A Case of Oral Squamous Cell Carcinoma in a Nontobacco Habitué

Abstract
India is considered to be the oral cancer capital of the world. Oral squamous cell carcinoma is a multifactorial disease with tobacco and alcohol being considered major risk factors. However, there is a growing incidence of nonhabit (i.e., the absence of tobacco or alcohol) associated oral cancer. Difference is noted in demographics, site predilection, grade, and stage while comparing habit associated and nonhabit associated oral carcinoma. This warrants a need for a greater understanding of carcinogenesis without a known carcinogen. This case adds to the sparse existing scientific literature on oral cancer in nonhabitues and reviews the possible etiopathogenic mechanisms underlying the disease process.

Keywords: Nonhabitues, oral carcinogenesis, trauma

Introduction
Oral squamous cell carcinoma (OSCC) is the eight most common cancer in the world.\[1-3\] A recent trend seen in India is the increased incidence of OSCC in females without a deleterious habit history.\[3\] However, the pathogenesis of oral carcinoma without a known carcinogen is yet to be elucidated. This case focuses on OSCC in a nonhabitué and dwells into the possible pathogenic molecular pathways for the same.

Case Report
A 53-year-old female patient reported to the Department of Oral Medicine and Radiology, with a complaint of a nonhealing ulcer on the left buccal mucosa. The patient was edentulous and a denture wearer for 10 years. She gave a 6 months history of loosening and impingement of her upper denture which caused discomfort while eating. As a result of the trauma caused by the loose denture, an ulcer developed over the left buccal mucosa which gradually increased in size and caused the patient severe pain because of which she had a limited mouth opening.

There was no history of any deleterious or pernicious habits and no relevant medical history.

The intraoral examination was difficult due to restricted and painful mouth opening which was <2½ cm. A single well-defined, ulceroproliferative lesion could be visualized, measuring approximately 1 cm × 2 cm in dimension, present over the left buccal mucosa, extending into the left posterior gingivobuccal sulcus [Figure 1].

The margins of the ulcer were everted; floor showed slough, and surrounding mucosa appeared erythematous. The ability of the patient to inflate her cheeks suggested that the left buccinator was negative for tumor infiltration. Palpation confirmed findings of the inspection and further revealed that the ulcer had indurated borders, bled easily, and appeared fixed to the underlying mucosa.

A single left submandibular lymph node was palpable, mobile, and tender and measured approximately 1 cm × 1 cm in dimension.

Complete hemogram, blood glucose, liver, and kidney function tests were normal. Fine-needle aspiration cytology of the clinically palpable lymph node showed reactive hyperplasia.

Incisional biopsy revealed a well-differentiated squamous cell carcinoma (i.e., by Broder’s histopathological grading system) [Figure 2]. A wide excision of the lesion along with modified radical neck dissection was performed. Clear margins were obtained and the lesion was diagnosed as stage II buccal carcinoma according to the STNMP staging system.\[4\]

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The patient was advised a monthly follow-up regime of 5 years with no evidence of recurrence to date.

### Discussion

Oral cancer represents a major subset of head and neck cancers.[1] Conflicting data exist with respect to the most prevalent age group affected by nonhabit associated OSCC.[2,3] While some authors state that nonhabit associated OSCC commonly affects young individuals, others state a bimodal age of predisposition, i.e., <40 years and >70 years of age. This case, however, does not follow the bi-modal age predisposition.[5,6]

The younger age for acquiring non habit associated OSCC is attributed to genetic predisposition, viral etiology (e.g., human papillomavirus and Epstein–Barr virus), immune-suppressive states, Fanconi’s anemia, and occupational exposures.[3,7,8] Older individuals are thought to be susceptible to malignancies due to the cumulative effect of environmental and ingested carcinogens. In this case, considering the age of the patient, repeated trauma could act as a mutagen initiating carcinogenesis in a conducive oral environment.[9]

Oral carcinoma without a habit history shows a higher incidence for the female gender.[8] It is known that cancer cell lines derived from head and neck carcinoma demonstrate estrogen metabolism genes, in particular, estradiol in tongue carcinoma. Other studies have attributed the altered levels of follicle-stimulating hormone, lutetizing hormone, prolactin, and testosterone in females with nonhabit associated OSCC.[1,8] This case adds to the existing voids in research related to the exact role played by estrogen receptors in nonhabit associated OSCC which seems to favor the female gender.

The oral cavity is exposed to different sources of trauma in the form of ill-fitting dentures, impinging dental restorations, sharp cusps, and root pieces. It has been established that chronic irritation results in the generation of reactive oxygen and nitrogen species (ROS and RNS, respectively) through a number of inflammatory cells such as macrophages and lymphocytes. When the concentration of free radicals (e.g., superoxide radical O2•, hydroperoxy radical HO2•, hydroxyl radical •OH, nitric oxide NO•, nitrogen dioxide NO2•) exceeds the body’s antioxidant defense mechanism, it induces mutations in the stem cell compartment resulting in oral carcinogenesis [Figure 3].[10]

In this case, the loose denture served as a source of chronic irritation and trauma to the buccal mucosa. The possible synergistic effect of long-standing trauma and faulty DNA repair mechanisms, seen in the older age group should be studied further to shed light on the cell signaling pathways, thus generated.[9]

It has also been documented that non habit associated OSCCs tend to have a negative nodal status and a tumor size which seldom exceeds T2 (STNMP staging). The phenotype of nonhabit associated OSCC is generally well to moderately differentiated carcinoma. Comparative analysis of the expression of p53 in habit and nonhabit associated OSCC show a significant decrease in expression in the latter. This could explain a good response to radiotherapy and thus an improved overall prognosis.[3‑5] However, some studies state the contrary, explaining that a poor 5 years survival rate in nonhabitues is attributed to a delay in therapy and at times inappropriate management.[6]

As a disease entity, nonhabit associated OSCC remains an enigma. The molecular pathways which trigger oncogenic mutation as a result of inflammation induced by trauma, micronutrient deficiencies, immune dysfunction, and hormonal imbalances could delineate a niche uniquely occupied by nonhabit associated OSCC.

This case highlights clear differences seen in demographics, grade, stage, and prognosis when comparing non habitué and habitué associated oral carcinogenesis.
The limitation in this paper was that investigations for a possible association of human papilloma virus with OSCC was not carried due to financial constraints of a government hospital set up.

With the recent rise in nonhabit associated OSCC, it is imperative to further research the molecular pathways which initiate cancer stem cells in the presence of an occult carcinogen. An increased awareness among medical and dental professionals will result in an efficient multitier approach to targeted therapeutics.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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