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Association between Clinical Manifestations and Candida Carriage in Patients with Oral Sub-Mucous Fibrosis

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ABSTRACT

A chronic, progressive disorder known as oral sub-mucous fibrosis causes the oral mucosa to become inflamed and fibrotic, which limits mouth opening, causes a burning sensation, and reduces salivary flow. **Objectives:** To assess the relationship between candida carriage in oral sub-mucous fibrosis patients and demographic traits, tobacco use, and clinical parameters such as burning sensation, salivary flow rate, and mouth opening. **Methods:** A comparative cross-sectional study was conducted from May 2024 to Oct 2024. This study was conducted in Multan Medical and Dental College. The total number of patients was 384 divided into 192 with oral sub-mucous fibrosis and 192 control participants split into groups with and without risk exposure. Clinical characteristics such as mouth opening, salivary flow rate, and burning sensation (measured using a visual analogue scale) were evaluated. Data were analyzed with descriptive, mean, Post Hoc analysis, and Chi-square tests. **Results:** Comparing the oral sub-mucous fibrosis positive group (93%) to the negative group (7%), the oral sub-mucous fibrosis group had a considerably greater prevalence of candida carriage. Reduced salivary flow rate (≤0.2 ml/min), restricted mouth opening (≤20 mm), and severe burning sensation (3-5 (Visual Analogue Scale)) were shown to be strongly correlated with candida positivity ($p<0.001$). A greater prevalence of candida colonization was also seen in patients who used tobacco more frequently ($p<0.001$). **Conclusions:** It was concluded that comprehensive treatment methods should include patient education on oral hygiene and quitting smoking, given the major impact that these behaviours play in candida's carriage.

INTRODUCTION

Oral Sub-Mucous Fibrosis (OSMF) is a progressive and painful condition predominantly affecting individuals who frequently consume areca nuts and tobacco products [1]. Symptoms include a burning sensation, reduced salivary flow, and restricted mouth opening, resulting from inflammation and fibrosis of the oral mucosa. As the disease advances, these symptoms worsen, significantly impairing patients' quality of life and increasing their susceptibility to infections, including fungal colonization [2]. Candida species, particularly candida albicans, are naturally present in the oral cavity but can become pathogenic under altered oral conditions, such as those seen in OSMF, where epithelial abnormalities, reduced salivary flow, and poor oral hygiene facilitate Candida overgrowth [3]. Despite studies indicating an elevated prevalence of Candida among OSMF patients, the relationship between Candida colonization and specific symptoms like burning sensation, salivary flow rate, and mouth opening remain underexplored [4]. OSMF is recognized as a chronic disorder of the oral mucosa that may affect any oral area and occasionally extends to the pharynx, larynx, and oesophagus [5]. OSMF is a chronic, progressive condition characterized by the fibrotic transformation of the oral soft tissues, severely hindering mouth opening. Its complex pathogenesis arises from an interplay of genetic susceptibilities and environmental exposures, predominantly triggered by areca nut and tobacco use. The hallmark is excessive, irregular collagen

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deposition and disrupted extracellular remodeling in the oral mucosa and submucosa, inducing stiffness and inflexibility. Chief among the triggers are areca nut's alkaloids and polyphenols, which spur fibroblast proliferation and rampant collagen synthesis [6]. Moreover, reactive oxygen species from areca nuts and tobacco provoke oxidative stress, exacerbating fibrosis. An imbalance of collagen-modulating enzymes like lysyl oxidase promotes insoluble collagen development through aberrant crosslinking, making it resistant to degradation over time. This accumulated, non-degradable collagen in the lamina propria and submucosa ultimately leads to rigidity and scarring [7]. Inflammation plays a pivotal role in OSMF progression. Chronic irritation of the oral lining by areca nut or tobacco sustains inflammatory cell infiltration, such as macrophages, lymphocytes and mast cells. These immune cells secrete pro-inflammatory cytokines including tumor necrosis factor-alpha and interleukin-6, amplifying fibroblast activation and collagen deposition. Tissue remodeling is further altered by disproportionate matrix metalloproteinase and its inhibitors. Typically, matrix metalloproteinase breaks down surplus collagen, but in OSMF their inhibitors overwhelm this function, letting collagen accumulate unchecked [8]. There is substantial evidence establishing a link between candida overgrowth and the epithelial alterations occurring in oral sub-mucous fibrosis. The dysfunctional oral environment present in OSMF, characterized by impaired integrity of the epithelium and diminished immunity, sets the stage for unchecked candida proliferation. By excreting toxins and enzymes, disrupting epithelial barriers, and promoting oxidative stress, candida can exacerbate mucosal inflammation and precancerous changes, fueling persistent inflammation that serves to further the fibrosis and malignant transformation seen in OSMF [9]. Certain debilitating symptoms of OSMF, such as limited jaw opening, fiery sensations, and blanched mucosa, help enable candida colonization by compromising oral cleanliness and defence mechanisms. The fiery pain and ulcerations could stem from damage inflicted by candida, while the fibrosis handicaps the mucosa's capacity to stave off colonization. This interplay highlights the potential role of candida in exacerbating OSMF symptoms and hastening the progression to a more advanced disease [10].

