Research Paper

A novel histological grading system for minor salivary gland involvement in oral submucous fibrosis patients with clinico-pathological validation

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ABSTRACT

Background: The involvement of minor salivary glands (MSGs) with fibrosis in oral submucous fibrosis (OSMF) pathology is a quite conceivable fact. However, very little attention has been given to the status of MSGs in OSMF.

Methodology: Total 53 cases of OSMF were recruited and demographic details, mouth opening, clinical oral dryness score (CODS), and buccal mucosal MSG flow rate were determined. The fibrosis around MSGs is categorized into three grades and compared with relevant clinicopathological parameters.

Results: Out of total 53 OSMF patients, there were 15 patients in grade I MSG involvement with fibrosis followed by 24 and 14 patients in grade II and grade III, respectively. Grade I MSG involvement showed maximum mouth opening (32 ± 3.87 mm) followed by Grade II (19.85 ± 4.31 mm) and Grade III (11.42 ± 5.21 mm) and the differences between them were statistically significant. The CODS score was more in grade III (5.5 ± 1.09 mm) as compared to Grade II (4.04 ± 0.62 mm) and Grade I (2.46 ± 0.74 mm) involvement of MSG. The flow rate was more in grade I (8.02 ± 2.99 mm) as compared to Grade II (3.97 ± 1.09 mm) and Grade III (3.4 ± 0.87 mm) involvement of MSG.

Conclusion: The fibrosis associated with OSMF can affect the MSGs located at mucosal and sub-mucosal levels. The clinical determinants such as mouth opening, salivary flow rate, and CODS corroborate with the grading of the degree of MSG involvement with fibrosis.

1. Introduction

Minor salivary glands (MSGs) are an integral part of the oral cavity and play a vital role in maintaining homeostasis in the oral cavity.¹ They are 400–500 in numbers and distributed in almost all the areas of the oral cavity except the gingiva and anterior part of the hard palate. Histologically, they are located in mucosal and sub-mucosal locations of the oral mucosa, and buccal and labial MSGs are specifically very close to stratified squamous epithelium.² Hence, it is quite conceivable that any pathology affecting the stroma of mucosa and sub-mucosa inadvertently involves MSGs as well.

Oral submucous fibrosis (OSMF) is a potentially malignant disorder with a high malignant transformation rate and compromised oral health-related quality of life.^{3,4} It is characterized by the deposition of dense bundles of collagen and sometimes hyalinization in the oral

mucosa. The other characteristic features include atrophic oral epithelium, loss of rete ridges, and juxta epithelial chronic inflammatory reaction.⁵ OSMF has undergone a lot of evolution in terms of grading the severity of the disease.⁶ Both clinical and histopathologic parameters have been part of the variety of grading systems proposed to date. Especially in histopathology parameters, the degree of fibrosis in the mucosa and submucosa, and around the blood vessels have been given due consideration.⁷ However, enough attention has not been given to the MSGs, which are a very vital part of the oral mucosa.

It is a well-known fact that as the OSMF disease progresses, the fibrosis increases in intensity and causes the involvement of deeper areas of sub-mucosa.⁷ Hence, it was quite conceivable to envisage the MSG involvement with the fibrosis from the OSMF. The involvement of MSGs in the OSMF has already been studied in the literature and was linked to the burning sensation and atrophy of the stratified squamous epithelium

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of the oral mucosa.⁸ Due to the vital importance of MSGs, it is imperative to grade the MSG fibrosis in OSMF patients for more elucidating the pathogenesis aspect and future development of therapeutics.

With this view in mind, the present study was designed to investigate MSGs histologically and establish a novel grading system that would be supported by correlation analysis with mouth opening, clinical oral dryness score (CODS), and MSG flow rate.

2. Materials and methods

The institutional ethics committee and university research and recognition committee approved the present study (DYPC/EC/99/18). Total 53 OSMF cases were recruited in the present study. The clinical criteria given by Pindborg et al.⁹ were used for the diagnosis. Before the incisional biopsy, all the demographic data and required clinical data were collected from the patient. The inter-incisal distance was measured using vernier caliper for obtaining the mouth opening measurement in millimeters. After obtaining all the demographic and clinical data, an incisional biopsy was performed on buccal mucosa using a 6 mm diameter punch under local anesthesia.

2.1. The clinical oral dryness score

To establish the quantitative measure for the dryness, CODS was used, which is based on the 10-point scale with each question expressing the dryness in the oral cavity.¹⁰ This questionnaire is well-established on the scientific ground after all the mandatory validation protocols. There are 10 well-defined questions and a score of 1 is given to each question. For statistical analysis, all the scores were added and a total score was determined. A high total score indicates increased severity of oral dryness. All the scores were given by the examiner (YI) based on the features observed in the patients' oral cavity and finally derived a score of 0–10.

