Original Study

CLINICOPATHOLOGICAL EVALUATION OF ORAL SUBMUCOUS FIBROSIS - A RETROSPECTIVE, SINGLE INSTITUTE STUDY

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ABSTRACT

Oral submucous fibrosis (OSMF) is a fibrotic, potentially malignant disorder of the oral cavity. The prevalence of OSMF in the south-east Asian population and the role of the areca nut in its pathogenesis are well documented. However, to understand the pathophysiology of the condition, it is necessary to study the risk factors and population characteristics of individuals affected by the condition. Thus, the present retrospective study aimed to evaluate the clinicopathological features of OSMF. Clinically and histologically diagnosed cases of OSMF reported from 1998 to 2018 were included in the present study. Clinicopathological parameters of gender, age, stage, grade, and habit history were included. To test the association, the chi-square test was used.

The OSMF cases showed a male predominance with the male to female ratio being 10.7:1. A wide age range from 14 years to 84 years was noted. Histological grade and clinical stage of OSMF showed significant association ($p<0.05$). The majority of cases (63 out of 141) showed advanced grades of OSMF. An association between gender and age ($p<0.05$) as well as between gender, habit history, and grade of OSMF ($p<0.05$) was observed. Betel nut and tobacco consumption in the younger age group and their significant association with advanced grade and stage of OSMF was observed in the present study. The study highlights a need for education of patients regarding the use of the substances and their deleterious effect on the disease progression and quality of life of the patient.

Key words: Oral Submucous Fibrosis, Carcinoma, Areca nut, Tobacco.

Introduction

Oral Submucous Fibrosis (OSMF) is a fibrotic condition of the oral cavity that occurs predominantly in the South-East Asian population. [1] It is also known as a potentially malignant disorder and causes debilitation due to the progressive fibrosis of the affected areas. [2] OSMF presents an array of clinical and histopathological features. [1, 2] Although multifactorial, the primary factor responsible for bringing about these changes is considered to be the persistent consumption of areca or betel nut. [2, 3] Commercially available forms of areca nut like gutkha, are implicated with the early presentation and progress of OSMF. [2, 4, 5] Consumption of Pan and gutkha are reported to be commonly associated with OSMF in the northern parts of India. [6] Although gutkha has been banned, the rising incidence of OSMF, its irreversible nature, and its malignant transformation deems essential the study of clinicopathological factors like patient age, gender, habits, stage, and grades of OSMF. Hence, the present retrospective study aimed to evaluate the clinical and histological features of reported cases of OSMF in a single institute.

Materials and Methods

After obtaining Institutional ethical clearance, the present retrospective study was undertaken. A total of 141 clinically and histologically diagnosed cases of OSMF reported from 1998 to 2018 were included in the study. Clinical data consisting of age, gender, clinical signs and symptoms, stage, and habits were retrieved. Habits documented were grouped as 0 - no documentation of history on patient record; 1- Betel leaf with or without lime; 2- Betel nut alone; 3- Gutkha; 4- Tobacco; 5- The combination of two or more and 6- No habit of addictive substance consumption. Clinical signs & symptoms as available from patient records were grouped into 0 - presenting with a sharp tooth, denture trauma, and other; 1- Burning sensation and blanching of mucosa with or without blisters; 2- Palpable bands in the buccal mucosa and/or circumoral mucosa with or without blistering and burning sensation, difficulty in mouth opening (26-35mm); 3- Palpable bands extending to raphe, uvula, tongue and difficult mouth opening (15-25mm) or one finger opening, erythematous areas; 4- Difficulty in mouth opening (less than 15mm) with ulcers/white lesions; 5- Difficulty in

mouth opening and associated with carcinomatous growth. For grading of OSMF, we used modified Pindborg and Sirsat classification and added categories of OSMF with dysplasia and OSMF with carcinoma. [1] The available clinical stage as mentioned on patient record as per Khanna JN and Andrade criteria was also included for comparison. [7] All the cases included were histologically evaluated by two trained pathologists of similar experience in diagnosing head and neck pathologies for confirmation of the histological grade of OSMF. The data was tabulated and Chi-Square analysis was performed to test the difference between the clinical and histopathological parameters ($P < 0.05$).

