International Journal of Dermatology

Report

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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Conflicts of interest: None.

doi: 10.1111/ijd.13265

Abstract

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

Methods Clinical data of patients with true oral lichen planus (LP) involving the lips, diagnosed and treated at our Oral Medicine Unit (University Federico II of Naples, Italy), 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 (female/male ratio 0.4) with a mean (± SD) age of 71.85 years (± 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 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, female/male ratio 0.4) with a mean (± SD) age of 45.35 years (± 16.19).

Conclusions In the 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 for 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.

Introduction

Lichen planus (LP) is a chronic T-cell-mediated mucocutaneous inflammatory disease with an etiology and pathogenesis that 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 band-like zone of cellular infiltration, predominantly lymphocytic, and the absence of epithelial dysplasia. An interruption of the basement membrane, 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 (OLP) 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 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 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, particularly if isolated, is not common, and few case reports are described. Lip lesions are probably subject to a variety of injuries, such as biting, application of makeup, or sun exposure, which can change the clinical features and mimic lesions of a different nature. Therefore, LP 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 Oral Medicine Unit of the University Federico II of Naples, Italy.

Contextually, a review of the literature about lip involvement in the 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.

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 teams experienced in oral medicine and dermatology from 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, 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, presence of any concurrent oral lesions, clinical form of LP, the symptoms, any skin involvement, systemic pathologies, hepatitis C virus (HCV) infection, drug therapy, realization of a biopsy specimen of the lip lesion, 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 (1950) to March 2014. The key words we have used are association, OLP and cutaneous LP, 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.

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

For each article reporting a case of LPL, these variables have been considered: year and country of publication, number of cases described, sex and age of the patient, presence of any concurrent oral lesions, clinical form of LP, symptoms, any skin involvement, systemic pathologies and HCV infection, a confirmatory biopsy, 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 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 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 and 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, i.e., tongue, buccal mucosa, gingiva, and mucobuccal fold; the other localizations of the lesions, in order of frequency (69.23% of cases for both tongue and buccal mucosa; 53.85%, the gingiva; 23.08%, 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 four of them were reported to be asymptomatic.

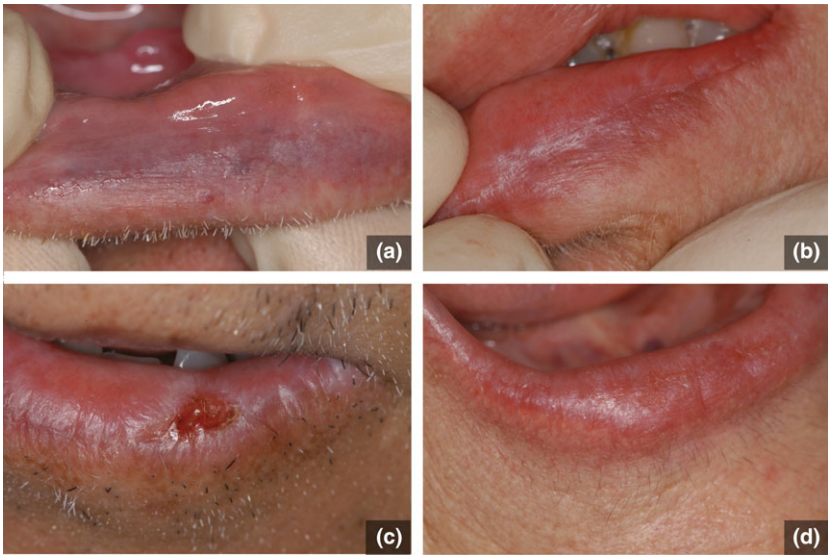

Figure 1 (a) Mild plaque keratosis with multiple micro-erosions of the vermillion. (b) White keratotic striae on labial mucosa with perilesional erythema–exfoliative features of the vermillion with skin inflammation. (c) Ulceration of the vermillion with peripheral keratotic striae. The rest of the lip shows erythema and mild keratosis with exfoliation of the vermillion border that appears undefined. (d) Multiple ulcerations of the mucosal border of the vermillion associated with keratotic isolated papules and striae

