Acta Derm Venereol 2006; 86: 433–438

CLINICAL REPORT

Unexpectedly High Frequency of Genital Involvement in Women with Clinical and Histological Features of Oral Lichen Planus

Olga DI FEDE[1], Pina BELFIORE[2], Daniela CABIBI[3], Stefano DE CANTIS[4], Emiliano MARESI[3], Alexander Ross KERR[5] and Giuseppina CAMPISI[1]

[1]Sector of Oral Medicine, Department of Oral Sciences, [2]Institute of Gynaecology and Obstetrics, Mother and Children Department, [3]Pathological Anatomy Institute [4]Department of Social Statistic, University of Palermo, Palermo, Italy, and [5]Department of Oral & Maxillofacial Pathology, Radiology, and Medicine, New York University College of Dentistry, New York, USA

The main aims of this cross-sectional study were: *(i)* to assess the frequency of genital (vulval) lichen planus (VLP) and vulval lichen sclerosus (VLS) in women affected with oral lichen planus (OLP), regardless of the genital symptoms reported; and *(ii)* to verify whether any demographic, clinical, or histological features of OLP are associated with a higher risk of vulvo-vaginal involvement. Fifty-five women, presenting OLP, consecutively underwent gynaecological examination and, if they demonstrated positive clinical signs of VLP, underwent biopsy. After a drop-out of 14 subjects, 31/41 (75.6%) were found to have signs of genital involvement, of which 13/31 (44.0%) were asymptomatic. Following genital biopsy, 27/31 (87.1%) had histologically confirmed VLP or VLS. Following both univariate and multivariate statistical analyses, no significant association was found between gynaecological concomitance and demographic, clinical, histological features of OLP. This unpredictably common genital involvement in females with OLP emphasizes the importance of routinely performing both oral and gynaecological examinations, to facilitate an early and correct therapeutic approach. *Key words: oral lichen planus; genital lichen planus.*

(Accepted March 31, 2006.)

Acta Derm Venereol 2006; 86: 433–438.

Olga Di Fede, Università di Palermo, Policlinico "P. Giaccone", Via del Vespro 129, IT-90127, Palermo, Italy. E-mail: odifede@odonto.unipa.it

Lichen planus (LP) is one of the most common idiopathic immune disorders, found in 0.5–2.3% (1) of the general population. LP may involve, separately or simultaneously, different muco-cutaneous sites (oral and genital mucosa, skin, scalp and nail). The concurrent involvement of oral and genital sites, in patients with mucosal burning and itching, has been reported, especially in females, usually showing a low percentage (3.7–19.3%) of double involvement for LP (2–4).

It is common for women in the general population, to present to healthcare providers with the non-specific symptoms of persistent and recurrent oral and/or genital burning infection, oral lichen planus (OLP), burning mouth syndrome, or drug-related conditions. Similarly, genital burning may be attributed to candidosis (5), desquamative inflammatory vaginitis (6), or dysaesthetic vulvodynia (7). Collectively, these symptoms are often misdiagnosed, particularly since biopsies are not performed on a regular basis (8).

In 1869, Wilson (9) described a case of a woman with LP and "pruritus vaginae"; more recently, Gardner (10) and Lynch (11) reported a "desquamative inflammatory vaginitis" in association with erosive OLP. This association was recognized and defined as "vulvo-vaginal-gingival syndrome" (12) or "plurimucosal LP" (13), and later its prevalence was established as between 3.7% and 19.3% in patients with OLP (2).

The main aims of this cross-sectional study were: *(i)* to evaluate the frequency of genital (vulval) LP (VLP) and vulval lichen sclerosus (VLS) in females affected by OLP; *(ii)* to verify whether any demographic, clinical, or histological features of OLP are associated with a higher risk of genital involvement.

PATIENTS AND METHODS

Between October 2001 and April 2004, following informed consent, female out-patients with clinical signs of oral lichenoid lesions were consecutively enrolled after histological confirmation of OLP. Patients were excluded, if on the basis of histopathological features and clinical data, they were found to have lichenoid reactions to medications or a dental material (e.g. amalgam).

