Well-armed is well started: A population-based study to assess risk stratification in potentially premalignant oral epithelial lesions

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Abstract

Background: The association between potentially premalignant oral epithelial lesions (PPOEL), oral squamous cell carcinoma and its higher incidence in South-East Asian population due to the use of arecanut, pan, slaked lime and tobacco is well known. The study was carried out in urban and rural population of Bengaluru, Karnataka, to assess and correlate the pattern of habit, clinical presentation and cytological grading of PPOELs, attempting at identifying the main arms associated with risk of malignant transformation.

Aims: Assessment of history, clinical presentation of PPOELs, co-relate with cytological grades and escalate to binary risk assessment.

Materials and Methods: One hundred and fourteen cytological smears received at the Department from screening camps were stained with Papanicolaou and hematoxylin-eosin stains and correlated with the clinical data.

Results/Statistics: Descriptive and inferential statistics were performed. 38% lie between 21 and 30 years, 76.3% males, 81 cases involved buccal mucosa with 51.1% Grade II cytosmear, 53.5% chewing tobacco habit, 10 cases involved multiple sites with 60% Grade II cytosmear and 6 cases showed Grade III cytosmear. Based on clinical risk factors and cytological grading, 15.3% were grouped under high risk lesions as against 5.4% when only cytological grading was considered.

Conclusion: The incidence of PPOELs is increasing in young males with chewing tobacco mainly in buccal mucosa associated with habit. Biopsy and definitive treatment is necessary when the lesions are red, nonhomogeneous, seen in multiple sites and concomitant lesions with higher grades of dysplasia. The use of cytosmears in screening camps helps to assess, affirm and stress on biopsy on higher dysplasia grades as biopsy is not an acceptable norm in camps.

Keywords: Cytosmear, dysplasia grades, potentially premalignant oral epithelial lesions, risk assessment, risk factors, screening camp

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INTRODUCTION

The best way to fight oral cancer, is to catch it at initial stages and exercise opportune intervention. Around 90%–95% of oral cancers are synonyms with oral squamous cell carcinoma (OSCC) and about 15%–48% of them present with pre-existing mucosal changes which have an increased risk of malignancy termed as oral potentially malignant disorders. Recently, a new term potentially premalignant oral epithelial lesions (PPOELs) has been presented for these lesions. The PPOELs include oral leukoplakia, erythroplakia, erythroleukoplakia, oral submucous fibrosis (OSMF), palatal lesions in reverse smokers, oral lichen planus, oral lichenoid reactions, graft versus host reaction, oral lupus erythematosus, dyskeratosis congenita and epidermolysis bullosa. Lately, tobacco pouch keratosis has also been added to the group of PPOELs though considered to be at low-risk for malignant transformation.

The estimated number of new cases of PPOELs per population range between 0.6/1000 and 30.2/1000 with a reported malignant transformation rate range of 0.13%–36.4%. By and large, the estimated malignant transformation rate of PPOELs is 1.36% per year. This suggests that not all cases of PPOELs transform into OSCC, but they still possess the potential to transform to malignancy and that potential is undetermined. The binary risk assessment based on whether it is at low risk, that is it may resolve over a period on cessation of causative agent or high risk that requires definitive treatment to prevent malignancy; is thus required.

Evidences and studies have shown association of PPOELs with a cause or an etiological factor which include smoking and smokeless tobacco use, arecanut use, alcohol and probably sexually acquired human papilloma virus infection. The site and presentation depends on the pattern in which these etiological factors are consumed. For example: oral leukoplakia is seen associated with the site of placement of the quid or the tobacco product in the oral cavity, reverse cigar smoking causes lesions on the palate, the presence of fibrous bands of OSMF depends on whether the betel nut is swallowed (posterior palate and soft palate involvement) or spit out (buccal mucosa and commissural involvement).

A population-based study on Taiwanese population showed a 2.7 relative risk of oral leukoplakia in cigarette smokers and arecanut chewers; smokeless tobacco users of rural United States presented with oral leukoplakias; and Yemenis population who use shammah a form of snuff dipping showed high incidence of PPOELs. A meta-analysis on studies in South-East Asian countries showed increased risk of PPOELs in individuals who use smoke-less tobacco. These features points to the fact that the prevalence of PPOELs varies from region to region and the related habit history.

