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HOT TOPIC

Oral lichen planus: controversies surrounding malignant transformation

MA Gonzalez-Moles[1], C Scully[2], JA Gil-Montoya[3]

[1]*Oral Medicine Department, Faculty of Dentistry, University of Granada, Granada, Spain;* [2]*Eastmant Dental Institute, London, UK;* [3]*Special Care in Dentistry Department, Faculty of Dentistry, University of Granada, Granada, Spain*

Studies of the malignant potential of oral lichen planus (OLP) have been hampered by inconsistencies in the diagnostic criteria used for OLP, the criteria adopted to identify a true case of malignant transformation in OLP, the risk factors for malignant transformation and the optimum management of patients to ensure the early diagnosis of transformation. Consensus remains elusive, and leading workers in this field have recently published conflicting reports on the malignant potential of OLP and on the important question of the advisability of excluding patients with epithelial dysplasia or a tobacco habit from studies on this issue. The present review outlines these debates and proposes a possible a molecular basis for the malignant transformation in this disease.
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Oral lichen planus – malignant potential?

Since the first report of the malignant transformation of oral lichen planus (OLP) (Hallopeau, 1910), numerous studies have attempted to address this issue. Table 1 lists the most significant studies of OLP patients published between 1924 and 2007, and shows a frequency of malignant transformation ranging from 0% to 12.5%. Although these findings appear to support the potentially malignant character of OLP, it remains a controversial topic. The first critical review appeared in the *Journal of Oral Pathology* about three decades ago (Krutchkoff *et al*, 1978), included data published up to 1977, and the authors recommended strict criteria (Table 2) be adopted to definitively accept the malignant transformation in OLP. After applying these new criteria, they concluded that only 15 of the 223 cases reported in the literature should be unquestionably accepted as malignant transformation in OLP. The remaining cases were excluded for at least one of the following reasons: (1) insufficient data to support the OLP diagnosis, (2) appearance of oral cancer in an area anatomically distant from the OLP and (3) inadequate historical data on previous exposure to carcinogens. The authors commented:

> If OLP prevalence is accepted to be 1–2% of general population over 15 years, and if malignant transformation rate is 1% in a mean period of 5 years, then, from 10 to 20 patients per 100 000 inhabitants should develop oral cancer in a mean period of 5 years. This would indicate that in many parts of the world all oral carcinomas should develop on an OLP, which is rather improbable.

Krutchkoff *et al* (1978) further drew the conclusion that there was insufficient evidence to accept an inherent biological potential of OLP to progress to cancer, but they acknowledged that OLP patients have a slightly higher tendency to develop carcinomas compared to individuals without OLP.

Almost a decade ago, van der Meij *et al* (1999a,b) reviewed studies on the malignant transformation of OLP published from 1977 to 1999, applying the Krutchkoff criteria. During this period, 98 new malignant transformations were reported, of which 33 (34%) met the proposed criteria. According to the authors, the high incidence of malignant transformation described in many studies may be due to the misdiagnosis of some lesions as OLP, or to the analysis of a highly selected study population (e.g. predominance of patients referred to specialists). van der Meij *et al* (1999a,b) further emphasized the need for standard criteria for a firm diagnosis of OLP to be universally adopted. Five years ago, a review by Mattsson *et al* (2002), largely based on follow-up studies, reported a higher incidence of oral cancer in OLP patients and concluded that OLP should be considered a potentially malignant condition with a transformation rate of 0.5–2%. Numerous other

Correspondence: MA Gonzalez-Moles, Facultad de Odontología, Paseo de Cartuja s/n, 18071 Granada. Spain. Tel/Fax: +34 958243796, E-mail: magonzal@ugr.es
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Table 1 Malignant transformation rate in oral lichen planus (OLP) patients

Reference	*Country*	*OLP patients (n)*	*Oral carcinoma*	*Malignant transformation rate*	*Observation period (years)*
Williger (1924)	Germany	20	2	10.0	–
Montgomery and Culver (1924)	UK	17	1	6.0	1–9
Schuermann (1939)	Germany	310	2	0.6	–
Dechaume *et al* (1957)	France	50	5	10.0	–
Sugar and Banoczy (1959)	Hungary	36	1	3.0	11
Warin *et al* (1958)	UK	53	5	9.0	1–10
Altman and Perry (1961)	USA	128	1	0.8	6–10
Andreasen and Pindborg (1963)	Denmark	115	0	0	2–5
Grinspan *et al* (1966)	France	114	8	7.0	–
Rhode (1966)	Germany	207	6	3.0	–
von Janner *et al* (1967)	Germany	585	9	1.7	1–24
Andreasen (1968)	Denmark	115	0	0	1–10
von Abramova (1968)	Russia	436	5	1.1	5–8
Cawson (1968)	UK	138	1	0.7	–
Shklar (1972)	USA	600	3	0.5	1–15
Fulling (1973)	Denmark	225	1	0.4	3.6
Kovesi and Banoczy (1973)	Hungary	274	1	0.4	1 > 10
Silverman and Griffith (1974)	USA	200	5	2.5	18
Holmstrup and Pindborg (1979)	Denmark	8	1	12.5	0.4–6.5
Vaskovskaya and Abramov (1981)	Russia	725	29	4.0	–
Kaugars and Svirsky (1982)	USA	30 920	71	0.23	–
Silverman *et al* (1985)	USA	570	7	1.2	6 months–10 years
Murti *et al* (1986)	India	722	3	0.4	5.1
Holmstrup *et al* (1988)	Denmark	611	9	1.5	1–26
Salem (1989)	Saudi Arabia	611	4	5.6	3.2
Vincent *et al* (1990)	USA	100	0	0	9.1 months
Silverman *et al* (1991)	USA	214	5	2.3	7.5
Sigurgeirsson and Lindelof (1991)	Sweden	2071	8	0.4	9.9
Voute *et al* (1992)	The Netherlands	113	3	2.7	7.8
Carbone *et al* (1992)	Italy	170	10	5.8	3.0
Barnard *et al* (1993)	UK	241	9	3.7	1–10
Brown *et al* (1993)	USA	193	0	0	8.0
Vescovi and Gennari (1996)	Italy	71	3	4.22	5.0
Gorsky *et al* (1996)	Israel	157	2	1.3	3 months–15 years
Markopoulos *et al* (1997)	Greece	326	4	1.3	6 months–10 years
Lo Muzio *et al* (1998)	Italy	263	10	3.80	1–10
Rajentheran *et al* (1999)	UK	832	7	0.8	–
Mignogna *et al* (2001)	Italy	502	24	4.7	–
Eisen (2002)	USA	723	6	0.8	–
Rode and Kogoj-Rode (2002)	Slovenia	55	0	0	25
Lanfranchi-Tizeira *et al* (2003)	Argentina	491	32	6.5	–
van der Meij and van der Waal (2003)	The Netherlands	173	3	1.7	–
Gandolfo *et al* (2004)	Italy	402	9	2.2	2–21
Rodstrom *et al* (2004)	Sweden	1028	5	0.5	6.4
Laeijendecker *et al* (2005)	The Netherlands	200	3	1.5	4.3
Xue *et al* (2005)	China	674	4	0.6	3–21
Mignogna (2006)	Italy	700	45	6.43	16
van der Meij (2007)	The Netherlands	192	4	2.1	5
Ingafou *et al* (2006)	UK	690	13	1.9	–
Bornstein *et al* (2006)	Sweden	141	4	2.84	–
Hsue *et al* (2007)	China	143	3	2.10	10

authors share this view (Silverman *et al*, 1985; Rajentheran *et al*, 1999; Silverman, 2000; Drangsholt *et al*, 2001; Mignogna *et al*, 2001; Gandolfo *et al*, 2004; Rodstrom *et al*, 2004).

