Ackerman’s Tumor and Field Cancerization with Emphasis on Chemoprevention

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ABSTRACT
Slaughter et al (1953) coined the term ‘field cancerization’ for the mucosa of head and neck region undergoing genetic transformation directly proportional to the intensity and duration of carcinogen exposure, making it more susceptible to develop many foci of premalignant lesions and malignant transformation. This increases the overall incidence and variety of oral cancers we encounter in our day-to-day practice.

We describe a patient with an exophytic oral lesion diagnosed as verrucous carcinoma, who was already undergoing treatment, regular follow-up and recovering well from speckled leukoplakia. The lesion was completely excised. The patient subsequently developed leukoplasias in the affected field which histopathologically showed mild to moderate dysplasia. This case shows that mucosa was breaking at different points into different premalignant lesions and neoplasm, in spite of patient’s abstinence from the habit and regular treatment with meticulous follow-up, chemoprevention is also briefly reviewed.

This report highlights two important aspects: (1) Site-specific treatment is not adequate and (2) Regular, close and meticulous follow-up is important for high-risk patients.

Keywords: Field cancerization, Chemoprevention, Premalignant lesions, Exophytic, Verrucous carcinoma, Follow-up.

INTRODUCTION
Epithelial carcinogenesis is a multistep process in which an accumulation of genetic events within a single cell line leads to a progressively dysplastic cellular appearance, deregulated cell growth and finally, carcinoma (Tsao et al 2004). 1 One way to explain the development of head and neck cancer is through the theories of field cancerization (Slaughter et al 1953) 2, i.e. the exposure of the entire field of tissue to repeated carcinogenic insult and multistep process, i.e. development of multiple cancers in a predisposed field through a series of recognizable states (Papadimitrakopoulou et al 1996). 3

Ha and Califano (2003) 4 stated that while Slaughter did not describe a molecular foundation for his observations, the term has taken on a slightly different meaning in today’s literature. This phrase has been used to describe three phenomena: (1) A wide field of aerodigestive mucosa that tends to be affected by premalignant disease, (2) the frequent occurrence of multiple primary tumors in this field and (3) the possibility of distant related primary tumors in the upper aerodigestive tract.

Given the above background information, we present a case, where in a single field multiple foci of dysplasia’s including a malignant lesion developed at sites independent of each other.

CASE REPORT
In August, 2009, 51-year-old male patient was incidentally diagnosed with speckled leukoplakia (mixed red and white lesion) on the right buccal mucosa. An incisional scalpel biopsy was performed after staining the lesion with vital dye (1% toluidine blue and destaining with 1% acetic acid) (Fig. 1). Histopathological report was suggestive of leukoplakia.
At that time, patient was a bidi smoker (10-15 bidi’s per day for 25 years). Being cancer phobic, he gave up smoking after counseling. He was prescribed antioxidant (lycopene 8 mg/day) and topical antimycotic (clotrimazole mouth paint) and was recalled after every 15 days for review. He was very regular in his follow-up schedules with repeated motivation from our side and was recovering well.

In July 2010, intraoral examination revealed a sessile, solitary exophytic growth, grayish white in color showing finger like projections, approximately 0.5 × 1.5 cm in dimension (Fig. 2). On palpation, the lesion was nontender, nonindurated, without cervical lymphadenopathy. A deep and wide excisional biopsy was performed with a clinical diagnosis of verrucous leukoplakia. Histopathological report was suggestive of verrucous carcinoma (Fig. 3). Patient was kept on antioxidant (lycopene 8 mg) and immunomodulator (levamisole 150 mg). Levamisole was given once a day for 3 days and repeated after 2 weeks. This was done four times. He was keeping his appointments and recovering well, when during one of his follow-up visits a pearly white plaque in the area of surgery extending from the alveolar ridge till right buccal mucosa involving the right aspect of oropharynx (Fig. 4). The lesion was surgically removed using wide and deep excisional biopsy, which was histopathologically suggestive of tobacco-induced leukoplakic patch with mild to moderate dysplasia. The patient was subjected to another excisional biopsy when in January 2011 it was incidentally noticed that patient had developed homogenous leukoplakia in right buccal mucosa in retrocommissural region, histologically showing mild to moderate dysplasia. After being on lycopene and regular intervals of immunomodulation with levamisole for 18 months, the patient was prescribed 4 to 5 cups of green tea and 1 gm of Spirulina fusiformis per day. The patient has responded well to the chemopreventive treatment and has shown remission of the preexisting lesions with no emergence of any new lesions. Follow-up is being meticulously maintained (Fig. 5).

**DISCUSSION**

A distinct clinicopathologic entity, verrucous carcinoma, was described in 1948 by Ackerman and is sometimes called...
Squamous cell carcinoma. It has a classic evolution and an excellent prognosis if treated correctly; therefore, it is important that it is recognized both clinically and microscopically. It is more common in Caucasians and in India approximately 7% of oral cancers are verrucous carcinomas.