Oral examination and diagnostic criteria

Anamnestic and clinical data for each patient was recorded on a clinical report form. Examinations were carried out by one of the authors (ODF) as described previously (14–15). Clinical features of OLP lesions were classified, as proposed by Rogers & Eisen (4), on the basis of the dominant variant into three forms: reticular, athrophic-erythematous, and ulcerative (including bullous) (Fig. 1).

Gynaecological examination and diagnostic criteria

After the histological confirmation of OLP, all patients (with or without genital symptoms) were evaluated by a trained vulvologist-gynaecologist (PB), as recommended by the European College for the Study of Vulval Diseases (ECSVD) (16). The

DOI: 10.2340/00015555-0116

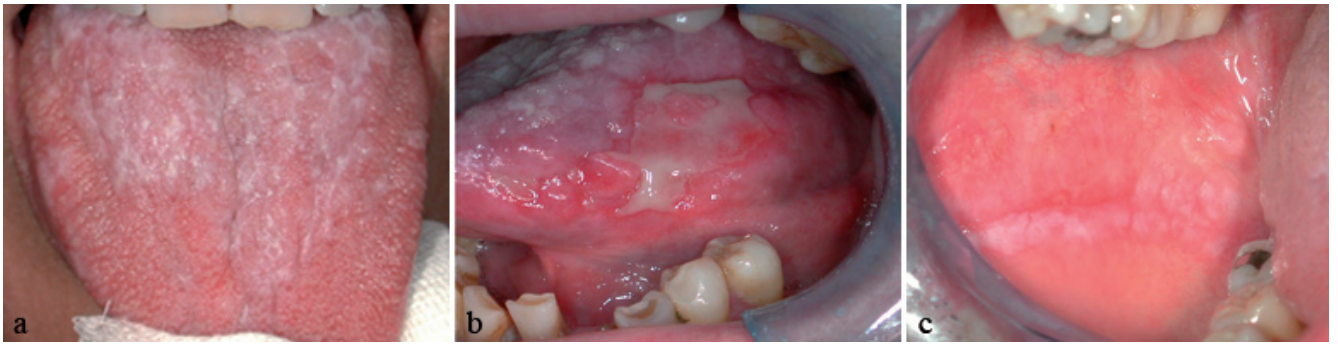

Fig. 1. Examples of oral lichen planus of (a, b) the tongue and (c) buccae.

medical history, genital symptoms, clinical and histological data were collected and recorded on a vulvologist's chart. Genital symptoms were described as itching, burning, dyspareunia, and/or vaginal discharge. Aided by vulvoscopy, genital signs were based on visual appearance (colour and surface changes) and palpation (texture and elasticity). Mons pubis, labia majora, labia minora, clitoris, vestibule, frenulum, perineum and perianal area were all examined closely. Genital lesions were defined as papular, erosive-atrophic or hypertrophic, according to the International Society for the Study of the Vulvovaginal Disease (ISSVD) (17). Examples of VLP and VLS are shown in Fig. 2. To reach histological confirmation of VLP, one or more biopsies were performed. In the presence of vaginal discharge from bacterial or candidal infection, a suitable treatment was given before performing biopsy.

Histological procedures and characteristics

For diagnosis of OLP and VLP, formalin-fixed and paraffin-embedded tissue sections were stained with haematoxylin-eosin and evaluated in a blinded manner by two pathologists (EM and DC). CD3 (pan T) and CD20 (pan B) immuno-stains were performed to confirm the predominance of T lymphocytes (CD3+) over B lymphocytes (CD20+), typical for LP (18–20); no assessment of sub-populations of T lymphocytes (CD4 or CD8) was routinely carried out.

