

# Oral Submucous Fibrosis - Correlation between Clinical Findings and Histopathological Grading

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## ABSTRACT

### Introduction

Oral Submucous fibrosis (OSMF) occurs in young adults, who are in the habit of chewing tobacco mixed with areca nut and its various commercially available preparations. The disease results in progressive inability to open the mouth due to the submucosal fibrosis initiated by chronic inflammation affecting mainly oral mucosa. Authors undertook the present study to correlate the clinical features of OSMF to histopathological features and to find out aetiopathological factors of this condition.

### Materials and Methods

A total of 123 clinically diagnosed OSMF patients, in the age range of 17 to 70 years were studied. Mouth opening was measured using a scale and was recorded in millimeters. Incisional biopsy was taken from the representative areas in the oral cavity. The patients were graded clinically and histopathologically and results were analyzed and discussed.

### Result

Most of the patients were in the age group of 20-30 years (37.4%) with male predominance. The duration of either tobacco or areca nut chewing ranged from 1 to 35 yrs. Most patients had these habits for 6-19 yrs. Majority (55.3% & 54.5%) of the patients belonged to grade-2 (clinical grading) and intermediate grade (HPE grading) respectively. The HPE grading showed significant and direct association with duration of ill habits. The HPE grading showed significant and direct association with clinical grading ( $\chi^2=204.08$ ,  $p<0.001$ ).

### Discussion

The HPE grading showed significant and direct association with duration of ill habits and also with clinical findings of restriction of mouth opening and inter incisal distance. The HPE findings showed significant and direct association with clinical grading i.e. when the clinical grading increases, the histopathological grading also increases.

### Conclusion

OSMF is a disease with a high incidence. It also carries a significant risk of transformation to oral cancer. As no effective medical and surgical treatment is available for this condition; it is desirable to diagnose OSMF at early stages.

### Keywords

Oral Submucous fibrosis

Oral submucous fibrosis (OSMF) is a chronic debilitating disease, which is characterized by mucosal rigidity of varying intensity due to fibroblastic changes of the juxta-epithelial layer, resulting in a progressive inability to open the mouth. It predominantly occurs in Indians and South East Asians. It mainly affects oral cavity and sometimes the pharynx and oesophagus.

The World Health Organization (WHO) defines precancerous oral lesion as "A generalized pathological state of the oral mucosa associated with a significantly increased risk of cancer." The characteristics of OSMF

comply well with the above definition.<sup>1</sup>

Over the past several years, many researchers studied different aspects of OSMF and gave their results to enrich the medical literature regarding the aetiopathogenesis and

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natural history of the disease. The evidence can be found in the form of simple case reports, population-based studies or hospital-based case control studies. With the advent of better diagnostic facilities, histopathological studies and scanning electron microscopy were also done by different authors.<sup>2</sup> Along with this animal experiments, in vitro human fibroblast culture studies and many Randomised Controlled Trials were carried out to analyze the effectivity of various management options available for OSMF.<sup>3</sup> However, there is a paucity of studies which correlate the clinical features to the various histopathological changes of OSMF. The present study was undertaken to correlate the clinical features of OSMF to histopathological features and to find answers to the questions of aetiopathogenesis of oral sub mucous fibrosis.

### Materials and Methods

The study was conducted from September 2014 to August 2015 at a tertiary care center in northern India. The study population consisted of clinically diagnosed OSMF patients attending the Outpatient department of Department of ENT & Head-Neck Surgery, who gave consent for biopsy. Individuals having habit of chewing commercially available areca nut and tobacco preparations (Gutkha) and using tobacco alone and having clinically confirmed oral submucous fibrosis were included in the study. Individuals not fit for biopsy or not giving informed consent and patients with associated illness (hypertension, myocardial infarction, renal, hepatic, pancreatic and pulmonary diseases) were excluded from the study.

A total of 123 clinically diagnosed OSMF patients who came for management of symptomatic OSMF were studied. Their ages ranged from 17 to 70 years, including both males and females. History of habits, including duration of use in months, duration of symptoms, oral mucosal sites of involvement, maximal mouth opening, tongue protrusion were recorded in a structured proforma designed for the study. Mouth opening was measured as the inter-incisal distance from the mesioincisal edge of the upper left central incisor tooth to the mesioincisal edge of the lower left central incisor tooth. Measurements were made using a scale

and recorded in millimeters.

