Acta Dermatovenerol Croat 2021;29(1):1-7 ORIGINAL SCIENTIFIC ARTICLE

Analysis of Coexistence of Oral and Cutaneous Lesions in 253 Patients with Lichen Planus – Single-center Retrospective Analysis

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Received: August 11, 2020
Accepted: March 15, 2021

ABSTRACT Lichen planus (LP) is a chronic inflammatory disorder that especially affects the skin, mucous membranes, or both. The aim of the study was to determine the clinical characteristics of patients with LP in the oral cavity and concomitant cutaneous lesions and compare their outcomes with those without cutaneous lesions. 253 records of patients with confirmed diagnosis of oral lichen planus (OLP) were retrospectively analyzed. The following clinical data were obtained from the medical charts: sex, age, clinical presentations of OLP, distributions of the lesions, presence of symptoms, extra oral manifestations of lichen planus, presence of systemic diseases, and treatment provided. The group of patients with cutaneous manifestations was compared for possible clinical differences to those without. Cutaneous lesions were present in 18.2% (46/253) of patients. Significantly more patients with cutaneous lesions had other extra oral manifestations (26.1% versus 1.0%, P<0.00001). Lips were significantly more affected in patients with cutaneous presentation (41.3% versus 16.9%, P=0.00006). Ulcerative OLP was more frequent in patients with cutaneous lesions (23.9% versus 10.6%, P=0.0266). Patients with cutaneous manifestations needed significantly more systemic treatment with systemic steroids (10.9% versus 3.4%, P=0.0466). Patients with cutaneous lesions were more symptomatic and tended to require more treatment than patients with OLP who only had oral involvement.

KEY WORDS: oral lichen planus, clinical features, extra-oral manifestation

INTRODUCTION

Lichen planus (LP) is a chronic inflammatory disorder that especially affects the skin, mucous membranes, or both (1). The most frequent form is oral lichen planus (OLP). It is characterized by a recurrent clinical course typically occurring in outbreaks. Its clinical presentation ranges from asymptomatic mild forms to more severe painful lesions requiring systemic treatment. The most frequently affected locations are oral buccal mucosa, the tongue, and the alveolar ridge (2).

The first description of lichen planus is usually credited to Ferdinand Ritter von Hebra, who introduced the term lichen ruber planus, and the disease was further described by Erasmus Wilson later on (3). White cutaneous striations were described by Louis Wickham in 1895 (4). It took more than 40 years to the

histopathological description by William Dubreuilh in 1906 (5). Efforts to standardize and ensure maximum clinicopathological correlation are still being discussed even now and have lasted over a century.

It is currently believed that LP is a T-cell-mediated immunopathology (6). The etiology remains unknown. The pathogenesis probably includes many pathways in specific as well as non-specific immunity. TNF-α and IFN-γ have been the most frequently reported cytokines in LP pathogenesis. Tissue disruption by various enzymes, including matrix metalloproteinases, has also been described (7). Histologically it is usually defined as liquefactive degeneration of the basal cell layer of the epithelium and the presence of an inflammatory infiltrate with a band-like appearance in the superficial chorion.

The diagnosis of OLP should be based on a combination of clinical and histopathologic criteria. Various classification criteria have been proposed, but none are currently considered the standard (8,9). OLP is now considered a potentially premalignant lesion with a low rate of malignant transformation generally ranging from 0-2% (10).

Cutaneous lichen planus is the most frequent site of LP together with the oral cavity. There are very few studies reporting the prevalence of cutaneous lesions in patients with OLP. Cutaneous lesions are usually observed in 4-44% of patients with OLP (11,12). It commonly affects flexor surfaces of the extremities. The most frequent manifestation are the so-called Wickham's striae (purplish, polygonal, planar, pruritic papules and plaques) (13). The traditional 6 Ps have been reported in cutaneous LP. These stand for Pruritic, Purple, Polygonal, Planar, Papules, and Plaques. Lesions are frequently bilateral and symmetric (14). Cutaneous LP can be the only presentation, but is frequently accompanied by OLP. Rarely, other mucosal surfaces such as the genitalia, gastrointestinal tract, or the eyes may be affected as well.

The aim of this study was to determine the clinical characteristics of patients with OLP and concomitant cutaneous lesions and compare their outcomes with those without cutaneous lesions.

