

Vulvar leukoplakia: therapeutic options

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Abstract

Vulvar leukoplakia is not a histological diagnosis and involves several diseases. Most commonly, these are vulvar lichen sclerosus and squamous cell hyperplasia of the vulva. These two conditions have similar aetiology, clinical presentation and treatment but different histopathological changes. They both lead to significant impairment of quality of life, risk of malignancy, as well as recurrence after treatment.

Treatment of these conditions includes topical corticosteroids as a first-line therapy, but they have their side effects and not all patients are receptive to this therapy. This requires the use of alternative therapeutic options such as topical calcineurin inhibitors, topical and systemic retinoids, other steroid creams, various destructive techniques and, as a last resort, surgical removal of affected tissues. Surgical treatment should be avoided, despite the malignant potential, because of recurrence risk in both diseases.

New therapeutic approaches are coming into effect in gynaecological practice due to potential risks of the above-mentioned methods. Platelet-rich plasma therapy, ablative and non-ablative laser treatment, and new topical medicines, are some of the new options applied to improve the efficacy of treatment avoiding the side effects of conventional medications. A number of them are still in their initial phase of application and time will tell their effectiveness.

Key words: vulvar leukoplakia, vulvar lichen sclerosus, squamous cell hyperplasia of the vulva, treatment.

Introduction

The term vulvar leukoplakia is not a histological but a descriptive diagnosis meaning "white spot". It is used for non-inflammatory diseases characterized by pathological modification of external genitalia multilayered flat epithelium that is accompanied by skin and mucosa cornification [1]. It combines various atrophic and hypertrophic diseases of the vulva classified in the past as vulvar dystrophies [2]. This group includes lichen sclerosus (LS), squamous cell hyperplasia, condyloma acuminata, psoriasis, lichen planus, mixed LS and atrophicus. White colouration is caused by excessive keratin, at times deep pigmentation, and relative avascularity [3]. Two non-neoplastic epithelial disorders of the vulva – vulvar LS (VLS) and squamous cell hyperplasia of the vulva (SCHV) – are generally referred to as vulvar leukoplakia. They have different anatomical and pathological features, but similar clinical manifestations. The frequency is 1 in 300 to 1,000 [4]. Treatment involves different approaches such as topical medications, platelet-

rich plasma (PRP) therapy, various destructive techniques, e.g. ablative and non-ablative laser treatments, alcohol-mediated denervation and, in the last instance, surgical removal of the affected tissues.

Aetiology

The two major diseases leading to white skin coloration in the external genitalia are VLS and SCHV. These are chronic conditions and their occurrence is determined by many factors such as immunity, sexual hormones, injuries, environment, enzymes, free radicals, and apoptosis. It is assumed that VLS and SCHV are genetic immune diseases [5].

VLS is the most common chronic lesion of the vulva and mainly affects the anogenital area [4, 5], but may have extragenital location as well. In 20% of patients with anogenital involvement extragenital involvement is found too [6-9]; in 6-15% of LS cases disease manifestations have extragenital locations only [8, 9]. The classical

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histological findings of LS are a thinned epidermis and/or the loss of rete ridges, hyperkeratosis, oedema and/or hyalinization, as well as chronic band-like inflammatory cell infiltrate of the dermis [10]. However, there are many variations to these classical histological characteristics leading to a myriad of lesions that may be classified as LS [11]. Macroscopically, the vulva is shiny and dry, with no creases. Lesions are often symmetrical. The disease is more common in postmenopausal women, but there is a peak in its development in pre-pubertal girls as well [7, 9, 12]. It affects mostly women aged 50-59 [4]. It is assumed to be of autoimmune genesis with a genetic predisposition [5, 13]. Autoimmune diseases are diagnosed in 21% of cases of VLS, and in 22% of cases family history of the disease [2] affects sisters, mothers and daughters, and twin sisters including both homozygotic and heterozygotic twins [5].

The aetiology of SCHV is not well known. It is supposed there is a role of chronic irritation of the skin. Irritants might include perfumed soaps, fabric conditioners and detergents used in the laundry of underwear or even excessive washing [14]. It is thought that SCHV is an autoimmune condition and it has been associated with other autoimmune diseases such as malignant anaemia, thyroid diseases, diabetes mellitus, systemic lupus erythematosus, primary biliary cirrhosis, and bullous pemphigoid [2].

