A Correlative Study of Smokeless Tobacco-induced Lesion and Smoke-induced Leukoplakia in Various Aspects

Parita K Chitroda, Jigna T Shah, Girish Katti, Sreenivas Ghali

1 Reader, Department of Oral Medicine and Radiology, Al-Badar Rural Dental College and Hospital, Gulbarga, Karnataka, India
2 Professor and Head, Department of Oral Medicine and Radiology, Government Dental College and Hospital, Ahmedabad, Gujarat, India
3 Professor and Head, Department of Oral Medicine and Radiology, Al-Badar Rural Dental College and Hospital, Gulbarga, Karnataka, India
4 Postgraduate Student, Department of Oral Medicine and Radiology, Al-Badar Rural Dental College and Hospital, Gulbarga, Karnataka, India

ABSTRACT

Various oral mucosal lesions are attributed to tobacco use. The presence of these conditions varies with particular type of tobacco used (smoking or smokeless) and the form in which it is used, such as cigarettes, pipes, cigars and chewing moist snuff. The frequency and duration of use as well as the ways in which the tobacco product is used also contributes to the clinical presentation and severity of the lesion. The present study is mainly focused on the correlation between the smokeless tobacco-induced lesion and smoke-induced leukoplakia on various aspects with an objective to determine smokeless tobacco as a possible cause for leukoplakia.

Keywords: Leukoplakia, Smokeless tobacco-induced lesion, Tobacco quid lesion.

INTRODUCTION AND REVIEW

The particular type of tobacco used and the form in which it is used do have a correlation between the developments of various oral mucosal lesions.

These lesions often take the form of white patch or plaque. These all lesions were referred to as leukoplakia. The role of smoking in development of leukoplakia is very well-established ever since it was first recognized by Sir James Paget in 1837 and has been supported by many with experimental evidences.1-4

However, the role of smokeless tobacco in the development of leukoplakia was found to be variable among various authors, the mucosal lesions so developed with their use were grouped under various synonyms like snuff-induced leukoplakia, smokeless tobacco induced keratosis, tobacco pouch keratosis, snuff Dipper's lesion, or chewer's mucosa. Few of them also suggested it to be as a variant of leukoplakia only occurring at the regular site of placement of quid.5-12

This led to a considerable confusion in replacing such type of cases. An attempt is made in present study to evaluate the correlation between the lesions caused by smokeless tobacco and smoke-induced leukoplakia with following aims and objectives.

AIMS AND OBJECTIVES

i. To assess the correlation in the clinical and histological appearance

ii. To estimate the effect of amount, duration and frequency of smokeless tobacco as a possible cause for development of leukoplakia

iii. To determine which one out of two, i.e. smokeless tobacco-induced lesion and smoke-induced leukoplakia is more premalignant in nature.

MATERIALS AND METHODS

Sample: The study was conducted among 105 patients, who came to the Department of Oral Diagnosis, Government Dental College and Hospital, Ahmedabad. All the patients who presented with the following inclusive criteria were only included.

1. Patients having either the lesions that is smokeless tobacco-induced lesion and smoke-induced leukoplakia or both together were selected

2. Patients having any other keratotic lesions of oral mucosa with leukoplakia or smokeless tobacco induced lesions were also included in the study.

Method of Examination

After selecting the patients for study, all patients were interviewed for a thorough medical and dental history. Clinical examination included detailed intraoral examination of the lesion. Data collected during the interview and clinical examinations were recorded in the specially prepared proforma for the study, and only those patients were included who were...
ready to undergo punch biopsy, radiographs. Ethical committee clearance and patient consent had been obtained.