The patients were graded clinically according to the following grading which was devised by Ranganathan K et al.<sup>4</sup>

**Group I:** Only symptoms, with no demonstrable restriction of mouth opening

**Group II:** Limited mouth opening 20 mm and above.

**Group III:** Mouth opening less than 20 mm.

**Group IV:** OSMF advanced with limited mouth opening. Precancerous or cancerous changes seen throughout the mucosa.

Incisional biopsy was taken from the representative areas in the oral cavity i.e. the fauces or retromolar trigone area under local anaesthesia; the areas where changes of OSMF occur early and prominently. Biopsy is taken deep enough to include the underlying changes of surface lesion. The biopsy tissue was processed and stained using H&E stains. The sections were studied under a binocular light microscope. The histopathological grading was done according to following classification given by Utsunomiya, Tilakaratne et al.<sup>5</sup>

**Early stage:** Large number of lymphocytes in sub-epithelial zone and connective tissue, along with myxedematous changes.

**Intermediate stage:** Granulation changes close to the muscle layer and hyalinization appears in sub-epithelial zone, where blood vessels are compressed by fibrous bundles. Reduced inflammatory cells in sub-epithelial layer.

**Advanced stage:** Inflammatory cell infiltrate hardly seen. Number of blood vessels dramatically low in subepithelial zone. Marked fibrous areas with hyaline changes extending from sub-epithelial to superficial muscle layers. Atrophic, degenerative changes start in muscle fibres.

**Statistical analysis:** Continuous data were summarized as Mean  $\pm$  SD (standard deviation) while discrete (categorical) in number and percentage. The categorical groups were compared by chi-square ( $\chi^2$ ) test. Pearson correlation analysis was used to assess association between the variables. A two-tailed ( $\alpha=2$ ) p value less than 0.05 ( $p<0.05$ ) was considered statistically significant. All analyses were performed on SPSS

software (Windows version 17.0).

**Result**

*I. Demographic characteristics:*

The frequency distribution of demographic characteristics (age, sex and location) of OSMF patients was studied. The age of patients ranged from 17 to 70 yrs with mean ( $\pm$  SD)  $33.91 \pm 11.21$  yrs and median 30 yrs. Most of the patients were in the age group of 20-30 yrs (37.4%) followed by 30-40 yrs (30.9%), 40-50 yrs (16.3%),  $\geq 50$  yrs (11.4%) and 10-20 yrs (4.1%). Among them, 79.7% were males and 20.3% were females. Further, 66.7% patients belong to rural background and 33.3% from urban background.

*II. Ill habits:*

It is clear that most of the patients are in habit of chewing commercially prepared areca nut preparation commonly known as pan masala or Gutkha (Table I).

**Table I: Frequency distribution of ill habits of OSF patients (n = 123)**

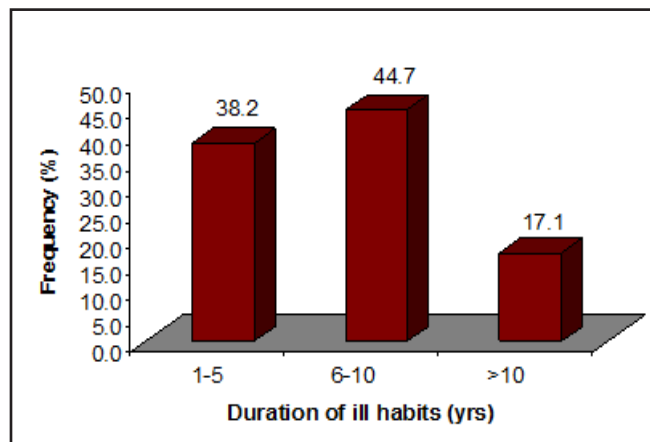
ILL HABITS	NO. OF PATIENTS WITHOUT HABIT (IN %)	NO. OF PATIENTS WITH HABIT (IN %)
Pan masala	30 (24.4)	93 (75.6)
Gutkha	34 (27.6)	89 (72.4)
Tobacco	35 (28.5)	88 (71.5)
Alcohol	93 (75.6)	30 (24.4)

*III. Duration of ill habits:*

The duration of either ill habit ranged from 1 to 35 yrs. Most patients had these ill habits for 6-19 years. (Fig. 1)

*IV. Clinical Findings:*

The frequency distribution of Clinical findings (restriction of mouth opening and inter incisal distance)



**Fig. 1. Distribution of duration of ill habit of OSMF patients.**

of OSMF patients are summarized in Table II. It can be observed that most patients had 2 finger opening only. Similarly, the inter incisal distance of patients ranged from 5 to 48 mm of which most number of patients i.e. 40 (32.5%) were found having had 20-30 mm of inter incisal distance.

