EDITORIAL

Why do Only Certain Cases of Oral Submucous Fibrosis Undergo Malignant Transformation?

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Background

Oral submucous fibrosis (OSMF) causes desmoplasia and rigidity of submucosa of the oral cavity, resulting in reduced mouth opening, and in advanced stage causes difficulty in swallowing. OSMF has poor morbidity in terms of oral function as well as general health due to loss of oral function, such as eating. In severe conditions, it can cause dysphagia and hearing loss. Various clinicians have tried the different treatment modalities to reverse the disease process, but with limited success and that too in alleviating the associated symptoms.

One most important risk of OSMF is the development of oral squamous cell carcinoma (OSCC). Further, there is no definitive time limit for malignant transformation of oral mucosa in OSMF. Usually, it can take 2–3 years to undergo malignant transformation. Prevalence of malignant transformation of OSMF stands at 7–13%. However, actual prevalence could be on a higher side in view of the number of areca nut (AN) users in the world. Considering the OSCC nature, it adds more difficulties to OSMF patients and decreases the prognosis and mortality.

In the past few years, researchers are trying to understand mechanism of carcinogenesis in OSMF. Although AN is strongly linked to OSMF and a certain extent to malignant transformation, how AN causes the malignant transformation in only a few numbers of cases (7–13% rate) has not been explained.

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Discussion

Numerous theories and mechanisms proposed are making rounds in the literature to explain the role of AN in the malignant transformation of OSMF. The studies suggested that AN or its constituents exert a carcinogenic effect on oral mucosa through various pathways.[1] AN or AN extract (ANE) has cytotoxic effects on oral epithelial cells.[2] and causes cell cycle arrest.[3] Any damaged cells are eliminated through the physiologic cell death process of apoptosis. The immune system continuously monitors and protects the body tissue from potential pathogens as well as abnormal self-cells by eliciting the inflammation. Inflammation involves various inflammatory cells (immune cells), such as natural killer cell lymphocytes, macrophages, neutrophils, and mast cells that especially involve T- and B-lymphocytes.

The immune cells are important for controlling tumorigenesis, but during early carcinogenesis, tumor-associated immune suppression cells inhibit these immune cells that are present in the extracellular matrix. How these immune suppression cells make their way in the extracellular matrix needs evaluation. Inflammation has complex nature as an immune response in the body and is difficult to analyze the role of immune cells. Although inflammation plays a defensive role, it is difficult to say when it crosses a thin line and starts harming own. Still these mechanisms have not explained why only a few cases of OSMF undergo malignant transformation and have a variable timeline for conversion. Most these evidence are from *in vivo* and *in vitro* laboratory conditions not mimicking the oral cavity environment as well as were carried out for a duration of few days. AN chewer usually keeps or eats AN in the oral cavity for a variable time duration ranging from few minutes to few hours.[4] Further, saliva may dilute the ANE released from AN chewing, and it may not be there for a longer time in the oral cavity to interact with oral mucosa since it may be swallowed or spitted by the AN chewer. This could partially explain the longer duration for malignant transformation of OSMF. However, still the question remains unanswered why certain OSMF cases undergo malignant transformation.

A recent study showed that ANE affects the neutrophils altering the defensive function of inflammatory cells that are a primary line of defence against oral microbes.[5] Inhibition of inflammatory cells may make a person susceptible to infections from oral microbes that are implicated in oral carcinogenesis.[6] It is known that OSMF patients develop opportunist microbial infections, such as candidiasis, during OSMF progression. *Candida albicans* role in

malignant transformation of oral leukoplakia (OL), another oral potentially malignant lesion, has recently been reviewed.[7] Candidal infection promotes cellular and dysplastic changes in OL. Further, there is an association between epithelial dysplasia in OL and candidiasis. Although the explicit correlation of candida infection with malignant transformation of OSMF has not been proven, few studies have studied candida in OSMF patients and *in vivo* or *in vitro* experiments.[8,9]

Candida produces its carcinogenic effect on oral mucosal cells through the production of nitrosoamines.[10] Further studies have shown that candida species can produce surface changes in oral mucosal cells.[11] These changes can then be susceptible to the carcinogenic effect of chemicals, such as AN. Moreover, the activity of the neutrophil influences the response of epithelial cells to candidal infection. The absence of an appropriate immune response can lead to hyperplastic candidiasis, resulting in a chronic hyperplastic change in the epithelium. This chronic hyperplastic epithelium can harbor the markers associated with malignancy, including p53.[12]

Considering the interaction of ANE with immune cells and the prevalence of candida infection in OSMF, it is interesting to explore it in the context of malignant transformation. Does ANE act synergistically with chronic candidal infection to induce malignant change in oral submucosa? Does surface change enhance ANE cytotoxic effects on epithelial cells producing the dysplastic changes? At present, no laboratory or observation study has been conducted to evaluate the role of candida infection in the malignant transformation of OSMF. Answer to these questions may help clinicians to focus on developing appropriate treatment protocol in OSMF patients and thereby reduce the morbidity and mortality caused by OSMF–OSCC.

Predisposing Factor Audit

Due to fact that only a few cases of betel quid chewing or OSMF patients undergo malignant transformation, it becomes mandatory to perform predisposing factor audit in such patients to find out exactly the reason for the same. This should involve assessment of candidal carriage, presence of sharp tooth, long-term use of alcohol-based mouthwash, nutritional deficiency, immunodeficiency, genetic susceptibility, and human papillomavirus expression.

Conclusion

It is important for the researcher to look into the aspect of malignant transformation of OSMF considering the increase in the number of OSMF patients, especially in later stages with OSCC. Future studies should consider the above-mentioned predisposing factors while considering *in vivo* or *in vitro* studies to explore carcinogenesis in OSMF to find out the variable that can bear on malignant transformation of OSMF.

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