Each case had to meet the inclusion and exclusion criteria. Cases were categorized as "histologically diagnostic of OLP/VLP" only when all three inclusion criteria were present (category 1); "compatible with OLP/VLP" when only two criteria were present (category 2) and "non consistent with OLP/VLP" when less than two criteria were evident (category 3). Only patients classified in category 1 or 2 were included in the study. The inclusion criteria were: (*i*) signs of "liquefaction degeneration" in the basal cell layer; (*ii*) presence of well-defined band of cellular infiltration, confined to the superficial part of the connective tissue; and (*iii*) strong predominance of T lymphocytes in the inflammatory infiltrate (Fig. 3 a). Each of these histological features was scored: 1=presence; 0=absence. Although criteria used were originally established for OLP, in our study they were considered also for genital lesions, in the absence of criteria more recent than 1909 (21). Exclusion criteria were the following: (*i*) epithelial dysplasia (defined as presence of nuclear enlargement and hyperchromatism, increased number of mitotic figures, aberrant mitoses, or dyskeratosis); (*ii*) absence of epithelial layers (for ulcers or erosions, inadequate sampling); (*iii*) deep extension of infiltration beyond superficial stroma; (*iv*) heterogeneous population in inflammatory infiltrate with B lymphocytes, neutrophils or plasma cells; (*v*) presence of lymphoid follicles in the infiltrate; or (*vi*) perivascular infiltration.

Cases of VLS were included in the study when they met the following morphological features: (*i*) homogenization of the dermis with a band of scattered lymphocytes beneath; (*ii*) spongiosis of basal cell layer; or (*iii*) loss of rete ridges and thinning of the epithelium (Fig. 3b).

Statistics

Data were analysed by SPSS 10.0 (Chicago, IL, USA.). The χ^2 test was used to assess statistical differences among categorical variables; Fisher's exact test was used when the frequency

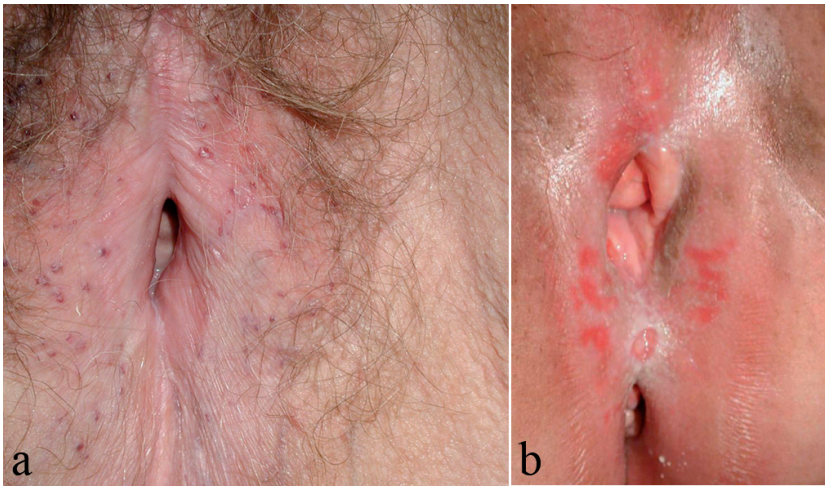

Fig. 2. Examples of (a) vulval lichen sclerosus and (b) vulval lichen planus.

