Vulvar lichen sclerosus, premalign inflammatory dermatosis

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Abstract

Vulvar lichen sclerosus (VLS) is a chronic inflammatory condition classified as precancerous dermatosis of the genital mucosa, associated with a risk of progression to in situ, then invasive vulvar squamous cell carcinomas. Although the etiology of this disease has not been determined, the factors involved in its pathogenesis are genetic, autoimmune, hormonal, infectious as well as environmentally-mediated. Given the risk of malign progression, these type of skin lesions have to be carefully watched by regular clinical exams, and a biopsy of the affected genital mucosa should be carried out whenever dysplasia or malign transformation is suspected. Vulvar carcinogenesis is a multistage process, regardless of the type (i.e. differentiated or not) of intraepithelial vulval neoplasia (IVN), which includes human papilloma viruses (HPV)-negative immune-mediated inflammatory disease, mainly the VLS. The involvement of HPV as main trigger in IVN has been clearly confirmed. The present paper comprises a synthetic review of the available literature on this borderline type of disease referred to as VLS, and looks at the mainly clinical and diagnostic aspects that need to be observed by the clinicians. Considering the potential for progression of the disease, it is of foremost importance to diagnose VLS in an early stage, to closely follow up with the gynecologist and dermatologist, while carefully and steadily monitoring these lesions and to initiate the appropriate disease-specific treatment.

Keywords: *vulvar lichen sclerosus, vulvar carcinoma, precancerous lesions, early diagnosis*

Introduction

Cutaneous and mucosal precancerous conditions are chronic dermatoses at risk to undergo malignant changes. These lesions share a similar pathological feature, namely the epithelial dysplasia revealing nucleocytoplasmic abnormalities in keratinocyte morphology[(1)]. In 2011, the International Society for the Study of Vulvovaginal Disease adopted a new classification of intraepithelial vulval neoplasia. Intraepithelial vulvar neoplasia (IVN) is now considered precancerous lesion and divided into 2 types: the common, undifferentiated type of IVN (i.e. mainly associated with oncogenic human papillomavirus (HPV) infection) and the differentiated type of IVN (i.e. associated with vulvar skin disorders, mainly the vulvar lichen sclerosus)[(2-4)].

The undifferentiated IVN type commonly occurs in smokers with HPV infection, whereas the differentiated type may develop from vulvar lichen sclerosus (VLS) (i.e. HPV-negative lesion) which is susceptible to progress more rapidly to vulvar carcinoma (i.e. approx. 5% of VLS lesions are likely to undergo malignant changes)[(5)].

Precancerous dermatoses of women genital mucosa include vulvar lichen sclerosus, erosive/ulcerative lichen planus of the vulva, extramammary Paget disease of the vulva, leukoplakia, giant Buschke-Löwenstein tumor, Bowenoid papulosis, and Bowen's disease. These conditions can progress to IVN or vulvar cancer.

Vulvar cancer accounts for 0.7% of the overall new cases of neoplasia in women[(6)] and for 6% of the total gynecological neoplasia cases[(7)]. Vulvar tumors having developed from VLS are the main cause of vulvar cancer in older women[(8)]. Therefore, early detection and proper diagnosis of VLS may reduce the incidence of vulvar cancer in older women, and have a positive impact on the burden of this disease and vulvar cancer mortality.

VLS is a chronic inflammatory dermatosis of the genital area[(9,10)]. Severe pruritus and soreness that are characteristic of this condition have a debilitating impact on the patients' quality of life, with significant psychological and psychiatric effects. A study conducted in 45 VLS patients showed that 16% of them feared they might transmit the disease, 27% experienced libido changes, 58% had anxiety attacks, 27% experienced depressive episodes, 19% suffered from insomnia, 23% reported stress and 11.5% were reluctant to involve in a new relationship[(11)]. Early diagnosis of this condition might help diminish these subjective complaints by initiating a treatment adapted to the specific form of the disease.

VLS most commonly occurs in postmenopausal women[(12)], however it was also reported in prepubertal children (i.e. in approximately 15% of the cases)[(13)].

