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Lichen Sclerosus and Lichen Planus in Women and Girls

BETHANEE J. SCHLOSSER, MD, PhD,* and GINAT W. MIROWSKI, DMD, MD† ‡

**Departments of Dermatology and Obstetrics and Gynecology, Northwestern University Feinberg School of Medicine, Chicago, Illinois; † Department of Oral Pathology, Medicine, Radiology, Indiana University School of Dentistry; and ‡ Department of Dermatology, Indiana University School of Medicine, Indianapolis, Indiana*

Abstract: Lichen planus and lichen sclerosus are common, chronic inflammatory vulvar dermatoses with significant morbidity. The course may wax and wane but disease often persists for decades. These autoimmune diseases have varied clinical presentations that extend beyond the genitalia. Management is best undertaken using a multidisciplinary approach and active patient involvement. The first-line treatment of both conditions is superpotent topical corticosteroids. Supportive measures and adjunct therapies can optimize patient outcomes. Patients who fail to improve despite correct medication use should be re-evaluated, and clinicians should be vigilant in detecting concomitant contact dermatitis, secondary infection, and malignancy.
Key words: lichen sclerosus, lichen sclerosus et atrophicus, lichen planus, vulva, vagina, dermatology

Introduction

Women with vulvovaginal lichen planus (VVLP) and/or vulvar lichen sclerosus (VLS) often present to their gynecologic providers with chronic vulvovaginal symptoms and may be refractory to initial and/or empiric treatments. It is imperative that providers take adequate time to thoroughly evaluate women with these challenging conditions.

A focused history including medications and complementary substances as well as personal hygiene regimens, a review of systems, and a directed physical examination are necessary to determine the extent of disease involvement and exacerbating factors. Patients themselves may not be aware that the root cause of their vulvovaginal complaints may affect other anatomic sites, and it is the responsibility of the clinician to query about and search for all potentially involved locations. Both lichen planus (LP) and lichen sclerosus (LS) exhibit the Koebner phenomenon, an isomorphic response in which lesions occur in areas of trauma. A thorough review of systems and directed laboratory testing should be obtained to

Correspondence: Bethanee J. Schlosser, MD, PhD, Department of Dermatology, 676 N St. Clair, Suite 1600, Chicago, IL 60611. E-mail: bschloss@nmff.org

The authors declare that they have nothing to disclose.

evaluate for potential associated systemic illnesses (ie, thyroid disease). Treatment should target both symptoms and clinical disease; asymptomatic patients require ongoing care to limit progressive disfigurement and to survey for premalignant and malignant disease. A multidisciplinary approach helps to establish the diagnosis, direct therapy, and maximize treatment success.

LP

INTRODUCTION

LP is an autoimmune inflammatory disorder that affects both the skin and mucous membranes. On the skin, LP is characterized by pruritic, violaceous, polygonal papules, and plaques associated with fine white striae. The presence of papules with scale results in the classification of cutaneous LP as a papulosquamous eruption.

The onset of cutaneous lesions may occur abruptly, and pruritus is typically severe. Despite the intense pruritus, excoriations are rarely found; when excoriations are present, other causes of pruritus such as scabies or folliculitis should be considered.

In contrast to cutaneous LP, VVLP is often characterized by painful erythema, erosions, and vaginitis. Similarly, oral LP also exhibits painful erythema and erosions of the mucous membranes and desquamation of the gingivae. Thus, LP with mucosal involvement is characterized most often as an erosive rather than a papulosquamous dermatosis. Other mucosal sites of involvement, including the conjunctiva, ear, esophagus, and larynx may precede, follow, or occur concurrently with vulvovaginal disease.

PATHOGENESIS

The etiology of LP is unknown. Evidence suggests that LP is a T-cell–mediated disease that is an autoimmune response to altered self-antigens or exogenous antigens.[1] Activated T cells in early lesions seem to target antigenically altered basal keratinocytes, whereas in older lesions, suppressor T cells predominate. Associated autoimmune conditions such as thyroid disease, vitiligo, alopecia areata, and celiac disease seem to be less prevalent for VVLP than for VLS.[2]

EPIDEMIOLOGY

There are no comprehensive population studies to establish the incidence or prevalence of LP. The incidence of oral LP is estimated to be 1/1000 patients, whereas the incidence of vulvar disease is believed to be less. Estimates of prevalence for VVLP vary but are generally $< 1\%$. Disproportionate prevalence rates are reported from specialty clinics. For example, in a large study of 3350 women attending a specialized vulvar clinic, 3.7% were documented to have LP based on vulvar histology. Of these women, 17.6% had erosive disease.[3] In a study of 37 women presenting with cutaneous LP to a dermatology department, 51% were found to have vulvar involvement.[4]

CLINICAL PRESENTATION

VVLP may present insidiously with painful erosions and desquamation of the vulva and vagina typically in the fifth or sixth decade though young adults and the elderly may be affected. Symptoms may last for decades and be misdiagnosed as "recurrent yeast" or "herpes" infections.

SYMPTOMS

VVLP is a common, mucocutaneous condition that is often misdiagnosed. Nonspecific symptoms include pain, discomfort, pruritus, burning, and rawness of the genitalia associated with dysuria, dyspareunia, and postcoital bleeding.

In a prospective study of 114 women with erosive VVLP seen in academic vulval clinics, the most frequent symptoms at presentation were vulvar pain/soreness

(80%), pruritus (65%), dyspareunia (61%), irritation (48%), dryness (27%), vaginal discharge (24%), dysuria (23%), perianal symptoms (21%), difficulty obtaining a cervical smear (18%), and poor urinary stream (11%).[5] Up to 21% of patients with VVLP may be asymptomatic.[4]

FINDINGS

The morphology of primary lesions on vulvar skin results in the recognition of 3 clinical types of vulvar LP. It is essential that clinicians are familiar with all of these varied presentations to optimally diagnose and treat affected patients. Patients may exhibit more than 1 morphology concurrently or sequentially (Fig. 1).

