Malignant Transformation of Oral Lichen Planus: A Retrospective Study of 565 Japanese Patients

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Abstract

Objective Oral lichen planus (OLP) is a chronic inflammatory oral mucosa disease that is recognized as an oral potentially malignant disorder. However, the potentially malignant nature of OLP remains unclear.

Materials and Methods We designed this study to examine the demographic and clinical characteristics of OLP and evaluate its malignant potential. A total of 565 patients with a clinical and histopathological diagnosis of OLP who presented at our department between 2001 and 2017 were retrospectively studied. Patients who had clinical and histopathological features of oral lichenoid lesions (OLLs) classified as oral lichenoid contact lesions (OLCLs), oral lichenoid drug reactions (OLDRs) and oral lichenoid lesions of graft-versus-host disease (OLL-GVHD) were excluded.

Results The study population included 123 men and 442 women aged 21-93 years (median, 62 years). The 565 patients were followed up for an average duration of 55.9 months, during which 4 (0.7%) patients developed squamous cell carcinoma (SCC). In three of these 4 patients who developed SCC, the clinical type of OLP was the red type.

Conclusions Our results suggested that OLP was associated with a low risk of malignant transformation. Further investigation of the clinical risk factors associated with malignant transformation is necessary.

Clinical relevance We recommend regular follow-up for OLP patients and clear differentiation of oral epithelial dysplasia (OED) and OLLs to enable early detection of malignant transformation.

Introduction

Oral lichen planus (OLP) is a chronic inflammatory oral mucosa disease of unknown etiology that has an estimated global prevalence of 1.01% [1]. The World Health Organization (WHO) Collaborating Center for Oral Cancer has defined OLP as an oral potentially malignant disorder (OMPD) [2]. Although Gonzalez-Moles et al in 2008 stated that malignant transformation of OLP is controversial [3], new evidence does not support their view. This controversy, if any, arose mainly due to the use of varied inclusion and exclusion criteria in previous follow-up studies [3]. In 1978, the WHO first published the clinical and histopathologic criteria for OLP diagnosis [4] that did not mention whether epithelial dysplasia was distinguished or excluded from the OLP diagnosis. In 2003, Van der Meiji and van der Waal proposed modifying the WHO diagnostic criteria [5] and confirmed the absence of epithelial dysplasia in OLP diagnosis, attempting to exclude lichenoid dysplasia from OLP. They also indicated that a diagnosis of OLP required the fulfillment of both clinical and histopathologic criteria. Furthermore, in 2016, the American Academy of Oral and Maxillofacial Pathology (AAOMP) proposed diagnostic criteria for OLP [6]. They emphasized clinical and histopathologic correlations in making the diagnosis of OLP. Therefore, they recommended that clinicians provide all relevant clinical information to pathologists to aid in accurate diagnosis and encouraged active discussion between clinicians and pathologists in situations of persistent doubt.

Oral lichenoid lesions (OLLs) have clinical and histopathologic similarities to OLP and have been classified as oral lichenoid contact lesions (OLCLs) caused by dental substances, oral lichenoid drug reactions (OLDRs) triggered by systemic drugs and oral lichenoid lesions of graft-versus-host disease (OLL-GVHD) at the 2006 World Workshop of Oral Medicine IV [7]. However, clear and reliable clinical and histological criteria were not obtained to fully differentiate OLLs from OLP. Recently, Carrozzo M et al [8] suggested pragmatic diagnostic criteria and a comprehensive classification of OLP and OLLs.

Based on six recent systematic reviews and meta-analyses, the malignant transformation rate of OLP ranges from 0.44–1.4% [9–14]. These results showed that OLP had malignant potential; however, the diagnostic criteria for OLP in each study were not unified. These studies also listed the following as clinical risk factors for the malignant transformation of OLP: tongue localization, red type (atrophic or erosive pattern), tobacco and alcohol consumption, and hepatitis C virus (HCV) infection.

This retrospective study aimed to investigate the demographic and clinical characteristics of OLP using the proposed diagnostic criteria and evaluate the malignant potential of OLP in a Japanese cohort of patients.

Materials And Methods

The diagnostic criteria for OLP

The diagnostic criteria for OLP were based on the following AAOMP proposed criteria [6]:

Clinical criteria

Clinical criteria included the presence of multifocal symmetric distribution and white and red lesions exhibiting one or more of the following forms: reticular/popular, atrophic (erythematous), erosive (ulcerative), plaque and bullous.

