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ORIGINAL ARTICLE

Course of oral lichen planus: a retrospective study of 808 northern Italian patients

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OBJECTIVES: To undertake a retrospective inspection of the general features, clinical presentation and outcome of 808 Italian patients with oral lichen planus (OLP), followed up from 6 months to 17 years.

RESULTS: The mean age was 61 years for women (*n* = 493) and 58 years for men (*n* = 315). More than 20% of the total cases had liver abnormalities (*n* = 164) of which 83.5% infected with hepatitis C virus (*n* = 137). The reticular and plaque form were the predominant type, affecting almost 60% of patients. 12.3% of patients had also extraoral manifestation, taking into account the skin (*n* = 63) and genital (*n* = 24). Symptoms were present in 40% of the total patients. Only less than 2.47% of patients underwent remission, whereas 78% still had oral lesions at the end of the follow-up period. Treatment was directed towards almost 42% of the patients, mainly using topical corticosteroids. Oral squamous cell carcinoma developed in 15 patients, commonly arising on the lateral border of the tongue.

CONCLUSION: This is one of the largest groups of OLP patients with such long a follow-up ever reported. We confirm the chronic nature of this disorder, rarely remissive and the treatment intend for alleviating symptoms. OLP is established to be a disease with small frequency of malignant transformation.

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Keywords: lichen planus; HCV; clinical features; treatment; outcome

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Introduction

Oral lichen planus (OLP) is a chronic inflammatory disease, affecting nearly 1–2% of the population. While in the majority of instances, cutaneous lesions of lichen planus (LP) are self-limiting and cause itching, oral lesions in OLP are chronic, potentially premalignant, hardly ever undergo spontaneous remission, and are frequently a source of morbidity. To date, the precise etiology remains unknown and most therapies are only symptomatic (Eisen *et al*, 2005). It possibly represents a cell-mediated immunological response to an induced antigenic change in the skin or mucosa in predisposed patients (Carrozzo *et al*, 2004). Numerous drugs have been used with shifting results; however, even if the best treatment remains high-potency topical corticosteroids, management is commonly empirical, with no adequate control groups or corrected study designs (Cribier *et al*, 1998; Carrozzo and Gandolfo, 1999; Chan *et al*, 2000; Scully *et al*, 2000).

Oral lichen planus is unlikely to be caused by a single antigen, given that studies of T-cell receptor variable region genes from lesional OLP T-cells have not revealed the use of a restricted number of different variable region genes (Thomas *et al*, 1997). Probably, OLP is the common outcome of the influence of a limited range of extrinsic antigens, altered self-antigens or superantigens. In a minority of patients, precipitating factors have been identified. These include dental materials (mainly dental restorative materials such as amalgam), drugs (such as non-steroidal anti-inflammatory drugs and angiotensin-converting enzyme inhibitors), stress, trauma and infectious agents (including herpes simplex virus I, herpes virus 6, cytomegalovirus, human papilloma virus, Epstein–Barr virus and *Helicobacter pylori* and hepatitis viruses) (Scully *et al*, 2000). Many studies have demonstrated an association of OLP and hepatitis C in southern Europe and Asia, implying that viral sequences can be discovered in the serum of patients with OLP and the virus was also shown to occasionally replicate in OLP tissue (Carrozzo and Gandolfo, 1999, 2003; Eisen *et al*, 2005).

The oral manifestations of OLP have been described in several large studies around the world (Silverman *et al*, 1985, 1991; Thorn *et al*, 1988; Bagan Sebastian *et al*, 1992; Brown *et al*, 1993; Gorsky *et al*, 1996; Eisen, 2002). Six clinical forms of OLP have been described (reticular, plaque-like, popular, atrophic, erosive and bullosus); whereas reticular form is generally asymptomatic, atrophic and erosive lesions result in profound discomfort. Skin lesions characteristically present as flat-topped, polygonal, violaceous papules regularly covered by a network of fine lines affecting usually wrists, ankles and genitalia.

The most important complication of OLP is the development of an oral squamous cell carcinoma, although this is a very controversial matter. Results from previous studies reported a large heterogeneity and the estimates of the frequency of malignant evolution vary between 0 and 12.5% (Gandolfo *et al*, 2004).

In this retrospective report, we reviewed different features of 808 northern Italian patients with OLP managed in an oral medicine unit. To the best of our knowledge, this is the largest number of patients with OLP, followed-up for 17 years. Based on these results, the current concepts for the clinical course, treatment and malignant potential of OLP are critically discussed.

