Case Report

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Malignant Transformation of Oral Submucous Fibrosis to Oral Squamous Cell Carcinoma: A Case Report.

Abstract:
Oral submucous fibrosis (OSMF) is a potentially malignant disorder with high rate of malignant transformation.Oral epithelium beingthin and atrophic becomes more vulnerable to attack of carcinogens. Malignant transformation in OSMF usually occurs gradually over a long period of time. Here, we reported a case of OSMF transforming into malignancy in a 27-year-old male patient.

Keywords: malignant transformation, premalignant, Oral cancer, Oral submucous fibrosis

Introduction:

Jens J. Pindborg in 1966 defined OSMF as "an insidious, chronic disease that affects any part of the oral cavity and sometimes the pharynx. Although occasionally preceded by, or associated with, the formation of vesicles, it is always associated with a juxtaepithelial inflammatory reaction followed by fibroelastic change of the lamina propria and epithelial atrophy that leads to stiffness of the oral mucosa and causes trismus and an inability to eat" [1]

Known for its significant malignant potential, the incidence of OSMF varies from one region to another. A series of epidemiological surveys conducted by Pindborgin India and South Africa reported malignant transformation in 3 to 6 % of patients having OSMF.[2]

Oral cancers arising from OSMF are believed to be distinct clinicopathological entities. The cellular DNA damage to oral epithelium occurs due to the constant challenge of excessive Reactive oxygen species, released cytokines and reactive intermediate metabolites of areca nut and betel quid. Nitrosation of areca alkaloids by nitrosamines causes tumour induction followed by tumor promotion by arecaidine. Also, areca nut-specific nitrosamines like N-nitrosoguvacoline, Nnitrosoguvacine, 3-propionaldehyde, and 3-propionitrile exerts genotoxic and mutagenic effects on oral mucosal fibroblasts and oral keratinocytes.[3]

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A distinct clinical presentation is seen in carcinoma arising from a background of OSMF.There is male predilection and younger age at presentation reported in such patients.[4] Here, we report a case of OSMF turning to Oral Squamous cell carcinoma(OSCC) in a 27-year-old male patient. The present case report tries to highlight the significance of periodic checkup and biopsy whenever needed to check any malignant transformation.

Case Presentation:

A 27 years old male reported to the outpatient department of the Oral Medicine & Radiology with the chief complaint of pain and discomfort over the left inner back side of the cheek since a month. He was relatively asymptomatic one month back then he noticed a solitary painful growth on the left side of cheek.The pain was insidious in onset, intermittent in a nature, of moderate intensity, aggravated while having hot and spicy food and no medication was taken for the same. He also

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complains of progressive difficulty in mouth opening and burning sensation on mucosa since one year but no treatment was taken for the same. There was no significant medical or family history.Patient was a chronic tobacco smoker since 5 years with daily consumption of 12 biddi/day.He is also having 7-10 packets gutka with tobacco and betelnut daily since 7 years. He quit gutka chewing one year back but continues to smoke. Patient consent was taken for publication of the case.

Patient was well built with normal gait and posture and was well oriented to time, place & person. His face appears symmetrical but was not able to blow out air with closed lips. Intraoral examination revealed pale, blanched buccal mucosa with palpable fibrotic bands running vertically extending from 14,15, to 44 45 and 24 25 to 34, 35. Mouth opening was 18 mm(interincisal distance)(fig 1)and tongue protrusion was restricted. The uvula was deformed and shrunken.

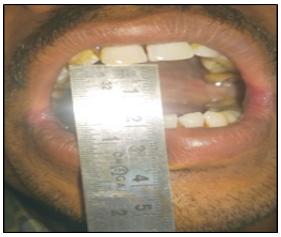

Fig.1: Photograph showing restricted mouth opening of 18 mm

On inspection a small round to oval, reddish white colour ulceroproliferative lesion of approx. 8mm x 9mm was present on left buccal mucosaone cm to the retrocommisure area.(Fig 2A) It was slight tender to palpate and firm in consistency. A provisional diagnosis of exophytic lesion on pre-existing OSMF (stage IV as per Ranganathan et al.[5]) was made. Verrucopapillary lesions like Oral verrucous hyperplasia and verrucous carcinoma were considered in differential diagnosis. Toluidine blue test was done to delineate the margins of the lesion and to identify the sites in need of biopsy. (Fig 2B) It is a useful way of demarcating the extent of a lesion prior to excision. Area of maximum intensity was selected for the punch biopsy

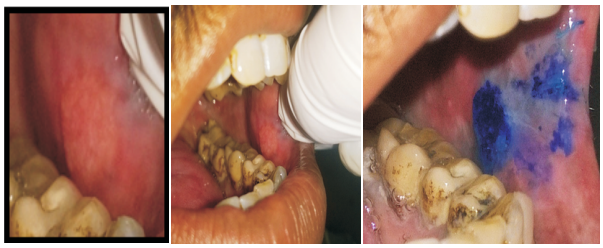

Fig 2A: Proliferative growth seen on the left buccal mucosa (seen in inset also) Growth was round and erythematous.Fig 2B: TB test highlighting the lesion area.

On haematological examination patient reported to be anaemic with Hemoglobin 10.4 gm%. An incisional biopsy was done from the margin of the lesion present on left buccal mucosa including the adjacent mucosa also. Gross Specimen measured around 1.5 cm × 0.8 cm was whitish gray in colour and firm in consistency.