PATIENTS AND METHODS

The study was approved by the local Ethics Committee. All consecutive patients at the Oral Medicine Unit at Department of Dentistry, Charles University in Prague, Faculty of Medicine and University Hospital in Hradec Králové in the Czech Republic diagnosed with OLP from January 2003 to December 2019 were included in the study. All patients had histologically confirmed clinical diagnosis of OLP according to the diagnostic criteria of the World health Organization (WHO) of 1978 modified by van der Meij *et al.* in 2003 (15). Patients without histological examination (and thus not meeting the diagnostic criteria) were excluded from the study. We excluded patients with oral lichenoid contact lesions caused by an identifiable cause such as a hypersensitivity reaction to dental restorative materials or patients with lichenoid dysplasia. Only patients with clinical and histological evidence of OLP were included in the study. The following clinical data were obtained from the medical records: sex, age, clinical presentations of OLP, distributions of the lesions, presence of the symptoms, extra-oral manifestations of lichen planus, oral hygiene and periodontal health status, presence of systemic diseases, medication history, treatment provided (topical corticosteroid in mucosal adhesive paste or as intralesional injection or systemic corticosteroid), adverse effects of treatment, tobacco use. The patients were divided into two groups: the first group comprised patients without cutaneous lesions, while the second group consisted of with cutaneous lesions. Retrospective charts were reviewed. We compared the groups for possible clinical differences. A descriptive statistical analysis was performed using Microsoft Excel 2003 (Microsoft, USA) and MedCalc 9.5.2.0 (MedCalc Software, Belgium). Data were described by absolute and relative frequencies of categorial variables and mean values (minimum-maximum) of quantitative variables The ML chi-square test was used. For comparison of categorical variables in groups, whereas the Mann Whitney U test was adopted in case of quantitative variables. P-values less than 0.05 were considered statistically significant (all tests were two-sided).

RESUTLS

Patient characteristics

A total of 253 charts of patients with confirmed diagnosis of OLP were retrospectively analyzed, of whom 65.2% (165/253) were women and 34.8% (88/253) were men, giving a female to male ratio of 1.9:1. All affected patients were white Caucasian. The mean age of the patients at presentations was 54.3 (18.9-85.0) years; mean age was 50.4 (18.9-74.1) for women and 56.3 (19.3-85.0) for men and was statistically significantly different (P=0.001). Details can be found in Table 1. 81.8% of patients (207/253) had oral LP only, while 18% (46/253) had various combinations of oral cutaneous and genital lesions. The combinations of lesions in all patients are depicted in Table 2.

Table 1. Comparison of patients with cutaneous involvement and oral LP only

	w/o skin	%	w skin	%	*P* value
Age mean range	54.3	(19.0-85.0)	54.4	(24.8-78.0)	0.952
Female sex	132	64.1	33	71.7	0.392
Male sex	75	35.9	13	28.3	
Systemic disorders					
Arterial hypertension	98	47.3	23	50.0	0.748
Diabetes mellitus	28	13.5	9	19.6	0.355
Cardiac disease	22	10.6	5	10.9	1.000
Psychiatric disease	16	7.7	5	10.9	0.553
Thyroid gland disease	41	19.8	9	19.6	1.000
Other	84	40.6	23	50.0	0.253
Confounding factors					
Drugs	143	69.1	33	71.7	0.860
Allergies	36	17.4	14	30.4	**0.064**
Smoking	33	15.9	14	30.4	**0.034**
Subjective symptoms					
No symptoms / occasional burning	23	11.1	6	13.0	0.798
Burning on food ingestion	137	66.2	25	54.3	0.174
Constant pain	47	22.7	15	32.6	0.185
Other extraoral lesions					
Genital	2	1.0	12	26.1	**< 0.001**
Lesions distribution					
Buccal	187	90.3	44	95.7	0.386
Alveolar ridge	66	31.9	21	45.7	**0.087**
Tongue	112	54.1	28	60.9	0.418
Palate	12	5.8	6	13.0	0.108
Lips	35	16.9	19	41.3	**0.001**
Mouth floor	7	3.4	5	10.9	**0.047**
OLP form					
Reticular	195	94.2	45	97.8	0.473
Erythematous	87	42.0	24	52.2	0.251
Erosive	102	49.3	25	54.3	0.625
Plaque	84	40.6	22	47.8	0.410
Ulcerative	22	10.6	11	23.9	**0.027**
Bullous	0	0.0	2	4.3	**0.033**
Desquamative gingivitis	38	18.4	10	21.7	0.678
Treatment required					
None	72	34.8	12	26.1	0.301
Topical steroid	134	64.7	34	73.9	0.301
Intralesional steroid	60	29.0	20	43.5	**0.079**
Systemic steroid	7	3.4	5	10.9	**0.047**

w/o: without; w: with

Table 2. Combinations of lesions

N = 253	n	%
Oral only	207	81.8
Oral + cutaneous	31	12.3
Oral + cutaneous + genital	10	3.9
Oral + cutaneous + nails	3	1.2
Oral + genital	2	0.8