Finally, the World Health Organization, in its latest volume on the Pathology and Genetics of Head and Neck Tumours (Gale *et al*, 2005), has recommended the development of diagnostic criteria to differentiate between OLP and oral lichenoid lesions (OLL) but it declared that both lesions should be considered at risk of malignant transformation until such criteria become available.

Drawbacks in the studies of OLP malignant transformation

Drawbacks related to diagnostic criteria

The main difficulty in studying the malignant transformation of OLP relates to the absence of universally accepted criteria for the diagnosis OLP (van der Meij *et al*, 1999a,b; Gandolfo *et al*, 2004). Not all patients with OLP have the classic clinical features of bilateral white striae/papules and the term OLL is then not uncommonly applied. A group of oral cavity lesions, including OLLs, graft-*vs*-host disease (GVHD) and

Table 2 Criteria for malignant transformation of oral lichen planus (OLP)

A. Original diagnosis must have been properly verified, with histological evidence demonstrating at least the last two of these four features
Hyperkeratosis or parakeratosis
Saw-toothed rete ridges
Superficial infiltrate of lymphocytes
Basal cell liquefaction
B. History and follow-up
Clinical and histological features of the alleged transformation must have been adequately described (information on age and sex of patient and on the precise location and clinical description of the lesion)
The reported transformation should have had proper follow-up (minimum of 2 years) with all changes in clinical features properly recorded
C. Tobacco exposure: Tobacco habits should have been properly documented to help distinguish between true malignant transformations and conventional carcinomas occurring in the mouths of patients who happen to have OLP

lichenoid contact reactions (LCR) or drug reactions, are generically known as lichenoid reactions and their clinical and histopathological features can closely resemble those of OLP.

Key authors in this field (Mattsson *et al*, 2002; van der Meij *et al*, 2003) are in agreement that OLP diagnostic criteria should be based on both clinical and histopathological data. The use of solely clinical criteria might result in false-positive findings for lesions that are similar to OLP and carry an inherent malignant potential (e.g. erythroleukoplakia and proliferative verrucous leukoplakia) (Rodstrom *et al*, 2004) (Figures 1 and 2). The presence of white striations and/or papules is the most characteristic clinical feature of OLP (Mattsson *et al*, 2002) and van der Meij *et al* (1999a,b) considered bilateral, often symmetrical reticular lesions to be an essential clinical criterion. Bilaterality is a strongly determining component of the clinical profile of OLP (Eisenberg, 2000). Plaques and atrophic, ulcerative or bullous lesions can also be observed at diagnosis or during the course of the disease (Thorn *et al*, 1988) but are not OLP specific and cannot assist the differential diagnosis between OLP and clinically similar disorders.

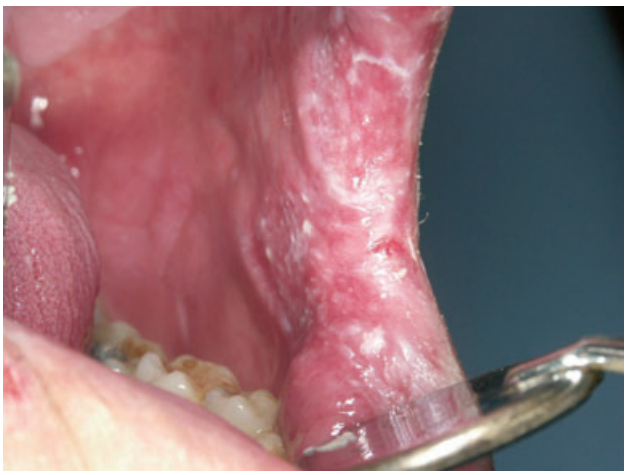

Figure 1 Leukoerythroplastic lesion of left buccal mucosa. In the absence of strict diagnostic criteria, this type of lesion, with inherent potential for malignant transformation, could be incorrectly considered an oral lichen planus, leading to overestimation of the malignant potential of this disease

That the lesion in question might represent a disease other than OLP is suggested by various clinical features (Krutchkoff *et al*, 1978; Eisenberg and Krutchkoff, 1987, 1992a; Eisenberg, 1992b), including: asymmetric lesions (unilateral, solitary or without bilateral involvement of buccal or gingival mucosa), especially if they appear in cancer-prone areas (floor of the mouth, lateral border and ventral surface of the tongue, retromolar trigone and soft palate–uvula complex); lesions accompanied or preceded by cutaneous manifestations suggestive of diseases other than LP (e.g. lupus erythematosus); lesions with specific surface characteristics, e.g. thickening, plaque-type keratosis, verrucous-papillary texture and mottled appearance, possibly related to oral mucosa atrophy (Eisenberg, 2000); and lesions located in areas that suggest direct relation with a causative agent, e.g. silver amalgam restorations (LCR) (Figures 3 and 4).

The histopathological criteria for a diagnosis of OLP pose a more complex challenge. Many histopathological alterations can appear in OLP, both in the epithelium and in the underlying corium. The epithelium may develop hyperkeratosis, atrophy, hyperplasia, acanthosis, saw-toothed rete ridges, keratinization of individual cells and/or liquefaction degeneration of the basal layer. The connective tissue typically shows a band-like inflammatory infiltrate dominated by lymphocytes and macrophages (Mattsson *et al*, 2002). Essential histopathological criteria for OLP diagnosis are: the presence of a well-defined band-like inflammatory infiltrate, confined to the connective tissue surface area and largely formed by lymphocytes; signs of liquefaction degeneration of the epithelial basal layer; and absence of epithelial dysplasia (Larsson and Warfvinge, 2003). Similar criteria were proposed by Eisenberg (1994) who also described possible but non-essential features, including Civatte bodies, saw-toothed rete ridges, parakeratosis and separation of the epithelium from lamina propria. Features considered by Eisenberg (1994) that would rule out OLP included atypical cytomorphology (nuclear enlargement or hyperchromasia, prevalent dyskeratosis, increased number of mitotic figures, aberrant mitosis), blunt rete ridges, absence of basal liquefaction, disordered stratification and lichenoid infiltration (heterogeneous population, deep extension below superficial stroma or perivascular infiltration). Hence, a biopsy can be regarded as an essential instrument for correctly diagnosing OLP, although diagnoses based solely on histopathological data can also be erroneous (Mattsson *et al*, 2002).

Eisenberg and Krutchkoff (1992) claimed that photomicrographs in some published reports corresponded to or suggested a non-OLP diagnosis, and intra- and inter-individual variations in interpretations by pathologists are now widely recognized (van der Meij *et al*, 1999a).