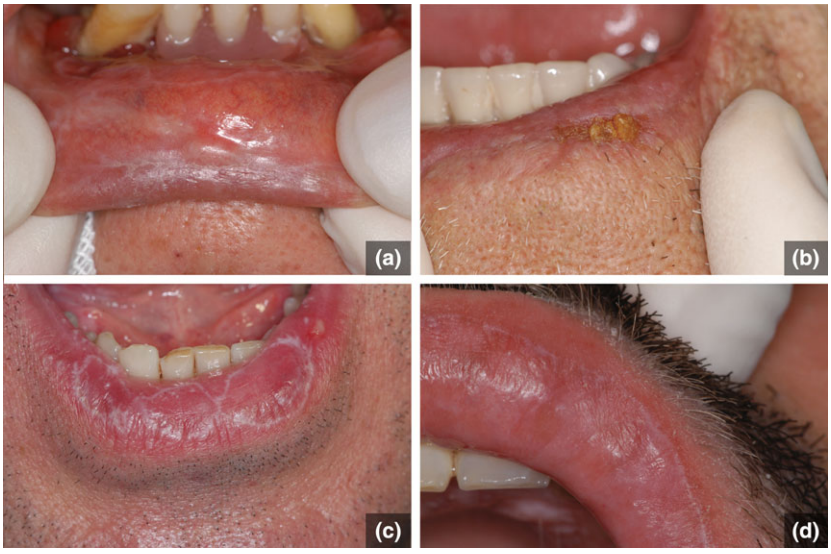

Figure 2 (a) Reticular keratotic lesions of the labial mucosa with keratotic plaques and exfoliation of the vermillion. (b) Squamous cell carcinoma of the lip. (c) Erythema, papules, annular keratotic striae, and erosions of the vermillion interesting also the mucosal side. (d) Linear keratotic lesion with mild plaque. Keratosis of the upper vermillion

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 six patients. Moreover, all but three patients showed some systemic pathologies and had followed some chronic, often multidrug therapy. Three patients were former smokers, but none reported smoking at the time of examination.

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

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

Most of the patients were treated with nystatin and cortisone ointments. One patient with OLP and cutaneous LP also reported a previous therapy with cyclosporine. 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 four 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.

In the review of the literature, the data of 17 case reports and four case series of LPL that met the inclusion criteria were analyzed, for a total of 35 patients

Table 1 Case series: LP of the lip

Case no.	Year of diagnosis	Patient	Age/ sex	Isolated (oral mucosa)	Symptoms	Clinical form	Skin involvement	Systemic pathologies
1	2002	G G	72/M	Yes (upper)	Burning	Erosive	No	Liver insufficiency
2	2003	C C	80/F	No (lower). Buccal, tongue	Burning	Erosive, keratosic	No	Osteoarthritis
3	2004	S G	78/M	No (lower). Buccal, fold, tongue	No	Atrophic, plaque, reticular	Previously legs and wrists	COPD, former smoker + alcohol, hiatal hernia, ischemic cardiopathy, kidney insufficiency, prostatic hypertrophy
4	2006	B G	77/M	No (lower + upper). Buccal, gingiva, tongue.	No	Erosive, plaque, reticular	No	Former smoker, hypertension, ischemic cardiopathy, prostatic hypertrophy
5	2007	N C	63/M	No (lower). Buccal, gingva	No	Plaque, reticular	Previously lichen ruber	Former smoker + alcohol. celiac disease, rheumatoid arthritis
6	2007	D C	61/F	No (lower). Diffused	Pain, xerostomia	Annular, bullous, LSA	Hands, feet, vagina, nails	Osteoarthritis, osteoporosis
7	2007	S A	77/M	No (lower). Gingiva	Burning	Erosive, keratosic	No	No
8	2007	R A	76/M	No (lower). Buccal, fold, tongue	Burning	Atrophic, erosive, reticular	No	Prostatic hypertrophy
9	2008	P C	78/F	No (lower). Buccal, gingiva, tongue	Burning	Plaque, reticular	Axillas, wrists	Aortic mechanic valve
10	2013	G C	62/M	No (lower). Buccal, tongue	Burning	Erosive, reticular	No	No
11	2014	F A	74/M	Yes (upper + lower)	Burning	Erosive	No	No
12	2014	G V	67/M	No (upper + lower). Gingiva, palate, buccal, tongue	Burning	Reticular, ulcerative	No	Liver insufficiency
13	2014	A A	69/F	No (lower). Gingiva, tongue	No	Keratosic	No	Hypertension

ASA, aminosalicylic acid; COPD, chronic obstructive pulmonary disease; HCV, hepatitis C virus; K lip, OSSC (oral squamous cell carcinoma) of the lip; LP, lichen planus; LSA, lichen sclerosis et atrophicus.

