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Oral Leukoplakia: An Overview of Histopathological Spectrum Focusing on WHO Grading System and Binary System of Oral Epithelial Dysplasia

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ABSTRACT

Oral leukoplakia by definition is a white patch with uncertain risk, not including other lesions that could develop into cancer. **Objectives:** To assess the histopathological spectrum of oral leukoplakia and focus on their relation with WHO-classified histological grades and binary system of dysplasia. **Methods:** This cross-sectional and multicenter study comprised patients diagnosed with oral leukoplakia. Hematoxylin and eosin-stained slides of 60 cases were assessed based on the World Health Organization 2005 classification system: epithelial precursor lesions and binary system of oral epithelial dysplasia. The chi-square test was used to compare different categorical variables related to oral leukoplakia. For analyzing data SPSS version 20.0 was used. **Results:** Of the 60 oral leukoplakia subjects 43 (71.7%) were found to be male while 17 (28.3%) were female. Whereas 26 cases showed dysplastic features (n=26, 43.3%) Among the cases of oral epithelial dysplasia, a higher number of cases of moderate dysplasia was observed (n=12, 46.1%) followed by severe dysplasia (n=10, 38.5%), and the least number of cases had mild dysplasia (n=4, 15.4%). There was a statistically significant relationship between the binary system of oral epithelial dysplasia and variants of oral epithelial dysplasia, mildly dysplastic, moderately dysplastic, and severely dysplastic epithelium ($p<0.04$). **Conclusions:** It was concluded that as oral leukoplakia is such a disorder having a high chance of conversion into cancer early detection is of utmost importance to prevent conversion into malignancy. In addition to the WHO Classification of the said lesions, a binary system of dysplasia can also be promoted.

INTRODUCTION

Oral leukoplakia (OL) is included among oral potentially malignant disorders so there is a significant chance that this potentially malignant oral cavity condition will progress to become a true malignancy [1, 2]. Depending on the location, the transformation rate of oral leukoplakia might vary from 0.13% to 34% [3]. The majority of research has demonstrated heterogeneity in the morphological and clinical features of OL. Its prevalence Varies from 0.2% to 11.7% worldwide. There is marked geographic variation in prevalence even in the different regions of the same country. Studies carried out in Pakistan indicate that the frequency is between 5 and 7% [4]. Mechanical trauma, tobacco use whether smoked or not, alcohol, fungal infections, and Epstein Barr virus are some of the associated etiological factors [5, 6]. As OL is included in oral potentially malignant disorders. So, it manifests

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histologically as an epithelial precursor lesion. Epithelial precursor lesions are categorized by the World Health Organization (WHO) as mild dysplasia, moderate dysplasia, severe dysplasia, and oral epithelial hyperplasia (OEH) [7]. The propensity for malignant transformation of oral leukoplakia is usually determined by the microscopic evaluation of epithelial dysplasia [3]. Dysplasia has been identified in several cytological and architectural changes affecting the oral epithelium, which is limited to the lower third, middle, and upper third layers [8, 9]. WHO grading system of dysplasia includes mild, moderate and severe dysplasia based on the layers of epithelium involved, however another system that is the Binary system of the dysplastic epithelium of the oral cavity has also been introduced to classify dysplasia into high-risk and low-risk [10]. The clinical outcome is that oral leukoplakia with moderate and severe dysplasia have high chances of conversion (potentially malignant) into malignancy so timely treatment of such lesions should be done to avoid such threat.

Oral leukoplakia, a common oral potentially malignant disorder, carries a significant risk of malignant transformation ranging from 0.13% to 34%, making its accurate histopathological characterization critically important for timely clinical intervention. Despite the availability of both the WHO grading system and the binary system of oral epithelial dysplasia, limited studies have simultaneously evaluated and compared both classification systems in the context of oral leukoplakia, particularly within the Pakistani population where prevalence ranges between 5–7%. This study therefore aimed to assess the histopathological spectrum of oral leukoplakia and explore the relationship between WHO-classified histological grades and the binary system of dysplasia, in order to determine which approach better predicts malignant transformation risk and guides clinical decision-making.