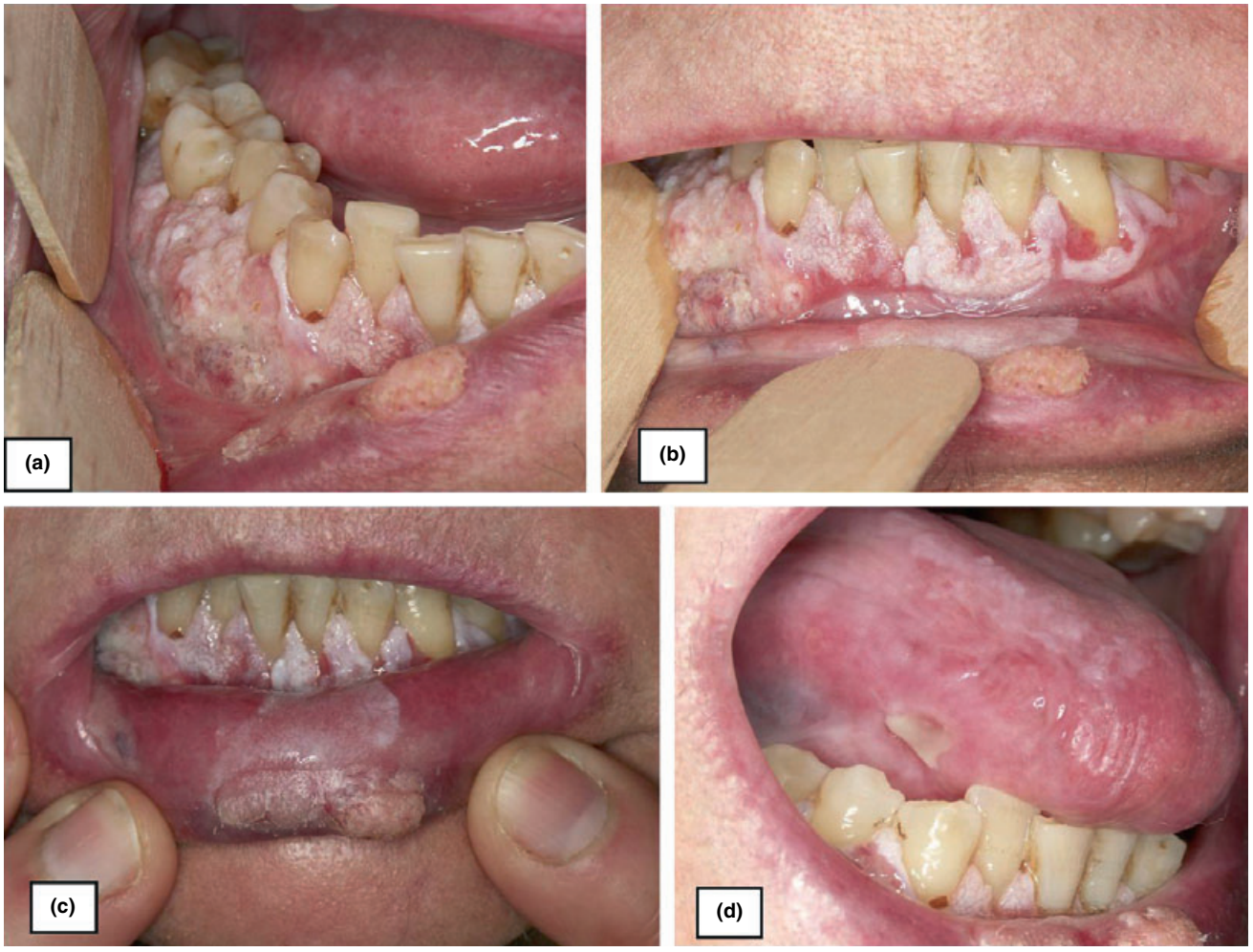

Figure 2 Patient with proliferative verrucous leukoplakia who has developed various carcinomas (**a**–**c**). The tongue shows reticular, atrophic, and erosive lesions that can be easily confused with oral lichen planus (**d**)

Immunosurveillance phenomena that can develop in response to a dysplastic epithelium can mimic those found in OLP. Studies that fail to take account of this aspect are therefore contentious (Krutchkoff and Eisenberg, 1985; Gandolfo *et al*, 2004), although the absence of well-defined criteria for epithelial dysplasia, especially in the presence of inflammation, contributes towards the conceptual disorder (Lodi *et al*, 2005). For some major authors in this field (Krutchkoff and Eisenberg, 1985; Holmstrup *et al*, 1988; Eisenberg, 1992, 2000; Eisenberg and Krutchkoff, 1992a; van der Meij *et al*, 1999a,b; Silverman, 2000; Mattsson *et al*, 2002), lesions that specifically demonstrate epithelial dysplasia should not be included in these studies, although others consider these criteria to be excessively rigid (Sigurgeirsson and Lindelof, 1991; Holmstrup, 1992; Camisa *et al*, 1998). So long as it is accepted that a diagnosis of OLP should be based on the clinico-pathological criteria described above, terms such as 'OLP with atypia' or 'OLP with dysplasia' (De Jong *et al*, 1984; Kaplan and Barnes, 1985; Odukoya *et al*, 1985; Sigurgeirsson and Lindelof, 1991; Camisa *et al*, 1998; Lo Muzio *et al*, 1998) should not be used. Eisenberg (2000), describing lesions designated as 'atypical or dysplastic lichenoid oral lesions', later referred to as 'atypical lichenoid stomatitis' and 'lichenoid dysplasia', suggested they occupied a specific pathological niche, probably representing a primary disturbance of epithelial maturation that indicates malignant potential (Eisenberg and Krutchkoff, 1987, 1992a; Lovas *et al*, 1989; Eisenberg, 1992, 1994; Barnard *et al*, 1993; Allen, 1998). In addition, these lesions are not characterized as lichenoid according to defined clinical data but simply because they show a band-like inflammatory infiltrate at the interface, and this diagnosis is often solely based on histomorphological observations (Figure 5).

The exclusion of cases that present epithelial dysplasia would eliminate false-positive cases of malignant transformation (lichen-like dysplastic lesions that carry inherent malignant transformation risk), as already discussed. However, it cannot be ruled out that the epithelium in OLP may develop epithelial dysplasia during the process of carcinomatous transformation and hence the exclusion of all lesions that resemble OLPs but exhibit epithelial dysplasia may lead to an underestimation of the rate of malignant transformation. Mignogna

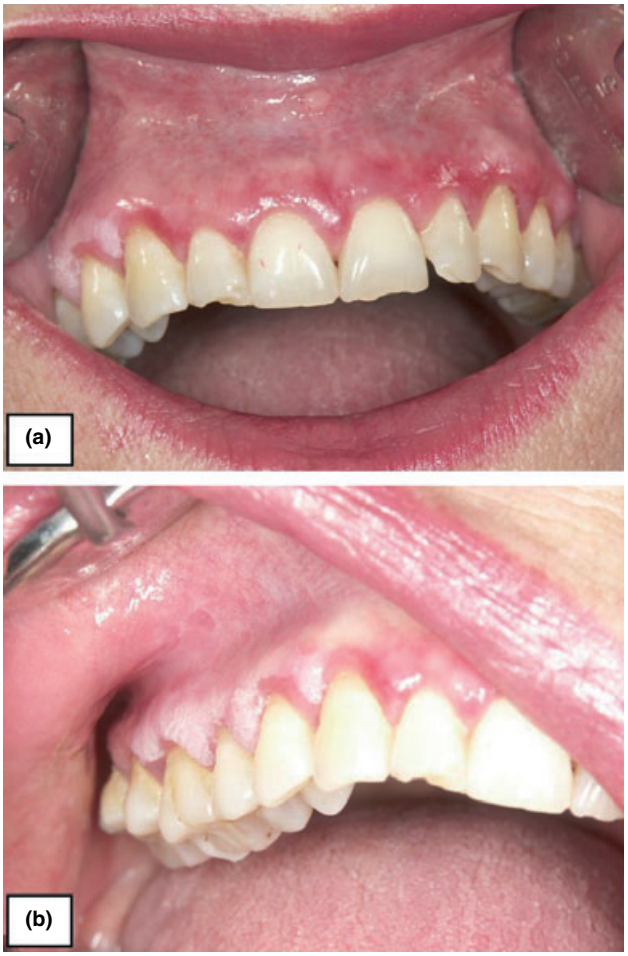

Figure 3 Gingival lesion that manifests as erythematous and atrophic areas (**a**) and verrucous plaque (**b**). Although some reticular images can be observed in (b), the verrucous appearance and unilateral localization are exclusion criteria for the clinical diagnosis of oral lichen planus