2.2. Measurement of minor salivary gland secretion

Saliva collection was performed between 8:00 and 10:00 a.m. Subjects were instructed not to smoke, eat, drink, or perform any oral hygiene procedures for at least 2 h before the measurements. Nevertheless, the individuals were instructed to drink 300 ml of water 2 h preceding saliva collections to avoid the variability in the hydration of the body which could affect the results. In cases with bilateral involvement, the side showing more fibrosis was taken for measurement of MSG secretion.

Cotton rolls were placed on Stensen's duct area to absorb the saliva from the parotid glands which could have influenced the results. Thereafter, the minor salivary gland regions were carefully dried with compressed air, and subsequently, the examiners placed a pre-weighed Schirmer's test strip. To avoid unwanted stimulation, strip positioning was gentle, with no finger or instrument pressure. The strip remained in place for 1 min and then, upon removal, it was immediately weighted again to avoid weight loss from evaporation. The net weight was obtained by calculating the difference between the second and the first weights (Fig. 1).

2.3. Calculation of salivary secretion

The weighing method was performed to assess salivary flow and an electronic balance was used for this purpose. Considering that each 1-g corresponds to 1 mL of saliva,¹¹ the difference in weight of the vial collection, before and after sampling, divided by the period time used, given the values. The samples of the saliva of each participant were performed in a single session.

As the total area covered by the strip was 3.5 cm², the value of the secretion rate will be divided by 3.5 to get the salivary flow rate per cm². The unit of measurement will be expressed in microliter per square

Fig. 1. Placement methodology for Shrirmer's strip on buccal mucosa of oral submucous fibrosis patient for estimation of salivary flow rate.

centimeter per minute ($\mu\text{L}/\text{cm}^2/\text{min}$).

2.4. Grading for the involvement of MSG with OSMF

The biopsy site for all the cases was buccal mucosa and hence, the entire analysis was for buccal MSGs. We observed fibrosis around the MSGs (peri-glandular) in all the cases while twenty cases showed fibrosis within the gland and surrounding the acini (intra-glandular). We also observed variation in the degree of fibrosis around the MSGs and categorized them into mild, moderate, and severe fibrosis. The criteria given by Ranganathan et al.⁷ was used to categorize the degree of fibrosis around MSG. To finalize the grading system for MSG involvement in OSMF, we considered two important points: 1) location of fibrosis (peri-glandular and/or intra-glandular) and 2) degree of fibrosis (mild, moderate, or severe) and developed a novel grading system. Further details of the classification are given in Table 1. Two investigators (YI and GS) performed the grading and any disagreement was solved by consultation with a third investigator (SS) until the consensus were reached (Fig. 2).

2.5. Statistical analysis

Mean and standard deviation was used to summarize the CODS, mouth opening, salivary flow rate, and other demographic data. The mean CODS, mouth opening, and salivary flow rate of different MSG involvement grades were compared with the use of one-way ANOVA and Tukey test (post hoc comparisons). All of the analyses were carried out with SPSS version 17.0 and the significance of all the tests was set at a p-value less than 0.05.

Table 1		
Grading for involvement of minor salivary gland in oral submucous fibrosis.		
Grade	Histopathology parameters	Number
I	Peri-glandular + mild fibrosis	15
II	Peri-glandular + moderate fibrosis/intra-glandular + mild fibrosis	24
III	Peri-glandular + severe fibrosis/intra-glandular + moderate to severe fibrosis	14

Fig. 2. Photomicrograph showing various grades of minor salivary gland involvement in oral submucous fibrosis patient: (A) Normal glandular architecture without fibrosis; (B and C) Mild minor salivary gland involvement; (D, E and F) Moderate minor salivary gland involvement; (G,H,I) Severe minor salivary gland involvement. (Hematoxylin and Eosin stain; 400x magnification).

3. Results and observations

3.1. Demographic data

The present study comprised 53 subjects, which were clinically and histopathologically diagnosed with OSMF. The mean age of the OSMF patients was 31.62 ± 11.01 years [age range = 16–70 years]. OSMF group comprised of 46 males and 7 females with a male-female ratio of 6.5:1. This corresponds with the higher prevalence of betel quid chewing habit in males in the Indian population. Mouth opening for OSMF patients ranged from 0 mm to 39 mm with a mean of 21.06 ± 7.9 mm. The most common habit was gutkha chewing (44), followed by gutkha + tobacco (6), gutkha + mawa (1), mawa alone (1), and areca nut alone (1) (Table 2).

3.2. Grading of MSG involvement with OSMF

On histopathological examination, fibrosis was predominantly seen located around the MSGs (27 cases) and around the acini (26 cases). Finally, by using the criterion (Table 1), out of a total of 53 OSMF patients, there were 15 patients in grade I followed by 24 and 14 patients in grade II and grade III, respectively.