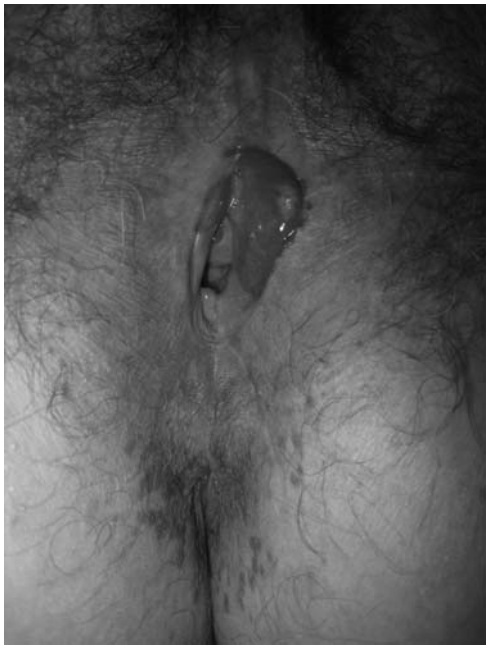

FIGURE 1. Vulvovaginal lichen planus with extensive erosion and agglutination of the left labium minus, near complete agglutination of the right labium minus and clitoral hood, introital narrowing, and flat-topped perianal papules.

Type I, classic LP, is identical to the typical papulosquamous LP of glabrous skin. This presentation is rarely seen on the vulva, but white reticulation may be seen on the labia minora and clitoral hood. Papular LP lesions may occur on the perineum and perianal skin.

Type II, hypertrophic LP, is the least common morphology of VVLP. Patients present with white thickened and hyperkeratotic violaceous plaques of the mucous membranes.

Type III, erosive LP, is the most commonly recognized presentation of VVLP. Clinical findings range from mild macular mucosal erythema to extensive erosions and scarring.[6]

Cooper and Wojnarowska[5] prospectively found that the most common vulvar findings in patients with erosive VVLP were erosions (97%), white reticulations (at the periphery of erosions; 82%), clitoral burying (59%), introital narrowing (59%), and erythema (45%). The differential diagnosis of VVLP is presented in Table 1.

Erythematous/violaceous papules and/or diffuse erythema without scale may be found in the inguinal and anogenital folds as well as in the axillae and inframammary creases. The inherent moisture and apposition of skin surfaces in these areas minimizes the finding of scale. This pattern is termed inverse LP.

Vaginal involvement has been reported in up to 70% of patients and may present as diffuse erythema, erosions, and/or ulceration.[7] Purulent vaginal discharge may be seen with involvement of the vagina, but its absence does not exclude vaginal disease.[8–10] LP of the uterine cervix has also been reported.[11]

As in all inflammatory dermatoses of the vulva, agglutination (partial or complete resorption) and loss of normal architecture may result in scarring of the clitoral hood with burying of the clitoris (68%) and narrowing of the introitus (59%) (Fig. 1). With vaginal inflammation, scars, synechiae, and

TABLE 1. Clinical Differential Diagnosis of Vulvovaginal Lichen Planus and Vulvar Lichen Sclerosus

Papules and plaques with or without scale	**Inflammatory:**
	Acrodermatitis enteropathica
	Chronic cutaneous lupus erythematosus
	Chronic graft vs. host disease
	Contact dermatitis (chronic, allergic or irritant)
	Eczematous dermatitis
	Lichen planus
	Lichen sclerosus (hypertrophic)
	Lichen simplex chronicus
	Lichenoid drug reaction
	Pityriasis rosea
	Prurigo nodularis
	Psoriasis vulgaris
	Seborrheic dermatitis
	Infectious:
	Candidiasis (intertrigo, pseudomembranous)
	Condylomata acuminata
	Condyloma lata/secondary syphilis
	Molluscum contagiosum
	Sarcoptes scabiei infestation
	Tinea cruris
	Neoplastic (benign or malignant):
	Extramammary Paget's disease
	Fox-Fordyce disease
	Squamous cell carcinoma
	Syringomas
	Vulvar intraepithelial neoplasia (Bowen's disease, bowenoid papulosis, squamous cell carcinoma in situ)
Erythematous patches	**Inflammatory:**
	Acute graft vs. host disease
	Chemotherapy-induced mucositis (mild)
	Contact dermatitis (acute, allergic or irritant)
	Intertrigo
	Inverse psoriasis
	Inverse seborrheic dermatitis
	Lichen planus
	Lichenoid drug reaction
	Plasma cell mucositis (Zoon's vulvitis)
	Infectious:
	Candidiasis (erythematous)
	Group A streptococcal infection
	Group B streptotoccal infection
	Tinea incognito
	Tinea versicolor
	Neoplastic (benign or malignant):
	Extramammary Paget's disease
	Vulvar intraepithelial neoplasia (Bowen's disease, bowenoid papulosis, squamous cell carcinoma in situ)
Erosions and ulcers	**Inflammatory:**
	Aphthae
	Chemotherapy-induced mucositis (severe)
	Contact dermatitis (acute, allergic or irritant)
	Hailey-Hailey disease (benign familial pemphigus)
	Lichen planus
	Lichen sclerosus
	Mucous membrane pemphigoid
	Pemphigus vulgaris
	Infectious:
	Candidiasis (erosive, ulcerative)
	Herpes simplex virus infection
	Varicella zoster virus infection
	Neoplastic (benign or malignant):
	Basal cell carcinoma