*V. Clinico-pathological findings:*

The frequency distribution of clinical and HPE grading of OSMF patients are summarized in Table III. Majority (55.3% & 54.5%) of the patients belonged to clinical grade-2 and intermediate HPE grade respectively. 23 patients (18.7%) had clinical grade 1, 68 (55.3%) had clinical grade 2, 25 (20.3%) had clinical grade 3 and 7 patients (5.7%) had clinical grade 4. Similarly, 26 (21.1%) patients had early HPE grade, 67 (54.5%) had intermediate HPE grade and 30 (24.4%) had advanced HPE grade.

*VI. Association of HPE with ill habits of OSMF patients:*

The association of HPE findings (grading) with ill habits of OSMF patients is summarized in Table IV. The HPE grading showed significant and direct association with duration of ill habits ( $\chi^2=11.88$ ,  $p=0.018$ ).

*VII. Association of HPE with clinical findings of OSMF patients:*

The association of HPE findings (grading) with Clinical

**Table II: Frequency distribution of clinical findings of study group**

CLINICAL FINDINGS	NO. OF PATIENTS (N = 123) (%)
<b>Restriction of mouth opening (no of fingers)</b>	
1	24 (19.6)
2	61 (49.6)
3	38 (30.9)
<b>Inter incisal distance (mm)</b>	
<10	5 (4.1)
10-20	22 (17.9)
20-30	40 (32.5)
30-40	26 (21.1)
≥ 40	30 (24.4)

Findings (restriction of mouth opening and inter incisal distance) of OSMF patients was seen (Table V) and they were found significantly associated to both restriction of mouth opening ( $\chi^2=181.66$ ,  $p<0.001$ ) and inter incisal distance ( $\chi^2=206.76$ ,  $p<0.001$ ).

#### *VIII. Association of HPE with clinical grading of OSMF patients:*

The association between HPE grading and clinical grading of OSMF patients is summarized in Table VI. The HPE grading showed significant and direct association with clinical grading ( $\chi^2=204.08$ ,  $p<0.001$ ).

#### **Discussion**

OSMF, a crippling disease of the oral mucosa, evokes the interest of medical professionals in different parts of the world. The peculiarity of the disease is that it is

**Table III: Frequency distribution of clinico-pathological grading among OSMF patients**

CLINICO-PATHOLOGICAL GRADING	NO. OF PATIENTS (N=123) (%)
<b>Clinical grading:</b>	
Grade 1	23 (18.7)
Grade 2	68 (55.3)
Grade 3	25 (20.3)
Grade 4	7 (5.7)
<b>HPE grading:</b>	
Early	26 (21.1)
Intermediate	67 (54.5)
Advanced	30 (24.4)
≥ 40	30 (24.4)

confined to a particular geographic region. The present study is undertaken to correlate the chewing habits, its duration and the ability to open one's mouth to various histopathological changes of OSMF. A total of 123 symptomatic patients of either sex were recruited and evaluated.

The primary objective of the study was to correlate histo-pathological findings (grading) with demographic criteria (age, sex and location), ill habits (pan masala, gutkha, tobacco, alcohol and duration), clinical findings (restriction of mouth opening and inter incisal distance) and clinical grading.

Of the 123 cases of OSMF studied, 79.7% were males and 20.3% were females. Some of the epidemiological surveys in India have shown a female predominance in the occurrence of this entity. A male predominance in OSMF cases was shown by others.<sup>6</sup> We also observed a male predominance with male to female ratio of 4:1.