METHODS

This cross-sectional and multicenter study was conducted at Khyber College of Dentistry and Peshawar Medical College. Data from 60 cases of oral leukoplakia that were diagnosed clinically and confirmed microscopically were collected over 7 months from August 2016–March 2017. Before the start of the study permission from the institutional review board was taken with an IRB number Prime /IRB/2016-0035. The sampling which was adopted was a non-probability convenient sampling technique, an online calculator, was used to determine the sample size with a 9.5% confidence interval, 0.05 chance of error and 2% prevalence. As the sampling which was adopted was a non-probability convenient sampling technique so 60 sample sizes were selected [11]. Inclusion criteria included clinically diagnosed and histopathological confirmed oral leukoplakia cases whereas individuals having microscopic features of anaplasia and invasion were excluded. Permission was granted by the Institutional review board before the commencement of the study. Written consent was taken from every participant on a pre-structured consent form. Separate codes will be given to conceal the identity of the patients. Data were handled by me being the PI of the study. Research data was secured in PI's laptop having a password. Laboratory techniques for biopsy specimens included grossing and processing followed by staining of slides by H and E stain. Two consultant histopathologists graded and assessed the histopathological findings of oral leukoplakia cases until they reached an agreement. When there was disagreement, a third observer, a senior, skilled oral pathologist reevaluated the slides and mediated the matter until everyone agreed. The WHO's 2005 classification method for epithelial precursor lesions was used to group oral potentially malignant disorders (OPMDs) including oral leukoplakia [12]. By this system, oral leukoplakia was categorized as Hyperplasia, or dysplasia, (mild, moderate, severe). The assessment of dysplastic epithelium of the oral cavity was based on cytological factors such as variable cells and nuclear size and shape, increased nucleus–cytoplasm ratio, aberrant mitosis, hyperplasia and hypertrophy of nucleoli, and darkly stained cytoplasm and nuclei) and alterations in epithelial architecture include hyper-cellularity, loss of polarity of basal cells, bulbous rete ridges, individual cell keratinization, and non-cohesive cells of epithelium) [13]. A binary system of oral epithelial dysplasia (OED) was also adopted, and cut-off points of four architectural and five cytological features were employed to classify OED as a high-risk lesion (those who have a potential for MT) and a low-risk lesion (those who do not have the potential for MT) [12]. Variables related to histopathological features of oral leukoplakia were included in the tabulation of data. The chi-square test was used to compare different categorical variables related to the lesion. Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) software version 21.0 (IBM Corp, Armonk, New York, United States America) with a significance level of $p \leq 0.05$.

RESULTS

Of the 60 oral leukoplakia cases 43(71.7%) were found to be in male patients while 17 (28.3%) were in female patients .2.5:1 was the computed ratio (Table 1).

Table 1: Gender Wise List of Oral Leukoplakia Patients

Gender	No. of cases n (%)
Male	43 (71.7%)
Female	17 (28.3%)

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Total	60 (100.0%)

The age range is shown which is from 30 to 90 years and the mean age is found to be 60 years (Table 2).

Table 2 : Oral Leukoplakia Cases Distributed by Age

Age	No. of cases
Minimum	30 Years
Maximum	90 Years
Mean	60 Years

The total number of oral leukoplakia cases was 60 out of which 26 were dysplastic (n=26, 43.3%). The dysplastic feature was observed in 26 (43.3%) individuals out of 60, whereas 34 cases showed hyperkeratotic and hyperplastic epithelium (56.6%) (Table 3).

Table 3: Frequency of Various Grades of Dysplasia

Frequency and Percentage of Grades of Dysplasia	n (%)
Mild Dysplasia	4 (15.5%)
Moderate Dysplasia	12 (46.1%)
Severely Dysplastic Epithelium	10 (38.5%)
Total	26 (100%)

There was a statistically significant relationship between the binary system of OED and WHO grading system of dysplasia, that is, mildly dysplastic, moderately dysplastic, and severely dysplastic epithelium ($p<0.04$) (Table 4).