Case reports

We selected two cases from our clinical practice, which are highly representative of the evolution of this medical condition. Our first case is a 70-year old women patient referred for dermatological examination by the gynecologist, with achromic scleroatrophic plaques that had emerged on her skin several years ago in the vulvar and perivulvar region. She had very severe pruritus that she tried to treat by following various non-specific therapies only to experience a worsening of her symptoms. When she decided to have

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a dermatological check-up, a sore, infiltrating tumor growth was detected in her labia minora and clitoris (Figure 1). She was diagnosed with VLS susceptible to transformation into squamous cell carcinoma, this diagnosis being further confirmed by histopathological examination. The treatment recommendation was total vulvectomy and specific oncological therapy.

Our second case is a 53-year old patient with known endocrine disorder (i.e. autoimmune thyroiditis complicated by hyperthyroidism) in premature menopause since the age of 32, diagnosed with depressive syndrome. She was referred by the gynecologist for dermatological examination of scleroatrophic lesions in the vulvar region, for which she received several topical treatments. The onset of the disease was 21 years ago, with the emergence of whitish, scleroatrophic, pruriginous plaques that have been spreading progressively. A significant edema of the right labia developed recently, showing purpuric lesions, blistering and secondary vulvar ulcerations (on the clitoris and labia), associated with severe pruritus and burning-like pain (Figure 2). A punch-biopsy was performed, followed by pathological examination of the tissue due to suspected dysplasia (the pathological appearance did not confirm the suspicion of malign transformation). Systemic and topical corticotherapy was initiated, leading to an alleviation of the symptoms. Further monitoring of the disease course is mandatory in order to prevent any malignant transformation of VLS.

Discussion

In VLS, achromic macules (i.e. discoloured patches on the skin) appear on the skin that further join together to form plaques and are associated with alteration of the teguments (i.e. cracks, telangiectases, purpuric, at times bullous skin lesions), that vary in terms of skin damage and disposition, typically involving the vulvar, perivulvar and perianal regions (hourglass appearance). The patients experience severe itching, dyspareunia, dysuria and genital bleeding. During the course of the disease, there may appear scaring of the labia minora and clitoris, synechias involving irreversible changes of the genital area (i.e. vaginal stenosis, urinary obstruction) and malignant transformation to vulvar squamous cell carcinoma[14]. The main pathological features are epidermic atrophy, hydropic degeneration of basal cells, collagen fibers packed into course bands within the superficial dermis and inflammatory lympho-monocyte infiltrate.

In terms of clinical presentation, VLS should be distinguished from the erosive vulvar lichen planus (EVLP). In EVLP of the vulvar and vaginal mucosa, former erythema leads to painful ulcerations, genital bleedings and white lesions with a lace-like, reticular appearance. As the disease progresses, there may appear scaring, strictures, vaginal obstruction or development of squamous cell carcinoma (a 2-3% risk)[15,16]. The patients complain of dysuria, intense itching and dyspareunia[17]. In 2/3 of the cases, the vulvo-vaginal lesions may be associated with oral lesions, which commonly precede genital lesions. Together are known as the vulvovaginal gingival syndrome[16,18,19]. As opposed to the VLS (i.e. in which the vaginal mucosa is not affected), with EVLP there is ulceration and scaring of the vaginal tissue as well. Rectal and esophageal mucosae may also be involved[16,20].

In addition to EVLP, the differential diagnosis of VLS also includes other precancerous dermatoses, of which one should consider the extra-mammary Paget disease of the vulva. This presents as erythematous, well demarcated, scaly infiltrative plaques, that may be eczematous, papillomatous or ulcerated in appearance, the affected area being hypo- or hyper-pigmented. Symptoms include intense burning or itching occurring locally[1,14].

Vulvar leukoplakia is yet another precancerous skin condition, characterized by white, well-demarcated plaques on the genital mucosa, which may have a verrucous or ulcerated appearance. Bowen disease of the vulvar mucosa, categorized as squamous cell carcino-