Various epidemiological studies have shown that a high percentage of cases of PPOELs are tobacco users and resolve after tobacco cessation. A regression of oral leukoplakias over a 6-week period after tobacco cessation has been shown in smokeless tobacco users. This assessment guides us to first remove any source of irritation (mechanical, thermal, or chemical) and encourage cessation of habit as initial treatment protocol. The point to be noted also is that overall risk of malignant transformation is approximately 1.36% which is relatively low; thus unnecessary aggressive interventions at the initial stages is not warranted. Hence, most clinicians assess the PPOELs at second visit based on the response of the lesion after removing the etiological agent - a wait and watch policy. If a lesion persists and/or demonstrates evidence of progression, a clinical diagnosis of PPOEL is made and mandates a biopsy to rule out dysplasia or OSCC.

Patients with unifocal PPOELs, small (<200 mm²) well-circumscribed, flat homogeneous leukoplakias, with histological diagnosis of mild dysplasias are termed low-risk lesions and are subjected to a wait and watch policy amenable later to excisional biopsy if the lesion does not regress on the removal of etiological agent.

Certain lesions present aggressively and require medical and surgical intervention at the initial presentation-termed as high-risk lesions. Currently, the factors used to stratify risk in PPOELs include clinical history, clinical presentation and cytological/histological examination (Table 1).

Since the habit history, clinical presentation and cytological/histological association vary from region to region, the risk factor determination also varies. The present study is a population based screening study done to identify such risk factors in urban-rural population in and around Bengaluru, Karnataka, India. The acceptance rate of biopsy and histopathological evaluation which is gold standard for risk assessment, is low in screening camps; in such situations cytological examination which is the next best adjunct to evaluate the PPOELs was carried out. This also helps to screen the PPOELs in the “silent period.”

This study was done to identify the arms or the risk factors associated with PPOELs in these regions since being
Venugopal, et al.: Risk stratification in PPOELs

well armed with these factors helps us to understand the disease process better, facilitate identification of cases which require mandatory biopsy and necessary treatment protocols, hence the saying ‘well armed is well started’. The main aim of the study was to assess the clinical presentation of PPOELs, its associated cytological grading and to attempt at identifying the parameters that might help us to categorize them as low-risk or high-risk lesions in relation to malignant transformation.

**MATERIALS AND METHODS**

A total of 114 cases with a clinical provisional diagnosis as PPOELs received by the Department of Oral and Maxillofacial Pathology from screening camps with appropriate clinical data were stained with Papanicolaou stain and hematoxylin-eosin stains. The clinical assessment was based on parameters as follows:

**Clinical history/habit history**

1. Tobacco use: smoking; smokeless: Chewing tobacco with or without arecanut or betel quid
2. Arecanut chewing habit
3. Betel quid chewing habit: Betel leaf + slaked lime + arecanut
4. Frequency and duration of habit.

**Clinical presentation**

1. Age, gender, site and size
2. **Type of mucosal change:** Leukoplakia: Homogeneous-predominantly white or grayish-white color: Thin (Flat) and Thick: Wrinkled/corrugated. Nonhomogeneous-mixed red and white presentation termed erythroleukoplakias or speckled, nodular and verrucous or exophytic. Erythroplakia, OSMF, lichen planus, preleukoplakia, tobacco pouch keratosis.

**Cytological assessment**

Grades of dysplasia:

- Grade I: Normal, only normal cells present
- Grade II: Atypical, indicates presence of minor atypia, no malignant changes
- Grade III: Indeterminate: Cells with wider atypia that may be suggestive of cancer, biopsy is recommended
- Grade IV: Suggestive of cancer: Few malignant cells or many cells of borderline atypia, biopsy mandatory
- Grade V: Positive for cancer: Malignant cells seen obviously, biopsy mandatory.

Grade I and Grade II were considered as low grade lesions since biopsy is not normally advised for such cases and Grade III to Grade V lesions are considered high grade as biopsy is advised for such cases [Figures 1-3].

Based on the clinical and cytological assessment, the lesions were considered high risk if 2 or more parameters of high risk lesions [Table 1] were present. For cases of OSMF, multiple sites of blanching were considered as a single site until unless they showed leukoplakic changes.

**OBSERVATIONS AND RESULTS**

Out of 114 cases, 76.3% were male and 38.6% were in the age group of 21–30 years. 62.3% were associated with chewing tobacco habit with 47.1% presenting duration of 1–5 years [Table 2].

