Premalignant Lesions of the Oral Cavity: Our Experiences at a Tertiary Care Teaching Hospital of Eastern India

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ABSTRACT

Background: Premalignant oral cavity lesions are potentially malignant diseases that include oral leukoplakia, erythroleukoplakia, oral submucous fibrosis (OSMF), and lichen planus. There are various etiological factors associated with premalignant lesions of the oral cavity. The most frequent etiological factors are tobacco use, consumption of alcohol, chewing of betel quid containing areca nut and solar rays.

Objective: To study details of the premalignant lesions, including their incidence, etiological factors and management at a tertiary care teaching hospital.

Materials and Methods: This is a retrospective observational study conducted between December 2018 to January 2021. There were 652 patients with oral cavity premalignant lesions enrolled in this study.

Result: There were 383 male and 275 females patients with a male to female ratio of 1.39:1. The majority of the patients with oral cavity premalignant lesions are in the age group 50 to 60 years. Out of 658 patients, 262 had oral leukoplakia, 149 had OSMF, 48 erythroplakia, 52 oral candidiasis and 25 had oral erythroleukoplakia.

Conclusion: Early diagnosis and prompt treatment are important steps for managing the premalignant lesions of the oral cavity as late stages may progress into severe dysplasia and even carcinoma in situ and/or squamous cell carcinoma in the oral cavity.

Key Words: Premalignant lesions, Oral cavity, Leukoplakia, Erythroleukoplakia, Oral submucosal fibrosis, Oral cancer

INTRODUCTION

Cancer of the oral cavity is the fifth most common cancer in the world.¹ The annual incidence of oral cancer is approximately 29,370 cases in the United States. ¹Oral cancer was the fourth important cause of death among males and sixth among both sexes in various cancers.² Leukoplakia, erythroplakia, erythroleukoplakia, oral submucosal fibrosis, oral lichen planus and oral candidiasis are common premalignant lesions of the oral cavity.³ These premalignant lesions are usually associated with and preceding squamous cell carcinoma of the oral cavity. The malignant potential of these premalignant lesions of the oral cavity is variable. In 2005, World Health Organization introduced the term "potentially malignant disorders" for the premalignant lesions to eliminate the terminological confusion in clinical practice.⁴ The buccal mucosa, lower lips and edges of the tongue are com-

monly affected regions for these premalignant lesions. The exact causes of the premalignant lesions of the oral cavity are often variable, which may be associated with betel nut chewing, cigarette smoking and alcohol consumption.³ However, tobacco chewing is a major risk factor for leukoplakia, oral submucosal fibrosis and erythroleukoplakia. The human papillomavirus (HPV) has been thought to play an important role in etiopathogenesis of the oral cavity premalignant lesions.³ There is also a high prevalence of p53 mutations in premalignant lesions like erythroplakia.¹ Patient under immunosuppressive drugs after organ transplant, human immunodeficiency virus patients and chronic graft versus host disease after stem cell transplantation are in the risk group for oral cavity premalignant lesions and oral cancer.³ The diagnosis is usually made during routine examination of the oral cavity. The diagnosis is based on the

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clinical presentations and histopathological reports. The premalignant lesions of the oral cavity may show changes such as squamous hyperplasia, mild dysplasia, moderate dysplasia, severe dysplasia and carcinoma in situ. Early detection of the oral cavity premalignant lesions is very important for getting a successful outcome. Therefore, different modalities such as oral cavity examination, supravital staining, cytology and optical technologies like spectroscopy, fluorescence spectroscopy, optical tomography, narrow-band imaging and multimodal optical imaging can be utilized.²

The treatment options include change of lifestyle factors like cessation of tobacco and alcohol, medication with retinoid or antimycotics and surgical treatment like excision, cryosurgery and laser.⁴ The outcomes of the treatment options vary, and long-term follow-up studies are also few in the literature. After surgical excision, the chance of recurrence and cancer development at the excision sites has also been reported. However, in the case of low to moderate grade, premalignant lesions of the oral cavity are often treated observation as well as ablation. Although there is advancement in the surgical technique, resection of the tissue from the oral cavity may negatively affect the mechanisms of swallowing and speech. Beta-carotene and retinoids are commonly used antioxidants for chemoprevention of the oral cavity premalignant lesions.⁵ Chemoprevention should be advised if the premalignant lesions and their sites in the oral cavity or medical status would make difficult surgical removal.⁵ The incidence, etiological factors and management of the oral cavity premalignant lesions are less studied in this region of the world. So, this study attempts to evaluate the details of the premalignant lesions of the oral cavity.

