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A Review of Vulvovaginal-Gingival Syndrome. Case Report

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Abstract: Vulvovaginal-gingival syndrome (VVGS) is a chronic mucocutaneous disease of unknown etiology, which consists of a triad of symptoms: vulvar, vaginal and gingival of lichen planus (LP) lesions. The evidence suggests an autoimmune response, a genetic and probably hormonal component. Associated factors observed in LP include stress/anxiety, hepatitis C virus (HCV) and autoimmune diseases, among others. The most serious complication of oral and possibly also vulvar Lichen Planus is the development of squamous cell carcinoma. Corticosteroids are the mainstay treatment for LP in order to control inflammatory activity. In case of failure, immunosuppressive agents can be used (Tacrolimus and Cyclosporine). We present an illustrated case of VVGS who over the years developed tongue cancer and, 10 years later, a vulvar cancer. Oral Lichen Planus (OLP) should be referred to the appropriate specialists to rule out involvement of other mucous membranes and track it early to diagnose a possible malignant transformation. The efficient management of VVGS involves a multidisciplinary approach involving gynecologists, dermatologists and stomatologists.

Key words: Vulvovaginal-gingival syndrome, oral lichen planus, complications, multidisciplinary treatment.

Abbreviations

ELVP	Erosive Vulvar Lichen Planus
HCV	Hepatitis C virus
HLA	Human leukocite antigen
LP	Lichen Planus
LUTS	Lower urinary tract symptoms
NK cells	Natural Killer cells
OLL	Oral Lichenoid Lesions
OLP	Oral Lichen Planus
Th	T helper
SCC	Squamous cell carcinoma
VVGS	Vulvovaginal-Gingival Syndrome
VVGS-LP	Vulvovaginal-Gingival Syndrome-Lichen Planus
WHO	World Health Organization

1. Introduction

Lichen Planus (LP) is a chronic inflammatory mucocutaneous and immune disorder of the skin, hair, nails and mucous tissue, which develops with periodic outbreaks. It was first explained in 1869 by Dr. Wilson as an inflammatory disorder of the stratified squamous epithelia with an unknown etiology.

Vulvovaginal-gingival syndrome-Lichen Planus (VVGS-LP) or Hewitt-Pelisse syndrome is a distinctive erosive form of Lichen Planus (LP). Pelisse was first delineated in 4 patients in 1982 and 19 patients in 1989 as a rare variant of LP. Pelisse et al. named “vulvovaginal–gingival syndrome” the triad of erosive or desquamative vulvitis, vaginitis and desquamative gingivitis [1]. Cribier et al. [2] reported a case of “peno-gingival syndrome” as the equivalent in males.

1.1 Epidemiology

LP is probably the most common non-infectious disease of the oral mucosa. Although the exact prevalence of LP is unknown, the estimated prevalence is in the range of 0.22% to 5% worldwide [3]. However, these figures should be taken with caution as large epidemiological studies population groups have not

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often been made by experts, as well as suspected cases of oral lichen planus (OLP) that have been detected, often received a clinical diagnosis without a histopathologic confirmation.

The age range in which the disease manifests itself is between 30 and 70 years old. The mean age is 52 years, more frequently affecting peri- or post-menopausal women. Nevertheless, some cases have been reported in children or the elderly [4]. For each affected man, there are about 3-4 women with the disease [5, 6].

In general, mucosal LP involves the oral cavity as the sole manifestation [7], while approximately 19%-25% of patients with oral involvement show concomitant genital lesions [8].

1.2 Etiology

The etiology of VVGS is unknown, although there is sufficient data suggesting that immunological mechanisms are essential in the initiation and perpetuation of the process. Today it is accepted that the OLP is a cell-mediated immune response, in which there is a lymphocyte interaction directed against epithelial antigens of the basal keratinocytes of the epithelium, leading to the degeneration of the basal layer of the epithelium.

