Malignant Transformation in Oral Lichen Planus and Lichenoid Reactions in Southern Thai Population

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Abstract

Objectives: This study aimed to determine the prevalence of malignant transformation (MT) and the incidence rate of oral squamous cell carcinoma (OSCC) in oral lichen planus (OLP) and oral lichenoid reaction (OLR) patients from southern Thailand.

Methods: This hospital-based retrospective cohort study comprised OLP/OLR patients who were treated between January 2016 and December 2022. Data on the general characteristics, clinical manifestations and laboratory investigations were obtained from the hospital records and analyzed. Descriptive and analytical statistics were performed to assess the demographic data, clinical profiles of the patients and the prevalence and incidence rate of MT.

Results: A total of 117 patients were included in the study; 103 (88%) were diagnosed with OLP, and 14 (12%) were diagnosed with OLR. The median follow-up time was 15.6 months (interquartile range; 6.1-46.0). The overall prevalence of MT in OLP/OLR was 1.71% (2/117 patients); specifically, MT in OLP was 1.94% (2/103 patients). The overall annual incidence rate of MT into OSCC was 0.0060 (95% confidence interval, 0.0015-0.0240).

Conclusions: These findings suggest that OLP is a potentially malignant disorder with an MT incidence of 1.94% in the southern Thai population. OLP patients must be regularly followed-up and advised about the risk of MT.

Keywords: lichen planus, lichenoid reactions, oral squamous cell carcinoma, southeast Asian people

Introduction

Oral lichen planus (OLP) is a chronic inflammatory and immune-mediated disease of the oral mucosa. A recent meta-analysis revealed that the global prevalence of OLP is 1.01%, with a remarkable difference based on the geographic location. Furthermore, the prevalence of OLP is known to increase with age, especially after the age of 40.[1] In the Thai population, OLP predominantly affects females with a 1:4 male-to-female ratio.[2] The clinical manifestations of OLP include white reticules, white patches, atrophic mucosa, and ulcerative areas.[3,4] Furthermore, OLP and oral lichenoid lesions (OLL) have been recently classified as oral potentially malignant disorders (OPMDs), which can transform into oral squamous cell carcinoma (OSCC). Additionally, OLP showed a cancer development rate of approximately 1-2%.[3]

However, the malignant transformation (MT) of OLP remains controversial. The rate of MT in OLP ranges from 0% to 12.5% across the world.[5] Previous studies, including systematic reviews and meta-analyses, have reported the following rates of MT for the OPMDs: 0.44%–2.28% for OLP, 1.88%–3.80% for OLL and 1.71% for OLR.[6-10] A multicenter study in Thailand reported an MT rate of 0.2% in Thai patients, based on data gathered from all regions, except southern Thailand.[2] In addition, a recent clinical study on OLP patients from northern Thailand found that none of the patients developed OSCC.[11] To the best of our knowledge, there are no reports on the MT of OLP in the southern Thai population. Therefore, this study aimed to raise awareness about this issue and provide supporting evidence by investigating the prevalence of MT and the annual incidence rate of OSCC associated with MT in OLP/OLR patients in the southern Thai population.

Materials and Methods

Study population and data collection

All patients diagnosed with OLP/OLR and treated between 2016 and 2022 at the Dental Hospital, Faculty of Dentistry, Prince of Songkla University, Thailand were identified via a hospital database search using the International Classification of Diseases, version 10- ICD-10 (L430-8). Patients with a biopsy report indicating OLP/OLR and the necessary follow-up records were included in the study. The OLP patients were diagnosed according to the clinical and histopathological criteria of van der Meij and van der Waal in 2003.[12] The diagnosis of OLR patients relied on the patient's history, clinical correlation with causative agents, and histopathological reports reviewed by clinicians. The clinicians in this setting did not use the term "OLL" in the retrospective hospital records, which means that the study population in this present study was defined only as "OLP" or "OLR". Furthermore, OLP/OLR with epithelial dysplasia was recorded and included to the study population as Gonzalez-Moles and Ramos-García's recommendation.[13]

