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Case Report

Snus (nass) and oral cancer: A case series report

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ABSTRACT

Snus (nass) is a form of snuff used in a similar manner to American dipping tobacco, but it does not typically result in a need for spitting. Possible hazards associated with this material include malignant and premalignant lesions in the oral cavity and gastrointestinal tract. The use of smokeless tobacco has increased in the Middle East in recent decades, particularly among teenagers and young adults. Therefore, practitioners must be able to recognize malignant and premalignant lesions. Although, an estimated 10-25% of the world's population uses smokeless tobacco, this practice is virtually unknown in Iran. The aim of this study is to report a series of cases of squamous cell carcinoma and verrucous carcinoma occurring in the users of snus, who referred to the Department of Oral Medicine in Kerman Dental School.

Key Words: Oral cancer, smokeless tobacco, snus, squamous cell carcinoma, verrucous carcinoma

INTRODUCTION

Tobacco use is one of the main factors that can lead to cancers of the oral cavity and pharynx.[1] There are many types of smokeless tobacco products such as chew, chewpoos, chits, chewsky, dip, smokeless tobacco keratosis, flab, chowers, snuff dipper, guy, snus or nass, which can be used by placing and chewing a small amount of the substance between the cheek and gum or teeth.[2]

In Europe and North America, chewing tobacco and snuff are two major products. Both, moist and dry snuff exists in this area, such that moist snuff is usually used in Scandinavia and the USA. It is generally placed under the upper lip, lower lip or kept in the buccal gingival area, but dry snuff is placed in the oral cavity or administered through the nose. A great number of users chew tobacco for several hours a day.[2]

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Snus (called "nass" in Iran, Afghanistan and Pakistan) or Swedish snuff is used by placing it under the lip for extended periods of time. It is a moist powder tobacco product produced from a variant of dry snuff in the early nineteenth century in Sweden. This material is a mixture of pan prague, coarse grains and red trees along with tobacco leaf, lime, ash aromatic spices, saccharin and various oils.[3,4]

During recent decades, the use of smokeless tobacco has increased in the Middle East, particularly among teenagers and young adults.[3] The prevalence of smokeless tobacco in relation to age reflects major changes over the decades in the use of smokeless tobacco. In 1970, 2.2% of white male adults aged 18 to 24 years used chewing tobacco or snuff. The prevalence was higher at successively older ages, peaking at 11.8% among white men 65 years or older. In 1991, the age trends were reversed, with 10.4% of 18-24 year-olds using the products and fewer older persons using them: 7.9% of 25-34 year-olds, 5.4% of 35-44 year-olds, 3.8% of 45-64 year-olds, and 5.5% of individuals 65 years of age and older.[5]

The relation between use of smokeless tobacco and cancer was noted as early as 1761, when a British

physician described nasal "polyposes", probably nasal cancer in several of his patients, which he attributed to the use of snuff through the nose.[6] The cancers often occurred precisely where tobacco had routinely been placed in the lower half of the mouth and in the buccal mucosa or gums.[7]

Here we report a series of cases of squamous cell carcinoma and verrucous carcinoma occurring in the users of snus, who referred to the Department of Oral Medicine in Kerman Dental School.

CASE REPORTS

Case 1

A 78-year-old Iranian female was referred to the Department of Oral Medicine, Kerman Dental School, by her dentist for evaluation of an exophytic lesion on the right buccal mucosa, which had been noticed 2 months previously. The lesion had rapidly increased in size. The patient did not have any systemic disease. In addition, the patient had a snus habit for the past 15 years in the right mandibular vestibule but no alcohol consumption.

On examination, there was a tender firm exophytic lesion with induration, measuring 8 cm by 4 cm, on the right buccal mucosa. The surface of the lesion was verrucous with a white color and no associated lymphadenopathy [Figure 1].

A diagnosis of verrucous carcinoma with differential diagnosis of a squamous cell carcinoma was made. Under local anesthesia, simple enucleation of the lesion was performed. Histological examination of the excised tissue showed features of a poorly differentiated verrucous carcinoma. In view of the diagnosis of verrucous carcinoma, further investigations including chest radiography and hematological and biochemical blood tests yielded negative results. Surgery, chemotherapy and radiotherapy were considered for the patient. Further, histological examination of the main specimen confirmed the presence of a verrucous carcinoma with parakeratin and the wide and elongated rete ridges that appear to push into the underlying connective tissue [Figure 2]. A year later, the patient passed away despite removal of the lesion and a relatively good response to treatment.

