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Clinical behaviour of malignant transforming oral lichen planus

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Aims: At present oral lichen planus (OLP) is classified among precancerous conditions but very few data are available in literature regarding prognosis of OLP-related cancers. The aim of this paper is to evaluate clinical long-term behaviour of OLP-related oral squamous cell carcinomas (OSCCs).
Methods: Clinical history and data from follow-up regarding 21 patients undergoing malignant transformation of OLP have been critically revised.
Results: In a mean time of 2.6 years from diagnosis of OLP, patients developed OSCCs. Histopathologically, two carinomas showed a moderate degree of differentiation, while the others were well differentiated. Six (28.5%) were *in situ* OSCC, in eight (30%) was found a microinvasive pattern of infiltration, one was a stage II tumour and the remaining (6 cases) were stage I tumours. During follow up, four patients (19%) have developed another OSCC in a mean time of 11 months from the first occurrence. In two men (10% of cases), multiple OSCCs occurred and in five cases (24%) lymph nodal metastases were detected.
Conclusions: Our study points out an alarming tendency in developing second primary metachronous tumours (33.3%) of the oral cavity and nodal metastases (23.8%), especially if we consider their early stages. Thus we always recommend a strict follow-up of OLP patients with clinical oral and neck examination every 2 months for 6–9 months since OSCC diagnosis is made and, after, three times a year.

Key words: oral lichen planus; oral squamous cell carcinoma; metastases; prognosis.

INTRODUCTION

Lichen planus is a chronic inflammatory autoimmune disease involving epithelia with squamous differentiation. Oral manifestations occur in at least six forms: reticular, papular, plaque, atrophic, erosive, and bullous, often simultaneously associated. At present oral lichen planus (OLP) is classified among precancerous conditions[1] and is generally accepted an increased risk of oral cancer development for patients affected by OLP diagnosed on the basis of clinical and histological manifestations, though necessity of a prospective multicenter case-control study has been pointed out.[2] Malignant transformation of OLP lesions has been reported with a wide range of frequency;[3–6] however it can be considered a relative uncommon eventuality, occurring in our series in about 3.7% of cases.[4] In fact, in the last 6 years 24 of our OLP patients developed oral squamous cell carcinomas (OSCCs). In this paper we analyse clinical history and data from follow-up data of 21 of these patients in order to evaluate clinical long-term behaviour of both OLP lesions and OSCCs.

PATIENTS AND METHODS

In last 6 years, 24 out of our 578 patients affected by OLP were diagnosed as having OSCC; among these 21 have developed OSCC in a site of preexisting OLP lesions, whereas in the remaining three cases diagnoses of OLP and OSCC were synchronous. Four were men with a mean age of 66.75 years (range 48–78 years) and twenty were women whose age ranged from 35 to 74 years, with a mean of 55.14 years. In all patients OLP diagnosis was based on clinical manifestations and confirmed by oral biopsy; histological features used as diagnostic criteria, in haematoxylin–eosin stained

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sections obtained from 10% neutral buffered formalin fixed specimens, were: hyperortho-hyperparakeratosis, a subepithelial lymphocytic band-like infiltrate, and the focal signs of basal layer degeneration. On the basis of the prevalent clinical morphology patients were categorised into six forms of OLP (reticular, plaque, atrophic, erosive, bullous, and mixed) after that all clinical factors that could modify clinical features were removed (e.g. candidiasis, calculus, etc.).[7] In a mean time of 2.6 years, the patients were known to have developed OSCCs. All were squamous cell carcinomas, staged as follows: six (28.5%) were *in situ*, eight (30%) with a microinvasive pattern of infiltration, one was a stage II tumour and the remaining (six cases) were stage I tumours. All were treated with a wide excision with a 0.5–1 cm region of clinical normal tissue around the lesion, except for the stage II cancer, in which neck dissection was also performed. The primary role of follow-up of OLP lesions in OSCC early detection and prognosis improvement has already been underlined in a previous our paper;[4] in fact, according to us, an extremely careful follow-up examination at least three times a year is absolutely required.

In this study, clinical history of 21 patients has been critically revised, including initial diagnosis of OLP, location, extent, morphological picture and modifications of OLP lesions, diagnosis of OSCC, and data from follow-up regarding occurrence of subsequent other tumours and prognosis. The other three patients, now deceased, were not included in the study because of the synchronous diagnosis of OLP and stage IV OSCC.

