Malignant Transformation of Oral Leukoplakia: Study of 50 Patients

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ABSTRACT:

Background: Oral leukoplakia (OL) is the best-known potentially malignant disorder. The objective of this study is to estimate the rate of malignant transformation in patients with leukoplakia for more than 5 years and identify significant risk factors of OL malignant transformation. Methods: A total of 50 patients with clinical and histopathological diagnosis of OL were retrospectively reviewed. The mean follow-up period was 5.3 years. Results: Among 50 cases, 10 (20%) OL patients developed oral cancer, with a mean duration of 5.2 years. Statistical analysis revealed that dysplasia was an independent risk factor for OL malignant transformation, but age, gender, lesion site, diet habit, smoking and ethanol intake were not risk factors. Consistent with this result, high-risk dysplastic OL had significantly higher malignant incidence than low-risk dysplasia, particularly during the first 2-3 years. Conclusions: The utilization of high-risk dysplasia as a significant indicator for evaluating malignant transformation risk in patients with OL was suggested, which may be helpful to guide treatment selection in clinical practice.

Key words: Leukoplakia, Oral squamous cell carcinoma, precancer.

INTRODUCTION:

Oral squamous cell carcinoma (OSCC) is widely recognized as the most common type of head and neck cancer, with a 50% survival rate over 5 years despite various treatments in the past three decades. Oral leukoplakia (OL) is defined as “A white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer”, which is the best-known potentially malignant disorder of the oral mucosa. Reports indicate that 15.8-48.0% of OSCC patients were associated with OL when diagnosed. Histopathologically, oral epithelial dysplasia currently is the most important prognostic indicator for determining the malignant transformation risk of OL. Traditionally, OL lesions are classified as non-dysplasia (hyperplasia) and dysplasia (mild, moderate or severe). The risk factors of clinical features and lifestyle habits associated with transformation of OL into carcinomas have been evaluated in previous studies. Studies suggest the clinical predictors of malignant transformation in oral leukoplakia, such as age, gender and lesion site, but the results from different study populations vary. The role of smoking and ethanol intake as important risk factors related to malignant transformation remains controversial and unclear. Thus, assessment of these factors for OL malignant transformation is still needed. The objective of the present study is to estimate the malignant transformation rate of 50 patients with OL (mean follow-up of 5.3 years), and identify significant risk factors of OL malignant transformation.
Figure 2 Low power photomicrograph shows changes from basal or parabasal layer.

Figure 3 Lesion shows hyperkeratosis of the surface epithelium (H & E, X 40) The fibrous connective tissue Stroma exhibit mild chronic inflammation.

METHODS
Study population
Information regarding gender, age, site of lesions at the time of the initial diagnosis of OL and diet habit, history of smoking and ethanol intake was all documented in detail.

Exclusion Criteria: 1) Patient without the initial histopathologic examination of OL and development of OSC. 2) Clinical history and histopathologic changes of oral white or predominantly white oral benign diseases, for example, linea alba, leukoedema, leukokeratosis; and oral precancerous conditions. 3) Patient with diagnosis of OSCC at first visit. 4) Patient with a follow-up period of less than 12 months. According to the binary grading system newly proposed by WHO, re-examination of the sample confirmed the diagnosis of epithelial dysplasia. The architecture (a total of 7 scoring) and cytology (a total of 9 scoring) criteria for epithelial dysplasia were as follows: Architecture: 1) Irregular epithelial stratification; 2) Loss of polarity of basal cells; 3) Drop-shaped rete ridges; 4) Increased number of mitotic figures; 5) Abnormally superficial mitoses; 6) Premature keratinization in single cells; 7) Keratin pearls within rete ridges. Cytology: 1) Abnormal variation in nuclear size; 2) Abnormal variation in nuclear shape; 3) Abnormal variation in cell size; 4) Abnormal variation in cell shape; 5) Increased nuclear-cytoplasmic ratio; 6) Increased nuclear size; 7) Atypical mitotic figures; 8) Increased number and size of nucleoli; 9) Hyperchromasia.

We reclassified all lesions as low-risk dysplasia and high-risk dysplasia in the present study. A low-risk lesion was based on observing less than four architectural changes or less than five cytological changes. A high-risk lesion was based on observing at least four architectural changes and five cytological changes.

Statistical analysis
A descriptive analysis was performed on clinical and pathologic factors and P values < 0.05 were considered statistically significant.

