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Lichen planus of the lips: an intermediate disease between the skin and mucosa? Retrospective clinical study and review of the literature

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Title

"Lichen planus of the lips: an intermediate disease between the skin and mucosa? retrospective clinical study and review of the literature**"**

Abstract

Background: Lichen planus of the lips (LPL) is not frequently described in literature. The objective of this study is to investigate the clinical outline, behaviour and prognosis of LPL.

Methods: Clinical data of patients with true oral lichen planus (OLP) involving the lips diagnosed and treated at our Oral Medicine Unit have been collected and analyzed. Concurrently, a PUBMED search was carried out from 1950 to March 2014 to assess epidemiological and clinical data about LPL.

Results: Our case series revealed 13 patients (F/M ratio=0.4) with a mean (±SD) age of 71.85 (±6.72). The lower/upper lip involvement ratio was 9, mainly with mixed clinical patterns (76.9%), generally including erosion and mild keratosis. In most of the cases the lips were involved with other oral sites, but displayed a better evolution of the lesions.
The literature review showed 21 reports of LPL (35 patients, F/M ratio=0.4) with a mean (±SD) age of 45.35 (±16.19).

Conclusions: In literature, erosive (28.57%) lower lip lesions showed a clear predominance (lower/upper lip ratio=6.5). One case of malignant transformation was also reported. The prevalence of isolated LPL was clearly reported only in two studies, ranging from 0.51% to 8.9%. In our patients lesions were mostly found at the inner border of the lower vermillion and presented a tendency to self-limitation, or to regression after treatment, like cutaneous lesions. The lip lesions were small and easy to overlook and therefore the prevalence of these lesions may have been underestimated.

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Introduction

Lichen planus (LP) is a chronic T-cell-mediated mucocutaneous inflammatory disease with an etiology and pathogenesis which is not completely understood [1]. It affects 1-2 % of the general adult population, with the highest frequency in women over 40[2].

Histological characters pathognomonic for LP are: the "liquefactive degeneration" of the basal cell layer, a juxtaepithelial bandlike zone of cellular infiltration, predominantly lymphocytic, and the absence of epithelial displasia. An interruption of the basement membrane, the appearance of eosinophilic civatte bodies, parakeratosis, acanthosis and histological cleft formation may also be present[2-3].

The clinical presentation is complex, with white, red or mixed lesions. Six variants for oral LP have been described: reticular, papular, plaque-like, erosive, atrophic and bullous. The reticular form, with white striations (Wickham's striae) is the most typical[4]. These variants can also coexist and change during the course of the disease[5].

Oral involvement (OLP) is quite common and is often the only site of manifestation of the disease. OLP typically affects the buccal mucosa, tongue and gingiva, with symmetrical and bilateral lesions, and less frequently the lips and the palate[1].

Coincident cutaneous lesions appear in approximately 15% of the patients[4], presenting as purple, polygonal, pruritic papules on the wrists, ankles and genitalia. Other dermatological features are nail pitting, pterygium formation, nail loss and scarring alopecia[2].

The diagnosis results from the integration of the histological and clinical data, as well as the medical history, which is necessary to exclude lichenoid reactions to drugs, dental materials or graft-versus-host disease[5].

Lip involvement, especially if isolated, is not common and few case reports are described. Lip lesions are likely to be subject to a variety injuries –such as biting, application of makeup or sun exposure, that can change the clinical features and mimic lesions of a different nature. Therefore, lichen planus of the lips (LPL) is difficult to detect and it is often misdiagnosed . On the other hand, it has been suggested that injuries acting on lip lesions in OLP could increase the risk of malignant transformation[6], so that the diagnosis and management of such lesions are mandatory.

In this paper we present a retrospective study of patients affected by LPL, who were diagnosed and treated at the Unit of Oral Medicine of the University Federico II of Naples.

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Contextually, a review of the literature about lip involvement in course of OLP has been performed to integrate the clinical data discussed. The purpose of this paper is to identify distinct features of LPL relating to its clinical presentation, evolution, and response to treatment, and concurrent oral or skin lesions.

