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Original Article

Exploring Status of Oral Submucous Fibrosis and its Association with C-Reactive Protein at a Public Sector Medical University

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ABSTRACT

Oral submucous fibrosis (OSMF) is a well-established precancerous condition affecting the oral mucosa. **Objective:** To explore serum C- reactive protein levels in healthy patients and their comparison with diagnosed patients having oral submucous fibrosis. **Methods:** Eighty-two patients of all age groups, irrespective of gender and clinically diagnosed with oral submucous fibrosis, without any other systemic problem were included in the study. Patients were divided into two groups i.e., Group A = normal healthy patients and Group B = clinically diagnosed oral submucous fibrosis patients. After taking detailed history of patients of both groups, blood samples were collected from all patients for C- reactive protein levels. **Results:** Out of 82 patients, male were 30 (73.2%) and 34 (82.9%) and female were 11 (26.8%) and 7 (17.1%) with mean age of 41.0 ± 6.6 years and 42.6 ± 7.4 years in group I (normal healthy patients) and group II (oral submucous fibrosis patients) respectively. All patients were long-term consumers of betel quid with or without tobacco [13 (31.7%) and 28 (68.3%)], whereas no healthy patient was using betel quid. CRP level was significantly high 3.62 ±1.02 mg/dl in OSMF patients as compared to normal healthy patients 0.40 ± 0.21mg/dl. Similarly, CRP level was significantly abnormal (raised) in all OSMF patients as compared to normal healthy patients where only 7 (17.1%) were reported with abnormal (raised) CRP levels. **Conclusions:** Serum C- reactive protein levels in oral submucous fibrosis patients were significantly high as compared to normal healthy patients.

INTRODUCTION

Oral submucous fibrosis (OSMF) is a precancerous condition of the oral cavity characterized by fibrosis of oral mucosa (in the juxta-epithelial layer), which has also been defined by world health organization (WHO) as "Pathological state of Oral Cavity with potential risk of oral cancer" [1]. This condition was first labeled by Schwartz in 1952 and the term-oral submucous fibrosis was first coined by Joshi in 1953 [2]. The literature studies confirms the areca nut as the main etiological factor in causing OSMF [3] and various autoantibodies and antigens such as human leucocyte antigens (HLA) has showed their autoimmune role in some patients as well, with some positive support for a genetic predisposition for occurrence of this potential premalignant oral disease [1]. Other etiological factors may include use of capsaicin in chilies, deficiency of iron, zinc and other vital trace elements and vitamins [4]. Areca nut relation with other disorders have been found like epilepsy, hepatocellular carcinoma, metabolic syndrome, impaired glucose tolerance (IGT), and diabetes [5]. Areca nut is obtained from the seed of the fruit of Areca Catechu (a

