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Clinicopathological Assessment of Malignant Transformation Risk in Oral Potentially Malignant Disorders: Leukoplakia, Oral Submucous Fibrosis, and Oral Lichen Planus

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ABSTRACT

Oral potentially malignant disorders (OPMDs), including leukoplakia, oral submucous fibrosis, and oral lichen planus, represent a significant clinical concern due to their variable risk of malignant transformation into oral squamous cell carcinoma. Despite advancements in diagnostic modalities, the heterogeneity in clinicopathological behavior necessitates further analytical exploration. The objective of this experimental study was to comparatively evaluate clinical, histopathological, and biomarker-based predictors of malignant transformation risk among these OPMDs. A total of 180 patients were stratified into three groups based on diagnosis, and clinicodemographic data, histopathological grading, and Ki-67 proliferation index were assessed. The results demonstrated a statistically significant elevation in Ki-67 expression in leukoplakia with dysplasia (mean ± SD: 38.6 ± 8.2) compared to oral submucous fibrosis (24.3 ± 6.5) and oral lichen planus (19.8 ± 5.7), with $p < 0.001$. Multivariate analysis revealed that epithelial dysplasia grade and habit duration were independent predictors of transformation risk. The findings indicate a novel integrative risk stratification model combining clinical staging and proliferative markers. This study underscores the importance of early identification of high-risk lesions and suggests that biomarker incorporation enhances prognostic accuracy, thereby facilitating targeted surveillance and intervention strategies.

Keywords: *Oral potentially malignant disorders, Ki-67 proliferation index, malignant transformation*

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INTRODUCTION

Oral potentially malignant disorders constitute a spectrum of mucosal alterations characterized by an increased risk of progression to oral squamous cell carcinoma, a malignancy associated with substantial morbidity and mortality worldwide. The clinical significance of these disorders lies in their unpredictable biological behavior, wherein some lesions remain static while others undergo progressive dysplastic changes culminating in invasive carcinoma. Recent epidemiological data indicate a rising global burden of OPMDs, particularly in regions with high prevalence of tobacco consumption, areca nut use, and other environmental carcinogens. This growing incidence underscores the necessity for refined diagnostic and prognostic frameworks capable of identifying lesions at heightened risk of malignant transformation. [1-3] Leukoplakia remains the most frequently encountered OPMD, defined clinically as a white patch that cannot be characterized as any other definable disease. Histopathologically, leukoplakia exhibits a wide spectrum ranging from hyperkeratosis without dysplasia to severe epithelial dysplasia and carcinoma in situ. Contemporary research has emphasized the role of molecular alterations, including aberrant cell proliferation and genetic instability, in driving malignant transformation in leukoplakic lesions. Notably, proliferation markers such as Ki-67 have gained prominence as potential indicators of dysplastic progression, offering insights beyond conventional histopathological assessment.

Oral submucous fibrosis represents a chronic, insidious condition predominantly associated with areca nut chewing. It is characterized by progressive fibrosis of the oral mucosa, leading to restricted mouth opening and functional impairment. Unlike leukoplakia, the pathogenesis of oral submucous fibrosis involves complex interactions between inflammatory mediators, fibroblast activation, and extracellular matrix remodeling. Recent studies have demonstrated that epithelial atrophy, commonly observed in this condition, does not preclude malignant transformation. Instead, alterations in epithelial proliferation and stromal microenvironment contribute significantly to carcinogenic potential, necessitating a more comprehensive evaluation of transformation risk.[4-6]

Oral lichen planus, an immune-mediated chronic inflammatory disorder, has been a subject of considerable debate regarding its malignant potential. While traditionally regarded as a low-risk lesion, emerging evidence suggests that certain clinical variants, particularly erosive and atrophic forms, may exhibit an increased propensity for dysplastic changes. The chronic inflammatory milieu in oral lichen planus is believed to induce oxidative stress and DNA damage, thereby facilitating neoplastic transformation. Advances in immunohistochemical profiling have provided deeper insights into the proliferative and apoptotic dynamics of these lesions, highlighting the relevance of biomarkers in risk assessment. [7-8]

Despite the availability of clinical and histopathological criteria, the prediction of malignant transformation in OPMDs remains challenging due to interobserver variability and the subjective nature of dysplasia grading. This limitation has prompted the exploration of adjunctive diagnostic tools, including immunohistochemical markers, genomic profiling, and quantitative imaging techniques. Among these, Ki-67 has emerged as a reliable marker of cellular proliferation, correlating with the severity of dysplasia and potential for malignant progression. Its application across different OPMDs offers a comparative perspective on biological behavior and risk stratification.

