

The Frequency and Malignant Transformation Rate of Oral Lichen Planus and Leukoplakia – A Retrospective Study

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ABSTRACT

The aim of this retrospective study was to determine the frequency and malignant transformation rate of oral lichen planus and leukoplakia in a large group of oral medicine patients. Study included 12 508 patients who were referred between 1998 and 2007 to the Department of Oral Medicine. The frequency of OLP was 4.30%, leukoplakia 1.11%, and combined diagnoses 0.14%. In primary biopsies dysplasia was found in 12.96% of patients with leukoplakia and not in one with OLP and combined lesions. The highest frequency of leukoplakia was found in smokers. Women were found as predominant sufferers of both diseases and their combination. During the observed period of ten years malignant transformation of OLP was not detected, unlike leukoplakia where it was 0.64%. The frequency of OLP and leukoplakia in our study are comparable to other similar studies. The highest frequency of malignant transformation was observed in those patients who did not respond to our invitation to regular check-up. It is therefore necessary to perform a detailed examination of the oral cavity in these patients and to raise patients awareness of the disease and the importance of regular follow-up.

Key words: study, retrospective, lichen planus, oral, leukoplakia

Introduction

Oral lichen planus (OLP) and leukoplakia (LPL) are considered as premalignant lesions. Oral lichen planus (OLP) is a relatively common mucocutaneous disease with varying prevalences (0.5–2.2%) in general population¹. Etiopathogenesis of OLP seems to be complex. Current data suggest that it is a T cell-mediated autoimmune disease in which auto-cytotoxic CD8+ T cells induce apoptosis of oral epithelial cells². Currently accepted patohistological criteria for oral lichen planus, cutaneous lichen planus and oral lichenoid lesion are those given by WHO^{3,4}.

Patients with OLP may also develop extraoral manifestations in one or more sites, such as cutaneous lesions in 15% of patients with oral lichen planus, genital lesions in 20% of women with oral lichen planus⁵ and, uncom-

monly, lesions in ocular, bladder, nasal, laryngeal, otic, gastric and anal structures (plurimucous lichen planus)². Therefore multidisciplinary approach is required to discover these sites. Oral lesions of lichen planus usually have characteristic clinical morphology and distribution, but it is not always the case, and other disorders may also clinically simulate OLP, such as lichenoid lesions, discoid lupus, leukoplakia and graft *versus* host disease (GVHD). Some studies have shown that risk of malignant transformation is independent of the clinical type of OLP^{2,6}, whereas other deny this assumption and suggest that the risk is the highest in erosive forms⁷. However, malignant potential of OLP is still controversial^{7–9}, reported from 0–5.3%³.

A global prevalence of LPL has been reported of 2.60%, with a high degree of heterogeneity¹⁰ and varying malignant transformation rate from 0.13–17.5%¹¹. A definitive clinical diagnosis of oral leukoplakia is made as a result of the identification, and if possible elimination, of suspected aetiological factors and, in case of persistent lesions (no signs of regression within 2–4 weeks), histopathological examination¹².

Since oral and pharyngeal carcinoma is the sixth most common cancer in the world and seventh in frequency among the most common cancers overall in EU¹³, determination of the frequency of premalignant lesions in general population is of particular clinical importance for early detection and prevention of oral cancer. As for the population of our oral medicine patients these data are not investigated by now, the aim of this study was to determine the frequency of oral lichen planus, leukoplakia and their combination in the population of oral medicine patients as well as to examine the frequency of malignant transformation of these lesions.

Subjects and Methods

Retrospective data were taken handsearching the medical records of total 12 508 patients attending Department of Oral Medicine, School of Dental Medicine, University of Zagreb between January 1st 1998 and December 31st 2007. This is the largest database of oral medicine clinics in Croatia where the largest number of patients are referred. Medical history and clinical examination data were taken from medical records from all patients for the observed period of ten years. The incidence of oral lichen planus and leukoplakia was recorded based on the verified diagnosis, which was set according to established clinical and/or histopathological criteria^{3,4,12}.

