Concurrent multiple oral malignant and potentially malignant lesions – The phenomenon of field cancerization

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Abstract- The incidence of oral cancer is increasing dramatically over the past years. According to National Cancer Registry Programme of Indian Council of Medical Research(ICMR), the mortality rate due to cancer has increased by approximately 6% between 2012 and 2014. The long term survival rates of oral cancer is less than 50%. Increased rate of morbidity and mortality is mainly due to the occurrence of multiple primary tumors and locally recurrent cancers. The concept of "field cancerization" by Slaughter *et al*. explains the mechanism by which second primary tumors develops. The presence of a 'field' with genetically altered cells appears to be a continuous risk factor for cancer. Detection and monitoring of these fields may have profound implications for cancer prevention. Here is a case report of "field cancerization" phenomenon.

Index Terms- Field cancerization, Multiple oral carcinomas, Oral cancer

I. INTRODUCTION

Worldwide incidence rate of oral cancer is escalating in such a rate that 1 in 8 men and 1 in 10 women can have this disease in their lifetime. It is estimated that a total of 18.1 million new cancer cases will be reporting in 2018[1]. In India, the rate of occurrence of oral cancer is high compared to western populations and oral cancer is the leading cause of cancer death in Indian male. This is due to high rate of tobacco usage in the sub-continent as part of custom and otherwise. The carcinomas associated with these habits shows comparatively good treatment response and prognosis than non-habit related cases. Also, habit associated lesion has got some particular pattern of occurrence – site of distribution, rate of locoregional progression, chance of distant metastasis etc. Multiple areas of cancers were observed in many patients with oral carcinomas, leading to the concept of 'Field cancerization'. This is relevant in oral carcinogenesis, which is described in this article along with a case study.

II. CASE PRESENTATION

An 80- year- old female reported at Department of Oral medicine and Radiology, Government Dental College Kozhikode, complaining of progressive painless swelling of right cheek since 2 weeks. There was no bleeding or discharge from the mouth. She was not experiencing numbness or parasthesia.

She was a chronic user of tobacco in chewable form, stopped the habit 7 years back. No other co-morbidities were present.

On extra oral examination, there was a firm, non tender swelling on the right cheek of size 6×5 cm, without superficial ulceration or discharge. There was no localised rise of temperature. Multiple level Ib lymph nodes were present bilaterally, which were firm, mobile and non tender and none were more than 1cm.

Intra orally, a proliferative growth was present over right buccal mucosa, of size 4×3.5 cm. It was having raised borders, granular surface and superficial fissures. It was non-tender without bleeding or discharge.

A minimally proliferative growth with superficial fissures and multiple nodularities was present over left buccal mucosa, extending into left upper mucobuccal sulcus and left maxillary posterior alveolar mucosa.

Another growth was present in the edentulous ridge of right mandibular premolar-molar region of size 1×0.8 cm. Its surface was granular and consistency was firm. There was no tenderness or bleeding from the growth on palpation.

A white, non- scrapable lesion was present in the attached gingiva of maxillary anterior region in relation to 21 & 22 teeth.

A mixed red and white lesion was present in the mandibular anterior gingiva, extending into the mucobuccal sulcus, which was non- scrapable. Inflamed gingiva covered with slough was noticed in the region. There was generalised gingival inflammation and oral hygiene status was poor (Figure 1).

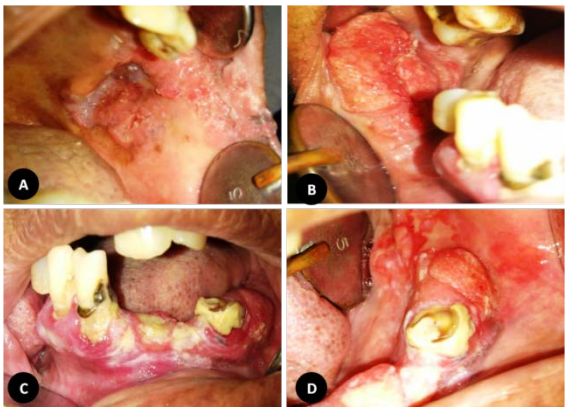

Figure 1: A)Lesion on left buccal mucosa B) Lesion on right buccal mucosa C) Lesion on mandibular anterior gingiva D) Lesion on mandibular posterior alveolar ridge

Radiographic investigation revealed no evidence of bone erosion in the alveolus. Blood parameters were also within normal limits.