Methods

Data collection

From a standardized computerized database (Gandolfo *et al*, 2004), the case records of all patients who had been initially referred to the Oral Medicine Unit of the main hospital of the city of Turin, Italy, for the diagnosis and management of OLP, from November 1987 to December 2004, were reviewed and relevant retrospective data selected and extracted. Included patients were those with a minimum follow-up of 6 months.

At baseline, demographic information, histological diagnosis, age at the time of diagnosis and gender, smoking (current or former smoker *vs* non-smoker), alcohol consumption (current of former drinker *vs* non-drinker), first oral symptoms referred, clinical aspect of the lesions, sites of oral involvement, eventually described extraoral manifestations, presence of any systemic disease and use of any drug were searched.

The majority of case files contained the required data for analysis. If necessary, patients were in due course re-contacted by telephone to revise and complete the information.

Subjects had to be resident in Piedmont region, Northwest Italy.

During the follow-up period, we analyzed the duration of the disease, its clinical evolution, treatment provided (e.g. topical, systemic and cryotherapy), any other systemic diseases occurred and other skin or mucosal involvement of lichen reported.

For every patient, we also analyzed the clinical form at the beginning and at the end of the follow-up period, to establish the clinical evolution of OLP in this study population.

We also estimated the risk for oral cancer. A latency time of at least 6 months between the diagnosis of OLP and the diagnosis of the oral carcinoma was considered to exclude concomitant presentation.

Diagnostic criteria for inclusion

According to Krutchkoff *et al*'s (1978) criteria and modified WHO diagnostic criteria (van der Meij and van der Waal, 2003), the diagnosis of OLP has to be based on the following criteria:

1. Presence of characteristic bilateral clinical signs of OLP [papular and/or reticular lesions (Wickham striae) alone or in association with atrophic or erosive lesions]
2. Histological confirmation of clinical diagnosis through incisional biopsy demonstrating the following microscopic characteristic
   - Presence of a well-defined band-like zone of cellular infiltration that is confined to the superficial part of the connective tissue, consisting mainly of lymphocytes
   - Signs of "liquefaction degeneration" in the basal cell layer
3. Absence of signs of epithelial dysplasia at the moment of first diagnosis
4. Absence of suspicion that oral lesions may be related to any drug or oral restoration.

According to the description done at the time of the diagnosis, the clinical forms of OLP were detailed and gathered in two categories: (i) white lichen, which included the papular, reticular and plaque forms; and (ii) red lichen, which included all the atrophic or erosive forms, irrespective of a contemporaneous presence of a white form (Gandolfo *et al*, 2004). In patients with more than one clinical type of lesion, such as reticular and erosive, the most severe form of the disease (e.g. erosive) was used to classify the lesions.

Data analysis

All analyses were performed using SPSS® software (SPSS for windows, version 11; SPSS Inc, Chicago, IL, USA). All different data collected from each patient were later analyzed using descriptive statistics. Continuous variables are expressed as mean ± s.d.

We estimated standardized incidence ratio (SIR) of development of oral squamous cell carcinoma with corresponding 95% confidence intervals. SIRs were obtained by comparison of the observed number of oral tumors with the expected number of cases in our study population. The latter was calculated using the gender and 5-year age class-specific incidence rate of mouth and tongue cancers provided by the Piedmont Cancer registry, city of Turin for the period 1993–1998, as already been previously described (Gandolfo *et al*, 2004).

Results

Patient characteristics at first visit

A total of 1448 patients have been initially selected but 410 patients were excluded because of non-conformation

of the diagnosis and 230 patients were excluded because follow-up period was less than 6 months. Finally, a total of 808 charts of patients with confirmed diagnosis of OLP were retrospectively analyzed, of whom 315 were men (~39%) and 493 women (f:m = 1.56:1). The mean age at presentation was 58.3 years for men (s.d. ± 12.4) and 61.4 years for women (s.d. ± 13.3), showing a high percentage of affected patients between V and VI decades.

Follow-up ranged from 6 to 204 months in our study population (median follow-up of 47.4 months for male and 44.8 for female patients). One hundred eighty-nine patients (23.4%) were followed-up for less than 2 years (median follow-up of 11.8 months), 381 (47.15%) for a long-lasting period of 5 years (median follow-up of 33.4 months) and 238 (29.45%) for more than 5 years (median follow-up of 84.5 months).

Most of the patients were non-smoker (77.8%) and non-drinkers (87.7%). The medical histories of the 808 patients included essential hypertension (20.5%), gastrodoudenal ulcer (10.2%), diabetes mellitus (8.1%), cardiomyopathies (7.6%), neoplastic diseases but not in the upper aereo-digestive way (3.8%), thyroid disease not autoimmune (3%), autoimmune diseases (RA, thyroiditis: 1.5%) and psoriasis (0.9%). Neoplastic diseases were detailed as follows: breast cancer (n = 12), lymphoma (1 f–3 m), uterine cancer (2) and bladder cancer (2 m). Medications above all taken by our cohort study population were anti-hypertensive (17.1%) and different types of ansiolitycs (6.4%).