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tropical palm tree) and ranks at fourth most widely used substance among tobacco, alcohol and caffeine and has more than 10% usage world widely as psychoactive component [6]. Limited research studies are documented in Pakistan regarding oral submucous fibrosis and its status associated issues in school going children, adults and their relation with periodic usage and rate related with areca nut [7]. Initial clinical features of Oral submucous fibrosis most commonly includes burning sensation in mouth and inability to eat spicy food also there can be inflammation along with hypovascularity, fibrosis, blanching (localized, diffused or reticular), small vesicle (that may rupture) and marble like manifestation of the oral cavity. The later stage of OSF includes presence of clinically palpable fibrous bands causing variable restricted mouth opening (trismus), inability to perform proper oral hygiene inspection, associated with speaking-chewing and difficulty in swallowing issues. Lip fibrosis may also cause its rubbery appearance and elliptical shape, other symptoms like fibrosis of soft palate, uvula and lesser extent fibrosis of gingival tissues, and sometimes blockage of Eustachian tube, labial, faucial and buccal bands may also be present [8, 9]. Many clinical and functional investigations have classified OSMF. In 2012, clinically staged OSF into four groups: S1, S2, S3, and S4 with subtypes S4 (a) and S4 (b). (S1) as stomatitis/blanching of the oral mucosa, (S2) as palpable fibrous bands in buccal mucosa/oro-pharynx with/without stomatitis, (S3) as palpable fibrous bands in buccal mucosa/oro-pharynx or in any part of oral cavity with/without stomatitis, (S4a) as any one of the above stages, along with other potentially malignant disorders, such as oral cancer, leukoplakia, erythroplakia, etc., (S4b) any one of the above stages. His Functional Staging uses inter-incisal measurement mouth opening up to or >35mm as M1, 25–35 mm as M2, 15–25 mm as M3, and <15 mm as M4 [10]. Different treatment modalities have been tried for OSF which includes administration of Steroids, Placental extracts, IFN Gamma, Pentaoxifyline, Lycopene enzymes, Antioxidants and Minerals, Surgical excision, but there is no global uniform treatment accepted [11]. There are approximately 600 million cases of OSMF reported [4]. Asian countries like India, Bangladesh, Sri Lanka, Pakistan, Taiwan and China have the significantly higher ratio of oral submucous fibrosis in comparison to west [12]. There is high risk of potential pre-malignant diseases to be converted in oral malignancy; therefore early assessment of high risk patients is very important [13]. Many researchers are searching for biomarkers that might distinguish healthy people from those at high risk of oral cancer [14]. The C - reactive protein or CRP is a useful and common biomarker. There is proven and well documented work of over 100 years is present that inflammation is related with cancer and that, C-reactive protein escalates in inflammatory conditions where either acute and chronic inflammation and in other conditions like cancer, heart diseases and surgeries [15, 16]. Furthermore, it is also a known absolute independent prognostic and pre-diagnostic factor for malignancies [17]. On the other hand, it is still unclear, and researchers doubt that CRP can be elevated before biological onset of cancer or it can be risk factor for the development of cancer [14]. As the frequency and habit of chewing Areca Nut, Ghutka, and Betel Quid increases, oral epithelium becomes more prone to oral cancer and oral submucous fibrosis increases in young patients. As there are few research on OSMF in Pakistan, we aim to investigate the association between CRP and OSMF instances in our community and its results at LUMHS.

METHODS

This comparative cross-sectional research with non-probability convenience sample was carried out at Liaquat University of Medical and Health Sciences Jamshoro's Oral and Maxillofacial Surgery Department OPD. The 2020 study was carried out between June and July. Rao Soft's sample size calculator was used to determine the sample size. The sample size was divided into two groups (Group I = Normal healthy patients and Group II = Oral Submucous fibrosis patients, 41 patients in each group) by lottery method/random number generator method. Patients with all age groups and either gender and clinically diagnosed with oral submucous fibrosis, without any other systemic problem were included in the study. All oral submucous fibrosis patients having any other systemic disorder or histopathology proven oral cancer, including surgically operated patients with Oral Cancer having associated diagnosed OSMF were exclude from study. Selected Patients were divided into two groups Group A = normal healthy patients and Group B = clinically diagnosed OSMF patients. A written informed consent was taken from adult patients and their parents/ attendants in case of children in both groups by researcher. For both groups, the whole patient history, including name, age, gender, hospital registration number, and any complaints made, was documented. Group B patients were enrolled after diagnosis of OSMF according to clinical and functional classification of OSMF. All the findings were recorded on Proforma (Annexure -1). After synopsis approval from ERC Prior written Permission was taken with a covering letter from Supervisor and reason for this study shared with in charge Pathology Lab, LUM & HS. CRP test was done after collecting blood samples from all study patients by the researcher and stored in test tubes collected if suitable, as per protocol of Pathology Lab, LUM & HS and finally

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submitted for reporting with patients details by the researcher. However, if this is not possible then the study patients were sent with request to collect blood sample and provide its report as per need of this research. CRP results of both groups were compared for respective results. After receiving clearance from the university's Ethical Review Committee, research was carried out. Patients from both groups were requested to undergo blood C-reactive protein testing after thorough clinical exams, and the results were analyzed and documented on Proforma. Data were analyzed by statistical package for social sciences (SPSS) software package version 20.0. Mean and standard deviation was calculated for continuous variables such as age and serum CRP. Frequencies and percentages were calculated for categorical variables such as gender, age in groups, habits, usage of betel nuts, symptoms of OSMF and serum CRP (normal/abnormal). Chi-Square Test and Independent Sample t-test was applied between both groups. Values for $p \leq 0.05$ were considered statistically significant.

