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Malignant transformation of oral leukoplakia and oral lichen planus: a retrospective cohort study of 293 Ukrainian patients

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Abstract

Background: The five-year survival rate of early stage (I and II) oral squamous cell carcinoma might be about 80%, but of advanced stage (III and IV) oral squamous cell carcinoma is only approximately 20%. Because most cases of oral squamous cell carcinoma are preceded by clinically evident oral potentially malignant disorders, it is important to prevent malignant change for those patients diagnosed with oral potentially malignant disorders. *Purpose*: to estimate the malignant transformation rate of a retrospective cohort of 293 patients with oral leukoplakia (OL) and oral lichen planus (OLP) (mean follow-up of 4,5 years) and identify significant risk factors of malignant transformation in Ukraine. *Materials and Methods*: All archived files of patients with the clinical and pathologic diagnosis of OL and OLP from 2011 to 2015 were retrospectively reviewed in Oncology Hospital in Zhitomir and Chernigov. All clinical history and follow-up data were obtained from the archived files. Information regarding gender, age, site of lesions at the time of the initial diagnosis of OL and OLP was all documented in detail. *Results*: Two important parameters should be considered when evaluating the potential for malignant transformation of OPMDs. First, the initial OPMD lesions should be confirmed using histopathological diagnoses; second, the amount of time it takes for the lesion to be transformed into a malignancy at the same location as the original OPMD lesion. *Conclusions*: In the current study, we analyzed and updated the data of malignant transformation of various OPMDs in a cohort of patients from Ukraine. Moreover, our data indicated that patients with OPMDs need a long-term clinical follow-up and histopathological examination is an important predictor of cancer development to monitor the possibility of malignant transformation.

Keywords: Oral squamous cell carcinoma, oral leukoplakia, oral lichen planus, risk factors, malignant transformation.

Introduction

Oral squamous cell carcinoma (OSCC) is widely recognized as the most common type of head and neck cancer, with a ~50% survival rate over 5 years despite various treatments in the past three decades [1, 2].

The five-year survival rate of early stage (I and II) OSCC might be about 80%, but of advanced stage (III and IV) OSCC is only approximately 20% [5]. Because most cases of OSCC are preceded by clinically evident oral potentially malignant disorders (OPMDs), it is important to prevent malignant change for those patients diagnosed with OPMDs [6].

In our review of the literature, we found only a few studies that focused on the malignant transformation potentials of various OPMDs. Hsue et al. [7] found that the malignant transformation rates of a cohort of 1458 patients with OPMDs were 5.4% for epithelial dysplasia with oral submucous fibrosis, 4.65% for epithelial dysplasia with hyperkeratosis/epithelial hyperplasia, 3.55% for hyperkeratosis/epithelial hyperplasia, 3.09% for verrucous hyperplasia, 2.1% for lichen planus, and 1.9% for oral submucous fibrosis; the overall malignant transformation rate was 3.02% and the average time for transformation was 42.64 months. In contrast, another study [8] reported that the malignant transformation rates of OPMDs in southern Taiwan were 24.24% for oral epithelial dysplasia, 20.00% for verrucous hyperplasia, 8.57% for hyperkeratosis/epithelial hyperplasia, and 0.00% for oral submucous fibrosis.

The objective of the present study is to estimate the malignant transformation rate of a retrospective cohort of 293 patients with oral leukoplakia (OL) and oral lichen planus (OLP) (mean follow-up of 4,5 years) and identify significant risk factors of malignant transformation in Ukraine.

Methods

All archived files of patients with the clinical and pathologic diagnosis of OL and OLP from 2011 to 2015 were retrospectively reviewed in Oncology Hospital in Zhitomir and Chernigov. All clinical history and follow-up data were obtained from the archived files. Information regarding gender, age, site of lesions at the time of the initial diagnosis of OL was all documented in detail. Diet habit, history of smoking and ethanol intake were also collated through the files. According to the definition of OL and OLP.

I. Any patient without the initial histopathologic examination of OL and OLP and development of OSCC during a follow-up period by biopsy or surgery.

II. Any patient with the clinical history and histopathologic changes of oral white or predominantly white oral benign diseases, for example OL and OLP.

III. Any patient with diagnosis of OL and OLP concomitant OSCC at the first visit.

IV. Any patient with a follow-up period of less than 12 months.

Based on these criteria, 293 patients with OL and OLP were selected to be retrospectively reviewed in the cohort. This study was approved by the institutional review board of Oncology Hospital in Zhitomir and Chernigov.

The duration required for malignant transformation is defined as the time from the initial biopsy of the OPMD to the additional biopsy that confirmed the diagnosis of oral cancer. Two criteria had to be met to confirm the actual malignant transformation to oral cancer: (1) a malignant transformation lesion had to occur at the same anatomical site as the precancerous lesion, and (2) a minimum of six months was required between the initial biopsy and the additional biopsy to confirm the malignant transformation.

