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RESEARCH PAPER

AN ANALYSIS OF RATE AND FACTORS AFFECTING MALIGNANT TRANSFORMATION OF ORAL SUBMUCOUS FIBROSIS IN PATIENTS ATTENDING THE ORAL MEDICINE CLINIC, DENTAL HOSPITAL PERADENIYA, SRI LANKA - A RETROSPECTIVE STUDY

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Abstract

Background: Oral submucous fibrosis (OSF) is a chronic, progressive, scarring and potentially malignant disease of the oral mucosa seen primarily in the Indian subcontinent and in South East Asia. OSF is a premalignant condition with a malignant transformation rate varying from 7-12%. Even though OSF and oral cancer are common in Sri Lanka, malignant transformation potential and rate have not been studied in our population.

Objectives: To identify the relationship of malignant transformation with age, gender, habits, amount of mouth opening, duration of follow up, presence of other oral potentially malignant disorders and dysplasia in a group of patients with OSF attending the Oral Medicine clinic, University Dental Hospital Peradeniya.

Methods: All the clinical files of patients with OSF attending the Oral Medicine clinic, University Dental Hospital Peradeniya were selected. Cases with OSF where histopathological diagnosis was not available, patients who had developed oral cancer before the diagnosis of OSF and patients who were diagnosed with OSF and received prior surgical therapy were excluded. Data were analysed to identify any relationship of malignant transformation with other variables.

Results: There were 135 patients with a follow up period ranging from 6 months to 23 years and average follow up period was 5.26 years. 75.6% of them were males. 42.2% of them presented with burning sensation as the main complaint. 96.3% of them chewed betel with all ingredients whereas the rest chewed only arecanut. Eight patients developed malignancy during the follow up period giving a malignant transformation rate of 5.9% after a mean follow up period of 6.5 years.

Conclusions: Malignant transformation in patients with OSF is significantly associated with presence of dysplasia on the initial biopsy, presence of any other potentially malignant disorder and the duration of betel chewing.

Introduction

Oral submucous fibrosis (OSF) is a chronic, progressive, scarring and potentially malignant disease of the oral mucosa seen primarily in the South and South East Asian regions of the world. OSF is characterized by

fibrosis of the submucosa, atrophy of the epithelium and reduction of vasculature. Schwartz first described this condition in 1952 and named it 'atrophica idiopathica mucosa oris' and Joshi in 1953 renamed it 'oral submucous fibrosis'. Although various factors have been proposed as aetiological factors in the past, areca nut use is the only proven factor in the aetiology of OSF[1,2]. Arecoline, an alkaloid found in areca nut stimulates fibroblastic proliferation and collagen synthesis leading to OSF. In addition to the local factors, various systemic factors have been suggested to play a role in the causation of the disease. These include anaemia, chronic iron and vitamin B complex deficiency and genetic predisposition[1,3,4].

Fibrosis and sub epithelial hyalinization account for most of the clinical features. OSF is diagnosed by its characteristic clinical features. Incisional biopsy may be needed in order to confirm the diagnosis. Clinical criteria for the diagnosis of OSF include mucosal blanching, hardening and the presence of characteristic vertical fibrous bands. Degree of mouth opening can be used as an objectively verifiable criterion to assess the severity of the disease (functional stage)[5]. Site of the fibrous bands can be used to classify the disease clinically (clinical stage)[5]. OSF starts at the back of the mouth and spreads to the anterior parts of the mouth as the disease progresses. Fibrous bands can be observed at the faucial, buccal and labial mucosae whereas involvement of the bands is minimal in mild disease. Mouth opening has been used as a predictor of the severity and extent of OSF[5].

OSF is a potentially malignant condition with a malignant transformation rate varying from 7-12%[1,6]. Not all the cases of oral potentially malignant disorders (OPMDs) transform into malignancy. Some of them can have dysplasia at the initial stage of the diagnosis whereas others are without any epithelial dysplasia. Histopathological diagnosis of squamous cell carcinoma (SCC) in patients with OSF without any clinical suspicion of SCC, high prevalence of leukoplakia in patients with OSF and high prevalence of epithelial dysplasia are the evidence to suggest premalignant nature of the disease.

