International Clinical and Medical Case Reports Journal
Research Article (ISSN: 2832-5788)

Evaluation of Malignant Transformation of Oral Submucous Fibrosis into Oral Squamous Cell Carcinoma: A Prospective study

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Citation: *Dipanshu Kumar, Vijendra Kumar Suman, Inzamamul Haque, Shafi Ahmad, Amrita Bharti, Kaihkashan Zabin, et al. Evaluation of Malignant Transformation of Oral Submucous Fibrosis into Oral Squamous Cell Carcinoma: A Prospective study. Int Clinc Med Case Rep Jour. 2025;4(10):1-8.*

Received Date: 03 October 2025**; Accepted Date:** 04 October 2025**; Published Date:** 06 October 2025

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ABSTRACT

Background: Oral submucous fibrosis is considered as a chronic debilitating condition with potential for malignant transformation. Squamous cell carcinoma arising from a background of oral submucous fibrosis presents clinically as a distinct clinical disorder due to different etiopathogenesis.

Aim: To assess the transformation of OSMF into OSCC

Methodology: This prospective case series describes sixty cases of oral squamous cell carcinoma (OSCC) that developed alongside oral submucous fibrosis (OSF). Patient clinical data were recorded that included type and duration of habits, location of tumor, size, histological grading and nodal status.

Results: A total of 78% patients were found in males and 22% in females. A total of 74.4% patients had a history of use of gutka of which 16.1% used only arecanut or gutka while the remaining used gutka along with smoking and quid habits and 26.8% cases smoked tobacco products or used smokeless tobacco. Primary site of presentation was buccal mucosa and seven cases of carcinoma at retromolar trigone (RMT) altogether accounting for 66.1% of the cases. 53.4% cases reported were advanced tumour T4 lesions, 10.1% T3 lesion, 30.1% reported as T2 lesions and 6.8% T1 lesion. 55% of cases showed nodal involvement of different level and 46.6% cases were N0. About 60.1% of cases were histologically well differentiated squamous cell carcinoma.

Conclusion: Carcinoma arising from a background of oral submucous fibrosis follows a distinct clinical presentation. Malignant transformation occurs in younger age group and with better histological grading. Overall malignant transformation of OSMF to OSCC was 12.24%

Keywords: Clinical presentation; Malignant transformation; Oral submucous fibrosis; Squamous cell carcinoma

INTRODUCTION

Oral submucous fibrosis (OSF) is a potentially malignant disorder prevalent in India and South Asian countries apparently because of chewing arecanut. In 1952, Schwartz for the first time reported a case of "Atrophica idiopathica mucosae oris" occurring in Indians in East Africa [1,2]. First described this condition in India and coined the term OSF. The World Health Organization [3] subsequently defined OSF as "a slowly progressive disease in which fibrous bands form in the oral mucosa, ultimately leading to severe restriction of movement of the mouth, including the tongue."

Paymaster[4] first described the malignant potential of OSF in 1956. Since then, malignant transformation of OSF into oral squamous cell carcinoma (OSCC) has become a topic of interest. [5]substantiated the malignant potential of OSF using five main criteria:

i. A high frequency of OSMF in patients with oral cancer
ii. Increased prevalence of OSCC in patients with OSMF
iii. Histological diagnosis of SCC in patients without any obvious tumors in OSF
iv. High frequency of epithelial dysplasia
v. A higher incidence of leukoplakia among OSMF patients [6].

Rate of transformation varies from 3% to 19%. [7,8,9]After comparing the risk ratio, it has been estimated that people with OSF are 19.1 times more likely to develop oral cancer than those without it [10].

Oral cancer has distinct clinical presentation patterns depending on the etiologic factor.

OSF is associated with chewing of arecanut and arecanut has been declared as Group 1 carcinogen by the International Agency for Research on Cancer. [11] Patients with OSF changing into OSCC is described to have different morphology, histology, and biology because of a distinct molecular pathway for carcinogenesis. [12] In this paper, we discuss the clinical presentation, histological grading, and tumor stages of OSCC arising from a background of OSF.

It has been described that the carcinoma arising from OSF is a pathologically distinct disease, and the clinical course of progression is not clearly discussed in the literature. There is a need to investigate the various aspects of this entity that occurs in the background of OSF.

METHODS AND MATERIALS

This is a prospective case series selected consecutively. The study describes sixty cases with OSCC with the presence of OSF concomitantly. Cases with previous history of treatment and radiation therapy were excluded. A biopsy was done to confirm the diagnosis.

Patients' clinical data were recorded including type and duration of habits. Site of tumor, size, and nodal status were discussed and staged according to the AJCC (2004). Related data on histopathology were collected, and all

parameters were tabulated and analyzed. Mouth opening was measured in each patient by measuring the maximum interincisal opening.

The parameters analyzed were age of presentation of the tumor, gender distribution, and type of habit. The primary site of the tumor, clinical tumor classification, histological grading, and mouth opening at the time of presentation were analyzed.

