An overview of the risk factors associated with multiple oral premalignant lesions with a case report of extensive field cancerization in a female patient

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Background. Field cancerization is a well-known and well-documented process of malignant transformation first coined by Slaughter et al. in 1953. Tobacco chewing was associated with the greatest increase in the risk of multiple oral premalignant lesions and may be the major source of field cancerization of the oral cavity in the Indian population. The field cancerization will probably help clinicians in complementing evaluation of pathologic biopsy specimens.
Material and Methods. We present a case report of field cancerization in a 63-year-old Indian female. She presented with an intra-oral generalized hyperkeratotic verruciform type white lesions involving right and left buccal mucosa, lower labial mucosa, upper and lower vestibule, dorsal, ventral and right lateral border of the tongue, hard and soft palate. Microscopic examination revealed features of verrucous carcinoma in one area, squamous cell carcinoma in another and carcinoma in situ in other areas. Based on the overall features in various areas of the oral cavity, the lesion was diagnosed as field cancerization.
Conclusion. Reviewing the literature revealed the presence of a field with genetically altered cells appear to be induced by tobacco (smoking/smokeless form). The large number of premalignant cells in the fields may increase cancer risk considerably. Thus screening and monitoring of the field may have serious implications for oral cancer prevention.

Key words: field cancerization, oral cancer, tobacco chewing, premalignant lesions

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INTRODUCTION

An important physiological function of epithelia is its protective role by its frequent self-renewal process. It also inevitably gets exposed to environmental substances, including carcinogens, leading to abnormal proliferation creating a vast area of genetically altered cancer fields. Such hyperplastic epithelia could form the basis of neoplastic transformation leading to the formation of the most common types of cancers of the human body.

Patients with head and neck squamous cell carcinoma often present with widespread multiple premalignant lesions in the upper aerodigestive tract[1]. A potential mechanism for the development of multiple oral premalignant lesions is explained by the field cancerization theory which proposes that carcinogenic exposure can cause simultaneous genetic defects in the epithelium of the upper aerodigestive tract, putting the epithelium at high risk, for the development of multiple lesions[2].

Field cancerization is a well-known and well-documented process of malignant transformation first coined by Slaughter et al. in 1953 (ref.[3]). Since then the term field cancerization is applied to explicate the oral cancer developing in multifocal areas of a precancerous change, abnormal tissues surrounding the tumor, oral cancer often consisting of multiple independent lesions that may coalesce and the persistence of abnormal tissue even after surgery[4]. Tobacco chewing was considered to be the major source of field cancerization of the oral cavity in the Indian population[5]. However certain carcinogens from tobacco chewing and tobacco smoking are identical, possibly the amount of exposure between these tobacco habits is different in the Indian population[5].

Currently, absence of abnormal cells reviewed by histology biopsies often precludes the diagnosis of cancer[6]. Nevertheless, histologically normal biopsy specimen that possess molecular signatures of cancer fields suggest either the tumor was missed by the biopsy procedure, or that some cells in the tissue are progressing towards malignancy[6]. Such high-risk patients will require close surveillance for early detection of disease. Thus this review highlights all the risk factors associated with multiple oral premalignant lesions with a case report of extensive field cancerization in a female patient. The field cancerization will probably help clinicians in complementing evaluation of pathologic biopsy specimen.

CASE REPORT

A 63 year old female patient with a low socio economic status residing in a remote rural area and working on a daily wage, reported with the chief complaint of pain for one and half years and growth on the lips and

