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Clinical Observation

Malignant transformation of oral leukoplakia with a focus on low-grade dysplasia

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ABSTRACT

Objective: Oral leukoplakia (OL) is classified as a precancerous lesion with potential for malignant transformation. No consensus has been reached regarding appropriate treatment for OL with low-grade dysplasia (LGD). We have often seen that OL with LGD that goes untreated or is excised with insufficient margins develops into squamous cell carcinoma. The aim of this study was to identify the rate of and clarify risk factors for malignant transformation of OL, with a focus on LGD.

Methods: Consecutive patients with OL with LGD treated between 2000 and 2011 were selected from the medical records of the Department of Oral and Maxillofacial Surgery at Tokyo Dental College, Chiba Hospital, Japan. Differences between clinical characteristics (age, sex, lesion site, smoking habit, alcohol intake, clinical appearance, lesion color, lesion surface, degree of dysplasia and treatment) and malignant transformation were analyzed using Fisher's exact test.

Results: A total of 115 OL patients with LGD were evaluated. Four cases (3.5%) showed malignant transformation to squamous cell carcinoma. No clinical characteristics showed any significant correlation with malignant transformation.

Conclusions: Strict follow-up is recommended for OL with LGD to detect oral cancer in the early stage. Biomarkers to identify malignant transformation of leukoplakia are needed to facilitate treatment of these patients and confirm the malignant transformation rate.

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1. Introduction

Oral leukoplakia (OL) is a precancerous or potentially malignant lesion, defined as a "white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer" [1]. A number of studies have reported that 3.5–17.9% of OL undergo malignant transformation into squamous cell carcinoma [2–6]. Various risk factors for malignant transformation have been suggested, such as age, sex, alcohol intake, tobacco habits, anatomical site and the presence of epithelial dysplasia. According to van der Waal, significant risk factors for malignant transformation of leukoplakia include female sex, long

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* Corresponding author. Tel.: +81 43 270 3901; fax: +81 43 270 3979. *E-mail address:* watabeyukio@tdc.ac.jp (Y. Watabe). duration of leukoplakia, leukoplakia in non-smokers (idiopathic leukoplakia), location on the tongue and/or floor of the mouth, size >200 mm², non-homogeneous type, presence of *Candida albicans*, and presence of epithelial dysplasia [7].

The degree of epithelial dysplasia represents a histopathological factor associated with the risk of malignant transformation of OL into squamous cell carcinoma. The risk of malignant transformation differs markedly between low-grade dysplasia (LGD) and high-grade dysplasia (representing severe dysplasia or carcinoma in situ) [8]. OL with high-grade dysplasia is therefore generally treated aggressively, such as by excision with wide surgical margins and strict follow-up. However, no consensus has been reached on appropriate treatment for OL with LGD. Most oral premalignant lesions represent OL and clinicians have many opportunities to diagnose and treat OL with LGD. We have often seen in our own clinical experience that OL with LGD that goes untreated or is excised with narrow margins develops into squamous cell carcinoma.

The aim of the present study was to facilitate the improvement of clinical approaches to OL with LGD, by retrospectively evaluating

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the rate of malignant transformation of OL with LGD and identifying significant risk factors for malignant transformation with a focus on LGD.

2. Patients and methods

Participants in this study were consecutive patients with OL with LGD selected from the 2000 to 2011 medical records of the Department of Oral and Maxillofacial Surgery, Tokyo Dental College, Chiba Hospital, Japan. Patients with malignancy in the initial histopathological examination of oral leukoplakia or with less than 2 months of follow-up were excluded from this study. The degree of dysplasia was determined from either incisional or excisional biopsy. We analyzed the following variables: age; sex; lesion site; smoking habits; alcohol intake; clinical appearance (homogeneous or non-homogeneous); lesion color; lesion surface; degree of dysplasia (mild or moderate); treatment; and presence of malignant transformation. The diagnosis of malignant transformation into oral squamous cell carcinoma was based on histopathological examination of a representative incisional or excisional specimen. For comparison, we calculated the malignant transformation rate in the group of OL with severe dysplasia. With regard to cases of malignant transformation, we analyzed the period until malignant transformation and TNM classification. All lesions were diagnosed by specialists in oral pathology and defined according to the criteria of classification of the World Health Organization (WHO) [9].