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Materials and methods

All the clinical records of OLP treated at the Oral Medicine Unit of the University Federico II were scanned, and all the cases in which lips (upper, lower or both) were involved were selected for a retrospective analysis. Cases of allergic mucositis, associations with dental fillings/amalgams, lichenoid lesions and graft versus host disease were excluded.

All the patients were diagnosed and treated by experienced teams of Oral Medicine and Dermatology of the University of Naples Federico II for oral and skin and genital exams, respectively.

The diagnostic pattern for LP at our Unit includes medical history, a thorough skin and oral exam and the realization of a biopsy for histomorphologic confirmation; no direct immunofluorescence is usually performed. If the case is consistent with a diagnosis of LP and oral lesions are present, a diagnosis of OLP is realized. Exclusion of allergic or lichenoid lesions is possible through confrontation of medical history and absence of local irritating factors (i.e. drugs, dental fillings); differential diagnosis with discoid lupus is done through the integration of clinical and histological data . Within the group of cases of OLP, if lesions on the lips were present, the case was considered as LPL.

For each file selected, these variables have been considered: age and sex, the presence of any concurrent oral lesions, the clinical form of LP, the symptoms, any skin involvement, systemic pathologies, HCV infection, drug therapy, the realization of a biopsy specimen of the lip lesion, the treatment and outcome.

Concurrently, a review of the literature has been realized using the Medline database via PubMed for articles about LPL published from inception to March 2014. The key words we have used are: association, oral and cutaneous lichen planus, lip, involvement, and clinical feature, in various combinations.

The inclusion criteria were the English language and the relevance of the title or the abstract to the field of research, including lip lesions in OLP/LP, both as sole manifestations of the disease and with concurrent lesions in other sites, in patients of either sex, and of any age and nationality.

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The exclusion criteria were papers describing oral lichenoid lesions, graft-versus-host-disease or other forms of lichen planus different from OLP.

For each article reporting a case of LPL these variables have been considered: the year and country of publication, the number of cases described, the sex and age of the patient, the presence of any concurrent oral lesions, the clinical form of LP, the symptoms, any skin involvement, systemic pathologies and HCV infection, a confirmatory biopsy, the treatment and outcome.

Epidemiological data about isolated lip lesions, or concurrent lip lesions in OLP have also been investigated and the related articles have been classified according to the year and country of publication, and the number of patients involved in the study. Articles producing only narrative data were excluded.

Two reviewers selected the studies, then extracted and classified the data. Another independent reviewer checked the selection and the data classification.

Results

Of the 388 OLP files recorded from 2002, 63 were excluded for incomplete information about the clinical data considered in this study. Thirteen clinical records of patients affected by true OLP involving the lips were found and reviewed, representing the 4% of the remaining 325 OLP files, which had been considered elective for the selection, with a mean follow up of 5.15 years (Figs.1,2) (Table 1). The patient's mean age at the last follow-up was 71,85 years and the female/male ratio was 0.4. In all but two cases, the lips were not the only site of oral involvement, being the tongue, the buccal mucosa, the gingiva, and the mucobuccal fold the other localizations of the lesions, in order of frequency (69.23% of cases for both tongue and buccal mucosa, 53.85% of the cases for the gingiva, 23.08% of the cases for the mucobuccal fold) . The lower lip was more frequently affected than the upper lip, with a ratio of 9:1. With the exception of two erosive forms and one keratotic form, all the other patients showed mixed clinical patterns, generally including erosion and mild keratosis. Nine patients complained of pain and burning (one also complained of xerostomia), while 4 of them were reported to be asymptomatic.

Only two patients showed concurrent skin lesions or lesions in other mucous epithelia. Two other patients reported a previous skin involvement which had spontaneously disappeared . HCV infection was detected in 6 patients. Moreover, all but three patients showed some systemic pathologies and had followed some chronic, often multi-drug therapy. Three patients were former smokers, but none reported smoking at the time of examination.

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No history of lichenoid lesions in near family members was recorded except for one doubtful case.