TABLE 1. (Continued)

	Extramammary Paget's disease
	Squamous cell carcinoma
Hypopigmented patches	**Inflammatory:**
	Atrophic vulva, estrogen deficiency
	Chemical leukoderma
	Chronic graft vs. host disease
	Lichen sclerosus
	Morphea
	Vitiligo
Purpura	**Inflammatory:**
	Atrophic vulva, estrogen deficiency
	Atrophy from topical corticosteroid use
	Lichen sclerosus
	Mucous membrane pemphigoid
	Venous varicosity
	Trauma
	Neoplastic (benign or malignant):
	Angiokeratoma
	Fabry's disease (angiokeratoma corporis diffusum)
	Kaposi sarcoma
Fissures	**Inflammatory:**
	Atopic dermatitis
	Contact dermatitis (allergic, irritant)
	Crohn's disease
	Inverse psoriasis
	Inverse seborrheic dermatitis
	Lichen planus
	Lichen sclerosus
	Lichen simplex chronicus
	Trauma
	Infectious:
	Candidiasis
	Group A streptococcal infection
	Group B streptococcal infection
	Staphylococcus aureus infection
Hyperpigmentation	**Physiological:**
	Physiological pigmentation
	Postinflammatory hyperpigmentation
	Tattoo
	Infectious:
	Condylomata acuminata
	Tinea versicolor
	Neoplastic (benign or malignant):
	Melanocytic nevus, benign or dysplastic
	Genital melanosis/lentiginosis
	Laugier-Hunziker syndrome
	Melanoma
	Peutz-Jeghers syndrome
	Pigmented basal cell carcinoma
	Seborrheic keratosis
	Vulvar intraepithelial neoplasia (Bowen's disease, bowenoid papulosis, squamous cell carcinoma in situ)

adhesions develop, and sexual function and urination become progressively more painful and difficult.[5,9,10] Urethral stenosis may also develop.

MULTIFOCAL LP

Pelisse and colleagues have documented that LP can and often does affect multiple mucosal sites within the same patient.[12–14]

Initially, this concept was best recognized as including oral and genital mucosa; current understanding of LP recognizes additional mucosal sites of disease. Patients may exhibit any combination of vulvar, vaginal, and oral involvement either sequentially or concomitantly. Disease morphology and severity may vary independently. When genital and oral involvement occurs, the term vulvo-vaginal-gingival LP has been invoked. However, oral disease may include sites other than the gingivae such as the buccal mucosa and tongue. Genital and oral involvement in men has been termed the peno-gingival syndrome with similar sequential or concurrent involvement.[13]

Although scarring rarely occurs in the oral cavity, scarring figures prominently at other mucosal sites such as the esophagus, larynx, middle ear, and conjunctivae. Nongenital involvement of LP is presented in Table 2.

DIAGNOSTIC EVALUATION

There are no serologic tests to support a diagnosis of LP. Patients with vaginal LP may exhibit variable degrees of vaginal discharge, ranging from normal to copious. The presence of an elevated pH, immature parabasal epithelial cells, white blood cells, and/or red blood cells should raise the possibility of vaginal involvement (Table 3).

HISTOPATHOLOGY

Histopathologic findings vary with the clinical presentation and site of involvement. In both the skin and mucous membranes, the presence of cytoid bodies (Civatte bodies, colloid bodies, eosinophilic hyaline spheres, dyskeratotic keratinocytes), wedge-shaped hypergranulosis, basal layer squamatization with liquefaction degeneration, loss of the basement membrane, and pointed rete ridges in the setting of a band-like lymphohistiocytic inflammatory infiltrate is highly suggestive of LP.

The histologic findings of erosive lesions often are not specific. A mixed lymphohistiocytic infiltrate can be seen in LS, allergic reactions, graft versus host disease, mucous membrane pemphigoid, lupus erythematosus, pemphigus vulgaris or LP.

TABLE 2. Nongenital Findings in Lichen Planus

Anatomic Site	Findings and/or Symptoms
Oral cavity: buccal mucosa, gingivae, lips, tongue	Reticulated: net-like, lacy or web-like appearance (Wickham's striae), typically asymptomatic Erosive/ulcerative: painful erythema, erosions, or ulcerations Papular: white papules Plaque-like: hyperkeratotic papules or plaques Atrophic: erythematous patches or desquamative gingivitis Bullous: fluid-filled vesicles
Esophagus: proximal and/or distal	Erosions, white pseudomembranes, strictures or webs Dysphagia, difficulty swallowing, globus sensation May require or have undergone repeated surgical dilatation
Conjunctivae	Conjunctival injection, erosion, pterygium formation, shortening of sulcus
Ear	Erythema, scaling, and cerumen accumulation Pruritus, decreased hearing acuity
Skin, scalp, nails	Pruritic purple polygonal papules on flexural areas Hypertrophic white plaques with severe itching Pink patches of scarring alopecia Pterygium formation at base of nails

TABLE 3. Microscopic Evaluation of Vulvovaginal Dermatoses and Infections

Feature	Vulvovaginal candidiasis	Bacterial vaginosis	Atrophic vaginitis	Lichen sclerosus	Lichen planus	DIV
Discharge amount, color, character	↑↑↑ or NL, white, curd-like	↑↑, gray	scant	NL	↑↑ or NL	↑↑, yellow-green
pH	NL	↑↑	↑↑	NL	↑↑	↑↑
Immature parabasal cells	—	—	↑↑	—	↑↑	↑↑
WBCs	↑↑ or NL	—	↑↑ or NL	—	↑↑, + RBCs	↑↑
Lactobacilli	NL	↓↓	↓↓	NL	↓↓	↓↓
Clue cells	—	+ +	—	—	—	—
Pseudohyphae, buds, or spores	+ +	—	—	—	—	—

Modified from Sobel.[15]

↑↑ indicates increased; DIV, desquamative inflammatory vaginitis; NL, normal; RBC, red blood cell; WBC, white blood cell.