RESULTS

The mean age of presentation was 45.6 years with two cases reported <30 years, most patients in their late 40s . Seventy eight percent of the cases occurred in males and 22% in females.

Table 1: Age distribution

Age (years)		**Frequency (%)**			
<30		4			
30-39		14			
40-49		24			
50-59		12			
60-69		6			
Total		60			
n	**Mean**	**SD**	**Median**	**Minimum**	**Maximum**
60	45.6	9.79	45.5	29	68

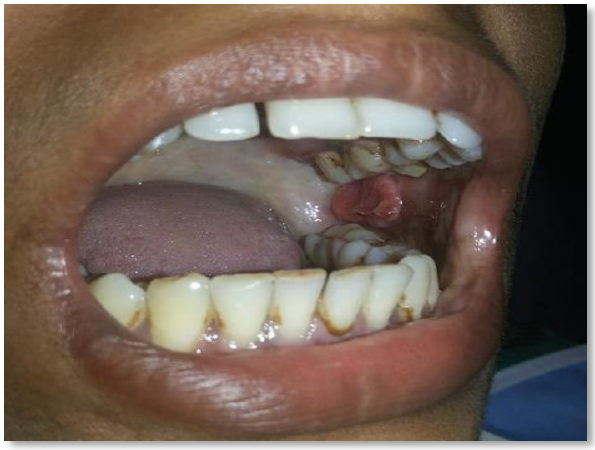

Figure 1: Proliferative lesion at the buccal mucosa

About 74.4% of the cases had a history of use of gutka, of which 17% of them were only arecanut or gutka users and the remaining were using gutka along with smoking and quid habits, and 27.8% of the cases were smoking and smokeless tobacco use **(Table 2)**.

Table 2: Type of habits in the study group

Habits	Frequency (%)
Arecanut	6
Gutka	8
Gutka + quid	2
Gutka + quid	2
Gutka + tobacco	6
Gutka + alcohol	2
Quid	2
Quid + arecanut	4
Gutka + smoker + alcoholic	2
Gutka + smoker	14
Gutka + smoker + pan	2
Gutka + smoker + tobacco	2
Tobacco + smoker + arecanut	4
Tobacco + smoker + alcoholic	4
Total	60

In 26 cases, the primary site of presentation was the buccal mucosa and seven cases of carcinoma at the retromolar trigone (RMT) , together accounting for 66.1% of the cases. Eight cases presented with carcinoma of gingivobuccal sulcus, excluding four of buccal mucosal lesions involving gingivobuccal sulcus. Two case reported was carcinoma of the floor of the mouth and one case of the lip.

About 54.4% of the cases reported as advanced tumor T4 lesions, 10% T3 lesion, 30.1% reported with T2 lesions, and 6.8% T1 lesion. Fifty-five percent of the cases showed nodal involvement of different levels and 46.5% of the cases were N0.

Sixty percent of the cases were histologically well-differentiated squamous cell carcinoma, 27.8% of the cases of moderately differentiated OSCC, 6.8% of the cases of poorly differentiated carcinoma, and 6.8% of the cases were carcinoma in situ.

Interincisal mouth opening reported from a minimum of 8 mm up to 35 mm. The degree of mouth opening and tumor stage compared had no significant relation between them **(Table 3)**. Generally, patients with reduced mouth opening presented with an advanced stage of tumor.

Table 3: Tumor size and interincisal mouth opening

	n	**Mean**	**SD**	**Minimum**	**Maximum**	***F***	***P***
T1	4	30.11	7.082	26	36	1.075	0.378
T2	16	23.61	9.938	13	41		
T3	6	23.78	6.221	17	29		
T4	32	19.42	8.257	9	36		
n	**Mean**	**SD**	**Median**	**Minimum**	**Maximum**		
58	22.39	8.621	21.11	9	80		

DISCUSSION

Oral cancers arising in OSF are said to constitute a clinicopathologically distinct disease, and morphologic, histological differences are attributed to the differential mechanisms of the carcinogenesis of areca nut. [13] It has been estimated that people with OSF are 19.1 times more likely to develop oral cancer than those without it, after adjusting for other risk factors. [10] reported 1.9% malignant transformation in OSF and 5.4% malignant transformation in patients with OSF and epithelial dysplasia. [14] In a large study of 5071 patients from Taiwan, Wang *et al.* have reported malignant transformation rate of 3.75% in OSF patients and also noted that malignant transformation is more common in male patients than in female patients. [8]

Age is an influencing factor in the development of oral cancer. In our study, the mean age of presentation was 44.5 years. Oral cancer in OSF has been described to occur in younger males, and early development of OSF accelerates progression into malignant transformation to OSCC. [12] Recent meta-analysis has shown the average age of OSF patients with oral cancer to be 48.78 years. [15]

In our study, 76% of the cases were male, which can be compared to other studies and predominantly can be attributed to adverse habits more common in men. [9,16] On the contrary to our study, a Pakistani study has reported 4 times more transformation in females than in males. [17] They documented that young females consumed betel nut more frequently and graduating to more toxic varieties as they grew with locally available ingredients, hence higher malignant transformation compared to males.

