Oral Oncology 133 (2022) 106025

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Overestimated risk of transformation in oral lichen planus

ARTICLE INFO

Keywords
Oral lichen planus
Oral leukoplakia
Proliferative verrucous leukoplakia
Oral squamous cell carcinoma
Malignant transformation

ABSTRACT

Objectives: Oral lichen planus (OLP) was classified as an oral potentially malignant disorder due to the association with oral squamous cell carcinoma (OSCC). However, the malignant potential of OLP has been controversial. Whether epithelial dysplasia should be differentiated from OLP and lichenoid dysplasia could be identified as a pathological entity has been the subject of debate.

Materials and methods: We recruited a large retrospective cohort with 3568 patients, and 10 of them developed OSCC. These cases were reviewed retrospectively to investigate association between OLP and OSCC.

Results: In 10 cases of OSCC, three of them were primary cancers distinct from the site with OLP, two were malignant transformation of proliferative verrucous leukoplakia, and five were malignant transformation of oral leukoplakia. All OSCC is not transformed from OLP. Therefore, previous insights into OLP might have overestimated its transformation risk. There may be the reasons: I. did not distinguish OLP from epithelial dysplasia, II. neglect of oral leukoplakia with dysplasia developed in the course after OLP, III. misdiagnosis in the early stage of proliferative verrucous leukoplakia.

Conclusion: The pathological and molecular biological features of OLP differed from those of oral leukoplakia and OSCC. Strict control of the diagnostic criteria for OLP and close surveillance during the course could contribute to correctly identify the origin of OSCC and avoid overestimating the risk of OLP transformation.

Introduction

Oral lichen planus (OLP) was a common chronic inflammatory disease occurred in the oral mucosa with a global incidence rate of 0.89% [1]. OLP was classified as one of the oral potentially malignant disorders (OPMD) by the WHO, which increased the risk of oral squamous cell carcinoma (OSCC) [2,3]. However, the malignant potential of OLP remained controversial [4,5], different studies have shown differential malignant risk [6–15]. On the one hand, the diagnostic criteria for OLP varied in different studies, and the term "lichenoid dysplasia" was mentioned in different studies, but its definition was vague [4,16]. On the other hand, the long course between OLP and OSCC lacked of the surveillance and biopsy of the intermediate process, and it was impossible to identify the actual biological process between OLP and OSCC. A retrospective study only starting with a diagnosis of OLP and with follow-up to the end of OSCC seemed to be insufficient. Given these shortcomings, in this study, we retrospectively analyzed a large-scale OLP cohort strictly in accordance with the criteria established by WHO [2,17], and diagnosed the entire disease course of OSCC which developed after OLP to explore the association between OLP and OSCC.

Materials and methods

The OLP cohort was recruited from Department of Oral Pathology, Peking University Hospital of Stomatology between 2010 and 2017. Inclusion criteria were as follows: I. all OLP cases were diagnosed and reviewed based on biopsies by two experienced pathologists according to the standard drafted by the WHO [17]. II. there were available clinical and pathological data of patients. The exclusion criteria were that, I. there were OSCC and other types of oral potentially malignant disorders before or concomitant with OLP. II. There were not medical records of patients. III. The diagnosis was histopathological descriptive terms without a clear disease. This research was a retrospective cohort study and has been approved by the institutional review board of the hospital (No. PKUSSIRB-202164075).

Results

A total of 3568 cases of OLP were recruited from the Department of Oral Pathology, Peking University Hospital of Stomatology for eight consecutive years. There were 1263 (35.40%) males and 2305 (64.60%) females, with an age range of 6–84 years and a median age of 46 years. 2254 (63.17%) cases occurred in the buccal, 1135 (31.81%) cases in the tongue, 112 (3.14%) cases in the gingiva, 66 (1.85%) cases in the lip, and 1 (0.03%) case in the palate.