RESULTS

At the time of diagnosis of OLP, mean age of patients was 64.5 years for men (range 46–68 years) and 54.1 for women (range 33–69 years). Morphological pictures and location of OLP lesions are detailed in Table 1. The most common involved sites were buccal mucosa bilaterally and tongue (71 and 57% of patients respectively). In both sites one third of patients had mixed lesions; the keratotic component (reticular and/or plaque) of these lesions had generally a wider extent, but while in the former site it was usually associated with erosive lesions, in the latter it was associated with atrophic ones. Furthermore, among patients with OLP lesions on the buccal mucosa, four (27%) had truly reticular lesions, in other four (27%) morphological picture was plaque/reticular, and only one patient (7%) had atrophic erosive lesions. Among patients with tongue involvement, only one (8%) showed truly reticular morphology, while plaque/reticular lesions were encountered in seven patients (58%). It is of great interest to underline the concept that when we talk about OLP plaque lesions, we mean a quite homogeneous keratinization, in an epithelium with a tendency to atrophy,[8] often with ray-like or reticular margins and surrounded by atrophy, which is clinically different from leukoplakia plaque (Fig. 1). An unusual involvement of midline structures (palatal arch, labial mucosa, gingiva of the frontal region), prevalently with reticular features has also been found. Medical history, careful clinical and histopathological examination, and laboratory investigations ruled out the possibility of drug- or restoration-related lichenoid reactions, and/or oral lichenoid manifestations of systemic diseases. Critical evaluation of histological slides confirmed that in all patients were satisfied above mentioned diagnostic criteria. Furthermore, in all patients there was no cytomorphological atypia or dysplastic features of the epithelium; only in four cases infiltrate was not really homogeneous and confined to the lamina propria, but in these cases a secondary micotic and/or bacterial infection could not be clinically excluded.[9] During the follow-up, which implies clinical examination three times a year, clinical features of OLP lesions have remained quite stable especially in keratotic forms, in which changes or loss of homogeneity is suspicious, while a little fluctuation has been observed in mixed lesions in relation to the extent of atrophic/erosive component which is generally directly proportional to the degree of symptoms.

From this point of view OLP lesions remained completely asymptomatic in 13 cases (62%); three patients had only non-specific discomfort, whose therapy was deemed unnecessary, whilst the remaining patients had moderate (four cases) or severe pain (one case), that required therapy with topical steroids (clobetasol ointment 0.05% mixed 1:1 in orabase). Remission of symptoms was obtained, so all of 21 patients were able to maintain a normal diet including fresh fruit and vegetables. In fact, all patients ate fresh fruit at least once a day and fish twice a week; vegetables were consumed three times (80% of patients) or twice a week. None of patients drank alcohol and only three (two women and a man) smoked about 15 cigarettes a day; none of the other common predisposing factors to oral cancer could be encountered.

In a mean time of 2.6 years from diagnosis of OLP the patients developed OSCC, diagnosed clinically and histologically. The most common locations were buccal mucosa (nine cases: 43%) (Fig. 2), tongue (seven cases: 33%; three on the margins and four the dorsum) and gingiva (four cases: 19%), palate has been involved in one patient. Histopathologically, only two carcinomas showed a moderate degree of differentiation, while the others were well differentiated; six (28.5%) were *in situ* OSCC, in eight (30%) was found a microinvasive pattern of infiltration, one was a stage II tumour and the remaining (six cases) were stage I tumours.

To date, ten (47%) out of these 21 patients have not had other OSCCs. Four patients (19%) have developed another OSCC in a mean time of 11 months from the

Table 1 Clinical data of OLP undergoing malignant transformation

Case	Sex	Age[a]	Site and type of OLP lesions							Site of SCC	Grading	Staging	Follow-up (years)[b]	Subsequent tumours and/or metastases
			Buccal mucosa bilaterally	Buccal mucosa monolaterally	Tongue	Palatal arch	Floor of mouth	Labial mucosa	Gingiva					
1	F	52		Reticular	Plaque/ reticular			Reticular		Margin of tongue (left)	G2	I	3	No SCC
2	F	65	Atrophic/ reticular						Reticular/ plaque	Gingiva	G1	I	3	No SCC
3	F	40			Plaque					Tongue	–	*in situ*	3	No SCC
4	F	50	Reticular/ plaque		Reticular/ plaque				Plaque/ reticular	Gingiva	G1	I	2	No SCC
5	F	70	Mixed		Atrophic/ plaque					Tongue	G1	microinv	2	No SCC
6	F	35		Mixed	Plaque					Buccal mucosa (right)	–	*in situ*	2	No SCC
7	F	71			Plaque/ atrophic					Tongue	G1	microinv	2	No SCC
8	F	61	Reticular		Reticular/ atrophic	Reticular			Reticular	Gingiva (right)	G1	I	4	No SCC
9	F	54		Reticular		Reticular/ plaque				Palate	–	*in situ*	3	No SCC
10	F	74	Mixed			Mixed		Reticular		Buccal mucosa (left)	–	*in situ*	4	No SCC
11	F	70	Atrophic/ erosive			Reticular			Atrophic/ erosive	Tuber (right) Palate (right)	G1	I	2	Yes (after 15 months)
12	F	45	Mixed		Plaque					Buccal mucosa (left) Buccal mucosa (right)	–	*in situ* *in situ*	3	Yes (after 1 year)
13	F	40	Reticular		Reticular					Buccal mucosa (left) Buccal mucosa (left)	–	*in situ*	2	Yes (after 1year)
14	F	46	Reticular		Reticular/ plaque					Tongue Tongue	G1	microinv	3	Yes (after 5 months)
15	M	70	Mixed						Mixed	Buccal mucosa (left)	G1	microinv	2	Yes (after 7 months)