Histopathologic criteria

Histopathologic criteria included the presence of a band-like or patchy, predominately lymphocytic infiltrate in the lamina propria confined to the epithelium-lamina propria interface; signs of “basal cell liquefactive (hydropic) degeneration;” presence of lymphocytic exocytosis; absence of epithelial dysplasia; and absence of verrucous epithelial architectural change.

OLP patients were excluded from this study for the following reasons: 1. Any patient who was not histopathologically examined; 2. any patient who had clinical and histopathological features of OLLs proposed by the 2006 World Workshop of Oral Medicine IV [7]; and 3. any patient who was followed up for <6 months.

Patients

This study retrospectively analyzed the records of 1430 patients with a clinical diagnosis of OLP between 2001 and 2017. The records were accessed from the archives of the Department of Oral and Maxillofacial Surgery, Graduate School, Tokyo Medical and Dental University. Of these, 1081 patients (75.6%) were subjected to histopathological examination. Two hundred ninety-four (27.2%) patients who were not diagnosed with OLP on histopathological examination were excluded from the analyses (Table 1). One (0.3%) patient was diagnosed with squamous cell carcinoma (SCC), and 81 (27.6%) were diagnosed with epithelial dysplasia or atypical epithelium; 3 (3.7%) of these 81 patients developed SCC during the follow-up. Furthermore, we excluded 86 OLL patients. Eighty-five patients who had positive metal or dental materials on patch test reactions, localizing adjacent to, and in contact with lesions were diagnosed with OLCL. One patient with chronic GVHD was diagnosed with OLL-GVHD. There were no OLDR patients due to systemic drugs. SCC did not develop in OLL patients. Seven hundred one (64.8%) patients were clinically and histopathologically diagnosed with OLP. Thereafter, 136 patients who were followed up for <6 months were excluded. Finally, 565 patients were analyzed in this study (Fig. 1).

Criteria of the malignant transformation of OLP

The criteria of the malignant transformation of OLP were based on the criteria given by Idrees et al [14]. The criteria were as follows: 1. The properly verified OLP diagnosis, 2. development of the cancerous lesion at the same site as the verified OLP lesion, and 3. follow-up duration of at least 6 months before SCC development.

Ethical considerations

This study was approved by the ethics committee board of the faculty of dentistry of Tokyo Medical and Dental University (D2015-575).

Results

Characteristics of OLP patients

Patient characteristics are summarized in Table 2. Of the 565 patients, 123 were male and 442 were female. The male/female ratio was 1:3.6. The patients were followed up for 6-220 months (mean, 55.9 months). The median patient age at initial presentation was 62 y (range, 21-93 y). One hundred eighteen (20.9%) patients had hypertension, 40 (7.1%) had diabetes mellitus, 31 (5.5%) had thyroid diseases, and 25 (4.4%) were seropositive for HCV. Eighteen (3.2%) patients had both hypertension and diabetes mellitus. Two patients (0.4%) had cutaneous LP, and no women had vulvovaginal lesions. All patients had multiple oral sites of involvement. The most common site was the buccal mucosa (50% of lesions), followed by the gingiva (37.7%), the lateral tongue (7.1%), the lips (4.5%), the dorsal tongue (3.5%), and the palate (3.4%). Of the gingival lesions, 85.6% accompanied the buccal mucosa. The red type was

predominantly involved in the palate, whereas the white type was predominantly involved in the lateral and dorsal tongue (Table 3). Regarding the predominant clinical type, 325 (57.5%) patients had the red type, and 240 (42.5%) had the white type. The prevalence of oral candidiasis in OLP patients was 34.3%.

The treatment of OLP was mostly performed using topical steroids, including 0.1% triamcinolone acetonide, to control inflammation and reduce painful symptoms. No side effects were observed during long-term treatment with topical steroids, except for oral candidiasis in 99 (17.5%) patients.

Characteristics of the four patients with transformation of OLP to carcinoma

SCC developed in four patients (0.7%) at sites clinically and histopathologically diagnosed with OLP (Fig. 2). There were no OLP patients who developed SCC from the original biopsy site. One of the four patients with SCC was male (1/123; 0.8%), and three were female (3/442; 0.7%). The mean patient age at the time of SCC development was 65 y. The development occurred after a mean period of 52.5 months (range, 25-129 months). The site of malignant transformation included the gingiva (2/341; 0.6%), buccal mucosa (1/547; 0.2%) and lateral tongue (1/77; 1.3%). The clinical types of OLP in malignant lesions were three red type (3/325; 0.9%) and one white type (1/240; 0.4%). No patient had a history of smoking, and 75% consumed alcohol (Table 4).