According to a diagnostic protocol published before (Carrozzo *et al*, 1996), a complete liver profile including serum transaminase levels, total bilirubin, antibodies to hepatitis B virus and hepatitis C virus, and hepatitis B surface antigen, as well as a complete blood cell count, were performed for each patient from 1992 onwards. Seventy-five patients were selected from 1987 to 1991: of those, 29 were lost to the follow-up, but 46 were reviewed and later the tests were performed on them. So, a total of 779 patients underwent a complete liver profile showing more than 21% of the total cases affecting by liver abnormalities (n = 164) of which 83.5% infected with hepatitis C virus (n = 137), 24 patients with non-viral hepatopaties and three cases infected with hepatitis B virus.

During the first visit, while history taking, 156 patients (19.3%) reported that their dentist noticed the lesions first, while the other patients were aware of the disease and they decided to be visited.

According to our clinical classification, 476 patients (58.9%) had white lichen and 332 the red one (41.1%) (Figure 1). Although most patients had multiple oral sites of involvement, among all cases, the buccal mucosa was the single most common site of involvement in each form (73%) followed by the tongue (44%), gingiva (33%), floor of the mouth (4,6%), labial mucosa (1,8%), palate (1,8%) and oropharynx (0,7%). Symptoms were present in 323 patients (40%) (e.g. pain, the single most frequent complaint, but also burning and irritation). Red lesions were easier to have symptoms: 167 patients with atrophic OLP (55 males; 112 females), and 75 with erosive form (30 males; 45 females). Isolated reticular lesions were generally asymptomatic: only 46 patients with reticular form (14 males; 32 females) and 35 with plaque like lesions (16 males; 19 females) complained.

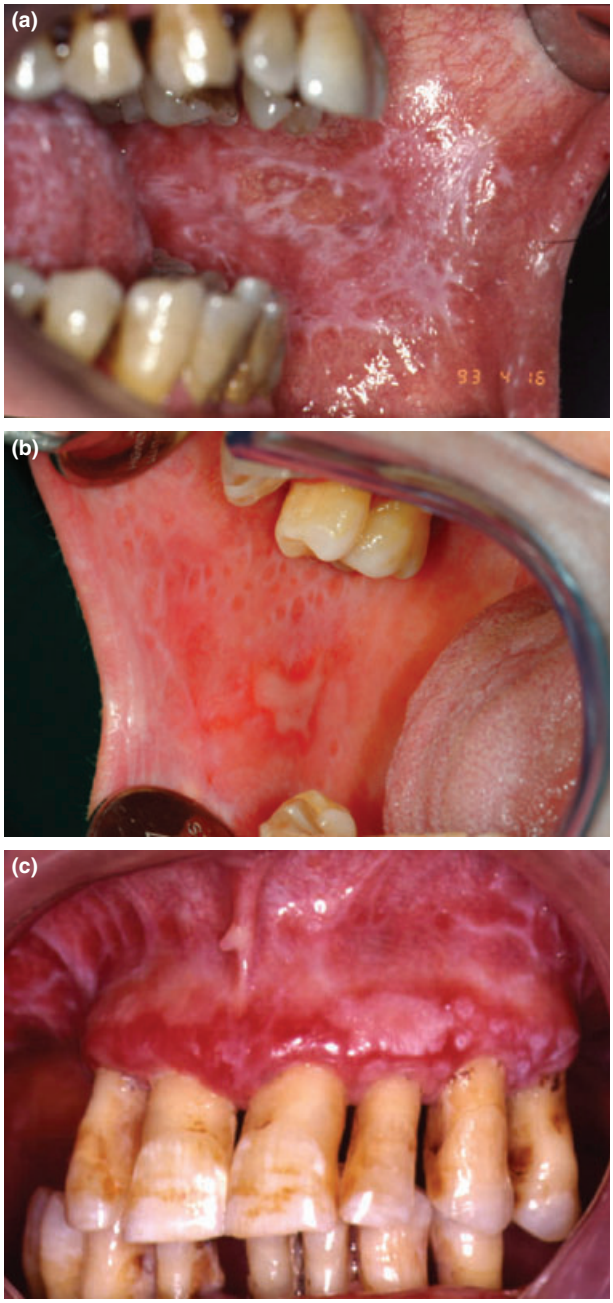

Figure 1 The clinical forms of OLP: **(a)** white reticular forms; **(b)** red lichen, which included all the atrophic-erosive forms, irrespective of a contemporaneous presence of a white form; **(c)** clinical picture of gingival involvement of OLP

More than 12% of patients had also extraoral manifestation; of those, 63 had skin involvement, 24 had genital involvement and 13 in other sites (e.g. scalp, nail, esophageal).