The usage of areca nuts is the main cause of oral sub-mucous fibrosis (OSMF), a progressive, potentially malignant illness with substantial morbidity. Investigating this connection may provide fresh perspectives on the pathophysiology and possible treatment modalities for OSMF.

This study aims to determine the prevalence of candida carriage in patients with OSMF and investigate any correlations between it and particular clinical characteristics of the illness. We anticipate that by comprehending these connections, we will be able to pinpoint important indicators of candida colonization, which could lead to more focused and efficient treatment plans for OSMF patients.

METHODS

A comparative cross-sectional study was conducted from May 2024 to Oct 2024 at the Department of Dentistry at Multan Medical and Dental College. The total number of participants was n=384 including both genders, which divided into 192 with OSMF and participants split into two control groups non-habitual and habitual control group (each group contain n=92 participants). The non-habitual group consists of individuals who do not have any habits that may negatively affect oral health, such as tobacco, or smoking. They serve as a control group representing the normal, unaffected population without exposure to these risk factors. The habitual group includes individuals who have habits such as tobacco, and smoking but do not exhibit clinical signs or symptoms of oral sub-mucous fibrosis (OSMF). They serve as a comparison group to assess the early or subclinical effects of such habits on oral health including breathing sensation, salivary flow rate and mouth opening. Patients diagnosed with oral sub-mucous fibrosis (OSMF) were further categorized into three stages—early, moderate, and advanced—based on clinical criteria. For consistency in comparative analysis, an equal sample size of 64 patients was allocated to each stage. Inclusion criteria: The age range of the patients was 18-50 years diagnosis was confirmed through clinical examination, history of smoking, burning, difficulty opening the mouth, and changed salivary flow rate and each patient had to provide written informed consent. Exclusion criteria were diabetes, immunosuppressive conditions, patients who had taken antifungal medicine last six months. The sampling technique adopted for this study was convenience sampling. To calculate the sample size for the relationship between clinical features and candida carriage in oral sub-mucous fibrosis (OSMF) patients the following formula applies: n= Z2. P. (1-P)/d2, where, n=sample size, Z= (1.96 or 95% confidence level), p=estimated prevalence ratio (0.5 or 50%), d=margin of error (0.05 or 5%). According to this study, the prevalence of candida carriage in OSMF patients was reported as 30% [11]. The required sample size was n=384. Mouth opening (MO) was measured three times using an electronic Vernier caliper (0.005 mm resolution). Unstimulated saliva flow rate (SFR) was assessed between 9:00 a.m. and 12:00 p.m., with participants instructed to avoid eating, drinking, and oral products for 60 minutes prior. Before testing, they swallowed all saliva and kept their tongue on the hard palate. SFR was measured using the modified Schirmer

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test (MST). For candida assessment, patients were rinsed with 10 ml PBS and expectorated into a container. Samples were centrifuged, suspended, and cultured on Sabouraud's Dextrose Agar at 37°C for 24–48 hours. Colony-forming units per mL (CFU/mL) were calculated. Candida species were identified using germ tube testing, Gram staining, and CHRO-Magar. For comparisons of quantitative clinical features across groups, ANOVA was used for normally distributed data, and the Kruskal-Wallis test was applied for non-normally distributed data. In cases where one-way ANOVA was used, Tukey's Honest Significant Difference (HSD) post-hoc test was performed to identify specific group differences. The Chi-square test was employed for categorical data analysis. A p-value of <0.05 was considered statistically significant. The study was approved by the Institutional Review Board number (No: C-76-1030), ensuring adherence to ethical standards. Informed consent was obtained from all participants before their involvement in the research.