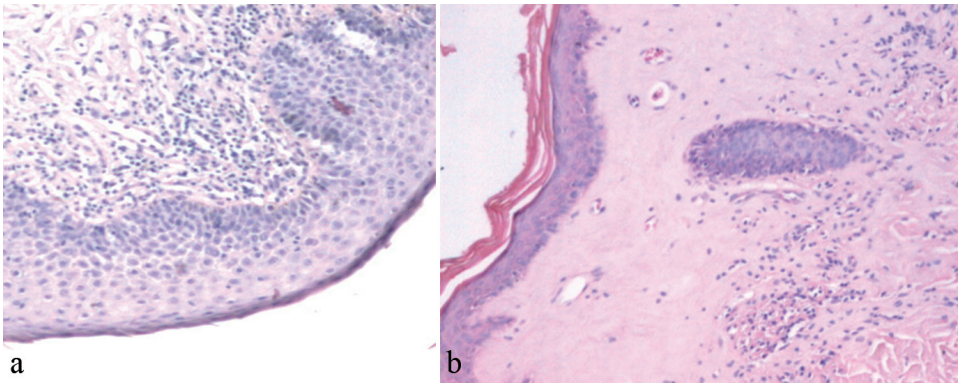

Fig. 3. Histological features of (a) vulval lichen sclerosus and (b) genital lichen planus. Original magnification, a: 200×, b: 100×.

observed was less than 5; Student's *t*-test was used for continuous variables; in all of evaluations *p*-values ≤ 0.05 were considered statistically significant. In particular, to measure the association level, crude odds ratio and the corresponding test-based 95% confidence interval were calculated. Reference groups were chosen as follows: for symptomatic category, the asymptomatic was chosen as the reference group; for ordinal variable (e.g. age) the first category was chosen as the reference group; for other features, the category with the largest number was chosen as the reference group.

RESULTS

As shown in Fig. 4, 55 females were enrolled with clinical signs of OLP (mean age 60.7 years, range 33–80 years). In all, 14/55 (26%) patients were dropped from the study. The remaining 41 patients all had histologically confirmed OLP (83% were OLP category 1 and 17% were OLP category 2). Of these 41 patients, 31 showed clinical signs of genital lichenoid lesions. All 31 patients underwent genital biopsy, and 27/31 patients (87%) showed histological confirmation of VLP, VLS, or both: 16/31 (52%) were VLP category 1, 6/31 (19%) were VLP category 2, 3/31 (10%) were VLS, and 2/31 were both VLP and VLS. Four of 31 patients had other diseases. Those with genital involvement (VLP or VLS) showed a wide range in scores equated with degree of narrowing of the vaginal orifice.

After stratifying by whether they experienced genital symptoms, the demographic, clinical and histological features of the 41 patients, are shown for OLP and VLP/VLS in Tables I and II, respectively. There were no significant associations with the presence of VLP/VLS in terms of the demographic, clinical and histological features of OLP, regardless of genital symptomatology.

