Concomitant Association of Oral Submucous Fibrosis and Oral Squamous Cell Carcinoma and Incidence of Malignant Transformation of Oral Submucous Fibrosis in a Population of Central India: A Retrospective Study

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Abstract

Aim To evaluate the incidence of oral squamous cell carcinoma concomitant with oral sub mucous fibrosis in central India and to correlate precipitating factors associated with oral submucous fibrosis and oral squamous cell carcinoma. This paper also aims to study the incidence of oral squamous cell carcinoma arising secondary to untreated oral submucous fibrosis.

Materials and Methods Two hundred and twenty five cases of oral squamous cell carcinoma and one hundred and nineteen cases of oral submucous fibrosis of various regions in oral cavity were included in the study. All the included cases were clinically and histopathologically diagnosed and retrospective data was retrieved.

Result In the present study of 119 patients of oral submucous fibrosis, 97.4 % were found to have betel nut chewing habit. Incidence of malignant transformation to oral squamous cell carcinoma in patients of untreated oral submucous fibrosis was found to be 4.2 % in the present study. The incidence of oral cancer concomitant with oral submucous fibrosis was found to be 25.77 %, which is statistically significant.

Conclusion From the present study, it is evident that the malignant potential of OSF is underestimated. However, considering the small sample size and the fact that the study was carried out in a small geographical area, further study with a larger sample size and longer duration of

follow up on a multicentric basis may be required to reveal the actual malignant potential of the disease.

Keywords Oral squamous cell carcinoma · Oral submucous fibrosis · Malignant potential

Introduction

Cancer is one of the main causes of death in all societies, its relative position varying with age and sex [1]. Globally, oral cancer is the sixth most common cause of cancer related- death, although many people are unaware of its existence [1]. In the International classification of diseases (ninth revision- WHO), oral cancer is classified under the *rubrics* 140 (lip), 141 (tongue), 143 (gingiva), 144 (floor of the mouth), and 145 (other parts of the mouth) [2]. Of all the histologic variants of oral cancer, oral squamous cell carcinoma is the fifth most common cancer worldwide [3]. OSCC is a also major cause of morbidity and mortality in the Indian subcontinent [3]. The high incidence of oral carcinomas in India can be contributed in part by the habit of tobacco and betel quid chewing [4].

Oral precancer is distinguished by WHO (World Health Organization) into ‘precancerous lesions’ (e.g. Leukoplakia, Erythroplakia) and ‘precancerous conditions’ (Eg. Oral submucous fibrosis, Lichen Planus) [5]. It has been documented in literature and frequently observed in clinical practice that many cases of OSCC are associated with or preceded by precancerous lesions and conditions for a varying length of time. Interestingly, they share the same etiologic factors with oral cancer, particularly the use of tobacco, and exhibit the same site and habit relationships. These precancerous lesions and conditions can therefore serve as a good model for investigating the chemopreventive approach for

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controlling oral cancer. The recognition and management of precancers, therefore, constitute a vital oral cancer control measure.

Oral sub mucous fibrosis (OSMF) may be defined as an insidious, chronic disease affecting any part of the oral cavity and sometimes pharynx. Although occasionally preceded by and/or associated with vesicle formation, it is always associated with a juxta—epithelial inflammatory reaction followed by fibro elastic change of the lamina propria, with epithelial atrophy leading to stiffness of oral mucosa and causing trismus and inability to eat [6, 7]. Worldwide, estimates of OSMF shows a confinement to Indians and Southeast Asians, with overall prevalence rate in India to be about 0.2–0.5 % and prevalence by gender varying from 0.2 to 2.3 % in males and 1.2–4.57 % in females [8]. It has been suggested that ingestion of chillies, genetic susceptibility, nutritional deficiencies, altered salivary constituents, autoimmunity and collagen disorders may be involved in the pathogenesis of this condition [7]. The condition is well recognized for its significant malignant potential, the incidence of which varies from one region to another, as shown by a number of studies [9–14]. Pindborg [13] in 1980, from a series of epidemiological surveys conducted in India and South Africa found malignant change in 3 to 6 % of patients having OSMF. In 1985, Murti et al. [14] assessed malignant transformation rate of 7.6 % in a 10-year mean observation period.

In view of increasing number of patients of OSCC who have associated OSMF in the clinical practice, the incidence of OSCC concomitant with OSMF seems to be much higher than that reported in the literature. To authenticate this clinical observation with a scientific statistical data, it was decided to carry out a study with the purpose of evaluating the incidence of OSCC concomitant with OSMF in a population of Central India. The authors also aimed to observe the incidence of malignant transformation in cases of OSMF and to investigate various precipitating factors associated with OSMF.

