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ORIGINAL ARTICLE

Clinicopathological features and malignant transformation of oral lichen planus: A 12-years retrospective study

ELENA BARDELLINI, FRANCESCA AMADORI, PIERANGELA FLOCCHINI, SARA BONADEO & ALESSANDRA MAJORANA

Dental Clinic, Department of Oral Medicine, University of Brescia, Brescia, Italy

Abstract

Objective. Oral lichen planus (OLP) is known to be associated with the risk of developing oral squamous cell carcinoma (OSCC). The objective of this study was to investigate the clinicopathological features of OLP and the prevalence of malignant transformation in this setting. ***Materials and methods.*** This retrospective study was carried out on 204 medical records of patients with histologically proven OLP who received long-term follow-up (range 6 months–12 years). Data were entered in an informatic database. The statistical analysis, when needed, was performed with the chi-squared test for significance ($p < 0.05$). ***Results.*** At the moment of the diagnosis, out of 204 patients (163 female and 41 male; mean age 54.5 years), 107 patients (52.45%) suffered from systemic chronic diseases, in particular 46 (22.5%) from hepatitis C. Clinically, the reticular form of OLP was the predominant one and most patients had multiple oral sites of involvement. Fourteen patients showed extra-oral lesions. A percentage of malignant transformation less than 1% was found. In fact, two patients (0.98%) underwent a malignant transformation at a site previously diagnosed as OLP. ***Conclusions.*** At present, OLP is accepted as being a potential malignant disorder, therefore lifelong follow-up is recommended.

Key Words: *cancer, epidemiology, oral mucosa*

Introduction

Lichen planus (LP) is an inflammatory dermatosis of stratified squamous epithelia which may involve skin, oral mucosa and/or genitalia. The disorder, with unknown etiology and immune pathogenesis, affects from 0.5–2% of population, with a predilection for women (63–67%). The mean age of onset is from the 4^{th} to the 5^{th} decade and it is extremely rare in childhood [1,2].

LP develops on the buccal mucosa in ~ 60–70% of cases. The oral manifestations of LP have been described in several large studies around the world [3,4]. Oral lichen planus (OLP) lesions have a chronic course, rarely undergo spontaneous remission and finally are potentially malignant disorders [2].

In 1978, the WHO classified OLP as a potentially malignant disorder, since it had been associated with a significantly increased risk of developing cancer. The possibility of developing an oral squamous cell carcinoma (OSCC) from OLP lesions was estimated between 0–12.5%. Although a number of studies have analyzed the malignant transformation of OLP, this remains a very controversial matter [5,6]. Prospective and retrospective epidemiological studies in several countries suggested that the patients with OLP present a higher risk for developing OSCC than the general population. Many of these studies were criticizable due to the lack of clear clinical and histopathological criteria for the diagnosis of OLP and also of data about the clinical history and the follow-up.

In fact, in 1978, Krutchkoff et al. [7] alerted about the lack of data to support the malignant transformation of cases of OLP described in the literature and van der Meij et al. [8] stated that two thirds of the malignant transformation cases of OLP were not sufficiently documented to be considered. The best way to establish the putative pre-malignant nature of OLP would be a prospective follow-up study of a group of affected patients vs a group of unaffected

Correspondence: Dott.ssa Elena Bardellini, Dental Clinic, P.le Spedali Civili 1, 25133 Brescia, Italy. Tel: +00393996521. Fax: +0039030303194. E-mail: bardelena@libero.it

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individuals including smokers and non-smokers. Unfortunately, given the low incidence of OSCC in the general population and in OLP, such a study would require a very large number of participants and a long-term follow-up, therefore it is not currently available [6].

The best evidence of the potentially malignant transformation of OLP is still derived from well-conducted retrospective studies.

The purpose of this study is to contribute to the epidemiologic assessment of OLP. We described a group of Italian patients with OLP, reporting the main clinico-pathological features (e.g. clinical form, histopathological diagnosis, site of the lesions, association with chronic systemic diseases, alcohol/tobacco exposure, etc.) and investigating the prevalence of the potential malignant transformation in our setting.

Materials and methods

This retrospective study was carried out on 204 medical records of patients with histological diagnosis of OLP who attended the Oral Medicine Department of the Dental Clinic of the University of Brescia, Italy, from January 1999 to December 2010.