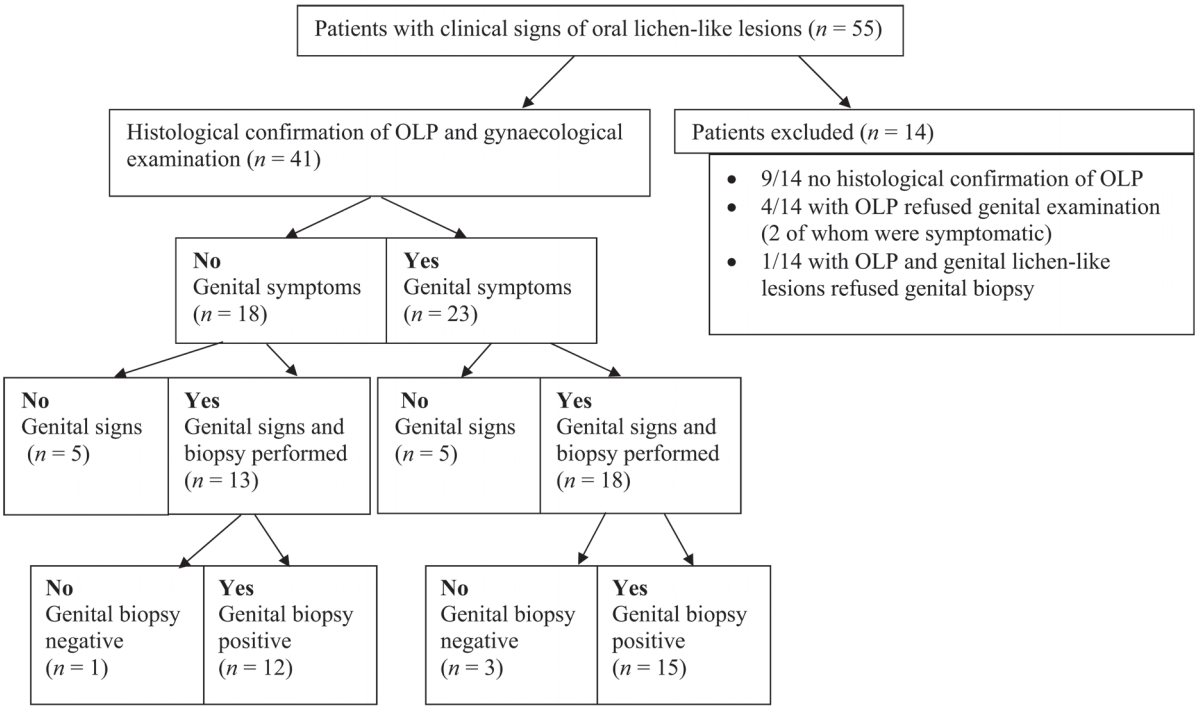

Fig. 4. Distribution of study population. OLP, oral lichen planus.

Table I. *Features of oral lichen planus (OLP) patients included in the study (n=41)*

	Genital symptoms:		Crude OR; (CI 95%)
	No *n* (%)	Yes *n* (%)	
Total	18 (44)	23 (56)	
Age (years) range	35–80	33–76	
(mean ±SD),	(62.8±11.7)	(59±12)	
HCV+	2 (11)	2 (9)	0.8 (0.1–6.0)
Dermal lichen planus	3 (17)	1 (4)	0.2 (0.0–2.4)
Oral histopathology:			
OLP1	16 (89)	18 (78)	2.2 (0.4–13.1)
OLP2	2 (11)	5 (22)	
OLP location:			
Gingival	11 (61)	16 (70)	1.5 (0.4–5.3)
Tongue	8 (44)	8 (35)	0.7 (0.2–2.4)
Buccal	15 (83)	18 (78)	0.7 (0.1–3.5)
Palate	7 (39)	6 (26)	0.6 (0.1–2.1)
OLP clinic:			
AE	10 (56)	14 (61)	1.2 (0.4–4.3)
R	14 (78)	14 (61)	0.4 (0.1–1.8)
E	4 (22)	2 (9)	0.3 (0.1–2.1)

OR, odds ratio; SD, standard deviation; CI, confidence interval; HCV, hepatitis C virus; AE, atrophic-erythematous; R, reticular; E, erosive/ulcerative/bullous

Only one woman presented a pure "vulvo-gingival" form of LP, with exclusive involvement of both gingival and vulval sites.

Isolated gingival localization was found in only 3/27 (11%) of patients.

Table II. *Features of genital involvement in patients grouped by symptoms (n=31)*

	Genital symptoms		
	No	Yes	p-value
	n (%)	*n* (%)	Crude OR (CI 95%)
Total	13 (42)	18 (58)	
Histopathological diagnosis			
VLP1	8 (61)	8 (44)	
VLP2	3 (23)	3 (17)	p>0.2
VLS	1 (8)	2 (11)	
VLP+VLS	0 (0)	2 (11)	
Other disease	1 (8)	3 (17)	
VLP/VLS location			
Clitoris	8 (62)	13 (72)	1.6 (0.4–7.4)
Fourchette/frenulum	7 (54)	11 (61)	1.4 (0.3–5.7)
Labia minor	13 (100)*	16 (89)	0.2 (0.0–2.1)
Labia maior	6 (46)	1 (6)	0.1 (0.0–0.7)
Perineum	3 (23)	3 (17)	0.7 (0.1–4)
Vestibule	8 (62)	10 (56)	0.8 (0.2–3.3)
Perianal	0 (0)*	2 (11)	2.5 (0.2–26.5)
VLP/VLS clinic			
AE	13 (100)	16 (89)	2.5 (0.2–26.4)
HY	4 (31)	8 (44)	0.6 (0.1–2.5)
P	1 (8)	0 (0)	2.9 (0.2–35.7)

OR, odds ratio; CI, confidence interval; VLP1, vulval lichen planus; VLP2, compatible with VLP; VLS, vulval lichen sclero-atrophicus; AE, atrophic-erythematous; HY, hypertrophic; P, papular.
*When a cell in a 2×2 table was equal to zero, a conventional value equals to 0.5 was added to cell frequencies to allow the calculation of OR.

