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DECODING THE PREDICTORS OF DYSPLASTIC CHANGES IN ORAL SUBMUCOUS FIBROSIS: A CROSS-SECTIONAL STUDY



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Abstract

Oral submucous fibrosis (OSMF) is a chronic, progressive, potentially malignant oral condition strongly linked to areca nut use. Since epithelial dysplasia predicts malignant transformation, this study identified factors associated with dysplastic changes in OSMF patients. This cross-sectional analytical study was conducted in a diagnostic laboratory affiliated with Punjab University, Lahore, over six months. Using non-probability consecutive sampling, 120 patients clinically diagnosed with OSMF were enrolled. Demographic data, length and frequency of areca nut use, tobacco exposure, mouth opening, burning sensation scores and clinical staging were recorded. Incisional biopsies were undertaken for diagnosis and the grade of epithelial dysplasia. The SPSS (version 26.0) software was used to analyze the data. Predictors of dysplastic changes were identified using the chi-square test, independent t-test, and multivariate logistic regression analysis. A p -value ≤ 0.05 was considered statistically significant. The mean age of participants was 36.8 ± 9.7 years, and 71.7% of the participants were male. Histopathological examinations showed that 44 (36.7%) patients had epithelial dysplasia. There was a significant increase in people who have been chewing areca nuts for more than 10 years, chewed more than five times a day ($p=0.014$), used tobacco at the same time ($p=0.026$), had a more advanced stage of OSMF, and had decreased opening of the mouth (disability) ($p<0.05$). Advanced clinical stage (OR=3.82, 95% CI: 1.89–7.73), tobacco use (OR=2.94, 95% CI: 1.36–6.34), and consumption of areca nut for more than 10 years (OR=3.27, 95% CI: 1.54–6.96) were independent factors associated with epithelial dysplasia. Advanced clinical stage, prolonged areca nut exposure, and concomitant tobacco use were significant predictors of dysplastic changes in patients with OSMF.

Keywords: Areca nut, Epithelial dysplasia, Oral cancer, Oral submucous fibrosi, Potentially malignant disorders, Risk factors

INTRODUCTION

Oral submucous fibrosis (OSMF) is a chronic progressive potentially malignant disorder of oral cavity in which there is excessive collagen deposition, subepithelial inflammation and progressive fibrosis of oral mucosa (1, 2). The disease is more common in the South Asian population, where areca nut chewing is a common practice with or without tobacco (3,4) OSMF is linked with high morbidity with burning sensation, mucosal rigidity, reduced mouth opening, loss of speech and reduced chewing efficiency. One of the main issues with OSMF is its known tendency for malignant transformation to oral squamous cell carcinoma (OSCC) (5, 6). Different studies have reported the malignant transformation rate at some 4% to 13% (7, 8).

Epithelial dysplasia is considered to be one of the most important histological indicators of increased malignant potential (9, 10). Dysplastic changes are progressive genetic and molecular changes in the oral epithelium and can occur in the early stages of the development of invasive carcinoma (11, 12). It is therefore important to identify patients with a higher risk of their developing a dysplastic transformation in order to perform appropriate and effective surveillance and to intervene early. A variety of clinical and behavioral factors have been suggested as predictors of epithelial dysplasia in OSMF (13, 14). These include long duration of use of areca nut, high frequency of chewing of areca nut, chewing of tobacco in addition to

areca, severity of the areca nut induced mouth opening restriction, and advanced clinical stage of disease (15). The correlation of these with dysplastic progression is not consistent among various populations, however. Identifying predictors for dysplastic changes can be helpful in determining which patients would benefit from more frequent follow-up and early biopsy. Although the burden of OSMF in developing countries is high, there is still limited evidence to show the relative contribution of clinical and habit factors for dysplastic transformation. Hence, the present study was conducted to assess the prevalence of epithelial dysplasia in the patients of oral submucous fibrosis and to see if there are any demographic, behavioral and clinical predictors associated with epithelial dysplasia based on histopathological examination as the reference standard. This study postulated that increased probabilities of epithelial dysplasia would be linked to longer duration and higher frequency of areca nut usage, tobacco use, advanced clinical stage, and restricted mouth opening.