Results and Discussion

Gender and Age

The gender distribution showed the male to female ratio of 10.7:1 indicative of a male predisposition. Males were predominantly in the younger age group of 40 years and less (97%), while the majority of females belonged to the more than 40 years age group (78.6%). The age range for the cases was from 14 years to 84 years. 70% of cases (99 out of a total of 141 cases) were noted in the less than 40 years age group **(Table 1)**.

Table 1. Distribution of OSMF cases according to Gender & Age groups

Gender	40 and fewer years of age (%)	More than 40 years of age (%)	Total no. of participants n (%)
Male	96 (97)	33 (78.6)	129 (91.5)
Female	3 (3)	9 (21.4)	12 (8.5)
Total	99 (100)	42 (100)	141 (100)

Habits and Grade

The majority of cases (63 out of 141 cases) presented with moderately advanced OSMF **(Table 2)**. A total of 116 cases gave the history of habits, 5 cases had no habit history given by the patient, amongst which one was associated with denture trauma. No habit history was documented for 20 cases. Maximum cases had a history of Gutkha chewing or a combination of two or more habits **(Table 3)**.

Table 2. Distribution of OSMF cases according to Histopathological grade

Histopathological Grade	No of participants n (%)
Very early OSMF	10 (7.1)
Early OSMF	34 (24.1)
Moderately advanced OSMF	63 (44.7)
Advanced OSMF	22 (15.6)
OSMF with dysplasia	6 (4.3)
OSMF with Carcinoma	6 (4.3)

Table 3. Distribution of OSMF cases according to habits

Habits (Score assigned)	No of participants n (%)
No history documented (0)	20 (14.2)
Betal leaf with or without lime (1)	2 (1.4)
Betal nut (2)	26 (18.4)
Gutkha (3)	32 (22.7)
Tobacco (4)	24 (17.0)
Combination of any two or more (5)	32 (22.7)
No habit of addictive substance consumption (6)	5 (3.5)

Gender and grade

More than 50% of cases with moderately advanced OSMF were noted in males, while females showed the majority of cases that were in the early grade. Out of the total 12 cases showing OSMF with dysplasia (6 cases) and OSMF with carcinoma (6 cases), the majority of them were noted in male patients (11 out of 12 cases).

Association between gender, habits, grade, and age

All gutkha chewers were males and about 50% of females showed a habit history of betel nut consumption. A significant association was noted between gender and habit ($p=0.046$) **(Table 4)**. Amongst Gutkha chewers, 50% of cases showed moderately advanced OSMF followed by advanced OSMF (28.1%). A significant association was noted between the habit history and grades of OSMF ($p = 0.048$) **(Table 5)**. Similarly, a significant association was noted between the histological grade and age of patients ($p=0.001$) **(Table 6)**.

Table 4. Comparison between Gender and Habit

Gender	Habit	Total

		0	1	2	3	4	5	6		p-value
Female	**Count**	0	0	6	0	3	2	1	**12**	**0.046***
	% within gender	0.0%	0.0%	50.0%	0.0%	25.0%	16.7%	8.3%	**100.0%**	
Male	**Count**	20	2	20	32	21	30	4	**129**	
	% within gender	15.5%	1.6%	15.5%	24.8%	16.3%	23.3%	3%	**100.0%**	
Total	**Count**	20	2	26	32	24	32	5	**141**	
	% within gender	14.2%	1.4%	18.4%	22.7%	17.0%	22.7%	3.6%	**100.0%**	

Chi-square test; * indicates a significant difference at p≤0.05.

Habits: 0 -No history documented; 1- betel leaf with or without lime; 2- betel nut; 3- Gutkha; 4- Tobacco; 5- the combination of two or more; 6 - no habit of addictive substance consumption.

Table 5. Association of Histopathological grades with habits

Histopathological Grade	Habit							Total	p-value
	0	1	2	3	4	5	6		
Very early OSMF	1 (5)	0	4 (15.4)	3 (9.4)	1 (4.2)	1 (3.1)	0	10 (7.1)	0.048*
Early OSMF	6 (30)	0	10 (38.5)	3 (9.4)	9 (37.5)	4 (12.5)	2 (40)	34 (24.1)	
Moderately advanced OSMF	9 (45)	2 (100)	11 (42.3)	16 (50)	11 (45.8)	12 (37.5)	2 (40)	63 (44.7)	
Advanced OSMF	2 (10)	0	1 (3.8)	9 (28.1)	2 (8.3)	7 (21.9)	1 (20)	22 (15.6)	
OSMF with dysplasia	2 (10)	0	0	0	1 (4.2)	3 (9.4)	0	6 (4.3)	
OSMF with Carcinoma	0	0	0	1 (3.1)	0	5 (15.6)	0	6 (4.3)	
Total	20 (100)	2 (100)	26 (100)	32 (100)	24 (100)	32 (100)	5 (100)	141 (100)	

Chi-square test; * indicates a significant difference at p≤0.05.