OLP involves a type IV hypersensitivity reaction to antigen which produces direct aggression against T lymphocyte cells of the basal epithelium of the oral mucosa. Inflammatory cells involved in this process consist of T helper and T cytotoxic lymphocytes, natural killer (NK) cells, and dendritic cells. T-cell activation is central to the pathogenesis of LP. Cytotoxic T-cell infiltration into the epithelium results in apoptotic basal keratinocytes. Theoretically, it may be induced by CXCR3 and CCR5 mediated signaling pathways initiated by both, T-cells and keratinocytes [9, 10]. There have been no previously reported HLA studies in this variant of LP. Setterfield et al. [11] found 80% positivity for the class II human leukocyte antigen (HLA) DQB1*0201 allele in 40 patients, which suggests a genetic predisposition [12]. An association of oral and cutaneous LP with HLADR1 suggests a genetic component [13].

Related to clinical factors, anxiety is a well-established risk factor or an accompanying factor in patients affected by LP. Apart from stress/anxiety, other associated factors and disease conditions include autoimmune diseases, internal malignancies and dyslipidemia.

The infectious factors are related to viral infections, specially the chronic hepatitis C virus (HCV). Epidemiological studies have demonstrated that there is a correlation between oral lichen planus and HCV infection. The pathogenesis of OLP induced by HCV is uncertain, but two hypotheses have been raised to explain the mechanism of the triggering of OLP by HCV. The first hypothesis suggests that virus replication is associated with the oral epithelium and thus contributes directly to the development of lesions. The second hypothesis proposes that the high mutation rate of the virus results in repeated activation of immune cells, increasing the probability of cross-reaction with its own tissue and, consequently, the risk of autoimmune disease. In certain genotypes, cross reactivity that activates immune cells against epithelial cells is favoured [14].

Arrieta et al. [15] have shown that oral biopsies performed on positive HCV patients in both, with and without OLP, demonstrated the virus replicating within the epithelial cells of all the oral biopsies taken, regardless of whether the patient had OLP or not. HCV- related LP may affect any oral site clinically. The reasons for such an association between HCV-related LP are still unclear; as HCV- related LP and idiopathic form LP share histological features, they may also share pathologic mechanisms [14, 16].

Finally, described factors may influence the initiation, perpetuation or worsening of oral Lichen planus lesions of the following [4]: (1) Local factors: mechanical (prosthesis, edges, metals), chemical (alcohol and tobacco [snuff]) or biological (bacterial plaque). (2) Drugs, among which we can find as the

most common: antimalarial (Chloroquine), antihipertensives (Methyldopa, Captopril, Enalapril, Propanolol), compounds of metal (salts gold, bismuth salts), nonsteroidal anti-inflammatories (Phenylbutazone, Ibuprophen) and diuretics (Furosemide, Spironolactone).

1.3 Diagnosis

The diagnosis of LP should be based on clinical observation and confirmed by the description of the histological changes observed in the biopsy. The histopathology is almost always conclusive. Even though there are still no universally diagnostic criteria of OLP accepted, so far can we follow the clinic pathological criteria described by World Health Organization (WHO), although some authors question it. The clinical criteria would lead to a presumptive clinical trial that would have to be confirmed by histopathology. Biopsy alone is never diagnostic for LP itself.

1.3.1 Diagnostic Criteria of OLP and OLL (Oral Lichenoid Lesions). Modified WHO (2003)

(1) Clinical criteria [17]: Presence of bilateral, more or less symmetrical lesions. Presence of a lacelike network of slightly raised gray-white lines (reticular pattern). Erosive, atrophic, bullous and plaque-type lesions are accepted only as a subtype in the presence of reticular lesions elsewhere in the oral mucosa. In all other lesions that resemble OLP but do not complete the aforementioned criteria, the term "clinically compatible with" should be used.

(2) Histopathologic Criteria [18]: Presence of a well-defined band-like zone a cellular infiltration that is confined to the superficial part of the connective tissue, consisting mainly of lymphocytes (mainly T cells). Signs of liquefaction degeneration in the basal cell layer. Variable degrees of ortho or parakeratosis. Frequently tooth-shaped interpapillary ridges. CD8 lymphocytes predominate in relation to the epithelium.