3.3. Mouth opening and MSG involvement with OSMF

To authenticate the proposed grading system, we compared MSG

involvement grading with the mouth opening status of the patient. The maximum mouth opening was reported in grade I (32 ± 3.87) followed by Grade II (19.85 ± 4.31) and Grade III (11.42 ± 5.21) involvement of MSGs and the differences between them were statistically significant. When compared with each other, all the three grades showed statistically significant differences between each other in terms of mouth opening (Table 3).

3.4. Clinical oral dryness score and grading of MSG involvement with OSMF

The CODS was more in grade III (5.5 ± 1.09) as compared to grade II (4.04 ± 0.62) and grade I (2.46 ± 0.74) involvement of MSG. A decreasing trend of CODS with the increasing grades of MSG involvement was observed which showed statistically significant differences. Moreover, when compared with each other, all the three grades showed statistically significant differences between each other in terms of CODS (Table 3).

3.5. MSG flow rate and grading of MSG involvement with OSMF

The buccal MSG flow rate was compared with the proposed grading system of MSG involvement with OSMF. The flow rate was more in grade I (8.02 ± 2.99) as compared to grade II (3.97 ± 1.09) and grade III (3.4 ± 0.87) involvement of MSG. The MSG flow rate in grade I vs grade II ($p < .00001^*$) and grade I vs grade III ($p < .00001^*$) showed statistically

Table 2

Demographic details of oral submucous fibrosis patients.

Parameter	n (%)	%
Age	Mean: 31.62 ± 11.01 years (range: 16–70 years)	
Gender		
Male	46	86.79
Female	7	13.2
Ratio	6.5:1	
Habit		
Duration		
Gutkha chewing	44	83.01%
Gutkha + tobacco	6	11.32
Gutkha + Mawa	1	1.88
Mawa alone	1	1.88
Areca nut alone	1	1.88
Range: 2–30 years; mean: 9.33 ± 6.24 years		
Site		
Buccal mucosa	15	28.3%
Buccal mucosa + Labial mucosa	10	18.86
Buccal + labial + Palatal + Uvula	20	37.73
Buccal + labial + Palatal + Uvula + Tongue	8	15.09
Side		
Mouth opening		
Unilateral	7	13.2
Bilateral	46	86.79
Mean: 21.06 ± 7.9 mm (range: 0–39 mm)		
Habit pattern		
Spitting	37	69.81
Spitting and swallowing	14	26.41
Swallowing	2	3.77
Clinical Grading		
Grade I	5	9.43
Grade II	4	7.54
Grade III	18	33.96
Grade IV	26	49.05

Table 3

Comparison of mouth opening, clinical oral dryness score and salivary flow rate in various minor salivary gland involvement grades.

MSG involvement Grade	n	Mean SD	F ratio	P value ^a
Mouth Opening				
I	15	32 ± 3.87	78.838	I and II: < .00001*
II	24	19.85 ± 4.31		I and III: < .00001*
III	14	11.42 ± 5.21		II and III: < .00001*
Clinical Oral Dryness Score				
I	15	2.46 ± 0.74	51.86	I vs II: p < .00001*
II	24	4.04 ± 0.62		I vs III: p = .00001*
III	14	5.5 ± 1.09		II vs III: p < .00001*
Salivary Flow Rate				
I	15	8.02 ± 2.99	30.38	I and II: < .00001*
II	24	3.97 ± 1.09		I and III: < .00001*
III	14	3.4 ± 0.87		II and III: p = .63189

^a One-Way ANOVA and Post Hoc Tukey HSD.

significant differences. However, there was no statistically significant difference between grade I and grade III involvement of MSG with fibrosis ($p = .63189$) (Table 3).

4. Discussion

Fibrosis of any organ of the body could occur due to fibrosis as a primary pathology or secondary involvement. The loss of functionality due to atrophy of the cellular elements is the ultimate outcome of fibrosis pathogenesis.¹² Salivary gland fibrosis as a secondary manifestation has been reported in many diseases such as sialadenitis, post-radiation salivary gland dysfunction, and Sjögren's syndrome.¹³ All these pathologies manifest in the form of decreased salivary secretion. However, to date, involvement of MSGs with fibrosis from OSMF has not been deeply investigated. However, Sarode et al.⁸ have proposed novel pathogenesis for burning sensation of the oral cavity and atrophic epithelium, which are the cardinal features of the OSMF, based on the involvement of MSGs with OSMF. To further explore the MSG

involvement in OSMF, we investigated the histopathology of OSMF tissues with a special focus on MSGs.