Diagnostic criteria for inclusion

(1) Diagnosis of OLP based on the following criteria:
   (a) clinical criteria for OLP, according to van Der Meij and van der Waal [9]:
   presence of bilateral, mostly symmetrical lesions;
   presence of a lacelike network of slightly raised gray-white lines (reticular pattern); and
   erosive, atrophic, bullous and plaque type lesions (accepted as sub-type only in the presence of reticular lesions elsewhere in the oral mucosa).
   (b) histological criteria for OLP, according to WHO [10]: hyperkeratosis and parakeratosis of epithelium surface layers, vacuolar degeneration in the basal layer of the epithelium, lymphocytic infiltration-band at the epithelial-stromal junction.

(2) Absence of clinical and histologic signs of oral lichenoid lesions (OLL). We excluded asymmetric lesions in which there was a direct topographic relation between the lesions and the causing materials. In addition, according to the diagnostic criteria proposed by Thornhill et al. [11], we excluded the lesions with the following histological findings for OLL: an inflammatory lymphocytic infiltrate deeply located in some or all areas; a focal perivascular infiltrate; the presence of eosinophils and plasmacells in the connective tissue and more colloid bodies than in classic LP.

(3) Absence of histological signs of epithelial dysplasia at the moment of the diagnosis. We excluded the lesions with a biopsy showing OLP and epithelial dysplasia.

(4) Follow-up longer than 6 months from the clinical and histological diagnosis.

The records of the patients that did not meet the clinical and the histological criteria were excluded from the study.

Compilation of the medical records

During the past 12 years, the medical records were filled up by the two clinicians who visited the patients. They both had undergone the same training to standardize their procedures and they had collected the medical history by asking the patients and perusing clinical and laboratory data. The extra-oral sites of involvement were evaluated by two dermatologists (to whom all the patients had been referred after the first visit).

Periodical visits of follow-up were conducted for all the patients, with a frequency established on the basis of the clinical features and the need of treatment. In general, the patients with white OLP were seen twice a year for the first two visits and then once a year; the patients with red OLP were seen twice a month; the patients under treatment were seen once or twice a month.

Data collection

For each patient's medical record, the following data were recorded: age at the time of the diagnosis, gender, smoking (current or former smoker vs non-smoker), alcohol consumption, systemic chronic diseases and use of drugs, clinical aspect of the lesions, sites of oral LP lesions, extra-oral sites of LP lesions, treatment provided and, if detected, malignant transformation of the lesions.

The clinical forms of OLP were recorded and detailed in 'white forms' which included the reticular, papular and plaque-like forms and 'red forms', which included the atrophic, erosive and bullous forms. As different type of lesions may occur in the same patient, for the classification we considered the most severe form shown at the first visit.

Data analysis

Data were entered in an informatic database. The statistical analysis, when needed, was performed with the chi-squared test for significance. The results were considered statistically significant for p-value < 0.05.

Results

Table I summarizes the profile of our study group and the age distribution at the moment of diagnosis. For each patient, habits about smoking and alcohol were analyzed. Among the 163 women, five (3.06%) smoked or were ex-smokers, four (2.45%) consumed alcohol and one (0.61%) smoked and consumed alcohol. Among the 41 men, five (12.2%) smoked or were ex-smokers, two (4.87%) consumed alcohol and three (7.31%) were smokers and consumed alcohol. Consumption of alcohol was considered to be more than 0.5 l/day of wine or intake of super-alcoholic drinks every day.

Out of the total sample (n = 204), 107 (52.45%) patients suffered from systemic chronic diseases (86 female and 21 men): 69 patients (33.82%) suffered from one systemic chronic disease, 30 patients (14.7%) from two systemic chronic diseases and eight patients (3.92%) from three systemic chronic diseases. Distribution of the chronic diseases is shown in Table II.

At the moment of the diagnosis, 68 patients (33.33%) suffered from hepatitis, 61 (29.9%) women and seven (3.43%) men. In particular, 18 women (8.82%) suffered from hepatitis B, 42 women (20.58%) from hepatitis C and one woman (0.49%) from both hepatitis B and C. Among men, four men (1.96%) had hepatitis B, two men (0.98%) had hepatitis C and one man (0.49%) had both the diseases.

As regards the clinical form, the reticular form of OLP was found in 46.56% (n = 95) of the patients; the plaque-like form in 23.03% (n = 47) of the patients; the atrophic form in 16.17% (n = 33) of the patients; the erosive form in 10.29% (n = 21) of the patients. In 62% of patients with the plaque-like form and in 12.3% of patients with atrophic lesions, reticular lesions were almost detected concomitantly. The less observed clinical forms were the papular (n = 6; 2.94%) and the bullous (n = 2; 0.98%) ones.