Identification of the lesion based on different patterns and clinical types;

Clinical features of leukoplakia:
1. Homogeneous leukoplakia: White opaque, slightly elevated, plaque-like with fissuring and irregular outline
2. Nodular leukoplakia: White or red and white, highly opaque with fissuring and irregular borders, proliferative, raised plaque-like lesion
3. Speckled leukoplakia: Red and white, flat ulcerative, velvety and granular appearance
4. Verrucous leukoplakia: Gray or grayish pink, thick, fissured, papillomatous, proliferative, indurated lesion with cauliflower-like appearance.3

Clinical features of smokeless tobacco-induced lesion:
Degree I: A superficial lesion with a color similar to the surrounding mucosa with slight wrinkling and no obvious thickening.
Degree II: A superficial whitish or yellowish lesion with wrinkling and no obvious thickening.
Degree III: A whitish yellow to brown wrinkled lesion intervening furrows of normal mucosal color and obvious thickening.
Degree IV: A marked whitish-yellow to brown and heavily wrinkled lesion with intervening deep and reddened furrows or heavy thickening.

INVESTIGATIONS

All the selected patients were subjected to routine blood investigations and punch biopsy. Other investigations were advised as and when indicated.

RESULTS

The present study was conducted in 105 patients who presented with 137 numbers of lesions. Out of which 83 (60.58%) were STIL and 54 (39.4%) were leukoplakia. Among leukoplakia, homogeneous variant was found to be more common followed by speckled, nodular and verrucous. Among STIL patients with clinical grade III were found to be more common and then followed by grade II, grade I and others. Leukoplakia was found to be more prevalent in between 31 and 60 years of age group, while STIL was recorded in age group between 16 and 45 years. Both were found predominantly more common in males.4,5,7

When the types of habits were analyzed among the patients with leukoplakia and STIL, it was found that all the lesions of leukoplakia were associated with smoking habits and particularly bidi smoking was more frequently recorded (i.e. 94.44%). Smokeless tobacco habits were also seen with leukoplakia (66.66%), which was mainly in the form of gutkha (20.37%). However, not a single case of leukoplakia with habit of only smokeless tobacco was recorded. While in STIL it was found that it was preferred more in combination with lime (50.60%) than alone or any other additives like betel nut, gutkha, pan or pan masala4,8,10 (Table 1).

On further analysis of pattern of habit it was found that patients with most of the habit preferred placement, chewing and spitting off the quid and few of them used to chew them with buccal vestibule as a preferred site of placement. Maximum number of patients after consideration of any pattern of habit were recorded under 5 years with frequency of at least 10 times/day.

The most common clinical findings noted in leukoplakia in the descending order of frequency proliferative one
Out of 20 patients, two (10%) were diagnosed as having Ca in situ and were sent to MP Shah Hospital for treatment.
In two patients (10%) having speckled leukoplakia, the epithelium was ulcerated.
In two patients, the biopsy results showed adipose tissues, of these one was having homogeneous leukoplakia and one had speckled leukoplakia.

HISTOPATHOLOGICAL EXAMINATION

Histopathological examination revealed epithelial changes mostly in the form of hyperparakeratinization. In leukoplakia and hyperorthokeratinization with STIL, interestingly chevron pattern of keratinization was recorded in few cases with STIL. Although acanthosis remained the predominant feature of leukoplakia, it was also seen in with STIL and mainly in GIIIa lesions. Dysplastic changes were recorded in 74.35% of patients with leukoplakia.

Severe dysplastic changes were noted in verrucous and speckled with less commonly in nodular and homogeneous variant.
While considering STIL, dysplastic changes noted were very few comparatively (Table 2).