After recruiting eligible participants, the hospital records were reviewed to extract the following information: general characteristics, clinical characteristics of OLP/OLR, review of biopsy report and laboratory investigations. Data on the general characteristics included sex, age, medical history, alcohol consumption, smoking, betel quid chewing, and total follow-up time. The clinical characteristics of the patients included the type of OLP/OLR, location of OLP/OLR and corticosteroid prescription, while the laboratory investigations included the presence of hepatitis C (HCV) and *Candida* superinfection. The following criteria were used to ascertain the primary outcomes[14]: (a) clinically and histopathologically verified OLP diagnosis; (b) development of OSCC at the site of OLP/OLR; and (c) follow-up at least 6 months prior to OSCC transformation.

Ethical Approval

This study was approved by the Human Research Ethics Committee (HREC) of the Faculty of Dentistry, Prince of Songkla University-EC6503-016 (amendment version). HREC is certified in full compliance with the international Guideline for Human Research Protection-the Declaration of Helsinki, the Belmont Report, CIOMS guidelines and the International Conference on Harmonization in Good Clinical Practice (ICH-GCP). HREC was approved for waiver of informed consent according to retrospective study design.

Statistical analysis

The STATA software, version 16.0 (StataCorp, College Station, TX, USA), was used for data analysis. The general characteristics, clinical characteristics of OLP/OLR and laboratory investigations were analyzed using descriptive statistics. Categorical data were described as frequencies/percentages and continuous data were described as mean/

standard deviation or median/interquartile range (IQR), depending on the data distribution. The prevalence of MT and the overall annual incidence of OSCC among the patients was determined across the study population with recorded follow-up time. The findings were reported with a 95% confidence interval (CI; α=0.05).

Results

A total of 207 patients with ICD 10 (L430-8) were selected, out of which 90 patients (43.5%) were excluded according to no histopathological diagnosis (50 patients), no follow-up data (16 patients), loss of dental records (12 patients) and biopsies showed as other conditions/ diseases (7 patients), respectively. As a result, a total of 117 (56.5%) patients met the eligibility criteria and were included in the study (Figure 1).

Among the 117 patients, 103 (88.0%) were diagnosed with OLP, while the remaining 14 (12%) were diagnosed with OLR. Two patients (1.7%) had OLP with mild epithelial dysplasia and none of OLP with epithelial dysplasia patients developed OSCC during the follow-up periods of 21.7 and 60.2 months. The median follow-up time for the study population was 15.6 months, with an IQR of 6.1-46.0 months.

The general characteristics of the OLP/OLR patients are summarized in Table 1. OLP/OLR was predominant in females with a male-to-female ratio of 1: 3.9. The mean age of the OLP patients at diagnosis was 55.4±11.1 years. Sixty-one patients (53.0%) had underlying systemic diseases (generally more than one disease). Hypertension (29.9%) and dyslipidemia (24.8%) were the most common systemic diseases in these patients. Assessment of the risk factors revealed that 7.7% (9/117) of the patients had a smoking habit, 6.0% (7/117) consumed alcohol, and 0.9% (1/117) chewed betel quid. However, the risk assessment was not performed in all the OLP/OLR patients due to missing data (Table 1).

The clinical characteristics of the patients are summarized in Table 2. The majority of patients presented with OLP/OLR lesions at multiple sites (76.9%) with multiple clinical manifestations (66.7%) in the oral cavity. The most common affected site was the buccal mucosa (83.8%), followed by the gingiva (67.5%) and tongue (20.5%). Reticular patterns were most commonly seen (89.7%), followed by the presence of desquamative gingivitis (41%) and atrophic lesions (35%). A variety of

corticosteroids were prescribed during the follow-up period, the most common being a 0.1% fluocinolone acetonide oral paste (56.4%), followed by a 10% triamcinolone acetonide (TA) mouthwash (31.6%) and a 0.1% TA oral paste (29.9%; Table 2). The clinicians usually started with high-potency steroids and subsequently changed to other lower-potency topical steroids depending on the severity of the lesions. Of the 117 patients, 5 (4.3%) were positive for HCV; the relevant data were missing in 82.9% of the patients. Of the two patients (1.7%) positive for HBV, one was co-infected with both HCV and HBV. Furthermore, *Candida* superinfection was detected in 42 patients (35.9%).