Table 1 Continued

Case	Sex	Age[a]	Site and type of OLP lesions							Site of SCC	Grading	Staging	Follow-up (years)[b]	Subsequent tumours and/or metastases
			Buccal mucosa bilaterally	Buccal mucosa monolaterally	Tongue	Palatal arch	Floor of mouth	Labial mucosa	Gingiva					
										Buccal mucosa (right)				Yes (after 16 months)
										Tuber (left)				Yes (after 21 months)
										Tuber (right)				
16	M	78	Plaque			Reticular		Reticular		Buccal mucosa (right)	G1	microinv	3	Yes (after 6 months)
										Buccal mucosa (right)				Yes (after 14 months)
										Tuber (right)				
17	F	74			Plaque/ atrophic		Plaque			Tongue	G1	II	5	Nodal metastases
18	M	48	Reticular		Plaque					Tongue	G1	microinv	2	Nodal metastases (after 3 months)
19	M	71	Reticular/ plaque							Buccal mucosa (right)	G1	microinv	2	Nodal metastases (after 6 months)
20	F	72	Mixed							Buccal mucosa (right)	G2	I	2	Nodal metastases (after 4 months)
21	F	59	Reticular/ plaque			Reticular			Plaque/ reticular	Gingiva (left)	G1	microinv	2	Yes (after 4 months)
										Tuber (left)	G1	microinv		Nodal metastases (after 6 months)

[a] Age at time of diagnosis of SCC.
[b] Time from diagnosis of OLP.
SCC, squamous cell carcinoma.

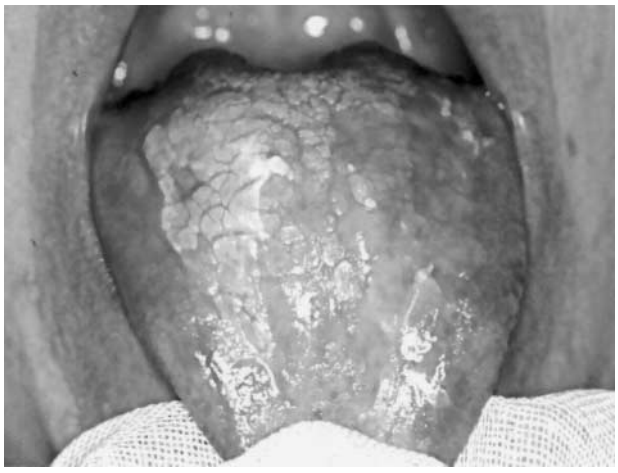

Figure 1 OLP plaque lesions of the dorsum of the tongue, with a quite homogeneous keratinization, surrounded by an atrophic epithelium.

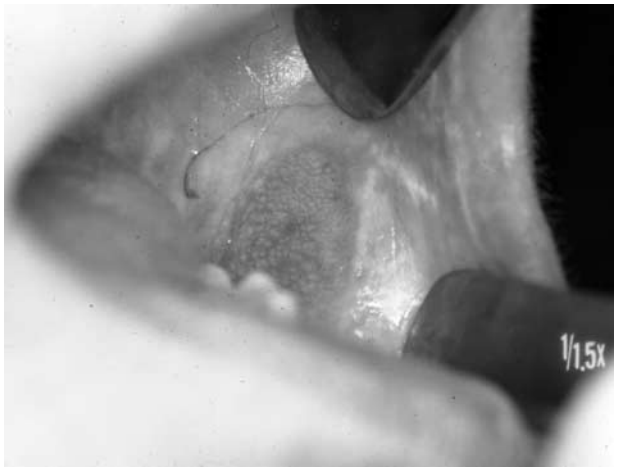

Figure 2 Microinvasive OSCC of the buccal mucosa arisen in keratotic plaque/reticular OLP.