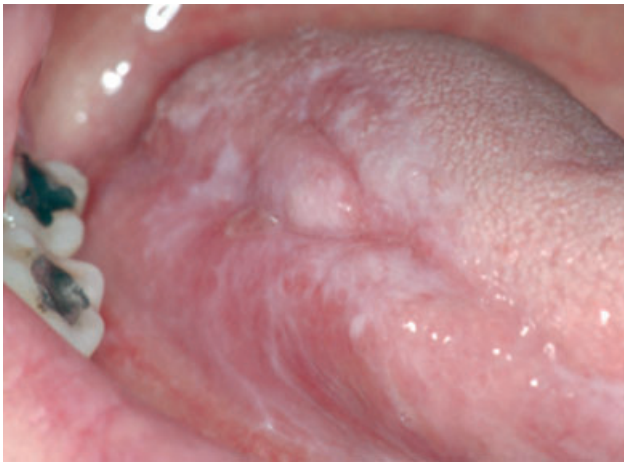

Figure 4 Silver amalgam-associated lichenoid reaction. This is a unilateral lesion in a characteristic localization for the development of this disease

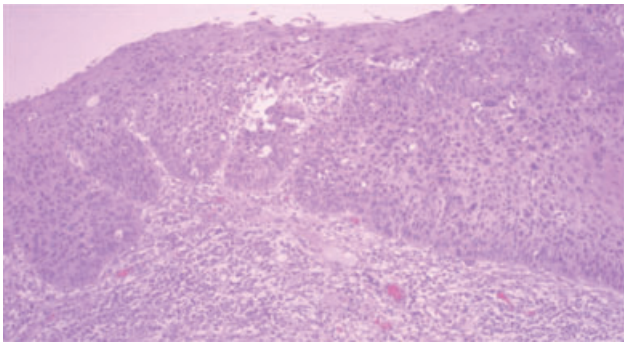

Figure 5 Oral epithelial dysplasia. Due to the immunosurveillance phenomenon, the histopathological image can sometimes simulate an oral lichen planus (OLP). This type of false-positive diagnosis overestimates the risk of OLP malignant transformation

et al (2007) recently reported the presence of severe epithelial dysplasia/carcinoma *in situ* in patients with OLP throughout the course of their disease. Therefore, OLP cases rejected solely for the presence of epithelial dysplasia might correspond to true cases of malignant transformation of OLP.

According to Lodi *et al* (2005), the presence of epithelial dysplasia in an OLP lesion may correspond to two types of conditions: lesions with clinical features of OLP but with dysplasia, and lesions with lichenoid histopathological features (especially band-like inflammatory infiltration) but without the classical clinical features of OLP (e.g. with unilateral distribution or absence of reticular lesions). The first type may represent an early phase of OLP malignant transformation, whereas the second may correspond to one of various clinical conditions with lichenoid histopathology (e.g. lichenoid reactions, lupus erythematosus, leukoplakia, erythroplakia, proliferative verrucous leukoplakia).

Lichenoid reactions are at risk of malignant transformation

Some lichenoid reactions carry a risk of cancer development. Their clinical and histopathological features can be closely similar to those of OLP.

van der Meij *et al* (1999a,b) proposed the designation OLL for cases that are clinically characteristic and histologically compatible, clinically compatible and histologically characteristic, or clinically and histologically compatible with OLP. It is currently proposed that OLL rather than OLP are at high risk of developing cancer (Figure 6). van der Meij *et al* (2007) estimated the number of expected oral carcinomas in 67 patients with OLP and 125 patients with OLL. All malignant transformations (4 of 192, 2.1%) appeared in OLL patients, i.e. an annual OLL malignant transformation rate of 0.71%. Hence, there was no increase in oral cancer risk for patients with OLP but a 142-fold increase for patients with OLL ($P = 0.04$).

There may be considerable overlap between the clinical and microscopic features of LCRs and OLP. Although no association has been established between LCRs and malignant transformation (Mattsson *et al*, 2002), Larsson and Warfvinge (2003) proposed that

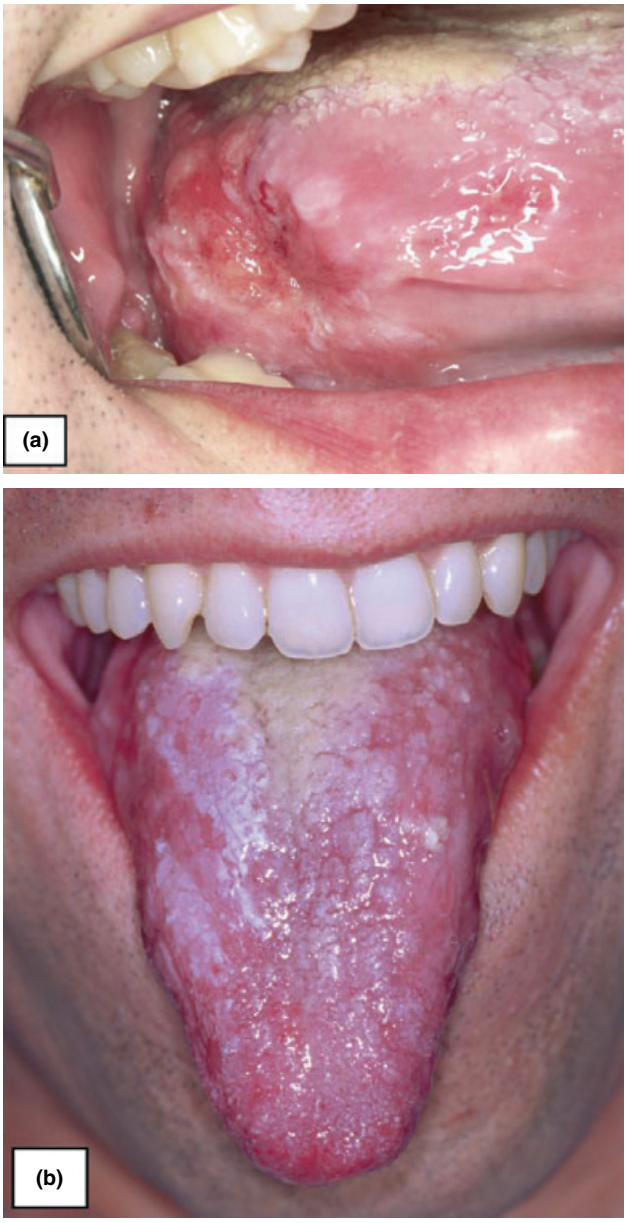

Figure 6 Oral lichenoid lesion that developed a squamous cell carcinoma on the right margin of the tongue (**a**). The lesion only involved the tongue and no typical clinical appearance of oral lichen planus (OLP) was presented (**b**), but a biopsy of the tongue dorsum revealed characteristic histopathological findings of OLP

there may be a similar rate of malignant transformation in LCRs to that observed in OLP, especially in lesions at the lateral border of the tongue, a frequent site for LCRs due to the close contact with silver amalgam restorations (Figure 4). In a subsequent study, Larsson and Warfvinge (2005) found that the cancer had developed on an LCR in 4 of 724 patients with tongue cancer.