MATERIALS AND METHODS

This is a single institutional prospective study from December 2018 to January 2021. This study was approved by our institutional ethics committee (IEC) with reference number IEC/IMS/SOA/112/2.12.2017. Patients with a clinical diagnosis of the premalignant lesions of the oral cavity of our tertiary care institute were enrolled in this study. There were 658 patients with oral cavity premalignant lesions who participated in this study. All the patients' data with oral cavity premalignant lesions were collected about age, sex, site of involvement and history of addiction. Patient records were compiled from the department of otorhinolaryngology and were retrieved manually. In this study, all the procedures were done with the involvement of human participants as per ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments. Detailed clinical examination of the oral cavity was done in each participating patient of this study. The patient's habits such as addiction to alcohol, smoking, betel nut chewing or tobacco chewing were evaluated. The

exact locations of the premalignant lesions of the oral cavity were assessed, such as buccal mucosa, the floor of the mouth, tongue, retro-molar area, mandibular mucosa and sulcus and maxillary mucosa and sulcus.

Patients diagnosed histopathologically as malignancy of the oral cavity or those who underwent surgery or radiotherapy in the past were excluded from this study. All of the cases underwent treatment, both surgical and conservative. All the premalignant lesions were biopsied before confirmation of the diagnosis. The surgical treatment options included laser (Lumenis CO₂ laser, New York) and coblation (Smith Nephew, Watford, United Kingdom). The premalignant lesions of the oral cavity, such as leukoplakia (Fig.1), erythroplakia (Fig.2), erythroleukoplakia, were excised with surgical interventions such as laser and coblation. The conservative treatment included maintaining good oral hygiene with mouth antiseptic gargles, anti-oxidants and cessation of smoking, alcohol, betel nut chewing, spicy food, tea and coffee. After the immediate postoperative period, the patients were examined every three months for the first year and every six months in the next year.

Statistical Analysis

In this study, all the data were recorded and analyzed using Statistical Package for Social Science (SPSS) software, v20.

RESULT

There were 658 patients diagnosed with premalignant lesions in the oral cavity. Out of 658 cases, 383(58.20%) were males, and 275(41.79%) were female. The male to female ratio is 1.39:1. The mean age of the patients was 53.40 years and age ranged from 20 to 72 years. The majority of the patients who participated in this study belonged to the 51 to 60 years of age group (Table.1). Out of the 658 patients, 502 patients (76.29%) had no complaints, whereas 110(16.71%) had a burning sensation in the throat and 24(3.64%) had foreign body sensation in the throat and odynophagia in 22(3.34%) patients. The majority of the patients (76.29%) with premalignant lesions of the oral cavity were asymptomatic. Out of the 658 patients with premalignant lesions, leukoplakia constitutes 39.82%, OSMF (Fig.3) constitutes 22.64%, lichen planus constitutes 18.54%, and oral candidiasis constitutes 7.90%(Table 2). Leukoplakia is the most common premalignant lesion of the oral cavity in this study. The most common addictions or habits of the patients associated with premalignant lesions of the oral cavity was consumption of alcohol (29.17%) followed by smoking (17.62%) and then betel nut chewing (15.50%)(Table 3). The typical locations of the oral cavity premalignant lesions include buccal mucosa (31.30%), the floor of mouth (25.53%), tongue (17.93%) (Table.4). Out of 262 cases of leukoplakia, 144 cases under-

went surgical excision, whereas 118 were treated conservatively. Out of 48 cases of erythroplakia, 32 cases underwent complete surgical excision of the lesion. Out of 25 cases of the erythroleukoplakia, 15 cases underwent complete surgical excision and 10 cases were treated conservatively. Out of 149 cases of OSMF, 32 cases underwent surgical treatment for mouth opening and the rest were treated with topical steroid injection, anti-oxidant vitamins and mouth opening exercises.