The aim of this study was to assess the rate of malignant transformation of OSF and analyse the possible contributory factors such as age, gender, habits, amount of mouth opening, duration of follow up, presence of other OPMD and dysplasia in a group of patients with OSF attending the Oral Medicine clinic, University Dental Hospital, Peradeniya.

Materials and Methods

A hospital-based observational retrospective study was designed to identify the malignant transformational rate of OSF. All the clinical files of patients attending the Oral Medicine clinic, University Dental Hospital, Peradeniya, Sri Lanka were searched and cases diagnosed with OSF were selected for the study.

Exclusion criteria for the study were:
1. Cases of OSF where histopathological diagnosis was not available
2. Those patients who had developed oral cancer before the diagnosis of OSF.
3. Patients who were diagnosed as OSF but had previously received surgical therapy
4. Follow up period of less than 6 months.

All the files were examined and general data including the age, sex, history of complaint, medical problems and habits (especially in relation to tobacco and areca nut usage and alcohol consumption) at the time of presentation were retrieved using a pre-prepared data sheet. Records were searched to identify the existence of potentially

malignant lesions other than OSF and development of cancer during the follow-ups. Functional staging and grading were done. The site in the mouth of any malignancy was also recorded. Patients who had not come to the clinic for a long period were recalled. Informed consent was taken from the patient and thorough clinical examination was carried out to identify the presence of potentially malignant lesions other than OSF or cancer. If a suspected lesion was present, a biopsy procedure was carried out to confirm the diagnosis.

This study was carried out using the retrospective details of patients and was in accordance with the Helsinki Declaration. Ethical clearance for the study was obtained from the Faculty Research and Ethics Review committee, Faculty of Dental Sciences, University of Peradeniya, Sri Lanka (Reference No- FDS-FRC/2014/01)

Data were analysed using SPSS version 17 to identify any relationship of malignant transformation with other variables. Chi-square test was performed to identify the statistical significance between malignant transformation and other different parameters.

Results

There were 135 patients. The majority (75.6%) were males. Age range of the sample was between 21 years to 81 years. Average age of a patient at the initial diagnosis was 49.3 years. Most of them were between 40 to 59 years (54.8%) but there were 24.4% (n=33) young patients who were less than 40 years. The follow up period of the cases studied ranged from 6 months to 23.0 years and average follow up period was 5.26 years. Almost 20% of patients were followed up for more than 10 years (**Table 1**).

The majority of the patients in the study used betel quid with all ingredients whereas 5 patients were using only areaca nut (**Table 1**). Among the patients who used betel quid, a substantial numbers of patients were either smoking or/and using alcohol together with betel quid. Burning sensation was the main complaint (42.2%) in these patients with OSF. Eighty percent of the participants in this study had fibrous bands, 50.8% had restricted tongue movements, 70.4% had depapillation of the tongue whereas depigmentation in lips/ buccal mucosa was found in 45.9% of them. Average mouth opening at the initial presentation in the present study was 31.6mm and the majority of the participants (57%) had 20mm-40mm mouth opening. Twenty three patients had leukoplakia whereas only one patient had erythroplakia in addition to the OSF (**Table 1**). Eight patients developed malignancy during the follow up period giving a malignant transformation rate of 5.9% (**Table 1**). Five of them (62.5%) were males. Average age at the diagnosis of malignancy was 55.4 years with the range of 44 to 68 years. Malignant transformation was observed after 0.9 years to 11.3 years of follow up with an average of 6.49 years (**Table 2**).

A statistically significant association was observed with the malignant transformation and duration of betel chewing ($p=0.018$). Presence of other potentially malignant disorders ($p=0.006$) and presence of dysplasia at the initial biopsy ($p<0.001$) were also significant. However the observed differences of the malignant transformation were not statistically significant with reference to the sex, age, type of habit, frequency of betel chewing, extent of mouth opening at the day of presentation or duration of follow up ($p>0.05$) (**Table 3**).