DISCUSSION

Smokeless tobacco-induced lesion was found to be more prevalent than leukoplakia, mainly because the habit of smokeless tobacco was found to be more prevalent than smoking. Also, because it takes longer exposure with smoke for a patient to develop leukoplakia while STIL develops sooner due to local irritation caused by the placement of quid.5,8,11,13

The most common age group in which leukoplakia was recorded was between 31 and 60 years and 31 and 45 years respectively for smokeless tobacco-induced lesion. The range reported in our study was 16 to 60 years and at least 11(13.25%) were reported above 60 years of age. Although significant difference in the common age of occurrence was noted, but both the lesions recorded with strong male predominance, which is also favored by others.3,5,10,14-16

The reason to this can be, the younger age of habit as compared to smoking habits. It has been suggested that smokeless tobacco has been finding its way on to the middle school, high school and college campus and as a socially acceptable and vastly popular habits that reflects a masculine image, which also explains high male predominance.
Table 1: The type of habits among patients with leukoplakia and smokeless tobacco-induced lesions

(n = 105, N* = 137)

<table>
<thead>
<tr>
<th>Habit</th>
<th>Leukoplakia</th>
<th>Smokeless tobacco-induced lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 43 (40.95), N* = 54 (38.41)</td>
<td>n = 71 (67.61), N* = 83 (60.58)</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td>S</td>
</tr>
<tr>
<td>-------</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Bidi</td>
<td>24%</td>
<td>44.44%</td>
</tr>
<tr>
<td>Cigarette</td>
<td>0%</td>
<td>1.85%</td>
</tr>
<tr>
<td>B + C</td>
<td>0%</td>
<td>10%</td>
</tr>
<tr>
<td>Tobacco alone</td>
<td>12.5%</td>
<td>5%</td>
</tr>
<tr>
<td>Betel nut</td>
<td>4%</td>
<td>16.66%</td>
</tr>
<tr>
<td>Lime</td>
<td>5%</td>
<td>20.83%</td>
</tr>
<tr>
<td>Gutkha</td>
<td>25%</td>
<td>6.66%</td>
</tr>
<tr>
<td>Pan</td>
<td>1%</td>
<td>4.16%</td>
</tr>
<tr>
<td>Panmasala</td>
<td>14.16%</td>
<td>4.81%</td>
</tr>
</tbody>
</table>

H–homogeneous leukoplakia; n–number of patients; S–speckled leukoplakia; N*–number of lesions; V–verrucous leukoplakia; B + C–bidi + cigarette; N–nodular leukoplakia
### Table 2: Histopathology of leukoplakia and smokeless tobacco-induced lesions

*(n = 105, N* = 137)*

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Leukoplakia n = 43 (40.95), N* = 54 (39.41)</th>
<th>Smokeless tobacco-induced lesion n = 71 (67.61), N* = 83 (60.58)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H   S V N   Total</td>
<td>I a   II b</td>
</tr>
<tr>
<td>Habit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homogeneous leukoplakia</td>
<td>9   20 4 6 39</td>
<td>8 10 13</td>
</tr>
<tr>
<td>Speckled leukoplakia</td>
<td>11.11</td>
<td>5%</td>
</tr>
<tr>
<td>Verrucous leukoplakia</td>
<td>44.44</td>
<td>4%</td>
</tr>
<tr>
<td>Nodular leukoplakia</td>
<td>33.33</td>
<td>3%</td>
</tr>
<tr>
<td>Total</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Hyperorthokeratinization</td>
<td>88.88%</td>
<td>75%</td>
</tr>
<tr>
<td>Hyperparakeratinization</td>
<td>20.93%</td>
<td>46.51%</td>
</tr>
<tr>
<td>Acanthosis</td>
<td>77.77%</td>
<td>10%</td>
</tr>
<tr>
<td>Mild</td>
<td>11.11%</td>
<td>5%</td>
</tr>
<tr>
<td>Moderate</td>
<td>33.33</td>
<td>45%</td>
</tr>
<tr>
<td>Severe</td>
<td>40%</td>
<td>50%</td>
</tr>
<tr>
<td>Hyalinization</td>
<td>22.22%</td>
<td>15%</td>
</tr>
<tr>
<td>Inflammatory changes</td>
<td>66.66%</td>
<td>40%</td>
</tr>
<tr>
<td>Melanin pigmentation</td>
<td>55.55%</td>
<td>20%</td>
</tr>
<tr>
<td>Salivary gland changes</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