Clinical follow-up changes

Periodical visits of follow-up were conducted for all patients, with a frequency established on the basis of the

clinical feature and the need for therapy. In general, patients with white lichen were seen twice a year for the first 2 years and then once; patients with red lichen were usually seen twice; patients on therapy were seen every 2 months.

During the follow-up period, 4.57% of the total study population developed: diabetes ($n = 1$), hypertension (12), cardiomyopathies (3), gastrointestinal disease (9), non-lichen dermatitis (8), chronic non-viral liver disease (2), HCV-related liver disease (2). Moreover, 11 patients developed cancer diseases: breast cancer ($n = 3$), liver cancer (one female and two males), bladder cancer (2 males), non-Hodgkin's lymphoma (1 female), esophageal cancer (1 female) and intestinal cancer (1 female).

Based upon the digital files, the evolution of the disease was detailed as follows:

- Clinical improvement: during the follow-up period, if it was possible to observe change of the lesion from red to white.
- Exacerbations: changing from asymptomatic to symptomatic lesions, or worsening of a symptomatic form (e.g. from atrophic to erosive form).
- Changes in the morphology of the lesions.
- Partial or complete remission.

Long-term surveillance of patients with LP revealed that exacerbations of the disease were uncommon (Figure 2); 421 patients (52.1%) did not have any changes in the morphology of their white lesions, of whom 350 without treatment (205 females; 145 males) and 71 under medication (44 females; 27 males). One hundred ninety-six patients (24.2%) had unchanged red lesions, of whom 45 without treatment (30 females; 15 males) and 151 under medication (107 females; 44 males). Twenty patients (2.47%) had a total remission (from any type of lesions for at least 12 months), of whom 13 from white lesions (seven females and six male patients) all without treatment, and seven from red lesions, of whom three without therapy (two females and one male) and four after treatment (three females and 1 male). One hundred twenty-two patients (15.1%) showed changes from red lesions to white ones, of whom 35 without treatment (21 females; 14 males) and 87 after therapy (53 females; 34 males). Forty-nine patients (6%) had white lesions transformed into atrophic-erosive ones with acute flare-up, of whom 25 without therapy (10 females; 15 males) and 24 under treatment (16 females; eight males).

Treatment outcome

Treatment was undertaken usually with the goal of achieving complete control of symptoms with minimal side-effects.

For topical treatment, we used clobetasol propionate ointment 0.05% (Clobesol®; Glaxo, Verona, Italy), cyclosporine 3% (Sandimmun Neoral®; Novartis, Origgio, Varese, Italy), fluocinonide ointment 0,05%, (Topsyn®; Teofarma, Valle Salimbene, Pavia, Italy) all mixed separately with 4% hydroxyethyl cellulose gel. Topical medications were usually applied twice daily for at least 2 months. Triamcinolone acetonide (10–20 mg ml^{-1}) injections have also been used as a unique administration eventually repeated after 4 weeks.

Treatment with systemic corticosteroids (prednisone at 1–1.5 mg kg^{-1} in a single morning dose per o.s.), depending on clinical severity, usually for no longer than 8 weeks, was sometimes used; topical corticosteroid therapy, using 0.05% clobetasol propionate ointment mixed in equal parts with 4% hydroxyethyl cellulose gel, twice daily for 2 months and once for another two, was also added in some cases usually to maintain the results.

Anti-mycotic treatment was used as prophylaxis against oropharyngeal candidosis. It consisted of miconazole gel (Micotef®; LPB, Cinisello B., Milano, Italy) applied once daily and 0.12% chlorhexidine mouthrinse