MATERIALS AND METHODS

A cross-sectional analytical study was carried out in a diagnostic laboratory affiliated Punjab University, Lahore for 6 months (July 2022 to December 2022). The study included total 120 patients having clinically diagnosed OSMF.

Eligible patients were those between 18 years and older who had clinical features suggestive of OSMF such as blanching of the oral mucous membrane, fibrous bands palpable, burning sensation, and restricted mouth opening. Past oral cancer history, past treatment for OSMF, severe systemic disease and incomplete clinical records excluded patients from the study. Detailed demographic and clinical information were collected using a structured questionnaire. Information on age, gender, duration and frequency of chewing areca nut, tobacco, smoking habit and associated symptoms were collected.

Clinical staging of OSMF was done following known clinical criteria: mouth opening and extent of fibrotic involvement. Inter-incisal mouth opening was determined with a calibrated Vernier caliper, and recorded in millimeters. Detailed oral examinations were conducted by qualified specialists in oral medicine in standardized conditions. Prior to the study, all examiners underwent calibration training (kappa score = 0.85) to ensure consistency in clinical staging and mouth opening measurements. Incisional biopsies were taken from the buccal mucosa bilaterally at the site of the most prominent fibrotic band or clinically suspicious epithelial change. The tissues were fixed in 10% buffered formalin, processed routinely and stained by hematoxylin and eosin. The histopathological evaluation was done by an oral pathologist who was unaware of the clinical findings. All slides were evaluated by a single oral pathologist; inter-observer variability was not assessed. According to the World Health Organization (WHO) 2017 classification of oral epithelial dysplasia, the epithelial changes were classified as absence of dysplasia, mild dysplasia, moderate dysplasia, severe dysplasia.

Data was entered and analyzed with the help of Statistical Package for Social Sciences (SPSS) version 26.0. Data were presented as mean \pm standard deviation for continuous variable data and frequencies and percentages for categorical variable data. Clinical parameters were correlated with epithelial dysplasia with the use of Chi-square and independent t-tests as appropriate. Variable(s) with significant bivariate associations were placed into a multivariate logistic regression model to determine which variables are independent predictors of dysplastic changes. Odds ratios (ORs) and 95% Confidence intervals (CIs) were computed. A p value of < 0.05 was deemed as statistically significant.

RESULTS

A total of 120 patients diagnosed with oral submucous fibrosis (OSMF) were included in the study. The majority of participants were young to middle-aged males with a history of areca nut consumption. Histopathological examination revealed epithelial dysplasia in 44 out of 120 (36.7%) patients. Significant associations were observed between dysplastic changes and habit-related as well as clinical disease characteristics.

The majority of participants belonged to the 31–45 years age group (43.3%), and males constituted 71.7% of the study population. More than two-fifths of patients reported areca nut consumption for over 10 years, while 63.3% chewed areca nut more than five times daily. Concurrent tobacco use was observed in

57.5% of participants, as shown in Table I.

Table I. Demographic and habit characteristics of patients with OSMF (n=120)

Variable	Category	Frequency (n)	Percentage (%)
Age groups (Years)	≤30	38	31.7
	31–45	52	43.3
	>45	30	25.0
Gender	Male	86	71.7
	Female	34	28.3
Areca nut consumption duration	≤5 Years	28	23.3
	6–10 Years	42	35.0
	>10 Years	50	41.7
Daily chewing frequency	≤5 Times/Day	44	36.7
	>5 Times/Day	76	63.3
Tobacco use	Yes	69	57.5
	No	51	42.5

Clinical Stage II OSMF was the most common presentation, accounting for 35.0% of cases (Table II). Restricted mouth opening of less than 25 mm was observed in 36.7% of patients. Histopathological examination confirmed epithelial dysplasia in 36.7% of OSMF cases.