Most patients had multiple oral sites of involvement. The buccal mucosa was the most common site of involvement in each form, apart from the plaque-like one that interested in particular the dorsum of the tongue and the hard palate. The dorsum of the tongue and the gingiva were similarly affected, followed by the hard palate and the lip mucosa. Lesions of the floor of the mouth and the soft palate were uncommon (Table III).

Table I. Profile of the patients affected by OLP.

	Female (n = 163) (79.9%)	Male (n = 41) (20.01%)	Total (n = 204) (100%)
Mean age at onset, years	55	54	59
Range, years	22–85	21–86	21–86

Statistical analysis performed for each of the three most prevalent sites did not show a significant association between the sites and the clinical forms of the disease. Fourteen patients showed extra-oral manifestations of OLP: 11 patients had cutaneous lesions, three patients had vaginal involvement and one patient nail lesions.

Treatment was usually undertaken with the goal of controlling symptoms with minimal side-effects. For topical treatment, clobetasol propionate ointment 0.05% or betamethasone rinses were used. Topical medications were usually applied twice a day for at least 2 months. Anti-mycotic treatment was used as prophilaxis against oral candidosis. It consisted in fluconazole rinses or miconazole gel, applied once a day. The treatment with systemic corticosteroids (prednisone at 1–1.5 mg/kg per os) was managed by the dermatologist who followed the patients for extra-oral manifestations of OLP and administered only in four cases (in which topical treatment was subsequently added to maintain results).

Out of 204 patients with OLP lesions, the majority (66,6%, n = 136) did not need any treatment (except, occasionally, for salivar substitutes in th case of oral xerostomia or for anti-mycotic rinses in the case of oral candidosis), while 68 patients (33.3%) needed to be treated with topical corticosteroids; in particular, 54 of them needed more than one therapeutic cycle. Twenty-three patients had a positive response (i.e. disappearance of any kind of lesion and symptom for at least 12 months or passage from a red form to a white one). In the remaining 45 cases, the therapy resulted in a reduction but not complete disappearance of the lesions. Most of the patients with white forms did not require any treatment.

During the follow-up period, two patients (0.98%) had histologically proven malignant transformation at a site previously clinically and histologically diagnosed as OLP. They were both female, respectively, 57 and 63 years old, non-smokers and HCV-positive. They displayed an erosive form of OLP and they developed OSCC, with a mean time of 50 months (SD ± 2) after the initial diagnosis of OLP. The last follow-up visit was, respectively, 10 months and 14 months before the diagnosis of OSCC, as both the patients had family problems and did not regularly attend the control visits. The sites of the carcinomas were single, respectively, the posterior mucosa of the cheek and the upper alveolar mucosa. Both sites were sized less than 2 cm and the lesions presented as dishomogeneous erythroplakia areas. There was no clinical evidence of multi-focality of the neoplastic lesions.

An incisional biopsy with 6 mm punch was performed in each case. The histopathological diagnosis was 'OSCC *in situ*' for both the lesions. The two patients underwent the ultrasonography of the neck which showed no lymph node metastases. The staging

Table II. Distribution of the systemic chronic diseases in the patients with OLP.

Diseases	Female (n = 86) (80.37%)	Male (n = 21) (19.62%)	Total (n = 107) (100%)
Ipertension	25 (23.37%)	10 (9.34%)	35 (32.71%)
Diabetes (type 2)	4 (3.73 %)	3 (2.8%)	7 (6.54%)
Cardiovascular diseases	9 (8.41%)	2 (1.87%)	11 (10.28%)
Autoimmune diseases	4 (3.73%)	1 (0.93%)	5 (4.67%)
Tiroiditis	5 (4.67%)	0 (0%)	5 (4.67%)
Hepatitis	61 (57%)	7 (6.54%)	68 (63.55%)
Respiratory diseases	2 (1.87%)	3 (2.8%)	5 (4.67%)
Gastroenteric diseases	9 (8.41%)	2 (1.87%)	11 (10.28%)
Neoplastic diseases	5 (4.67%)	1 (0.93%)	6 (5.6%)

was carried out according to the TNM classification and resulted TisN0M0 for both patients.

The two patients were addressed to the Otolaryngology Department where they were subjected to pre- and intra-operative high definition television (HDTV) Narrow Band Imaging (NBI) endoscopy and to surgical excision of the lesions [12].

No other therapies were needed. The patients were followed-up every 2 months for the first year after the intervention, undergoing the ultrasonography at every control. Then they attended 3-month follow-ups for the second and third year. Both the patients were alive at the last visit, respectively, 26 and 34 months after the surgical excision of the lesions.