The most common PPOEL observed was homogeneous leukoplakia (55.3%) corrugated type, followed by leukoplakia flat type, preleukoplakia (16.7%), tobacco pouch keratosis (7.9%) and OSMF (6.1%) [Table 2]. There were 5 cases of homogeneous leukoplakia which presented with denuded epithelium. There were 8 cases of nonhomogeneous leukoplakia and a single case of erythroplakia which was also associated with tobacco pouch keratosis, there were 3 cases of OSMF associated with leukoplakia (homogeneous - 1.8%, nonhomogeneous 0.9%) [Table 2].

Among 114 cases, 53.5% were Grade II lesions, 38.6% Grade I, 5.3% Grade III lesions and in 2.6% (3 cases) of cases the grade was inconclusive [Figure 1].

Further analysis was performed on 111 cases which had conclusive cytological grading. When habit history and cytological grading were compared, individuals who had both smoking and tobacco chewing habit predominantly presented with Grade II cytosmear (100%), those with gutka, tobacco + arecanut chewing habit presented with Grade II cytosmear (60% each) and 58% of pan chewers showed Grade II smears. 20% of betel quid chewers presented with Grade III smears as against 80.0% who

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**Table 1: Risk factors associated with potentially premalignant oral epithelial lesions**

| Clinical features                                                                 | Histological features                                                                 |
|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Size of lesion >200 mm²                                                            | DNA aneuploidy                                                                         |
| Nonhomogeneous texture of the lesion                                               | Loss of heterozygosity involving many genes                                            |
| Red color or speckled with mixed red and white lesions                             | HPV: Human papilloma virus                                                             |
| Lesions involving tongue or floor of the mouth                                     |                                                                                       |
| Age >45-50 years                                                                   |                                                                                       |
| Associated with nonsmokers                                                         |                                                                                       |
| Higher grades of dysplasia                                                         |                                                                                       |
| Lesions associated with HPV-1                                                      |                                                                                       |
| HPV: Human papilloma virus                                                         |                                                                                       |
showed Grade I smear. 16.7% of pan chewers presented with Grade III cytosmear. These results were statistically significant with a $P = 0.03$ [Table 3]. Comparison of site of lesions ($n = 111$) with cytological grades showed that buccal mucosa was most commonly involved and this was statistically significant with a $P = 0.001$ [Table 3].

On comparing the clinical types, the following data were obtained: Erythroplakia and OSMF with nonhomogeneous leukoplakia was predominantly associated with higher grades of dysplasia-Grade III (100%); and 59.7% of homogeneous leukoplakia and 55.6% of nonhomogeneous leukoplakias were associated with Grade II cytosmears. These results were statistically significant with a $P \leq 0.001$.

Figure 1: (a) Photomicrograph showing clumps of uniform epithelial cells displaying Grade I cytosmear (H and E, ×40), Inset: High power view of cells showing normal nuclear cytoplasmic ratio (H and E, ×100). (b) Photomicrograph showing epithelial cells with normal nuclear cytoplasmic ratio and equal ratio of cells with bluish tinge and pink tinge suggesting they are superficial well-differentiated cells (Pap stain, ×40)

Figure 2: (a) Photomicrograph showing clumps of epithelial cells with very few cells showing mild increase in nuclear cytoplasmic ratio displaying grade II cytosmear (H and E, ×100), Inset: High power view of the cells showing mild increase in size of nucleus in few cells (H and E stain, ×200). (b) Photomicrograph showing more cells with blue tinge than cells pink tinge with very few cells showing mild increase in size of the nucleus (Pap stain, ×40)

Figure 3: (a) Photomicrograph showing clumps and scattered epithelial cells with few cells showing increase in nuclear cytoplasmic ratio (H and E, ×40). (b) High power view showing few cells showing increased nuclear cytoplasmic ratio (H and E, ×100). (c) Photomicrograph showing increased cells with blue tinge as compared to cells with pink tinge suggesting the presence of lesser differentiated cells (Pap stain, ×40)

Risk assessment as high risk or low risk lesions was carried out using both clinical and cytological grading parameters as mentioned in materials and methods. Three cases which showed inconclusive results were omitted from this assessment. When the cases presented with 2 or more risk factors (both clinical and cytological) they were categorized as high risk lesions. Around 15.3% of cases were grouped as high risk lesions as against binary categorization (where only cytological grading was used) where 5.4% were considered high grade lesions [Table 5].
A sensitivity and specificity test was carried out to assess the potential of cytological grading as either low grade or high grade (binary system) alone to detect risk assessment (low risk/ high risk). Sensitivity determines the true positive cases of high risk cases that can be identified through any of the methods. It was observed that cytological grading alone showed a sensitivity of 35%, but the specificity of binary grading to detect low risk lesions was 100% and the accuracy level was 90.1% which signifies that binary grading system accurately detects low risk lesions but its ability in grading high risk lesions is less. Hence, the risk assessment should be carried out using both clinical and cytological/histopathological parameters.