In both mucosal and cutaneous LP, direct immunofluorescence studies often reveal a shaggy band of IgG, IgM, IgA, C3, and fibrin at the basement membrane. Civatte bodies may stain positively with IgG, IgM, IgA, or C3. Immunofluorescence findings may help to exclude other autoimmune erosive disorders (ie, mucous membrane pemphigoid, pemphigus vulgaris).[16]

TABLE 4. Consensus Clinical and Pathologic Diagnostic Criteria for Erosive Vulvar Lichen Planus

Clinical Features	Histologic Features
Well-demarcated erosions or glazed erythema at the introitus	Well-defined inflammatory band below the dermoepidermal junction
Hyperkeratotic white border to erythematous areas or erosions with/without Wickham striae in surrounding skin	Lymphocytic inflammation
Pain and burning	Lymphocytic inflammation
Scarring or loss of normal architecture	Basal layer degeneration
Vaginal inflammation	
Involvement of other mucosal sites	

Simpson RC, et al 2013.[17]

In 2012, an electronic Delphi consensus exercise was completed to develop diagnostic criteria for VVLP. A series of surveys were administered to 73 experts in vulvar disease.[17] Nine clinical and/or histologic criteria were identified as being important for the diagnosis of VVLP by at least 75% of the participants (Table 4).

MALIGNANCY

In patients with VVLP, the development of premalignant intraepithelial neoplasia and squamous cell carcinoma (SCC) of the vulva and at other mucosal sites has been documented. This risk seems to be low. It is hypothesized that dysplasia and malignant transformation result from a dysregulation in cellular replication, DNA damage, and altered epithelial integrity due to the oxidative stress, cytokines, and transcription factor signals seen in chronic inflammation in mucosal LP. Despite a growing appreciation for the occurrence of vulvar SCC in women with VVLP, the incidence of this rare condition is not known. In 1 survey, 10 of 145 patients with LP had a history of or current genital malignant neoplasm.[10] This included 7 new cases of vulvar intraepithelial

neoplasia (VIN), 2 cases of genital/SCC, and 1 oral SCC. In a study of 95 patients, 2 new cases of vulvar SCC were found.[18] In the retrospective evaluation of 131 patients with VVLP, 2 patients had VIN at presentation. These 2 patients did not develop a recurrence, and no other malignancies developed in any other patients.[8]

LS

INTRODUCTION

LS is the most common vulvar inflammatory dermatosis with the potential exception of contact dermatitis. LS was first described in 1887 and over time has also been termed kraurosis vulvae, vulvar dystrophy, guttate scleroderma, lichen albus, and LS et atrophicus. LS is a chronic inflammatory, lymphocyte-mediated dermatosis that predominantly affects the genital skin and mucosa. LS occurs 6 to 10 times more frequently in females than males and typically exhibits a chronic, relapsing course.

PATHOGENESIS

LS is believed to be autoimmune in nature. However, the exact pathogenesis and target antigen are not known. Familial predisposition has been reported in LS; 1 study demonstrated that 12% of 1000 VLS patients in the UK had a positive family history of LS.[19] The inheritance pattern has not been established.

A study of human leukocyte antigen associations demonstrated that LS patients had a statistically significant difference in expression of DQ7, DQ8, or DQ9 antigens compared with controls.[20] Another study demonstrated that haplotype DRB1*12/DQB1*0301/04/09/010 confers susceptibility to LS, whereas haplotype DRB1*0301/04/DQB1*0201/02/03 seems to offer protection.[21]

Circulating IgG antibodies to the basement membrane zone proteins BP180 and BP230 have been detected in 30% of VLS patients.[22] In addition, circulating autoantibodies to extracellular matrix protein 1 have been demonstrated in 74% of patients with VLS (vs. 7% of controls) and were associated with more extensive disease and disease duration of more than 1 year.[23]

Multiple studies have demonstrated a strong association between LS and other autoimmune disorders (28.4% of 190 adult women with VLS vs. 8.7% of controls),[2] specifically autoimmune thyroid disease, vitiligo, alopecia areata, and pernicious anemia.[2,24,25]

A role for hormones in the pathogenesis of LS has been postulated. Reduced numbers of androgen receptors in VLS have been shown in a small number of studies.[26,27] Other studies have shown that estrogen receptor beta is highly expressed in VLS but is absent in normal tissues. Estrogen receptor alpha was not expressed in the fibrovascular layer of diseased vulvar tissue.[28]

Similar to LP, LS exhibits koebnerization with an inherent tendency to occur in areas of trauma or chronic irritation as well as after radiation therapy. There are no data to support a role for any infectious agent in the pathogenesis of VLS including *Borrelia burgdorferi*.