DISCUSSION

LP is a muco-cutaneous disorder that can affect several body sites, showing a wide range of clinical variants and symptoms. Yet, a routine team approach by various specialists (i.e. oral medicine practitioner, gynaecologist and dermatologist) has not been adopted. Eisen (3) observed that in many OLP patients with genital symptoms, evaluation by physicians other than dermatologists, often led to misdiagnosis. Furthermore, diagnosis is rarely definitive when based on procurement of biopsy tissue and strict histological criteria.

Since 1869 (9), when the first report appeared of a patient with LP in different mucosal sites, simultaneous involvement of different mucosal sites was taken into account. There are many case reports about simultaneous oral–genital involvement (4, 12, 13, 22–28), but only few systematic studies have reported prevalence data, with frequencies ranging from 3.7% to 19.3% (2–3). Notably, Eisen (3) identified, in a series of 399 women with OLP, 77 cases (19.3%) of vulval and vaginal LP, presenting mainly with erosive or erythematous genital lesions. Interestingly, all of the 77 patients with genital involvement displayed gingival OLP; however, the severity and clinical oral variants were not correlated to the genital involvement. Ramer et al. (23) reported data regarding patients with severe oral lesions and a mild genital disease, as well as patients with asymptomatic gingival involvement but with severe erosive vulvo-vaginal disease.

In the present study, authors assessed frequency of VLP/VLS (87.1%) in OLP patients and verified that there were no demographic, clinical or histological features of OLP that were significantly associated with genital disease. This was contrary to the reported association in the literature of vulvo-vaginal and gingival disease. Indeed, only a few cases of the vulvo-vaginal-gingival syndrome were found (11.1%), suggesting a casual association rather than a well-defined syndrome.

As Eisen reported (3), sometimes this syndrome is not correctly recognized and the affected women suffer the lack of an appropriate medical therapy. Also, in our experience, the majority of women with genital symptoms reported a long history of such symptoms prior diagnosing the condition, suggesting a period of unsolved unspecified problems. Furthermore, all asymptomatic patients with VLS or/and VLP would have had no reason to consult a gynaecologist if not recruited for the study. In fact, unexpectedly, the highest frequency of genital lichen-like lesions was registered in the asymptomatic group (92.3%), but without any statistically significant difference, suggesting that lack of genital symptoms does not exclude *per se* the involvement of the district.

Previous studies have highlighted the need for histological evaluation in every case in which the features of the history and physical examination are suggestive of

LP (29). The histological diagnostic criteria of OLP were formulated first by the World Health Organization (WHO) (15) in 1978. However, strong inter- and intra-observer variability in the clinical and histological assessment of OLP, based on the WHO definition (30, 31) led to the development of more stringent diagnostic criteria (29), allowing a more reproducible diagnosis of OLP. Lotery & Galask (27) propose that the diagnosis of VLP may be based clinically on the presence of vulvo-vaginal signs alone, and the discovery of oral lesions is particularly supportive of this diagnosis. Additionally, they proposed that vulval or vaginal biopsy is generally non-contributory and may be misleading because, in presence of erosion, the histological features are variable. Conversely, in our experience described here, the diagnosis of LP (vulvo-vaginal or oral) should always be confirmed by biopsy on the basis of a set of reproducible clinical and histopathological criteria; and also, in doubtful cases, additional biopsies should be performed to establish the diagnosis.

