Carcinoma on oral lichen planus: report of four cases and review of literature

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Summary

Background. Oral lichen planus (oLP) is a chronic inflammatory disease which has been associated with an increased risk of malignant transformation.

Objective. We report our experience and review cases of oLP with malignant transformation in the English and German literature.

Methods. We report four cases of oLP with malignant transformation. Cases were evaluated for age, sex, location of LP, biopsy results, and medical history.

Results. Results according to methods.

Limitations. Retrospective analysis of four cases of squamous cell carcinoma (SCC) on oLP and cases in the German and English literature.

Conclusion. Patients affected by oLP require treatment and close monitoring for early diagnosis and treatment of SCC.

KEY WORDS: oral lichen planus; SCC; premalignant lesion; cancer.

Capsule Summary

- Oral lichen planus (oLP) is a chronic mucocutaneous disease that has been associated with the risk of malignant transformation.
- We report our experience and review the cases of oLP with malignant transformation in the English and German literature.
- Until a consensus on the malignant potential of oLP is established, dermatologists should closely follow-up on patients affected by oLP to ensure early diagnosis and treatment of squamous cell carcinoma (SCC).

Introduction

Lichen planus (LP) is a chronic inflammatory disease of the stratified squamous epithelium that affects 2 to 3% of the population (1). LP was first described by Erasmus Wilson (1869), but to date the etiology has remained unknown. Common clinical manifestations include cutaneous LP as well as genital and oral LP (oLP). However, involvement of the hair follicles, nails, esophagus, larynx, and nasal mucosa can occur (2-7). Between 50 and 70% of patients with cutaneous LP shows involvement of the oral mucosa (8, 9). Oral LP usually onsets in patients between 40 and 60 years of age, particularly in perimenopausal women (7). OLP occurs in erosive, bullous, papular, reticular, and atrophic forms (2).

Since Hallopeau in 1910 first reported a case of malignant transformation of oLP to carcinoma (10), a controversial discussion has been led regarding the malignant potential of oLP. A number of sporadic case reports and retrospective studies have since associated squamous cell carcinoma with oLP. The percentage of malignant transformation varies from 0 to 10%, depending on the study population (11-15). Although oLP is a common muco-cutaneous disorder, reports of malignant transformation of oLP are rare in the literature. Here, we report our experience with four patients who developed oral squamous cell carcinoma arising from oLP to raise awareness of the malignant transformation potential in patients suffering from LP with oral involvement.

Methods

We reviewed the medical charts of four patients with oLP and histopathologically proven squamous cell carcinoma, who presented to our Dermatological Department between 2011 and 2015. Additionally, we reviewed the English and German literature on oLP associated with oral squamous cell carcinoma.
This study did not need approval by the institution’s review board as it was a study conducted retrospectively on medical charts of patients treated in our Department.

**Case 1**

In 2011, a 65-year-old female patient presented to our Dermatological Department with typical reticular-type oLP affecting both sides of the buccal mucosa and tongue. There were no clinical signs of cutaneous or genital LP (Figure 1a). Punch biopsies taken from both the tongue and buccal mucosa confirmed the clinical diagnosis histopathologically. Serological tests excluded infectious liver diseases. No history of alcohol intake or smoking was found. Mycological oral swabs showed a secondary infection with Candida albicans, which was treated with amphotericin B lozenges. Topical treatment with tacrolimus was initiated. The patient was followed up twice per year. By November 2013, the lesion on the left side of the tongue became resistant to topical therapy, had significantly grown in size, and had changed its morphology (Figure 1b). We decided to repeat the histopathological examination by taking biopsies from both the tongue and buccal mucosa, which confirmed the presence of squamous cell carcinoma (Figure 1c). Immunohistochemical staining for P16 was negative showing no sign of Human Papilloma Virus (HPV) infection.