in the oral cavity for three years (Fig. 1A). She visited a local doctor for the same problem for which she was prescribed with a topical application of candid- mouth paint, which relieved the pain for some time. She gave a history of tobacco chewing 5-6 times /day for 22 years and smoking 10-15 bidis a day for 15 years. On examination multiple brownish yellow papular proliferative growths were seen on the right upper and lower lip for 3 years measuring approximately 1x1.5 cm, 0.5x1 cm respectively, which were firm and non-tender (Fig. 1B). Upon intraoral examination generalized hyperkeratotic verruciform type white lesions involving right and left buccal mucosa, lower labial mucosa, upper and lower vestibule, dorsal, ventral and right lateral border of the tongue, hard and soft palate were evident. The lesion involving the hard (5x3 cm) and soft palate (3x2 cm) was verruco-papillary intermixed with erythematous areas, tender, with irregular surface (Fig. 2A). In the right buccal mucosa hyperkeratotic white lesion extended from commissure to retromolar area antero-posteriorly, upper to lower vestibule supero-inferiorly measuring 6x4 cm with irregular surface, non-tender, non scrapable, with pebbly appearance (Fig. 2B). The dorsum and lateral border of the tongue showed a thick whitish, verruciform, non scrapable growth measuring about 3x3 cm and 3x4 cm respectively (Fig. 2C and 2D). There was marked restriction in the movement of the tongue. On palpation there were three palpable, tender, mobile right submandibular lymph nodes. A provisional diagnosis of verrucous carcinoma of the lip, proliferative verrucous leukoplakia of oral mucosa and field cancerization was made. Routine blood investigations revealed that the patient was anaemic and positive for Monteux test. The postero-anterior view of the patient's chest radiograph revealed bilateral hyper-inflated lungs with pulmonary parenchymal calcification and cardiomegaly. The patient was referred to a general physician and following the additional investigations like sputum examination, aspiration from lymph nodes, and echocardiogram. The patient was diagnosed with pulmonary tuberculosis with cardiomegaly and advised on treatment. She was subjected to incisional biopsy of right buccal mucosa, hard palate, right labial mucosa, and lateral border of the tongue, under the physicians' supervision. The tissues were processed and stained with hematoxylin and eosin stain.

Section of the lesion on the upper lip mucosa of right commissural area revealed hyperparakeratinized stratified squamous epithelium with broad pushing rete ridges devoid of connective tissue. The surface parakeratin plugging with hyperplastic epithelial cells with occasional inflammatory cells suggested a diagnosis of verrucous carcinoma (Fig. 3A). Tissue from hard palate revealed invading islands and sheets of dysplastic epithelial cells showing features of nuclear hyperchromatism, abnormal mitotic figures, loss of cohesion, and altered nuclear cytoplasmic ratio with prominent keratin pearls in the connective tissue with mild inflammatory reaction from which the diagnosis of well/differentiated squamous cell carcinoma was made (Fig. 3B).

The hematoxylin and eosin stained sections from right lower labial mucosa revealed top to bottom dysplastic epithelium with features of loss of basal cell polarity, nuclear hyperchromatism, abnormal mitotic figures, and loss of cohesion with thin dropshaped rete ridges the features of which were suggestive of carcinoma in-situ (Fig. 3C). A diagnosis of severe dysplasia was made for the tissue from the lateral border of the tongue which showed hyperplastic parakeratinized stratified squamous epithelium with the dysplastic features extending to 2/3rd of the epithelium with thin long rete ridges with minimal amount of papillary connective tissue (Fig. 3D). The overall features in various areas of the oral cavity led us to make a diagnosis of field cancerization. Because of extensive involvement of the oral cavity and her systemic illness, the patient was referred to a regional cancer center for further treatment.

DISCUSSION

Field cancerization is used to explain the existence of preneoplastic processes at multiple sites often with the hypothesis that these have developed independently. The multiple premalignant lesions in the entire oral cavity could result from exposure to carcinogens that can cause multiple genetic abnormalities in the whole tissue region. Another hypothesis for the development of multiple squamous cell lesions could be the pervasive migration of tumor cells through the whole aerodigestive tract either via saliva (micrometastasis) or via intraepithelial migration of the progeny of the initially transformed cells. An exogenous agent like tobacco is strongly associated with increase in the risk of multiple oral preneoplastic lesions and may be the major cause of field cancerization of the oral cavity in the Indian population. The risk of multiple oral premalignant lesions for lifetime chewers was reported as intermediate when compared to single lesions of leukoplakia, oral submucous fibrosis, and erythroplakia. The major carcinogens recognized in chewing tobacco, comprise tobacco-specific N-nitrosanes predominantly N-Nitrosononicotone and 4(Methyl nitrosamino)-1-(3-pyridyl)-1-butanone[7]. Studies done in the Indian population have reported that tobacco smoking is a weak risk factor for multiple oral squamous cell lesions[5]. Possibly, smoking involves the inhaling of smoke, which may have less contact with the mouth and more contact with the throat and lungs than tobacco chewing. However some of the carcinogens from smoking and smokeless tobacco are the same, perhaps the amount of exposure between these tobacco practices is different in the Indian population. The association between alcohol drinking and multiple oral premalignant lesions was not evident.

Various authors have stated several oral field changes in tumor distant mucosa and tumor adjacent mucosa in OSCC patients associated with different risk factors.