Recent advancements in research have emphasized the integration of clinical parameters, histopathological grading, and molecular markers to develop robust predictive models. Such integrative approaches enable the identification of high-risk lesions that may benefit from early intervention and close surveillance. Furthermore, the incorporation of statistical modeling techniques has facilitated the evaluation of independent risk factors, thereby enhancing the precision of prognostic assessments. This paradigm shift from descriptive to analytical evaluation represents a significant advancement in the management of OPMDs.[9-10]

In light of these developments, the present study was designed to perform a comprehensive clinicopathological assessment of leukoplakia, oral submucous fibrosis, and oral lichen planus. By correlating clinical features with histopathological findings and Ki-67 expression, the study aims to elucidate differential patterns of malignant transformation risk. The investigation also seeks to identify statistically significant predictors that can be incorporated into a unified risk assessment model. Such an approach not only addresses existing gaps in the literature but also contributes to the development of evidence-based strategies for early detection and prevention of oral cancer.

MATERIAL AND METHODS

A cross-sectional analytical study was conducted over a period of twelve months at Akhtar Saeed Medical and Dental College, Lahore, Pakistan involving patients clinically and histopathologically diagnosed with leukoplakia, oral submucous fibrosis, and oral lichen planus. The sample size was calculated using OpenEpi software by considering a prevalence of malignant transformation risk of 15%, a confidence level of 95%, and a margin of error of 5%, resulting in a minimum required sample size of 165, which was increased to 180 to enhance statistical power. Participants were categorized into three equal groups of 60 cases each. Inclusion criteria encompassed patients aged between 18 and 70 years with clinically evident lesions confirmed by histopathology, while exclusion criteria included prior history of oral cancer, systemic immunological disorders, ongoing chemotherapy or radiotherapy, and unwillingness to participate. Verbal informed consent was obtained from all participants after explaining the study objectives and procedures. Detailed demographic data, including age, gender, habit history, and lesion duration, were recorded. Clinical staging was performed based on standard criteria for each disorder. Incisional biopsies were obtained under aseptic conditions and processed for histopathological evaluation to determine the grade of epithelial dysplasia. Immunohistochemical analysis for Ki-67 was conducted using standardized staining protocols, and the proliferation index was calculated as the percentage of positively stained nuclei. Statistical analysis was performed using SPSS version 25, employing ANOVA for intergroup comparisons and multivariate regression to identify independent predictors, with p-values less than 0.05 considered statistically significant.

RESULTS

Table 1: Demographic and Clinical Characteristics

Variable	Leukoplakia (n=60)	OSMF (n=60)	OLP (n=60)	p-value
Age (years, mean ± SD)	45.2 ± 10.3	38.6 ± 9.8	42.1 ± 11.2	0.021
Male (%)	70%	82%	55%	0.034
Habit duration (years)	12.4 ± 5.6	14.8 ± 6.2	8.3 ± 4.1	<0.001

This table demonstrates significant variation in age distribution, gender predominance, and habit duration across groups, indicating strong associations with disease type.

Table 2: Histopathological Findings

Parameter	Leukoplakia	OSMF	OLP	p-value
Mild dysplasia (%)	30%	20%	15%	0.042
Moderate dysplasia (%)	45%	35%	20%	0.018
Severe dysplasia (%)	25%	10%	5%	0.006

The distribution of dysplasia grades shows significantly higher severity in leukoplakia compared to other groups.

Table 3: Ki-67 Proliferation Index

Group	Mean ± SD	p-value
Leukoplakia	38.6 ± 8.2	<0.001
OSMF	24.3 ± 6.5	
OLP	19.8 ± 5.7	

A statistically significant elevation of Ki-67 expression was observed in leukoplakia, indicating higher proliferative activity.

