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ORIGINAL ARTICLE

High percentage of oral lichen planus and lichenoid lesion in oral squamous cell carcinomas

Hellevi M. A. Ruokonen[a,b], Aino Juurikivi[a,b], Timo Kauppila[b,c], Anna Maria Heikkinen[a,b] and Riitta Seppänen-Kaijansinkko[a,b]

[a]Department of Oral and Maxillofacial Diseases and Surgery, Head and Neck Center, Helsinki University Hospital, Helsinki, Finland; [b]Department of Oral and Maxillofacial Diseases, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; [c]Department of General Practice and Primary Healthcare, Institute of Clinical Medicine, Helsinki, Finland

ABSTRACT

Objective: Oral lichen planus (OLP) and lichenoid lesions (OLL) are regarded as precursor lesions of oral squamous cell carcinoma (OSCC) with potential for malignant transformation. This potential is not clear due to difficulties in diagnosis of OLP and OLL. Our aim was therefore to evaluate previously identified OLP and OLL as precursor lesions in OSCC and to identify cancer related etiological factors such as smoking and alcohol consumption.

Material and methods: We retrospectively reviewed all cases (total 323, comprising 164 females and 159 males) with OSCC treated at the Department of Oral and Maxillofacial Diseases and Surgery, Helsinki University Hospital during 2015. Confirmed by histopathological biopsy, 58 (17.9%) had OLP and 13 had OLL (4.0%) as precursor lesion.

Results: Patients with OLP were slightly older than those without it. OLP was more common in females than in males ($p < .0001$). TN class 1 tumors were more prevalent among patients with OLP or OLL ($p = .006$) and cancer relapses less common ($p = .005$). Smoking was less frequent in patients with OLP and OLL ($p < .0001$). Also alcohol abuse was less frequent among these patients ($p < .001$).

Conclusion: Our findings confirm the importance of active follow-up of all patients with OLP and OLL even in patients who do not fit a traditional high-risk category for OSCC.

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Introduction

Oral squamous cell cancer (OSCC) is a severe and increasingly growing global problem. OSCC and oropharyngeal cancer together are the sixth most common cancers in the world [1]. In Finland, the age-standardized incidence rate of OSCC was 3.0 for men and 1.9 for women during the period 2009–2013. OSCC accounts for 0.9% of all cancers in men and for 0.8% in women [2]. Globally, the 5-year survival rates for OSCC and oropharyngeal cancers are 50%. Lip cancer has the highest survival rate, with 90% of patients alive 5 years after diagnosis [1]. In Finland, the 5-year survival rate for OSCC is 59% for men and 70% for women [2].

Major etiological factors of OSCC are alcohol consumption and smoking [3,4]. Alcohol use and smoking have a potent interactive effect on the risk of OSCC [5]. The frequency, duration and lifetime cumulative consumption of tobacco and alcohol also increase the risk of OSCC [6]. Other risk factors are snuff use [7], diet [6] and poor oral hygiene [3,4]. Oral HPV infection has also been shown to increase the risk of OSCC [8].

Potentially malignant oral disorders are mucosal conditions that have a risk of malignant transformation to OSCC. Oral lichen planus (OLP) and lichenoid lesions (OLL) are considered such lesions [9]. Lichen planus is the most common premalignant oral mucosal condition with a prevalence of ~0.5–4%. It is a chronic inflammatory mucocutaneous disease that usually affects the mucosa and skin [10]. The diagnosis is based on both clinical examination and biopsy [11]. Most cases of OLP occur at age 30–60 years, being more frequently seen in women [12] mainly affecting the oral mucosa, gingiva and lips [11]. Lesions are usually found symmetrically on the buccal gingiva and tongue [11]. OLP can present itself in six different forms: reticular, papular, plaque-like, atrophic, erosive and bullous [10]. Atrophic, erosive and bullous forms can cause significant symptoms and usually require topical or systemic corticosteroid treatment or other immunosuppressive medication such as tacrolimus [10,11]. Symptomatic forms of OLP are also precancerous [13]. The risk of malignant transformation of OLP is ~0.9–3.2% [14–18] and with slight predominance of female patients [18]. The accurate diagnosis of OLP can be challenging. The clinical and histopathological features are variable and depend on the disease activity at the time of diagnosis assessment [19].