**DISCUSSION**

Increasing incidence of PPOELs in South East Asian countries has emphasized the need to identify them at early stages to prevent further progression to OSCC. As stated previously, these lesions possess the potential to transform to malignancy, but such potential cannot be defined adequately and is relatively low as per previous studies (1.36%). Some of these lesions may show signs of regression once the provocative agent has been removed as was observed in studies done by Mehta et al. and Silverman et al. Mehta et al. inferred that on cessation of cause of leukoplakias, 42.5% of lesions healed in 5 years and 45.3% in 10 years. Silverman et al. stated that 31.6% decreased in size or healed while 11% progressed to increase in size and 57.3% remained unchanged. The fact is also that some of these lesions transform to malignancy and lesions that are at higher risk for malignant transformation needs to be identified. Certain factors have been put forth recently as risk factors [Table 1]. These factors mainly depend upon the habit history and clinical presentation of the lesions and this pattern varies in different regions.

The best way to identify the factors for a particular region is through mass/community/population screening programs where the target group is invited to participate specifically for the purpose of detecting prevalence of PPOELs. The present study is one such attempt, where the cases identified through community screening were analyzed based on the habit history, clinical presentation and cytological features, for risk factors.

Histopathological analysis and detection of dysplasia are gold standard for assessing the malignant risk potential, but this could not be carried out in the current mass screening program due to patient noncompliance. Hence the next best adjunct which is cytological testing was carried out. Studies have shown that 92% of patients with clinically evident, suspicious lesions of PPOEL or OSCC will be classified correctly and 94% of patients who are healthy will be classified correctly using cytological technique. The patients who test positive for the target condition via cytologic testing are 14 times more likely to have the disease than are those without the disease.

The current study showed that mucosal changes were detected at early ages in young men and the age of prevalence was predominant in 20–30 years which correlates with the recent study done by Hosagadde et al. The use of tobacco (chewing and smoking) was significantly associated with development of higher cytological grades suggesting a definite risk associated with tobacco use. The risk factors mentioned by Speight et al. do not include use of chewing form of tobacco as a risk factor. In the current study, most of the cases with

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**Table 2: Distribution of demographic, habit history and different potentially premalignant oral epithelial lesions among study populations**

| Variables                  | Category                        | n (%) |
|----------------------------|---------------------------------|-------|
| Age (years)                | <20                             | 8 (7.1)|
|                            | 21-30                           | 44 (38.6)|
|                            | 31-40                           | 25 (21.9)|
|                            | 41-50                           | 25 (21.9)|
|                            | >50                             | 12 (10.5)|
| Sex                        | Males                           | 87 (76.3)|
|                            | Females                         | 27 (23.7)|
| Habit history              | Areca nut chewing               | 5 (4.4)|
|                            | Betel quid chewing              | 5 (4.4)|
|                            | Pan chewing                     | 12 (10.5)|
|                            | Gutka chewing                   | 61 (53.5)|
|                            | Tobacco + arecanut chewing      | 10 (8.8)|
|                            | Cigarette/bidi smoking          | 6 (5.3)|
|                            | Smoking + tobacco chewing       | 3 (2.6)|
|                            | No habits                       | 12 (10.5)|
| Duration (years)           | 1-5                             | 48 (47.1)|
|                            | 6-10                            | 38 (37.3)|
|                            | 11-15                           | 11 (10.7)|
|                            | 16-20                           | 2 (2.0)|
|                            | >20                             | 3 (2.9)|
| Clinical presentation      | PPOELs                          |       |
|                            | Preleukoplakia                  | 19 (16.7)|
|                            | Homogeneous leukoplakia         | 63 (55.3)|
|                            | Flat                            | 26 (41.3)|
|                            | Corrugated                      | 32 (50.8)|
|                            | Wrinkled                        | 5 (7.9)|
|                            | Nonhomogeneous leukoplakia      | 8 (7.0)|
|                            | Speckled                        | 5 (62.5)|
|                            | Nodular                         | 3 (37.5)|
|                            | Verrucous                       | 0 (0.0)|
|                            | Erythroplakia                   | 1 (0.9)|
|                            | OSMF                            | 7 (6)|
|                            | OSMF + homogeneous leukoplakia  | 2 (18)|
|                            | OSMF + nonhomogeneous Leukoplakia| 1 (0.9)|
|                            | TPK                             | 9 (7.8)|
|                            | TPK + Erythroplakia             | 1 (0.9)|
|                            | Desquamative Gingivitis         | 1 (0.9)|
|                            | Lichen planus                   | 1 (0.9)|
|                            | Smoker’s melanosis              | 1 (0.9)|