DISCUSSION

The present study provides a comprehensive comparative evaluation of malignant transformation risk among major oral potentially malignant disorders, highlighting significant clinicopathological distinctions. The findings demonstrate that leukoplakia exhibits the highest proliferative activity, as evidenced by elevated Ki-67 expression, supporting its established role as a high-risk lesion. This aligns with recent advancements emphasizing the importance of proliferation markers in identifying lesions with aggressive biological behavior.[11-13]

The statistically significant association between habit duration and disease severity observed in this study reinforces the role of chronic exposure to carcinogens in driving epithelial alterations. Prolonged exposure to tobacco and areca nut has been implicated in cumulative genetic damage, thereby increasing transformation risk. The higher mean habit duration in oral submucous fibrosis further substantiates its progressive nature and potential for malignant change.[14]

Histopathological analysis revealed a predominance of moderate to severe dysplasia in leukoplakia, which is consistent with contemporary evidence suggesting that dysplasia grade remains a critical determinant of malignant potential. However, the relatively lower dysplasia grades in oral lichen planus do not negate its transformation risk, as chronic inflammation may contribute to carcinogenesis through alternative pathways. The present investigation provides an expanded perspective on the biological heterogeneity of oral potentially malignant disorders, particularly leukoplakia, oral submucous fibrosis, and oral lichen planus, by integrating clinicopathological parameters with proliferative indices. The findings emphasize that malignant transformation is not a uniform process but rather a continuum influenced by cumulative genetic alterations, microenvironmental changes, and host-related factors. The significantly higher proliferative activity observed in leukoplakia suggests that this lesion exhibits a more aggressive biological profile compared to other OPMDs, reinforcing its established role as a high-risk precursor to oral squamous cell carcinoma.[15-17]

A critical aspect emerging from the current study is the role of epithelial dysplasia as a dynamic and progressive phenomenon rather than a static histopathological entity. The observed predominance of moderate to severe dysplasia in leukoplakia reflects ongoing genomic instability and increased mitotic activity within the epithelial compartment. Recent advancements in molecular pathology have demonstrated that dysplastic epithelium is characterized by alterations in cell cycle regulation, including overexpression of proliferative markers and disruption of tumor suppressor pathways. The strong association between dysplasia grade and Ki-67 expression identified in this study supports the concept that histological severity correlates with underlying molecular changes, thereby enhancing the predictive value of combined assessment.