Intriguingly, we observed varying degrees of fibrosis in and around MSGs, which formed the basis for classifying them into three different grades (Table 1). In the present study, the biopsy site was from the buccal mucosa and hence the present results are exclusively attributed to the degree of involvement of buccal MSGs. Nonetheless, as OSMF causes generalized involvement of the oral cavity, there could be involvement of other MSGs such as labial, palatal, and tongue. However, buccal mucosa is the most common site for the OSMF^{14,15} and hence, we believe that these MSGs are the most effective as compared to other glands. Out of the total of 53 OSMF patients, there were 15 patients in grade I followed by 24 and 14 patients in grade II and grade III, respectively. It was imperative for the present study to authenticate the grading system on the clinical ground, and hence we compared the values of mouth opening, CODS, and flow rate with the different grades.

The CODS value gives the status of the dryness in the oral cavity and was the most appropriate parameter for comparison with the various grades of MSG involvement with OSMF.¹⁰ In the present study, it was observed that the CODS value increased with an increase in the grade of MSG involvement with OSMF. These findings suggest that MSG fibrosis might have caused the decrease in the functioning of the glandular secretory cells leading to a reduction in salivary secretion. But only involvement of buccal MSG will not majorly contribute to oral cavity dryness. However, OSMF is a generalized pathology of the oral cavity and hence, involvement of other MSGs of other locations is also possible. Because of this generalized effect on the MSGs of the oral cavity, there is an overall reduction in the salivary flow leading to dryness. Moreover, it can also be concluded that buccal mucosa MSG fibrosis can be an indicator of the status of other MSGs of the oral cavity. Future studies are recommended on the comprehensive assessment of all the salivary glands that can be performed in OSMF patients and comparisons with different modalities of dryness assessments.

In the present study, it was observed that with decreasing mouth opening, the grade of MSG involvement with fibrosis increased. When compared with each other, all the three grades showed statistically significant differences with each other in terms of mouth opening. It is usually a perceived fact that as the fibrosis increases it will cause a reduction in the mouth opening.^{9,14,15} Inverse correlation of the mouth opening and degree of fibrosis has already been reported in the literature.¹⁶ Mouth opening measurement in OSMF patients represents the status of the disease progression. In fact, grading based on the mouth opening, which is proposed by Lai et al.¹⁷ has been widely used in the literature. Thus, the present study results depict that the proposed grading system of MSG involvement with fibrosis corroborate with the clinical status of the OSMF and thus can be a very good marker for disease progression.

In the present study, the MSG flow rate was calculated using Schirmer's test strip method, which was widely used in the literature.^{18,19} This methodology is useful in determining the flow rates of individual MSGs of the oral cavity with a high degree of accuracy and reproducibility. Other methodologies such as strips that incorporated the iodo-starch reaction are not widely used in the literature.²⁰ In the present study, the MSG flow rate was compared with the proposed grading system of MSG involvement with OSMF. The flow rate showed decreasing trend as the grade of MSG involvement with fibrosis increased. This finding was quite evitable as the flow rate considered for the present study was from the buccal mucosal MSGs and the same areas later considered for the biopsy. Hence, these results are a classical example of cause and effect relationship depiction.

There are some limitations to the present study. Although fibrosis gives a good indication of the functional status of the MSG, it does not give the exact degree of degeneration causes at the molecular level. This can only be measured with the help of the study of molecular markers associated with degeneration, perhaps the proliferative and survival markers. The second limitation was the consideration of only buccal

mucosa MSGs as it was the most common site for biopsy in OSMF patients, which does not depict the complete status of all the MSG functional impairment. However, it is also equally true that examination of all the MSGs histologically is not practically possible at the incisional biopsy level. However, salivary flow rates can be studied for MSGs of different locations of the oral cavity. We recommend future studies on the role of TGF-beta in MSG fibrosis, as it is the main driver for the initiation, activation, and propagation of fibrotic diseases in the body. In addition to the CODS value, future studies should also incorporate the measurement of wettability of oral mucosa as a comparative indicator for MSG involvement with OSMF. Finally, the salivary flow rate in apparently healthy individuals is not assessed in the present study, which could have been done for comparison with OSMF patients.

5. Conclusion

To the best of our knowledge, this is the first study that investigated the status of MSGs in OSMF and proposed a novel classification system for the same. The fibrosis associated with OSMF can affect the MSGs located at mucosal and sub-mucosal levels. The clinical determinants such as mouth opening, salivary flow rate, and CODS corroborate with the grading of the degree of MSG involvement with fibrosis and hence, it should be a part of assessment during the routine histological examination of OSMF. Lack of assessment of the status of other MSGs and correlation with other clinicopathological parameters are the major limitation of the present study. We recommend future studies on in-depth analysis of fibrosis-relevant signaling pathways to better understand the mechanism of fibrosis in MSGs. Corollary to this proposition; MSGs should also be investigated for possible signs of degeneration by using suitable markers.

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Declaration of competing interest

All the authors associated with the present manuscript declared no potential conflict of interest concerning research, authorship, and/or publication of this article.

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