There is thinning of the affected skin in VLS, while the opposite is observed in SCHV – an abnormal growth of the skin of the vulva. The histological features are as follows: widening of the rete ridges and irregular thickening of the Malpighian layer of rete ridges (acanthosis); hyperkeratosis and chronic inflammation in the dermis; possibly increased mitotic figures in basal and prickle cell layers but no atypia; possible parakeratosis.

This condition is characterized by a pink-red vulva with overlying grey-white keratin and involved labium majus, nympholabial furrow, preputium clitoridis, and commissura labiorum posterior. In the early stage of the disease, the skin might appear dark red or pink, while hyperkeratotic skin might appear white.

The disease is predominant in postmenopausal women but can be observed in any lifetime period [15-17]. The average age of its occurrence is between 42 and 53 years of age according to research literature [18, 19].

Clinical manifestation

The clinical picture in both conditions is similar, and its main manifestation is itching in the vulva which is more expressed in SCHV than in VLS [5]. Other less common symptoms are dyspareunia and dysuria.

Rarely VLS can be asymptomatic. Usual symptoms are pruritus, burning, or stinging of the vulva, white or grey patches of thickening or thinning on the vulvar skin. At the early stage of VLS the symptoms are swell-

ing and redness of the skin and the lesion can further progress to white, thin, dry, and chapped skin and mucosa with a loss of elasticity as the disease advances. There can be atrophy or even a reduction in the labiorum minus [5].

VLS and SCHV may cause significant vulvar changes affecting quality of life. Anatomical changes that are caused by both conditions, especially from VLS, may lead to sexual dysfunction [13]. Both conditions have an opportunity to relapse after treatment, and this is related to the method of treatment and patients' age [20, 21].

They have a malignant potential: 3 to 6% for VLS and 2 to 4% for SCHV [5]. It has been established that VLS patients can develop vulvar squamous cell carcinoma for several years – from 3.3 to 8.8 years [22, 23]. About 80% of the cases of invasive squamous cell carcinoma (SCC) of the vulva in elderly patients are associated with untreated, long-term VLS conditions [4].

Because of the malignant potential of these diseases, many clinicians advocate that active management of VLS and SCHV can reduce the risk of malignant transformation [22].

Diagnosis

The diagnosis of both diseases is clinical, which is sufficient in routine clinical practice. It is very easy to diagnose then when the clinical presentation is typical, especially for VLS [24-26]. In some cases such as atypical features, uncertainty of diagnosis, concern for malignancy, or in failed response to treatment, biopsy is mandatory. The gold standard to differentiate these conditions is histological – biopsy [22, 27]. Because biopsy is the only way to exclude SCC of the vulva and vulvar intraepithelial neoplasia, it is necessary in our opinion.

Treatment

Both diseases have similar treatment, but different therapeutic options are available as well. The main goal of therapy is to control genital itching, which is a major problem for the patient. Management of pruritus vulvae can be divided into four stages: (1) identification of underlying disease; (2) restoration of the skin barrier function; (3) reduction of any inflammatory complication; and (4) elimination of the itch-scratch cycle by psychological methods [28]. Asymptomatic VLS cases should be treated too.

The first course of action in both conditions is to minimize irritants, soap substitution, avoidance of urinary contact, moisturization with emollients, and treatment of co-infections [29].

Topical corticosteroids are the gold standard for treatment of these patients. Ultra-potent corticosteroid

ointments or creams are used as there are not enough randomized controlled trials providing records on how often, how long, and in what potency the corticosteroids are to be applied [16]. In the last few years some trials were published about what kind of corticosteroids has to be used for VLS treatment, the duration of the treatment period and the safety of treatment. They all reported no differences in results depending of different types of steroids or different ways of application and they did not report any serious adverse events [30-32]. It should be noted that long-term use of steroid creams or ointments can cause reddening or thinning of the skin, stretch marks and genital yeast infections. They relieve the symptoms in nearly all patients; in about 70% of the cases, symptoms disappear completely, and in 20% complete recovery of the skin is observed [29]. The British Association of Dermatologists guidelines advocate their use and propose a detailed dosing regimen [27]. The recommendations for newly diagnosed cases are: application of clobetasol propionate 0.05% ointment once daily at night time for the duration of 4 weeks, followed by application on alternate nights for 4 weeks, and then twice weekly for a further 4 weeks. In recurrence of symptoms with reduced frequency, the patient should apply treatment until symptoms resolve. An ointment formulation is usually better tolerated than a cream base [29]. Other corticosteroids may be used in doses twice daily for several weeks and then twice weekly. Overuse of superpotent topical corticosteroids may induce atrophy, telangiectasia, and striae as early as 2-3 weeks following daily application. Treatment of SCHV is similar and corticosteroid creams are applied [20].

