ORAL MUCOSAL LESIONS ASSOCIATED WITH TOBACCO AND BETEL-CHEWING HABITS : A NEPALESE EXPERIENCE

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EXTENDED ABSTRACT

A pre-existing potentially malignant lesion or condition, often associated with tobacco or betel-quid habit, may constitute, if not in all cases, pre-malignant stages of oral squamous cell carcinoma. However, their natural history, prevalence and their transformation into a malignant lesion vary between different population groups, geographical distribution, lifestyles and other predisposing or risk factors. A hospital-based study in Kathmandu, on the basis of malignant tumours diagnosed by the biopsy service at one of the tertiary care centre of the country, has shown that oral cancer accounts for 14 and 7.3 percent of all cancers in males and females, respectively[1].

The present study evaluates for the first time the prevalence and characteristics of oral mucosal lesions associated with tobacco and betel-quid chewing habits in a population-based random sample in three geographic regions of Nepal with different social and economic backgrounds. Firstly, a village in Dolkha in the mountainous region; secondly, Butwal and surrounding areas in the plains near the southern border and lastly, the city of Kathmandu, were selected for the study. An adult population of above 20 years were interviewed, examined and information recorded according to the Criteria for Diagnosis of Oral Mucosal Lesion prepared by Ikeda et al. with slight modifications[2]. The interview and examination of each individual was carried by one examiner (PS) in June and July 1996. Oral examination was performed in natural light with an additional torch light using two mouth mirrors. For comparison of several parameters the Kruskal-Wallis test and the chi-square tests were used. The critical value for statistical significance was considered as $p<0.05$. Futhermore, patients presenting with oral mucosal lesions in a hospital setting were analysed. Cellular proliferation and presence of mutant form of p53 oncosuppressor gene product, known to affect or play a role in the process of carcinogenesis[3], in a number of these lesions were assessed by immunohistological methods as described elsewhere[4].

The sample population was 1,421 adults (760 male and 661 female) with age range from 20-85 years (mean age 42.6). The commonest tobacco habit was smoking in both the sexes where more than 70% of the women in rural areas were smokers (49.2% male and 18.3% female). The most common constituents of the tobacco or betel quid habits, predominantly among men, was a mixture of tobacco and lime (23% male, less that 1% female) followed by betel quid with or without areca nuts and tobacco or areca nuts only (22% male vs. 6.2% female).

The most frequently found lesion associated with the habit was white or red lesions in 70.4% of tobacco and lime users (n=186) who frequently place the quid in their labial or buccal sulcus as a mucosal pouch. Betel-chewer's mucosa was found in 23.8% of betel quid chewers with or without areca nuts and/or tobacco (n=143), leukoplakia in 2.4% of smokers (n=495) and submucous fibrosis in 3 subjects who were all areca nut chewers.

Tobacco and lime user's lesion, localized at sites where the quid is most frequently placed, often resembled homogeneous and/or non-homogeneous leukoplakia. The lower labial and gingival or alveolar mucosa was the most preferred site for placing the quid and the lesion was more common ($p<0.001$) than any other sites. The lesion typically was velvety with fissured or rippled surface often showing white or red patches with frequent destruction of the periodontium resulting in gingival recession with exposure and yellow to brown staining of the root surfaces of the affected teeth. The appearance of the lesion was associated with the duration of the habit ($p < 0.05$) and frequency and duration of quid in the oral cavity ($p < 0.01$).

The prevalence of leukoplakia was nearly 1%, and was most frequent in men where the buccal mucosa, lateral border of the tongue and floor of the mouth were most commonly affected and was associated with smoking habit.

Based on the natural history and clinical appearance, the tobacco and lime user's lesions may demonstrate a different behaviour from leukoplakia classified according to the WHO criteria[5] and therefore we believe it is reasonable to segregate this particular habit associated lesion from other tobacco associated or idiopathic leukoplakia. The relative risk of malignant potential of these lesions, believed to be much less than leukoplakia but adequate enough to be classified as a potentially malignant lesion, may however never be known as many of these lesions disappear after cessation of the habit or will be treated before it is too advanced.

Betel-chewer's mucosa due to the direct action of the quid or traumatic effects of chewing or both results in a tendency to desquamation or peeling off of the oral epithelium. Loose or detached tags of epithelium may be seen or felt. This lesion was associated with the areca nuts or betel quid chewing habit with or without tobacco and/or slaked lime. Betel-chewer's mucosa was most significantly associated with the duration and frequency of the habit ($p<0.001$). Among the betel quid chewers, yellow or brown encrustations were found on the oral mucosal surfaces.