Discussion

In this study, the malignant transformation rate of OLP was 0.7%. The overall average malignant transformation rate cited in six recent systematic reviews and meta-analyses [9–14] was 1.09%. Our percentage is slightly lower than the overall average percentage. However, Idrees et al [14] showed the lowest malignant transformation rate of 0.44%, indicating that the rates cited by other authors were based on studies that included ineligible cases with nonconfirmed OLP, those with epithelial dysplasia at the initial diagnosis, and those with a follow-up duration of < 6 months. Gonzales-Moles et al [3] suggested that the high incidence of malignant transformation described in many studies might be attributable to the misdiagnosis of some lesions as OLP. Therefore, based on these diagnostic criteria, the malignant transformation of OLP may be ≤ 1%.

The differentiation between OED and OLLs is important for the diagnosis of OLP. OED is a well-known precursor of SCC, and its presence and dysplasia grade influence the malignant transformation potential of OPMDs [15]. Iocca et al [13] reported that the malignant transformation rate of OLP was the lowest in OMPDs, indicating the absence of epithelial dysplasia in OLP. In this study, 3 (3.7%) out of 81 OED patients developed SCC. This rate was considerably higher than the rate in patients with OLP, suggesting a low malignant potential of OLP.

However, Lodi et al [16] noted that lesions with clinical features of OLP but with dysplasia may represent an early phase in the malignant transformation of OLP. Thus, excluding OLP with epithelial dysplasia

from these studies may still be debatable.

In this study, no OLL patient developed SCC. However, some studies have reported that OLCLs might possess malignant potential similar to that of OLP [17, 18]. Therefore, regular follow-up is required for OLCL patients with malignant transformation as well as OLL-GVHD patients who are known to be at risk of SCC development. We did not find any OLDR suspected lesions because OLDR can occur at any time during the disease course, even > 1 y after initiating medication. No standard diagnostic criteria for OLDR have been established, and further research on this subject is necessary.

Based on six recent systematic reviews and meta-analyses [9–14], tongue localization, red type (atrophic or erosive pattern), tobacco and alcohol consumption, and HCV infection significantly heighten the risk of the malignant transformation of OLP. In the present study, we could not investigate the clinical risk factors associated with malignant transformation due to the relatively small study population, which did not allow statistically meaningful analyses. However, we found that age ≥ 62 y, lateral tongue site, and red-type OLP tended to have a higher risk of SCC development (Table 2). Further research on this subject is needed.

Regarding age and sex, the risk of the malignant transformation of OLP is believed to be higher in women than in men in the age group of 60–70 y [3]. Demographically, OLP is more common in women aged > 40 y. Furthermore, Gonzales-Moles et al [1] reported a significantly higher prevalence in subjects aged > 50 y or > 60 y. Thus, age and sex associated with the malignant transformation risk were suggested to be linked to demographics.

Regarding the clinical type and site, Aghbari et al [10] reported that the rates of malignant transformation were 1.7%, 1.3%, and 0.1% in erosive, atrophic, and reticular patterns, respectively. The most common site was the tongue (1.05%), followed by the buccal mucosa (0.7%), the gingiva and the lips (0.6%), and the floor of the mouth (0.5%). With respect to the clinical type and site, the results of this study were almost consistent with previous results. In addition, the mean duration until malignant transformation was much shorter in those with red-type OLP than in those with white-type OLP. Red-type OLP was suggested to have a higher malignant potential than white-type OLP.

Research has demonstrated a strong association between HCV infection and OLP, which is explained by the ability of the virus to replicate in oral mucosa cells and attract HCV-specific T lymphocytes [19]. Furthermore, HCV is an oncogenic virus and might be involved in oral carcinogenesis [20]. In our study, 4.4% of the OLP patients had an HCV infection; none developed SCC. Further studies on this subject are required.

The treatment of OLP involves the use of corticosteroids, cyclosporin, azathioprine, and retinoids. However, immunosuppressive agents may trigger malignant transformation, and the treatment of OLP patients with topical and/or systemic steroids did not influence the risk of malignant transformation [16]. Thus, we believe that in our study, the treatment did not affect the risk of malignant transformation.