Discussion

According to the literature, we found that OLP typically arises in female and middle-aged patients [3,4,13]. In fact, in our study we observed that the women outnumbered the men (ratio F:M = 3.98:1) and the largest number of cases occurred at a mean age of 59 years while the youngest patient was 21 years old. We did not find OLP lesions in children, even if recent studies [14,15] reported some cases of the disease in childhood.

In our survey, no correlation between OLP and smoking and/or alcohol was found. Even if it is well documented that they are important risk factors for OSCC and for potentially malignant disorders [16] there are no data in the literature showing an increase of OLP lesions associated to smoking and alcohol [3,13].

As regards the association between OLP and the systemic chronic diseases, we observed that hypertension and hepatitis were the two most common findings in our patients.

Among our study population, 17.15% of the patients (n = 35) with OLP suffered from hypertension. This percentage being lower than the mean (49–63%) of the Italian population [17], it could be assumed that there is not a link between OLP and hypertension. In fact, it is well-known that the antihypertensive drugs are more frequently associated with oral lichenoid lesions (OLL) than with OLP [11].

In recent years, several authors have reported a relationship between OLP and hepatitis C (HCV) infection [3,18]. According to the current view, the host immune response rather than the viral factors is of greater importance in the development of OLP lesions in HCV infected patients [3,19,20]. Our data confirm the association between OLP and HCV with a percentage of 22.55% (n = 46), one of the highest in a retrospective study.

Mega et al. [21] found that some OLP-HCV cases showed in the lamina propria a deeper and more extensive lymphocyte infiltration, which often clinically corresponds to an erosive form. Considering that in our study the erosive forms were in total 21 cases, it

Table III. Distribution of the sites of the lesions in each clinical form of OLP.

	Reticular (n = 95)	Plaque-like (n = 47)	Papular (n = 6)	Atrophic (n = 33)	Erosive (n = 21)	Bullous (n = 2)	Total
Buccal mucosa	95	23	6	30	21	2	177
Tongue (dorsum)	7	45	4	27	3	0	86
Tongue (lateral-ventral)	54	0	3	19	8	1	85
Gingiva	47	25	0	7	7	0	86
Hard palate	22	36	0	0	8	0	75
Soft palate	4	0	0	0	0	2	6
Floor of the mouth	1	0	0	0	4	0	5

means that as much as 71.4% of them had HCV. This percentage seems to suggest a link between the erosive form of OLP and the HCV infection.

The association between diabetes and OLP has been the subject of many researches, but the reports which investigated the presence of OLP in diabetic patients [22] or the presence of diabetes in patients with OLP [10] did not find any association between the two diseases.

However, most reports do not differentiate between the two types of diabetes. Petro-Amerikanou et al. [23] reported a significantly higher prevalence of OLP in type 1 diabetic patients vs a control population, but not in type 2 diabetic patients. Our findings confirmed the prevalence of diabetes type 2 recently estimated in the Italian population [24] supporting the data available in the literature about the lack of association between the two diseases. Eventually, no evidence suggesting a link between OLP and the remaining other chronic diseases was found.

In the literature, the predominance of the forms of OLP is controversial. Although some authors such as Eisen [4] found the red ones to be the most common clinical forms of the disease, most authors [3,25] recorded the white forms as the most frequent clinical presentations. In agreement with this last finding, we observed a prevalence of the white forms (72.6%), compared to the red forms (27.4%). In particular, the most common type of lesion that we detected was the reticular one (46.56%), followed by the plaque-like one (23%).

According to the literature, we found that the buccal mucosa was the most common site of involvement (34%), followed by the dorsum of the tongue (16.5%), the lateral-ventral tongue (16.3%), the gingiva (16.5%) and the hard palate (14.4%). While the dorsal tongue was predominantly interested by plaque-like lesions, the lateral-ventral tongue showed mostly reticular lesions. This is probably due to the different grade of keratinization of the epithelium in the two sites. Lesions on the palate and on the floor of the mouth were uncommon.

Cutaneous and genital involvement can precede, arise concurrently with or appear after the development of OLP lesions [26]. Different studies reported an incidence of cutaneous and/or genital lesions in OLP variable from 12% to up 50% [3,19]. Among our sample, only the 6.86% (n = 14) of the patients showed extra-oral manifestations. This discrepancy could be explained by the fact that we did not record the patients' past medical history about extra-oral lesions but we only noted the dermatologic findings after the first visit at our department.