With a mean follow-up of 8 years, ten of them developed OSCC after OLP (Table 1), accounting for 0.28%. Among them, six cases occurred in the tongue, three cases in the buccal, and one case in the gingiva. The age range of primary diagnosis was 36–72 years old, and the median age was 58 years old. The age range at the development of cancer was 40–77

Abbreviations: OLP, oral lichen planus; OSCC, oral squamous cell carcinoma; OPMD, oral potentially malignant disorders; PVL, proliferative verrucous leukoplakia; OLK, oral leukoplakia; MT, malignant transformation; MPC, multiple primary cancers.

https://doi.org/10.1016/j.oraloncology.2022.106025
Received 7 July 2022; Received in revised form 10 July 2022; Accepted 13 July 2022
Available online 17 July 2022
1368-8375/

Table 1
Retrospective diagnosis of oral cancer after oral lichen planus.

Patients		P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
Sex		Female	Female	Female	Male	Female	Female	Male	Male	Female	Male
Age at first diagnosis		56	65	60	53	41	36	72	64	48	60
Smoking and drinking		No	No	No	Smoking	Drinking	No	No	No	No	No
First	Site	Buccal	Tongue	Tongue	Tongue	Tongue	Buccal	Buccal	Gingiva	Tongue	Tongue
	Pathology	OLP	OLP	OLP	OLP	OLP	OLP	OLP	OLP	OLP	OLP
	Treatment	Drug	Drug	Drug	Drug	Drug	Drug	Drug	Drug	Drug	Drug
Second	Interval	5 months	63 months	17 months	115 months	67 months	54 months	53 months	16 months	10 months	67 months
	Site	Lip	Tongue	Tongue	Tongue	Tongue	Tongue	Buccal	Gingiva	Tongue	Buccal
	Pathology	OSCC	OLK	OLK and OSCC	OLK and OSCC	OLK and OSCC	OLK and OSCC	OLK and OSCC	OSCC	OLK and OSCC	OLK
	Treatment	Surgery	Drug	Surgery	Surgery	Surgery	Surgery	Surgery	Surgery	Surgery	Surgery
Third	Interval		87 months	23 months			73 months	87 months	22 months	22 months	79 months
	Site		Tongue	Tongue			Tongue	Buccal, gingiva	Gingiva, buccal	Tongue	Buccal, gingiva
	Pathology		OSCC	OLK			OSCC	OSCC	OLK	OLK and OSCC	OSCC
	Treatment		Surgery	Drug			Surgery	Surgery	Surgery	Surgery	Surgery
Fourth	Interval			33 months					39 months	52 months	
	Site			Tongue					Gingiva	Gingiva	
	Pathology			OLK and OSCC					OSCC	OSCC	
	Treatment			Surgery					Surgery and radiotherapy	Surgery	
Fifth	Interval			41 months					48 months		
	Site			Tongue					Neck		
	Pathology			OSCC					OSCC		
	Treatment			Surgery					Surgery and radiotherapy		
Sixth	Interval			50 months							
	Site			Gingiva							
	Pathology			OLK and OSCC							
	Treatment			Surgery							
Seventh	Interval			62 months							
	Site			Tongue							
	Pathology			OLK							
	Treatment			Laser							
Eighth	Interval			86 months							
	Site			Tongue							
	Pathology			OLK and OSCC							
	Treatment			Surgery							
Ninth	Interval			110 months							
	Site			Tongue							
	Pathology			OLK and OSCC							
	Treatment			Surgery							
Tenth	Interval			119 months							
	Site			Tongue							
	Pathology			OSCC							
	Treatment			Surgery							
Retrospective diagnosis		Primary OSCC	MT of OLK	MT of PVL, MPC	MT of OLK	MT of OLK	MT of OLK	MT of OLK, MPC	MT of PVL	MT of OLK, MPC	MT of OLK, MPC
Comorbidities		Hypertension, diabetes mellitus	No	Uterine fibroids, high cholesterol, chronic gastritis	No	Diabetes mellitus, bronchiectasis, iron deficiency anemia	No	Hypertension, atrial fibrillation, varicose veins	No	Diabetes mellitus	No
Family history		No	No	Father with rectal cancer, mother with breast cancer	No	Mother with breast cancer and bladder Cancer	No	No	No	No	No

Notes: Interval: the interval time between each diagnosis and the first diagnosis. OLP: oral lichen planus, OLK: oral leukoplakia, PVL: proliferative verrucous leukoplakia, MT: malignant transformation, OSCC: oral squamous cell carcinoma, MPC: multiple primary cancer.