Histopathological Findings:

The epithelium overlying the connective tissue is thin on one side and increases in the thickness with prominent rete ridges towards lesion.Epithelial cells invade the connective tissue in form of sheets, islands and cords. There is submucosal deposition of collagen in the connective tissue with presence of chronic inflammatory cells.(Fig 3). Dysplastic features like cellular pleomorphism, increased n/c ratio, *nuclear hyperchromatism*, prominent nucleoli, mitotic figures *and* intraepithelial keratinization can be seen in the overlying epithelium.(Fig 4) Round focus of concentrically layered keratinized cells of different size and shape known as keratin pearls can be seen in the underlying connective tissue. Based on these findings, final diagnosis of well differentiated oral squamous cell carcinoma in the background of fibrosis was given. Patient was referred to higher centre for further management.

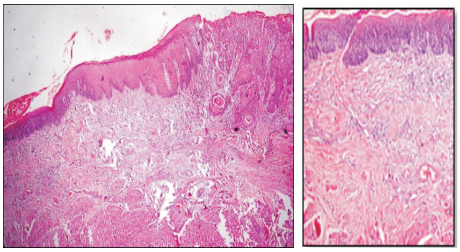

Fig 3: Photomicrograph showing atrophic thin epithelium on one side and invading epithelial cells in form of sheets, stands and cords on the other.(H & E, [4x]). The underlying connective tissue below the atrophic epithelium shows deposition of thick collagen fibres. (inset- fig 3, H & E , 10x).

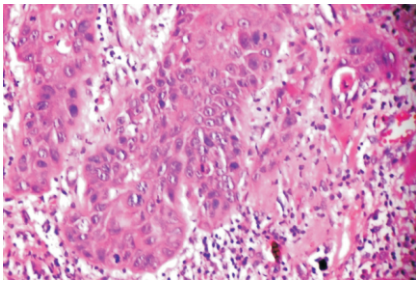

Fig 4: Photomicrograph showing dysplastic changes in the overlying epithelium. (H & E; 40x)

Discussion:

OSMF is a potentially malignant disorder with disturbance in collagen metabolism. There are distinct changes in the underlying connective tissue resultant to chewing of areca nut which further affects the overlying surface epithelium[6]. People with OSMF are 19.1 times more likely to develop oral cancer compare to those without it, after regulating other risk factors.[7] The prevalence of OSMF in India has increased from 0.03% to 6.42% over the past four decades. The malignant potential rate of 7-30% has been report for this condition[8].

Chuang et al reported the malignant transformation rate of 8.6 (per 1000 person-years) in patients of OSMF.[9] Another hospital based study done by Chiang et al. shown the rate of carcinoma development from oral submucous fibrosis to be 13.6%.[10] Yang et al in their cohort study, observed 71 (9.13%) of 778 cases of OSF transforming into oral cancer.[11] Chaurasia et al reported the incidence of 4.2% of malignant transformation to oral cancer in patients of untreated OSMF.[12] Wang et al in a reterospective hospital based study observed malignant transformation of 3.72% (37/994) in OSMF patients.[13] Hsue et al. found malignant transformation in 5.2% cases of OSMF with dysplasia.[5] As reported by Murti et al about 10% of OSMF cases may show malignant transformation.[14]

Betel quid (BQ) containing areca nut is the strongest risk factor for OSMF. Malignant transformation was more commonly seen in males of young age group similar to present case.[15] Shah et al. also reported younger age as starting point for areca nut chewing habit.[16] This might be due to psychopharmacological effects of areca nut as a popular pleasure giving substance and increase in concentration, mild mood elevation, enhanced satisfaction after eating and relaxation.[17] The amount of areca nut, frequency and duration of chewing the BQ are linked to the development of OSMF. Tobacco usage duration and betel nut chewing habit was reported to be considerably higher in OSCC compared to OSCC arising from pre-existing OSMF[18]

Buccal mucosa is the most common site for malignant transformation in OSMF since this region is stimulated by arecanut. Malignant transformation is seen as ulceroproliferative lesion, suggesting more of exophytic growth.[15] Five cases of exophytic verrucopapillary lesion arising in from OSMF has been reported by Jayasingle et al. Histologically, these lesions revealed dysplasia only without deeper invasion even with the large size of the lesions. It has been hypothesized that abnormal bundles of collagen may resist the invasion of epithelial cells.[19]

Areca nut as a carcinogen, Hypoxia, and epithelial–mesenchymal transitions are the main etiologies that have been extensively studied to elucidate the possible pathway of malignant transformation of OSMF. Arecoline, major alkaloid of arecanut, affects key proteins that regulate cell cycle against various stresses such as reactive oxygen species (ROS), cyclin-dependent kinase p21 and p27. Also, high copper content of arecanut activate several angiogenic factors that activate proliferation of endothelial cells stimulating tumour angiogenesis.[20] Extensive fibrosis of the connective tissue reduces the vascularity, resulting in subsequent hypoxia in surface epithelium. Hypoxia leads to over expression of Hypoxia inducible factor-1α which helps cell proliferation promoting tumorigenesis.[21]

Gadbail et al reported 60.95% of cases as well differentiated OSCC arising from OSMF.[18] Zhou et al. also testified more differentiated OSCC arises from OSMF cases.[22] This difference may occur due to protective effect of OSMF because of presence of fibrosis in the connective tissue stroma. Abnormal cross-linkage of collagen may resist the process of invasion. Matrix metalloproteinases also may fail to destroy the abnormal collagen to enhance the process of invasion.[23] Hence, OSCC with OSMF can be described as a distinct tumor, with less rapid growth, more differentiation, less metastasis, fewer chances of postoperative recurrence hence better prognosis and better survival rate.[18]

Conclusion:

The malignant potential of OSMF should not be under estimated. OSCC arising in the background of OSMF has better prognosis when detected at an early stage. Since dentists are usually the first to diagnose the condition; therefore, they should have a basic knowledge and awareness about this condition. Regular screening without negligence is recommended for these patients so as to identify early occult cancers and to treat them promptly.

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