Shear and Pindborg coined the term verrucous hyperplasia of the oral mucosa in the year 1980 to describe a distinct clinical form of oral leukoplakia. However, some authors regard verrucous hyperplasia to be a morphological variant of verrucous carcinoma. Others consider verrucous hyperplasia to be an irreversible precursor of verrucous carcinoma and recommend that both lesions should be managed in the same manner.

Neville et al (2007) stated it is found predominantly in men older than 55 years of age (average age 65-70 years). However, in areas where women are frequent users of spit tobacco, elderly females may predominate. Common sites are mandibular vestibule, buccal mucosa and hard palate. Site of occurrence often correspond to the site of chronic tobacco placement.

Etiology is not completely established but risk factors such as tobacco use, including both inhaled and smokeless tobacco and opportunist viral activity associated with HPV 16 and 18,7,11 may play an important role in the pathogenesis. Tumors at anatomic sites other than mouth are unrelated to tobacco use. They are locally invasive. If there is a concomitant infection, the draining lymph nodes, particularly submandibular and submental become enlarged and tender could lead to a misdiagnosis of metastatic carcinoma. This knowledge is important so that elective neck dissection may be avoided.

Although, verrucous carcinoma is frequently curable in the precocious stage, the neoplasm may become locally aggressive if not treated. Jacobson and Shear (1972) reported a 40% recurrence rate. Oliviera et al (2006) reported a 38.5% recurrence rate and compared it with Ackerman who reported a 29% recurrence rate, Jyothirmayi et al (30.1%)13, Kraus and Perez-Mesa (6.93%) and Rajendran et al (6.12%).

Treatment of choice is wide and deep excision of the lesion. Chen et al (2005) successfully treated an extensive verrucous carcinoma with 20%w/w topical ALA-photodynamic therapy with a 6 months postoperative period free of any recurrence. Jacobson and Shear (1972) reported that anaplastic transformation following radiotherapy occurs. However, Jyothirmayi (1997) and Nair MK (1988) treated verrucous carcinoma with radiotherapy and stated that oral verrucous carcinoma appears to have similar radioresponsiveness and improved disease-free survival compared to well-differentiated squamous cell carcinoma.

Ha and Califano (2003) stated that it would not be feasible to remove all of the area with molecular alterations surgically. Lodi and Porter (2008) further stated that this is also not likely to reduce the risk of later recurrence nor malignant transformation at the same or another site. Hence, preventive strategies are clearly desirable. Thus, using the knowledge gained from molecular studies, researchers have attempted to come up with protective measures that could render the mucosa less sensitive to DNA alterations.

13-cis-retinoic acid has probably been the most widely studied compound in the upper aerodigestive tract. A landmark study conducted by Hong et al (1986) showed regression of oral leukoplakias as compared with placebo as well as regression of SPTs (Hong et al, 1990). However, Ha and Califano (2003) in their review noted that despite clinical regression, genetic alteration in the mucosal field remained unchanged. Additionally, the toxicities associated with high-dose retinoids have prevented them from becoming the standard of care, while low doses have been shown to be ineffective.

However, lycopene may have some efficacy for the short-term resolution of oral epithelial dysplasia. Epigallocatechin-3-gallate (EGCG) in green tea seems to work as an antioxidant and inhibit cell proliferation, invasiveness and angiogenesis. However, several cups a day must be consumed to achieve pharmokinetically active levels. Sun et al (2010) studied ZengShengPing which is a mixture of six medicinal herbs in a randomized clinical trial on patients with oral leukoplakia. ZSP reduced the size of the lesion in 67.8% patients. The chemopreventive activity of Spirulina fusiformis (SF) 1g/day for 12 months in reversing oral leukoplakia was evaluated by Mathew et al (1995). Complete regression of lesions was observed in 20 of 44 (45%) evaluated subjects supplemented with SF. It also did not result in increased serum concentration of retinol or beta-carotene, nor was it associated with toxicity.

The regular use of aspirin is associated with an almost 25% decrease in the risk for most head and neck cancers, especially oral cancers. Another natural compound, guggulsterone, has been shown to have a potent inhibitory effect on the head and neck cancers by the activation of c-Jun N-terminal kinase and the subsequent increase in apoptosis. Similarly, genistein has been shown to inhibit head and neck cancers by activation of the nuclear transcription factor, nuclear factor κB (Kapoor 2008).

Biochemoprevention therapy combining high-dose tretinoin, α-TF and interferon-alpha (IFN-α) has shown a markedly better inhibition of cell growth but it’s efficacy needs to be determined in phase III trials. In addition, the investigation of biomarkers, latest being podoplanin (Kawaguchi et al 2008) has led to the development of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and farnesyl transferase inhibitors (FTIs) that target EGFR and H-ras and cox-2 inhibitors (Singh et al 2010) are new promising agents for chemoprevention.

Inspite of advances in research of carcinogenesis, chemoprevention for head and neck cancer remains investigational. Thus, clinical judgment and meticulous follow-up remain the best course.
REFERENCES