Table 4: Relation of Binary Grading System and WHO Categorization of Dysplastic Epithelium

Variables		WHO Classification			Total	Pearson's Chi-Square Test
		Mildly Dysplastic Epithelium n (%)	Moderately Dysplastic Epithelium n (%)	Severely Dysplastic n (%)		
Binary Grading System	Low Risk	4 (15.4%)	7 (26.9%)	2 (7.7%)	13 (50.0%)	0.04
	High Risk	0 (0%)	5 (19.2%)	8 (30.8%)	13 (50.0%)	
Total		4 (15.4%)	12 (46.1%)	10 (38.5%)	26 (100.0%)	

DISCUSSION

The WHO grading system for epithelial precursor lesions, the binary system for grading of OED, and other histomorphological features of oral leukoplakia are included in this study for the first time. According to the current study, men are more likely than women to have oral leukoplakia. This gender-related observation contradicts the findings of Pires *et al.*, the number of female with the habit of tobacco use is increasing in certain populations and secondly, there is the likelihood that the female lesions would be diagnosed and treated earlier. The result of our study is consistent with the findings reported by Saldivia *et al.*, and Pires *et al.*, [13, 14]. This may be explained by the fact that in certain regions men are more exposed to the risk factors of oral leukoplakia such as smoking habits and outdoor jobs. The majority of cases of oral leukoplakia were found to be in the older age group according to the current study. This is in line with research by Khan *et al.* and Mello *et al.*, who found that growing older may be a determinant of OPMDs [15, 16]. This study found that among the oral epithelial dysplasia cases, moderate dysplasia was the most common, severe dysplasia was the second most common, and cases with mildly dysplastic epithelium were the least common. This is consistent with [12]. Additionally, cases of severe dysplasia were documented by other researchers in comparison to mild and moderate dysplasia [17]. Epithelial Dysplasia has been identified microscopically as one of the predictive markers for the development of cancer from such lesions having chances of conversion into cancer, including oral leukoplakia [18]. A statistically significant correlation was found between the grades of dysplastic epithelium and the binary grading system of dysplastic epithelium. All the cases of mild dysplastic were placed in the low-risk category while the majority of cases of moderately dysplastic and severely dysplastic epithelium were placed in the high-risk category. This is due to the results of international literature about the probable chance of conversion into cancer of such lesions having the potential to show a certain degree of dysplastic [19]. 50% of cases in this study were classified as high-risk lesions and 50% as low-risk. Its results are similar to the international study by Câmara *et al.*, however, are in contrast to research by Kujan *et al.*, [20, 21], binary grading system. Leukoplakia of the oral cavity was classified by the Binary system as high risk and low risk. International studies noted that oral cancers can also occur in low-risk OPMDs but high-risk oral epithelial dysplasia has a much higher chance of conversion into cancer [12]. In line with the finding of Câmara *et al.*, the current investigation discovered a statistically significant association between the oral epithelial dysplasia binary system and oral epithelial dysplasia introduced by the WHO grading system [20]. WHO grading system classifies dysplasia into mild, moderate and severe dysplasia whereas the binary grading system classifies dysplasia into low risk and high risk. The high-risk category includes moderate and severe dysplasia. In this study, there were more cases of severe and moderate dysplasia and the clinical outcome is that oral leukoplakia with moderate and severe dysplasia have high chances of conversion (potentially malignant) into malignancy so timely diagnosis and treatment of such lesions should be done to avoid such threat.

This study is constrained by its relatively small sample size of 60 cases, non-probability convenience sampling, limited geographic representation from only two centers in Peshawar, and a short data collection period of seven months, all of which reduce the generalizability of findings.

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Furthermore, the retrospective nature of histopathological reassessment and inter-observer variability, despite mediation protocols, may have introduced some degree of diagnostic inconsistency. Future studies should employ larger, multi-center, longitudinal designs with standardized biopsy protocols to track malignant transformation rates over time across dysplasia grades. Additionally, integrating molecular and immunohistochemical biomarkers alongside conventional grading systems could significantly enhance the predictive accuracy of both the WHO and binary classification systems in identifying high-risk oral leukoplakia cases.

CONCLUSIONS

It was concluded that oral leukoplakia was the most common in males, mostly in age ≥50 years. Timely diagnosis and treatment of oral leukoplakia with dysplastic features are of utmost importance to avoid the conversion of these premalignant lesions into cancer and ultimately decrease the mortality rate.

Authors' Contribution

Conceptualization: TN
Methodology: TN, ZI, SM, MUH
Formal analysis: ASK, UM, TK, MM
Writing and Drafting: TUH, ASK, UM, TK, MM
Review and Editing: TUH, ASK, UM, TK, MM

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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