Habits: 0 -No history documented; 1- betel leaf with or without lime; 2- betel nut; 3- Gutkha; 4- Tobacco; 5- the combination of two or more; 6 - no habit of addictive substance consumption.

Table 6. Association of Histopathological grade of OSMF with age groups

Histopathological grade	Age group		Total	p-value
	40 or less	More than 40 yrs		
Very early OSMF	6 (5.9)	4 (10)	10 (7.1)	0.001*
Early OSMF	19 (18.8)	15 (37.5)	34 (24.1)	
Moderately advanced OSMF	56 (55.4)	7 (17.5)	63 (44.7)	

Advanced OSMF	15 (14.9)	7 (17.5)	22 (15.6)
OSMF with dysplasia	1 (1)	5 (12.5)	6 (4.3)
OSMF with Carcinoma	4 (4)	2 (5)	6 (4.3)
Total	101 (100)	40 (100)	141 (100)

Chi-square test; * indicates a significant difference at p≤0.05

Stage of OSMF, Clinical presentation, and grade

According to the staging criteria used, 79 out of 141 total participants presented with Stage 2 OSMF (56%), while 11 out of 141 cases presented with Stage 4 OSMF (7.8%) **(Table 7)**. Clinically, 53 out of 141 cases presented with reduced mouth opening, few erythematous areas, and palpable bands extending to involve the raphe, uvula, and tongue **(Table 8)**.

Table 7. Distribution of OSMF cases according to the clinical stage

Stage	No of participants n (%)
Stage 1	30 (21.3)
Stage 2	79 (56.0)
Stage 3	21 (14.9)
Stage 4	11 (7.8)

Table 8. Distribution of OSMF cases according to clinical presentation

Clinical signs and symptoms (Score)	No of participants (%)
Not relevant to OSMF/other symptoms like a sharp tooth, denture irritation, etc (0)	6 (4.3)
Burning sensation, blanching of the mucosa, and blistering (1)	14 (9.9)
Palpable bands in BM and/or circumoral, difficulty in mouth opening [26-35mm], blistering, burning sensation (2)	47 (33.3)
Palpable bands extending to raphe, uvula, tongue, and difficult mouth opening [15-25mm] or one finger opening, erythematous areas (3)	53 (37.6)
Restricted mouth opening [<15mm] with Ulcers/white lesions (4)	15 (10.6)
Restricted mouth opening and associated cancer [5]	6 (4.3)

Association between Grade, stage, and Clinical signs - symptoms

Clinical signs and symptoms, as well as clinical stage, showed significant association with the histopathological grade of OSMF (p=0.001) **(Tables 9 and 10)**. The majority of patients presented with stage 2 OSMF and amongst these 70% of cases had a histological grade of moderately advanced OSMF. 50% of cases with stage 1 OSMF showed histological features of early OSMF whereas stage 3 & 4 OSMF cases showed either advanced OSMF or dysplasia and carcinoma with OSMF **(Table 10)**.

Table 9. Association of Histopathological grades with clinical signs and symptoms

Histopathological Grade	Clinical Signs & symptoms						Total	p-value
	0	1	2	3	4	5		
Very early OSMF	1 (16.7)	4 (28.6)	5 (10.6)	0	0	0	10 (7.1)	0.001*
Early OSMF	5 (83.3)	4 (28.6)	18 (38.3)	3 (5.7)	4 (26.7)	0	34 (24.1)	
Moderately advanced OSMF	0	6 (42.9)	23 (48.9)	28 (52.8)	6 (40)	0	63 (44.7)	
Advanced OSMF	0	0	1 (2.1)	21 (39.6)	0	0	22 (15.6)	
OSMF with dysplasia	0	0	0	1 (1.9)	5 (33.5)	0	6 (4.3)	

OSMF with Carcinoma	0	0	0	0	0	6 (100)	6 (4.3)
Total	6 (100)	14 (100)	47 (100)	53 (100)	15 (100)	6 (100)	141 (100)

Chi-square test; * indicates a significant difference at p≤0.05.