Graft-*vs*-host disease, seen mainly in recipients of bone marrow transplants (BMTs), is clinically and histopathologically similar to OLP, and there are numerous reports of the development of oral cancer (mainly oral squamous cell carcinoma) in this lichenoid reaction (Lowsky *et al*, 1994; Deeg *et al*, 1996; Curtis *et al*, 1997; Millen *et al*, 1997; Otsubo *et al*, 1997; Abdelsayed *et al*, 2002; Zhang *et al*, 2002). Indeed, oral cancer was the most frequent cancer found in a study of 20 000 BMT recipients, who showed a 11.1-fold higher than expected risk of developing this disease (Curtis *et al*, 1997). In another study, head and neck squamous carcinoma was the only type of solid cancer found in 78 patients receiving BMT for Fanconi anaemia, with a 167-fold higher frequency than expected (Deeg *et al*, 1996). Nevertheless, strict comparison with OLP patients is hampered by the numerous risks for cancer development in BMT recipients, e.g. primary immunodeficiency, immunosuppressant treatment, viral infections and possible genetic predisposition to cancer.

Follow-up period in studies of malignant transformation
The length of follow-up is an important issue. A short follow-up has major drawbacks and may underestimate the incidence of transformation (Gandolfo *et al*, 2004). Moreover, a short interval between OLP/OLL diagnosis and cancer onset may be the source of problems related to the synchronism of the two lesions. Thus, lichenoid lesions that appear on oral mucosa synchronously with a cancer might be the consequence of a cellular immune response against tumour antigens (Helm *et al*, 1994; van der Meij *et al*, 1999a,b; Rajentheran *et al*, 1999). In addition, initial stages of the cancer, with erythroplastic and leukoerythroplastic lesions (with or without small ulcerations), may resemble and be misdiagnosed as OLP/OLL (Andreasen and Pindborg, 1963; Andreasen, 1968; Shklar, 1972; Voute *et al*, 1992; Lo Muzio *et al*, 1998).

Malignant change in tobacco smokers
Another relevant issue is whether to include patients with chronic oral exposure to carcinogens as it will probably be impossible to differentiate between the transformation caused by tobacco and that secondary to OLP. For this reason, some authors recommend the exclusion of smokers with OLP from studies (van der Meij *et al*, 1999a,b; Lozada-Nur, 2000). However, according to Lodi *et al* (2005), although some cases described may be mainly related to tobacco consumption, the exclusion of one putative risk factor based on the presence of another appears inappropriate and could prevent the identification of new risk factors. Thus, for example, this approach would have impeded identification of the supermultiplicative risk of combined tobacco and alcohol consumption for oral and oropharyngeal cancer development.

Types of studies of malignant transformation
As pointed out by Markopoulos *et al* (1997), study of an inadequate number of patients may not reflect the true percentage malignant transformation of the disease. Reports of isolated cases are of little value, while retrospective studies frequently contain incomplete data. Prospective studies are the most appropriate (Mattsson *et al*, 2002). Thus, the best method to determine the potentially malignant nature of OLP lesions would undoubtedly be by the prospective follow-up study of a

series of patients with OLP and a control group without OLP, including in both groups tobacco smokers and non-smokers. Given the low incidence of oral cancer in the general population, especially in OLP patients, a large number of patients (many thousands) would need to be followed up for at least 5 years (Lodi *et al*, 2005). Retrospective incidence studies also contribute to clarifying the malignant potential of OLP lesions, although they offer less precise information (Silverman *et al*, 1985; Murti *et al*, 1986; Holmstrup *et al*, 1988; Salem, 1989; Voute *et al*, 1992; Barnard *et al*, 1993; Brown *et al*, 1993; Gorsky *et al*, 1996; Vescovi and Gennari, 1996; Silverman and Bahl, 1997; Lo Muzio *et al*, 1998; Cowan *et al*, 1999; Rajentheran *et al*, 1999; Chainani-Wu *et al*, 2001; Eisen, 2002; Rode and Kogoj-Rode, 2002; Yaacob *et al*, 2002; van der Meij *et al*, 2003; Gandolfo *et al*, 2004; Rodstrom *et al*, 2004), and most of them have reported a malignant transformation rate in a narrow range of 0–5.3%, which does not substantially differ from the findings of prospective studies (Lodi *et al*, 2005).

According to Lozada-Nur (2000), prospective studies on the malignant potential of OLP should address whether OLP is a premalignant lesion and whether OLP patients are at risk of developing oral cancer, and they should be designed to identify risk factors of oral cancer in OLP patients after controlling for tobacco and alcohol consumption. As the author acknowledged, such studies are rare. Moreover, many investigations do not adequately document demographic information that might be related to oral cancer development, e.g. socioeconomic status or ethnicity (Lozada-Nur, 2000). There is often no specific reference to the role of diet, probably because food is very abundant in advanced societies (Lozada-Nur, 2000) and researchers may assume, not necessarily consciously, that food deficiencies only arise in resource-poor countries. It should be borne in mind that the diet of patients with OLP may be deficient in fresh fruit and vegetables because of the discomfort and pain caused by their consumption (Lozada-Nur, 2000). The importance of diet in oral cancer aetiology has been addressed in some epidemiological analyses (McLaughlin *et al*, 1988; Gridley *et al*, 1990; Block *et al*, 1992). Finally, no or little cognizance has been taken of the possible effects of topical immunosuppressants used in the treatment of these lesions.

Malignant transformation risk factors in patients with OLP

Numerous studies (Silverman *et al*, 1985; Barnard *et al*, 1993; Markopoulos *et al*, 1997; Hietanen *et al*, 1999; Eisen, 2002; van der Meij *et al*, 2003; Rodstrom *et al*, 2004; Mignona *et al*, 2006) have been unable to identify risk factors for cancer development in patients with OLP. It has therefore been proposed by some authors that carcinomatous transformation is part of the natural history of the disease or is attributable to unknown risk factors (van der Meij *et al*, 2003).

With regard to tobacco use, it is tempting to speculate that the development of cancer in OLP could result from an interaction of the clinical and histological atrophy with tobacco carcinogens, enhancing the action of these agents (Kaugars and Svirsky, 1982; Kaplan and Barnes, 1985; Lind *et al*, 1985). However, many authors (Murti *et al*, 1986; Barnard *et al*, 1993; Eisen, 2002; van der Meij *et al*, 2003; Gandolfo *et al*, 2004) found no relationship between tobacco and/or alcohol consumption in patients with malignant transformation in OLP. Results published by Rajentheran *et al* (1999) indicated that tobacco and alcohol consumption may even be lower in these patients than in patients developing oral cancer in the absence of OLP. In fact, as already commented, many authors exclude cases of malignant transformation of OLP in smokers from their analysis, hampering assessment of the combined risk of OLP and tobacco for cancer development.