Cutaneous manifestation

Cutaneous lesions were present in 18.2% (46/253) of patients, with women being equally affected as men (20.0% in women versus 13.6% in men, P=0.277). No difference in age was observed between patients with and without cutaneous lesions (54.3 years without skin lesions and 54.4 years with lesions, P=0.952). There were slightly more patients reporting allergies with cutaneous lesions (30.4% and 17.4%, P=0.064) and significantly more smokers (30.4% versus 15.9%, P=0.034). Significantly more patients with cutaneous lesions presented with other extra oral manifestations (26.1% versus 1.0%, P<0.001). The lips were significantly more affected in patients with cutaneous presentation (41.3% and 16.9%, P=0.001), as was the floor of the mouth (10.9% versus 3.4%, P=0.047). Ulcerative presentation was much more frequent in patients with cutaneous lesions (23.9% versus 10.6%, P=0.0266). 2 women (4.3%) with cutaneous lesions were affected by the most serious bullous form of OLP, compared with no patients without cutaneous lesions (P=0.002). Patients with cutaneous manifestations did not need significantly more topical treatment than those without, but a trend towards higher treatment need was observed with intralesional steroids (43.5% versus 29.0%, P=0.079) and needed significantly more systemic steroids (10.9% versus 3.4%, P=0.047). No specific treatment other than steroids (either local, intralesional, or systemic) was administered. All details are shown in Table 1. Distribution of cutaneous lesions was predominantly found on the extremities, most frequently on the arms and hands. Genital lesions were observed in 12 patients (8 women and 4 men), accounting for 26.1% of all patients with cutaneous lesions. The nails (3/46 patients, 6.5%) and hair (2/46 patients, 4.3%) were the least commonly affected sites. Both patients with lesions in hair manifested as lichen planopilaris. See Table 3 for lesions distribution.

Systemic diseases, medication, smoking

The most prevalent concomitant systemic disorders included arterial hypertension in 47.8% (121/253), thyroid gland disorders in 19.8% (50/253), diabetes mellitus in 14.6% (37/253), and other various diseases in 41.9% (106/253) patients. Positive allergy history was present in 19.8% (50/253) patients. 69.9% (176/253) patients were on regular medication. The medications taken by the patients primarily included ACE inhibitors in 22.2%, beta blockers in 14.6%, calcium channel blockers and statins in 11.6%, and levothyroxine in 10.2% of patients. Other drugs were taken by less than 10% of patients. 18.6% (47/253) of patients were smokers. There were no significant differences in these parameters between patients with and without cutaneous lesions.

Malignant transformation rate

Overall, 0.8% (2/253, 1 man, 1 woman) of patients developed squamous cell carcinoma during the observation period. No patient with cutaneous lesions developed squamous cell carcinoma. The female patient was a smoker, and the male patient had quit smoking 15 year before diagnosis. The time from diagnosis to transformation was 2.4 years in the female and 8.6 years in the male patient.

DISCUSSION

Lichen planus is a disease affecting both the skin and mucosal surfaces. It is a common disease with a worldwide prevalence ranging from 0.49-1.43% according to a recent meta-analysis (16). This data

Table 3. Distribution of cutaneous changes in evaluable patients

N = 28	n	%	Women	%	Men	%
Wrist/hand	20	71.4	16	76.2	6	85.7
Legs/foot	6	21.4	4	19.0	2	28.6
Nail	3	10.7	2	9.5	1	14.3
Hair	2	7.1	2	9.5	0	0.0
Other skin (chest, back, etc.)	10	35.7	7	33.3	3	42.9

Detailed cutaneous distribution was not available in the records for 18 patients

confirm higher LP prevalence among women compared with man (female to male ratio 1.9:1). This observation is similar to data reported previously by various groups (11).

The cutaneous involvement varies considerably across the published data. Historical data have reported a prevalence of cutaneous lesions from 4 to 44% (8,17). More recent publications reported prevalence ranging from 6 to 48% (18-20). In our current report, the most patients were found to have oral involvement only, whereas 18.2% of patients had cutaneous involvement concomitantly with oral lesions. The wide range of cutaneous involvement across the studies may be due to the nature of the populations examined, such as tertiary care centers possibly focusing on more severe cases or differences across geographic regions that may exist. Patients with cutaneous lesions presented much more frequently with involvement of other sites, especially the genitalia. The presented data showed genital lesions in 26.1% of patients with cutaneous lesions compared with only 1.0% of those without cutaneous lesions. Overall, 4.7% of patients had localization in a combination of all three sites (oral, cutaneous, and genital). Similar data were reported by Cassol-Spanemberg *et al.*, where 2.6% of all patients reported had all three sites involved (20). Our data also suggest that there is no difference between men and women in genital involvement. The most frequent localization of cutaneous lesions was the wrist/hand, accounting for 71.4% of patients. The arms were the predominant location for LP lesions across the presented studies. In what is probably the largest published cohort reported by Eisen *et al.*, 63% of patients were found to have lesions on the arms (19). Similar data were reported in a study by Stojanovic *et al.*, where around 80% of patients presented with arm lesions (21). We reported 3 patients being affected by nail LP, which is a very rare clinical condition. So far, there has been very few studies about nail LP. It has been reported in as few as 10% of patients with cutaneous LP (22). Piraccini *et al.* reported 105 such patients during 20 year follow up of all patients with LP (23). It is notable that nail LP can be found in the pediatric population (24).