When the histopathologic features are less obvious, the term "histopathologically compatible with" should be used. Fig. 1 shows the classic histological features.

To achieve the final diagnosis of OLP or OLL, clinical, as well as, histopathologic criteria should be included [17]: (1) OLP. A diagnosis of OLP requires fulfillment of both clinical and histopathologic criteria. (2) OLL. The term OLL will be used under the following conditions: Clinically typical of OLP but histopathologically only compatible with OLP; Histopathologically typical of OLP but clinically only compatible with OLP; Clinically compatible with OLP and histopathologically compatible with OLP.

Oral Lichen Planus has many different forms of presentation, being the reticular form and the erosive form the most common.

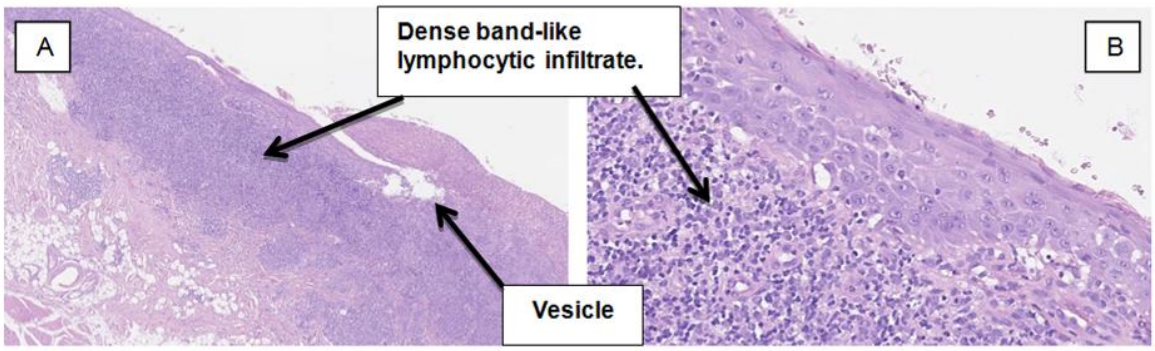

Fig. 1 H&E- × 5 (A) and H&E- × 40 (B), Histology of oral lichen planus. The classic histopathologic features of OLP include a dense band-like lymphocytic infiltrate at the interface between the epithelium and the connective tissue, which produce a hydropic degeneration of basal layer. In these images, neither the apoptosis of the keratinocytes nor the focal areas of hyperkeratinized epithelium can be well seen, as it may be in the very beginning of the process. In the first image it can be seen a stop in the squamous layer, as a consequence of the presence of a vesicle and its perilesional infiltrate.

1.3.2 Reticular LP

It is the most common clinical form of the disease and it presents with fine, intertwined white striae, called “Wickham striae”. It occurs more often in the posterior region of the oral mucosa bilaterally (Figs. 2 and 3), and also in other regions such as the side and back of the tongue edge, gums, palate and lips. This form is usually asymptomatic. In some patients, reticular OLP may eventually progress to the more severe subtypes, such as the erosive form.

1.3.3 Erosive/Ulcerative LP

It is the second most common form of oral LP, and it is characterized by oral ulcers presenting with persistent, irregular areas of redness, ulcerations and erosions covered with a yellow slough. Typically, it has a multifocal pattern of distribution. It is clinically important because the lesions can be quite painful and therefore it may negatively affect the patient’s quality of life. The symptoms may range from discomfort to severe, painful episodes. Involvement of the dorsum of the tongue might cause dysgeusia [9].

Forms of red predominance (erythematous and erosive) are symptomatic (Fig. 4). Symptoms include increased sensitivity to food (especially contact with acidic or salty food), intense local pain, and burning. The disease occurs in outbreaks and the number of outbreaks in a year, and periods between outbreaks vary in each patient. Chronicity is characteristic and almost always there is some kind of injury.