With respect to the clinical form of OLP, numerous authors (Silverman *et al*, 1985; Murti *et al*, 1986; Barnard *et al*, 1993; Duffey *et al*, 1996; Markopoulos *et al*, 1997; Hietanen *et al*, 1999; Rajentheran *et al*, 1999; Silverman, 2000; Eisen, 2002; Lanfranchi-Tizeira *et al*, 2003; van der Meij *et al*, 2003) found that atrophic-erosive forms predisposed to cancer development, but this remains controversial. In some series (Barnard *et al*, 1993; Markopoulos *et al*, 1997; Lo Muzio *et al*, 1998; Hietanen *et al*, 1999; Mignogna *et al*, 2001, 2007; Lanfranchi-Tizeira *et al*, 2003), keratotic forms (plaques) were also relevant, both when they appeared alone and when associated with atrophic-erosive lesions. In contrast, Gandolfo *et al* (2004) found that non-reticular OLP cases were not more prone to malignant change than reticular forms and suggested that the idea of atrophic-erosive or plaque forms being more frequently related to cancer development was based on non-controlled studies and isolated case reports (Silverman *et al*, 1985, 1991; Murti *et al*, 1986; Porter *et al*, 1997). Mattsson *et al* (2002) reported that specific clinical features cannot explain the transformation of this disease, as the percentage transformation was similar among the different types of OLP.

Analyses of malignant transformation risk factors have also considered the different intraoral localizations of LP. The tongue appears to be the preferred site for the emergence of a cancer (Holmstrup *et al*, 1988; Barnard *et al*, 1993; Duffey *et al*, 1996; Markopoulos *et al*, 1997; Silverman and Bahl, 1997; Lanfranchi-Tizeira *et al*, 2003) but Mignogna *et al* (2001) found a significantly higher frequency of carcinomas at the midline of the palate, gingiva and lips, and Rajentheran *et al* (1999) reported the buccal mucosa to be the site with the highest risk of cancer appearance in OLP.

Regarding gender and age, there appears to be a general consensus that the risk is higher in women than in men (Duffey *et al*, 1996; Hietanen *et al*, 1999; Mignogna *et al*, 2001; Gandolfo *et al*, 2004). Some authors reported that an oral cancer most frequently develops on an LP between the sixth and seventh decade of life (Barnard *et al*, 1993; Duffey *et al*, 1996; Hietanen *et al*, 1999; Lanfranchi-Tizeira *et al*, 2003), although much lower mean ages have also been documented (Marder and Deesen, 1982; Murti *et al*, 1986). The mean

interval between OLP diagnosis and cancer diagnosis ranges widely from 20.8 months (Lanfranchi-Tizeira *et al*, 2003) to 10.1 years (Holmstrup *et al*, 1988), although the maximum risk is reportedly between 3 and 6 years after OLP diagnosis (Duffey *et al*, 1996; Hietanen *et al*, 1999). In contrast, Silverman *et al* (1985) concluded that disease duration is not a transformation risk factor.

It has been suggested that OLP malignant transformation may be associated with modifications in diet imposed by symptoms. Thus, Lozada-Nur (2000) and Gandolfo *et al* (2004) postulated that patients with OLP probably consume less fresh vegetables and fruit, especially citrus fruit, which may itself increase cancer risk (McLaughlin *et al*, 1988).

Some infectious factors have also been implicated. A study by Hietanen *et al* (1999) in patients with OLP and cancer demonstrated, using periodic acid-Schiff staining, vigorous fungal growth in culture in five of eight cases and hyphae in two of eight cases, significantly more frequent than in controls. It is thought that *Candida albicans* may be an important factor in OLP malignant transformation (Eisen, 2002; van der Meij *et al*, 2003) as a consequence of *N*-nitroso benzylmethylamine production (Krogh *et al*, 1987). The treatment of oral fungal infection has been specifically recommended for OLP patients (Hietanen *et al*, 1999). Hepatitis C virus (HCV) infection has also been considered as a factor, and there have been reports, mainly in southern Europe and Japan, of a higher prevalence of this infection in OLP patients (Del Olmo *et al*, 2000). The appearance of carcinomas in patients with HCV infection has been reported (Nagao *et al*, 1995; Carrozzo *et al*, 1997; Porter *et al*, 1997; Lo Muzio *et al*, 1998), suggesting that HCV infection might increase the risk of oral cancer in patients with OLP (Gandolfo *et al*, 2004). Gandolfo *et al* (2004) observed that four of nine OLP patients who developed carcinomas were infected with HCV, although no significant relationship was found, probably because of the small sample size. Lo Muzio *et al* (1998) found anti-HCV antibodies in 22.4% of patients with malignantly transformed OLP, and Nagao *et al* (2005) proposed that HCV secreted in saliva may play a role in OLP malignant transformation. Nevertheless, as acknowledged by Sorensen *et al* (1998), results are difficult to interpret because HCV is a common cause of hepatic cirrhosis, itself an independent risk factor for oral cancer.

Finally, there is considerable and increasing interest in the possible influence of immunosuppression on the malignant transformation of OLP lesions. The treatment of choice, mainly topical corticosteroids (Lozada-Nur, 2000; Gonzalez-Moles *et al*, 2002, 2003; González-Moles and Scully, 2005a,b), may, it has been proposed, make patients more vulnerable to malignant transformation (Duffey *et al*, 1996). Some immunosuppressants, such as cyclosporin, may promote cancer progression both by direct cellular effect and by effect on host immune cells (Hojo *et al*, 1999). Azathioprine, used for chronic GVHD treatment in BMT patients, may be a risk factor for squamous cell carcinoma (Deeg *et al*, 1996), although this is controversial (Lowsky *et al*, 1994; Curtis *et al*, 1997). Tacrolimus, a powerful macrolide immunosuppressor, has also been associated with cancer development in some patients (Hernandez *et al*, 2003; Becker *et al*, 2006). It has also been proposed that immunosuppression, by reducing symptoms, might increase the probability of progression to an advanced stage before diagnosis and treatment of the cancer (van der Meij *et al*, 2003). However, other authors consider that immunosuppressant therapy does not increase the risk of transformation (Barnard *et al*, 1993; Hietanen *et al*, 1999; Rajentheran *et al*, 1999; Gandolfo *et al*, 2004; Mignogna *et al*, 2007) and might even reduce it (Eisen, 2002). Thus, it has been proposed that a microenvironment rich in proinflammatory cytokines may be especially favourable for neoplastic promotion, suggesting that more aggressive immunosuppressant treatments against the inflammatory response in OLP might restore normal immunosurveillance and interrupt neoplastic progression (Eisen, 2002).

Clinicopathological characteristics of tumours developing in OLP

Clinically, carcinomas that appear on OLP are mainly exophytic keratotic lesions (Lo Muzio *et al*, 1998; Fatahzadeh *et al*, 2004) but sometimes show endophytic growth patterns (Lo Muzio *et al*, 1998). Markopoulos *et al* (1997) suggested that rapid expansion of the lesion should raise suspicion of malignant transformation but Mignogna *et al* (2001) found neither the extension nor severity of symptoms a useful indicator of transformation – rather they considered the loss of lesion homogeneity at a specific site to be most relevant. This clinical sign is especially useful when only a small area is involved, as OLP usually affects various areas or a large area.