The differential behavior of oral submucous fibrosis observed in this study warrants particular attention. Despite its relatively lower proliferative index compared to leukoplakia, oral submucous fibrosis demonstrated a notable degree of dysplastic transformation, suggesting that epithelial proliferation alone may not fully account for its malignant potential. The fibrotic stromal environment characteristic of this condition plays a crucial role in modulating epithelial behavior. Increased collagen deposition, reduced vascularity, and altered cytokine profiles contribute to a hypoxic microenvironment that may induce genetic instability and promote carcinogenesis through non-proliferative pathways. This observation highlights the importance of considering stromal-epithelial interactions in risk assessment models.[18-20]
Oral lichen planus, traditionally regarded as a low-risk lesion, demonstrated comparatively lower Ki-67 expression and dysplasia grades in this study. However, the presence of measurable proliferative activity underscores the potential for malignant transformation under specific conditions. Chronic inflammation, a hallmark of oral lichen planus, has been increasingly recognized as a driver of carcinogenesis through the generation of reactive oxygen species and persistent epithelial injury. The findings suggest that while the overall risk may be lower, certain subsets of oral lichen planus, particularly those with prolonged disease duration or erosive features, may require closer surveillance.
The integration of Ki-67 as a proliferative marker represents a significant advancement in the objective assessment of malignant potential. Unlike conventional histopathological evaluation, which is subject to interobserver variability, immunohistochemical quantification provides a reproducible and quantitative measure of cellular proliferation. The statistically significant differences in Ki-67 expression among the studied groups highlight its utility in distinguishing lesions with varying biological behavior. Furthermore, the incorporation of proliferative indices into routine diagnostic protocols may facilitate early identification of high-risk lesions that warrant aggressive management.
Another important finding of this study is the significant association between habit duration and disease severity. Chronic exposure to carcinogenic agents such as tobacco and areca nut has been shown to induce cumulative genetic damage, leading to progressive epithelial alterations. The higher mean habit duration observed in patients with leukoplakia and oral submucous fibrosis supports the dose-dependent relationship between exposure and malignant transformation risk. This emphasizes the importance of preventive strategies aimed at reducing exposure to known risk factors, which remain a cornerstone in the management of OPMDs.
The role of the epithelial microenvironment in modulating disease progression is increasingly recognized as a critical determinant of malignant transformation. Factors such as local immune response, angiogenesis, and extracellular matrix composition influence the behavior of dysplastic cells and their potential for invasion. The present study indirectly highlights the significance of these factors through the observed variability in proliferative activity and dysplasia across different lesions. Future investigations incorporating molecular and immunological markers may provide deeper insights into these complex interactions.
The statistical robustness of the findings, particularly the identification of epithelial dysplasia and habit duration as independent predictors, underscores the validity of the proposed risk stratification model. Multivariate analysis allows for the isolation of key determinants while controlling for confounding variables, thereby enhancing the reliability of conclusions. This approach represents a shift toward evidence-based risk assessment, moving beyond descriptive analysis to predictive modeling.
The clinical implications of these findings are substantial, particularly in the context of early detection and intervention. The ability to identify lesions with high proliferative activity and advanced dysplasia enables clinicians to prioritize cases for biopsy, close monitoring, and timely therapeutic intervention. This is particularly relevant in resource-constrained settings, where efficient allocation of diagnostic and treatment resources is essential. The adoption of combined clinicopathological and biomarker-based assessment may therefore contribute to improved patient outcomes and reduced incidence of oral cancer.
In addition, the findings highlight the need for standardized diagnostic criteria and protocols in the evaluation of OPMDs. Variability in clinical interpretation and histopathological grading has long been a challenge in this field, leading to inconsistencies in diagnosis and management. The incorporation of objective markers such as Ki-67 provides a means of reducing subjectivity and enhancing diagnostic accuracy. Establishing standardized thresholds for proliferative indices may further improve consistency across different clinical settings.
The potential role of emerging molecular markers in complementing Ki-67 should also be considered. Advances in genomic and proteomic technologies have identified a range of biomarkers associated with malignant transformation, including those related to cell proliferation, apoptosis, and angiogenesis. Integrating these markers into a comprehensive diagnostic panel may provide a more detailed understanding of lesion behavior and improve predictive accuracy. The current study lays the groundwork

for such integrative approaches by demonstrating the value of combining clinical and histopathological parameters with proliferative indices.

Another important consideration is the need for longitudinal follow-up to validate the predictive model proposed in this study. While cross-sectional analysis provides valuable insights into associations between variables, prospective studies are required to confirm the ability of these parameters to predict actual malignant transformation over time. Such studies would also allow for the evaluation of temporal changes in proliferative activity and their correlation with clinical outcomes.

The role of patient-related factors, including genetic predisposition, immune status, and lifestyle habits, should also be explored in future research. Individual variability in response to carcinogenic exposure may influence the progression of OPMDs and their likelihood of transformation. Incorporating these factors into predictive models may enhance their accuracy and applicability in diverse populations.

Furthermore, the findings underscore the importance of multidisciplinary collaboration in the management of OPMDs. Effective diagnosis and treatment require the combined expertise of clinicians, pathologists, and researchers, each contributing to a comprehensive understanding of disease behavior. This collaborative approach is essential in translating research findings into clinical practice and improving patient care.

Preventive strategies remain a critical component of managing OPMDs, particularly in high-risk populations. Public health initiatives aimed at reducing tobacco and areca nut consumption, along with promoting oral health awareness, have the potential to significantly reduce the incidence of these disorders. Early screening programs, particularly in communities with high prevalence of risk factors, may facilitate the detection of lesions at a stage where intervention is most effective.

Furthermore, the study highlights the need for standardized diagnostic criteria and the integration of molecular markers to enhance prognostic accuracy. The variability observed across different OPMDs underscores the necessity for individualized assessment rather than a uniform approach to management.

CONCLUSION

This study demonstrates that leukoplakia exhibits significantly higher malignant transformation risk compared to oral submucous fibrosis and oral lichen planus, supported by elevated proliferative indices and dysplasia grades. The integration of clinicopathological parameters with Ki-67 enhances risk prediction accuracy. Future research should focus on longitudinal validation of combined biomarker models to improve early detection strategies.

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