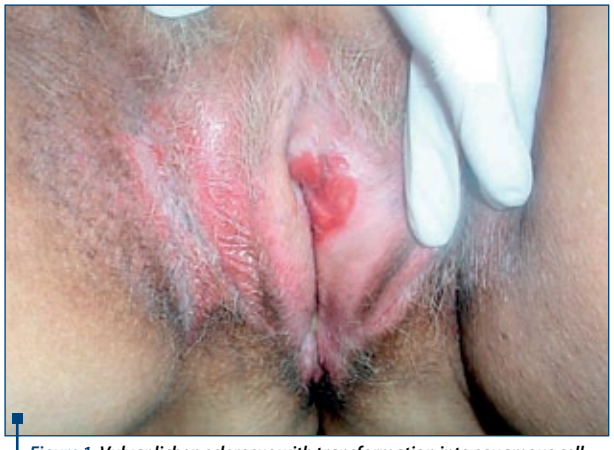

Figure 1. Vulvar lichen sclerosus with transformation into squamous cell carcinoma

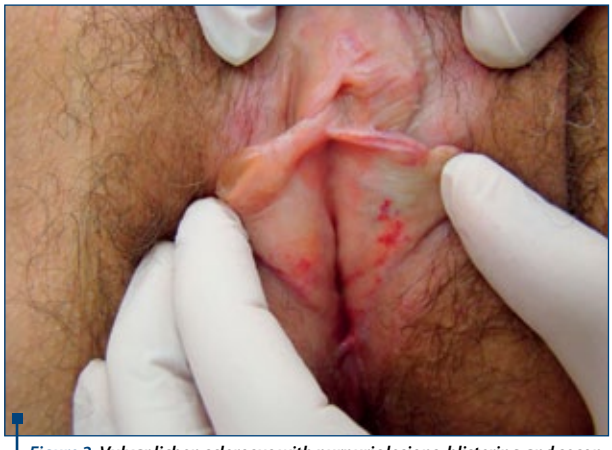

Figure 2. Vulvar lichen sclerosus with purpuric lesions, blistering and secondary vulvar ulcerations on the clitoris and labia

ma in situ, is rarely located in this area, most usually involving photo-exposed areas of the skin.

Clinically, it manifests as a single erythematous scaly plaque, well-defined in appearance and sometimes showing multiple lesions. Bowenoid papulosis presents as small, flat-topped hyper-chromic papules, with a 2.6% risk of progression to squamous cell carcinoma[21-24].

Buschke-Löwenstein giant condyloma is also a precancerous condition affecting genitalia. It is characterized by a pseudo-tumoral cauliflower-like proliferation that progresses rapidly. Malignant transformation to verrucous squamous cell carcinoma may be suspected when there is tissue hardening of the tumor base and signs of infiltration are observed[21-23].

Etiopathogeny

The etiopathogenesis of VLS has not been clearly determined until present date, since it comprises a multitude of causal factors like genetic factors, autoimmune factors, hormonal, infectious or environment-mediated factors[25].

The question of genetic factors involvement of was raised and confirmed by the identification of VLS cases in members of the same families. A study in 1052 women suffering from VLS, which was published in 2010, showed that 12% of the subjects had a family medical history of lichen sclerosus (i.e. of the vulva or penis). Furthermore, vulvar cancer development was more frequently reported in families with lichen sclerosus cases (4.1%) than in families with a negative family history of lichen sclerosus (1.2%)[26].

Another study that was published in 2014 and enrolled 117 patients, of which 114 were women with VLS, revealed the fact that 8.6% of them had a positive family history of lichen sclerosus, and a further 30% were suspected to have such cases in their family[27].

The role of immune-mediated factors has not been clearly delineated as yet, however there is a great amount of serological evidence that have showed a connexion between VLS and autoimmune disorders like thyroiditis[28], morphea, alopecia areata, diabetes miellitus, pernicious anemia, vitiligo[29] and have established the serological markers of autoimmunity.

A retrospective study in 532 patients with lichen sclerosus investigated the association of VLS with autoimmune disorders and the serological markers of autoimmunity in a subgroup of 322 patients. As many as 18.9% of the patients in the VLS group had at least one VLS-related autoimmune disorder (i.e. immune-mediated thyroiditis, morphea, rheumatoid arthritis and psoriasis). Several serological markers of autoimmunity were detected: anti-thyroid antibodies (11.1%), antinuclear antibodies (9.8%), circulating immune complexes (8.6%), anti-smooth muscle antibodies (4.3%), extractable nuclear antigens (3%), the C3 fraction of the complement (2.8%), the rheumatoid factor (1.8%), and the C4 fraction of the complement (0.5%)[30].