Morphological changes

These include increase in nuclear size, discontinuous nuclear membrane, numerous Feulgen-negative areas, increased associated chromatin surrounding the clear areas, absence of a single large nucleolus, altered nuclear to cy-

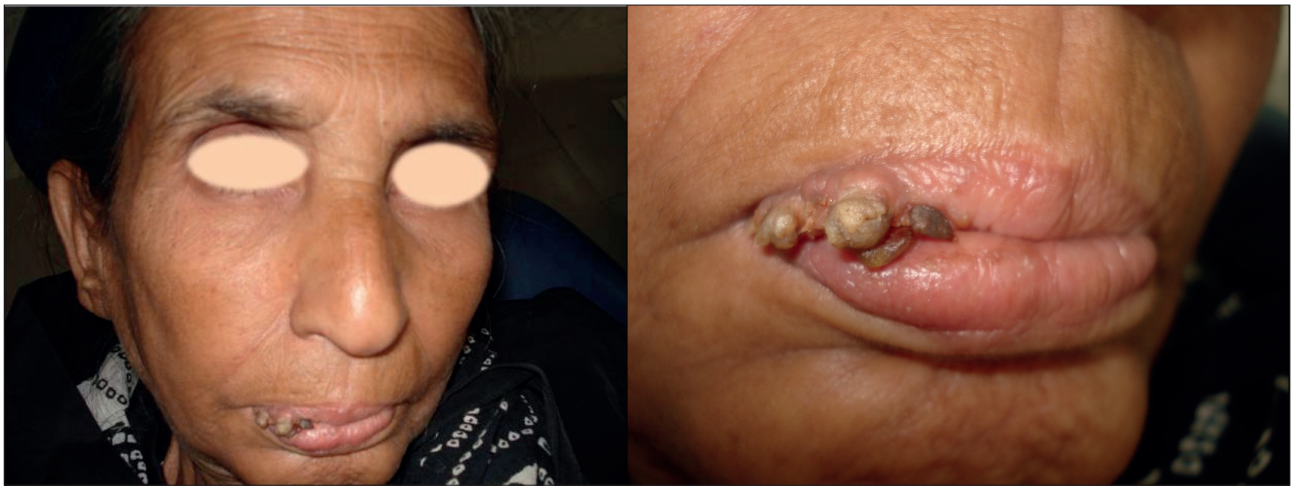

Fig. 1.