Out of the 484 cases of leukoplakia, OSMF, erythroplakia and erythroleukoplakia, 223 cases were treated with surgical techniques, which included laser and coblation assisted excision. All these cases that underwent surgical excision showed malignant changes in 5 cases, confirmed by histopathological study. These five malignant cases were treated with surgery and radiotherapy. All 52 cases of oral candidiasis were treated with the application of the antifungal topical mouth paint with the treatment of diabetic patients with anti-diabetic medications. All 122 cases of oral lichen planus were sent to the dermatology department for treatment, where all of them were treated with topical steroids with the maintenance of good oral hygiene.

Out of 658 cases, 11 cases (5 leukoplakia, three erythroplakia, one erythroleukoplakia, two lichen planus) showed malignant transformation at one year follow up, which was confirmed by histopathological examinations.

DISCUSSION

Premalignant lesions of the oral cavity are often called potentially malignant disorders and include a group of diseases that should be diagnosed in an early stage.⁵ The premalignant lesions of the oral cavity include oral leukoplakia, oral submucous fibrosis, lichen planus and oral candidiasis.⁵ The premalignant lesions can be seen in any part of the oral cavity, and the anatomical landmark for the oral cavity includes lips, the mucosal lining of the cheek, the floor of the mouth, anterior two-thirds of the tongue, upper and lower gingiva (gums) and hard palate.⁶ The premalignant lesions of the oral cavity are found in association with and preceding oral squamous cell carcinoma.⁶ Oral cancer is one of the tenth common cancer in the world. Oral cancer ranks fifth among males and sixth among females and seventh among both sexes.² Leukoplakia, erythroplakia, lichen planus and OSMF are well known premalignant lesions of the oral cavity.⁷ As per the WHO definition, oral leukoplakia is defined as a predominantly white lesion of the oral cavity mucosa, which cannot be characterized as any other definable condition, constitutes a worldwide prevalence of approximately 2%.⁸ However, the malignant transformation of the oral leukoplakia varies from 2.2 to 17.5%.⁹ As per the appearance of the lesion, leukoplakia is divided into four types such as early

or thin, homogenous or thick, granular or verruciform and speckled or erythroleukoplakia.¹⁰ Each type of leukoplakia lesion has a different potential for malignant transformation.¹¹ In this study, the most common premalignant lesion of the oral cavity was leukoplakia followed by OSMF and lichen planus.

Erythroplakia is defined as a red patch in the oral cavity that cannot be characterized clinically or pathologically as any other definable disease. Erythroplakia appears as red, discrete, velvety macule or plaque, <1.5cm in diameter on the floor of the oral cavity, soft palate or buccal mucosa.¹² The prevalence of erythroplakia is lower than leukoplakia and constitutes 0.02% to 0.83%.¹² Tobacco chewing and alcohol consumption are two strong risk factors for the development of erythroplakia in the oral cavity. A high prevalence of p53 mutations is reported for the origin of this oral erythroplakia.¹³ However, the erythroplakia has a higher risk for malignant transformation than oral leukoplakia.¹³ In this study, the patients with oral cavity erythroplakia include 7.29%.

Erythroleukoplakia carries a higher risk for malignant transformation in comparison to other potentially premalignant lesions such as leukoplakia, lichen planus and OSMF.¹⁴ The histopathological study of the erythroplakia or erythroleukoplakia often show squamous cell carcinoma in situ or invasive squamous cell carcinoma.¹⁴ OSMF is a condition that is characterized by alteration in the fibroelastic qualities in the submucosal soft tissues of the oral cavity. Areca nut with or without tobacco chewing often acts as an etiological agent for OSMF. Betel quid and Gutkha are commonly available products in the market which contain areca nuts. OSMF is documented to malignant transformation at a rate of 7 to 30%.¹⁵ In this study, OSMF is the second most common premalignant lesion of the oral cavity, which constitutes 22.64% among all types of the premalignant lesions found in the oral cavity.