(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] A histological specimen was provided in 17 articles.[7–23]

The age of the patients ranged from 7 to 75 years (mean ± SD 45.35 ± 16.19), and the female/male ratio was 0.4. As for the geographical distribution, nine reports were from Europe,[8,15,19,21–23,25–27] seven from Asia,[7,9–12,16,20] and five 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/upper lip involvement ratio was 6.5, while in two cases both the lower and upper lip presented lesions.[11,25]

HCV	Drugs	Biopsy	Diagnosis	Familial	Treatment	Outcome	Notes
Yes	No	Yes	K lip, lichenoid infiltrate	No	Surgical excision	Remission	Died in 2004 of liver insufficiency
Yes	ASA, bisphosphonates	No	LP	No	Cortisone + nystatin	Stable	
No	Antihypertensives, anti-H_2, allopurinol, ASA, beta blockers, statins	Yes	LP	Yes?	Cortisone + nystatin	Stable	Skin involvement appeared and disappeared spontaneously several times
No	Antihypertensives, ASA, beta blockers, statins, nitroglycerin, silodosin	No	LP	No	Nystatin	Regression	
No	No	Yes	LP	No	Nystatin	Stable	Spontaneous remission of skin lesions. Koebner + (buccal lesions)
No	No	Yes	LP	No	Cortisone, nystatin, cyclosporine	Worsening in the mouth, Stable on the lip	Keratosis on the lip only. Skin lesions appeared after oral lesions
Yes	No	Yes	LP	No	Cortisone + nystatin	Remission	LP lasted 10 years, then disappeared
No	Alfuzosin, ASA	No	LP	No	Cortisone + nystatin	Stable	Koebner +
Yes	Allopurinol, bisoprolol, warfarin	No	LP	No	Nystatin	Stable in the mouth, regression on the lips	Skin lesions appeared after oral lesions
No	No	No	LP	No	Cortisone + nystatin	Stable	Lip lesions appeared after oral lesions
No	No	No	LP	No	Cortisone + nystatin	Stable	
Yes	Immunosuppressors	No		No	Cortisone + nystatin	Stable	
Yes	Amiloride + hydrochlorothiazide	No	LP	No	None	Stable	

Discussion

In the 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 (three),[10,11,21] nodular (one),[23] and bullous (one).[15] Accordingly, symptoms such as pain, burning, bleeding, and crusting were reported in 13 cases,[7,14–22,27] while only two cases were completely asymptomatic.[10,11] Only four cases of concurrent skin lesions have been described.[15,20,23,24]

It is worth noting 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]