Case 2

A 53-year-old female presented for routine examinations with his general dental practitioner, complaining of a sore area on the right side of the buccal mucosa, present for about 4 weeks. The patient had hypertension for the past 10 years and had become addicted to opium 15 years previously. She had a snus habit from 5 year ago in the right mandibular vestibule with no alcohol consumption. The practitioner diagnosed a leukoplakia and the patient was referred to the dental school for biopsy. In the intraoral examination, a 5 cm-diameter white verrucous area extended from the right buccal mucosa into the alveolar ridge, which was tender to palpation. The tissue proximal to the lesion was erythematous and atrophic in appearance with indurations [Figure 3].

The lesion was biopsied and histological examination of the excised soft tissue showed features of a early squamous cell carcinoma with some cell degeneration, keratin pearls, nests and cords of malignant epithelial cells with wide cytoplasm, round or oval nuclei, with prominent nucleoli and mitotic figures [Figure 4].

The patient underwent total excision of the lesion with reconstruction using a split skin graft. At 3-year follow-up the patient was free from the disease.

Case 3

A 35-year-old female was referred urgently having presented to her general medical practitioner complaining of an ulcer on her tongue of about 2-month duration. The patient was complaining of an ulcer on the right side of her tongue, which had previously been asymptomatic but had begun to cause occasional discomfort as it increased in size. The ulcer was interfering with the patient's ability to eat. Previous medical history revealed that the patient was suffering from hyperthyroidism. Otherwise, her medical history was clear, and the patient had a snus habit for the previous 3 years in the right mandibular lingual vestibule. Intraorally, there was evidence of a crater-like ulcer (prominent border and depressed base) on the right lateral border of the tongue extending into the dorsal surface of the tongue with a diameter of 6 cm, which was tender and indurated [Figure 5].

An incisional biopsy was performed, which revealed poorly differentiated squamous cell carcinoma histopathologically. CT revealed two abnormal nodes in the right submandibular region, which were needle-biopsied; metastatic squamous cell carcinoma was detected. Following surgery and radiotherapy the patient survived for only 5 months.

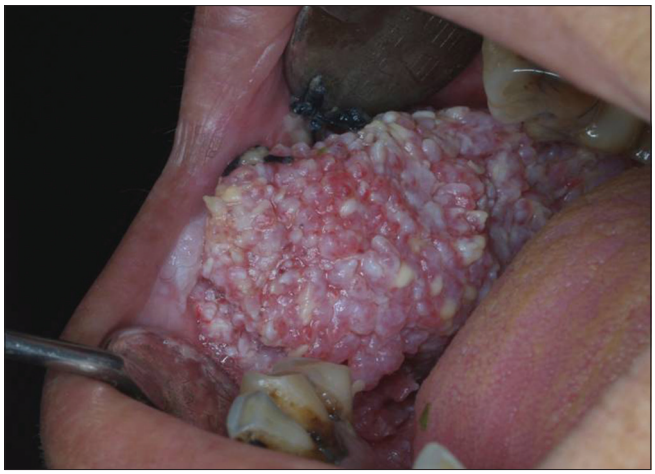

Figure 1: A exophytic lesion with measuring 8 cm by 4 cm at the right of the buccal mucosa. The surface of lesion is verrucous

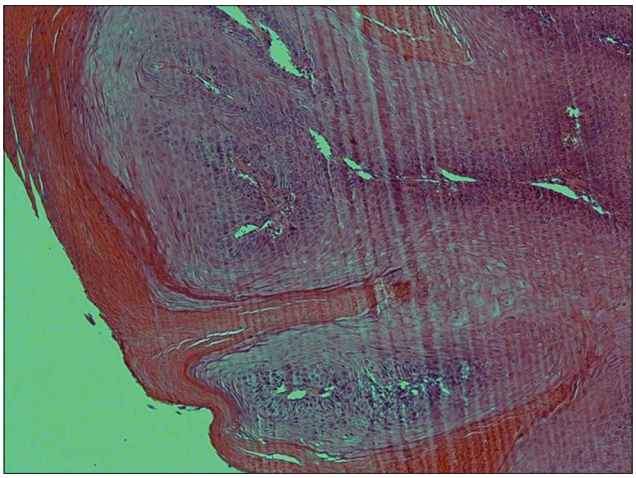

Figure 2: A verrucous carcinoma with parakeratin and the wide and elongated rete ridges that appear to push into the underlying connective tissue