Clinical Signs & symptoms: 0 - Sharp tooth, denture trauma and other; 1- Burning sensation and blanching of mucosa with or without blisters; 2- Palpable bands in the buccal mucosa and/or circumoral mucosa with or without blistering and burning sensation, difficulty in mouth opening (26-35mm); 3- Palpable bands extending to raphe, uvula, tongue and difficult mouth opening (15-25mm) or one finger opening, erythematous areas; 4- difficulty in mouth opening (less than 15mm) with ulcers/white lesions; 5- difficulty in mouth opening and associated with carcinomatous growth.

Table 10. Association of Histopathological grades with stages of OSMF

Histopathological Grade	Stage				Total	p-value
	Stage 1	Stage 2	Stage 3	Stage 4		
Very early OSMF	8 (26.7)	2 (2.5)	0	0	10 (7.1)	
Early OSMF	15 (50)	16 (20.3)	3 (14.3)	0	34 (24.1)	
Moderately advanced OSMF	7 (23.3)	56 (70.9)	0	0	63 (44.7)	
Advanced OSMF	0	5 (6.3)	16 (76.2)	1 (9.1)	22 (15.6)	0.001*
OSMF with dysplasia	0	0	2 (9.5)	4 (36.4)	6 (4.3)	
OSMF with Carcinoma	0	0	0	6 (54.5)	6 (4.3)	
Total	30 (100)	79 (100)	21 (100)	11 (100)	141 (100)	

Chi-square test; * indicates a significant difference at p≤0.05

The pathogenesis of OSMF is considered to be multifactorial. However, the areca nut is implicated as the key etiological agent for OSMF. [2, 3, 5] In India, the habit of betel leaf and betel or areca nut consumption is common. Recently, an upsurge has been observed concerning the consumption of various commercially available products of Areca nut alone or in association with other agents like lime and tobacco. [6, 8] With the change in available forms and accessibility of these substances, there is a need to evaluate the association between the consumption of these Areca nut products along with the study of characteristics of the population affected by OSMF.

Previous studies showed a female preponderance for OSMF, however, recently more number of OSMF cases are reported in male patients. [6] Hazarey VK et al, suggested this could be attributed to easy access to the commercially available areca nut products. [6] Our cases showed a male predisposition, with the male to female ratio being 10.7:1. This was following the findings of More CB et al[4], Biradar S et al [9], Srivastava R et al [10], Angadi PV et al [11], Cai X et al [12], and Yang SF et al [13] who also found a male predominance in OSMF cases.

In our present study, the OSMF cases showed an age distribution ranging from 14 years to 84 years. Recently, studies have shown that OSMF commonly affects individuals in the younger age group. [6, 14] A few Indian and Chinese studies have reported OSMF in children and young patients with ages ranging from 9 to 16 years. [12, 14, 15,16] Our study showed similar results wherein maximum cases were seen in the less than 40 years age group. Further, the age-wise distribution showed that the younger age group was predominantly comprised of male patients and showed moderate to advanced clinical grade and stage of OSMF. This was in concordance with the results of Angadi PV et al [11] and Cai X et al [12], who noted a similar association between age, gender, and clinicopathological features. Furthermore, it has been reported that OSMF with carcinoma is more common in the younger age groups. [15]

In our study, the most common clinical presentation noted was restricted mouth opening (between 15 to 25mm) with palpable bands and burning sensation. Angadi PV et al [11] also found mouth opening to be most affected in OSMF patients.

In the present study, we found that the female patients majorly presented with an early grade of OSMF, and only half of the female patients had a history of areca nut consumption. Contrary to this, all gutkha chewers were male and showed an advanced grade of OSMF. More CB et al [5] and Hazarey VK et al [6] also found a similar habit-gender association in their studies. The consumption of commercial

areca nut products like gutkha has been linked to the presentation of advanced grades of OSMF. [5, 17] OSMF being a potentially malignant disorder, can present with dysplasia or transformation of OSMF to carcinoma. In our study, we found 4.2% cases in both, OSMF with dysplasia and OSMF with carcinoma groups. Interestingly, all cases of OSMF with carcinoma had a history of consumption of two or more substances like betel nut, tobacco, and/or gutkha for longer than 10 years. While, amongst the 32 gutkha chewers, 78.1% of cases developed moderately advanced to advanced OSMF and 75% of cases of these cases reported less than 10 years of gutkha consumption history. Our study supports the findings of Hazarey VK et al [6], Angadi PV et al [11] and Avinash Tejasvi ML et al. [18] who found similar results. It can be hypothesized that consumption of commercial products with high levels of arecoline and tobacco or the consumption of two or more such agents could lead to persistent chemical and mechanical irritation, early progression, and a possible malignant transformation of OSMF.