EPIDEMIOLOGY

Peak incidence of VLS has a bimodal distribution, most commonly occurring during the prepubertal and midlife (perimenopausal and newly postmenopausal) years.[29] Of notable importance, however, a substantial number of women (17% to 40%) will experience onset of symptoms and cutaneous changes of VLS during the reproductive years.[25,30]

One study from a pediatric vulvar clinic found the prevalence of premenarchal LS to be 1 in 900.[31] The mean age of presentation of VLS was 5 years (range, 1 to 12 y), whereas the mean age at diagnosis was 6.7 years (range, 3 to 14 y).[31] A majority of girls with

prepubertal onset of LS have persistent activity after puberty and are at risk for progressive agglutination.[32,33]

In a 3-year study of a general gynecology clinic, the prevalence of VLS was 1.7%.[34] The prevalence of VLS among a population referred to a dermatology clinic was between 1/300 and 1/1000 women.[29] In women, the mean age of symptom onset is 45 to 55 years.[25,30] However, the mean age at diagnosis is 60 years suggesting a significant delay in diagnosis.[30] Extragenital (cutaneous) LS occurs in 9% of girls[31] and 6% to 15% of women with VLS.[25,30,35]

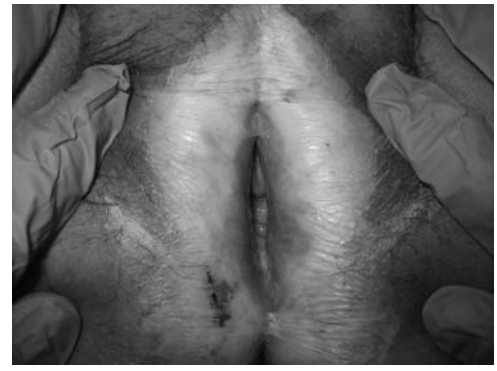

FIGURE 2. Severe vulvar lichen sclerosus demonstrating hypopigmented plaques with cigarette paper atrophy, complete agglutination of the clitoral hood and labia minora, burial of the clitoris and purpura at the right inferior medial labium majus.

CLINICAL PRESENTATION

Symptoms

The most common presenting symptom in patients with LS is pruritus, often worse at night. Such nocturnal pruritus should raise a suspicion for infestation including *Sarcoptes scabiei* (scabies) and *Enterobius vermicularis* (pinworms). Pain, dysuria, urinary retention, and dyspareunia due to fissures and/or erosions are also common. Painful defecation due to perianal fissures can result in constipation, often the presenting symptom in young girls, and stool retention. It is important to note that symptom severity does not necessarily correlate with clinical disease severity. Some patients (7% of children, up to 39% of adults) may be asymptomatic, even in the setting of advanced disease.[31,34]

Progressive vulvar agglutination may result in dyspareunia and apareunia. Patients may also experience abnormal micturition, decreased strength of urinary stream, dysuria, and hematuria; increased urinary frequency is not typical of VLS and its associated scarring.

Findings

LS characteristically exhibits ivory white (hypo/depigmented) patches and plaques with a waxy texture and/or epidermal wrinkling prototypically described as having a "cigarette paper" appearance (Fig. 2). Additional clinical findings include fissures, erosions, superficial ulcers, purpura, and hyperkeratosis; bullae are less common. Clitoral hood edema and follicular accentuation of depigmentation and waxiness comprise more subtle findings. Lichenification, the result of scratching and rubbing, may confound the clinical picture. In a prospective cohort study of 225 VLS patients, clinical disease severity was not associated with patient age or disease duration.[36]

VLS most commonly affects the modified mucous membranes, ie, the medial labia majora, interlabial creases, labia minora, clitoral hood, clitoris, and posterior fourchette. Skin changes may also involve the genitocrural creases, perineum, and perianal skin. Perianal LS occurs in 30% to 60% of women. In girls and women, a figure-of-eight or hourglass configuration with vulvar and perianal involvement is common.

Current dogma holds that LS does not affect the vaginal mucosa. However, 2 case reports (n = 3 women) have demonstrated that LS may affect the vaginal mucosa; vaginal prolapse was documented in 2 patients and was not commented on in the third.[37,38]

LS exhibits variable degrees of agglutination/scarring with loss of tissue mass, tissue resorption, and destruction of normal vulvar architecture; scarring most frequently affects the clitoral hood, labia minora, posterior fourchette, and vaginal introitus (Fig. 2). Agglutination of the clitoral hood may result in complete burial of the clitoris such that it is no longer visible though still palpable and neurologically intact. Clitoral hood agglutination may also result in the formation of a clitoral pseudocyst characterized by accumulation of keratin debris with variable pain. Similarly, the labia minora may be reduced in size or completely absent. Scarring of the introitus may result in decreased introital aperture (both superiorly above the level of the urethra and at the posterior fourchette) with potential sexual dysfunction. In severe cases, the introitus may be almost completely sealed, thereby compromising the patient's ability to urinate.

Active or resolving LS can present with patchy hyperpigmentation. This pigmentation can exhibit variable shades of brown, black, or gray pigmentation and can be strikingly irregular and varied. Biopsy may be required to differentiate postinflammatory hyperpigmentation from genital lentiginosis (melanosis) and atypical melanocytic proliferations including melanoma.

Cutaneous LS manifests as hypopigmented/white, waxy, wrinkled papules and plaques, often with follicular plugging. Preferential locations include the neck, upper back, breasts, axillae, abdomen, and thighs. Rare sites of involvement include the scalp, face, mouth (manifesting as white firm plaques on the lips, buccal mucosa, dorsal tongue, attached gingivae), and nails. Extragenital lesions are typically asymptomatic.

The clinical differential diagnosis of VLS is presented in Table 1.

Diagnostic Evaluation

There are no serologic tests to support a diagnosis of LS. Diagnostic biopsy is ideal but may not always be practical or necessary. For pediatric patients, a clinical diagnosis of LS with a trial of topical corticosteroids (TCS) is a reasonable initial approach. Biopsy should be performed if: (1) the disease fails to respond to appropriate treatment, (2) there is suspicion for malignancy (including VIN, SCC, melanoma), or (3) there is concern for possible overlap with morphea (for extragenital lesions). Clinically suspicious findings include nonhealing erosions and ulcers, hyperkeratotic papules, friable nodules and areas of irregular pigmentation.