RESULTS

In this study 30 (73.2%) and 34 (82.9%) patients were male and 11 (26.8%) and 7 (17.1%) patients were female in group I (Normal Healthy Patients) and group II (Oral Submucous Fibrosis Patients) respectively. Patients were grouped ≤ 40 years in 23 (56.1%) and 16 (39.0%) and > 40years in 18 (43.9%) and 25 (61.0%) patients in group I and group II respectively (Table 1).

Gender	Group I	Group II	p-Value
Male	30 (73.2%)	34 (82.9%)	0.286
Female	11 (26.8%)	7 (17.1%)	
Age Groups	**Group I**	**Group II**	**p-Value**
≤ 40	23 (56.1%)	16 (39.0%)	0.122
> 40	18 (43.9%)	25 (61.0%)	

Table 1: Patients Distribution According to Gender and Age Groups

Patient's distribution in relation to different habits like betel quid, tobacco, chilies, alcohol, and smoking has been documented in table 2.

	Group I	Group II	p-Value
Betel Quid with Tobacco			
Yes	0 (0.0%)	13 (31.7%)	<0.001
No	41 (100.0%)	28 (68.3%)	
Betel Quid Without Tobacco			
Yes	0 (0.0%)	28 (68.3%)	<0.001
No	41 (100.0%)	13 (31.7%)	
Chilies			
Yes	4 (9.8%)	7 (17.1%)	0.331
No	37 (90.2%)	34 (82.9%)	
Smoking			
Yes	10 (24.4%)	35 (85.4%)	<0.001
No	31 (75.6%)	6 (14.6%)	
Alcohol			
Yes	0 (0.0%)	9 (22.0%)	0.002
No	41 (100.0%)	32 (78.0%)	
Usage of Betel Nut (Years)			
< 5 Years	0 (0.0%)	3 (7.3%)	----
> 5 Years	0 (0.0%)	6 (14.6%)	
> 10 Years	0 (0.0%)	20 (48.8%)	
> 15 Years	0 (0.0%)	12 (29.3%)	

Table 2: Patients distribution according to habits

Patients reported various symptoms like burning sensation, difficulty in mouth opening, difficulty in swallowing, taste change, dryness of mouth and appearance of ulcers. Details of these symptoms in both groups have been shown in table 3.

Variables			p-Value
Burning Sensation			
Yes	0 (0.0%)	41 (100.0%)	<0.001
No	41 (100.0%)	0 (0.0%)	
Difficulty In Mouth Opening			
Yes	0 (0.0%)	41 (100.0%)	<0.001
No	41 (100.0%)	0 (0.0%)	
Difficulty In Swallowing			
Yes	0 (0.0%)	6 (14.6%)	0.025
No	41 (100.0%)	35 (85.4%)	
Taste Change			
Yes	2 (4.9%)	6 (14.6%)	0.137
No	39 (95.1%)	35 (85.4%)	
Dryness Of Mouth			
Yes	6 (14.6%)	17 (41.5%)	0.007
No	35 (85.4%)	24 (58.5%)	
Vesicles And Ulcers			
Yes	1 (2.4%)	28 (68.3%)	<0.001
No	40 (97.6%)	13 (31.7%)	

Table 3: Patients distribution according to symptoms

Mean and standard deviation of CRP was 0.40 ± 0.21 (0.03-0.8) mg/dl and3.62 ±1.02 (1.2-5.45) mg/dl in group I and group II respectively (Table 4).