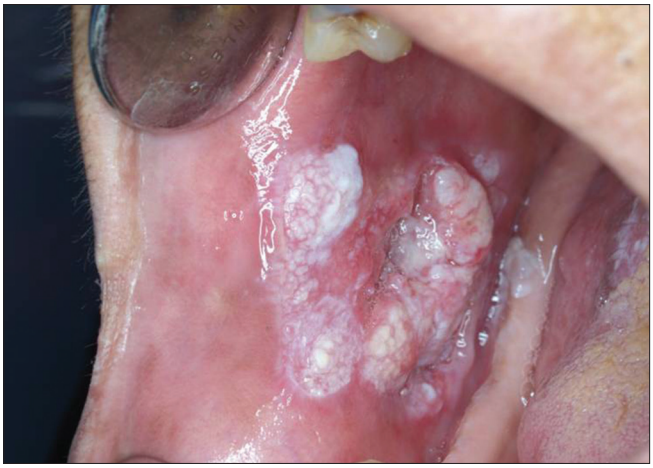

Figure 3: A verrucous area extended from the right buccal mucosa into the alveolar ridge, which tender to palpation. The tissue proximal to the lesion is erythematous and atrophic in appearance with indurations

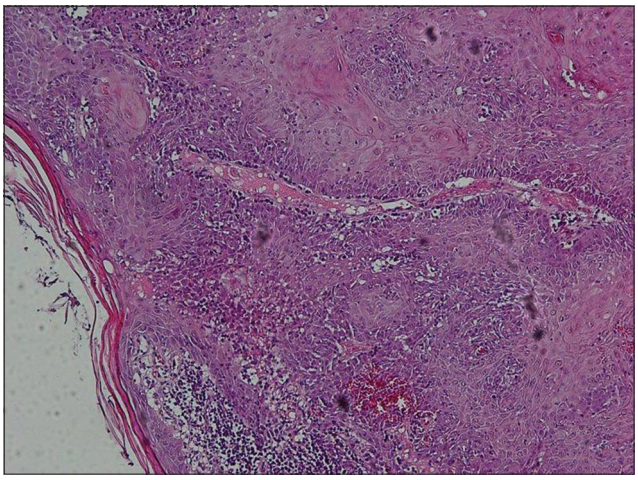

Figure 4: A early squamous cell carcinoma with some cell degeneration, keratin pearls, nests and cords of malignant epithelial cells with wide cytoplasm, round or oval nuclei, with prominent nucleoli and mitotic figures

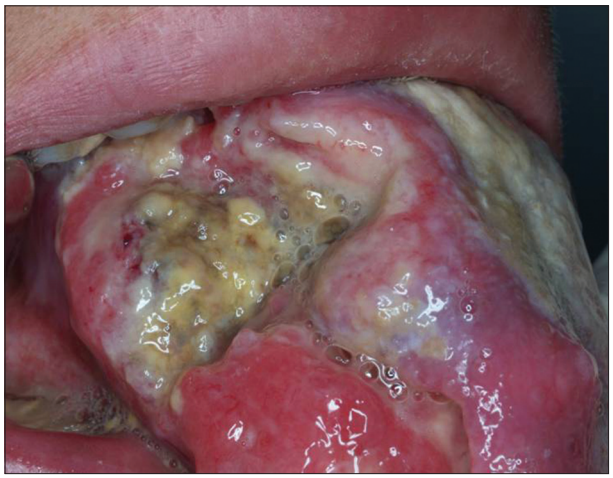

Figure 5: A crater like ulcer on the right lateral border of the tongue that extending into dorsal surface of the tongue

Case 4

An 82-year-old female, from Zahedan province, was referred by her general dental practitioner in relation to a complaint of a growth in the lower right alveolar left region since 3 months previously. The growth was insidious initially and gradually increased in size. Since the first week, the growth was associated with localized severe throbbing and pain. There was no relevant medical history. The patient had smoked up to 5 cigarettes per day for the past 20 years and had the habitual use of snus 4-5 times a day for the past 20 years in the left mandibular vestibule.

A solitary submandibular lymph node was palpable on the left side, measuring 4 cm in size, which was tender and hard boney in consistency and fixed. Intraorally,

an ulcero-proliferative lesion was evident on the left mandibular ridge area, measuring about 4 × 5 cm in size. It was irregular in shape with rolled-out edges extending to the floor of the mouth. The center of the lesion was composed of a whitish-yellow slough. The lesion was tender on palpation with an indurated base; in addition, there was evidence of a crater-like ulcer on the left vermilion border of the lip [Figures 6 and 7].