Even with the ban of Gutkha [19], the easy availability of commercial as well as natural areca nut products, tobacco, and other addictive substances highlights the need for regular awareness programs for the youth regarding the association between these habits and potentially malignant disorders like OSMF [6, 15]. The impact on the quality of life and the economical burden of treatment needs as well as the possible malignant transformation of OSMF needs to be addressed. [20-23] A strict scrutiny to regulate the availability of these natural and commercial betel nut/tobacco products needs to be implemented all over the country.

As the present study is a retrospective study, factors like nutritional status, general health, frequency of habit for all patients, and their socioeconomic status were not available. Being a single institute study, a fewer number of cases with the dysplastic and malignant change in OSMF were observed. To study the associations and enable research to discern the pathogenesis of OSMF, further multicentric studies should be undertaken.

Conclusion

The present retrospective study analyses the various clinicopathological features of OSMF and highlights the key associations observed in these patients. Clinically, restricted mouth opening was found to be the most common presentation of OSMF while, histologically, advanced grades of OSMF were observed in male patients of less than 40 years of age. History of consumption of gutkha or more than two substances like betel nut and tobacco was observed in patients with advanced, dysplasia and carcinoma-associated OSMF cases.

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Ethics statement: As the study is a retrospective research study, the ethics review board approved the waiver of written informed consent.

References

1. Pindborg JJ, Sirasat SM. Oral submucous fibrosis. Oral Surg Oral Med Oral Pathol. 1966 Dec 1;22(6):764-79.
2. More CB, Rao NR. Proposed clinical definition for oral submucous fibrosis. J Oral Biol Craniofac Res. 2019 Oct 1;9(4):311-4. doi: 10.1016/j.jobcr.2019.06.016. Epub 2019 Jul 2. PMID: 31334003; PMCID: PMC6614531.
3. Rao NR, Villa A, More CB, Jayasinghe RD, Kerr AR, Johnson NW. Oral submucous fibrosis: a contemporary narrative review with a proposed inter-professional approach for an early diagnosis and clinical management. J Otolaryngol Head Neck Surg. 2020 Dec;49(1):3. doi: 10.1186/s40463-020-0399-7. PMID: 31915073; PMCID: PMC6951010.
4. Hande AH, Chaudhary MS, Gawande MN, Gadbail AR, Zade PR, Bajaj S et al. Oral submucous fibrosis: An enigmatic morpho-insight. J Cancer Res Ther. 2019 Jul 1;15(3):463-9. doi: 10.4103/jcrt.JCRT_522_17. PMID: 31169205.
5. More CB, Rao NR, More S, Johnson NW. Reasons for Initiation of Areca Nut and Related Products in Patients with Oral Submucous Fibrosis within an Endemic Area in Gujarat, India. Subst Use Misuse. 2020 Jun 1;55(9):1413-21. doi: 10.1080/10826084.2019.1660678. PMID: 32569538.
6. Hazarey VK, Erlewad DM, Mundhe KA, Ughade SN. Oral submucous fibrosis: Study of 1000 cases from central India. J Oral Pathol Med. 2007 Jan;36(1):12-7.
7. Khanna JN, Andrade NN. Oral submucous fibrosis: A new concept in surgical management. Report of 100 cases. Int J Oral Maxillofac Surg. 1995 Dec 1;24(6):433-9.
8. Jha VK, Kandula S, Ningappa Chinnannavar S, Rout P, Mishra S, Bajoria AA. Oral Submucous Fibrosis:Correlation of Clinical Grading to Various Habit Factors. J Int Soc Prev Community Dent 2019 Jul;9(4):363-71. doi:10.4103/jispcd.JISPCD_92_19. PMID: 31516870; PMCID: PMC6714423.
9. Biradar SB, Munde AD, Biradar BC, Shaik SS, Mishra S. Oral submucous fibrosis: A clinico-histopathological correlational study. J Can Res Ther. 2018 Apr 1;14(3):597-603.
10. Srivastava R, Jyoti B, Pradhan D, Siddiqui Z. Prevalence of oral submucous fibrosis in patients visiting dental OPD of a dental college in Kanpur: A demographic study. J Family Med Prim Care. 2019 Aug;8(8):2612-7. doi: 10.4103/jfmpc.jfmpc_465_19. PMID: 31548942; PMCID: PMC6753822.