Data were analyzed using the StatFlex statistical software package (version 6.0; Artiteck, Osaka, Japan). We analyzed differences in clinical characteristics and malignant transformation using Fisher's exact test to analyze the association or independence of the different variables. Values of P<0.05 were considered to indicate statistical significance.

3. Results

3.1. Patient characteristics

A total of 115 OL patients with mild and moderate dysplasia were evaluated and their characteristics are shown in Table 1. Mean age of the 115 patients was 62.8 years (median, 63 years), with a range of 34–81 years. The patients comprised 65 men (56.5%) and 50 women (43.5%), corresponding to a male-to-female ratio of 1.3:1. Fig. 1 illustrates the relationship between age and sex of participants. The majority of patients were men between 60 and 69 years old.

The gingiva was the most common lesion site (37.4%), followed by tongue (36.5%), palate (11.3%), buccal mucosa (10.4%), and finally, floor of the mouth (3.5%). The lesion site was unknown for 1 patient.

Past or present history of smoking and alcohol intake were observed in 26 patients (22.6%) and 44 patients (38.3%), respectively. Past or present history of smoking and alcohol intake were unknown in 37 patients and 38 patients, respectively.

According to clinical appearance, 69 patients (60.0%) showed homogeneous type and 12 patients (10.4%) showed nonhomogeneous type. Clinical appearance was unknown in 34 patients. Color of the lesion was defined as white or a mixture of white and red (white/red). No patients showed only red lesions. White lesions were seen in 75 cases (65.2%) and white/red lesions in 6 cases (5.2%).

Lesion surface was divided into two types: flat or rough. If the same lesion included both flat and rough surfaces, the surface was defined as rough. A flat lesion surface was seen in 78 patients (67.8%), with a rough surface in only 3 patients (2.6%). However,

Table 1

Baseline characteristics of oral leukoplakia.

Characteristic	All cases
Patients	115
Age (years)	
Mean age	62.8 ± 10.2
Median	63
Sex	
Male	65(56.5%)
Female	50(43.5%)
Lesion site	
Gingiya	43(37.4%)
Tongue	42(36.5%)
Palate	13(11.3%)
Buccal mucosa	12(10.4%)
Floor of the mouth	4(3.5%)
Missing	1(0.9%)
Smoking	
Never	52(45.2%)
Past and present	26(22.6%)
Missing	37(32.2%)
Alcohol intake	
Never	33(28.7%)
Past and present	44(38.3%)
Missing	38(33.0%)
Clinical appearance	()
Homogenous	69(60.0%)
Non-homogenous	12(10.4%)
Missing	34(29.6%)
Color of lesions	()
White	75(65.2%)
White/red	6(5.2%)
Missing	34(29.6%)
Surface of lesions	()
Flat	78(67.8%)
Rough	3(2.6%)
Missing	34(29.6%)
Degree of dysplasia	
Mild	89(77.4%)
Moderate	26(22.6%)
Treatment	
Excision	70(60.9%)
Incisional biopsy	45 (39.1%)
Outcome	× /
Malignant transformation	4(3.5%)
Non-transformation	111 (96.5%)

clinical appearance, color of the lesion and lesion surface was not recorded on the chart for 34 patients.

According to the classification criteria of the WHO, 89 (77.4%) of the 115 OL patients showed mild dysplasia and 26 (22.6%) had moderate dysplasia.



Fig. 1. The relationship between age and sex of participants. The majority of patients were men between 60 and 69 years old.

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