An important feature of the presentation and clinical course of carcinomas that arise on OLP is their tendency to multiplicity. Mignogna *et al* (2002) found that 29% of patients developing carcinomas in OLP had two or more independent neoplastic lesions (19% with a second tumour, 10% with >2 metachronous tumours). This finding confirmed previous reports by Duffey *et al* (1996) (20% of patients with second primary tumours) and Lo Muzio *et al* (1998) (35.7% of patients with second primary tumours). The most recent study of multiple malignant transformation in patients with OLP (Mignogna *et al*, 2007) found that out of 45 transformed cases, 20 (45%) presented with a single 'neoplastic event' (severe dysplasia/carcinoma *in situ* or invasive carcinoma) and 25 (55%) with at least two neoplastic events: nine patients (36%) with two events, 14 (56%) with three to six events and two (8%) with 12 and 16 neoplastic events respectively. In 20% of the patients with multiple neoplastic events, new malignancies appeared in the same site as the primary tumour but in 80%, the second and subsequent neoplastic events appeared at other sites in the oral cavity, with a tendency to a greater variety of affected sites with a larger number of events. They also reported that

tumours usually appeared in areas with clinical OLP. According to the authors, this high frequency of multiple intraoral localizations of second primary tumours is consistent with the field cancerization phenomenon and indicates that OLP may have an intrinsic predisposition to tumour development.

The metastatic capacity of carcinomas developing in OLP has been addressed by Mignogna *et al* (2002), who showed that 24% of these patients had detectable lymph-node metastases at the time of diagnosis. More recently, the same authors (Mignogna *et al*, 2007) reported that 94% of 97 neoplastic events observed were TisN0M0 or T1N0M0 (intraepithelial neoplasia or microinvasive carcinoma < 1 mm), and 6% were stage III (three tumours) or IV (three tumours). Histopathologically, most tumours detected in OLP are well-differentiated squamous cell carcinomas [70% in the study by Lo Muzio *et al*, (1998); 100% in the study by Markopoulos *et al*, (1997)].

Finally, there are conflicting results on the prognosis of patients with neoplasia in OLP, some indicating a poor prognosis (Hietanen *et al*, 1999; Mignogna *et al*, 2001, 2002), but Mignogna *et al* (2007) reported 100% 3-year and 97% 5-year survival, although there may have been a bias in this study as the neoplastic events corresponded to severe dysplasias/carcinomas *in situ* in most patients, thanks to a meticulous follow-up programme.

Management of patients with OLP in relation to malignant transformation risk

Several authors (Scully *et al*, 1998; Mignogna *et al*, 2001, 2002; Gandolfo *et al*, 2004) recommend the careful and regular follow-up of OLP patients to ensure early detection of any cancer. This approach is also justified by the frequent appearance of second primary tumours in these patients. According to Gandolfo *et al* (2004), all OLP patients should be followed up regardless of the presence/absence of other risk factors for oral cancer development or the clinical presentation of the disease, based on reports of similar frequencies of malignant transformation on reticular and non-reticular lichen planus (Mattsson *et al*, 2002; Gandolfo *et al*, 2004). There is no consensus on the annual frequency of follow-up but van der Meij *et al* (2007) proposed two visits and Scully *et al* (1998) two to four visits per year. However, Lo Muzio *et al* (1998) found no significant reduction in recurrence or mortality with three visits per year compared with the results observed with a lower frequency of visits. Frequent follow-up examinations appear fully justified in patients who already have a carcinoma because of the high risk of developing a second tumour. Mignogna *et al* (2002) proposed the strict follow-up of patients with oral and neck examinations every 2 months during the 5- to 9-month period after the diagnosis of oral carcinoma, when the risk of metastasis or second primary tumour is maximum. The same authors subsequently reported (Mignogna *et al*, 2004, 2006 Mignona *et al*, 2006) that a programme of three follow-up examinations a year enables detection of malignant transformation in early or microinvasive intraepithelial states, which generally have a very good prognosis. However, their programme did not provide early detection of malignant transformation in a small group (6/25) of their patients who developed multiple carcinomas, which were detected only in advanced stages, and this group showed a 50% mortality at 5 years (3/6 patients). It is evident that malignant transformation cannot readily be visibly detected in all patients, probably reflecting a rapid transition from intraepithelial neoplasia to invasive carcinoma within a few months.

In relation to the healthcare professionals who should be involved, there is to date no strong scientific evidence to support that the examinations should be performed by oral medicine specialists. According to Gandolfo *et al* (2004), these procedures should be performed by general dentists, using available economic resources to educate and train them in early detection of cancer. Besides undergoing a meticulous clinical examination to assess OLP lesion modifications and transformation signs (Mignogna *et al*, 2001), OLP patients should be specifically examined at each appointment to detect and resolve additional factors that may predispose to cancer, including treatment of *C. albicans* infections (Mignogna *et al*, 2001), calculus removal, and repair of poorly fitting prostheses.

Possible molecular bases for an epithelium prone to malignant transformation: role of the inflammatory infiltrate

Malignant transformation of OLP may be related to, or dependent on, a series of molecular stimuli originating in the inflammatory infiltrate (Mignogna *et al*, 2004). Chronic inflammation has been associated with various types of cancer (Coussens and Werb, 2002; Clevers, 2004; Philip *et al*, 2004), and it has been widely reported that the inflammatory infiltrate can be a strong risk factor for cancer development in ulcerative colitis, atrophic gastritis and Barret's oesophagus, among other diseases (Balkwill and Mantovani, 2001; O'Byrne and Dalgleish, 2001). In fact, it was recently proposed that OLP could be included in this group of diseases (Mignogna *et al*, 2004). Some molecules and radicals generated by inflammatory cells can act as mutagenic agents for epithelial cells or influence important cell cycle regulation mechanisms, e.g. apoptosis, cell cycle arrest and cell proliferation, among others.

Mutagenic mechanisms on epithelial cells in OLP

Reactive oxygen species and reactive nitrogen species appear to play a key role in this association between chronic inflammation and cancer (Chaiyarit *et al*, 2005), as observed in the biliary epithelium of hamster chronically inflamed by repetitive parasitical infection (Pinlaor *et al*, 2003), gastric epithelial cells of patients with *Helicobacter pylori* (Ma *et al*, 2004) and hepatocytes of patients with hepatitis C (Horiike *et al*, 2005). In patients with OLP, inflammatory cells may contribute an excess of nitric oxide (NO) via expression of inducible

nitric oxide synthetase (iNOS) (Chaiyarit *et al*, 2005). The NO generated by iNOS reacts with O_2 to produce $ONOO^-$ (Wink and Mitchell, 1998), which induces the formation of both 8-oxo-7,8-dihydro-2′-doxyguanosine (8-oxodG) and 8-nitroguanine (Yermilov *et al*, 1995) in the nucleus of epithelial cells. Formation of 8-oxodG is a known cause of G-T transversion, which can promote carcinogenesis (Shibutani *et al*, 1991; Normark *et al*, 2003). 8-nitroguanine undergoes a spontaneous depurination that leads to apurinic sites of the DNA (Yermilov *et al*, 1995). The resulting apurinic sites can also give rise to G-T transversion (Loeb and Preston, 1986), therefore 8-nitroguanine is a potential DNA mutagen.