Patients and Method

The present study was undertaken by the department of Oral and Maxillofacial Surgery, Sharad Pawar Dental College and associated Acharya Vinobha Bhave Rural Hospital, Sawangi, Wardha after achieving clearance from the ethical board of the institute. Two hundred and twenty five patients with OSCC of various regions in oral cavity (buccal mucosa, tongue, palate, alveolus, floor of mouth, lip) and one hundred and nineteen cases of OSMF were included in the study after obtaining informed consent from them. All the included cases were clinically and histopathologically diagnosed; but not treated at the stage

when OMSF was detected, due to denial by the patients for personal/social reasons and fear of undergoing surgery. However, they were on a follow-up on a six-monthly basis. But, for patients diagnosed as OSCC also having concomitant OSMF, and who gave their consent for surgery, wide excision of lesion along with partial or hemimandibulectomy and modified radical neck dissection surgery was done, so that neck nodes also could be taken care of. The retrospective data from the year 1999 to 2006 was retrieved from the central medical record section of our institute.

Observation

As computed from Table 1, the age group of 21–30 years showed the highest number of cases suffering from OSMF i.e. 52 patients (44.06 %), of which 36 were males and females were 16. Overall occurrence of the disease was higher in males (73.72 %) than females (26.27 %) patients i.e. 97.47 % of the total OSMF cases had an associated habit of betel nut chewing (Table 2). Table 3 shows that 13 out of 119 OSMF patients i.e. 10.92 % showed other existing premalignant disease i.e. leukoplakia (9 cases) and erythroplakia (4 cases). Out of 225 patients who presented with OSCC, 58 patients also had OSMF (Table 4), thus revealing the incidence of concomitant OSMF with OSCC as 25.77 % in our study, which is statistically significant. Out of 119 patients with OSMF, 5 cases i.e. 4.2 % of OSMF cases transformed into OSCC (Table 5). Of the 58 OSMF patients having OSCC, the majority cases (26 patients) had malignancy of buccal mucosa, followed by tongue (15 patients), followed by other sites (17 patients)

Table 1 OSMF transforming into OSCC (malignancy)

	No. of patients	Percentage	Incidence (%)	z-value
Total number of patients with OSMF	119	–	4.2	2.28
Transformation of OSMF into OSCC	05	4.2		S
				$P < 0.05$

Critical value = 1.96

Table 2 Incidence of concomitant OSCC with OSMF

	No. of patients	Percentage	Incidence (%)	z-value
Total number patients with OSCC	225	100	25.77	7.98
Patients of OSCC secondary to OSMF	58	25.77		S
				$P < 0.05$

Critical value = 1.96

Table 3 Associated habit of betel nut in patients with OSMF

Habit	No. of cases (119)	Percentage	z-value
Betel nut/tobacco chewing	116	97.47	62.02
			$P < 0.05$

Critical value $Z\alpha = 1.96$

Table 4 Associated lesions in patients with OSMF

Lesions	No. of cases (119)	Total no. of patients with premalignant lesions	Percentage
Leukoplakia	9	13	10.92
Erythroplakia	4		

Critical value $Z\alpha = 1.96$

Table 5 Age-wise and sex-wise distribution of patients of OSMF

Age group (years)	Male (%)	Female (%)	Total (%)
10–20	16 (18.39 %)	1 (3.22 %)	17 (14.40 %)
21–30	36 (41.37 %)	16 (51.61 %)	52 (44.06 %)
31–40	18 (20.68 %)	6 (19.35 %)	24 (20.33 %)
41–50	11 (12.64 %)	6 (19.35 %)	17 (14.40 %)
51–60 and more	6 (6.89 %)	2 (6.44 %)	8 (6.77 %)
Total	87 (73.72 %)	31 (26.27 %)	119 (100.00 %)
Mean age	33.80	30.70	31.51
SD	11.61	11.16	11.31

as depicted in Table 6. Figure 1 depicts blanching on oral tissues and fibrotic buccal mucosa, which is typical to OSMF. OSCC of buccal mucosa, tongue, labial mucosa concomitant with OSMF can be observed in Figs. 2, 3 and 4 respectively.

Discussion

The clinical grading of the disease was proposed in literature by Borle et al. [15] in 1991 as eruptive phase and fibrosis induction phase. Khanna and Andrade [16] in 1995 classified the disease on the basis of severity and histopathological findings. They defined the disease as “A

chronic, progressive premalignant condition, with juxta-epithelial deposition of fibrotic tissue followed by muscular degeneration and limitation in oral opening” [16].