1.3.4 Vulvovaginal LP

In comparison with the other forms of LP, VVG-LP is considered to be a multisystemic disease, revealing a strong association with scar formation and mucous stenosis [11]. Vulvar LP can affect peri- or postmenopausal women. It has three major subtypes: erosive, papulosquamous, and hypertrophic. Erosive vulvar LP is the most frequent subtype, involving the mucous membranes exclusively.

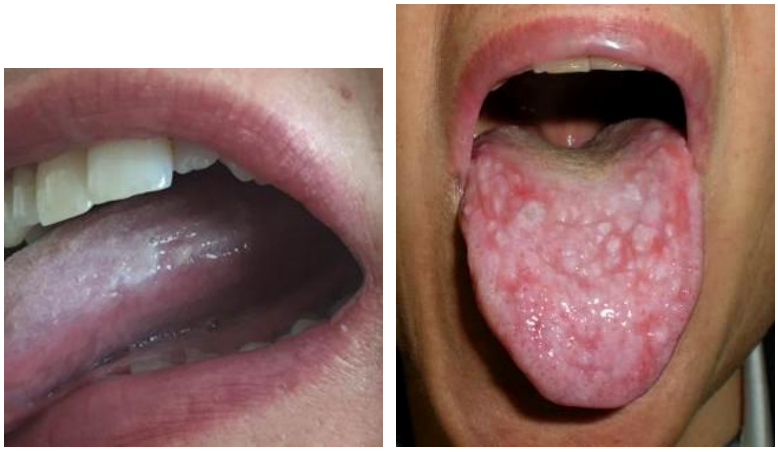

Fig. 2 Confluent white reticulated plaques of the lateral and dorsum of the tongue.

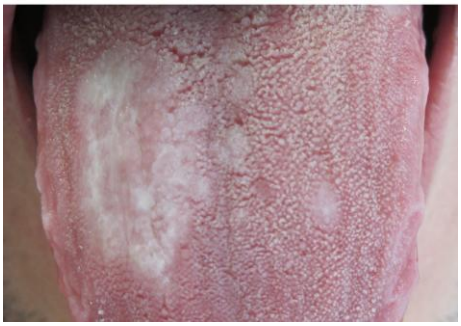

Fig. 3 Keratotic areas of LP lesions located in the dorsum of the tongue.

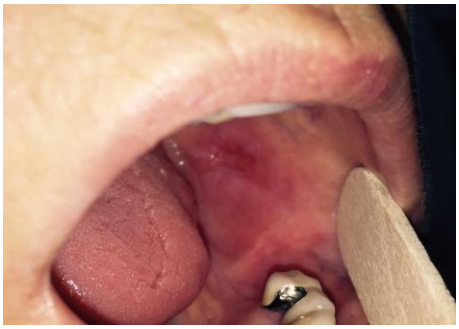

Fig. 4 Bright red bucal mucosal erosions with typical white reticular marginans.

The condition is chronic and painful, causing an increase in vaginal discharge, dysuria, burning, dyspareunia, and postcoital bleeding. The vaginal lesions are velvety red erosions or bright red, glazed erythema, which are friable and bleed when touched (Fig. 5). The most significant sequelae of chronic erosive vulvar LP is scarring, which can result in resorption of the labia minora (agglutination) and clitoral hood, with subsequent clitoral burying (synechiae,), stenosis of the introitus, and potentially total obliteration of the vagina (Fig. 6). The associated scarring and adhesions affecting the vagina may interfere with sexual intercourse [9]. Vaginal synechiae and adhesions develop, leading, in some cases, to vaginal stenosis [11]. These lesions may seriously compromise the quality of life.

Clinical differential diagnosis of lesions of LP should be made [4]: (1) OLP: Leukoplakia, candidiasis, multiform erythema, pemphigus vulgaris, bullous pemphigoid, lichen sclerosus, secondary syphilis, bite trauma, lichen sclerosus and atrophicus, lupus, ashy dermatosis. (2) Vulvar LP: Lichen sclerosis, vulvovaginal blistering diseases.