Histopathology

Classic histopathologic findings of LS include an atrophic epidermis with loss of rete ridges, hyperkeratosis, and a band-like lymphocytic inflammatory infiltrate in the upper to mid dermis. Interface dermatitis and dermal melanophages are also seen. The papillary and upper reticular dermis initially shows edema but eventually the collagen becomes more dense, homogeneous, and deeply pink. This hyalinized collagen typically sits above the lymphocytic infiltrate. Histologic features that help to differentiate LS from LP include a psoriasiform lichenoid infiltrate, basilar epidermotropism, loss of papillary dermal elastic fibers, basement membrane thickening and epidermal atrophy.[16] Use of TCS results in resolution of the lymphocytic inflammation and normalization of dermal collagen hyalinization.[39–41]

Evidence of squamous cell hyperplasia with acanthosis of the epidermis represents an increased risk for developing SCC and warrants further investigation.[42]

Malignancy

The risk of developing vulvar SCC is generally quoted as 2% to 5%, but estimates vary significantly depending on study design.[25,30] The risk of developing vulvar SCC is 246 to 300-times greater in women with VLS compared with women who do not have VLS.[43,44] Retrospective

evaluation of excised vulvar SCC specimens has revealed the concomitant presence of LS in 34% to 61%.[45,46] Risk factors for developing vulvar SCC include elderly age (possibly a surrogate marker for longer duration of disease), hyperkeratotic clinical lesions, and the presence of squamous dysplasia on histopathology. Malignant transformation has been reported in patients with poorly controlled or untreated VLS. It has not been determined whether effective treatment of VLS reduces the risk of malignant transformation. The mean time interval between onset of VLS and diagnosis of vulvar SCC has been estimated to be 4 to 10 years but varies considerably.[43,47] Verrucous carcinoma, basal cell carcinoma, melanoma, and Merkel cell carcinoma have been reported in patients with VLS; there seems to be no increased frequency of these malignancies relative to the general population. Vulvar malignancy in pediatric-onset VLS has not been reported.

TABLE 5. Vulvar Allergens and Irritants

Chronic moist environment: sweat, vaginal secretions (normal and pathologic), semen, urinary or fecal incontinence
Soaps, washes, cleansers
Feminine hygiene products: tampons, sanitary pads, vaginal douches, hygiene sprays, suppositories, lubricants
Topical medications: anesthetics (ie, benzocaine), antifungals, antihistamines (ie, diphenhydramine), corticosteroids, estrogen
Contraception: condoms, vaginal sponge, spermicides
Toilet paper
Synthetic fabrics (ie, polyester)
Underwear elastic/latex

General Approach to the Treatment of Inflammatory Vulvar Dermatoses

Goals of treatment are to relieve local and extragenital symptoms and to minimize further scarring and morbidity. Once the diagnosis of VVLP or VLS is made and before treatment is initiated, all potential etiologic and exacerbating factors should be determined and addressed (Table 5). A multidisciplinary approach is imperative and should include gynecologists, dermatologists, dentists, physical therapists with proficiency in women's health/pelvic floor, ophthalmologists, otolaryngologists, gastroenterologists, urologists, neurologists, and pain specialists to maximize treatment success and reduce morbidity for these complex patients. Supportive care by a psychologist, sexual therapist, and relationship counselor is often helpful for some patients.

For topical therapy of vulvar inflammatory dermatoses, ointment formulations are preferred as they provide increased potency, increased absorption and act as water-insoluble emollients. In contrast to creams, ointments are less likely to contain preservatives, alcohol, or propylene glycol thus reducing the risk of intolerance due to burning and secondary allergic or irritant reactions. We instruct our patients to apply a pea-sized amount of TCS to the affected areas of the vulva; if perianal disease is also present, use of an additional pea-sized amount on the perianal skin may be warranted. Patients with vaginal disease require additional therapy and instruction (see below). Areas for topical therapy are demonstrated to the patient during the examination utilizing a hand mirror, and patients may also be provided with clinical photographs or an anatomic diagram demonstrating areas of disease involvement. The patient's vision, mobility, and habitus should be considered when formulating a treatment plan; patients must be able to see and reach the targeted treatment areas. Patient educational handouts are available through the International Society for the Study of Vulvovaginal Disease (http://www.issvd.org).

In general, superpotent TCS, the gold standard of care for both VVLP and VLS, are initiated twice daily and subsequently tapered, both in frequency of use and potency of TCS, as the patient's symptoms and

TABLE 6. Clinical Pearls for the Treatment of Vulvovaginal Lichen Planus and Vulvar Lichen Sclerosus

Medications	Dose	Clinical Pearls
Clobetasol propionate ointment (0.05%)	Apply BID initially; as symptoms improve, taper to QHS, then QOHS, then alternate QOHS with midpotency topical corticosteroid	Reevaluate every 2-4 wk If symptoms worsen, consider HSV or *Candida* infection
Desonide ointment (0.05%)	Apply QOHS or 2-3 × /wk	Given low potency, use for maintenance treatment but not for initial therapy Reevaluate every 3 mo
Hydrocortisone acetate suppositories (25 mg)	Insert per vagina BID initially; as symptoms and signs improve, taper to QHS, then QOHS Taper to 2 × /wk over several months	Rectal formulations are commercially available Vaginal suppositories may be compounded at various doses Hallmarks of control include decreased number of immature parabasal epithelial cells, reduction in vaginal pH, and reduced WBCs and/or RBCs on normal saline wet mount examination
Triamcinolone acetonide (3-10 mg/mL)	Intralesional (intradermal, submucosal) injection of < 10 mg total every 4 wk, not to exceed 4 times per year	Indicated for recalcitrant or hyperkeratotic lesions after malignancy has been excluded by histopathology
Oral prednisone or prednisolone (0.5-1.0 mg/kg/d)	Taper over 2-4 wk	Use for acute flares to transition to topical corticosteroids or systemic steroid-sparing agents
Tacrolimus 0.03% and 0.1% ointment topically and per vagina	Use BID for 4 wk until symptoms improve then taper to QHS, 3 × /wk or weekly	Burning may limit use

BID indicates twice daily; HSV, herpes simplex virus; QHS, once daily at bedtime; QOHS, every other day at bedtime; RBC, red blood cell; WBC, white blood cell.

examination findings improve (Table 6). Thirty grams of corticosteroid ointment should be an adequate amount for once-daily treatment of genital skin for 3 months. Maintenance therapy with 30 g used over 6 to 12 months is considered to be safe.