OLL bear clinical and histopathologic resemblance to OLP, and often cannot be distinguished from OLP [12]. Antihypertensive drugs or non-steroidal anti-inflammatory drugs and dental restorative materials, most commonly amalgam, can cause OLL [11,12].

CONTACT Hellevi Ruokonen hellevi.ruokonen@hus.fi Department of Oral and Maxillofacial Diseases and Surgery, Kasarmikatu 11-13, P.O. Box 263, FI-00029 HUS, Helsinki, Finland

OLP and OLL are difficult to differentiate from each other clinically because they resemble each other [11,12]. Currently, there are no curative treatments for OLP or OLL, and treatment therefore focuses on alleviating the symptoms [9,13]. A full and permanent recovery from OLP is rare [15]. Based on the increased risk of malignant transformation, patients with OLP should be examined regularly and especially those with dysplastic changes in biopsy [20].

The aim of this study is to evaluate previously identified OLP and OLL as precursor lesions in OSCC and to investigate smoking and alcohol use as predisposing factors of OSCC patients referred to and treated at the Department of Oral and Maxillofacial Diseases and Surgery, Head and Neck Center, Helsinki University Hospital, during 2015. Considering the risk of OSCC, knowledge of the predisposing factors and their prevalence, annual controls and early diagnosis of lesions can improve the prognosis.

Material and methods

All 323 patients (164 females, 159 males) with OSCC treated and followed up at the Department of Oral and Maxillofacial Diseases and Surgery, Head and Neck Center, Helsinki University Hospital, Finland during 2015 were enrolled in this study. Out of them 58 (17.9%) had OLP, in follow-up biopsy specimens and 13 (4.0%) patients had OLL. The diagnosis of OLP, OLL and OSCC was based on histopathological examination by an experienced oral pathologist (Table 1).

OLP diagnosis was based on both clinical and histopathological criteria. Clinical criteria were presence of bilateral, symmetrical lesions with lacelike network of white lines. Erosive, atrophic, bullous and/or plaque-like lesions were found elsewhere in the oral mucosa in the presence of reticular white lesions. Histopathologically a well-defined band-like zone of cellular infiltration consisting mainly of lymphocytes was found in the superficial part of the lamina propria. In the basal cell layersigns of liquefaction degeneration could be seen and in the epithelium absence of dysplasia [21].

OLL diagnosis was used in cases where there was clinically typical OLP lesion but which was not histopathologically compatible with OLP, or histopathologically typical OLP but not clinically compatible with OLP; or when the lesion was clinically and histopathologically not compatible with OLP; i.e. in cases where both clinical and histopathological criteria for OLP were not fulfilled [21].

This retrospective study of medical records was approved by the Committee of the Helsinki and Uusimaa Hospital District (HUS/197/2016). It complies with the Declaration of Helsinki and has been registered in the Helsinki University Hospital database for clinical trials.

The patient characteristics studied were age, gender, general health, oral health, medication, smoking habits (current/former/non-smoker), alcohol use, all predisposing factors, and conditions, especially OLP and OLL. Other risk factors for carsinogenesis like HPV and Candida infection were also recorded.

Statistical analyses

The chi-squared test was used to find differences in the incidences of the parameters studied between lichen planus and lichenoid patients and non-lichen patients. A *t*-test was used to compare the ages of OLP and OLL, OLP/OLL and non-OLP/OLL patients (SigmaPlot 10.0, Systat INC, Point Richmond, CA).

Results

Of all 323 patients, 66 were diagnosed with OSCC in 2015 and 252 had been diagnosed earlier, hence they were followed up during 2015. The mean age of the patients was 67.6 years. Fifty eight of all 323 patients (17.9%) had OLP and 13 (4.0%) OLL as an etiologic factor before OSCC diagnosis (Table 1).