1.4 Treatment

Due to chronicity of mucosal LP and in particular the scarring potential of the VVGS, treatment is often challenging. The treatment of erosive vulvar LP is empirical and not curative. The most frequent first-line treatment is a potent topical corticosteroid.

The main problems of current treatments are the side effects and recurrence of lesions after treatment is stopped. Complications of corticosteroid therapy (topical or systemic) are common. These include superimposed candida vulvovaginitis and, occasionally, bacterial superinfection.

The main objectives of the current therapy of OLP are controlling the painful symptoms, resolution of mucosal lesions, reducing the risk of malignant transformation and maintenance of good oral hygiene.

It is important to identify factors that contribute to the maintenance of LP, so that, remove local, mechanical, physical, chemical and biological factors that may be involved (polish sharp edges of teeth, tooth extractions, dentures and adjust good oral hygiene). It is advisable to eliminate the consumption of tobacco and alcohol and the establishment of a proper diet. If it is suspected that the cause of lichenoid oral lesions is a drug, the charge should be removed or changed. There are some diseases which can contribute to the maintenance of LP, such as: HCV, diabetes, anxiety and stress management, and hypertension.

Treating oral lesions, also, is often difficult because of tongue movements and salivary flow which easily clear drugs [21]. Conventional treatment of OLP is based on the application of corticosteroids as a basic

Fig. 5 Characteristic clinical findings in erosive vulvovaginal lichen planus. White, reticulated lesions at the periphery. Introital erosion and extensive architectural change with labial resorption, buried clitoris and introital stenosis.

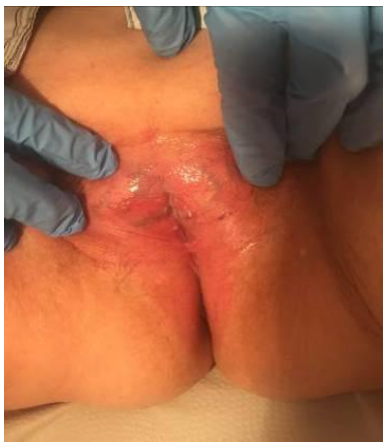

Fig. 6 Intense erythema and velvety red erosion of the vulva.

medication to control inflammatory activity. The most commonly topical steroids used are (low to high anti-inflammatory potency): Triamcinolone acetonide 0.1%-0.3%, Fluocinolone acetonide 0.05%-0.1% and Clobetasol propionate 0.025%-0.05%. Intraorally, in aqueous suspension for orabase or gel, betamethasone mouthwashes (0.5 mg dissolved in 10 mL of water) should be swished and spilled for 2 to 3 minutes between 1 to 4 times per day according to the severity of injuries [4].

After the prescription of local corticosteroids for a genital use, it is recommended to reduce its application gradually if the symptoms improve. Initially, one dose is applied every night during the first month, then in alternate nights during the following month and finally continue this procedure twice a week for one more month. The highest dose to be applied/administrated should be 30 gr. in a 3 month term [11].

Systemic medications (prednisone, metronidazole, azathioprine, and mycophenolate) can be added for severe or resistant cases. The use of prednisone 1-1.5 mg/kg per day in single dose early in the morning is recommended. This dose is used for 2-3 weeks and then, the same dose on alternate days or gradually decreasing [4].

In case of failure, immunosuppressive agents, such as Tacrolimus and Ciclosporin could be used. The molecular mechanism for the anti-inflammatory action of tacrolimus is similar to that of ciclosporin. However, unlike ciclosporin, tacrolimus is able to penetrate the epidermal barrier, thus exerting immunosuppressive action after topical use [19]. Tacrolimus and Pimecrolimus are inhibitors of topical calcineurin that bind macrophilin and subsequently inhibit dephosphorylation of nuclear factor of activated T cells by calcineurin.This significantly reduces the production of cytokines T. Given pathogenesis mediated by T cells, the application of calcineurin inhibitors seems a promising therapeutic option for LP [20].