LP is frequently associated with various other systemic conditions (25). Our data do not show any significant differences in systemic disorders associated with the presence or absence of cutaneous lesions. The most frequently associated conditions include hypertension, diabetes mellitus, thyroid dysfunction, and various other immunopathological conditions. Ebrahimi *et al.* reported 28% of patients with OLP having at least one associated autoimmune disease (26). A significant proportion of patients in our cohort suffered from diabetes mellitus (almost 20% of patients with cutaneous lesions). Diabetes may trigger immune dysregulation, thus predisposing patients to various immunopathological conditions including LP (27). Numerous thyroid gland disorders are of autoimmune origin and are frequently associated with other immune-mediated disorders such as LP (28). Our data support this hypothesis, with a more than 20% prevalence of thyroid gland diseases in our cohort of patients. Psychiatric disorders have also been repeatedly reported as one of the most significant associated conditions. Our cohort of patients with cutaneous LP showed a 10% prevalence of psychiatric conditions. Depression, anxiety, and other similar diseases have all been described together with LP (29,30). We observed significantly more patients reporting allergy together with cutaneous LP (30.4%). The overlap between cutaneous and oral contact allergic syndromes was reported by Chen *et al* (31). We also observed significantly more smokers in patients with cutaneous LP compared with those who had OLP only (30.4%). Even though smoking remains one of the most significant factors for malignant squamous cell carcinoma development, we were not able to demonstrate this association in our cohort of patients. We observed only 2 patients with malignant OLP transformation (0.8%), 1 smoker and one non-smoker, none of whom had cutaneous lesions present. Generally, it is believed that OLP carries a risk of malignant transformation of about 1.95% (16).

Based on our data, the majority of patients presented with white OLP lesions. The combination of red and white lesions was also common, which is similar to previously published data. Around 50% of patients presented with erosive OLP, with the same prevalence in patients with and without cutaneous lesions. In large series of 808 patients, Carbone *et al.* reported a prevalence of red lesions of 41.1% in the studied population (32). We also observed that more patients with cutaneous lesions suffered from more serious clinical forms of OLP. Ulcerative lesions were present in 23.9% of OLP with cutaneous lesions, compared with 10.6% in patients without cutaneous lesions, and 2 patients (4.3%) suffered from a bullous lesion compared with none in the group with OLP without cutaneous lesions. The fact that this rare variant of OLP has been associated with cutaneous lesions has been documented in study by Varghese *et al.*, where all 3 patients with bullous OLP had concurrent cutaneous lesions (33). Obviously, patients with red lesions tend to be more symptomatic (32). Our data, however, did not show any significant differences between oral symptoms in patients with and without cutaneous LP lesions. On the other hand, the need for

systemic treatment with oral steroids was higher in the group of patients with cutaneous LP compared with those who had OLP only. Usually, only up to 5% of patients with OLP need systemic steroid treatment (32), but our patients with cutaneous LP lesions needed systemic treatment in 10.9% of cases. The majority of patients had multiple oral site involvement. The most frequently affected sites that appeared to be significantly more common in patients with cutaneous lesions were the lips and floor of the mouth. The lips are generally involved in only a minority of patients (32), but our cohort of patients showed more than 40% lip involvement with concomitant cutaneous lesions. The same was true for involvement of the floor of the mouth, where generally around 4% of patients are affected (32), but our data with concomitant cutaneous lesions showed floor of the mouth involvement in 10.9% of patients, which was again statistically significant. We did not observe any of the more serious complications of LP, such as esophageal disease, which is a very rare complication (34).

CONCLUSION

OLP is a disease with a variable clinical picture. Patients with cutaneous lesions present different distribution patterns as well as distinctive types of lesions. The need for systemic treatment tends to be higher in those with cutaneous lesions. We did not observe more malignant transformations in patients with OLP and cutaneous lesions.

Acknowledgements:

The work was supported by the PROGRES Q40/13 (Charles University, Faculty of Medicine in Hradec Králové) project and MH CZ - DRO (UHHK, 00179906).

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