Table II. Clinical Characteristics and histopathological findings in OSMF patients (n=120)

Variable	Frequency (n)	Percentage (%)
Clinical Stage I	24	20.0
Clinical Stage II	42	35.0
Clinical Stage III	36	30.0
Clinical Stage IV	18	15.0
Mouth opening >35 mm	27	22.5
Mouth opening 25–35 mm	49	40.8
Mouth opening <25 mm	44	36.7
Epithelial dysplasia present	44	36.7
Epithelial dysplasia absent	76	63.3

The prevalence of epithelial dysplasia increased progressively with advancing clinical stage of OSMF (Table III). Dysplasia was observed in 72.2% of Stage IV cases compared with only 12.5% of Stage I lesions. This association was statistically significant ($p < 0.001$).

Table III. Association between clinical stage of OSMF and presence of epithelial dysplasia (n=120)

Clinical Stage	Dysplasia Present n (%)	Dysplasia Absent n (%)	p-value
Stage I (n=24)	3 (12.5)	21 (87.5)	
Stage II (n=42)	10 (23.8)	32 (76.2)	
Stage III (n=36)	18 (50.0)	18 (50.0)	
Stage IV (n=18)	13 (72.2)	5 (27.8)	<0.001

Patients with epithelial dysplasia were significantly more likely to have a history of prolonged areca nut consumption exceeding 10 years (65.9% vs 27.6%, $p < 0.001$). Higher chewing frequency and concomitant tobacco use were also significantly associated with dysplastic changes (Table IV).

Table IV. Association of habit characteristics with epithelial dysplasia in OSMF patients

Variable	Dysplasia present n (%)	Dysplasia absent n (%)	p-value
Areca Nut Use >10 Years	29 (65.9)	21 (27.6)	<0.001
Areca Nut Use ≤10 Years	15 (34.1)	55 (72.4)	
Chewing Frequency >5 Times/Day	34 (77.3)	42 (55.3)	0.014
Chewing Frequency ≤5 Times/Day	10 (22.7)	34 (44.7)	
Tobacco Use Present	31 (70.5)	38 (50.0)	0.026
Tobacco Use Absent	13 (29.5)	38 (50.0)	

Multivariate analysis demonstrated that advanced clinical stage, prolonged areca nut use, and tobacco consumption were independent predictors of epithelial dysplasia. Advanced OSMF stage exhibited the

strongest association with dysplastic transformation (OR=3.82, $p<0.001$), highlighting its importance as a clinical marker of malignant potential (Table V).

Table V. Multivariate logistic regression analysis for predictors of epithelial dysplasia in OSMF

Variable	Adjusted OR	95% CI	p-value
Clinical Stage III–IV OSMF	3.82	1.89–7.73	<0.001
Areca nut use >10 Years	3.27	1.54–6.96	0.002
Tobacco use	2.94	1.36–6.34	0.006
Mouth opening <25 mm	2.41	1.12–5.17	0.024
Chewing frequency >5 Times/Day	2.18	1.01–4.69	0.047

Among the 44 patients with epithelial dysplasia, mild dysplasia was the most frequently observed grade (47.7%), followed by moderate dysplasia (34.1%) and severe dysplasia (18.2%). These findings indicate that although most dysplastic lesions were detected at earlier stages, a considerable proportion had already progressed to advanced dysplastic changes requiring close surveillance and intervention (Table VI).

Table VI. Severity of dysplasia among histopathologically positive cases (n=44)

Dysplasia grade	Frequency (n)	Percentage (%)
Mild dysplasia	21	47.7
Moderate dysplasia	15	34.1
Severe dysplasia	8	18.2

DISCUSSION

In this cross-sectional study of 120 OSMF patients, 36.7% had histologically confirmed epithelial dysplasia. This prevalence is consistent with published literature, which reports epithelial dysplasia in approximately 30–45% of OSMF patients across different populations (16, 17). The results showed that there was a significant association between dysplasia and the clinical stage, increased areca nut consumption, increased frequency of chewing areca nut, concomitant tobacco use and decreased mouth opening (18,19). In multivariate analysis, these factors remained significantly associated with the outcome, with advanced clinical stage, areca nut use for over 10 years, tobacco use, mouth opening less than 25 mm and chewing frequency more than five times per day remaining significant. The results indicate that clinical severity and habit-related exposure are both factors in dysplastic transformation in OSMF (20,21).