Side effects of TCS such as atrophy and striae formation may be magnified due to physiological occlusion (eg, at inguinal crura, proximal medial thighs, gluteal cleft). This is true for all TCS potencies including over the counter therapy. Close observation is warranted with all TCS to limit atrophy, striae, and telangiectasia formation. Secondary infection with *Candida* species or dermatophytes (tinea incognito) and reactivation of herpes simplex virus may occur with the use of TCS.

Topical calcineurin inhibitors (tacrolimus, pimecrolimus) applied twice daily may be used as second-line therapy for those patients who do not respond to or experience adverse effects from TCS. An increased risk of cutaneous malignancy with the use of topical calcineurin inhibitors has been suggested.[48]

In postmenopausal patients, hormone replacement therapy with topical or systemic estrogen ameliorates underlying atrophy due to estrogen deficiency. Many patients find estradiol vaginal tablets (10 mcg/tablet, Vagifem®) easy to use, and this formulation decreases the risk of secondary irritation due to creams. Despite its historical use, topical testosterone is ineffective for and has no role in the management of VLS. In addition,

adverse effects including clitoromegaly may result from its use.

Preferential use of systemic/oral treatments when available (ie, oral antihistamines, oral antifungals, etc.) can also limit irritant or allergic reactions. Nonsedating (loratadine 10 mg, fexofenadine 180 mg, cetirizine 10 mg daily in morning) and sedating antihistamines (diphenhydramine 25 to 50 mg, hydroxyzine 10 to 50 mg, doxepin 10 to 30 mg daily at bedtime) can be used for associated pruritus while topical medications are initiated.

In severe or acute exacerbations of symptoms, secondary infection (ie, *Candida* species, herpes simplex virus) or concomitant contact dermatitis/mucositis (ie, irritant, allergic) must be considered (Table 5). Infectious agents should be treated systemically when possible and may require ongoing suppressive therapy. If contact dermatitis is suspected, all topical products should be discontinued, and the patient should be advised to use only water for hygiene. Causative irritants may be identified by sequential reintroduction of individual products. Cutaneous patch testing may be indicated to further evaluate for allergic contact dermatitis.

Patients should be evaluated for concomitant infection (impetigo, candidiasis, herpes simplex virus infection, etc.) and other dermatologic (allergic or irritant contact dermatitis, LP, etc.) or gynecologic (atrophic vaginitis, bacterial vaginosis, etc.) conditions upon initial evaluation and during all subsequent encounters. Any identified pathology should be treated, preferentially with oral medication to avoid potential for developing allergic or irritant contact dermatitis.

SUPPORTIVE MEASURES

Supportive measures are an important adjunct in the care of these complex patients. Patients should be instructed to avoid contact with extraneous substances on the vulva. After bathing with water, the area should be patted dry, not rubbed. To further minimize koebnerization, irritants, potential allergens, and physical manipulation should be avoided. Burning and pain may be minimized with Sitz baths, ice packs, cool compresses, and application of oatmeal solutions. Systemic antihistamines will control itching and limit rubbing. Topical emollients such as petrolatum, A and D ointment or Aquaphor® decrease friction, increase hydration, and may be soothing to the patient.

Patients may develop persistent vulvar pain (secondary vulvodynia) despite adequate resolution of skin changes; treatment with topical anesthetics (lidocaine ointment 5%) or systemic neuropathic pain modulators (amitriptyline, gabapentin, pregabalin, etc.) may be considered after other causes of vulvar pain have been excluded.

TREATMENT OF VVLP

Medical Therapy

Although no single therapeutic regimen has been shown to be universally effective in the treatment of mucosal LP, the first-line treatment of VVLP is the application of superpotent TCS.[8–10] Most patients can be successfully managed with TCS alone. In a retrospective review of 131 patients from a private dermato-gynecology practice, TCS were effective in inducing good control of symptoms in conjunction with good clinical improvement in 55% of patients. In the same series, to achieve a similar degree of improvement, 23.7% of patients required both TCS and oral prednisolone, whereas 16.8% responded to oral prednisolone alone.[8] In a separate study of erosive VVLP in an academic center, 75% of patients had good or partial improvement in symptoms with TCS monotherapy.[5]

Women with vaginal involvement require intravaginal therapy in addition to topical vulvar treatment. In 1 study, 60 women were treated with intravaginal hydrocortisone 25 mg (1/2–1) suppositories twice daily.[49]

The frequency was tapered to twice weekly after several months of improvement. Overall, 81% of these women reported significant improvement of burning, pruritus, dyspareunia, and vaginal discharge, and 76.8% improved objectively on examination (ie, erythema, erosion). Vaginal stenosis did not significantly improve.[49]

Various systemic treatments including griseofulvin, dapsone, minocycline combined with nicotinamide, oral retinoids, hydroxychloroquine, azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil, methotrexate, etanercept, adalimumab, and thalidomide have been tried with varied and often disappointing results. Cytotoxic and systemic immunosuppressive agents may be beneficial, but adverse effects limit their use to cases of severe and refractory disease.