RESULTS

The study included participants with an average age of 34 years (standard deviation: 9.24), consisting of 201 female (52.3%) and 183 male (47.6%), indicating a slight female predominance. Tobacco use was reported by 200 participants (52%), while 184 (47%) indicated they did not use tobacco, suggesting that over half of the sample has a tobacco habit, which may impact the study's focus on candida carriage and related health outcomes. Most participants (60.94%) reported using tobacco more than 12 times daily, with 26.04% using it 7 to 12 times and only 13.02% using it 1 to 6 times per day. Regarding symptom duration, 39.06% reported experiencing symptoms for 3 years, 34.90% for 6 years, and 26.04% for 1 year. These findings underscore the significant role that tobacco use may play in influencing health outcomes related to candida carriage (Table 1).

Table 1: Demographic Characteristics (n=389)

Characteristics	Category	Frequency (%)
Age Range	-28 Years	110 (28.6%)
	29-39 Years	138 (35.9%)
	40-50 Years	137 (35.6%)
Gender	Male	183 (47.6%)
	Female	201 (52.3%)
Tobacco Habit	Yes	200 (52%)
	No	184 (47%)
Frequency/Day	1-6	50 (13.02%)
	7-12	100 (26.04%)
	>12	234 (60.94%)
Duration	1 Year	100 (26.04%)
	3 Year	150 (39.06%)
	6 Year	134 (34.90%)

The analysis showed significant differences between the groups for all clinical features. OSMF patients had higher burning sensation (Visual Analogue Scale (VAS): 7.5 ± 1.2), lower salivary flow rate (0.2 ± 0.05), and reduced mouth opening (28 ± 5 mm) compared to both non-habitual and habitual control groups, with p-values of 0.001 for all variables. These results highlight the discomfort and functional impairments in OSMF patients (Table 2).

Table 2: Comparison of Clinical Features Between OSMF Patients with Non-Habitual Control Group and Habitual Control Group

Sign and Symptoms	OSMF Group (n=192)	Non-Habitual Control Group (n=96)	Habitual Control Group (n=96)	p-Value
Burning Sensation (VAS)	7.5 ± 1.2	1.2 ± 0.8	2.0 ± 1.0	0.001
Salivary Flow Rate (ml/min)	0.2 ± 0.05	0.5 ± 0.1	0.4 ± 0.1	0.001
Mouth Opening (mm)	28 ± 5	45 ± 3	42 ± 4	0.001

As the disorder evolves, the burning sensation gets progressively worse, acquiring its highest VAS evaluations in the more severe phase (p=0.001). As OSMF expands, the salivary flow rate declines; the stage of advanced disease has among the lowest values (p=0.001). When the OSMF condition advances, mouth opening significantly decreases (p=0.001). Significant differences between all stages are shown by post-hoc analysis, the following a significant result in the initial analysis (p=0.001), a post-hoc test (Tukey's HSD) was applied to further analyze pairwise comparisons between the stages. The post-hoc results indicated significant differences across all pairwise comparisons (p<0.05), which reflects the symptoms' growing intensity (Table 3).

Table 3: Clinical Feature Comparison Across Early, Moderate, and Advanced Stages of OSMF

Variables	Early Stage (n=64)	Moderate Stage (n=64)	Advanced Stage (n=64)	p-value	Post Hoc Analysis
Burning Sensation	3.5 ± 0.8	5.8 ± 1.0	7.2 ± 1.2	0.001	Early vs Moderate, early vs Advanced, Moderate vs. Advanced (all significant)
Salivary Flow Rate	0.5 ± 0.1	0.3 ± 0.05	0.1 ± 0.02	0.001	
Mouth Opening	38 ± 3	30 ± 4	22 ± 5	0.001	

In our study sample, candida-positive cases were found in a high proportion of participants. Specifically, 93% of the sample tested positive for candida, while only 7% tested negative (Figure 1).