**Case 2**

A 61-year-old male patient presented to our outpatient Clinic in September 2014. Oral papular LP was first diagnosed in 1979 and multiple therapies had been implemented without any major benefit. A squamous cell carcinoma of the tongue was first diagnosed in 2011 and primary surgery performed at the University Hospital in Düsseldorf. After two relapses in 2012 and 2014, neoadjuvant chemotherapy with cisplatin and radiotherapy was applied. On first inspection, the patient presented with dystrophy of the nails as well as reticular and partially erosive plaques on both the tongue and the buccal mucosa (Figure 2). Histopathological examination showed no sign of malignant transformation at this point, but confirmed the underlying diagnosis of oLP. Serology regarding hepatitis infection was negative. No history of smoking and alcohol abuse was found. We initiated topical treatment with glucocorticosteroids as well as extracorporeal photopheresis and the patient presented for regular checkups in our outpatient clinic. In November 2014, follow-up biopsies were done at the University Hospital in Düsseldorf during routine follow-up. They confirmed a fourth relapse of a squamous cell carcinoma of the tongue.
Case 3

A 55-year-old female patient presented with oral reticular LP to our outpatient Clinic first in 2011 (Figure 3a). Biopsies taken from the buccal mucosa confirmed the clinical diagnosis. There were no signs of cutaneous, genital or follicular LP involvement. Serology showed antibodies to hepatitis virus types B and C. The patient did not smoke. The history of alcohol consumption is unknown.

Unfortunately, the patient was incompliant and for nearly three years neither received treatment nor returned for follow-ups to our Clinic. In 2014, she presented to our Department because of a rapidly growing, erosive, bleeding plaque on the left side of her tongue (Figure 3b). Histology confirmed a malignant progression to squamous cell carcinoma (Figure 3c). Immunohistochemical staining for P16 was negative showing no sign of HPV infection.

Case 4

On first presentation in 2013, this 59-year-old male patient showed typical cutaneous, nail and oral lesions that he had been suffering from for over ten years (Figures 4a). A biopsy was taken, which confirmed the diagnosis of oLP. Serology was negative regarding infectious liver diseases. No history of alcohol consumption was found, but the patient was a regular cigarette smoker (20 pack years). Under regular topical treatment with tacrolimus, systemic retinoids and extracorporeal photopheresis, the symptoms initially improved. However, in January 2015, the patient developed a rapidly growing tumor on the left side of his tongue (Figure 4b). A biopsy confirmed the diagnosis of a squamous cell carcinoma on oLP (Figure 4c).
Discussion

Since the first report of an oral squamous cell carcinoma (SCC) in a patient with oral lichen planus (oLP) (16), numerous others have been published discussing the potential of oLP for malignant transformation. In fact, oLP is considered a premalignant condition of oral SCC according to the WHO criteria (1, 17). However, to date even expert groups disagree about the malignant potential of LP and the screening of patients with oLP, which is not standardized. Due to the low incidence rates of oral cancer in the general population as well as in patients with oLP, a prospective study would require a very large number of participants and a long follow-up time. Several prospective and retrospective studies have tried to substantiate the discussion, but to date consent has not been achieved on the subject (18).

In support of the malignant transformation potential of oLP, few large-scale prospective studies have been published. One study (19) found a 50-fold increase in the incidence of SCC among 611 patients with oLP followed up for 24 years. One of the largest retrospective studies evaluating 2,071 patients with LP reported a risk of 5.9% (20) of developing oral cancer for oLP patients. Several case reports and reviews have supported this thesis so far (11, 21-24).

In contrast, several studies, of note two prospective studies by van der Meij et al. with 192 patients (25) and with 173 patients (26), detected no increased risk of malignant transformation in oLP (27), but found an increased risk in patients with other oral lichenoid lesions.

The discrepancy between different study populations highlights the importance of clarifying both the histopathological criteria for the diagnosis of oLP as well as the defining criteria for the differentiation between lichenoid dysplasia as a separate clinical entity as opposed to variable degrees of dysplasia in oral LP (13). Agreement on the concise and specific histopathological terminology and diagnostic criteria has not been achieved yet (28). Diagnostic errors due to unspecific histopathology have been reported in between 11 and 25% of cases (24). In addition, distinguishing malignancy within the dense inflammatory infiltrate, which represents a fundamental feature of LP (29), is a challenge in itself, even to the experienced pathologist (15, 28, 30). Recently, oral proliferative verrucous leukoplakia has been described as a distinctive entity, which in an early phase can exhibit an interface lymphocytic infiltrate that may mimic oral lichenoid stomatitis, such as lichen planus (31, 32). Oral proliferative verrucous leukoplakia should also be taken into consideration as a clinical differential diagnosis when confronted with oLP.