Biopsies were made on the lip lesions in oder to exclude actinic cheilitis in some cases with medical history of prolonged UV exposition.

Most of the patients were treated with nystatin and cortisone ointments. One patient with oral and cutaneous LP also reported a previous therapy with cyclosporin. One asymptomatic patient was given no treatment, and only scheduled for a regular follow-up. One patient with a solitary lesion on the upper lip was treated with surgical excision, due to the suspicion of malignancy, which proved positive.

Most of the lesions remained constant during the course of time, while 4 of them showed signs of regression or complete remission. Interestingly, the lip lesions in a few cases showed a different and more favorable course than other lesions of the mouth in the same patient, appearing later on in the development of the disease, or regressing earlier.

As for the review of the literature, the data of 17 case reports and 4 case series of LPL meeting the inclusion criteria were analyzed, for a total of 35 patients (Table 2). All the cases were presented as true LP, but in three cases the lesions were diagnosed as concurrent LP and fungal infection[7], morphea[8] and systemic lupus erythematosus[9], respectively. A histological specimen was provided in 17 articles[7-23].

The age of the patients ranged from 7 to 75 years (mean value 45.35 years, SD±16.19) and the female/male ratio was 0.4. As for the geographical distribution, 9 reports were from Europe[8, 15, 19, 21-23, 25-27], 7 from Asia[7, 9, 10-12, 16, 20] and 5 from America[13, 14, 17, 18, 24].

Of the 21 case reports and series, 17 described an isolated lip involvement[7-12, 14, 17-22, 24-27]. The lower to upper lip involvement ratio was 6.5, while in 2 cases both the lower and upper lip presented lesions[11,25].

Comment

In literature, the most frequently reported clinical form of LPL is the erosive (10 cases)[7, 14, 16-20, 22, 24, 25], followed by the reticular/annular (3 cases)[10, 11, 21], nodular (1 case)[23] and bullous (1 case)[15]. Accordingly, symptoms such as pain, burning, bleeding and crusting were reported in 13 cases[7, 14-22,27], while only 2 cases were completely asymptomatic[10 11]. Only in 4 cases concurrent skin lesions have been described[15, 20, 23, 24].

It is worth noticing that for two reports it was impossible to determine if a confirmatory biopsy had been made for the diagnosis[25,26], while two other papers describe cases in which the diagnosis was only clinical[24,27].

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Most of the patients are reported to have no systemic pathology, and only for 6 cases a serological positivity for HCV infection was reported[17, 25].

As for the treatment, tacrolimus was used in 5 cases[10, 11, 14, 16, 17], and the reported outcome was regression in two cases[11, 16], remission in one case[17], and the persistence of the lesion in one case[14] (there was one not reported outcome); corticosteroids, alone or in association with other drugs, were reported to have been used in 10 articles[7, 13, 15, 18, 19, 21-25], causing a remission of the lesion in most cases[7, 13, 15, 18, 19, 21-24]. However, in one article, recurrence and malignant transformation was described[25]. Imiquimod and chloroquine phosphate were also reported to have been used[12, 26]. In the first reported uncertain case of LPL, Whittle et al. described the use of mercury, arsenic, and X-rays for the treatment[27].

Few data about the prevalence of lip involvement in LP can be found in literature (Table 3). The prevalence of isolated LPL was assessed only in two studies, with very different results: Aminzadeh*et al*. in 2009[28] reported a prevalence of 0.51% in a total of 186 Iranian patients, while Xue*et al*. in 2005[29] reported a prevalence of 8.9% in a total of 674 Chinese patients. Lip involvement, concurrently with other oral sites, is reported to have a prevalence between 32.3 % and 6.3%[28-32], being the third most common site of involvement according to Xue's epidemiolocal study, or the fourth according to Eisen and Carrozzo's reviews[33, 34]. LPL is unanimously considered to affect far more frequently the lower than the upper lip.

In accordance to these data, in the case series described the lesions were almost always erosive, or erosive and keratotic, and consequently symptomatic.