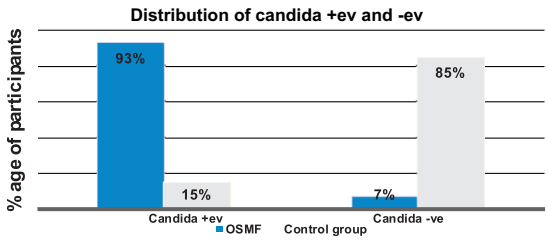

Figure 1: % Age of Patients Represent Distribution of Candida Positive and Negative Sample

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In the OSMF group, the highest number of candida colonies (83%) was 1-200 CFU/mL. Six patients (79%) had candida carriage with a colony count ranging from 201 to 400 CFU/mL. (85%) of the research group's participants showed colony counts between >400 CFU/mL (Figure 2).

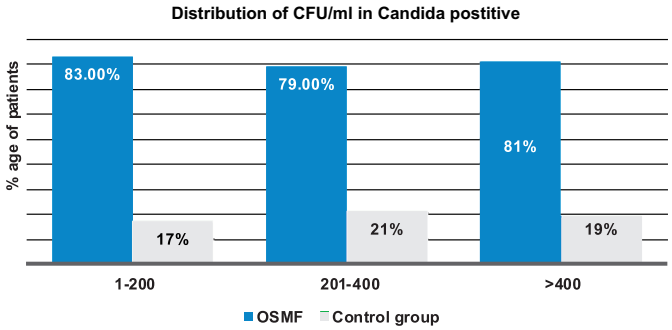

Figure 2: % Age of Patients Represent Candida Colonies

In this study, candida positivity was higher among OSMF patients aged 29-39, predominantly male, with a significant association with tobacco use (p=0.01). Higher tobacco frequency (1-6 times/day) and longer duration (over 1 year) were strongly linked to candida positivity (p<0.001), highlighting the role of demographic factors and tobacco use in candida carriage (Table 4).

Table 4: Impact of Demographic Factors and Tobacco Use on Candida Carriage in OSMF

Characteristics	Candida Positive (n=179)	Candida Negative (n=13)	p-value
Age			
18-28	60 (33.5%)	4 (30.8%)	0.11
29-39	80 (44.7%)	6 (46.2%)	
40-50	39 (21.8%)	3 (23.1%)	
Gender			
Male	90 (50.3%)	6 (46.2%)	0.55
Female	89 (49.7%)	7 (53.8%)	
Tobacco Habit			
Yes	120 (67.0%)	5 (38.5%)	0.01
No	59 (33.0%)	8 (61.5%)	
Frequency of Tobacco Use			
1-6	90 (50.3%)	2 (15.4%)	<0.001
7-12	50 (27.9%)	6 (46.2%)	
>12	39 (21.8%)	5 (38.5%)	
Duration of Tobacco Use			
1 Year	30 (16.8%)	4 (30.8%)	<0.001
3 Years	70 (39.1%)	5 (38.5%)	
6 Years	79 (44.1%)	4 (30.8%)	

Candida positivity was significantly associated with burning sensation (VAS 3-5) at 5.59%, low salivary flow rate (≤2 ml/min) at 27.93%, and mouth opening ≤20 mm at 39.11%. No significant association was found in other categories (Table 5).

Table 5: Association of Oral Symptoms and Candida Isolation in Patients with OSMF

Variables	Subgroups	OSMF (n=192)	Candida Positive (n=179)	Candida Negative (n=13)	X^2	p-value
Burning Sensation (VAS)	≤2 (VAS)	85	80(44.69%)	5(38.46%)	0.56	0.454
	3-5 (VAS)	11	10(5.59%)	1(7.69%)	5.52	0.019
	≥6 (VAS)	96	89(48.65%)	7(53.84%)	0.56	0.454
Salivary Flow Rate	≤2 ml/min	52	509(27.93%)	2 (15.38%)	9.34	0.011
	0.3-0.5 ml/min	105	100(55.87%)	5(38.46%)	15.2	0.001
	≥0.6 ml/min	35	29 (16.19%)	6 (46.15%)	0.79	0.374
Mouth Opening	≤20 mm	73	70 (39.11%)	3 (23.08%)	12.5	0.001
	21-30 mm	75	70 (39.11%)	5(38.46%)	0.78	0.376
	>30 mm	44	39(21.79%)	5 (38.46%)	0.43	0.514