Statistical analysis was done by use of MedCalc version 9.2.0.1 statistical software (MedCalc Software, Mariakerke, Belgium). Descriptive statistics was employed to describe characteristics and measured variables, presented in tables. On comparison of distribution of category variables according to groups, χ^2 -test was used. The level of statistical significance was set at $p < 0.05$.

Results

Table 1 shows distribution of patients with OLP, LPL and combined lesions regarding gender. Women were found as predominant sufferers of both diseases and combined lesions with a statistically significant difference ($p < 0.05$). The mean age of patients with OLP was 52 ± 15 years, age range 19–91 (median 54.0). The mean age of patients with LPL was 49 ± 17 years, age range 22–70 (median 41.1), and in patients with OLP and LPL the mean age was 55 ± 13 years, age range 32–65 (median 48.0).

Table 2 shows distribution of patients with OLP, LPL and their combination regarding smoking habits. Most of our patients with OLP were non-smokers (77%) unlike

TABLE 1
THE DISTRIBUTION OF PATIENTS WITH OLP, LPL AND COMBINED LESIONS REGARDING GENDER

	OLP (N, percentage)	LPL (N, percentage)	OLP+LPL
Females	379 (71%)	79 (57%)	11 (61%)
Males	158 (29%)	60 (43%)	7 (39%)
Total	537 (100%)	139 (100%)	18 (100%)

$\chi^2 = 9.871$; $df = 2$; p -value < 0.05

TABLE 2
THE DISTRIBUTION OF PATIENTS WITH OLP, LPL AND COMBINED LESIONS REGARDING SMOKING HABITS

	OLP (N, percentage)	LPL (N, percentage)	OLP+LPL
Smokers	96 (18%)	65 (47%)	3 (17%)
Non-smokers	413 (77%)	53 (38%)	12 (66%)
Unknown data	28 (5%)	21 (15%)	3 (17%)
Total	537 (100%)	139 (100%)	18 (100%)

$\chi^2 = 79.989$; $df = 4$; p -value < 0.0001

TABLE 3
TYPE OF ORAL LICHEN PLANUS LESIONS IN OUR PATIENTS

Type of lesions	Patients (N, percentage)
Reticular	351 (65.36%)
Atrophic-erythematous	72 (13.41%)
Ulcerative-erosive	67 (12.47%)
Plaque	30 (5.58%)
Papular	17 (3.16%)
Bullous	0
Other	0

leukoplakia where almost half of the patients were smokers (47%) and the difference is statistically significant ($p < 0.0001$).

According to the clinical and/or histopathological criteria most of the patients with OLP had a distinctive reticular type of lichen (351 out of 537, 65.36%; Table 3). Biopsies were taken in 223 cases of OLP (41.52%), 54 leukoplakias (38.8%) and 11 out of 18 combined lesions (61.1%) and the diagnoses were histopathologically proven. Clinical types of leukoplakia are shown in Table 4. A biopsy was always performed in non-homogeneous leukoplakias and in some homogeneous.

In primary biopsies dysplasia was found in 12,96% of patients with LPL and not in one with OLP and combined lesions. During the follow-up period three patients with OLP showed dysplasia but none of these lesions transformed to carcinoma. During completion of this manuscript two patients occurred with OLP at buccal mucosa and vestibular mucosa respectively diagnosed as

squamous cell carcinoma. One of them was a female, which has already been a patient of the Department, and was included in this study, but has not come to a recall appointment for more than ten years. At first examination years ago lesions of lichen planus were located on the dorsum of the tongue, gingiva, alveolar ridge and buccal mucosa and on her primary biopsy dysplasia was not found. The last control examination showed lesions of lichen and squamous cell carcinoma on upper right alveolar ridge mucosa which was histopathologically proven.

The other patient was a new OLP patient, a male 60 years of age, whose lesions were diagnosed as squamous cell carcinoma at the first appointment. He had a history of cutaneous lichen planus from adolescent age and treated only by a dermatologist. Since his oral lesions of OLP were asymptomatic, he did not seek further professional help.