Incisional biopsy of the lesion was performed, which provided a histopathological diagnosis of poorly differentiated squamous cell carcinoma. The patient was reviewed at monthly intervals. Despite radical surgery and radiotherapy, the patient died 5.5 months after presentation.

DISCUSSION

The present study presented 4 cases of oral cancer occurring in the users of snus. Oral carcinoma in these patients had occurred at anatomic locations where this material is routinely placed.

A recent evaluation by the international agency for research on cancer (IARC) has confirmed that smokeless tobacco is also carcinogenic.[8,9] A recent meta-analysis showed a two-fold increase in risk of oral cancer with the use of smokeless tobacco in the United States and Canada, a five-fold risk increase for India and other Asian countries and a seven-fold risk increase in Sudan. No risk increase for oral cancer was shown with smokeless tobacco use in the Nordic countries.[10] In the UK and Europe (with the notable exception of Sweden) the use of smokeless tobacco is rare except in minority ethnic groups.[11] In the USA, it is a major problem with 6% of the adult male population as regular users.[12] In some areas, particularly the southern states, the prevalence is much higher with up to one-third of young men using smokeless tobacco.[13]

The primary cause of the very high incidence of oral cancer in South Asia is the widespread habit of chewing betel quid (or paan) and related areca nut use (areca nut is the seed of the fruit of the oriental palm, areca catechu).[14] Chewing betel is thought to date back to at least 2000 years and worldwide an estimated 200-400 million people practice the habit.[15] The components of the betel quid vary between different populations but the main ingredients are the leaf of the vine, piper betel, areca nut, slaked lime (calcium hydroxide) and spices.[16] Tobacco was introduced to South Asia in the seventeenth century. Areca nut is carcinogenic to humans and the risk of oral cancer is increased with chewing of paan without tobacco, although the risk is higher for paan-containing tobacco.[17-20] As with smoking tobacco, the risk is dependent on dose and duration of use. Among Asian communities in the UK, Bangladeshis are the most likely to retain the habit of betel quid chewing with 9% of men and 16% of women using smokeless tobacco. The most commonly used chewing tobacco product is betel quid with tobacco.[21]

Therefore, smokeless tobacco use occurs in many cultures throughout the world, resulting in the incidence of oral cancers in these countries. For example, in India and other Asian countries, smokeless tobacco in combination with areca nut, piper betel leaf, lime, and other ingredients has been strongly linked to oral cancer

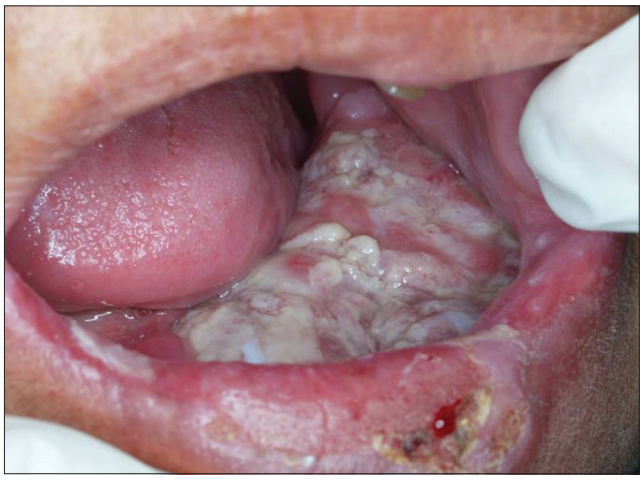

Figure 6: An ulcero-proliferative lesion in the left mandibular ridge area

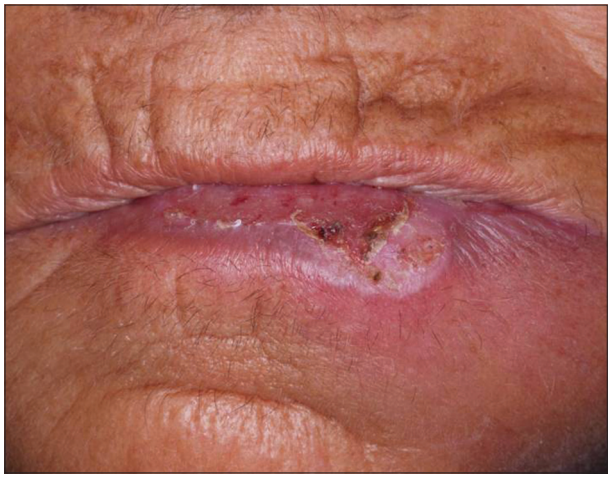

Figure 7: A crater like ulcer on the left vermilion border of lip

risk. Recent carefully conducted studies outside of the US continue to indicate that tobacco used in a variety of unsmoked forms confers an oral cancer risk on the user. The extent of cancer risk might depend on the products or combinations of products used or the way the user takes the product. Therefore, the risk of oral cancer increases with an increase in the product dose.[4]