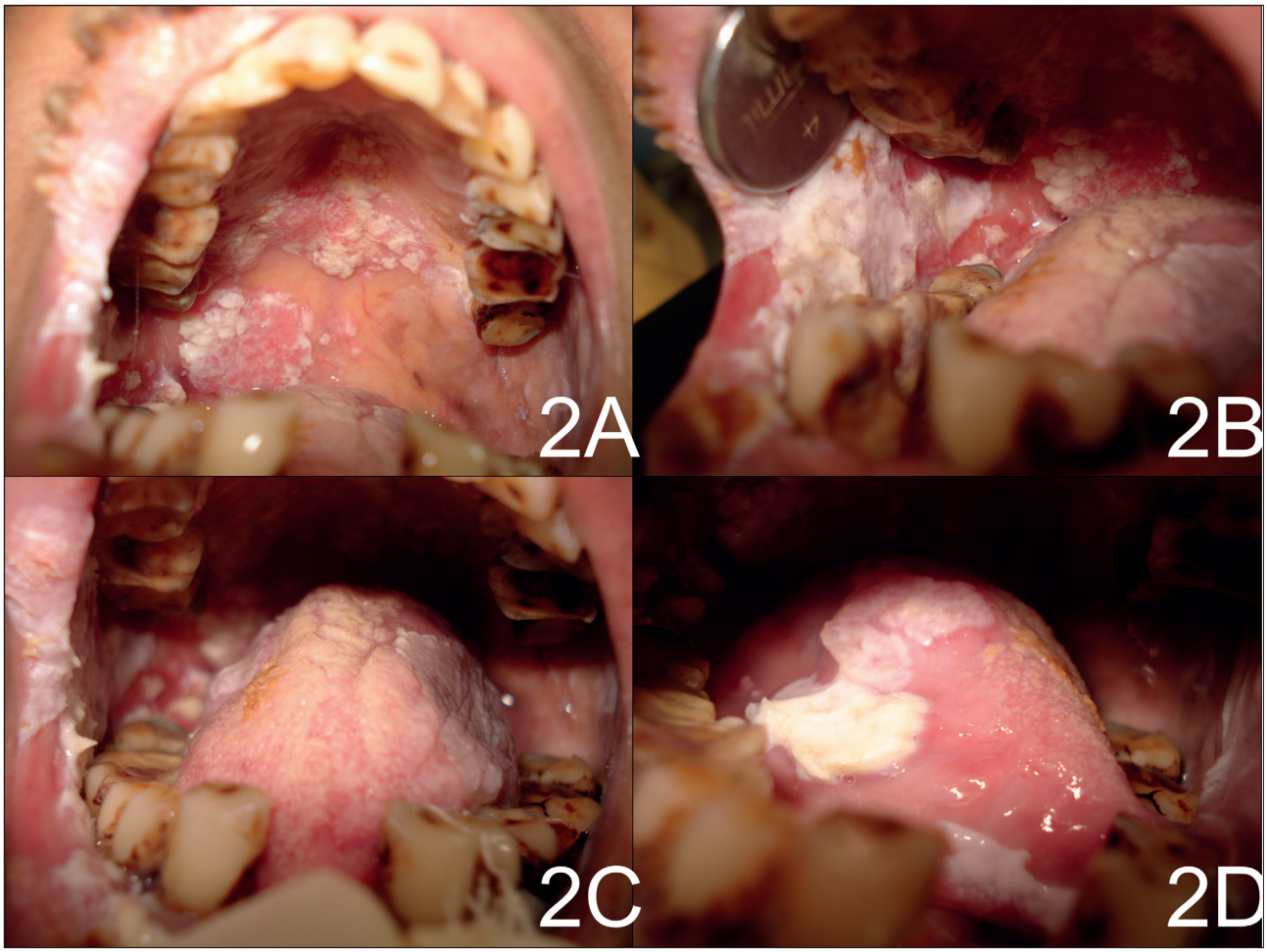

Fig. 2.

toplasmic area ratio and reduction in cytoplasmic area in the normal buccal mucosa of patients with SCC (ref.[8-11]).

Molecular changes

Studies have reported aneuploidy in hyperplastic/ inflammatory mucosa in tumor distant areas which later developed into an invasive carcinoma[12].

Chromosomal aberrations:

Various chromosomal aberrations were seen in the normal mucosa opposite the side of OSCC (ref.[13]). Polysomies of chromosomes 7 and 17 and a significant loss of chromosome Y was observed in tumor adjacent mucosa from OSCC patients with a history of smoking

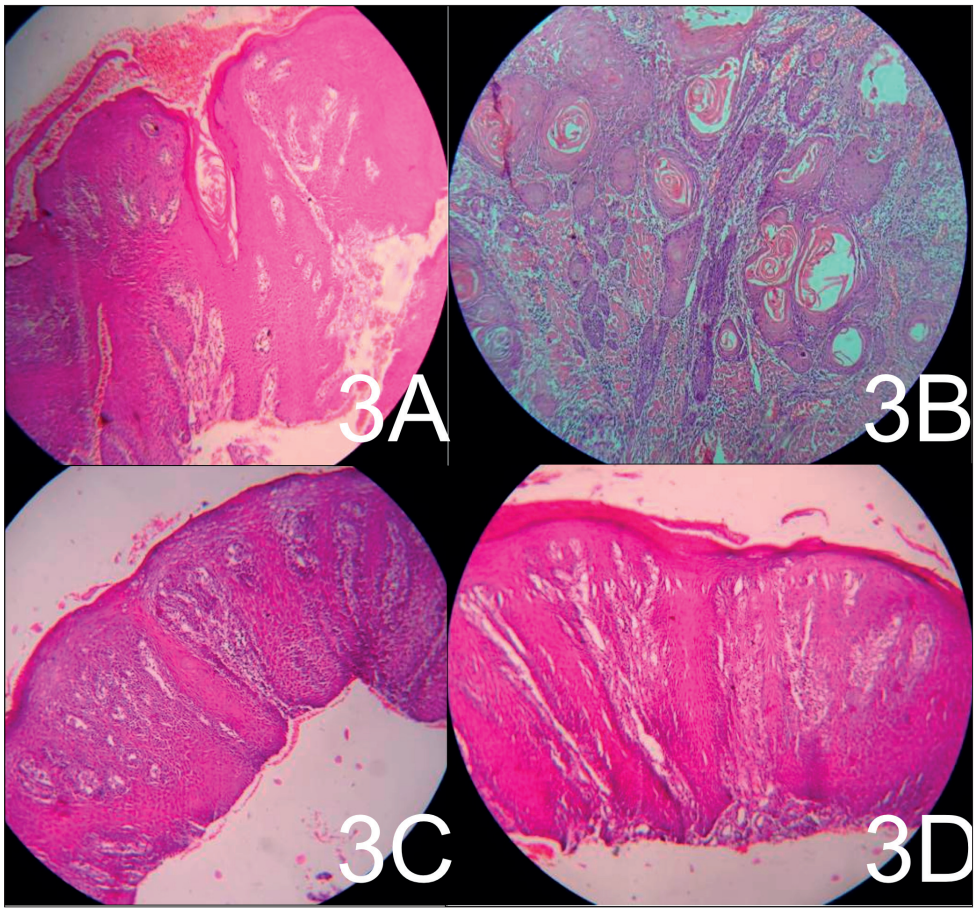

Fig. 3.

but this loss appeared not to be present in nonsmoking patients[14-16].