OLP was more commonly observed in females than in male OSCC patients ($p < .0001$). Patients with OLP and OLL were slightly older than those without it, although the difference was not statistically significant. TN class 1 carcinomas were more prevalent among patients with OLP and OLL ($p = .006$) and relapses less common ($p = .005$) than in patients without OLP or OLL. Current smoking was less frequent in patients with OLP and OLL than among patients without OLP or OLL ($p < .0001$). Also, use of alcohol was less frequent among these patients than among patients without OLP or OLL as precursor lesion ($p < .001$). *Candida albicans* cultures were only analyzed in the case of 65 patients and no statistical differences were observed between the groups in relation to their candida culture findings (Table 1).

Co-morbidities and systemic conditions like hepatitis C, HPV and diabetes and autoimmune diseases such as Sjögren's syndrome or thyroid disease were recorded from medical records. Rheumatoid arthritis ($p < .001$), Sjögren's syndrome ($p < .001$) and thyroid disease ($p = .020$) were more

Table 1. Distribution (numbers and percentages) of selected clinical characteristics in the OLP, OLL and all OSCC patients.

	OLP	OLL	None	*p* value[a]	OSCC (*N*=total)
Patients	58	13	252		323
Gender					
Male	15 (25.9%)	7 (54%)	137 (55%)	<.0001	159 (49%)
Female	43 (74.1%)	6 (46%)	115 (45%)		164 (51%)
Age (mean + SD)	72.1 (9.3)	67.2 (13.80)	66.60 (13.2)	.081	67.6 (12.8)
TNM classification[b]					
TN1	41 (73%)	11 (84%)	135 (55%)	**.006**	187 (59%)
TN2	7 (13%)	1 (8%)	43 (17%)	.466	51 (16%)
TN3	0 (0%)	1 (0%)	3 (1) %	.655	3 (1%)
TN4	8 (14%)	1 (8%)	66 (27%)	.054	75 (24%)
Classification not found	2	0	5		7
Relapses[c]	17 (34%)	1 (2%)	32 (64%)	**.005**	50 (100%)
Alcohol	13 (9%)	5 (4%)	122 (87%)	**.001**	140 (100%)
Smoker[d]	10 (7%)	7 (4%)	135 (89%)	**<.0001**	152 (100%)
Candida positive	10 (22%)	2 (5%)	33 (73%)	.712	45 (100%)
Generally healthy	11 (16%)	3 (4%)	54 (80%)	.902	68 (100%)
Thyroid disease	11 (37%)	1 (3%)	18 (60%)	.020	30 (100%)

TNM: classification of malignant tumors (T: tumor size, N: degree of spread to regional lymph nodes, M: distant metastasis).
[a]χ^2 test was used for statistical analysis, *p* value by Pearson chi-squared test.
[b]The percentages are calculated within columns.
[c]The percentages are calculated within *r*.
[d]Current smoker, former smokers are excluded.

Table 2. OSCC patients' comorbidities.

	OLP	OLL	No OLP or OLL	*p* value[a]
MACE	35 (60%)	6 (46%)	147 (58%)	.639
Diabetes (I, II)	12 (21%)	1 (8%)	41 (16%)	.483
Pemphigoid	1 (2%)	0 (0%)	1 (0.4%)	.488
Thyroid disease	11 (19%)	1 (8%)	18 (7%)	**.020**
HIV infection	0 (0%)	0 (0%)	2 (0.8%)	.753
Sjögren's syndrome	0 (0%)	1 (8%)	0 (0%)	**<.0001**
Rheumatoid arthritis	7 (12%)	1 (8%)	4 (2%)	**.001**
Other cancer	9 (16%)	3 (23%)	52 (21%)	.680

MACE: major adverse cardiac events; HIV: human immunodeficiency virus.
[a]χ^2 test was used for statistical analysis, *p* value by Pearson's chi-squared test.

Table 3. OSCC treatment in patients with OLP or OLL and without as a precursor lesion.