The results of our study reveal that 96.6 % of the patients having OSMF had the habit of betel nut chewing in different forms. The areca alkaloids in betel nut are known for their action on energy release mechanism in the central nervous system as gamma amino inhibitors [17]. Thus, any major change in the attitude and habit of betel nut chewing in the society is unlikely to happen without the help of adequate health care campaigns.

In the present study, the sex predilection is in favour of males. This coincides with the result of the studies carried out by Sumathi et al. [18]. The majority of patients with OSMF belonged to younger age group (15–30 years), as also observed by Sumathi et al. [18]. The reason could be attributed to the habit of betel nut chewing; which can be deleterious in all the sexes, and particularly at an early age. Due to precipitation of this disease at an early age, the progression & severity of fibrosis in younger patients is more. This leads to malnourishment secondary to trismus, wasting of cheek muscles [18] and esthetic compromise.

OSMF is also found to be associated with other premalignant lesions [14, 19] like leukoplakia and erythroplakia and in the present study the incidence of the same was found to be 11 %. Normally in the OSMF, the oral mucous membrane is found to be severely atrophic and development of such lesions like leukoplakia and erythroplakia associated with acanthosis and proliferation of epithelial lining warrants serious thought and early intervention, as it could be a transition from fibrosis to a frank squamous cell carcinoma. From the above findings it is evident that the risk of developing OSCC with OSMF is significantly higher, endorsing its carcinogenic potential at designation as a premalignant condition.

Incidence of malignant transformation of OSMF was found to be 4.23 % in the present study which is significantly higher than few studies carried out in the past, but is in conformity with the studies of Pindborg et al. [19] in 1984, whereas less than the incidence found by Murti et al. [14] in 1985. Both these studies were carried out in the Indian subcontinent, where betel nut chewing with or without tobacco is commonly seen in the society.

In the Indian circumstances, the transformation of OSMF into OSCC and its incidence is difficult to calculate

Table 6 Sites involved in patients of OSCC concomitant with OSMF

	Number of patients	Percentage
Patients of OSCC concomitant with OSMF	58	100
Site involved: <i>Cheek</i>	26	44.8
Site involved: <i>Tongue</i>	15	25.86
Other sites	17	29

Fig. 1 Photograph showing blanching and fibrotic buccal mucosa in a patient of OSMF

Fig. 2 Photograph showing OSCC of buccal mucosa concomitant with OSMF

Fig. 3 Photograph showing OSCC of tongue concomitant with OSMF

as most of these patients are socioeconomically poor, ignorant and illiterate. Therefore, keeping long term follow up is a challenging task. However, the concomitant OSCC with OSMF can be easily demonstrated from the clinical and histopathological observations. The concomitant association of OSCC with OSMF was 25.77 % in the present study. This is significantly less than the findings observed by Zachariah et al. [20] in 1966, who found such

Fig. 4 Photograph showing OSCC of labial mucosa concomitant with OSMF

association to be as high as 40 %. Shiau et al. [12] in 1979 observed the incidence of OSMF with oral malignancy to be 23 % in their study, but the sample size was very small i.e. 100 patients.

A definite site predilection was observed in our study. The posterior buccal mucosa was the most commonly involved site (44.8 %). Moreover, it was observed that such patients often reported with advanced stage of the disease extending to the retromolar trigon. In such patients, owing to the stiffness of mucosa and constant trauma from occlusion due to malpositioned lower and upper third molar, the OSCC could precipitate owing to chronic irritation. As the diagnosis is often delayed due to trismus, proper oral examination is not possible. To add to the clinical difficulties, the consistency of tissues involved in OSMF becomes firm to hard and an early sign of carcinoma, i.e. induration is often masked, thus making an average clinician misdiagnose the condition very often. The concept of field cancerization is also well executed in patients with submucous fibrosis [21]. Two OSMF patients in our study had double primary malignant lesions and one patient had multiple primary lesions.

Since many of the cases reported as stage III and stage IV malignancies at the time of first diagnosis, the surgical excision of these lesions was inadequate as almost all of them involved the retromolar region. Clinical assessment of surgical margins was extremely difficult when surgery was undertaken for malignant cases, owing to alteration in the consistency of tissues and unavailability of facilities for frozen section at our institute to establish adequate surgical clearance.

Conclusion

From the present study, it is evident that the malignant potential of OSMF is underestimated. However, considering the smaller sample size and the fact that the study was carried out in a small geographical area, further studies with larger sample sizes and longer duration of follow up on

multicentric basis may be carried out to reveal the actual malignant potential of the disease. It is therefore empirical to highlight the malignant potential of OSMF and take all the necessary steps towards prevention of the disease through public awareness rather than waiting for futile effort to treat the same ineffectively. The caption “prevention is better than cure” becomes more relevant for such complicated clinical premalignant conditions.

Conflict of interest None.

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