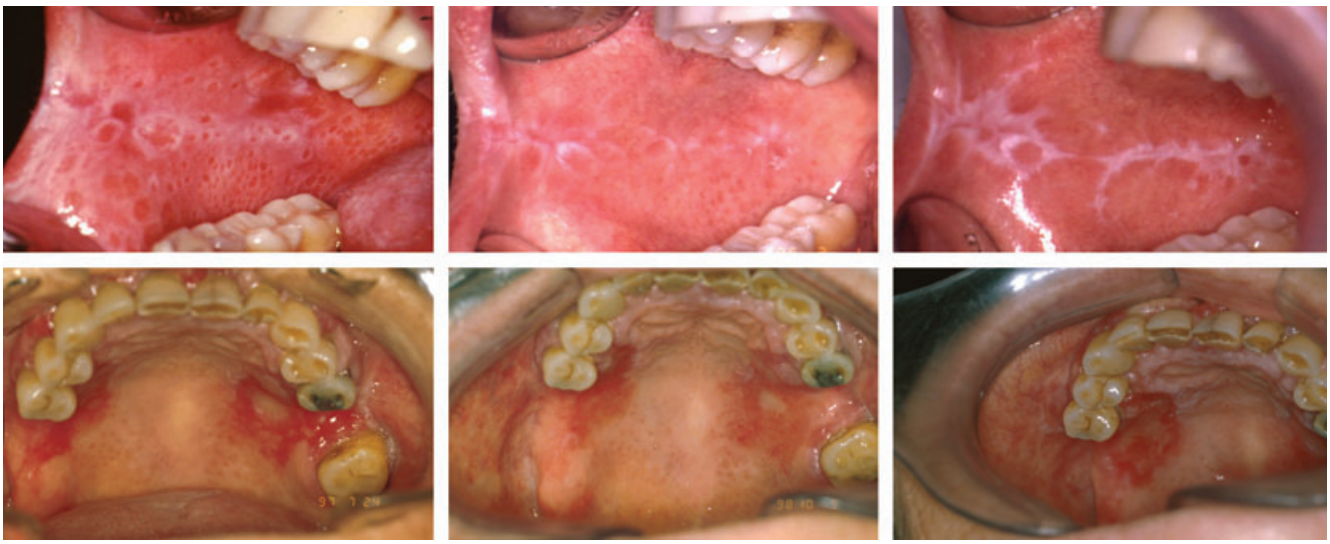

Figure 2 Clinical pictures revealing that usually white and red lesions did not have any changes during the follow-up period (from the left to the right a 5-year timing)

(Plack-out®; BYK, Gulden Italia, Cormano, Milano, Italy) thrice daily.

To evaluate any possible systemic absorption, blood cortisol levels taken at 8:00 AM and blood cyclosporine levels were monitored (Monoclonal antibodies AXSYM; Abbott Laboratories, Abbott Park, IL, USA) at the beginning and at the end of the each protocol. Moreover, blood pressure, weight, blood glucose levels, serum electrolytes, serum creatinine and urea levels, and full blood counts were also recorded at baseline and at the end of treatment, as previously reported (Frances *et al*, 1988). At each subsequent check-up visit, patients were also asked to refer any abnormal effects that may possibly have been linked to OLP therapy.

Cryotherapy was used to treat OLP in our department before 1990, only to promote the cicatrization of erosive lesions (Vercellino *et al*, 1980) and 17 patients were treated with this modality.

Three hundred thirty-three patients (41.2%) needed to be treated, of whom, 138 (41.4% of treated ones) needed more than one therapeutic cycle. One hundred fifty-nine patients (47.7%) had a good response (e.g. a total remission of any kind of lesion for at least 12 months or the passage from a red form to a white one). Two hundred forty-three patients (72.9%) received clobetasol once or more, of whom, 69% had a positive and stable response. Thirteen patients received fluocinonide once (77%) or more and 41% had a positive outcome. Twenty patients took cyclosporine and 85% had a positive response. Eighteen (5.4%) patients had to take prednisone and later clobetasol; of whom 41% had a positive response. Seventeen patients (5.1%) underwent cryotherapy once or more, of whom 64.7% had a good response. Three patients received intralesional triamcinolone, without any positive clinical response. Moreover, 33 patients (9.9%) received several different drugs, sometimes combined, because of recalcitrant lesions and of frequent recurrences.

Malignant transformation

During the follow-up period, three men and 12 women developed an oral squamous cell carcinoma, with a mean time of 52.33 months after the initial diagnosis of OLP (s.d. ± 39.14). The mean age of these patients was 67 years (s.d. ± 9.31). The clinical features of the tumors and some lifestyle characteristics of these subjects are reported in Table 1; tumor grade according to the WHO classification (Pindborg *et al*, 1997) was also detailed as well, moderately or poorly differentiated (G1, G2 or G3 respectively). Fourteen patients had an invasive squamous cell carcinoma whereas one had a verrucous carcinoma. Only four patients had the carcinoma in the same site of the initial biopsy. The overall SIR was 45.3 (95% CI: 21.2–87.3), being higher among women rather than among men, irrespective to the clinical type of OLP and therapy. Moreover, the malignant transformation of the group was calculated at 0.69% per year.