The highest frequency of leukoplakia was found in smokers and two thirds (66.66%) of patients with dysplastic leukoplakias were smokers. Neither one of verified dysplastic LPL were candidal leukoplakia as confirmed by histopathology. Oral clinical examination was performed at least three times a year in a majority of our OLP and LPL patients, and those who did not come regularly for check-ups were invited with letter.

During the follow up period, control biopsies were performed in patients with erosive lichen and non-homogeneous and previously histopathologically proven dysplastic LPL. In patients with dysplasia biopsy was repeated every 6 months.

Three leukoplakias altered to severe dysplasia and one to squamous cell carcinoma in the period of four years.

At the moment of writing this article, in one of the patients from the observed period, leukoplakia with severe dysplasia progressed to squamous cell carcinoma during 15 months as the patient did not come up for regular check-up. The patient was a male smoker and leukoplakia was located in sublingual area and on edentulous lower alveolar ridge.

During the observed period of ten years malignant transformation rate of leukoplakia was 0.64%, but this rate is slightly higher considering described case.

Discussion

This retrospective study included all 12 508 patients who attended Department of Oral Medicine during 10 years, among which we wanted to find out the frequency of OLP and LPL and the malignant transformation rate in these lesions since these data are lacking. The study was prompted with our previous research performed on a small sample of subjects only with OLP¹⁴.

The total number of patients with established diagnoses of oral lichen planus, leukoplakia, and their combination 5.6%. Among these, 4.30% was diagnosed with oral lichen, 1.11% with leukoplakia and 0.14% with combined diseases.

In general, reports from the literature regarding frequency vary due to limitations in data collection methods and sampling methods. There are only few dental schools with whom we can compare our results which included selected population of oral medicine patients^{15–17}. OLP was observed in 4.30% of our patients, which is higher than frequency described in Southern India (1.26%)¹⁵. It is expected that prevalence data for Croatia would be lower and comparable with the prevalence data from other European countries-Germany (1%)¹⁸, Italy (1.46%)¹⁹ or Slovenia (2.3%)²⁰. We found that OLP is predominant in women, which is consistent with data from the literature^{2,3,7,8,15,20,21}. Our patients with OLP were mostly non-smokers (77%) which is in agreement with data from the literature indicating a negative correlation between OLP and smoking^{6,20}. Malignant transformation in OLP patients was not detected in the observed period and considering the female patient who came at the end of the study the rate would be 0.37%, which is in agreement with similar studies²². Although in our patients reticular type was predominant type of OLP (65.36%), it is known that different clinical types may coexist in the same patient and may change in time to another clinical type^{1,2}.

The frequency of leukoplakia observed in our study was 1.11%, which is lower than the frequency reported in Southern India (1.59%)¹⁵, Thailand (1.7%)¹⁶ and Germany (4.26%)¹⁷. It could be expected that these data on a national level would be lower, but they are still unknown so we can not compare them with epidemiologic studies and prevalence data from Turin (Northwest Italy) (1.15%)¹⁹, Hungary (1.3%)²³, Chile (1.7%)²¹, Slovenia (3.1%)²⁰, Southern Italy (13%)²⁴ or Western India (11.7%)²⁵.

Reported data of global prevalence of leukoplakia are very heterogeneous with no consistent geographic differences between the countries, irrespective of continents. Our data have shown that half of the patients with leukoplakia are smokers, and this number would probably be higher if medical records for all of our patients would be completely fulfilled regarding this information. Data from the literature emphasize that patients with leukoplakia are mostly smokers²³ or all are smokers^{15,20}, but according to this rule there is also an exception²¹.

Women were significantly more affected with OLP, LPL and their combination (Table 3) which is an interesting datum because leukoplakia is more often seen in men^{10,23,26}, which can be connected with tobacco consumption, although some studies have reported equal distribution among gender^{16,27,28}. The results of our study could be explained with the fact that most of our patients are women and leukoplakia is often an accidental finding after patients complaint about another symptom.