RESULTS
Patient Characteristics
A total of 50 patients were enrolled in this retrospective study, with a mean follow-up period of 5.3 years. Of these, 10 (20%) patients developed invasive oral cancer, with the mean time of malignant transformation of 5.2 years. For all the subjects, the gender ratio was equal (40 males: 10 females). The average age at diagnosis was 42.7 years old (range 21-84). The peak incidence was the fourth decade of life (33.0%). Tongue was affected in 51.4% patients with OL, followed by buccal mucosa (32.6%). Few lesions were located on the floor of mouth and lip. There were 12.8% patients with spicy dietary habit. The history of smoking and ethanol intake were observed in 29.8% and 6.9% cases, respectively. We found 41 (82.6%) OL cases were low-risk dysplastic lesions and 9 (17.4%) OL cases were high-risk dysplastic lesions. Among 50 OL lesions, 6 of 41 low-risk dysplasia and 5 of 9 high-risk dysplasia developed into cancer, respectively. We observed that a high-risk dysplastic OL was associated with an increased oral cancer risk.

<table>
<thead>
<tr>
<th>L</th>
<th>Size of OL</th>
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<tbody>
<tr>
<td>L1</td>
<td>Lesion less than or equal to 2</td>
</tr>
<tr>
<td>L2</td>
<td>Lesion of 2-4 cm</td>
</tr>
<tr>
<td>L3</td>
<td>Lesion greater than 4 cm</td>
</tr>
<tr>
<td>LX</td>
<td>Site of lesion not specified</td>
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<thead>
<tr>
<th>P</th>
<th>Histopathological picture</th>
</tr>
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<tbody>
<tr>
<td>P0</td>
<td>No dysplasia</td>
</tr>
<tr>
<td>P1</td>
<td>Dysplasia</td>
</tr>
<tr>
<td>PX</td>
<td>Presence of dysplasia not specified</td>
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</tbody>
</table>

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<tr>
<th>C</th>
<th>Clinical presentation</th>
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<tr>
<td>C1</td>
<td>Homogenous leukoplakia</td>
</tr>
<tr>
<td>C2</td>
<td>Non-homogenous leukoplakia</td>
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</tbody>
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| Stage of leukoplakia | Evaluation of leukoplakia based on histopathological examination | Evaluation of leukoplakia based on clinical manifestation |

Table 1 Staging of OL
DISCUSSION
In the present study, we evaluated the malignant transformation rate of patients with OL, and identified the risk factors of malignant transformation during a relatively long follow-up period. Of the 50 cases, 39 (17.9%) patients developed invasive cancer, with a mean malignant transformation period of 5.2 years. Dysplasia was an independent risk factor for OL malignant transformation, but age, gender, site, diet habit, smoking and ethanol intake were not risk factors. In our series, according to the WHO criteria, we considered the time elapsed from the initial diagnosis of OL to the development of cancer. In this context, we excluded patients with diagnosis of OL concomitant OSCC at the first visit or patients with a followed-up period of less than 12 months after the initial diagnosis of OL. Although it is a well-known fact that the histological classification of OL lesions is imperfect, which may involve subjectivity, we cannot do without it to date.12 Notwithstanding it had been elucidated that oral lesions with epithelial dysplasia more often develop into cancer than those with hyperplasia in previous findings13 few studies have examined the risk of malignant development in different grades of dysplastic OL. In an American population, moderate or severe dysplastic OL was associated with 2.30-fold increased risk of malignant transformation, compared with mild dysplasia or hyperplasia14. In a Dutch study15, OL diagnosed with moderate or severe epithelial dysplasia had a significantly higher risk of malignant development than leukoplakia with lower dysplasia grades (P < 0.01). These findings were similar to ours. Consistent with this result, patients with high-risk dysplastic OL had significantly higher oral cancer incidence than low-risk dysplasia, particularly during the first 2-3 years of follow-up. It is suggested that rigorous follow-up in the first 2-3 years for patients with diagnosis of dysplastic OL may be important to detect early malignant events. We observed the average age at diagnosis of OL is 52.7 years, while other study populations had an average age closer to 60 years15. The peak incidence of OL was in the fifth decade of life in our study, earlier than the sixth decade in other reports16. The predominant sites of lesions are the tongue and buccal mucosa, and few lesions were located on the floor of mouth, whereas the tongue and floor of mouth were reported as the most common sites in Western countries17. Moreover, it may be generally accepted that smoking and ethanol intake play significant roles in the development of OL, but the roles of those in the malignant transformation of OL is conflicting and yet unclear. Studies 18 have demonstrated an increased risk of malignant transformation in the non-smoking cohort, while the study by Ho et al14 and our present study found smoking was not a significant factor in transformation risk. Further studies are needed to investigate the roles of lifestyle habits in the malignant process of OL.

CONCLUSIONS
In summary, we evaluated the usefulness of the new system of grading dysplasia proposed by WHO in prediction of OL malignant transformation risk. High risk dysplasia was a significant indicator for OL malignant transformation. It is thus important to detect early malignant events of OL with the diagnosis of high-risk dysplasia.

REFERENCES

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Conflict of interest: None declared

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