Snus (nass) or Swedish snuff, is a moist tobacco powder product extracted from a variant of dry snuff in the early nineteenth century in Sweden; it is consumed by placing it under the lip for extended periods of time. Nass is a mixture of tobacco, ash, cotton oil, and lime.[22] In some areas where nass is taken orally, such as in the Central Asia, the prevalence of leukoplakia is high, and oral cancer incidence is moderately high relative to other former Soviet republics.[23]

Three studies were identified that have attempted to understand the cellular mechanisms involved in snuff-induced epithelial changes using oral tissues or cells.[16,24,25] These studies examined the effect of Swedish snuff on indicators of cellular proliferation (e.g., Ki-67) and on tumor suppressor and differentiation markers (e.g., p53 tumor suppressor gene). This study shows overexpression of Ki-67 protein and mutant tumor suppressor p53 protein in the biopsy samples from the snus users and no expression in the control biopsies.

Also, Merne and colleagues[25] evaluated the expression of proteins involved in cell proliferation (Ki-67, PCNA), cell cycle regulation (p53, p21), and keratins in biopsy specimens from 14 men with SIL to 12 biopsy specimens from normal buccal mucosa of men who had never used any type of tobacco products. All participants in the snuff group had used "loose non-fermented Scandinavian moist snuff" and three were also using portion-packed snuff.

In addition, in the assessment of the epidemiologic evidence on carcinogenicity of smokeless tobacco, it is of interest to consider some local effects in the oral cavity. Oral leukoplakia is a common finding in snuff users and is sometimes referred to as 'snuff dipper's lesion'. There is a close correlation between exposure (duration and intensity) and prevalence, as well as severity of lesions. The prevalence of micronuclei and other nuclear anomalies is increased in the oral mucosa of snuff users, and the tumor suppressor gene p53 appears to accumulate in oral leukoplakias of snuff users. A large number of case reports have described oral carcinomas in smokeless tobacco users, occurring at anatomic locations where tobacco is routinely placed.[1,26]

In the mid-1980s, it was concluded from a large number of literature reviews that smokeless tobacco is a cause of oral cancer in humans. These evaluations relied on case reports and epidemiologic studies in humans and on laboratory studies demonstrating that N-nitrosamine compounds are present in high levels in smokeless tobacco and that these compounds produce cancer in laboratory animals. Based on evidence from smokeless tobacco manufacturing statistics, the renewed popularity of smokeless tobacco among youth started in the late 1960s and early 1970s. Concern has been expressed that this trend could lead to an epidemic of oral cancers among young men.[26]

A total of 6 case-control studies are available from Sweden and the USA on oral snuff use and oral cancer.[1] One early Swedish study indicated an increased risk of buccal and gum cancer in snuff users. Three of the US studies provided evidence of an association between snuff use and oral cancer.[1] Cohort studies on the use of snuff and oral cancer provide inconclusive evidence, but the interpretation is often difficult because of limited statistical power. The data from Scandinavia and the US on smokeless tobacco and cancer of sites other than the oral cavity are relatively sparse.

For carcinoma of the upper digestive tract and pancreas, excess risks have been reported, but the evidence is not conclusive. In India, Afghanistan and Pakistan, use of nass is associated with an increased risk of oral cancer. Relative risks exceeding 10 may be observed in regular users, indicating that a substantial proportion of the oral cancers are attributed to the exposure in populations where the habits are widespread.

In addition, two of their patients had other risk factors similar to smoked tobacco consumption and addicted to opium, which might probably cause oral cancer. Although, cancer in these patients had occurred at anatomic locations where this material is routinely placed, oral cancer most commonly involves the tongue and floor of the mouth.

CONCLUSION

Evidence from human population shows that smokeless tobacco users have risks of cancer several times higher than those of nonsmokers. Smokeless tobacco is very strongly correlated with cancers of the

cheek and gums. Finally, preliminary work on cancers in other anatomic sites suggests that smokeless tobacco may also be related to other upper digestive tract cancers.

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