A further source of possible mutation in OLP derives from the action of cyclooxygenase-2 (COX-2) that is also produced by inflammatory infiltrating cells. Among other actions, COX-2 intervenes in the metabolism of arachidonic acid, generating the carcinogenic metabolite malondialdehyde, which can damage DNA (O'Byrne and Dalgleish, 2001; Mignogna *et al*, 2004).

Apoptotic response in OLP

Despite the intense lymphocyte attack suffered by basal cells in OLP and the mutagenic effects to which they are exposed, remarkably few apoptotic phenomena are observed in this cell compartment. This has been demonstrated by several researchers (Dekker *et al*, 1997; Bloor *et al*, 1999; Neppelberg *et al*, 2001; Tobón-Arroyaye *et al*, 2004), including our own group (Bascones-Ilundain *et al*, 2005, 2006, 2007; González-Moles *et al*, 2006) by application of the TdT-mediated x-dUTP nick end labelling (TUNEL) technique and analysis of the immunohistochemical expression of caspase-3. There is growing support for the idea that the scarcity of epithelial apoptotic phenomena may be a consequence of stimuli from the inflammatory infiltrate itself (O'Byrne and Dalgleish, 2001; Mignogna *et al*, 2004). Thus, it has been shown that the macrophage migration inhibitory factor and the chemokine Regulated on Activation, Normal T Expressed and Secreted (RANTES), which are released by the infiltrate, can exert anti-apoptotic effects on epithelial cells (Mignogna *et al*, 2004). A low frequency of apoptotic phenomena has also been observed in the inflammatory infiltrate of OLP (Bascones-Ilundain *et al*, 2006; González-Moles *et al*, 2006), which may contribute to generating persistent and massive infiltrates in this disease and enhance anti-apoptotic or other effects of the inflammatory infiltrate on underlying epithelial cells..

Proliferative response in OLP

Most studies on cell proliferation in OLP have reported a marked increase in the proliferation rate of basal epithelial cells (Maidhof *et al*, 1981; Schifter *et al*, 1998; da Silva Fonseca and do Carmo, 2001; Valente *et al*, 2001; Taniguchi *et al*, 2002; González-Moles *et al*, 2006), and some authors have proposed that this might be an important event in the development of cancer in OLP (Taniguchi *et al*, 2002). Valente *et al* (2001) found that the cell proliferation rate, according to the ki-67 expression, was significantly higher in OLP patients who developed cancer than in patients who did not. This increase in the proliferation rate is probably produced by stimuli from the inflammatory infiltrate. Thus, RANTES triggers a cascade of proliferative transduction signals via induction of phosphatidylinositol 3 kinase and Akt/protein kinase B. COX-2 can also increase the cell proliferation rate in neoplastic and normal epithelial cells (Mignogna *et al*, 2004).

Role of p53 protein

Analyses of the expression of the p53 protein and interpretation of its function in OLP have yielded conflicting results. Most authors (Ogmundsdottir *et al*, 2002; Hofseth *et al*, 2003; Meek, 2004; Chaiyarit *et al*, 2005; Ebrahimi *et al*, 2006), including our group (González-Moles *et al*, 2006), found a significantly higher immunohistochemical expression of this protein in the basal layer of affected *vs* normal oral mucosa samples (Ogmundsdottir *et al*, 2002; Lee *et al*, 2005; González-Moles *et al*, 2006). These findings suggest that p53 expression is induced by damage to DNA (Meek, 2004). However, there is no consensus on the mechanism that would explain this overexpression. For some researchers (Chaiyarit *et al*, 2005), the immunohistochemical detection of p53 is due to a mutation of the gene secondary to oxidative and nitrative damage. This might lead to a mutant form of the protein that is unable to exert its function of surveillance of the integrity of the genome, which might have important repercussions for the development of cancer in OLP. However, this high frequency of p53 expression is not consistent with the much lower frequency of malignant transformation of OLP than would be expected with the mutation of a key genome protection gene shown to be altered in more than 50% of oral carcinomas (Gasco and Crook, 2003). The very few mutational analyses of the p53 gene in OLP have produced contradictory results. Whereas Ogmundsdottir *et al* (2002) observed mutation of this gene in 30% of OLP cases, Schifter *et al* (1998) detected no cases with this mutation. Our group (González-Moles *et al*, 2006) and other authors (Dekker *et al*, 1997; Tanda *et al*, 2000) have proposed that the frequent overexpression of p53 largely corresponds to the wild type of the protein, which may act preferentially to halt the cell cycle for DNA repair. The observations that led to this conclusion were as follows: the much lower OLP malignant transformation rate than could be expected if the p53 gene was truly mutated; the lack of association between p53 expression and apoptosis markers (González-Moles *et al*, 2006); and the significant association in OLP between the expression of p53 and that of p21, which arrests the cell cycle for DNA repair via a pathway dependent from that of p53 (González-Moles *et al*, 2006).

Hypothesis on the possible molecular bases of OLP malignant transformation

Various researchers (Schifter *et al*, 1998; da Silva Fonseca and do Carmo, 2001; Valente *et al*, 2001; Taniguchi *et al*, 2002), including our group (Bascones-Ilundain *et al*, 2005, 2006, 2007; González-Moles *et al*,

2006), consider that the response of epithelial cells to intense T lymphocyte attack in OLP, with scarce apoptosis and increased cell proliferation, is aimed at preservation of the epithelial structure. Thus, if most attacked basal cells died of apoptosis, the result would be the loss of epithelial regenerative capacity and the appearance of erosive lesions, the most severe clinical situation in OLP. We hypothesize that anti-apoptotic and proliferative stimuli are generated by the inflammatory infiltrate as a defence against this possibility, activating the p53-related DNA repair system in a high proportion of cells. Consequently, the malignant transformation rate is very low in an epithelium that would theoretically be prone to this phenomenon. Everything would change if the genome protection mechanisms failed, when the anti-apoptotic, proliferative and mutagenic stimuli to which OLP-affected oral epithelium is subjected would act synergistically, favouring carcinogenesis. Moreover, as these disorders affect wide areas of the oral mucosa, field cancerization phenomena would be produced, explaining the appearance of multiple secondary tumours once a primary tumour is established (Mignogna *et al*, 2007).

Conclusion

The malignant potential of OLP remains controversial, and different research groups have proposed distinct approaches and interpretations. In order to elucidate this issue, a worldwide multi-centre study of a large number of patients is required after agreement has been reached on the inclusion and exclusion criteria to be adopted. The objectives of such a study should be to establish consensus on some critical questions, including the true frequency of malignant transformation, the risk factors for cancerization, the influence of immunosuppressant treatment on the development of cancer on OLP and the most appropriate clinical management of these patients. Until this consensus is fully established, it appears advisable to carry out a meticulous follow-up of patients with OLP, similar to the recommended approach for early detection of the malignant transformation of other suspect lesions.

Author contributions

Gonzalez-Moles and Gil-Montaya were responsible for critical reading of all the mentioned works in the bibliography and for the redaction of the manuscript. Scully was responsible for a critical reading of all the mentioned works and reviewed the final version of the manuscript.

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