first occurrence; in two of them the second tumour occurred in different sites from the first, whereas in the others two were involved sites near the first cancer, even if histopathological examination of the previous specimens revealed margins of resection free of tumour and/or dysplasia. In two men (10% of cases), multiple OSCC occurred: after the initial OSCC a second primary tumour was found within 7 months. Other subsequent second primaries were detected in a mean time of 7 months, generally, without relationship for their location. In the remaining five cases (24%) lymph nodal metastases were detected by FNAC after that clinical and imaging techniques revealed nodal enlargement. One of these cases was a 74 year old female affected by a stage II OSCC diagnosed after that the patient had autonomously stopped follow-up examinations for 4 years; in the other four cases nodal metastases occurred in microinvasive carcinomas, with a mean thickness of 1.75 mm, in a mean time of 4.75 months after that diagnosis of OSCC was made, and one of them had also a second primary tumour before developing nodal metastases.

DISCUSSION

Even if OLP is classified among precancerous conditions,[1] the question of its malignant transformation does not find unanimous consent.[10,11] This leads to a very precarious condition, especially in clinical practice, because of the necessity to counsel patients about their disease and its management. Thus, a discerning evaluation of the evidence available points out that the real question seems to be related to the diagnosis of OLP itself. This one must be based on characteristic clinical features, history, and histopathology. The dynamic nature of OLP, related to its immunological pathogenesis, may produce multiple combination patterns of these factors. This may confuse diagnostic process and resemble at static and unilateral analysis, a group of lichenoid disorders,[11] with similar general features, suspected different behaviour and prognosis, but without a defined parameter suggesting alternative diagnoses among them. Scientific research has to clarify whether such a parameter exists, or not, by evaluating patients and their disease with the auxilium of strict and reasoned criteria; however, until this aim is not achieved, we cannot disregard clinical evidence of an increased, even if small, risk of oral cancer development in OLP. So, adequate managing OLP at a clinical level absolutely requires follow-up of patients for early detection of OSCC and prognosis improvement. In this study we retrospectively analyse clinical behaviour of malignant transforming OLP in 21 cases. First of all, we revised diagnosis of OLP: combination of clinical, microscopic and follow-up data confirmed it. OLP features in patients developing OSCC did not show rilevant clinical differences from our others OLP patients; however, a high incidence of multiple OSCC characterises them. In fact, in our patients, tendency to develop two or more OSCC on OLP amounts to 53% of cases. More specifically, analysis of this tendency allows us to retrospectively divide patients with malignant transforming OLP in four groups (Table 1). The first includes patients (47%) without second tumours; the second includes patients (19%) with only one further tumour. To the third group belong patients (10%), exclusively men, with multiple metachronous OSCC; in the fourth group are included patients (24%) with nodal metastases occurred in small thickness OSCC.[12] No differences among the four groups, were observed as

regard the length of follow-up and the exposure to oral cancer risk factors. In fact, smoking (three cases) was equally distributed in the first, second and fourth group, and mean follow-up time for each group was 2.8, 2.5, 2.5 and 2.6 years.

Actually, very few data are available in literature as regards OLP-related OSCC behaviour, although some reports suggest a worse prognosis.[12,13] Our study seems to confirm these data, pointing out an alarming tendency in developing second primary metachronous tumours (33.3%) of the oral cavity and nodal metastases (23.8%), especially if we consider stages of cancers in our series (Table 1). In fact, the overall tendency toward the development of multiple mucosal cancers is well known, but, in very large groups of oral and pharyngeal cancer patients, it has been estimated to be 3.7% per year.[14] For this reason an extremely careful management of OLP patients is mandatory and probably a more radical treatment of OSCC arisen in OLP should be performed. OLP patients developing OSCC cannot be prospectively included in any of the abovementioned groups because we have no useful criteria to predict recurring potential. Thus we always recommend a strict follow-up with clinical oral and neck examination, possibly every 2 months for 6–9 months since OSCC diagnosis is made: in fact, in our experience, the risk is high for second primary tumours or metastases in this period. Subsequently, clinical examination three times a year is required for early detection and adequate treatment: we analyse morphology, location, extent, and homogeneity of lesions, and whenever suspicious signs of malignant transformation are found frequency of follow-up examination, are increased or an additional oral biopsy was directly performed.[4]

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