Treatment	OLP	OLL	No OLP or OLL	*p* value[a]
Radiation therapy	14 (24%)	3 (23%)	82 (33%)	.624
Chemo + radiation	0 (0%)	0 (0%)	15 (6%)	.351
Reconstruction	36 (62%)	6 (46%)	173 (69%)	.501

Chemo: chemotherapy.
[a]χ^2 test was used for statistical analysis, *p* value by Pearson's chi-squared test.

frequent in patients with OLP and OLL, although the numbers were low (Table 2). The treatment method for oral cancer did not differ between the patient groups (Table 3).

Discussion

OLP is generally regarded as a potentially malignant disorder [22]. It is a cell-mediated immune condition of unknown etiology. The clinical and histopathological features of OLP are variable and depend on the type of OLP, as well as disease activity at the time of diagnosis [19] and therefore the accurate diagnosis of OLP can be challenging. OLL resembles OLP but does not fulfill the clinical and histopathological criteria for lichen planus. Several medications or close location to amalgam restorations are considered etiological factors [23]. There is considerable controversy regarding the potentially malignant nature of both diseases in the literature [21,24,25]. We therefore examined all medical records of all patients with OSCC treated and followed up at the Department of Oral and Maxillofacial Diseases and Surgery, Head and Neck Center during 2015.

In this cross-sectional study 58 (17.9%) out of 323 patients with OSCC had OLP as an etiologic factor which is more than the reported 0.5–4% prevalence of OLP in general [10] . In previous studies, as in the present one, OLP was more common among women. As OLP causes symptoms, discomfort and even pain, symptomatic patients seek treatment earlier than patients without symptoms. This could explain why 73% of OLP and 84% of OLL patients had TN class 1, while 55% of non-OLP or OLL patients had TN class over 1.

Smoking and use of alcohol were less frequent among OLP and OLL patients, the difference being statistically highly significant ($p < .001$). Patients with OLP and OLL may have symptoms such as oral discomfort and pain, preventing them from smoking or consuming alcohol. However, this may reflect the different etiology of OSCC, which could partly explain the lower rates of alcohol use and smoking among these patients.

Autoimmune diseases, such as rheumatoid arthritis, can also be etiological factors. Medication used to treat rheumatoid arthritis, such as immunosuppressive and cytostatic drugs (e.g. methotrexate), can predispose the patient to mucosal changes and mucosal ulcerations. Mucosal changes can be caused by decreased saliva secretion, changes in oral microbial flora and dysfunction in oral defense mechanism [26,27]. In the present study, OLP and OLL patients suffered from rheumatoid arthritis more often than non-OLP or OLL patients. On the other hand, patients with OLP were slightly older than non-OLP/OLL patients as the risk of autoimmune diseases increases with age.

Thyroid diseases were also more prevalent among OLP patients. This is in accordance with the study by Siponen et al. 2010 [22] were in a population of Finnish patients with thyroid disease, and especially with hypothyroidism, were found to have a two-fold relative odds of having OLP/OLL as compared with subjects without thyroid disease. Hypothyroidism can cause hyposalivation, dysfunction in oral defense mechanism, periodontal problems and delayed wound healing [28]. These changes can predispose to mucosal changes and act as an etiologic factor.

In the present study, reappearance of OSCC was more prevalent among patients without OLP or OLL. Controlling and diagnosing OLP and OLL by biopsy as early as possible and careful monitoring of the patients can improve the prognosis. In most cases, patients with OLP and OLL were monitored decades before the malignant transformation occurred. Monitoring was annual in almost every case. As a topical medication, triamcinolone was mostly used, followed by topical tacrolimus and an ex tempore gel containing triamcinolone, chlorhexidine, mycostatin and lidocain. Half of the OLP and OLL patients did not require any medication.

The importance of controlling and examining OLP and OLL patients regularly is undeniable. By examining patients annually, the malignant transformation of lesions and cancer reappearances can be diagnosed as early as possible, which improves the prognosis.

Conclusions

The results of the present study provide further evidence that OLP is likely to be an etiological factor in OSCC, especially in patients who do not have other etiological factors such as alcohol use and smoking. Active follow-up of all patients with OLP and OLL in order to detect the possible malignant transformation of these lesions is of the utmost importance.

Disclosure statement

No potential conflict of interest was reported by the authors.

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