Provisional diagnosis of carcinoma of bilateral buccal mucosa and right mandibular alveolar mucosa (T1N0M0), speckled leukoplalia of mandibular anterior region and homogeneous leukoplakia of maxillary anterior gingiva was made.

Histopathologic examination was done to diagnose the possibile malignancy. Samples were collected separately from each site. The report came as squamous cell carcinoma moderately differentiated on right buccal mucosa, Severe epithelial dysplasia with indistinct basement membrane on left buccal mucosa and moderately differentiated squamous cell carcinoma on right mandibular alveolar mucosa.

III. DISCUSSION

In 1953, Slaughter *et al*[2] observed several peculiar findings regarding oral cancer like,

- The linear spread of oral cancer compared to deeper extension (lateral cancerization) , which can be due to carcinogenic change of surrounding cells rather direct spread of pre-existing malignancy
- Independent foci of in situ cancer islands in surrounding area of large primary squamous cell carcinoma lesion
- Selective or Guided missile type carcinogenic activity in a pre-conditioned epithelium

He proposed the idea of 'field cancerization'. Although this concept was put forward to explain high local recurrence rate in oral cancer, it was also applicable in oropharynx, larynx, colon, breast, prostate, esophagus, skin, urinary bladder, vulva and cervix[3].

Various theories were formulated to explain this phenomenon. Slaughter's concept (classic theory) was that as a result of exposure to carcinogens, mucosa develops carcinomatous changes by independent mutations. Alternate theories came later (clonal theory) saying that altered cell leads to formation of expanding fields with premalignant potential and having same clonal origin[4].

A normal tissue will become dysplastic through 'multistep carcinogenesis', by the accumulation of genetic alterations both molecular and phenotypic progression of the neoplasm(4). These altered epithelial cells forms a 'patch' by clonal expansion, which later becomes a 'field' of epithelial cells with genetic alterations but without histologically evident changes. These fields contain genetic alterations that can be demonstrated by Tp53 immunostaining, where carcinomas may develop later.

Molecular studies provided sufficient evidences for establishing monoclonal origin for preneoplastic cells in a field, which was confirmed by presence of early markers of carcinogenesis. Thus 'field cancerization' was defined as "the presence of one or more areas consisting of epithelial cells that have genetic alterations. A field lesion (or shortly 'field') has a monoclonal origin, and does not show invasive growth and metastatic behaviour, the hallmark criteria of cancer."[3]. Widely accepted experimental animal model for field cancerization is 'hamster cheek pouch model', where carcinogenic agents were injected to cheek pouch of this animal and proliferative growth were developed in the site. Using this model, we could study regarding molecular markers, ploidy analysis, therapeutic response etc[5].

Detailing molecular concept of field cancerization is much complicated. Biomarkers like Cytokeratin -7,8,13,16,19, Cyclin D1, increased levels of isoenzyme glutatione s-transferase, vascular markers (vwf and cd31) and p53(most promising marker) are noticed in the 'fields'. Allelic loss can predispose to carcinogenesis[5].

Clinical application of this concept comes in early detection of oral cancer in a patient who already had carcinoma of head and neck. There is 20% chance for development of a second primary tumor in these patients [5], which can be monitored by identifying molecular markers in peri-tumoral cancer field. This can significantly reduce tumor progression and can modify treatment options, resulting in good prognosis. Identification of tumor markers are usually done by polymerase chain reaction (PCR), in situ hybradisation and immunohistochemistry. Commonly assessed markers are loss of heterozygosity, microsatellite alterations, mutations in p53 gene and chromosomal instability. Another important clinical application is in chemoprevetion of the disease, which aims to ablate altered cell population and repair the genetic damages. Most common chemotherapeutic agents are 13-cis retinoic acid and cyclooxygenase-2 (COX-2) inhibitors[6].

The idea of field cancerization evolved so much in the past 50 years and is currently exploring its molecular aspects. The most common agent causing altered fields in normal oropharyngeal mucosa is tobacco. Appropriate chemopreventive measures has to be taken in such patients to avoid development of multiple tumors. Contributions from molecular and genetic studies may help us to form a management protocol in such cases, which in turn improve the survival rates.

CONFLICTS OF INTEREST
The authors disclose the absence of any conflicts of interest.

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