JMP version 9.0.1 for Windows (SAS Institute, Cary, NC, USA) was used for all differences in the distribution of related factors in OPMDs and in the group with malignancies was estimated using a chi-square test. Time-to-event analysis involved estimating the probability that an event will occur at different points in time. The end point of follow-up in those developing cancer was the date of detection of oral malignancy, and in those lost to follow up were coded by the date of last visit, to arrive at "censored" data. Kaplan-Meier estimate was computed to estimate the probability of cancer-free survival. Cox proportional hazards model was applied to analyze the

effect of single and multiple covariates in predicting cancer development. The results were considered significance when the p-value was < 0.05.

Results

In the current study, 1159 patients were diagnosed with various OPMDs (749 males and 410 females). Additionally, a majority of these OPMD lesions were in the buccal mucosa (60.51%), followed by the gingiva (13.65%), and the tongue (12.46%) (Table 1). Most of these 1159 patients presenting various OPMDs were males with the majority had the oral risk factors (alcohol drinking, betel-quid chewing, and cigarette smoking) (Table 2).

Table 1

Location of the 293 potentially malignant oral mucosal disorders in the current study

Histological diagnosis	Upper lip	Lower lip	Buccal	Mouth floor	Hard palate	Soft palate	Gingiva	Tongue	Total
OL	0 (0.00)	19 (7.31)	189 (72.69)	4 (1.54)	0 (0.00)	4 (1.54)	18 (6.92)	26 (10.0)	260 (100.00)
OLP	1 (3.03)	2 (6.06)	24 (72.73)	1 (3.03)	1 (3.03)	0 (0.00)	1 (3.03)	3 (9.09)	33 (100.00)
Total	1 (0.34)	21 (7.16)	213 (72.70)	5 (1.71)	1 (0.34)	4 (1.37)	19 (6.48)	29 (9.90)	293(100.00)

Data are N (%).

Table 2

Age, gender and oral risk factors of the 293 potentially malignant oral mucosal disorders in the current study

		Age	Gender		Alcohol drinking		Betel-quid chewing		Cigarette smoking	
	N	Mean ± Standard deviation	Male N (%)	Female N (%)	Yes N (%)	No N (%)	Yes N (%)	No N (%)	Yes N (%)	No N (%)
OL	260	47.74 ± 11.84	247 (95.0)	13 (5.0)	197 (75.77)	63 (24.23)	28 (10.77)	232 (89.23)	229 (88.08)	31 (11.92)
OLP	33	51.08 ± 13.22	13 (39.39)	20 (60.61)	24 (72.73)	9 (27.27)	3 (9.09)	30 (90.91)	29 (87.88)	4 (12.12)

Data are N (%).

Two hundred ninety three patients (260 males, 33 females) underwent malignant transformation to oral cancers. The overall transformation rate was 25.28% and the mean duration of transformation was 18.56 months (Table 3). Two hundred sixty (22.54%) of the 1159 patients with oral leukoplakia developed oral cancers. However, only 33 (2.73%) of the 1159 patients with lichen planus developed oral cancer) (Table 3).

Table 3

Number, percentage and mean duration of the malignant transformation for the 219 potentially malignant oral epithelial lesions with different histological diagnoses

Histological diagnosis	Malignant transformation	Mean duration of malignant transformation
	N (%)	(months)
OL	260/1159 (22.54)	17.86
OLP	33/1159 (2.73)	8.07
Overall	293/1159 (25.28)	18.56

The most common sites for these 157 malignant transformation cases were the buccal mucosa (53.43%), the tongue 52-- (17.81%), and the gingiva 39 (13.24%). Of the 45 cases on the tongue, the predominant sites were the tongue border (n = 22), the tongue ventrum (n = 9), and the tongue dorsum (n =14).

Cox regression analysis of risk factors for OL and OLP malignant transformation

An analysis of risk factors of the transformation of OL and OLP into cancer was performed by the cox proportional hazards model (Table 4). In the cox regression analysis, age, gender, lesion site, diet habit, smoking and ethanol intake were not found to be significantly associated with the malignant development. The risk of malignant transformation of OL and OLP located at tongue may be higher than at other sites (HR = 1.97, 95% CI, 0.99-3.93; P = 0.053). Importantly, the degree of dysplasia was an independent risk factor associated with malignant transformation. The high-risk dysplastic lesions were associated with 4.57-fold (95% CI, 2.36-8.84; P < 0.001) increased the risk of malignant transformation, when compared to the low-risk dysplastic lesions. Table 4.