Table 1 Characteristics of OLP patients with malignant development

Patient	*Sex*	*Age (years)*[a]	*General diseases*	*OLP clinical form*	*Biopsy site for diagnosis*	*OLP therapy*	*Site of OSCC*	*TNM*[b]	*Grading*	*Tobacco usage*	*Daily alcohol consumption*	*Latency time*[c]
1	F	80	None	Red OLP	Right border of tongue	Systemic	Left buccal mucosa	T4 N1M0	G3	None	None	108
2	F	75	None	Red OLP	Left border of tongue	Topical	Left buccal mucosa	T1 N0M0	G2	Yes/1 pack daily	None	36
3[d]	F	73	Diabetes, hypertension	White OLP	Right buccal mucosa	None	Left buccal mucosa	T2 N0M0	G2	Yes/>1 pack daily	None	12
4[d]	F	67	Hypertension	Red OLP	Right buccal mucosa	Topical	Left buccal mucosa	T2 N0M0	G1	None	None	37
5	F	67	None	Red OLP	Right buccal mucosa	None	Left border of tongue	T1 N0M0	G1	None	None	8
6	F	49	None	Red OLP	Left buccal mucosa	Topical	Left border of tongue	T2 N1M0	G1	None	None	84
7	F	71	Arthritis	Red OLP	Right buccal mucosa	Topical	Right buccal mucosa	T2 N0M0	G3	Yes/3–4 cigarette daily	None	62
8	F	52	Hypertension	Red OLP	Right border of tongue	Topical	Right border of tongue	T1 N0M0	G1	Yes/1 pack daily	None	62
9[d]	F	69	None	Red OLP	Right border of tongue	Topical	Right border of tongue	T1 N0M0	G2	None	None	10
10	F	65	None	White OLP	Left buccal mucosa	None	Gingiva	T1 N0M0	G1	None	None	24
11	F	67	None	White OLP	Left border of tongue	None	Left buccal mucosa	T2 N0M0	G2	None	None	84
12	F	80	None	White OLP	Left border of tongue	None	Left border of tongue	T2 N0M0	G2	None	2 units daily	24
13	M	72	None	White OLP	Left border of tongue	None	Left buccal mucosa	T1 N0M0	G1	None	None	132
14	M	64	Chronic bronchitis	Red OLP	Left buccal mucosa	None	Right buccal mucosa	T2 N0M0	G1	Yes/>1 pack daily	3–4 units daily	17
15[d]	M	54	Hypertension	White OLP	Left buccal mucosa	None	Left border of tongue	T1 N0M0	G1	None	2 units daily	85

[a]At malignant development.
[b]T classification and neck nodes involvement at the time of diagnosis (Pindborg *et al*, 1997).
[c]In months, excluding the first 6 months of follow-up.
[d]HCV-positive patients.

Discussion

The clinical features of patients in our survey share many similarities with those reported previously, but we also reported some crucial differences.

Oral lichen planus is a relatively common disease, usually affecting women more than twice as men (Silverman *et al*, 1985; Thorn *et al*, 1988; Eisen, 2002; Xue *et al*, 2005). In our cases, the predominance of female patients is not so evident but still is more than 60%. Patients of all ages may be affected, most commonly in the fifth to sixth decades of life, developed at an earlier age in men, and this was confirmed in our study.

As reported previously, most patients with OLP show no increased prevalence of cigarette smoking or alcohol consumption (Eisen, 2002).

Although OLP patients do not appear to have an increased risk of diabetes, diabetics who develop OLP have an increased frequency of atrophic-erosive lesions and a greater proportion of lesions on the tongue (Bagan *et al*, 1993). The correlation of OLP and hypertension has also been proposed (Lowe *et al*, 1976). In our patients, presence of hypertension and diabetes mellitus appeared similar to previous finding, inferior regarding the data attended on the general population, in consideration of the elevate medium age of the group (Silverman *et al*, 1985; Eisen, 2002); moreover, the presence of gastrointestinal peptic disease appears to be a fortuitous association and usually this has never been reported. The common association of LP with chronic liver disease is well established (Carrozzo and Gandolfo, 2003). In particular, several epidemiological data suggests the involvement of HCV in the pathogenesis of oral lichen lesions, although the association appears proven only in some geographical areas, such as Japan and southern Europe, but not others (Lowe *et al*, 1976; Bagan *et al*, 1993; Scully *et al*, 2000; Eisen *et al*, 2005). We have already showed that HCV may occasionally replicate in the oral lichen mucosa (Carrozzo *et al*, 2002). This study again showed a high percentage (16.95%) of patients HCV positive with OLP and this data could not be confirmed by other extensive retrospective study, which did not analyze this correlation.