CRP Finding	Group I	Group II	p-Value
	Frequency (%)	Frequency (%)	
Normal	34 (82.9%)	0 (0.0%)	<0.001
Abnormal	7 (17.1%)	41 (100.0%)	
Total	41 (100.0%)	41 (100.0%)	
Descriptive Statistics of CRP			
Minimum	0.03	1.2	<0.001
Maximum	0.8	5.45	
Mean ± SD	0.40 ± 3.62		
	0.21 ± 1.02		

Table 4: Patients distribution according to CRP finding and descriptive statistics

DISCUSSION

Mouth submucous fibrosis is a chronic, slow-moving condition that may affect any portion of the oral cavity and,

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sometimes, the throat. As a result of the subepithelial and submucosal myofibrosis, the oral mucosa and deeper tissues become stiff, and the mouth gradually becomes more tough to open and the tongue protrudes, making it harder to eat, swallow, and speak [18]. A premalignant condition of the oral cavity is oral submucous fibrosis. It is crucial to keep an eye on these patients to spot any early changes into OSMF patients since different studies have indicated that the malignant transformation rate of OSMF ranges from 7 to 13% [19-21]. Relationship between serum CRP and oral submucous fibrosis is very much important and should be studied. In this regard, as very limited studies are documented on OSMF in Pakistan, so we want to explore the relationship of CRP with OSMF cases in our population and explore its associated findings at LUM & HS. OSMF is a significant health concern particularly in men and women belonging to low socio-economic status and should be considered as a major public health issue. In this study 34 (82.9%) patients suffering from OSMF were male and 7 (17.1%) patients were female. Different studies from Pakistan on OSMF patients also reported higher male and lower female prevalence such as Shaikh *et al.*, [22] reported 88.0% male and only 12.0% female patients, and Memon *et al.*, [23]. reported 66.7% male and only 33.3% female patients. A study by Gosavi and Torkadi from India on OSMF patients also reported higher male prevalence 80.0% and lower female prevalence 20.0% [24]. All similar studies on OSMF patients reporting that male patients are mostly suffering from OSMF as compared to female patients. Different studies including current study suggested that betel nut is the main causative factor for OSMF disease. Betel nut is a potent carcinogen next to tobacco in subcontinent. OSMF starts as a simple superficial mucosal lesion to invade wide area of oral cavity and pharyngeal structures causing significant morbidity leading to mortality in the form of squamous cell carcinoma [25]. In this study all of the participants suffering from OSMF were long-term consumers of betel quid with or without tobacco 13 (31.7%) vs 28 (68.3%)]. Other similar studies also reports that all OSMF patients were involved in using betel nuts [23-25]. OSMF shows a complex pattern of inflammation, so it is very interesting and yet challenging to explore relationship of OSMF and to establish a cause–effect relationship. Inflammation reflects its presence in serum in the form of various chemokines and various other molecules including raised CRP. CRP is one such nonspecific inflammatory marker. In humans, the CRP level is low under normal conditions, but increases up to approximately 1000-fold during inflammation, making CRP probably one of the most useful molecules for monitoring inflammation present in many diseases and conditions. Hence, in the present study, serum CRP levels in OSMF were estimated as compared to apparently healthy individuals [25, 26]. In this study CRP level was significantly (p-value=<0.001) high 3.62 ± 1.02 mg/dl in OSMF patients as compared to normal healthy patients0.40 ± 0.21mg/dl. Similarly, CRP level was significantly (p-value=<0.001) abnormal (raised) in all OSMF patients as compared to normal healthy patients where only 7 (17.1%) were reported with abnormal (raised) CRP levels. Different similar studies also reported the higher mean of serum CRP levels in OSMF patients as compared to normal healthy patients such as Kaja *et al.*, reported the CRP mean 0.58 ± 0.83 mg/dlas compared to controls 0.26 ± 0.05 mg/dl and Kohli reported the CRP mean 4.3708 ± 3.9279mg/dlas compared to controls 3.505 ± 1.4449 mg/dl [21, 27]. Similar to this research, Kumar reported significantly high CRP levels in OSMF patients0.68±0.10 mg/dl as compared to controls [14]. All findings help to conclude that mean serum CRP levels can be a useful prognostic marker in early diagnosis of OSMF.

CONCLUSIONS

It was concluded from the study that serum C- reactive protein levels in oral submucous fibrosis patients was significantly high as compared to normal healthy patients. CRP level was also significantly abnormal (raised) in all oral submucous fibrosis patients as compared to normal healthy patients where only few were reported with abnormal (raised) CRP levels.

Conflicts of Interest

The authors declare no conflict of interest.

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