Cox regression analysis of risk factors for OL and OLP transformation

Characteristic	Hazard Ratio (95%CI)	P-value
Age, y		
< 60	1.00	
>= 60	1.87 (0.92-3.80)	0.086
Gender		
Female	1.00	
Male	0.56 (0.29-1.08)	0.084
Site		
Other sites	1.00	
Tongue	1.97 (0.99-3.93)	0.053
Diet habit		

Characteristic	Hazard Ratio (95%CI)	P-value
Bland	1.00	
Spicy	0.41 (0.10-1.70)	0.217
Smoking		
Never	1.00	
Past and present	0.60 (0.26-1.36)	0.222
Ethanol intake		
Never	1.00	
Past and present	1.19 (0.42-3.37)	0.075
Epithelial dysplasia		
Low-risk	1.00	
High-risk	4.57 (2.36-8.84)	< 0.001

Discussion

Two important parameters should be considered when evaluating the potential for malignant transformation of OPMDs. First, the initial OPMD lesions should be confirmed using histopathological diagnoses; second, the amount of time it takes for the lesion to be transformed into a malignancy at the same location as the original OPMD lesion. In the present study, we included a wide spectrum of histopathologically diagnosed OPMDs and specified that the time from the initial presentation of the precancerous lesion to the malignant transformation must be at least six months and that the transformation must occur at the same site as the initial biopsy. We found that the overall malignant transformation rate of the OPMDs in our cohort was approximately 22.2%, which was higher than that of other studies [11-14] on the malignant transformation of precancerous lesions of leukoplakia. The reason for this difference may be that our study was based on the histopathological diagnoses of different kinds of precancerous oral lesions.

Oral lichen planus is an inflammatory mucocutaneous condition; its etiological factors are not yet completely certain [21]. It tends to occur in the buccal mucosa of 40-50-year-old women (female:male ratio = 2:1), [22]. In our study, women (average age at onset: 51.08 years) accounted for 60.89% of the cases of oral lichen planus, and 73.22% were in the buccal mucosa. The World Health Organization (WHO) recognizes oral lichen planus as an OPMD [6]. In the present study, the mean time needed for oral lichen planus to malignantly transform was 18.07 months.

We found that the average duration of malignant transformation was 18.56 months, shorter than in other studies [7,8]. Most of the OPMDs in our cohort were in the buccal mucosa (60.15%), the gingiva (13.65%), and the tongue (12.46%). Most of the 293 OPMDs with a malignant transformation in our cohort were in the buccal mucosa (53.43%), the tongue (17.81%), and gingiva (13.24%). However, we found that OPMDs in the tongue had a higher malignant transformation potential than those in the buccal mucosa (HRR = 1.83),.

In our series, according to the WHO criteria, we considered the time elapsed from the initial diagnosis of OL and OLP to the development of cancer. In this context, we excluded patients with diagnosis of OL and OLP concomitant OSCC at the first visit or patients with a followed-up

period of less than 12 months after the initial diagnosis of OL and OLP. Our recorded annual malignant rate of 22.2% is higher than the rate documented in the literature (0.69%-2.03%) [9, 10, 11]. Herein, various treatments on the OL and OLP patients were not considered because few prevention studies have shown effectiveness in preventing the transformation of OL and OLP to cancer [18].

We observed the average age at diagnosis of OL and OLP is 52.7 years, while other study populations had an average age closer to 60 years [16, 20]. The peak incidence of OL and OLP was in the fifth decade of life in our study, earlier than the sixth decade in other reports [20, 23]. The predominant sites of lesions are the tongue and buccal mucosa, and few lesions were located on the floor of mouth, whereas the tongue and floor of mouth were reported as the most common sites in Western countries [6, 16, 20]. These were probably due to the ethnic population and geographic difference in our cohorts compared to previous reports. Nevertheless, these factors were not related to malignant transformation of OL and OLP in our series. Moreover, It may be generally accepted that smoking and ethanol intake play significant roles in the development of OL and OLP, but the roles of those in the malignant transformation of OL and OLP is conflicting and yet unclear. The studies by Silverman et al [16] and Schepman et al [20] demonstrated an increased risk of malignant transformation in the non-smoking cohort, while the study by Ho et al [14] and our present study found smoking was not a significant factor in transformation risk. Ethanol intake was also not a risk factor for malignant transformation of OL and OLP [14, 15]. Further prospective cohort studies are needed to investigate the roles of lifestyle habits in the malignant process of OL and OLP.

Conclusion

In the current study, we analyzed and updated the data of malignant transformation of various OPMDs in a cohort of patients from Ukraine. Moreover, our data indicated that patients with OPMDs need a long-term clinical follow-up and histopathological examination is an important predictor of cancer development to monitor the possibility of malignant transformation.

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