Submucous fibrosis was associated with the history of areca nut chewing ($p<0.001$) with a prevalence rate of nearly 0.2% in the population. There was a clear association between submucous fibrosis and areca nut chewing habit with or without betel quid or tobacco. Betel-chewer's mucosa, may be a reversible condition, and could possibly be a precursor of submucous fibrosis especially among areca nut chewers. However the relationship, if any, is yet unknown. The chemical and mechanical trauma inflicted on oral mucosa resulting in the betel chewer's mucosa will need further studies to define the effects on the mucosa.

In patients presenting with tobacco associated lesions in a hospital setting - the tobacco and lime users (n=35) showed complete remission of their lesions with the discontinuation of the quid for 1-3 weeks (n=33). In one patient, the hyperkeratosis remain unchanged and gradually became thickened after cessation of the habit during a follow up of 3 months. Betel-chewers mucosa (n=12) also showed remission with the discontinuation of the habit (n=11) but one patient, a 36 year old male with the habit of areca nut and tobacco chewing, has multicentric squamous cell carcinoma on left and right lateral borders of the tongue at the time of presentation. The commonest sites involved in betel chewers mucosa (n=48) were the buccal mucosa in 60% of the cases, lateral border of the tongue (21%), floor of the mouth (6%), gingivae (4%), palate and dorsum of the tongue (3%). All patients presenting with submucous fibrosis (n=12) had areca nut chewing habit of various duration and may suggest a relationship, yet unknown, with the betel chewers mucosa. One of the patient, a 52 year old female, was diagnosed as having carcinoma of the buccal mucosa.

Using immunohistochemical methods, all these tobacco and betel quid associated lesions or conditions were found to be hyperproliferative with a statistically significant difference in labelling index of PCNA when compared with clinically healthy mucosa ($p<0.001$). The epithelial proliferation index assessed on the basis of nuclear immunostaining for proliferating cell nuclear antigen PCNA (mean percentage ± standard deviation) in the oral mucosa from healthy subjects was 7.2 ± 1.96 (n=16) compared with the lesional mucosa of tobacco and lime user 21.5 ± 1.96 (n=16), submucous fibrosis 28.2 ± 4.10 (n=12), betel-chewer's mucosa 25.4 ± 3.20 (n=12), and leukoplakia 18.8 ± 4.85 (n=8). Mutant form of p53 was detected in a number of these lesions including nearly 60% of OSF and 25% of clinically healthy oral mucosa restricted to subjects of over 40 years old with some form of tobacco, areca nut or betel quid habits. No significant correlation was observed between the growth fraction of cells and p53 status in any of these lesions. The role of mutant form of p53 in the transformation of a potentially malignant lesion into a malignant one needs further evaluation during oral carcinogenesis.

Ethnic variations, geography, lifestyles, nutritional, immune-modulating and many other factors may affect the ultimate outcome of tobacco and betel-quid related lesions. The results in the present study reasonably allowed us to conclude that due to a very high incidence of oral lesions among tobacco and lime users, these lesions may be evaluated as a separate lesion from leukoplakia (as defined by the WHO criteria) in order to clarify its nature and potential for malignant transformation. The tobacco and betel-quid associated lesions or conditions are indeed hyperproliferative disorders. The clinically healthy oral mucosa in elderly individuals with tobacco or betel quid habit as well as other quid-related oral lesions may be considered as a high risk mucosa on the basis of detection of mutant form of p53.

REFERENCES

1. Shrestha P. Incidence and pattern of cancer with special reference to oral cancer at Tribhuvan University Teaching Hospital, Kathmandu, Nepal. Oral and Maxillofacial Surgery - Proceedings of the 16th IAMFS, Oita, Japan, 1991; 197-200.

2. Ikeda N, Zain R, Handa Y, Axell T. Criteria for diagnosis of oral mucosal lesion - an aid for examiners of epidemiological surveys in South East Asia, 1995. In : Oral Mucosal Lesions Survey of Adults in Malaysia Oct 1993 - Feb 1994. Eds. Zain RB, Ikeda N, Yaacob M. Kuala Lumpur : Ministry of Health, Malaysia; University of Malaya, Malaysia and Aichigakuin University, Japan 1995; 61.

3. Coltrera MD, Zarbo RJ, Sakr WA, Gown AM. Markers for dysplasia of the aerodigestive tract. Suprabasal expression of PCNA, p53 and CK19 in alcohol fixed, embedded tissue. Am J Pathol 1992; 141: 817-825.

4. Lan H A, Zain RB, Saitoh M, Muramatsu Y, Shrestha P, Mori M. Proliferating cell nuclear antigen (PCNA) and p53 in epithelial dysplasia and squamous cell carcinoma of the oral mucosa - a marker for poor tumor differentiation, increasing nuclear atypia and invasiveness? Anticancer Res 1996; 16:3059-3066.

5. Kramer IRH, Pindborg JJ, Brezrukov V, Infirri JS. Guide to epidemiology and diagnosis of oral mucosal diseases and conditions. Community Dent Oral Epidemiol 1980; 8: 1-26.

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