Oral lichen planus is a premalignant lesion with characteristic lacy, white, reticular, which is classically found in the buccal mucosa.¹⁶ Oral lichen planus of the oral cavity may be found clinically as six different subtypes such as popular, reticular, plaque-like, atrophic, erosive and bullous types.¹⁶ The most common type of oral lichen planus is a reticular pattern which shows as fine white striae called 'Wickham's striae'. Typically these lesions are asymptomatic and may present bilaterally and symmetrically. The erosive pattern is often found as irregular erosion or ulceration covered by a fibrinous plaque or pseudo-membrane. Both erosive and atrophic types are usually associated with a burning sensation and pain, which can be exacerbated by trauma, spicy, hot or acidic diet. The atrophic and erosive varieties of the oral lichen planus have a greater chance of malignant transformation in comparison to other types. In this study, oral lichen planus was the third most common oral cavity pre-

malignant lesion, which constitutes 18.54% of all varieties of premalignant lesions of the oral cavity. Oral candidiasis is an opportunistic infection of the oral cavity by *Candida* species, the commonest being *Candida albicans*. This lesion is considered a premalignant lesion of the oral cavity. There are three types of oral candidiasis such as acute candidiasis, chronic candidiasis and angular cheilitis. The risk factors for oral candidiasis include impaired salivary gland function, dentures, drugs, high carbohydrate diets, old age, smoking and diabetes mellitus.^{17,18} In this study, patients with oral candidiasis include 7.90%.

The exact cause for the development of the premalignant lesions of the oral cavity is not well-known.¹⁹ The risk factors associated with premalignant lesions of the oral cavity are tobacco chewing, cigarette smoking and alcohol.²⁰ Tobacco chewing is an important factor resulting in the OSMF and erythroplakia. Cigarette smoking may be a very important risk factor for leukoplakia. In this study, 17.62% of patients were addicted to cigarette smoking. Tobacco chewing is important to risk factors for the development of the oral premalignant lesions and may be a major source for transformation to the malignancy in the oral cavity in the Indian population. Betel nut chewing is an important aetiology for the development of the premalignant diseases of the oral cavity.²¹ The important chemical components of the betel nut are polyphenols, tannins and alkaloids. Arecoline is the primary alkaloid present in the betel nut.²² Regular chewing of the betel nut may induce chronic irritation and inflammation of the mucosal lining of the oral cavity. In this study, 15.50% of patients were addicted to betel nut chewing. Alcohol consumption may increase the risk by 1.5 fold for oral leukoplakia, by two folds for OSMF and three folds for erythroplakia.²³ In this study, tobacco chewing, cigarette smoking and alcohol were important risk factors for the development of the premalignant lesions of the oral cavity. The human papillomavirus (HPV) may also play a role in the etiopathogenesis of the premalignant lesions of the oral cavity.²⁴

Timely diagnosis and treatment of the premalignant lesions of the oral cavity help in the prevention of the development of squamous cell carcinoma in the oral cavity.²⁵ The diagnosis is usually confirmed by the biopsy for evaluation of the degree of dysplasia. The treatment modalities for oral cavity premalignant lesions are lifestyle factors like cessation of tobacco and alcohol, medical treatments with retinoid or antimycotics, surgical excision, laser surgery and cryosurgery.²⁶ The treatment outcomes of these treatment options appear to vary and require long-term follow up. After surgical treatment, the chances of recurrence and malignant transformation have been documented as 10-20% and 3-9%, respectively.²⁷ But there is no randomized clinical study reported so far.²⁸ The standard gold treatment for clinically high-grade premalignant lesions of the oral cavity includes surgical excision or laser ablation. However, the low-grade

premalignant lesions may be treated with observation. Despite advancement in surgical techniques, the resection of the soft tissues of the oral cavity may cause a negative impact on deglutition, speech and swallowing.