DISCUSSION

The demographic profile of patients with Oral Sub-Mucous Fibrosis (OSMF) reveals critical insights into factors influencing candida carriage. Patients often show a high prevalence of tobacco use, a slight female predominance, and an age range from young to middle-aged. Given the substantial rates of tobacco consumption, health interventions should focus on educating individuals about the risks associated with tobacco use, particularly concerning OSMF, candida infections, and general oral health [12, 13]. Data highlight the significant impact of OSMF on oral health, showing marked differences in clinical features between OSMF patients and control groups. The intense burning sensation reported by patients is likely due to inflammation and fibrosis in the oral mucosa, which can impair sensory perception. Previous research indicates that Candida infections may exacerbate these symptoms, highlighting the need for comprehensive management strategies that address both sensory and physical components associated with OSMF [14, 15]. Decreased salivary flow is another common issue among OSMF patients, leading to dry mouth (xerostomia) and an increased risk of oral infections, including candidiasis. Saliva is vital for maintaining oral health, as it lubricates teeth, neutralizes acids, and possesses antibacterial properties [16]. Therefore, interventions aimed at enhancing salivary output are essential to mitigate complications associated with dry mouth in these patients. Additionally, the characteristic limited mouth opening in OSMF results from fibrous bands in the submucosal layer, which can hinder normal oral functions such as eating, speaking, and maintaining dental hygiene, ultimately reducing the quality of life [17]. Addressing the trismus linked to OSMF through physical therapy or surgical options is critical to improving patient outcomes [18]. As OSMF progresses, mucosal alterations and inflammation can worsen, intensifying discomfort and burning sensations. Patients in advanced stages may experience increased

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nerve damage and inflammatory responses, necessitating tailored management strategies for effective pain relief [19]. The loss of salivary flow can further worsen the quality of life and heighten the risk of opportunistic infections like candidiasis. Therefore, clinicians should prioritize treatments that boost salivary production or manage dry mouth symptoms, particularly for patients in intermediate to advanced stages of OSMF [20]. In this study, candida positivity was observed in 93% of OSMF patients, which is higher than the 60-70% prevalence suggesting a stronger association between candida and OSMF in our population. This difference may be due to variations in diagnostic methods or patient demographics. Regarding colony counts, 83% of Candida-positive cases had counts between 1-200 CFU/mL, low to moderate colonization. However, 81% of our participants had counts exceeding 400 CFU/mL, which is notably higher than where fewer than 50% showed high fungal loads. This suggests more persistent candida overgrowth in our study population, potentially contributing to OSMF progression [21]. Interestingly, the study found a statistically significant correlation between tobacco use and candida carriage; however, a significant relationship between the frequency of tobacco use and candida carriage was established ($p<0.001$). This intriguing result suggests complex interactions between tobacco use and oral microbiota dynamics that require further investigation. Moreover, compared to the control group, OSMF patients exhibited a significantly higher presence of candida ($p=0.048$), with 93% testing positive for candida versus only 15% in the control group [22]. These findings emphasize how decreased salivary flow can exacerbate oral infections and reinforce the importance of saliva in maintaining oral health, particularly in preventing candida colonization. Overall, these insights underscore the need for targeted interventions and comprehensive management approaches to address the multifaceted challenges faced by individuals with OSMF [23]. It is important to highlight in the discussion that cross-sectional study design restricted the capacity to demonstrate temporal or causal links between OSMF and candida carriage, whereas a case-control study may more robustly discern causative associations. This restriction implies that although correlations were noted, more case-control designs or longitudinal studies would be required to verify causality and examine the course of candida colonization in OSMF.

CONCLUSIONS

It was concluded that the study highlights how important it is to monitor patients' oral health closely when they have OSMF, especially when fungal infections are present. Candida colonization can be lessened by early detection and treatment of symptoms like a burning feeling, decreased salivary flow, and restricted mouth opening.

Authors Contribution

Conceptualization: MZUA
Methodology: MZUA, MTR, SL, MAW, MMR
Formal analysis: MTR, MAW
Writing review and editing: MAW

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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