As mentioned above, many definitions have been proposed to describe a multifocal presentations of LP, from "vulvo-vaginal-gingival syndrome" (12), to "plurimucosal lichen planus" (13), to "oro-vaginal-vulvar lichen planus" (28). In our opinion, the term "plurimucosal lichen planus" used by Bermejo et al. (13) is appropriate only to describe the simultaneous (synchronous or metachronous) sites without specifying gingival or vaginal sites, since they are not always the areas affected. In fact, evaluation of our data (Tables I and II) suggests that no dominant site exists, and several sites may be involved at the same time.

Regarding overlapping syndrome VLP/VLS, some authors (8, 32, 33) have suggested that these two aspects may represent a transitional stage to a unique disease rather than the coexistence of two distinct entities (8). In our opinion, differential diagnosis between VLP and VLS is difficult, particularly in the late stage of disease when fibrosis aspects, typical of VLS, are sometimes overlapping. Indeed both pictures are based on a similar immunological pathogenetic mechanism.

This cross-sectional study shows a higher frequency of concomitant VLP or/and VLS in women with OLP than previously reported in the literature; yet stringent exclusion histological criteria were applied. On the basis of our data, we suggest that all women with any clinical variant of OLP, even in the absence of genital symptoms, should undergo a thorough multidisciplinary evaluation with a strict protocol for LP diagnosis. Even in the absence of genital signs, long-term surveillance of the same patients should be planned in order to prevent multi-site involvement and possible malignant transformation (34, 35).

REFERENCES

1. Huber MA. Oral lichen planus. Quintessence Int 2004; 35: 731–752.
2. Micheletti L, Preti M, Bocci C, Bogliatto F, Condello V, Chieppa P. Vulval lichen planus in the practice of a vulval clinic. Br J Dermatol 2000; 143: 1349–1350.
3. Eisen D. The evaluation of cutaneous, genital, scalp, nail, esophageal, and ocular involvement in patients with oral lichen planus. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999; 88: 431–436.
4. Rogers RS, Eisen D. Erosive oral lichen planus with genital lesions: the vulvovaginal-gingival syndrome and the penogingival syndrome. Dermatol Clin 2003; 21: 91–98.
5. Eschenbach DA. Chronic vulvovaginal candidiasis. N Engl J Med 2004; 351: 851–852.
6. Murphy R. Desquamative inflammatory vaginitis. Dermatol Ther 2004; 17: 47–49.
7. Lotery HE, McClure N, Galask RP. Vulvodynia. Lancet 2004; 363: 1058–1060.
8. Marren P, Millard P, Chia Y, Wojnarowska F. Mucosal lichen sclerosus/lichen planus overlap syndromes. Br J Dermatol 1994; 131: 118–123.
9. Wilson E. On lichen planus. J Cutan Med Dis Skin 1869; 3: 117–132.
10. Gardner H. Desquamative inflammatory vaginitis: a newly defined entity. Am J Obstet Gynecol 1968; 102: 1102–1105.
11. Lynch P. Erosive lichen planus. Proc Int Soc Study Vulval Dis 1975: 30–31.
12. Pelisse M, Leibowitch M, Sedel D, Hewitt J. A new vulvo-vaginogingival syndrome. Plurimucous erosive lichen planus. Ann Dermatol Venereol 1982; 109: 797–798.
13. Bermejo A, Bermejo M D, Roman P, Botella R, Bagan JV. Lichen planus with simultaneous involvement of the oral cavity and genitalia. Oral Surg Oral Med Oral Pathol 1990; 69: 209–216.
14. Axell T, Rundquist L. Oral lichen planus – a demographic study. Community Dent Oral Epidemiol 1987; 15: 52–56.
15. WHO. Guide to epidemiology and diagnosis of oral mucosal diseases and conditions. Community Oral Epidemiol 1980; 8: 1–26.
16. Micheletti L. Clinical approach to vulvar diseases. Proceedings of the 4th Congress of the ECSVD 2002. Edizioni MAF Servizi, Turin, Italy, 2002; 55–56.
17. Neill S. Vulval Lichen Planus. Proceedings of the ISSVD Post-Congress Postgraduate Course, 1997 Edizioni MAF Servizi, Turin, Italy, 1197; 55–58.
18. Yamamoto, T, Nakane T, Osaki T. The mechanism of mononuclear cell infiltration in oral lichen planus: the role of cytokines released from keratinocytes. J Clin Immunol 2000; 20: 294–305.
19. Hirota J, Osaki T, Tatemoto Y. Immunohistochemical staining of infiltrates in oral lichen planus. Pathol Res Pract, 1990; 186: 625–632.
20. Mega H, Jiang WW, Takagi M. Immunohistochemical study of oral lichen planus associated with hepatitis C virus infection, oral lichenoid contact sensitivity reaction and idiopathic oral lichen planus. Oral Dis 2001; 7: 296–305.
21. Darier J. Precis de Dermatologie 1909. Paris: Masson, 1909.
22. Edwards L, Friedrich EG Jr. Desquamative vaginitis: lichen planus in disguise. Obstet Gynecol 1988; 71: 832–836.
23. Ramer MA, Altchek A, Deligdisch L, Phelps R, Montazem A, Buonocore PM. Lichen planus and the vulvovaginal-gingival syndrome. J Periodontol 2003; 74: 1385–1393.
24. Soper DE, Patterson JW, Hurt WG, Fantl JA, Blaylock WK. Lichen planus of the vulva. Obstet Gynecol 1988; 72: 74–76.
25. Eisen D. The vulvovaginal-gingival syndrome of lichen planus. The clinical characteristics of 22 patients. Arch Dermatol 1994; 130: 1379–1382.
26. Mous HV, Helmerhorst TJ, den Hollander JC, van der