PPOELs: Potentially premalignant oral epithelial lesions, OSMF: Oral submucous fibrosis, TPK: Tobacco pouch keratosis.
chewing tobacco habit presented with higher cytological grades which was statistically significant ($P = 0.03$); hence, the addition of this parameter would increase the arms in our armor. In females, the changes were predominantly seen in tobacco/pan chewing individuals in 40–50 years age group. As per the study by Hari Vinay et al., the PPOELs are more prevalent in third decade of life in women in Telangana state.\(^\text{[16]}\)

The most common site of presentation was buccal mucosa which correlated with the habit of quid or tobacco placement-cause and effect. The other studies conducted
in South-East Asian countries also show prevalence of PPOELs in buccal mucosa as against western countries where the prevalence is more in floor of mouth or tongue.\[9,15\]

The most common PPOEL was leukoplakia (64%) as compared to the study by Sandeep et al. in Madhya Pradesh and Kumar et al.\[17\] who found OSMF to be more prevalent and Gowhar et al. who found Lichen planus to be more prevalent.\[1,18\] The increased incidence of leukoplakias in the current study correlated with the study done by Hosagadde et al.\[15\]. Leukoplakias clinically are categorized as homogeneous and nonhomogeneous. These are further sub-classified as homogeneous-flat (thin), thick (corrugated or wrinkled) and nonhomogeneous as erythroleukoplakia, nodular and verrucous variants. The present study showed increased prevalence of homogeneous leukoplakias, subcategorizing them just increased the ambiguity but did not help in risk assessment as even flat homogeneous leukoplakias presented with higher cytological grades (Grade II, 57.7%). As suggested by various studies, our study also showed non-homogeneous leukoplakias presenting with higher grades of dysplasia, grade III smear in 22.20% of cases as against 3.2% of homogenous leukoplakias presenting with grade III cytosmears.\[6,9,19\]

An important clinical presentation of homogeneous leukoplakias observed in the current study was the presence of desquamation of epithelium in 5 cases [Figure 4]. Cytologically, these cases did not show any higher grades of dysplasia, two cases showed Grade I with hyperkeratosis, two showed Grade II atypia and none of them showed candidal hyphae. It could be hypothesized that such lesions are normal processes of desquamation of the epithelium which has just thickened as a response to the irritating agent or a caustic change with the use of lime as 2 cases were associated with use of gutka which has slaked lime in it. Further studies along with histopathological assessment are required to arrive at exact pathogenesis for such lesions.

Multiple sites of involvement should also be treated as these suggest field cancerization process. The present study showed 10 cases where there were multiple sites of involvement with Grade II cytosmears seen in 60% of cases [Table 4].

As seen in previous studies, a case of erythroplakia showed higher grades of dysplasia. Cases of lichen planus showed Grade II dysplasia. The risk of malignant transformation of lichen planus is around 1.09% and 0.9% which is very low and these correlates with the current cytological grades observed.\[9\]

The present study showed higher incidence of PPOELs in young individuals with chewing tobacco habit. Higher grades of dysplasia were observed in erythroplakias, nonhomogeneous leukoplakias and OSMF associated with leukoplakia.

**CONCLUSION**

The main aim of the study was to identify the risk factors associated with malignant transformation of PPOELs in the population group studied. Young men (20–30 years) with chewing and smoking tobacco habit, red lesions, nonhomogeneous leukoplakias, OSMF associated with leukoplakia and PPOELs involving multiple sites need to be treated at the earliest as they presented with higher grades of dysplasia on cytosmears and can be considered as high risk factors or arms which need definitive treatment. The incidence also emphasizes on the cause (tobacco) and effect relationship and the importance of prevention or cessation of habit to decrease the occurrence of PPOELs. The incidence of high risk lesions was 15.3% (n = 114). It also implies that in screening camps where biopsy acceptance rate is low, the use of cytosmears helps to identify the high risk lesions and also to study the PPOELs in its latent stages.

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Conflicts of interest
There are no conflicts of interest.

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