The overall prevalence of MT in the OLP/OLR patients was 1.71% (2/117 patients; 95% CI, 0.21-6.03). Specifically, the prevalence was 1.94% (2/103 patients; 95% CI, 0.24-6.84) in the OLP patients and 0% in the OLR patients. The overall annual incidence rate of OSCC, related to the MT of OLP/OLR, was estimated at 0.0060 (95% CI, 0.0015-0.0240). The general and clinical characteristics of patients who developed OSCC in this study are described in Table 3. Both patients developed OSCC at the site of the OLP lesion and other sites in the oral cavity were verified to be free of any cancer cases. One patient, who presented with red/ulcerative lesions, had a smoking habit and experienced an HCV infection, developed OSCC within a short time during the follow-up period (6.3 years). The other patient developed OSCC 17.5 years after being diagnosed with OLP.

Discussion

The overall prevalence of MT in OLP and OLR patients was 1.71%, and it was observed only in the OLP patients (prevalence, 1.94%). It is noteworthy that this study was the first to investigate the MT in OLP and OLR in the southern Thai population. The finding is consistent with previous studies, which reported MT rates ranging from 0.44 to 2.28%.[9,10,14] However, the MT in the present study is slightly higher than those reported previously in Asian populations, such as Iran, Taiwan, China and Japan (range, 0.07-0.7%).[15-18] A multicenter study, which investigated the prevalence of MT in all the regions of Thailand, except the southern region, reported an MT rate of 0.2% in the population.[2] Alternatively, another study reported no incidence of MT in OLP in the northern region of Thailand; however, one case of MT in

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│   Patients identified with ICD10     │
│       (L430-8) of OLP/OLR            │
│           (n = 207)                  │
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Patients excluded (n = 90)
No histopathologic diagnosis (n = 55)
Lack of follow-up data (n = 16)
Loss of dental records (n = 12)
Biopsy results showed
- Chronic inflammation (n = 2)
- Ulceration (n = 1)
- Mucous membrane pemphigoid (n = 1)
- Pemphigus vulgaris (n = 1)
- Erythematous candidiasis (n = 1)
- Hyperplastic candidiasis (n = 1)

