interpretation of epithelial dysplasia, and contrasting opinions present themselves, due to a discrepancy in observation patterns of epithelial and cellular maturation pattern. Hence, giving an exact grading based on optimum and defined parameters is a monumental task for the pathologist. A complex amalgamation of chromosomal, genomic and molecular factors lead to dysplasia, and in the long run, even malignancy, and standardization of key parameters in this regard is the need of the hour, so as to rule out inter- and intra-observer variations in between clinician and pathologists. In this regard, further future molecular biological and genetic studies will certainly broaden the horizon regarding the diagnosis of cancerous and pre-cancerous disorders.

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