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<td>桃崎, K; 瀬木, K; 中島, K; 保川, T; 小久保, K; 矢野, H; 坂本, M; 村川, S; 野祝, T; 資原, K; 保戸, A; 柴原, T; 瀬木, S; 井戸, T</td>
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Morphological analysis of relationship between oral cytology and biopsy in diagnoses of leukoplakia or oral lichen planus

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Abstract
Squamous cell carcinoma (SCC) is the most common cancer among oral malignant tumors. Oral lichen planus and leukoplakia are known as precancerous conditions / lesions. Recently, oral cytology has been incorporated in the examination to improve early detection and early treatment. The purpose of this study was to investigate the cytological diagnosis based on the final diagnosis of SCC when the clinical diagnosis was leukoplakia or oral lichen planus. Fifty-nine cases of clinically diagnosed leukoplakia or oral lichen planus from the Department of Oral Surgery, Hospital of Tokyo Dental College, with cytological examination and a biopsy were analyzed. The ratios of cases of diagnosed SCC in cytologically negative, doubtful or positive cases were calculated. Further, eight distinguishing cases were introduced. The ratio of histologically SCC in cytological negative cases was 18%, that in cytological doubtful cases was 78%, and that in cytological positive cases was 84%. Morphologically, most cytological negative cases showed a histologically surface differentiated SCC. However, in cytological positive cases, various atypical cells in the superficial area of SCC could be observed. In conclusion, although the cytology of oral precancerous lesions / conditions plays an important role and is a useful technique in view of screening and minimally-invasive procedures, some cases show a false-negative. The frequency of false-negative cases is higher in the cases of surface differentiated SCC.

Key Words: Leukoplakia, Oral lichen planus, cytology, biopsy

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Introduction
Although it is possible to observe the oral mucosa by direct observation, oral exploration is important for the early detection of oral cancers while general dental treatment or care is needed to address the social problem of oral cancer. However, the complex morphological configuration of the oral cavity often delays the detection of oral cancers, which can interrupt functions relevant to the quality of life such as talking, smiling, eating food, and so on. Oral lichen planus and leukoplakia are the most common lesions in oral mucosal diseases. They are known as precancerous conditions. Squamous cell carcinoma (SCC) is most common type of cancer among oral malignant tumors. Recently, oral cytology has been incorporated in the examination to improve early detection and early treatment. Cytology is advantageous, as it is a painless, bloodless, non-invasive, quick and simple procedure. The cytology of mucosa has been developed in the field of gynecology. The cytology of uterine cancer has an established role, but that of oral SCC has not been characterized yet. Although cervical cytology is a standardized diagnosis for dysplasia, intraepithelial neoplasm, SCC, and so on, oral SCC is unstandardized because of the presence of a superficial differentiation type in some cases. It is very important to understand the concordance rate for the diagnosis between cytology and biopsy.

So, the purpose of this study is to investigate the cytological diagnosis based on the final diagnosis of SCC when the clinical diagnosis was leukoplakia or oral lichen planus.

Materials and methods
From cases clinically diagnosed as leukoplakia or oral lichen planus in the Department of Oral Surgery, Suidobashi and Chiba Hospitals of the Tokyo Dental College from April 2014 to March 2015, fifty-nine cases, which had carried out a cytological examination and a biopsy, were analyzed. The ratios of cases of diagnosed SCC in cytologically negative, doubtful or positive cases were calculated. Further, morphological observations of the clinical features and the cytological and histological findings were observed. Further, eight cases were shown with clinical, cytological and histological findings. Cytological observation was carried out using a liquid based cytological (LBC) system (BD SurePath™, Tokyo, Japan). Cells that were obtained by LBC were stained by Papanicolaou staining, and biopsy specimens which were fixed with 20% formalin were paraffin sectioned at approximately 5 μm in thickness and stained with hematoxylin and eosin.