However, OLP patients have an increased prevalence of Candida infection and are predisposed to candidiasis with topical or systemic immunosuppressive therapy. Candida generates chronic inflammation and can produce carcinogenic N-nitrosobenzylmethylamine [21] and mutagenic amounts of acetaldehyde [22]. Although Candida strongly contributes to carcinogenesis, its association with carcinoma remains unclear. Further studies on this subject that may clarify these limitations are needed.

Conclusions

Our results showed a malignant transformation rate of 0.7%, suggesting that OLP is associated with a low risk of malignant transformation. Therefore, we recommend regular follow-up for OLP patients and clear differentiation of OED and OLLs to enable early detection of malignant transformation. Further investigation of the clinical risk factors associated with malignant transformation is needed.

Declarations

Conflict of interest:

The authors declare that they have no conflict of interest.

Funding:

There are no funding sources.

Ethical approval:

All procedures performed in studies were in accordance with the ethical standards of the institutional research committee (The ethics committee board of the faculty of dentistry of Tokyo Medical and Dental University, D2015-575) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent:

For this type of study, formal consent is not required.

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Tables

Due to technical limitations, tables are only available as a download in the Supplemental Files section.

Figures

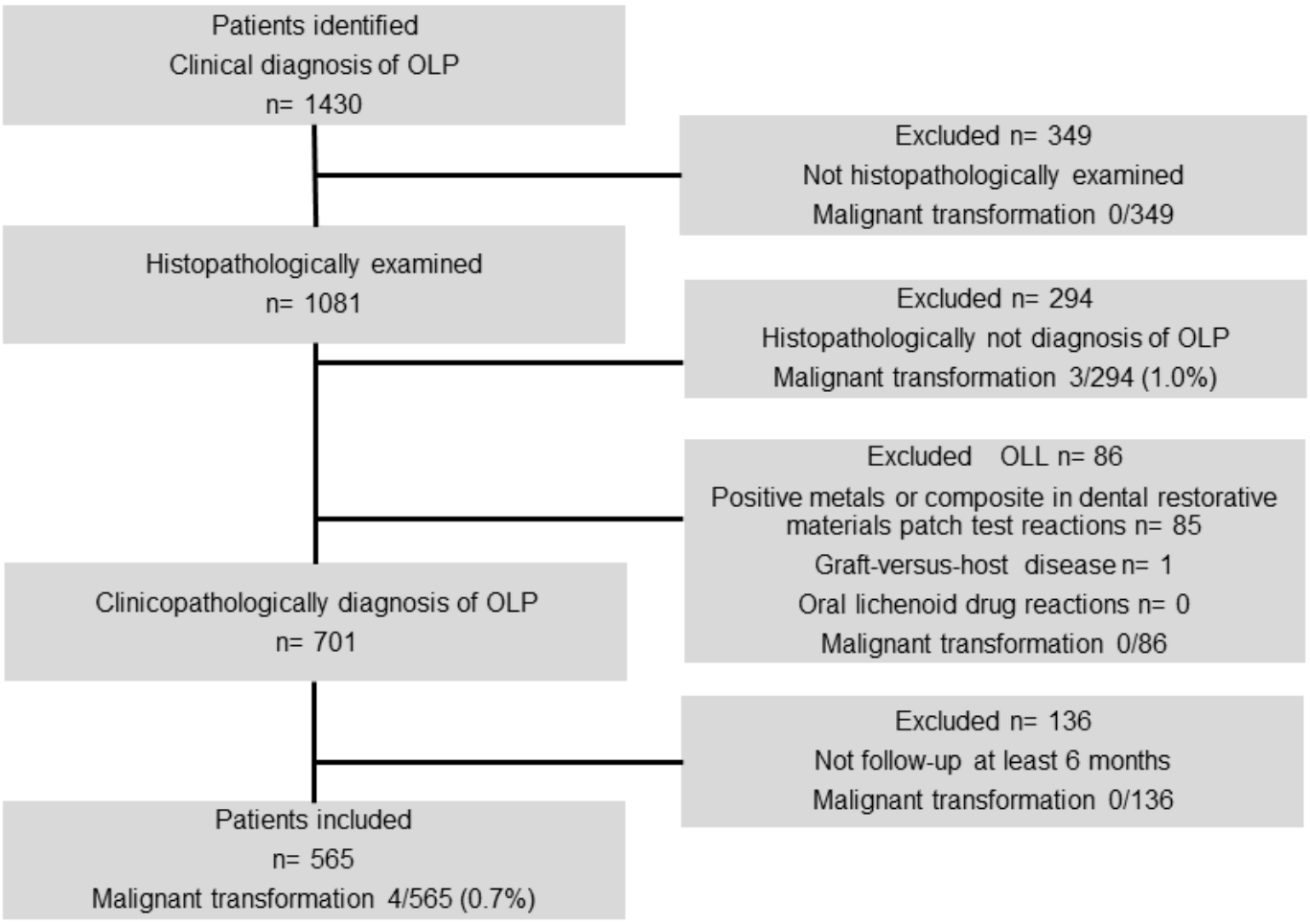

Figure 1

Flowchart of patients inclusion

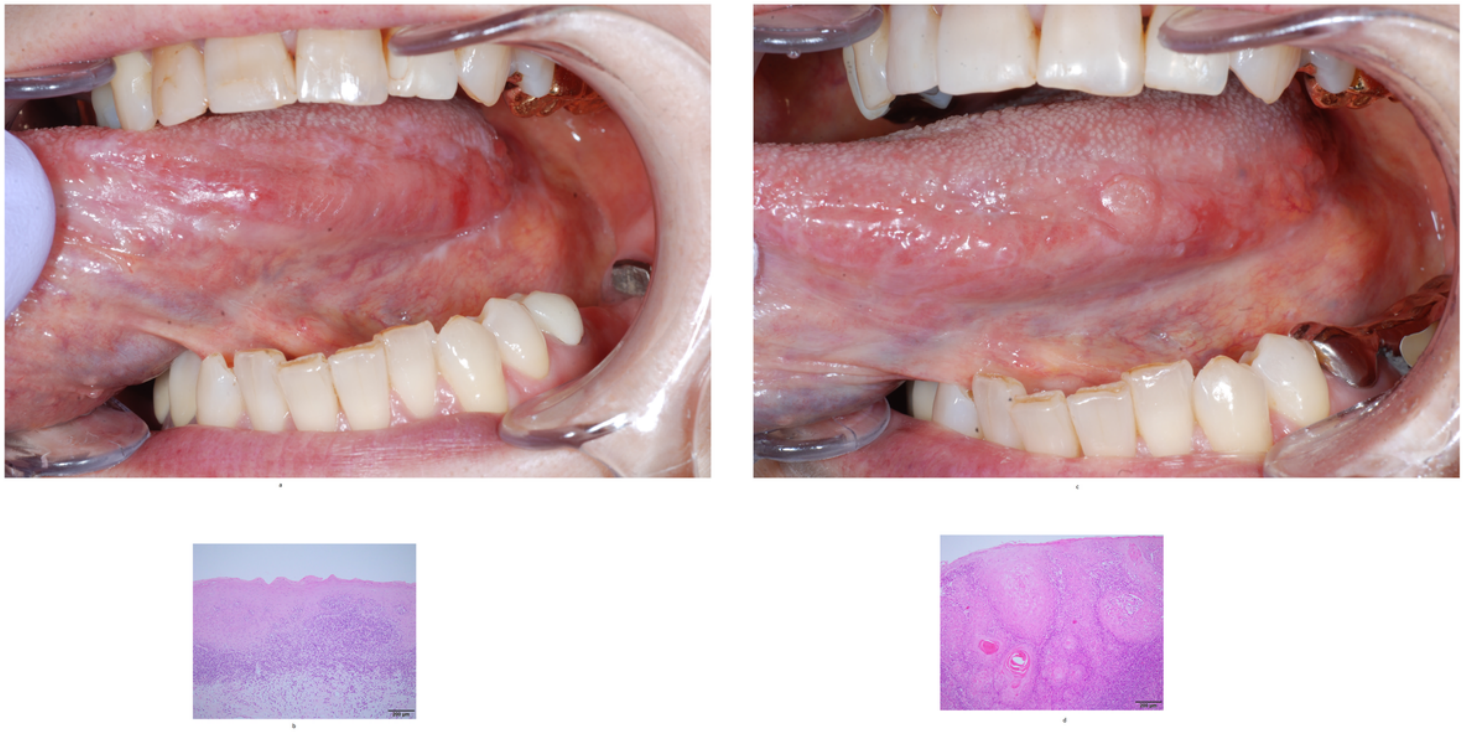

Figure 2

Malignant transformation in Case 4 showing clinical pictures and correlating histopathologic features in biopsy (haematoxylin-eosin staining) at initial presentation (a, b) and malignant transformation (c, d).

Supplementary Files

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