Our patients had been followed up from 6 months to 12 years, in particular 68 patients for more than 5 years. The considerable analyzed period of follow-up confirms the chronic nature of this oral disorder. Among our sample, two patients (0.98%) developed an OSCC during the follow-up period; they were both female, HCV-positive and non-smokers. The two malignant lesions were histopathologically diagnosed as 'OSCC *in situ*' and did not present any lymph node metastasis associated; thus, apart from the surgical excision, no other type of treatment was needed.

The malignant transformation of OLP is still controversial. Many series of cases have been published in relation to the malignant transformation in this pathology [2–8,12,26–33]. Although the malignant transformation rate varies widely in the literature from 0.4–6.5%, in most studies it does not exceed 1%.

In the review by Lodi et al. [6] that gathered studies published between 1985–2004, with a follow-up of 4.5–7.5 years, they observed a malignant transformation rate between 0–5.3%. In support of the malignant potential of OLP, the meta-analysis made by de Sousa et al. [27], that included the epidemiological studies from 1988–2008, revealed a malignant transformation rate of 1.63% (0.27% per year). Two recent studies, respectively in Italian and Chinese patients, provided further evidence of the potentially malignant nature of OLP [28,29].

Even if most studies are quite heterogeneous and differ in source of data, inclusion criteria, length of follow-up, design and geographical origin, they move in a malignant transformation rate of ~ 1% over 5 years. However, considering an OLP prevalence of ~ 1% and a transformation rate of 0.2% per year, it would mean that nearly every OSCC worldwide should develop from OLP lesions and this is unlikely.

One of the major problems of interpretation of malignant potential studies of OLP is the inexistence of strict diagnostic criteria to differentiate lichenoid processes [9]. Some studies have included cases of OLP with OLL and vice versa. The differentiation between OLP and OLL has become important, since the latter might have a greater malignant potential [6,30,31]. For this reason, it is important to establish precise clinical and histopathological criteria of differentiation of the lesions. Therefore, in order to assess the real malignant potential of OLP lesions, we decided to exclude the cases of OLL from the study.

The percentage of malignant transformation found in our survey is in the range (0.4–3.3%) of those reported in previous studies [13,32,33], but lower when compared to that (1.85%) in a large cohort of Northern Italian patients [3]. However, while they did not find an increased risk of malignant transformation for the red forms (if compared with the white ones), in our study the OSCC developed from erosive lesions. This is in agreement with the literature, according to which the clinical presentation of the disease seems to be relevant for potential malignancy. The red forms (erosive, atrophic and ulcerative) would in fact have a

higher risk of transformation than the white ones [13,27,30]. Eisen [4] found that the six (0.8%) patients who developed a malignant transformation had atrophic erosive lesions.

This circumstance could be related to a greater chronic inflammatory response behaving similarly to other inflammatory diseases also associated with neoplastic malignant growth, such as inflammatory intestinal disease, chronic esophagitis or chronic colicystitis: the increase of cytokines and growth factors would promote the malignant transformation [31,34,35].

Some authors [32] identified the basis of the malignant transformation of OLP in the accumulation in the oral epithelium of the inducible nitric oxide synthase with 8-oxodG (8-nitroguanine and 8-oxo-7,8- dihydro-2′- deoxyguanosine), which could reflect the oxidative and nitrative DNA damage.

Regarding the potential risk factors in the two patients, they both were non-smokers, HCV-positive and treated with topical steroids.

In our study, smoking was not observed in the OLP patients with transformation. As recently reported by a group of Italian authors [36], tobacco seems not to be associated with OSCC development from OLP lesions, above all in female patients. This may further support the true potentially malignant nature of OLP.

The link between HCV and malignant transformation is difficult to interpret. There is some evidence that HCV-associated OLP may have a clinically significant premalignant potential. Nagao et al. [37] found a high incidence of oral pre-cancerous lesions in a hyperendemic area of HCV infections and demonstrated the replication of HCV-RNA in OLP and OSCC tissues, but the issue is still controversial.

As most of the patients were treated with topical steroids plus anti-mycotics, we could assume that these treatments do not affect the risk of malignant transformation; indeed, in the two patients with OSCC, we suspected a lack of adherence to therapy because they did not attend the control visits regularly.

Until further knowledge is derived from large prospective studies, the data supporting or negating a potential malignant character of OLP lesions remains uncertain. Special emphasis should be directed toward unified inclusion and exclusion criteria, regarding the clinical and histological aspects and the possible risk factors, in order to allow for comparison among different studies.

For now, it should be critical that the patients with OLP be followed-up for all their lives by clinicians for the potential risk of malignant transformation.

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