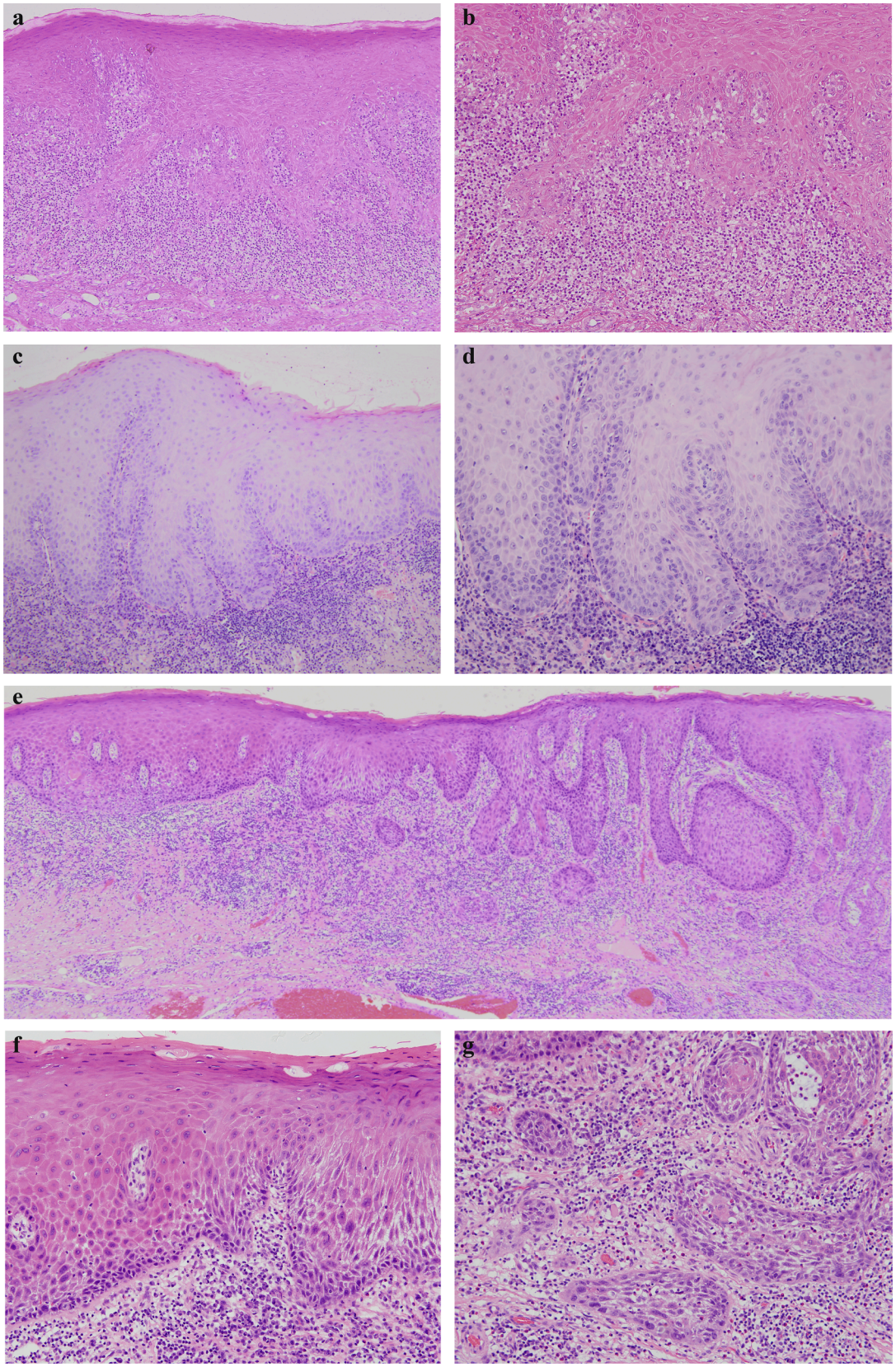

Fig. 1. The hematoxylin and eosin staining showed different pathological features in the course of P2. a (100×) and b (200×): oral lichen planus with liquefaction degeneration of basal cells layer and a zone of lymphocytic infiltration in connective tissue. c (100×) and d (200×): oral leukoplakia with mild epithelial dysplasia after 63 months, without liquefaction degeneration of basal cells layer. e (40×), f (100×), and g (200×): malignant transformation of oral leukoplakia with epithelial dysplasia transforming into invasive carcinoma after 87 months, without liquefaction degeneration of basal cells layer.