Table 2 Review of literature: Case reports/series of LPL

Year	First author/ reference	Country	No. of patients	Age/ sex	Isolated (oral mucosa)	Symptoms	Clinical f eatures	Skin involvement	Systemic pathologies	HCV	Biopsy	Diagnosis	Treatment	Outcome
2012	Domingues[24]	USA	1	44/M	Yes (lower)	Painful, bleeding	Erosive	Yes	Treatment with imiquimod	No	No	LPL	Clobetasol	Remission
2012	Holmukhe[10]	India	1	40/M	Yes (lower)	No	Annular	No	No	No	Yes	LPL	Tacrolimus	NA
2012	Sugashima[11]	Japan	1	32/F	Yes (lower + upper)	No	Annular atrophic	No	Allergy to zinc	NA	Yes	LPL	Tacrolimus	Regression
2011	Gencoglan[12]	Turkey	4	NA	Yes	NA	NA	NA	NA	NA	Yes	LPL	Imiquimod	Recurrence in 1/4
2011	De Moraes[13]	Brazil	1	7/F	No (upper)	NA	NA	NA	NA	NA	Yes	OLP	Corticosteroid	Remission
2008	Johnson[14]	USA	1	42/F	Yes (lower)	Dryness, peeling	Erosive	No	No	No	Yes	LPL	Tacrolimus	Stable
2007	Petruzzi[25]	Italy	10	NA	Yes (lower and/or upper)	Erosions and crusting	Erosive	NA	NA	5/10	NA	LPL	Clobetasol + tocopherol	Remission in 8/10
2007	van Tuyll[15]	Netherlands	1	75/F	No (lower)	Burning, bleeding	Bullous	Yes	No	NA	Yes	OLP	Tretinoin + triamcinolone	Remission
2006	Shichinohe[16]	Japan	2	64, 68/M, M	No (lower), no (lower)	Painful	Erosive	No	NA	NA	Yes	OLP	Tacrolimus	Regression
2005	Donovan[17]	USA	1	51/M	Yes	Painful	Erosive	NA	NA	Yes	Yes	LPL	Tacrolimus	Remission
2003	Yu[18]	USA	1	44/M	Yes (lower)	Burning	Erosive	No	Hypertension	No	Yes	LPL	Clobetasol	Remission
2002	Chiang[7]	Taiwan	1	36/F	Yes (lower)	Painful	Erosive	No	No	NA	Yes	LPL + mycosis	griseofulvin + prednisolone	Remission
2002	Cecchi[19]	Italy	1	45/M	Yes (lower)	Burning, swelling	Erosive	No	No	No	Yes	LPL	Betamethasone	Remission, recurrence on the limbs
2000	Melato[8]	Italy	1	NA	Yes (upper)	NA	NA	NA	Vitiligo	NA	Yes	LPL + morphea	NA	NA
1997	De Argila[26]	Spain	1	51/F	Yes (lower)	NA	NA	No	NA	NA	NA	LPL	Chloroquine phosphate	Regression
1997	Isogai[20]	Japan	1	54/M	Yes	Painful	Erosive	Yes	NA	NA	Yes	LPL	NA	NA
1996	Allan[21]	UK	1	51/M	Yes (lower)	Irritation, scaliness	Reticular	No	No	NA	Yes	LPL	Betamethasone	Remission
1995	Itin[22]	Switzerland	1	44/NA	Yes (lower)	Burning	Erosive	No	NA	NA	Yes	LPL	Acitretin + steroid	Remission
1992	Harland[23]	UK	1	23/M	No (lower)	NA	Nodular	Yes	Former smoker	NA	Yes	OLP	Corticosteroid	Regression, recurrence, K
1978	Piamphongsant[9]	Thailand	2	NA	Yes (lower)	NA	NA	NA	LES	NA	Yes	LPL + LES	NA	NA
1937	Whittle[27]	UK	1	69/M	Yes (lower)	Irritation	Plaque	Anal mucosa	No	NA	No	LPL?	Mercury, arsenic, x-ray	Stable

LES; LPL, lichen planus of the lip; NA, not applicable; OLP, oral lichen planus.

Table 3 Prevalence of lip involvement in oral LP

Year	First author/ reference	Country	No. of patients	Age range	Female/ male	Isolated lip	Lip involvement	Cutaneous involvement (% of patients)
2010	Bajaj[30]	India	95	17–62 (34–36 mean value)	55/40	NA	29.4%. Upper 7.4% (reticular). Lower 22.1% (reticular, erosive)	NA
2009	Carrozzo[34]	Italy	Review	NA	NA	NA	Lower lip 4th most involved site	15
2009	Aminzadeh[2]	Iran	187	46 (mean value)	72%/28%	0.51%	6.3%	1.25
2005	Xue[29]	China	674	10–78 (49–52 mean value)	66%/34%	8.9%	Upper 1.91% (erosive). Lower 32.3% (reticular). Third most common site of involvement	11
2005	Eisen[33]	USA	Review	NA	NA	NA	4th most common site of involvement	15
2002	Eisen[31]	USA	723	13–82 (57–47 mean value)	75%/25%	NA	Upper 2%. Lower 14%	NA
2001	Romero[32]	Spain	62	63 (mean value)	52%/48%	NA	28.6% LP HCV+ vs. 7.3% LP HCV-	NA
1992	Bagan-Sebastian	Spain	205	NA	NA	NA	NA	NA

HCV, hepatitis C virus; LP, lichen planus; NA, not applicable.

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

As for the treatment, tacrolimus was used in five cases,[10,11,14,16,17] and the reported outcome was regression in two cases,[11,16] remission in one,[17] and the persistence of the lesion in one[14] (in one there was no 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 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 described the use of mercury, arsenic, and x-rays in its treatment.[27]

Few data about the prevalence of lip involvement in LP can be found in the 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 *et al*.'s epidemiological study, or the fourth according to Eisen and Carrozzo's reviews.[33,34] LPL is unanimously considered to affect the lower lip far more frequently 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 *et al*.[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 oral lesions, even though skin involvement affected only a small percentage of patients. In accordance with this finding, the isolated lip lesions described in the 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 LP and OLP, between which LPL might stand, is to be found

in the immunological composition and molecular expression of the two epithelia. T-helper 22 cell-produced interleukin-22 and -23 have been proven to be more expressed in oral lesions,[35] probably because of the massive presence of T-helper 22 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. In addition, 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 behavior 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: ultraviolet B 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 multiple ways, 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 the 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.

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