The azathioprine associated with corticosteroids used in order to increase the immunosuppressive effect.

The metronidazole has a good safety profile, low cost, and has been recommended (level C of recommendation) for LP therapy (in VVGS-LP, no studies or case reports have been cited in the medical literature) [21]. It is probable that metronidazole acts as an immunomodulator, decreasing the activity of inflammatory diseases [12].

2. Materials and Methods. A Case Report

We report an illustrated case of a patient with VVGS diagnosed of LP, where genital lesions preceded oral lesions. Over the years she developed tongue cancer and 10 years later vulvar cancer.

An 89-year-old white woman. No toxic habits. Her medical history was significant for hypothyroidism, hypertension treated with Lisinopril and anxiety depressive disorder treated with Paroxetine 20 mg/day and Lorazepam 1 mg/day. B and C hepatitis markers were negative. Thirty-two years prior she suffered a total hysterectomy for post-menopausal bleeding. Afterwards, she never performed any controls.

When the patient was 78 years old, she suffered from white tongue lesions treated as oral thrush, with no improvement. Afterwards, she was diagnosed of erosive LP through biopsy. Three years later she developed lingual squamous cell carcinoma (SCC) in left lateral border of the tongue, which was surgically taken out and analyzed. Surgical margins were deemed as negative and there was no evidence of nodal disease. Two years later, after surgery, she suffered from node recurrence (Fig. 7).

3. Results

In March 2015, after some episodes of dysuria and itching treated as LUTS (lower urinary tract symptoms), was unresponsive to several medications including antibacterial and antifungal tablets and creams. Clinical examination revealed alteration of the normal vulvar architecture with loss of the labia minora and clitoris, presenting circumferential 3×3 cm exophytic

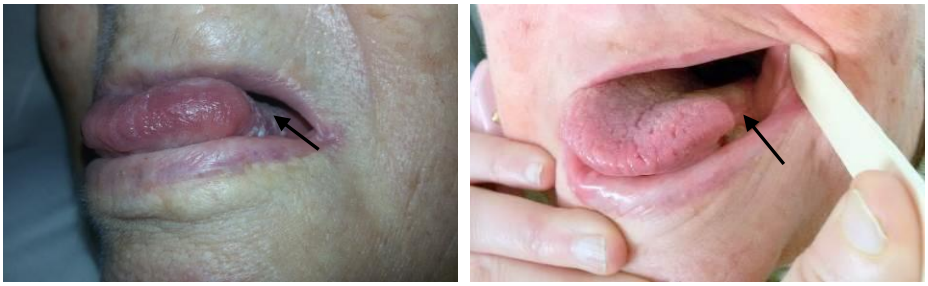

Fig. 7 Partial glosectomy for lingual squamous cell cancer.

Fig. 8 SCC of vulva. Labia resorption and buried clitoris.

tumor in the lower third of the right vulva (Fig. 8).

The result of the biopsy was a moderately differentiated squamous cell carcinoma, infiltrating on scleral-erosive and atrophic lichen. Radical surgery was performed with femoral bilateral inguinal lymphadenectomy.

Seven months after the vulvar surgery developed inguinal ganglionic recurrence. Her health deteriorated progressively and the patient died 10 months after the diagnosis of squamous vulvar carcinoma.

3.1 Complications

The most significant sequelae of chronic erosive vulvar LP is scarring, which can result in resorption of the labia minora (agglutination) and clitoral hood, with subsequent clitoral burying (synechiae), stenosis of the introitus and potentially total obliteration of the vagina [22]. The associated scarring and adhesions affecting the vagina may interfere with sexual intercourse [23, 24].

It is also beneficial to document the extent and location of the lesions in the vulva and examine other mucocutaneous sites of LP at each visit. In addition to dyspareunia, erosive LP may also result in very severe itch, which is one cause of vulvodynia (burning discomfort of the vulva) with chronic vaginal discharge and postcoital bleeding.

It is essential to consider the patient's psychological status and quality of life, which can be deeply affected by the disease.