The elevated number of patients affected by systemic diseases, in our group, explains the various drugs chronically taken: some of them, in special way antihypertensive are possible related to drug-induced oral lichenoid reactions (Lodi *et al*, 2005a,b). Clinical identification of lichenoid drug reactions has been based mainly on subjective criteria although there may sometimes be a predisposition for the oral lesion to be unilateral and erosive (Eisen *et al*, 2005), histologically having a more diffuse lymphocytic infiltrate and contain eosinophils and plasma cells. Our patients taking angiotensin-converting enzyme inhibitors did not showed those clinico-pathological features.

Twenty percent of the patients have been introduced in our unit because of referral by the general dentist practitioner, being therefore the first one to be aware of the disease. These patients usually suffered of white OLP, more frequently asymptomatic, than otherwise they would not be joints to the clinical observation. This finding shows that there is a high awareness of the issue of OLP among Northern Italian dentists and doctor.

The clinical features of oral lesions of patients in this survey share many similarities with those reported previously, in particular the prevalence of white lesions (58.9%) and the major involvement of buccal mucosa (Silverman *et al*, 1985, 1991; Thorn *et al*, 1988; Bagan Sebastian *et al*, 1992; Brown *et al*, 1993; Gorsky *et al*, 1996). In a different way, we also reported a larger incidence of white and red tongue lesions. The gingiva is generally one of the oral sites with the greatest incidence of OLP after the buccal mucosa and the tongue. OLP gingival involvement is very frequently observed, and it is characterized by wide variations in clinical appearance and symptoms, leading, in many cases, to misdiagnosis or undiagnosis (Mignogna *et al*, 2005).

Gingival involvement was reported in 33% of cases. As recently reported (Camacho-Alfonso *et al*, 2007), white lesions were the most frequently observed in the gingiva (almost 70% of the total cases), and the most frequent gingival location was the coincident involvement of the attached and marginal gingiva.

In this study, oral soreness was a common finding only in 40% of total cases; this can be explained because of the large number of white OLP usually asymptomatic.

Specific importance assumes in our study the duration of the follow-up, than concurs us to gain precious data on the clinical course, the necessity of treatment and the eventual complications of the disease. Our patients have been followed up from 6 months to 17 years; in particular 238 patients have been followed for more than 5 years. A single study in literature (Thorn *et al*, 1988) boasts advanced periods but on a smaller number of patients.

During the follow-up period, 4.6% of the patients have developed other pathologies (e.g. hypertension, cardiomyopathies, gastrointestinal disease, diabetes); this is compatible with the medium age of the patients and seems to have a fortuitous relation with the oral disease.

More than 12% of patients had also extraoral manifestation. Different studies reported a larger incidence (up to 50%) (Silverman *et al*, 1985, 1991; Thorn *et al*, 1988; Gorsky *et al*, 1996) and we tried to explain this with two considerations: our patients were evaluated to uncover potential sites of extraoral involvement at the time of diagnosis of OLP without considering the past medical history; moreover, most of the reported studies are dermatological and this could explain the differences of the studied population.

The considerable analyzed period of follow-up in our patients concurs us to confirm the chronic nature of this oral disorder, with a trivial percentage of patients who have shown complete and definitive healing (2.47%), the overwhelming majority that has shown a steady clinical appearance (76.6%) and a minority of patients who got worse (6%). Similar results have been reported by

Silverman *et al* (1985) showing a 3% of spontaneous remissions, and 8% of patients who got worse. Differently, Thorn *et al* (1988) reported a 17% of spontaneous remissions, being this data possibly explained by the longest time of the follow-up (1–26 years).

Patients with OLP are treated with medications that were neither developed nor proposed for oral diseases and, therefore, most lack satisfactory efficacy studies. The most regularly employed and useful agents for the treatment of LP are topical corticosteroids. Patients, who demonstrate desquamative gingivitis, widespread oral disease, or diffuse ulcerations, may not respond effectively to topical corticosteroids alone. The addition of potent immunosuppressant or immunomodulatory agents such as cyclosporine, tacrolimus, pimecrolimus or tretinoin, in topical formulations, may be beneficial in this group of patients (Scully *et al*, 1998, 2000; Eisen *et al*, 2005).