Arecanut has been proven as an etiologic agent for OSF and Class 1 carcinogen which might contribute to early development of OSCC in younger age group. Gutka was the most common habit recorded in this present study, and 73.3% of the cases were chewing arecanut in this form. About 13.3% of the cases were using arecanut alone and others with quid keeping habit. About 34.3% of the cases were smokers in the group and 13.3% smokers and alcoholics. The relative risk of the habit is difficult to assess because of combination of ingredients in gutka preparations and varied chewing habits. [18] A case–control study proves the synergistic effects of smoking, betel quid chewing, and alcohol consumption on risk of malignant transformation of OSF to OSCC with odds ratio of 13.3 for betel chewing, 5 for smoking, and 3.1 for alcohol consumption. [19]

Gingivobuccal complex that is buccal mucosa, RMT, and gingivobuccal sulcus was the most common occurrence (in total), and only buccal mucosa accounted for 38.3% as reported by Chaturvedi *et al.* [20] They also reported that carcinoma of the tongue was more common in patients with OSF compared to oral cancer without submucous fibrosis ($P = 0.003$). Similar to this study, our study showed 28 of 30 cases to occur in gingivobuccal complex, but we did not observe carcinoma of the tongue in any of the cases. Four cases had the second primary on the soft palate and floor of the mouth. This can be attributed to quid keeping habit and more constant trauma due to the third molars. A study of 5071 patients by Wang *et al.* has shown 53.43% involvement of the buccal mucosa in malignant transformation of OSF. [8] OSF is associated with malignant transformation more commonly in the buccal mucosa because that is the region stimulated by arecanut. [21,22] Chronic mucosal inflammation may be a contributing factor in case of OSF as it exposes the deeper tissue to the carcinogen. Retromolar area and buccal mucosa are highly prone for such inflammation because of the third molars. [23]

OSCC cases clinically presented with ulceroproliferative lesion, suggesting more of exophytic growth. Five cases of exophytic verrucopapillary lesion in the background of OSF have been reported,[24] which histologically showed only dysplasia without deeper invasion despite the large size of the lesions. The authors hypothesize that abnormal bundles of collagen may resist the process of invasion.

Simultaneous occurrence of leukoplakia and OSF leads to a higher risk of malignant transformation to squamous cell carcinoma compared to OSF alone. [25] Eleven of thirty cases had leukoplakia concurrent with OSF in our study. The malignant transformation risk for the group with epithelial dysplasia was 1.89 times more than those without epithelial dysplasia as described by Wang [8] Hsue [14]found 5.4% malignant transformation in patients with epithelial dysplasia with OSF compared to 1.9% in OSF without epithelial dysplasia.

About 53.3% of the cases presented as T4 lesions with involvement of the pterygomandibular space or mandible. Ten percent of the cases were with T3, 30% with T2, and 6.7% of the cases with T1 lesion, suggesting that late presentation of these cases may be attributed to failure to observe the area due to restricted mouth opening. In 46.5% of our cases, there was no nodal involvement.

Although there is no statistical difference between the grade of the tumor and mouth opening in our cases, mouth opening ranged between 8 mm and 40 mm, with mean mouth opening of 21 mm. T4 lesions had a severe reduction in mouth opening. Our study is comparable to Chourasia *et al.* [9] with similar presentation. The consistency of tissues involved in OSF masks the induration, the early sign of carcinoma.

Histologically, 60% of the cases were well-differentiated squamous cell carcinoma. OSCC in the background of OSF is said to be clinicopathologically distinct entity with better grade of differentiation and less nodal metastasis and early clinical stage detection and better prognosis. The lesser incidence of nodal metastasis is explained by blockage of submucosal lymphatics by fibrosis and reduced submucosal vascularity. [12] suggested that during carcinogenesis, the epithelial cells may retain the genetic memory of differentiation leading to better tumor grade. [26] According to Chaturvedi *et al.*, [12] most malignant transformations occur in younger males with better prognostic features: Better grade of tumor differentiation, lower incidence of nodal metastases, and less extracapsular spread.

On the contrary, another study has described OSCC with OSF to be clinically more invasive with higher metastasis and recurrence rate. [27] Gadbail *et al.* [28] described OSCC with OSF as a distinctive tumor, as well-differentiated tumor indicating less rapid growth less metastasis, fewer chances of postoperative recurrence hence better prognosis and survival rate.

CONCLUSION

Carcinoma arising in the background of OSF follows a distinct clinical presentation, usually missed at early diagnosis. Exophytic lesion arising in cases of OSF should raise the suspicion of squamous cell carcinoma. There is a need for multicentric study to understand OSCC arising from OSF as different molecular mechanism and clinical entity.

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