Table IV: Association of HPE with ill habits of OSMF patients

ILL HABITS	N	HPE GRADING			$\chi^2$ VALUE	P VALUE
		EARLY (N=26) (%)	INTERMEDIATE (N=67) (%)	ADVANCED (N=30) (%)		
<b>Pan masala:</b>						
No	30	6 (20.0)	19 (63.3)	5 (16.7)	1.57	0.457
Yes	93	20 (21.5)	48 (51.6)	25 (26.9)		
<b>Gutkha:</b>						
No	34	10 (29.4)	16 (47.1)	8 (23.5)	2.01	0.366
Yes	89	16 (18.0)	51 (57.3)	22 (24.7)		
<b>Tobacco:</b>						
No	88	18 (20.5)	49 (55.7)	21 (23.9)	0.19	0.911
Yes	35	8 (22.9)	18 (51.4)	9 (25.7)		
<b>Alcohol:</b>						
No	93	20 (21.5)	52 (55.9)	21 (22.6)	0.68	0.711
Yes	30	6 (20.0)	15 (50.0)	9 (30.0)		
<b>Duration (yrs):</b>						
1-5	47	14 (29.8)	29 (61.7)	4 (8.5)	11.88	0.018
6-10	55	8 (14.5)	29 (52.7)	18 (32.7)		
>10	21	4 (19.0)	9 (42.9)	8 (38.1)		

The age of patients ranges from 17 to 70 yrs. This observation is different from another study which reported most common age group to be 40 to 49 years in their study.<sup>7</sup> Increase in the chewing habit of the areca nut without any tobacco and the use of various commercial products containing areca nut may explain the decrease in the age of OSMF cases due to various chewing habits.

Correlating the HPE grading with demographic characteristics,  $\chi^2$  test revealed insignificant ( $p>0.05$ ) association between demographic characteristics and HPE finding except sex. In females, the frequency (%) of intermediate and advanced HPE finding were significantly higher (21.5%) as compared to males.

This is due to the fact that females are associated with nutritional deficiencies which are responsible for their intermediate and advanced stages.

More (66.7%) patients belong to rural background than urban background (33.3%). This is mostly due to the illiteracy among rural people and due to lack of health education and awareness of the ill-effects of the chewing habits. People in the urban background indulge in those habits due to peer pressure, misguiding by the social media. In recent years, commercial preparations like pan masala have become available in India and abroad. The main ingredient of these products is areca nut along with lime and catechu with or without tobacco. Many patients with OSMF give a history of chewing

Table V: Association of HPE with clinical findings of OSMF patients

CLINICAL FINDINGS	N	HPE GRADING			X <sup>2</sup> VALUE	P VALUE
		EARLY (N=26) (%)	INTERMEDIATE (N=67) (%)	ADVANCED (N=30) (%)		
Restriction of mouth opening (no of fingers):						
1	12	0 (0.0)	1 (8.3)	11 (91.7)	181.66	<0.001
1.5	12	0 (0.0)	1 (8.3)	11 (91.7)		
2	61	0 (0.0)	53 (86.9)	8 (13.1)		
2.5	10	0 (0.0)	10(100.0)	0 (0.0)		
3	28	26 (92.9)	2 (7.1)	0 (0.0)		
Interincisal distance (mm):						
<10	5	0 (0.0)	0 (0.0)	5 (100.0)	206.76	<0.001
10 - 20	22	0 (0.0)	0 (0.0)	22 (100.0)		
20 - 30	40	0 (0.0)	37 (92.5)	3 (7.5)		
30 - 40	26	0 (0.0)	26 (100.0)	0 (0.0)		
≥ 40	30	26 (86.7)	4 (13.3)	0 (0.0)		

Table VI: Association of HPE with clinical grading of OSMF patients

CLINICAL FINDINGS	N	HPE GRADING			X <sup>2</sup> VALUE	P VALUE
		EARLY (N=26) (%)	INTERMEDIATE (N=67) (%)	ADVANCED (N=30) (%)		
Grade 1	23	22 (95.7)	1 (4.3)	0 (0.0)	204.08	<0.001
Grade 2	68	4 (5.9)	64 (94.1)	0 (0.0)		
Grade 3	25	0 (0.0)	2 (8.0)	23 (92.0)		
Grade 4	7	0 (0.0)	0 (0.0)	7 (100.0)		

pan masala, gutkha, tobacco.