Infectious exogenous factors may also act as triggers for VLS. Among those, a particular attention was given to *Borrelia burgdorferi*. The studies investigating *Borrelia burgdorferi* involvement in the pathogenesis of VLS have yet to be conclusive. Using focus-floating microscopy to examine 61 VLS cases and 118 control cases, investigators identified species of *Borrelia burgdorferi* in 63% of the patients in the VLS group and in 57% in the control group[31]. However, other studies dismiss any active involvement of *Borrelia* in VLS etiopathogenesis.

Hormonal etiology of VLS is also considered a possibility given the prepubertal and postmenopausal onset of this disorder. In addition, deficiencies of 5-alpha-reductase activity were singled out at this level, which is suggestive of a hormonal imbalance underlying VLS. Oral contraceptives taken during post-menopause have also been found to play a role in VLS onset. A study in 40 patients with VLS and 110 healthy ones investigating the role of oral contraceptive in the early onset of VLS condition revealed that 70% of VLS patients used oral anti-androgen contraceptives, compared to 47.9% of the subjects in the control group. These findings suggest that the alteration of the androgen-signaling axis may be a possible factor of early VLS onset in a certain category of women who are susceptible to the disease[32].

Many researchers consider VLS to have pathogenic features similar to scleroderma[33]. This opinion is supported by published clinical cases revealing the association between VLS and scleroderma. VLS is characterized by inflammation in the papillary dermis and fibroblast function deterioration, associated with secondary fibrosis. The published studies indicated the presence of IgG autoantibodies to extracellular matrix protein1 (ECM1)[34] in 67% of the cases[35] and basement membrane zone antibodies to BP180 and BP230 in 30% of the cases[36].

When ECM1 becomes a target for certain antibodies (i.e. as is the case with VLS), this causes changes in the mucosal and cutaneous microcirculation (i.e. thickening of the basement membrane around vascular walls and the enlargement of vascular structures in the middle and deep layer of the dermis)[37].

Considering the involvement of autoimmune mechanisms in VLS, known to be mediated by lymphocytes activity, Regauer and contributors carried out a study with 90 VLS cases and 72 cases of penile lichen sclerosus, in which they examined vascular changes using antibodies to T-cells and B-cells and to antigen presenting cells. They noticed that dendritic cells antigens, once infiltrated into the affected tissue structures, initiate an immune response by interacting with T and B cells specific antigens, which suggests a type of mechanism that is similar to immune-mediated vasculitis[38].

The examination of vascular changes in the affected tissues has called into question the role of ischemia and tissue hypoxia in the detected damage to vascular structures. A study published by Li et al. revealed ultrastructural changes in the cellular organelles (i.e.

alterations of the mitochondrial structure, of the endoplasmic reticulum and ribosomes). Regarding the cutaneous vascular structures, there is damage of the vascular endothelium and capillaries, and disruptions of the capillary morphology. Hypoxia markers were suggestive of hypoxia involvement in the VLS pathogenesis[39].

Treatment of VLS

Given that the most severe complication of VLS is its malignant transformation (i.e. around 5% of the cases)[40] and the subsequent development of vulvar carcinoma, it is of uttermost importance to recognize its clinical symptoms so as to diagnose it early and initiate the appropriate treatment. Even more important yet it is to regularly monitor this condition in order to prevent scarring and detect any changes that might suggest a malign evolution of the lesions.

Treatment of VLS may include potent topical corticosteroids, vitamin D analogues combined with corticosteroids, calcineurin inhibitors, laser therapy (carbon dioxide or nonablative laser treatment), cryotherapy[41], phototherapy[42], and photodynamic therapy[43]. Systemic corticosteroids and retinoids, even methotrexate may be a considered as an option of treatment for the severe forms of the disease. In case of malign transformation, a partial or total vulvectomy needs to be performed, depending on the degree of tumor invasion of the tissue.

Conclusions

To conclude, a clear knowledge of the symptoms of vulvar lichen sclerosus that will help to diagnose it in its early stages, followed by adequate monitoring of this disease is critical for the initiation of a treatment that is adjusted to the progression stage of the disease in order to avoid potential complications, among which its malign transformation into vulvar cancer is the most severe. The optimal management of vulvar lichen sclerosus ensures the reduction of the disease burden and mortality and, indirectly, a decrease of the incidence of vulvar cancer in older women. ■

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