n–number of patients; N*–number of lesions; H–homogeneous leukoplakia; S–speckled leukoplakia; V–verrucous leukoplakia; N–nodular leukoplakia; T–total
In the present study, smoking was found to be associated with all the cases of leukoplakia. Although, some of them were also noted with the habit of smokeless tobacco mainly in the form of gutkha. While not a single case of leukoplakia was noted in those who consumed only smokeless tobacco. However, some of the lesions of smokeless tobacco were also found to be associated with leukoplakia. But, however, in these kinds of patients, habit of smoking was also always present. Thus, it can be suggested that leukoplakia is always associated with smoking habits only. The results of Roffo’s experiment and studies of most of the other also support our findings.1,2,5,7,17-19

Among the habits, bidi smoking was found to be the most prevalent by FS Mehata et al in the Indian population and also is ours.

With regards to the habit of smokeless tobacco, it was found that tobacco was preferred more in combination over its usage as alone. It was found that smokeless tobacco-induced lesions occurred more in number when tobacco was used with lime. These findings are consistent with that of RB Bhonsle et al, and thus also favor the theory of caustic action of lime, which inflicts the toxic effects on the oral mucosa. However, the assumption of direct chemical and mechanical injury to the oral mucosa by the placement of quid is also considerable.

The reason to why these lesions were predominantly white is that, whenever there is an increase in the thickness of the epithelium particularly of keratin, it would mask the pink color of the mucosa imparted by underlying vascular bed and giving white color. This increase in the thickness of epithelium gives it white, raised and elevated appearance as compared to the surrounding mucosa, thus giving it a plaque-like appearance. While in the speckled presumably represents sites in which epithelial cells are so immature that they are no longer be able to produce keratin giving intermixed red and white appearance to the lesion. Now, the most of the authors consider speckled and nodular leukoplakia as same entity and not to be a different variant.

In the present study, smokeless tobacco-induced lesions were found to have variable clinical presentation which were described separately by few authors but did not have place for Axell’s classification. Accordingly, lesions that were associated with minor salivary gland changes did not have any place in group. Although changes do occur in the minor salivary gland due to tobacco quid and it has been mentioned by other authors also. Also, no place for the lesions like lichenoid reactions caused by smokeless tobacco was found in his classification. The literature has mentioned the occurrence of oral lichenplanus like lesion occurring purely among smokeless tobacco users having the placement of quid. Similarly, various authors have also mentioned, leukoplakia like lesion occurring in association of tobacco quid habits. The present study showed that most common clinical variant was grade IIIa having plaque-like appearance resembling leukoplakia. As suggested by Mehta et al, the mixture of tobacco-lime exerts a keratinizing and a caustic influence on the oral mucosa, producing a yellowish-white to brown lesion that can be scrapped off. This finding could be duplicated in some of our patients.

According to our findings, epithelial changes noted in leukoplakia were mainly in the form of hyperparakeratinization and hyperorthokeratinization irrespective of their clinical variants except on verrucous leukoplakia, which predominantly presented with hyperparakeratinization with parakeratin plugging. Other features noted were anacanthosis and various grades of dysplasia, changes that varied in different clinical forms. Changes in the connective tissue noted were mainly in the form of infiltration of chronic inflammatory cells, melanin pigmentation and hyalinization, although not always. Only difference noted in the histology regarding the clinical variants were in the form of dysplastic changes, which was found to be present more in conjunction with speckled leukoplakia. Another feature found with speckled leukoplakia was presence of ulcerated epithelium.5

