Oral potentially malignant disorders: Revisited

Dear Readers,

In 1805, a panel of European physicians suggested that oral precancers are benign diseases which will always develop into invasive malignancies, if followed long enough. In 1978, the WHO proposed the terms "precancerous conditions" and "precancerous lesion" and defined precancerous lesion as "a morphologically altered tissue in which cancer is more likely to occur than in its apparently normal counterpart." Confusion prevailed over this terminology, and many opined that the prefix "pre" quotes that all precancerous lesions will eventually become cancer, whereas literature argues against this general belief. In 2005, the WHO recommended abandoning this terminology and instead proposed to use the term "oral potentially malignant disorders" (OPMDs), which is defined as "the risk of malignancy being present in a lesion or condition either at the time of initial diagnosis or at a future date." It has been well established by researchers that virtually all oral cancers are preceded by visible clinical changes in the oral mucosa usually in the form of white or red patches which may or may not be associated with additional features of significant discomfort. Information about the real prevalence of OPMDs among the general population worldwide is scarcely available; however it is reported to be from 1% to 5%. The average age of patients with OPMDs is 50–69 years. However, recent studies suggested that about 5% of OPMDs had been observed in persons under the age of 30 years. A 10-year survey in our referral center (Dr. R. Ahmed Dental College, Kolkata) comprising 1874 patients from eastern part of India showed a significant increase of oral submucous fibrosis (OSMF) cases, specifically among males, in the last 4–5 years. We observed pan masala and gutkha to be the main causative agents for the development of OSMF. However, the most alarming fact was that about 67% of OSMF cases were of age within 40 years. Among these relatively younger OSMF cases, ~76% were males and the remaining 24% were females. Among the genders, OPMDs have traditionally shown a predilection for males. However, recent studies show a 1:1 male-to-female ratio. We also observed OSMF cases, only above 40 years of age, with 1:1 male-to-female ratio. This could be due to the increased habitual use of areca nut products, tobacco and alcohol among women. Premalignant disorders are usually found on the buccal mucosa, followed by gingivae, tongue and floor of the mouth. Prevention and early detection of OPMDs have the potential of not only decreasing the incidence, but also in improving the survival of those who develop oral cancer in later stages.

Several lines of evidence, including clinical, experimental and morphological data, support the concept that squamous cell carcinoma of the upper aerodigestive tract arises from noninvasive lesions of the stratified squamous epithelium. These lesions encompass a histological continuum between the normal mucosa at one end and high-grade dysplasia/carcinoma *in situ*, at the other end, establishing a model of neoplastic progression. The identification of preneoplastic lesions of the upper aerodigestive tract, through clinical, morphological and more recently, molecular means, helps in the early detection and treatment of head-and-neck squamous cell carcinoma.

The most common OPMD lesions are oral leukoplakia, OSMF, erythroplakia and verrucous carcinoma. Some miscellaneous inherited/acquired diseases such as xeroderma pigmentosum, dyskeratosis congenita, Fanconi's anemia, chronic iron deficiency anemia and immunodeficiency are the other potentially malignant disorders for oral carcinoma. OSMF is a precancerous condition which is a chronic, complex and irreversible

condition characterized by juxta-epithelial inflammation and progressive fibrosis of the submucosal tissues. As the disease progresses, the fibrotic bands become rigid such that the patient is unable to open his/her mouth. The condition is habit dependent where the main component is areca nut. Leukoplakia, literally meaning "white patch," is an OPMD occurring in those individuals having either tobacco smoking or tobacco chewing habits. Leukoplakia results from chronic irritation of mucous membranes by carcinogens, stimulating the proliferation of epithelial tissue. Leukoplakia also reveals hyperkeratosis variably associated with the underlying epithelial hyperplasia. The chance that oral leukoplakia will convert into oral carcinoma is reported to be ~20%. Erythroplakia is a bright red velvety plaque. It is generally associated with the underlying epithelial dysplasia and has a greater potential to turn into malignancy than leukoplakia. Almost 40%–50% of erythroplakia cases turn into carcinoma. Verrucous carcinoma, characterized by a warty, bulky, elevated, fungating appearance, is a condition occurring predominantly in elderly patients with poor oral hygiene and tobacco abuse. The chance that verrucous cancers will show metastasis is rare though conflicting reports are seen in the recent literature which includes hybrid carcinomas. Genetic events such as silencing of tumor suppressor genes and activation of oncogenes play key role in the etiology of oral cancer. In our recent genome-wide DNA methylation study, we identified several novel differentially methylated genes associated with OSCC. We identified a unique set of hypomethylated immunoresponse genes among OSCC patients in India, which might be attributed to different oral habits observed in Indian patients.

Pathway analysis of these hypomethylated genes indicated that the OSCC patients in India induce an antitumor T-cell response, with mobilization of T-lymphocytes in the neoplastic environment. Recent studies also implicated a role of both genetic and epigenetic alterations and their complementary roles regarding the current understanding of the molecular pathogenesis of OPMD. However, we are far away from understanding the actual molecular mechanism of these potentially malignant disorders. More focused studies, considering both genetic and epigenetic alterations along with several environmental factors, may help us to unravel the molecular mechanism behind their potential for transforming into malignant lesions.

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