Reported malignant transformation rate of leukoplakia varies from 0.13–17.5%¹¹ and in our study it was 0.64%. Leukoplakia which progressed to squamous cell carcinoma was found in a woman patient, non-smoker, and was located in sublingual area.

This confirms data from previous studies that malignant transformation is more likely to develop in female patients and non-smokers²⁶. Given the localization of leukoplakia, data from the literature are inconsistent. Some studies emphasize that malignancy is more likely to develop on the tongue, floor of mouth, gingiva and retromolar or soft palate complex^{29,30}, whereas other deny that and say that the risk is independent of localization^{12,21}.

In concordance with previous reports our results also confirm that »predictors« of malignant transformation, such as presence of dysplasia, localization, type of lesion, age and gender²⁶ do not obligatory determine the malignant outcome. Follow-ups and clinical examinations are mandatory for early diagnosis and to prevent disease progression. A biopsy should be performed in patients with oral lichen and leukoplakia taking into consideration clinical picture and economical reasons²². When there is evidence of changes in clinical appearance, the follow-up period should be shortened and additional biopsy should be performed³.

Above-mentioned examples of patients who developed squamous cell carcinoma accentuate the importance of regular, long-term follow-ups entailing complete data about possible risk factors for the development of oral carcinoma, including tobacco and alcohol consumption. The clinician has a very important role because although the importance of regular follow up (2–4 times per year) is emphasized for early detection of malignant change, often it is economically unsustainable²².

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Conclusion

Our study comprised the highest number of examined oral medicine patients in our population and regarding this the frequency of OLP and leukoplakia can be comparable to other similar studies. Among potentially premalignant lesions, the most frequent lesion was OLP, followed by leukoplakia. None of OLP patients and only a small percent of leukoplakias (0.64%) during the observed period of ten years progressed to squamous cell carcinoma. The most frequent type of OLP was reticular type, followed by atrophic-erosive type.

Most of the leukoplakias were homogeneous leukoplakias. The highest frequency of leukoplakia was found in smokers. Among patients with dysplastic leukoplakias two thirds were smokers. Our results have shown that the highest frequency of malignant transformation was observed in those patients who did not respond to regular follow-up. Therefore, it is important to raise patients conscience about the significance of the disease per se and the necessity of regular follow-up. We suggest that acute inflammatory lesions with erosive or atrophic mucosa should be followed-up monthly, until remission; keratotic OLP and homogeneous LPL lesions should be monitored at least once a year and non-homogeneous lesions should be monitored every 6 months.

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UČESTALOST I STOPA ZLOČUDNE PREOBRAZBE ORALNOG LIHENA PLANUSA I LEUKOPLAKIJE – RETROSPEKTIVNA STUDIJA

S A Ž E T A K

Cilj ovog retrospektivnog istraživanja bio je utvrditi učestalost i zloćudne preobrazbe oralnoga lihena planusa i leukoplakije u velikoj grupi oralno-medicinskih bolesnika. Istraživanje je uključilo je 12 508 pacijenata koji su upućeni na Zavod za oralnu medicinu između 1998. i 2007. godine. Učestalost oralnoga lihena planusa bila je 4,30%, leukoplakije 1,11% i kombiniranih lezija 0,14%. Na primarnoj biopsiji displazija je nađena u 12,96% pacijenata s leukoplakijom i u nijednog pacijenta s oralnim lihenom i kombiniranim lezijama. Najveća učestalost leukoplakije nađena je u pušača. Žene su dominantno zahvaćene objema bolestima i njihovom kombinacijom. Tijekom promatranog razdoblja od deset godina zloćudna preobrazba OLP-a nije otkrivena, za razliku od leukoplakije gdje je bila 0,64%. Učestalost OLP-a i leukoplakije u našem istraživanju usporediva je s drugim sličnim istraživanjima. Zloćudna preobrazba bila je najučestalija u onih pacijenata koji se nisu odazvali na poziv za redoviti kontrolni pregled. Stoga je uz detaljan oralni pregled potrebno podići razinu svijesti pacijenata o značaju bolesti i nužnosti redovite kontrole.