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│ Eligible OLP/OLR patients (n = 117)  │
│      Subgroup of diagnosis;          │
│          OLP (n = 103)               │
│           OLR (n = 14)               │
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│     Data collection (n = 117)        │
│ Outcome: Malignant transformation on │
│ areas affected by OLP in two verified│
│ OLP patients after more than 6 months│
│        of follow-up.                 │
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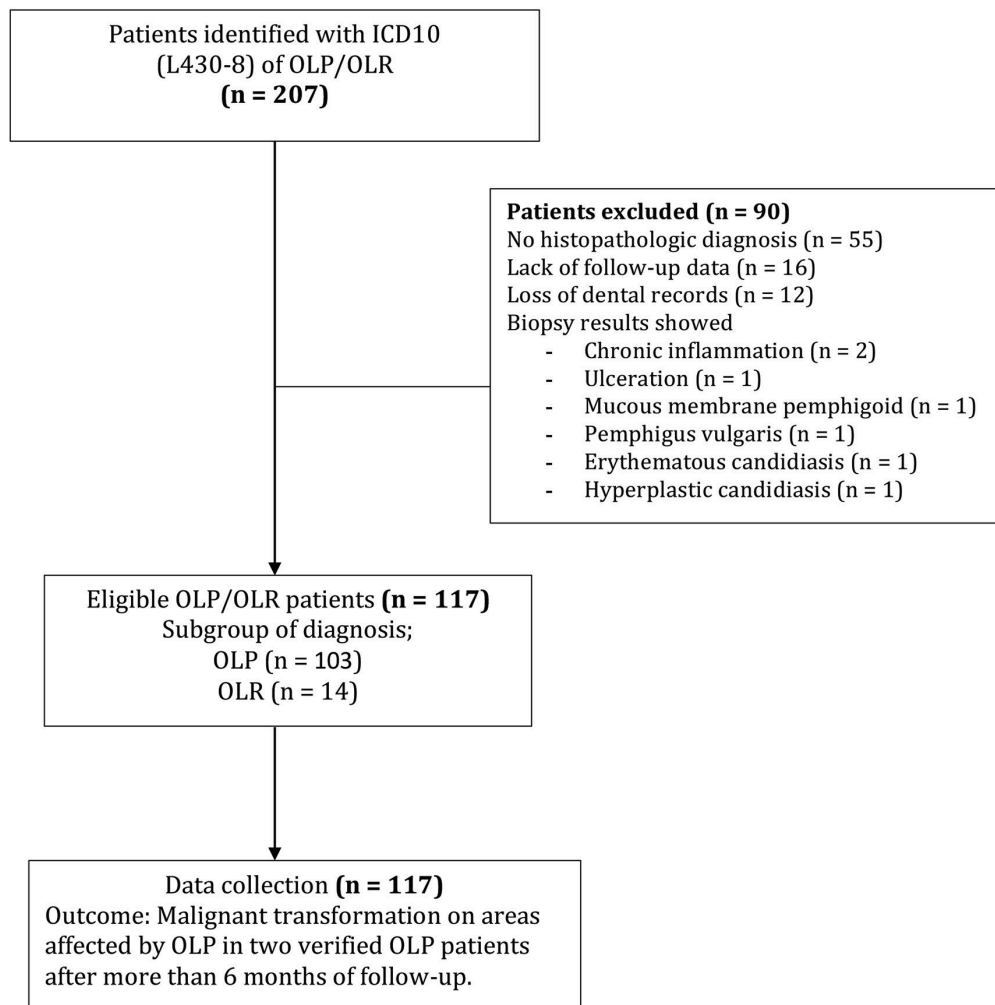
Figure 1: Study flowchart with inclusion and exclusion criteria

OLP was subsequently reported in the same population during the COVID-19 crisis.[11,19] The discrepancy in the MT rates observed in this study and other studies, which revealed a higher malignization rate compared to other regions of Thailand or Asian populations, may be due to differences in diagnostic criteria or the exclusion of epithelial dysplasia as a diagnostic criterion. Therefore, its inclusion or exclusion of study criteria can affect the MT rates observed in studies. Furthermore, although previous studies have suggested that OLL and OLR lesions have a slightly higher malignant potential than OLP lesions[6-10], no study has specifically determined the potential for MT in OLL and OLR in the Thai population. Although the study found no cases of MT in OLR patients, the findings may be considered as inconclusive owing to the limited number of OLR patients in this study (n=14). Further multicenter studies in Thailand are necessary to investigate the prevalence of MT in OLR and OLL

patients, highlighting the need for calibrated diagnostic criteria for OLP, OLR and OLL. Therefore, based on the study's result and previous studies in Thailand[2,19], OLP is considered a potentially malignant disorder (OPMD) with an overall MT rate ranging from 0.2 to 1.94% in the Thai population.

Certain risk factors can increase the malignant potential in OLP, OLL and OLR patients. Previous studies have suggested that clinically red/erosive forms, the location of the lesion, smoking and alcohol consumption and HCV infection are associated with an increased risk of MT in OLP patients[7,10,20], which odd ratio (OR) and risk ratio (RR) were reported OR=2.70 and RR=2.80-4.09 for red/erosive, OR=2.0-4.62 and RR=1.98 for smoking, OR=3.22-3.52 and RR=2.28 for alcohol consumption, and OR=5 and RR=3.77-4.46 for HCV infection, respectively.[10] In the present study, two OLP patients demonstrated MT to OSCC; one patient had presented

Table 1: General characteristics of the study population.