Table 1. Demographic and other characteristics of the patients, n=135

Variable		N (%)
Sex	Male	102 (75.6)
	Female	33 (24.4)
Age Category	Below 40	33 (24.4)
	40-59	74 (54.8)
	60 and above	28 (20.7)
Follow up	Less than 2 years	38 (28.1)
	2-5 years	31 (23)
	5-10 years	40 (29.6)
	More than 10 years	26 (19.3)
Main complaint	Burning sensation	57 (42.2)
	Difficulty in mouth opening	55 (40.7)
	Pain	0 (0)
	Ulceration	14 (10.4)
	White or Red patch	4 (3.0)
	Referral	3 (2.2)
	Other	2 (1.5)
Habits	Areca nut only	5 (3.7)
	Betel quid	130 (96.3)
	Betel quid only	80 (59.3)
	Betel and smoking	10 (7.4)
	Betel and alcohol	21 (15.6)
	Betel, smoking, alcohol	19 (14.1)
Frequency of habit (n=130)*	Less than 5 quids per day	49 (38.6)
	5-10 quids per day	46 (36.2)
	11-15 quids per day	21 (16.5)
	16-20 quids per day	7 (5.5)
	More than 20 quids per day	4 (3.1)
Duration of habit (n=130)*	0 - 5 years	38 (29.7)
	6-10 years,	37 (28.9)
	11-15 years	12 (9.4)
	16-20 years	29 (22.7)
	21-25 years	10 (7.8)
	over 25 years	2 (1.6)
Clinical features **	Fibrous bands	108 (80.6)
	Restricted tongue	68 (50.8)
	Depapillation on tongue	95 (70.4)
	Depigmentation on lips	62 (45.9)
Extent of mouth opening at The presentation	Less than 20mm	26 (19.3)
	20mm-40mm	77 (57.0)
	More than 40mm	32 (23.7)
Other OPMD	Leukoplakia	23 (17)
	Erythroplakia	01 (0.7)
	Ulceration	09 (6.7)
Malignant transformation	Yes	8 (5.9)

*System missing n=3 **Some patients had more than one symptoms of OSF

Table 2: Characteristics of the patients with malignant transformation (n=8)

Malignant transformation	
Male	5 (62.5%)
Female	3 (37.5%)
Age at malignant transformation	
Mean (SD)	55.38 (10.042)
Age range	44 - 68
Duration of follow up at malignant transformation (years)	
Mean (SD)	6.49 (4.157)
Range	0.92 - 11.3

Discussion

Oral submucous fibrosis (OSF) is a chronic progressive potentially malignant disorder predominantly seen in India, Bangladesh, Sri Lanka, Pakistan, Taiwan, Southern China, Polynesia and Micronesia. Clinical presentation of OSF depends on the stage of the disease. The majority of patients present with burning sensation to spicy food, blanching and stiffening of the oral mucosa and oropharynx, loss of stretchability of buccal mucosa, lip and tongue leading to limitation of mouth opening and tongue movement[1,7]. Even though OSF is common among adults, it has been reported among children as well[8].

OSF has been identified as a potentially malignant disorder for a long time. Paymaster in 1956 first reported the precancerous nature of OSF and it was confirmed later by many other investigators[6,9]. Several findings including high occurrence of OSF in patients with oral cancer, higher incidence of oral cancer in patients with OSF, histological diagnosis of cancer without any clinical suspicion in OSF, high frequency of epithelial dysplasia in cases of OSF and higher prevalence of other potentially malignant disorders specially leukoplakia among OSF cases are considered to be some evidence to suggest the precancerous nature of OSF[1].

Malignant transformation rate of OSF has been reported to be in the range of 7–13%[1,6]. Malignant transformation rate in the present study was 5.9% which is almost within the range reported. But a much lower value of 3.3% has been reported by Hazarey et al., in 2007[10]. The average age of patients with OSF at the diagnosis was 49.3 years in the current study and the average age at diagnosis of malignancy was 55.4 years. This is lower than the values reported by Murti et al (64.6 years) in 1985[6]. There was no gender difference in the malignant transformation where five out of eight patients who developed malignancies (62.5%) were males and it follows the pattern seen in the sample where majority (75.6%) were males. A similar follow up study done in India by Murti et al in 1985[6] demonstrated a female predilection in malignant transformation where all patients who developed cancers in their study were females.