Meijden WI. Vulvovaginal complaints, dyspareunia and oral mucosa abnormalities: erosive lichen planus. Ned Tijdschr Geneeskd 2002; 146: 881–885.
27. Lotery HE and Galask RP. Erosive lichen planus of the vulva and vagina. Obstet Gynecol 2003; 101: 1121–1125.
28. Petruzzi M, De Benedittis M, Carriero C, Giardina C, Parisi G, Serpico R. Oro-vaginal-vulvar lichen planus: report of two new cases. Maturitas 2005; 50: 140–150.
29. van der Meij EH, van der Waal I. Lack of clinicopathologic correlation in the diagnosis of oral lichen planus based on the presently available diagnostic criteria and suggestions for modifications. J Oral Pathol Med 2003; 32: 507–512.
30. van der Meij EH, Reibel J, Slootweg PJ, van der Wal JE, de Jong WF, van der Waal I. Interobserver and intraobserver variability in the histologic assessment of oral lichen planus. J Oral Pathol Med 1999; 28: 274–277.
31. van der Meij EH, Schepman KP, Plonait DR, Axell T, van der Waal I. Interobserver and intraobserver variability in the clinical assessment of oral lichen planus. J Oral Pathol Med 2002; 31: 95–98.
32. Holmes SC, Burden AD. Lichen sclerosus and lichen planus: a spectrum of disease? Report of two cases and review of the literature. Clin Exp Dermatol 1998; 23: 129–131.
33. Yashar S, Han KF, Haley JC. Lichen sclerosus-lichen planus overlap in a patient with hepatitis C virus infection. Br J Dermatol 2004; 150: 168–169.
34. Zaki I, Dalziel KL, Solomonsz FA, Stevens A. The under-reporting of skin disease in association with squamous cell carcinoma of the vulva. Clin Exp Dermatol 1996; 21: 334–337.
35. Gandolfo S, Richiardi L, Carrozzo M, Broccoletti R, Carbone M, Pagano M, et al. Risk of oral squamous cell carcinoma in 402 patients with oral lichen planus: a follow-up study in an Italian population. Oral Oncol 2004; 40: 77–83.