Results
The numbers of cytological diagnosis while clinical diagnosed as leukoplakia or oral lichen planus from April 2014 to March 2015 are shown in table 1. The ratio of histologically diagnosed SCC in cytological negative cases was 18%, that in cytological doubtful cases was 78%, and that in cytological positive cases was 84%. Morphologically, most cases that were cytological negative showed a histologically surface differentiated SCC. However, in cases that were cytological positive, various atypical cells in the surface area of the SCC could be observed. Further, eight typical cases are presented below; the clinical diagnosis was oral lichen planus in cases 1 and 2, and was leukoplakia in cases 3 to 8.

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<tr>
<th>clinical diagnosis</th>
<th>cytological diagnosis</th>
<th>number of cases</th>
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<td>leukoplakia (275 cases)</td>
<td>negative</td>
<td>256</td>
</tr>
<tr>
<td></td>
<td>doubtful</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>positive</td>
<td>5</td>
</tr>
<tr>
<td>oral lichen planus (137 cases)</td>
<td>negative</td>
<td>124</td>
</tr>
<tr>
<td></td>
<td>doubtful</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>positive</td>
<td>4</td>
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Case 1 (Fig. 1)
Gender: male
Age: 75-year-old
Region: left margin of the tongue to the oral floor
Clinical diagnosis: oral lichen planus
Cytological diagnosis: negative
Pathological diagnosis: squamous cell carcinoma
First visit: April, 2014
History of present illness: aware of haphalgesia 20 years ago, and disappeared a bit later
Date of cytology: April, 2014
Date of biopsy: May, 2014
Induration: negative

Case 2 (Fig. 2)
Gender: female
Age: 44-year-old
Region: right buccal gingiva of the premolar to molar region
Clinical diagnosis: oral lichen planus
Cytological diagnosis: positive
Pathological diagnosis: squamous cell carcinoma
First visit: April, 2014
History of present illness: smarting pain from 2013
Date of cytology: April, 2014
Date of biopsy: May, 2014
Induration: negative

Fig. 1: Case of a 75-year-old male clinically diagnosed with oral lichen planus arising from the left margin of the tongue to the oral floor. a: intraoral photograph, b: cytological finding (Original magnification X100), c: histochemical finding (Original magnification X20)

Fig. 2: Case of a 44-year-old female clinically diagnosed with oral lichen planus arising from the right buccal gingiva of the premolar to molar region. a: intraoral photograph, b: cytological finding, c: histochemical finding (Original magnification X20)
Case 3 (Fig. 3)
Gender: female
Age: 61-year-old
Region: right margin of the tongue
Clinical diagnosis: leukoplakia
Cytological diagnosis: negative
Pathological diagnosis: squamous cell carcinoma
First visit: November, 2014
History of present illness: white lesion noticed by primary care stomatologist
Date of cytology: January, 2015
Date of biopsy: February, 2015
Induration: negative

Case 4 (Fig. 4)
Gender: female
Age: 57-year-old
Region: right margin of the tongue
Clinical diagnosis: leukoplakia
Cytological diagnosis: negative
Pathological diagnosis: squamous cell carcinoma
First visit: May, 2014
History of present illness: conscious of white lesion from 2014
Date of cytology: May, 2014
Date of biopsy: June, 2014
Induration: doubtful

Fig. 3: Case of a 61-year-old female clinically diagnosed with leukoplakia arising from the right margin of the tongue. a: intraoral photograph, b: cytological finding (Original magnification X100), c: histochemical finding (Original magnification X20)

Fig. 4: Case of a 57-year-old female clinically diagnosed with leukoplakia arising from the right margin of the tongue. a: intraoral photograph, b: cytological finding, c: histochemical finding (Original magnification X20)
Case 5 (Fig. 5)
Gender: male
Age: 67-year-old
Region: right margin of the tongue
Clinical diagnosis: leukoplakia
Cytological diagnosis: doubtful
Pathological diagnosis: Verrucous carcinoma
First visit: October, 2014
History of present illness: conscious of mass from September 2014
Date of cytology: October, 2014
Date of biopsy: January, 2015
Induration: negative

Case 6 (Fig. 6)
Gender: male
Age: 54-year-old
Region: left margin to the under-surface of the tongue
Clinical diagnosis: leukoplakia
Cytological diagnosis: doubtful
Pathological diagnosis: squamous cell carcinoma
First visit: September, 2014
History of present illness: white lesion noticed by primary care stomatologist in July 2014
Date of cytology: September, 2014
Date of biopsy: September, 2014
Induration: negative