The traditional treatment of the premalignant lesions of the oral cavity such as leukoplakia, erythroplakia, and erythro-leukoplakia is total surgical excision, which may cause a scar formation in case of the large lesion.²⁹ Another treatment option is photodynamic therapy which helps to excise the premalignant lesions of the oral cavity as it can be used repeatedly without cumulative side effects and cause little or no scar formation.³⁰ Currently, there are three treatment modalities for OSMF such as surgery, physical and medical. The surgical treatment is done to improve the mouth opening and movements. The physical treatment includes a physical exercise regimen, splints or different mouth opening devices and microwave diathermy. There are several medical treatments which include steroids, interferon-gamma, placental extracts, beta carotene, lycopene vitamins, immunized milk, collagenase, hyaluronidase, chymotrypsin and aloe vera.³¹ In this study, out of 149 cases of OSMF, 32 cases underwent surgical treatment for mouth opening and the rest were treated with topical steroid injection, anti-oxidant vitamins and mouth opening exercises.

There is the possibility of recurrence of the premalignant lesions after its treatment, so monitoring of the patient should be needed. The important part of the treatment is always advise the patient to stop the habits of betel nut chewing, gutkha chewing, cigarette smoking and alcohol consumption. Mass screening of the oral cavity should be done for early detection of the premalignant lesions and prompt treatment. There should be intensive public education for changing the lifestyle for preventing such premalignant lesions of the oral cavity. The legislative measures like the control on the production or banning and restriction on the sale of tobacco products and alcohol should be strictly applied.

CONCLUSION

Premalignant lesions of the oral cavity often present with visibly abnormal areas on the mucosal lining and may result in significant anxiety of the patients. The diagnosis of the premalignant lesions is based on the clinical presentations and histopathological report. Clinicians should perform the oral cavity examination properly and alert for the patient's addiction to smoking, alcohol consumption and betel nut chewing. The suspicious lesions in the oral cavity are usually biopsied to evaluate for dysplasia. The treatment of choice is surgery, and it should be initiated early for preventing malignant transformation. Oral cancer does not originate as an isolated cellular phenomenon, rather as an anaplastic tendency affecting many cells at once and leads to multifocal develop-

ment of cancer at various rates in response to carcinogen like tobacco. So, multiple primary cancers and recurrence can occur after the complete excision of oral cancer.

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Figure 1: Oral cavity showing leukoplakia on the tongue.

Figure 2: Buccal mucosa of the oral cavity showing erythroplakia.

Figure 3: Oral cavity showing OSMF with trismus.

Table 1: Age wise distribution of patients along with symptoms with oral premalignant lesions

Age group	Male (%)	Female (%)	Total number	Percentage (%)
20 to 30	66(58.92%)	46(41.07%)	112	17.02
31 to 40	82(55.40%)	66(44.59%)	148	22.49
41 to 50	62(57.40%)	46(42.59%)	108	16.41
51 to 60	112(58.33%)	80(41.66%)	192	29.17
Above 60 years	61(62.24%)	37(37.75%)	98	14.89

Table 2: Different types of the premalignant lesions in the oral cavity

Premalignant lesions	Number of patients (n=658)	Percentage (%)
Leukoplakia	262	39.82
Oral submucous fibrosis (OSMF)	149	22.64
Lichen planus	122	18.54
Oral candidiasis	52	7.90
Erythroplakia	48	7.29
Erythroleukoplakia	25	3.79

Table 3: Distribution of habits of the patients with oral premalignant lesions

Habits	Number of patients	Percentage (%)
Betel nut chewing	102	15.50
Smokers	116	17.62
Alcohol consumption	192	29.17
Both tobacco chewing and smoking	78	11.85
Both tobacco chewing and alcohol consumption	56	8.51
All three habits tobacco, smoking and alcohol consumption	46	6.99
No addiction to tobacco chewing, smoking and alcohol	68	10.33

Table 4: Location of the oral premalignant lesions

Location	Number of cases	Percentage (%)
Buccal mucosa	206	31.30
Floor of mouth	168	25.53
Tongue	118	17.93
Mandibular mucosa and sulcus	55	8.35
Maxillary mucosa and sulcus	34	5.16
Retromolar region	22	3.34
Palate	20	3.03
Lip	12	1.82
Bilateral involvement	23	3.49