In our study group, the patients mostly had the habit of chewing commercial areca nut products (Pan masala and Gutkha). The duration of either ill habit ranged from 1 to 35 yrs. On correlating, the HPE findings were not found to be associated ( $p>0.05$ ) with types of ill habits,

however HPE grading showed significant and direct association with duration of ill habits ( $\chi^2= 11.88$ ,  $p = 0.018$ ).

In our study, it was observed that as the duration of the chewing habits increases, the histopathological grading also increases. Another study noted opposing

observation, stating that the total duration of the chewing habit was not significantly correlated to OSMF.<sup>8</sup> A similar observation was also reported in another study that the daily consumption rate appears to be much more significant with respect to risk than the lifelong duration of the habit.<sup>9</sup>

It is well-documented that in OSMF, there is a progressive inability to open the mouth and tongue movement gets restricted to varying degrees depending on the severity of the disease process. In a study of 800 normal patients in South India, it is reported that the average size of the mouth opening was 47.5 mm and 44.6 mm in males and females respectively.<sup>4</sup>

Based on inter-incisal distance, we grouped our OSMF patients into four clinical grades. Most of the patients had inter-incisal distance of 20-30 mm followed by 40 mm. This is due to the fact that the majority of patients usually report late for treatment as the symptoms in earlier stage of disease are very subtle. So most of the patients are in clinical grade 2 (68) followed by grade-3 (25), grade-1 (23) and grade-4.

It can be seen from above findings that 37.4% of the total study population was in the age group of 20-30 years and 55% of the patients are in Grade II who had a habit of chewing commercially available areca nut products (Pan masala and Gutkha). These findings are of great concern because younger individuals are at greater risk and it has been well established that OSMF is a premalignant and crippling condition of the oral mucosa.<sup>7</sup>

In our study, 26 (21.1%) patients had early HPE grade, 67 (54.5%) had intermediate HPE grade and 30 (24.4%) had advanced HPE grade. The HPE finding showed significant and direct association with clinical grading ( $\chi^2 = 204.08$ ,  $p = 0.001$ ). Similar findings were shown in another study which concluded that the bands formed initially in the fauces, followed by the buccal and labial areas.<sup>10</sup> Another study did not find any association between clinical staging and histopathological grading.<sup>11</sup>

This is accompanied by an increase in the severity of the disease as measured by restriction in the ability to open the mouth. It has been postulated that areca nut products exacerbate the submucosal fibrosis initiated by chronic inflammation. The inflammatory cells seen

predominantly were lymphocytes and plasma cells. The presence of a large number of lymphocytes and the production of cytokines play significant roles in the tissue reaction in OSMF.<sup>12</sup> In our study, all three histological grades had diffuse chronic inflammation as a common feature, it shows a reduced presence in advanced stage as a result of the stabilization of the lesion and reduction in levels of pro-inflammatory mediators.

## Conclusion

In our study, the occurrence of OSMF was higher in the younger age group of 20-30 years. The prevalence of OSMF was more in males than in females with a ratio of 4:1 hence showing a significant association of HPE grading with sex. In females, the occurrence of intermediate and advanced HPE findings were significantly higher (21.5%) as compared to males. In our study, most patients were found to be having clinical grade 2 followed by grade 3, grade 1 and grade 4. The commonest histo-pathological grade was intermediate followed by advanced and early grade. The HPE grading showed significant and direct association with the duration of ill habits of chewing pan masala and Gutkha.

The HPE findings were also found significantly associated to both severity of restriction of mouth opening and inter incisal distance. The HPE findings showed significant and direct association with Clinical grading i.e. when the Clinical grading increases, the Histopathological grading also increases. The findings of this study will help to enable clinicians, involved in the management of OSMF patients, to formulate better treatment for their patients. As higher clinical grade is found to be associated with advanced histopathological grade, patients of that group may be advised strict follow up and treatment, so that these patient can be saved from advancing to malignancy.

OSMF is a disease with a high incidence which also carries the risk of significant morbidity from oral cancer. As no effective medical and surgical treatment is available for this condition it is desirable to diagnose and provide the management of OSMF at early stages. Patient should be advised about cessation of the areca nut and Gutkha chewing and other factors should

be advised. Intervention studies and public health awareness program linked with OSMF may prove the best way to control disease process at the community level.

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