The main complaint in most of the patients in the present study was burning sensation of the mouth particularly for spicy food but Hazarey et al., 2007[10] reported it to be difficulty in mouth opening. Average mouth opening at the initial presentation in the present study was 31.6mm. This difference may be due to the duration of the disease prior to the presentation to the clinic. Progression of the disease with time leads to restricted mouth opening whereas at the early part of the disease process, burning sensation is more problematic for the patients.

Table 3: Association of malignant transformation with the different parameters of the patients

	Malignancy transformation				Significance
	No (n=127)		Yes (n=8)		
	Number	%	Number	%	
Sex					
male	97	76.4%	5	62.5%	*χ^2 =0 .785
Female	30	23.6%	3	37.5%	df=1
					p= 0.376
Age category					
Below 40	33	26.0%	0	0.0%	*χ^2 =5.625
41-59	70	55.1%	4	50.0%	df=2
60 and above	24	18.9%	4	50.0%	p=0.060
Habits					
Areca nut only	5	3.9%	0	0.0%	*χ^2 =1.508
Betel quid only	76	59.8%	4	50.0%	df=4
Betel and smoking	9	7.1%	1	12.5%	p=0.825
Betel and alcohol	20	15.7%	1	12.5%	
Betel, smoking and alcohol	17	13.4%	2	25.0%	
Frequency of betel quid chewing					
Less than 5 quids per day	47	38.8%	2	33.3%	*χ^2 =1.680
5-10 quids per day	44	36.4%	2	33.3%	df=4
11-15 quids per day	19	15.7%	2	33.3%	p=0. 794
16-20 quids per day	7	5.8%	0	0.0%	
More than 20 quids per day	4	3.3%	0	0.0%	
Duration of betel quid chewing					
0 - 5 years	38	31.1%	0	0.0%	*χ^2 =13.605
6-10 years,	36	29.5%	1	16.7%	df=5
11-15 years	12	9.8%	0	0.0%	p=0. 018
16-20 years	24	19.7%	5	83.3%	
21-25 years	10	8.2%	0	0.0%	
over 25 years	2	1.6%	0	0.0%	
Extent of mouth opening at the presentation					
Less than 20mm	24	18.9%	2	25.0%	*χ^2 =0.640
20mm-40mm	72	56.7%	5	62.5%	df=2
More than 40mm	31	24.4%	1	12.5%	p=0.726
Follow up Period					
Less than 2 years	36	28.3%	2	25.0%	*χ^2 =1.966
2-5 years	30	23.6%	1	12.5%	df=3
5-10 years	38	29.9%	2	25.0%	p=0.579
More than 10 years	23	18.1%	3	37.5%	
Other OPMD					
presence	26	20.5%	5	62.5%	*χ^2 =7.515
absent	101	79.5%	3	37.5%	df=1
					p=0.006
Grading of OSF					
1	37	29.1%	0	0.0%	*χ^2 =43.754
2	34	26.8%	2	25.0%	df=4
3	12	9.4%	0	0.0%	<0.001
4A	4	3.1%	5	62.5%	
4B	40	31.5%	1	12.5%	

**chi-square test was performed*

Malignant transformation was observed after 0.9 years to 11.3 years with an average of 6.49 years. Four out of 8 patients who developed cancer in the current series were either smokers or consumers of alcohol or used both other than betel quid. Similar results had been demonstrated by many others[10, 11]. Malignant transformation in OSF would be enhanced due to smoking having a modifying effect. One of the most important predictors of malignant transformation of OSF is the presence of epithelial dysplasia at the initial biopsy. This fact was confirmed by the present study as well as the study done by Shue-Sang Hsue et al., in 2007[12].

Conclusions

This study shows that the malignant transformation rate of OSF was 5.9% after a mean follow up period of 6.5 years. The most important factor associated with malignant transformation was the presence of dysplasia in the initial biopsy followed by the presence of other potentially malignant disorder and duration of betel quid chewing.

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