The particular predilection for the male gender and lower lip, as well as the clinical features of the lesions, seem to suggest some environmental and behavioral influence on the development of these lesions, such as solar radiation, wind exposure, air pollution and the habit of smoking. For this reason, attention has been focused on detecting the cancerization of LPL, reported, in fact, in a 23 year old former smoker by Harland[23] as well as in one of our patients.

LPL seems to be rare, but still somewhat underestimated. In our case series, the lesions appeared as small areas of mild keratosis and/or moderate erosion, often associated with atrophy, erythema and exfoliation and were mainly located at the limit between the vermillion and the labial mucosa. This is a very rough area due to the exposure of the inner part of the vermillion to oral irritants, such as saliva, food and tooth margins. Clinical features could be a combination of dystrophia and inflammatory conditions overcoming the lichenoid aspects. Additionally, the lip involvement in more than one case resembled the course of cutaneous LP, disappearing or regressing spontaneously after some years, or appearing after the other

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oral lesions, even though skin involvement affected only a small percentage of patients. In accordance with this finding, the isolated lip lesions described in literature underwent remission or regression.

The transitional mucosa of the lip, with its distinct antigenic structure, might be responsible both for the mildness of the lesions and for their cutaneous-like progression.

Another possibility, supported by more evidence, is that the difference in the clinical behavior of cutaneous and oral LP, between which LPL might stand, is to be found in the immunological composition and molecular expression of the two epithelia. Th22 cell-produced Interleukin 22 and 23 have been proven to be more expressed in oral lesions[35], probably because of the massive presence of Th22 cells in the oral mucosa. In the same way, the cytotoxic molecules Interleukin-17 and Foxp3[36], perforin and granzyme B [37], and finally caspase 3, Bax and Bcl-2 -associated with apoptosis [38] have been found to be highly expressed only in oral lesions. Also, a concentration of CD4-positive cells in the oral mucosa has been related to the entity of these lesions[37]. Possibly, the turning point between these different molecular patterns, which can be related to the different clinical behaviour of the skin and oral lesions, might be at the interface of the skin and oral mucosa, namely the vermillion.

On the other hand, the milder presence of microbiota and environmental factors might act on lip lesions, with a beneficial effect: UVB radiation is known to reduce the lesions in LP and phototherapy is also used to treat skin lesions[39] . It is possible that such factors act in a multiple way, on the one hand, controlling the immunological response of the epithelia, but also, on the other hand, acting as a chronic irritating stimulus on the lesions.

Given all these considerations, lip lesions in LP, showing transitional characteristics between oral and cutaneous forms, might need independent categorization and could be the starting point for a better understanding of the immunopathogenesis, prognosis and treatment of this disease. They should be detected very carefully by the clinician, because they are insidious and easily overlooked, and might undergo malignant transformation.

Legend:

Table 1: Case series of LPL. Listed by year of diagnosis. The lip involved (upper, lower or both) is indicated between parentheses. The erosive form on the lip is indicated with capital letter

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Table 2: Case reports and case series: review of the literature. Listed by year of publication. NA = not available; K= cancerization; LPL= lp with isolate lip involvement; OLP= lp with lip and other oral sites involved. The lip involved (upper, lower or both) is indicated between parentheses.

Table 3: Prevalence of lip involvement in OLP

Figure 1A: Mild plaque keratosis with multiple micro-erosions of the vermillion.

Figure 1B: White keratotic striae on labial mucosa with perilesional erythema-exfoliative features of the vermillion with skin inflammation.

Figure 1C: Ulceration of the vermillion with peripheral keratotic striae. The rest of the lip shows erythema and mild keratosis with exfoliation of the vermillion border that appears undefined.

Figure 1D: Multiple ulceration of the mucosal border of the vermillion associated with keratotic isolated papules and striae.

Figure 2A: Reticular keratotic lesions of the labial mucosa with keratotic plaques and exfoliation of the vermillion.

Figure 2B: Squamous cell carcinoma of the lip.

Figure 2C: Erythema, papules, annular keratotic striae and erosions of the vermillion interesting also the mucosal side.

Figure 2D: Linear keratotic lesion with mild plaque. Keratosis of the upper vermillion.

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