Fig. 5: Case of a 67-year-old male clinically diagnosed with leukoplakia arising from the right margin of the tongue. a: intraoral photograph, b: cytological finding (Original magnification X100), c: histochemical finding (Original magnification X20)

Fig. 6: Case of a 54-year-old male clinically diagnosed with leukoplakia arising from the left margin to the under-surface of the tongue. a: intraoral photograph, b: cytological finding (Original magnification X100), c: histochemical finding (Original magnification X20)
Case 7 (Fig. 7)
Gender: male
Age: 62-year-old
Region: left of soft palate
Clinical diagnosis: leukoplakia
Cytological diagnosis: positive
Pathological diagnosis: squamous cell carcinoma
First visit: September, 2014
History of present illness: white lesion noticed by primary care stomatologist in December 2013, and consciousness of smarting pain in June 2013
Date of cytology: June, 2014
Date of biopsy: July, 2014
Induration: positive

Case 8 (Fig. 8)
Gender: male
Age: 82-year-old
Region: left under-surface of the tongue
Clinical diagnosis: leukoplakia
Cytological diagnosis: positive
Pathological diagnosis: squamous cell carcinoma
First visit: January, 2014
History of present illness: consciousness of fiery pain
Date of cytology: January, 2014
Date of biopsy: February, 2014
Induration: positive

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Fig. 7: Case of a 62-year-old male clinically diagnosed with leukoplakia arising from the left side of the soft palate. a: intraoral photograph, b: cytological finding (Original magnification X100), c: histochemical finding (Original magnification X20)

Fig. 8: Case of a 82-year-old male clinically diagnosed with leukoplakia arising from the left under-surface of the tongue. a: intraoral photograph, b: cytological finding (Original magnification X100), c: histochemical finding (Original magnification X20)
Discussion

White lesions in the oral cavity are common, and while most intraoral white lesions are benign, some are premalignant and/or malignant at the time of clinical presentation, making it extremely important to accurately identify and appropriately manage those lesions 6). It is known that oral lichen planus is a precancerous condition and that leukoplakia is a precancerous lesion. The manifestations of oral lichen planus, which is an inflammatory dermatosis of the stratified squamous cell epithelium, have been reported around the world 7, 8). In 1978, the WHO classified oral lichen planus as a potentially malignant disorder, since it had been associated with a significantly increased risk of developing cancer. Based on a 12-year retrospective study, Bardellini et al. reported that patients with oral lichen planus should be followed-up for all their lives by clinicians for the potential risk of malignant transformation 3). Leukoplakia is a premalignant lesion that has long been considered to confer an increased risk for the development of oral cancer 9, 10). Leukoplakia is a diagnosis made by excluding all other known diseases or disorders, and may be characterized by a range of disorders of epithelial renewal and maturation, such as hyperkeratosis, acanthosis or epithelial dysplasia 9, 11, 12).

Oral mucosal cytology, which is a minimally-invasive procedure compared to a biopsy, could be useful for the detection of oral cancer in oral mucosal exploration 13). Precancerous lesions or conditions are necessary to be followed-up for early detection and early treatment of SCC. The rate of malignant transformation in leukoplakia has been reported as 5 to 10 percent, and that in lichen planus has been reported as a few percent 14). In this study, the technique of cytology used was liquid-based cytology. Navone reported about the comparison of conventional cytology and liquid-based cytology, which gives better results than conventional cytology for oral SCC 13). The false-negative rate in the cytological diagnosis of oral cancer was shown to exceed 30%, while that of oral precancerous/dysplasia was found to be 63% 14). Our study reveals that the false-negative rate, which is the ratio of histologically SCC in cytologically negative specimens, is 18%. This investigation found a similar rate compared with the previous report 16).

In conclusion, although the cytology of oral precancerous lesions/conditions, such as oral lichen planus, leukoplakia and erythroplakia, plays an important role and is a useful technique for minimally-invasive screening. The frequency of false-negative cases is higher in the case of surface differentiated SCC.

References