The dysplasia in OSMF ranges from Stage I to Stage IV, with the severity increasing along with the potential for malignancy, which shows the close relationship between the severity of the disease and the potential for malignancy (22). Only 12.5% of the cases were detected as dysplasia in Stage I cases while 72.2% of Stage IV cases were detected as dysplasia. The pattern would indicate that the severity of fibrosis and/or mucosal restriction could be a sign of chronic epithelial damage and of chronic exposure to carcinogenic agents. Mouth opening was also significantly associated with reduced mouth opening, an association that may be accounted for by the fact that the presence of severe fibrosis may indicate a longer duration of disease and a more persistent mucosal damage (23,24). Thus, clinical staging and inter-incisal mouth opening should be taken into account as important indicators to identify high-risk OSMF patients to be subjected to biopsy and more frequent follow-up of these patients (25).

Habit related factors also had high associations with dysplastic changes. Areca nut consumers who have used the nut for over 10 years showed significantly higher levels of dysplasia than those who used it for less than 10 years. Likewise, higher risk was related to frequent chewing each day, indicating that duration and intensity of exposure resulted in an alteration of the epithelium (26,27). Alkaloids and other irritant constituents of the Areca nut have been found to stimulate collagen deposition and oxidative stress and epithelial injury. The risk of dysplasia further increased if tobacco use was also accompanied by areca nut chewing. The synergistic action may be attributed to the extra carcinogenic and inflammatory effect of tobacco that can accelerate the epithelial atypia and malignant transformation (28).

Dysplasia grades were distributed as follows: mild dysplasia most common, moderate, severe. Although most dysplastic lesions were detected at an earlier grade, almost a fifth of dysplastic lesions were

severe dysplasia. This is clinically significant as those with severe dysplasia have a greater likelihood of developing malignancy, and it is essential that they are actively monitored, along with the need for cessation counselling and timely intervention. Additionally, moderate and severe dysplasia were detected in some cases with clinically diagnosed OSMF, indicating the need for histopathological diagnosis and not just clinical diagnosis (29). Mild dysplasia predominated (47.7%), suggesting most OSMF patients present at an early stage of epithelial change, probably prompted by symptoms such as oral burning and restricted mouth opening. This early presentation enables intervention through habit cessation and monitoring before progression to higher-grade dysplasia and increased cancer risk.

There were some limitations in this study. Because of its cross-sectional design, it was not possible to establish causal relationships between risk factors and dysplastic transformation. The study was done in one tertiary care centre and may not be generalisable. Non-probability consecutive sampling can also cause selection bias. Furthermore, data regarding habits was self-reported; this could be influenced by recall bias. Histopathological assessment was performed by a single oral pathologist without inter-observer variability analysis. Additionally, the cross-sectional design precludes assessment of progression from dysplasia to malignancy. Although these are limitations, the use of histopathological assessment enhanced the validity of the detection of dysplasia.

There is a need for future studies with bigger multicentre cohorts and with long-term follow-up to identify the progression from OSMF to the appearance of oral squamous cell carcinoma. In addition to clinical predictors, molecular markers (e.g., Ki-67, p53, CD44) could be combined to further improve risk stratification (30). High-risk patients may be identified early along with cessation of the habits and regular surveillance with biopsy can help limit malignant transformation in OSMF.

CONCLUSION

The study found that epithelial dysplasia occurs among OSMF patients, and in more than one-third of such cases. Dysplastic changes were significantly associated with areca nut use at advanced clinical stage, tobacco use together with areca nut chewing, higher frequency of chewing and lower mouth opening. Advanced OSMF stage and areca nut use for over 10 years and tobacco use were important independent predictor variables. These risk factors, if recognized early, and followed with timely biopsy and frequent surveillance, may help to identify those at high risk and minimize malignant transformation. High-risk patients (Stage III/IV, areca nut use >10 years, tobacco use) should undergo surveillance every 6–12 months with low-threshold biopsy for any clinical change.

Conflict of interest:

The authors declare no conflict of interest.

Authors' contribution:

AE Conducted the study; WAR Conceptualized and analyzed data; RK Performed statistical analysis

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