11. Angadi PV, Rekha KP. Oral submucous fibrosis: A clinicopathologic review of 205 cases in Indians. Oral Maxillofac Surg. 2011 Mar;15(1):15-9.
12. Cai X, Yao Z, Liu G, Cui L, Li H, Huang J. Oral submucous fibrosis: A clinicopathological study of 674 cases in China. J Oral Pathol Med. 2019 Apr;48(4):321-5.
13. Yang SF, Wang YH, Su NY, Yu HC, Wei CY, Yu CH, et al. Changes in prevalence of precancerous oral submucous fibrosis from 1996 to 2013 in Taiwan: A nationwide population-based retrospective study. J Formos Med Assoc. 2018 Feb 1;117(2):147-52. doi: 10.1016/j.jfma.2017.01.012. Epub 2017 Apr 5. PMID: 28390753.
14. More CB, Rao NR, Hegde R, Brahmbhatt RM, Shrestha A, Kumar G. Oral submucous fibrosis in children and adolescents: Analysis of 36 cases. J Indian Soc Pedod Prev Dent. 2020 Apr 1;38(2):190-9. doi: 10.4103/JISPPD.JISPPD_173_20. PMID: 32611867.
15. Chaturvedi P, Vaishampayan SS, Nair S, Nair D, Agarwal JP, Kane SV, et al. Oral squamous cell carcinoma arising in background of oral submucous fibrosis: a clinicopathologically distinct disease. Head Neck. 2013 Oct;35(10):1404-9.
16. Jain A, Taneja S. Oral Submucous Fibrosis in Pediatric Patients: A Systematic Review and Protocol for Management. Int J Surg Oncol. 2019 Apr 1;2019:3497136. doi: 10.1155/2019/3497136. PMID: 31057961; PMCID: PMC6463605.
17. Ali FM, Aher V, Prasant MC, Bhushan P, Mudhol A, Suryavanshi H. Oral submucous fibrosis: comparing clinical grading with duration and frequency of habit among areca nut and its products chewers. J Cancer Res Ther. 2013 Jul 1;9(3):471-6.
18. Avinash Tejasvi ML, Anulekha CK, Afroze MM, Shenai KP, Chatra L, Bhayya H. A correlation between oral mucosal lesions and various quid-chewing habit patterns: A cross-sectional study. J Cancer Res Ther. 2019 Jul 1;15(3):620-4. doi: 10.4103/jcrt.JCRT_620_14. PMID: 31169230.
19. Pai SA. Gutkha banned in Indian states. Lancet Oncol 2002 Sep 1;3(9):521.
20. Yang PY, Chen YT, Wang YH, Su NY, Yu HC, Chang YC. Malignant transformation of oral submucous fibrosis in Taiwan: a nationwide population-based retrospective cohort study. J Oral Pathol Med. 2017 Nov;46(10):1040-5.
21. Speight PM, Khurram SA, Kujan O. Oral potentially malignant disorders: risk of progression to malignancy. Oral Surg Oral Med Oral Pathol Oral Radiol. 2018 Jun 1;125(6):612-27.
22. Acharya S, Rahman S, Hallikeri K. A retrospective study of clinicopathological features of oral squamous cell carcinoma with oral submucous fibrosis. J Oral Maxillofac Pathol. 2019 Jan;23(1):162. doi: 10.4103/jomfp.JOMFP_275_17. PMID: 31110444; PMCID: PMC6503806.
23. Chaudhry K, Bali R, Patnana AK, Chattopadhyay C, Sharma PP, Khatana S. Impact of Oral Submucous Fibrosis on Quality of Life: A Multifactorial Assessment. J Maxillofac Oral Surg. 2020;19:251-6. doi: 10.1007/s12663-019-01190-4. Epub 2019 Jan 25. PMID: 32346236; PMCID: PMC7176758.