General characteristics	OLP/OLR (n=117)
Gender (n, %)	
Female	92 (78.6%)
Male	25 (21.4%)
Age (years; mean±SD)	
Female	56.0±11.0
Male	53.2±11.2
Systemic diseases (n, %)	
Hypertension	35 (29.9%)
Dyslipidemia	29 (24.8%)
Diabetes mellitus	11 (9.4%)
Thyroid diseases	5 (4.3%)
Allergic rhinitis	3 (2.6%)
Hepatitis B infection	2 (1.7%)
Arthritis	2 (1.7%)
Asthma	1 (0.9%)
Liver cirrhosis	1 (0.9%)
HIV	1 (0.9%)
Osteoporosis	
Risk factors for OSCC (n, %)	
Smoking	9 (7.7%)
Alcohol	7 (6.0%)
Betel quid chewing	1 (0.9%)

*Smoking, alcohol, and betel quid chewing had missing data of about 24.8%, 24.8%, and 60.9%, respectively.

Abbreviations: OLP/OLR, oral lichen planus/oral lichenoid reaction; HIV, human immunodeficiency virus; OSCC, oral squamous cell carci

with the red/ulcerative forms of OLP, while the other had the white form of the disease. The patient with the red/ulcerative form was a heavy smoker (10 packs/year) and had an HCV infection. During the follow-up, the OLP transformed into OSCC within a short period of 6.3 years. However, the other patient with the white form of OLP had no remarkable risk factors and the transformation to OSCC occurred over several years (17.5 years). These findings agree with those of previous studies, which show that the clinical forms, smoking habits and presence of HCV infection can influence and increase the potential for MT in OLP.

OLP with epithelial dysplasia was observed in 1.7% (2/117) of the patients in the current study. This finding was consistent with a previous study which reported a prevalence of 1.7% (9/533 patients) in Thai patients.[2] The presence of epithelial dysplasia was associated with an increased rate of MT.[10,18,21] Gonzalez-Moles and Ramos-García proposed that the presence of dysplasia should be included while investigating the prevalence of

MT in OLP; such cases should be defined as 'OLP with epithelial dysplasia', which was different from the van der Meij and van der Waal criteria that they did not consider epithelial dysplasia in histopathological criteria.[13] Gonzalez-Moles and Ramos-García also pointed out that there is no current literature proving that OLP lesion itself cannot progress to epithelial dysplasia.[12,13] In contrast, a model indicating that dysplastic changes could occur in OLP before transforming into OSCC due to chronic inflammation was introduced in the past[22] and there was a previous study suggested that OLP lesions with dysplasia could indicate early-phase MT in OLP.[23] The model was summarized that the presence of dysplasia or development oral cancer in OLP cases resulted from cell DNA damages, loss of epithelial integrity due to inflammatory cytokines, or oxidative stress.[22] However, detecting epithelial dysplasia remains challenging. As expressed in a recent publication, the evaluation of epithelial dysplasia, especially mild forms of dysplasia in OLP, is controversial and requires experienced pathologists.[24] Because, it is

Table 2: Clinical characteristics of the study population.

Clinical characteristics	OLP/OLR (n=117)
Follow-up (months; median with IQR)	15.6 with an IQR of 6.1-46.0
Clinical manifestations (n, %)	
Reticular type	105 (89.7%)
Desquamative gingivitis	48 (41.0%)
Atrophic type	41 (35.0%)
Erosive type	22 (18.8%)
Plaque type	
Clinical sites (n, %)	
Buccal mucosa	98 (83.8%)
Gingiva	79 (67.5%)
Tongue	24 (20.5%)
Lip	19 (16.2%)
Alveolar ridge	16 (13.7%)
Floor of the mouth	8 (6.8%)
Palate	7 (6.0%)
Labial mucosa	6 (5.1%)
Corticosteroid prescription (n, %)	
0.1% FA oral paste	66 (56.4%)
10% TA mouthwash	37 (31.6%)
0.1% TA oral paste	35 (29.9%)
10% Dexamethasone mouthwash	24 (20.5%)
0.05% CP oral paste	2 (1.7%)
Systemic prednisolone	5 (4.3%) with a range of 10-40 mg/day
HCV investigation (n, %)	
Negative	15 (12.8%)
Positive	5 (4.3%)
Missing data	97 (82.9%)
Presence of *Candida* Superinfection (n, %)	42 (35.9%)

Abbreviations: OLP/OLR; oral lichen planus/oral lichenoid reaction; IQR, interquartile range; FA, fluocinolone acetonide; TA, triamcinolone acetonide; CP, clobetasol propionate; HCV, hepatitis C virus

Table 3: General and clinical characteristics of patients who developed oral squamous cell carcinoma.