More than 40% of our patients have been treated, of whom more than 40% needed more than one therapeutic cycle during the follow-up period. The greater therapeutic experience has been obtained with clobetasol, used in approximately 73% of the treated patients, alone or in sequence with other active principles; it has been showed as the more effective and more manageable drug, with the greater percentage of immediate therapeutic answers (70% approximately of complete remission of signs and symptoms). In our experience, no serious side-effects arise with this topical corticosteroid (Carbone *et al*, 1999, 2003; Conrotto *et al*, 2006). Recently, we showed that clobetasol propionate in 4% hydroxyethyl cellulose gel, independently from the concentration used, would currently appear to be a treatment of choice for patients with atrophic-erosive OLP, providing comparable clinical efficacy, being safe and well tolerated (Carbone *et al*, 2009). Furthermore, systemic prednisone, followed by topical maintenance therapy with clobetasol, was useful in 70% of treated patients but it showed a greatest number of adverse effects (Carbone *et al*, 1998). Systemic corticosteroids should be reserved for recalcitrant erosive or erythematous OLP, where topical approaches have failed to be effective, or for extensive oral OLP with simultaneous skin, genital, esophageal or scalp involvement (Scully *et al*, 2000).

It has been reported that one-third of OLP patients treated with topical corticosteroids develop secondary candidosis (Lodi *et al*, 2007). Our antimycotic treatment has been effective in preventing iatrogenic oral candidosis.

However, finally, the stability of the therapeutic result turned out quite disappointing: independently from the active principle used and the way of administration, beyond the half of the responsive patients showed again active symptomatic disease, and can need new therapeutic participation, confirming the chronic course of the oral disease and the essentially symptomatic character of therapeutic treatments.

It has been reported that the most important complication of OLP is the development of an oral squamous cell carcinoma, although this is a very controversial matter (Gandolfo *et al*, 2004). We found that 1.85% of the subjects in the cohort developed an oral carcinoma during the follow-up period, mainly female subjects and rarely heavy smokers, of whom six have been treated with topical steroids. As recently reported by our group (Arduino *et al*, 2008) and similar to former current studies, tobacco is not so often associated with oral cancer development, above all in female patients. To date, the best evidence currently available on the potentially malignant nature of oral LP is from follow-up studies and retrospective incidence studies (Lodi *et al*, 2005a,b), and our data are similar to previous one estimating the frequency of malignant evolution between 0.4 and 3.3%, mostly involving female patients. This study did not find an excess of risk for the atrophic-erosive form (red lichen) as compared with white lichen. Moreover, immunosuppressive therapy did not seem to influence the risk for oral cancer. As most of the patients were treated with topical and sometime systemic steroids plus antimycotics, our study suggested that these therapeutic modalities do not affect the risk of malignant transformation of OLP. We also tried to analyze the role of HCV infection on OLP outcome. Although the percentage of HCV-positive patients who developed an oral carcinoma is higher in comparison with HCV-negative patients, the increased risk was not significant, possibly because of low statistical power. This result is difficult to interpret, because HCV is a common cause of liver cirrhosis, which may represent itself an independent risk factor for the development of oral cancer (Sorensen *et al*, 1998). We were not able to disentangle between the effect of HCV and the effect of cirrhosis, as only few patients had a liver biopsy or were screened for liver cirrhosis.

In conclusion, this is one of the largest groups of OLP patients with such long follow-up ever reported. We can confirm the chronic nature of this disorder; only 2.47% of patients underwent spontaneous remission, whereas 78% still had oral lesions at the end of the follow-up period, independently of the treatment proposed. The contemporary presence of different systemic pathologies seemed to be of all accidental and compatible with the medium age of the patients; only the hepatitis C virus infection seemed to be significantly associated with the OLP. The use of alcohol and tobacco and the chronic drug assumption do not seem to play a role in the pathogenesis of OLP. More than one-third of the patients need a specific treatment during their life. Moreover, independently from the proposed medication, treatment should be focused at achieving definite goals after considering the degree of clinical involvement, the main clinical type of lesions and, above all, the patient's symptoms. Reticular lesions generally require no therapy but only observation for change. In general, all treatment should be aimed at eliminating atrophic and ulcerative lesions, alleviating symptoms, and potentially decreasing the risk of malignant transformation. Superpotent halogenated corticosteroids such as clobetasol, in adhesive pastes, showed to be the most effective treatment modality to control OLP, even if it is complicated to evaluate dissimilar treatment modalities

such as we used during the follow-up period. Probably, future prospective studies, with large number of patients, could give more valuable information.

Retrospective observational studies such as the present survey may have different limitations; however, we added new information regarding the long-term behavior of OLP, which has rarely been reported. As the greater part of patients will have long-lasting OLP, and possibly a risk of malignant transformation, there is a crucial need for patients to be reviewed clinically by correctly trained clinicians, not only oral medicine clinician but also primary dental healthcare workers, for very many years.

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