While considering the histology of smokeless tobacco-induced lesions various studies have been performed, accordingly, the most consistent finding is the increase in the total thickness of the epithelium, which is predominantly in the form of hyperkeratinization or hyperorthokeratinization. These findings could be duplicated in our specimen of smokeless tobacco-induced lesions. The other feature that was consistent with our findings was the presence of anacanthosis. Mild to moderate dysplasia were recorded in all the clinical grades, which is a debatable finding with some of the literature. According to Anderson et al, increased mitotic rates and basal cell hyperplasia increased with higher clinical grades, however, he also emphasized that there was no clear cut difference between each of the clinical degrees, either clinically or histologically and thus, overlapping between the degrees is logical and sometimes do occur. This holds very much true for our findings. There was no clear cut difference in either epithelial changes or dysplastic changes.11,19,20

Chevron pattern, which is reported to be characteristic of smokeless tobacco-induced lesion, was not found to be present in all the cases. Connective tissue changes noted in our findings included inflammatory cell infiltration and sometimes with hyalinization that had no connotations with clinical grading. These findings are mentioned in the literature but hyalinization is reported with higher clinical grades.

Changes in the minor salivary glands were noted but not in the form of degenerative changes or fibrosis as mentioned in the literature but in the form of squamous metaplasia.

Thus, the results show that almost similar kind of histologic changes were found in both the lesions but certain difference like higher grades of dysplasia occurring with leukoplakia and the appearance of chevron keratinization in smokeless tobacco-induced lesion occur. The involvement of minor salivary glands was also noted with smokeless tobacco only and not with leukoplakia.
The results showed that dysplastic changes were found in variable degrees in both the forms of the lesions. Although, they were noticed more with leukoplakia.

Carcinoma in situ was to be found be occurring only with speckled leukoplakia. With homogeneous variant only mild to moderate dysplasia was found. Thus, our findings are in accordance with the literature, the data collected from the literature suggests, nonhomogeneous variants to be of more premalignant potential than homogeneous and among the non-homogeneous, speckled variant having the most premalignant potential.9,15,20

Regarding smokeless tobacco-induced lesions; variation in the presence of dysplastic changes has been reported. Dysplastic changes of mild to moderate degrees were found with grade I and as well as in grade IIIb, although dysplastic changes of variable degree were found with smokeless tobacco-induced lesions, not even in single case with carcinomatous changes was recorded in our study. Thus, leukoplakia is a well-established premalignant lesion while debate continues on whether to consider smokeless tobacco related oral mucosal lesions to be premalignant or not.

According to our findings, smokeless tobacco-induced lesions can be stated as premalignant, as variable degree of dysplasia was found in all the clinical grades. Although no carcinomatous changes occurring with these lesions were found, but it was also noted that some of our patients presented with leukoplakia as well as smokeless tobacco does not cause leukoplakia but significantly predisposes a person for the development of leukoplakia, which is already stated before by many authors. As such not a single patient from our study population having smokeless tobacco-induced lesions was found to have carcinomatous changes, but at least one patient in the literature has been reported to develop squamous cell carcinoma because of smokeless tobacco, hence these lesions cannot be neglected and definitely demands attention.3,4,10,11,17-19

**SUMMARY AND CONCLUSIONS**

The present study on correlation between smokeless tobacco-induced lesion and smoke-induced leukoplakia in various aspect was conducted among 105 patients, selected on the basis of predetermined criteria.

The following conclusions were drawn from the presented study:

1. Smokeless tobacco-induced lesions are separate entity that is caused with the use of smokeless tobacco.
2. Leukoplakia is essentially caused by smoking only, although smokeless tobacco can increase the risk of an individual to develop leukoplakia with minimum frequency of smoking as compared to a person who does use smokeless tobacco.
3. Amongst both the lesions smokeless tobacco-induced lesions are more prevalent than leukoplakia.
4. The basic clinical difference between the two lesions is scrapability of smokeless tobacco-induced lesion.
5. Regarding histological features, no remarkable difference was noted between these two lesions.
6. Considering premalignant nature, leukoplakia is found to be more premalignant than smokeless tobacco-induced lesion.

**REFERENCES**

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