years old, with a median age of 61.5 years old. The interval between OLP and OSCC ranged from 5 to 115 months, with a median interval of 4.5 years.

The OSCC cohort has experienced a long course with follow-up, and we could retrospectively review the records of the disease development as presented in Table 1. From the biological process, the cancer did not appear to be derived from the malignant transformation of OLP. Specifically, three cases of OSCC (P1, P6, and P10) were derived from a primary cancer at another site without OLP. Two cases of OSCC (P3 and P8) derived from malignant transformation of proliferative verrucous leukoplakia (PVL) with multiple sites of leukoplakia and cancer. The remaining five cases of OSCC were derived from the malignant transformation of oral leukoplakia (OLK), and one case (P2) among them was recorded by biopsy before OSCC. Fig. 1 showed the pathological features in the course of patient 2 (P2). Figure 1a and b showed the first diagnosis of OLP with liquefaction degeneration of basal cells layer and a zone of lymphocytic infiltration in connective tissue. Figure 1c and d shows the diagnosis of OLK with mild epithelial dysplasia after 63 months, without liquefaction degeneration of basal cells layer. Figure 1e-g showed malignant transformation of OLK into OSCC with epithelial dysplasia transforming into invasive carcinoma after 87 months, without liquefaction degeneration of basal cells layer. The others were observed with OLK concomitant with OSCC, indicating that OLK occurred after OLP (P4, P5, P7, and P9), and persisted in the subsequent course of disease. There were no cases diagnosed with malignant transformation of OLP in the retrospective study. Moreover, four cases of OSCC were diagnosed with multiple primary cancers (P3, P7, P9, and P10).

Discussion

In this retrospective study of a large-scale OLP cohort, no cases of cancer were found deriving from OLP. Except for one primary OSCC from a site without OLP, dysplasia was observed in the remaining nine cases, reflecting the association of dysplasia in the malignant transformation of OPMD. Comparative studies of OLP cohorts with/without malignant transformation showed that dysplasia increases the risk of transformation [6,18]. The rate of malignant transformation decreased when cases of OLP concomitant with dysplasia were excluded [7–9,13]. Patients with OLP might develop OLK with dysplasia during disease course, and then transformed into OSCC [19–21]. Also, some cases of PVL at an early stage could be misdiagnosed as OLP [22–24]. Combining these studies and our retrospective cohort, we summarized three factors that may lead to overestimation of the risk of transformation in OLP: I. OLP concomitant with dysplasia, II. neglect of OLK with dysplasia developed years after OLP, III. misdiagnosis in the early stage of PVL. Therefore, long-term surveillance of the biological course after occurrence of OLP was necessary. In our opinion, if there were epithelial dysplasia concomitant with some similar pathological features of lichen planus in oral mucosa, it should be diagnosed as epithelial dysplasia instead of OLP, which is in line with the WHO criteria [17]. Pathologists should cooperate with clinicians when diagnosing OLP, with full compliance with the clinical and histopathological criteria, conduct strict follow-up and differential diagnosis, exclude OLK and PVL in the disease course, and do not use so-called lichenoid dysplasia.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Not applicable.

Author contributions

Tiejun Li, Heyu Zhang, and Xinjia Cai: Contributed to conception, design, data acquisition and interpretation, drafted and critically revised the manuscript. Jianyun Zhang: Contributed to conception, design, data acquisition and interpretation.

Funding

This work was supported by research grants from the National Nature Science Foundation of China (81671006, 81300894), CAMS Innovation Fund for Medical Sciences (2019-I2M-5-038) and Innovation Fund for Outstanding Doctoral Candidates of Peking University Health Science Center (BMU2022BSS001).

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