Case	Demographics and Risk factors	Site of OLP malignization and time to MT	Staging and treatment
1	Male, 58 years with liver cirrhosis, diabetes mellitus, and hypertension **Risk factors:** Hepatitis C and smoking 10 packs/year	Right buccal mucosa (Previous red/ulcerative clinical form of OLP) **Time to MT:** 75.2 months (6.3 years)	T3N1M0; He underwent wide excisional surgery with a right modified radical neck dissection and immediate reconstruction with a right pectoralis major myocutaneous flap followed by chemoradiotherapy.
2	Female, 64 years with unremarkable medical history **Risk factors:** None	Lower anterior labial gingiva/vestibule (Previous white lesion site of OLP) **Time to MT:** 209.9 months (17.5 years)	Not applicable: She was referred to a tertiary hospital for further investigations and treatment, which were covered by her health insurance.

Abbreviations: OLP, oral lichen planus; MT, malignant transformation; TNM, Tumor-Node Involvement-Metastasis staging

crucial to differentiate the actual epithelial dysplasia from reactive epithelial atypia that responses to inflammatory stimuli, which is common in OLP lesion.

The present study found no MT in OLP with epithelial dysplasia (2/117 patients) during the current study's follow-up periods (1.8 and 5 years). This is in concordant with other expert experiences that epithelial dysplasia even high grade may not progress to malignancy.[25] On the other hand, this lack of MT may be due to the limited sample size of the OLP with epithelial dysplasia population and the short follow-up periods. Nonetheless, it is necessary to monitor patients with OLP/OLL/OLR with epithelial dysplasia in the long term, as previous studies have recommended.

This study has some limitations. The sample size was relatively small, and there was an issue that should be addressed, as shown in Figure 1. Of 207 patients, a high proportion of excluded patients (55/90 patients; 61.1%) had been diagnosed with OLP based on the clinical findings only. According to previous study, both clinical and histopathological examinations are essential to confirm a diagnosis of OLP/OLL/OLR[13] and ascertain the actual MT of OLP. Furthermore, it is also important to rule out other OPMDs that clinically resemble OLP. Previous studies have shown that lesions resembling early-stage OLP could develop into proliferative verrucous leuko-plakia (PVL), or that the clinicopathological features of OLL could be similar to those of PVL.[26-28] Therefore, we recommend that patients with clinical signs of OLP undergo an incisional biopsy to determine the definitive diagnosis, assess the presence of epithelial dysplasia as a potential risk for MT and plan appropriate treatment accordingly. Furthermore, the assessment of risk factors was not possible in all patients in the current study due to missing data on smoking, alcohol consumption, betel quid chewing and HCV testing. Comprehensive clinical records for OLP, OLL and OLR should be used to ascertain the effect of these risk factors on MT in the Thai population. Additional multicenter studies must be conducted using appropriate criteria for histopathological diagnosis that clearly discriminate among OLP, OLL and OLR across all regions of Thailand. This will aid in determining the rate of MT and raise awareness about its potential in patients with these lesions.

Conclusions

The prevalence of MT in OLP was 1.94% with the overall annual incidence rate was estimated at 0.0060 in the southern Thai population, based on the study. We recommend that all OLP/OLR patients undergo regular follow-ups; a comprehensive history of the patient, including the cancer risks, must be taken to enable the early detection of OSCC transformation. Furthermore, OLP patients should be counseled about the potential for MT, even if the symptoms are controlled.[29] Therefore, clinicians should communicate with OLP patients, inform them about the risks and address the importance of long-term follow-up.

Acknowledgments

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data are available from the corresponding author upon reasonable request.

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