If VLS treatment fails, there are some alternative, less popular options such as the use of topical calcineurin inhibitors (TCIs). Pimecrolimus and tacrolimus are used. These drugs have a pronounced anti-inflammatory effect, an immunomodulatory effect and a weakly pronounced immunosuppressive effect; adverse effects of these agents have not been described. Some authors believe that they may increase the risk of VLS progression to malignancy [34, 35]. The described dose of tacrolimus ointment is twice daily until symptoms disappear [36, 25], and the course of treatment should not be too long. It should only be used in patients refractory to corticosteroid treatment.

The use of topical testosterone in the treatment of VLS has already stopped due to worse results compared to those of ultrapotent topical corticosteroids and its side effects: systemic absorption and virilizing effects in female patients [37-41].

Local oestrogens are another treatment option for SCHV. However, they have serious adverse effects such as increasing the risk of endometrial hyperplasia and overstimulation [42].

Another option for vulvar leukoplakia treatment is the topical and systemic retinoids. They are not widely used because of adverse effects such as skin irritation and low tolerance to sunlight exposure for the topical forms; and mucocutaneous side effects, cheilitis, dryness of the oral mucosa, epistaxis, xerophthalmia, xerosis and fissuring of fingertips, hair loss, nail fragility, periungual granuloma, and paronychia manifested in patients treated with systemic retinoids [43].

Further treatment options for VLS are UV-A1 phototherapy, photodynamic therapy, oral acitretin, and topical progesterone/testosterone, but they should only be used as 3rd-line therapy [44, 45]. These methods have been described in extremely few patients and cannot be routinely applied.

Increasingly, reports of successful PRP treatment of VLS [46] have appeared in the literature. However promising it may be, this is not a standard treatment.

With the advent of medical lasers, reports of their use in the treatment of VLS have appeared frequently lately. They are less commonly used in SCHV treatment. Ablative lasers (carbon dioxide laser) [47-50], and non-ablative neodymium: yttrium aluminium garnet (Nd: YAG) lasers [51] are used in different operating modes. Both types of lasers have positive results, but non-ablative ones, unlike ablative lasers, have no side effects such as pain, discomfort, scars, infections, pigmentation or bleeding.

Vaporization, ultrasonic surgical aspiration, loop excision, simple lesion excision, and cryotherapy are some further therapeutic options to broaden the spectrum of SCHV treatment options.

Itching appears to be patients' main discomfort, and the use of some other types of non-steroid agents is another option. There have been reports of isolated cases of VLS and SCHV successfully treated with Theresienol herbal oil [48]. The treatment course with Theresienol herbal oil lasts for several months, but with no side effects as described with corticosteroid treatment [52]. This product is for topical administration and has the following mechanism of action: it hydrates the tissues; reduces bacterial invasion and inflammation; stimulates fibroblast and endothelial cell migration and proliferation; and stimulates epithelialization. Thereby, it has analgesic, antiseptic and moisturizing effects and reduces skin itching.

Surgical treatment of both diseases should be avoided because of recurrence risk and should only be used in certain cases, such as patients with malignancy, or to correct irreversible scarring, adhesions and micturition difficulties or sexual dysfunction caused by the subsequent anatomical changes [29]. If all conservative treatment measures have failed, surgical treatment is indicated. However, vulvectomy and skinning vulvectomy should be avoided because of recurrence rates and disfigurement.

Conclusions

The term leukoplakia should not be used in medical practice and should be replaced by the name of the condition that leads to coloration of the vulva. Most commonly there are two conditions that lead to white discoloration of the external genitalia: vulvar LS and SCHV. Both diseases have similar clinical features and malignant potential and therefore should be treated. Histological diagnosis is not necessary in clinical practice (but this is the only way to exclude SCC or VIN) since topical corticosteroids are the first-line therapy for these conditions. Histological verification is important in cases of corticosteroid-resistant patients, as they are subject to different therapeutic methods. Increasing numbers of new and alternative treatments such as PRP, Nd: YAG laser, Theresienol, and avoiding the side effects of conventional treatment, have been reported lately in research literature. Surgical treatment should be avoided, despite the malignant potential, because of recurrence risk in both diseases.

Disclosure

The authors report no conflict of interest.

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