Cytokeratins: Aberrant expression of cytokeratins was observed in the mucosa of patients during development of OSCC (ref.[17,18]). Normal mucosa from OSCC patients showed the presence of cytokeratin 7, 8, 13, 16, and 19 at abnormal intraepithelial sites or at abnormal intraepithelial levels[19-22].

Abnormality with cell cycle regulation: Overexpression of the proto-oncogene cyclin D1 has been reported in about half of the OSCC (ref.[23]). The amplification frequency of Cyclin D1 progresses from premalignant lesions to invasive carcinoma[23]. Cyclin D1 expression was observed in sections of normal mucosa adjacent to OSCC and was absent in sections from healthy individuals[24].

The proto-oncogene product eIF4E or mRNA 5′ cap-binding protein plays a key role in the regulation of translation in cell growth and proliferation[25]. OSCC patients and histologically normal margins of resected OSCC show increased expression of this protein[26].

Growth factors: Epidermal growth factor mRNA overexpression as well as protein overexpression, which indicates proliferation, has been demonstrated in nearly all OSCC (ref.[27-29]). Epidermal growth factor receptor expression increases during the progression of normal epithelium to dysplasia to carcinoma[30]. Several authors have reported increased expression of Epidermal growth factor receptor, Transforming growth factor-α mRNA levels and proteins in normal tumor adjacent mucosa (TAM) of OSCC patients[27-31].

Increased proliferation: Furthermore TAM from OSCC patients showed an increased number of proliferating epithelial cells[32], loss of function of the tumor suppressor p53 (ref.[33]), focal p53 positivity[34-36] and mutations in the *p53* gene[34,37] which can lead to uncontrolled cell division and progressive genomic instability. Literature reveals that frequency of p53 positive cells gradually increases as oral epithelium progresses from normal to hyperplasia to dysplasia to carcinoma[36,38].

Inhibition of apoptosis: Additionally, studies have reported absence of bcl-2 (an apoptosis inhibitor) expression in oral cancer and in normal tumor adjacent mucosa compared to control group.

Genetic polymorphism of drug metabolizing enzymes: Besides the expression of glutathione *S*-transferase isoenzymes which are detoxification enzymes were significantly higher in the normal oral mucosa from OSCC patients who later developed a second primary tumor than in normal oral mucosa from OSCC patients who stayed free of disease for at least 7 years[39].

Numerous studies have performed molecular analyses on tumor-adjacent "normal tissue" and surgical margins to assess the presence of a field lesion using markers for loss of heterozygosity, microsatellite alterations[40], chromosomal instability[41], and mutations in the TP53 gene[42]. These studies reported that one-third of unselected tumors

of OSCC have tumor-associated genetic alterations in a biopsy taken from the macroscopically normal TAM.

Studies have also reported that tobacco smoking is a risk factor for pulmonary tuberculosis as seen in the present case, with a dose-response relationship with the number of cigarettes consumed daily[43,44]. This could be attributed to nicotine that turns off the production of Tumor necrosis factor-α by the macrophages in the lungs, making the patient more susceptible to the *tuberculosis* infection. Molecular and histopathologic alterations identified in the bronchial epithelium of tobacco smokers suggest that smoking exerts field cancerization effects on bronchial epithelium increasing the risk for the subsequent development of lung cancer[45,46].

Further research is required to detect the fields carrying the high risk for cancer. Besides host factors, like tobacco consumption, the biological characteristics of the field also plays a important role in OSCC development. Clinical trials should be performed to identify approximately where the lesion will develop and to monitor the disease process. Moreover, knowledge of the tumor associated genetic alterations that precede the development to cancer will provide a basis for a rational therapy of the premalignant lesions.

CONCLUSION

The presence of a field with genetically altered cells appear to be induced by tobacco (smoking/smokeless form), which indicates field cancerization induced by carcinogens rather than due to migration of transformed cells. The large number of premalignant cells in the fields possibly can increase cancer risk considerably. This also clarifies the high incidence of secondary cancers in post-treated oral cancer patients. Thus screening and monitoring of the field may have serious implications for oral cancer prevention.

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