Overall, 76 patients with oLP were treated in the outpatient Department of our Clinic between 2010 and 2015. A total of 6 patients developed oral SCC during this period (7.9%), 4 of whom we are presenting here. However, other carcinogenic factors, such as chronic infectious diseases and smoking, must be considered. To our knowledge, only 3 patients showed no carcinogenic factors other than oLP to explain the development of SCC (3.95%).

With respect to the specific type of oral LP and its individual malignant transformation potential, to our knowledge no systematic review has been done to date. It seems that erosive type LP has a slightly higher malignant transformation potential than other subtypes of oLP. However, large-scale studies proving a clear connection are missing (33). Predominantly women are affected by oLP and conse-
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Frequently more female patients with oral SCC on LP have been reported (34). Patients’ average age at onset of SCC is usually between 60 and 65 years, which is consistent with our patient subset. Of the 76 patients with oLP seen in our Clinic, only 9 were male (11.8%), but 3 of them developed SCC (33.3%). In line with the literature, we had more female patients affected by oLP (88.2%) but 3 transformations suggest a lower SCC incidence in our population (4.5%). The most common site of malignant transformation was the tongue, which is consistent with the literature so far (33).

Chronic inflammation has been accepted as a major risk factor for the development of cancer in different tissues. However, the molecular and cellular mechanisms that connect both processes are yet to be clarified (35). The chronic inflammatory process associated with oLP is believed to play a key role in the development of oral cancer. Therefore, anti-inflammatory treatment with glucocorticosteroids has been considered an option to possibly reduce the risk of malignant transformation (35).

In refractory cases of oLP, extracorporeal photopheresis (ECP) has been used as an alternative treatment option with good response rates. By reducing inflammation, ECP might affect malignant transformation in oLP (36-38). However, clinical experience is limited to single case reports and small case series, and further studies are needed to assess the effect of extracorporeal photopheresis on oLP.

Similarly, two of the patients we present here were treated with oral tacrolimus, an immunosuppressive drug that reduces the inflammatory response and is commonly used for treatment of inflammatory and autoimmune skin diseases. However, as immunosuppression has also been suggested as a specific risk factor in carcinogenesis, such treatment needs to be acknowledged as an additional potential risk factor. Few case reports have discussed the suspected causal relationship between application of tacrolimus and SCC and have suggested an impact of tacrolimus on cancer signaling pathways such as p53 (39, 40). Nevertheless, in order to assess the risk of tacrolimus and other immunosuppressive treatments for the progression of LP to SCC, further studies need to be conducted (41, 42). However, it might be difficult to evaluate the extent of treatment or inflammation in causing malignant transformation (43). In our opinion, the major focus in oLP therapy should be put on reduction of the chronic inflammation, which is a known key promoter of carcinogenesis in numerous cancer models. In addition to chronic inflammation several other risk factors for the development of oral cancer need to be taken into consideration. For patients with coincidence of external risk factors and oral LP a retrospective study with 200 subjects conducted by Laejendecker et al. in 2005 concluded that it is impossible to define the contribution of each individual factor due to the low incidence rates of oral cancer (44). Tobacco use surely may be considered the most common risk factor for the development of oral leukoplakia and oral cancer. Specific criteria have been established by Krutchkoff evaluating the proper documentation of tobacco habits in studies on oral LP in order to distinguish between true malignant transformation and conventional carcinomas occurring in the mouths of patients who happen to have oral LP (11, 18). Nonetheless, numerous studies fail to mention tobacco use and other risk factors. Alcohol use also needs to be considered, although uncertainty exists about its independent influence on cancer progression. In the developing countries areca nut use is another common predisposing factor (45). Liver diseases have also been associated with LP and may play an important role in immunosuppression and carcinogenesis (46). The association between human papilloma virus infection and oropharyngeal cancer development is well established, while the possible association of HPV infection and oral SCC is still being discussed (24). Recently, attention has been drawn to the effect of chronic inflammation on carcinogenesis, but further research in this field is needed (29, 30, 47-49).

Concluding, discussion about whether oral LP may be considered a premalignant condition will continue until large, randomized prospective studies with sufficient follow-up time have been performed and risk factors have been unequivocally identified. Until a consensus on the malignant potential of oral LP is established, dermatologists should closely follow up on patients affected by oral LP to ensure early diagnosis and treatment of SCC.

Conflicts of interest disclosure

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