The incidence of vulval carcinoma varies from less than 1 in 100,000 women in developing countries to more than 1.5 in 100,000 women in North America, South America, and Europe. There is clear evidence that certain vulval inflammatory disorders, such as lichen sclerosus, predispose to the development of malignancy [25]. The malignant transformation rate of vulvar LP seems to be 1.1% [9, 30]; although there is not yet a formal consensus on whether ELPV (Erosive Vulvar Lichen Planus) is a premalignant condition [26].

Accurate diagnosis and follow-up of any vulvar lesion is important, particularly when symptoms of vulvovaginitis are persistent [27].

The most serious complication of oral lichen planus (OLP), is the development of oral SCC.

Mignona et al. [28] has suggested that currently there is sufficient evidence demonstrating that chronic inflammation, which is the case of OLP, generates a cytokine-based microenvironment that affects cell survival, growth, proliferation and differentiation. This may consequently contribute to cancer initiation, promotion and progression.

The malignant potencial of OLP still remains uncertain, with studies reporting malignant transformation rates between 0.4% and 0.56% [16].

From 1910 when was reported the first case in a woman suffered OLP, many cases and cases series have been reported with values from 0 to 12.5%, and with follow-up ranking from 0,5 to 20 years. But many of these cases not had been accepted by some authors who disagree with the diagnostic criteria employed [33].

In one recent study reported by Tomaz Aline et al. [30] of the LP (85 cases) 1 patient presented a SCC 4 years after the initial diagnosis of OLP, (malignant transformation corresponded to 0.85% of the cases). In addition, three patients showed moderate cellular atypia.

The malignancy potential of LP, especially in the erosive form, is not yet fully understood and has been a longstanding topic of debate [9]. The greatest problem of studying the potential of malignancy of OLP is the lack of objective and unanimous criteria for its diagnosis. Some studies base the diagnosis only on clinical characteristics; others, on histopathological findings and others still on both. In addition, many lesions clinically and/or histologically diagnosed as OLP may, in reality, be dysplastic leucoplakias with lichenoid appearance and secondary lichenoid inflammatory infiltrate similar to lichen planus (lichenoid dysplasia). It is important to stress that histological characteristics of epithelial dysplasia are not exclusively premalignant. Changes in the histological pattern may occur in response to low intensity chronic stimuli; for instance, in the reactive hyperplasia induced by prosthesis with epithelial dysplasia. Another limiting factor of studies about the malignant transformation of OLP is the lack of documentation about the associated smoking [7, 16, 31].

Based on the variant of OLP, the atrophic, ulcerated and erosive types show greater incidence of malignant transformation. The most common sites are the tongue, gingiva and mucosa of the cheek [32].

For this reason, The WHO has classified the OLP as a potentially malignant disorder [30, 33]. Thus we always recommend a strict follow-up.

Clinical examination is required three times a year for early detection and adequate treatment. We analyze the morphology, location, extent, and homogeneity of lesions. Whenever suspicious signs of malignant transformation are found, frequency of follow-up examination has to be increased, or an additional oral biopsy has to be directly performed [34].

4. Conclusions

The coexistence of oral and genital lesions is known as vulvovaginal-gingival syndrome and it is a distinct type of erosive LP.

The most significant sequelae of chronic erosive vulvar LP is scarring, which can result in resorption of the labia minora (agglutination) and clitoral hood, with subsequent clitoral burying (synechiae), stenosis of the introitus and potentially total obliteration of the vagina.

The most serious complication of oral and possibly also vulvar LP is the development of SCC (there is not yet a formal consensus on whether ELPV is a premalignant condition).

Gynecologists do not routinely examine the mouth, while dentists do not inquire about possible genital symptoms. You must always examine all mucous. The dentist must inquire about possible genital involvement in course of OLP as to avoid diagnostic delay and complications, mostly at the genital level.

Therefore, a multidisciplinary approach is required for an efficient management of VVGS with the involvement of gynecologists, dermatologists and stomatologists.

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