Vaginal dilators are used to both treat and prevent adhesions and synechiae due to apposition of inflamed and/or eroded vaginal mucosa. The dilator is coated with corticosteroid ointment or estrogen vaginal cream and used on a tapering schedule. In a small case series of patients (n = 3) treated with tacrolimus 0.1% ointment on the vulva, 2 patients also utilized a graduated vaginal dilator coated with estrogen cream twice daily for 1 week, followed by 3 times weekly.[50] All patients reported significant improvement in vulvovaginal symptoms, and those who utilized dilator therapy experienced increased diameter and depth of dilator insertion and were able to resume sexual intercourse.[50]

Surgical Therapy of the Vagina

Surgical intervention for vaginal synechiae is contraindicated in patients with active, ongoing inflammatory VVLP. Premature surgical intervention will worsen activity of VVLP resulting in more challenging disease control and greater morbidity. Surgical lysis of synechiae is recommended only once VVLP is under excellent control. This surgery requires general anesthesia and involves blunt and sharp dissection carefully undertaken to limit the risk of rectal perforation and to assist in successfully lysing adhesions. Intraoperative and postoperative vaginal dilators and TCS with or without local estrogen therapy must be used routinely and diligently to prevent new adhesions and scars from forming.

In a small case series from Finland, 5 patients with stenosing VVLP who had been treated with methotrexate and both superpotent corticosteroid cream and tacrolimus ointment were then treated with surgical dilatation. All patients reported symptomatic relief and only minimal to moderate restenosis of the vagina after 2 to 41 months.[51] In a retrospective self-administered survey, 11 women who had undergone surgery for VVLP-associated adhesions, 55% of patients were able to engage in sexual intercourse and were sexually active, whereas 75% had decreased urinary symptoms or infections. Most (91%) stated that they were happy with the results and would recommend the procedure to others despite persistent sexual difficulties.[52]

TREATMENT OF VLS

There are few randomized, controlled trials to support the therapeutic approach to LS.[53] VLS typically is very responsive to TCS. Extragenital LS is generally resistant to treatment.

Medical Therapy

Complete or partial relief of symptoms has been reported in 95% of 255 girls and women with VLS after 3 months of daily use of superpotent TCS. Complete clinical response was demonstrated in 23% of patients, and partial clinical response occurred in 68% reinforcing that treatment of VLS must be determined based on a combination of both patient-reported symptoms and clinical examination findings.[30] Long-term use of TCS as regular maintenance therapy is required for

sustained disease control in the great majority of patients. Prolonged use of TCS including clobetasol propionate 0.05% ointment has been shown to be safe and effective.[54]

A double-blind, randomized, prospective study of 55 girls and women (mean age, 46.6 y; age range, 4 to 73 y) with VLS demonstrated that clobetasol propionate 0.05% ointment was significantly more effective than tacrolimus 0.1% ointment. After 3 months of treatment, both treatment groups experienced improvement in symptoms and signs of LS, but significantly greater numbers of patients treated with clobetasol propionate 0.05% ointment experienced complete resolution of LS-associated symptoms and signs.[55]

Topical cyclosporine (200 mg/d of cyclosporine oral solution, 50 mg 4 times daily for 8 wk) had minimal impact on VLS in a single small pilot study.[56] Cost may be prohibitive.[56]

Positive impact of calcipotriol 0.005% ointment applied twice daily under occlusion to extragenital LS lesions for 12 weeks has been documented in a single case report. Irritation may limit use of calcipotriol ointment on genital skin.[57]

Systemic retinoids may have a role in hyperkeratotic or hypertrophic disease that is refractory to superpotent TCS after malignancy has been excluded. In a double-blind, placebo-controlled study of refractory VLS, 63% of patients responded to acitretin (20 to 30 mg/d for 16 wk) compared with 25% of those receiving placebo.[58] Acitretin is a teratogen and should not be used in women of childbearing potential. Acitretin is considered standard of care for reducing the risk of SCC in select populations (ie, post-solid organ transplantation); its impact on malignant transformation in VLS is not known but may be protective.

Oral cyclosporine (3 to 4 mg/kg/d tapered over 3 mo) was used in an open label, uncontrolled trial of 5 patients with refractory VLS. At the end of 3 months of treatment, symptoms and clinical findings were improved. Adverse effects included nausea, mild hypertrichosis, and mucositis but did not result in interruption of treatment.[59]

For VLS, increasing age (above 70 y) is associated with poor response to treatment and failure to remit.[43]

SURGICAL INTERVENTION

Surgical treatment is only indicated for functionally significant vulvar and introital scarring once active inflammation has resolved. Patients should be monitored for at least 6 months for recurrence of active disease before undergoing surgery. Regular use of superpotent/potent TCS after vulvar surgery is essential to prevent flares of LS (given the Koebnerization phenomenon) and to minimize the risk of reagglutination and stenosis.

PHYSICAL TREATMENT MODALITIES

The use of phototherapy (narrowband UVB, psoralen-UVA, and UVA1) for extragenital LS has been reported in case reports and small case series. A randomized trial comparing 3 months of medium-dose UVA1 phototherapy (4 times/wk) to once daily clobetasol propionate 0.05% ointment in 30 women with VLS revealed that the 2 treatments had similar impact on clinician grading of VLS but that UVA1 had less impact on pruritus and quality of life.[60]

Summary

Management of patients with VVLP and VLS can be challenging. The importance of the doctor-patient relationship cannot be overemphasized. These patients can and do improve and often return to normal function.

Patients with VVLP often have or may develop widespread, frequently debilitating disease at additional mucosal sites, and patients with VLS may develop extensive cutaneous involvement. Thus,

it is imperative that patients undergo a complete mucocutaneous evaluation to identify other sites of involvement and potential malignant lesions.

With appropriate medication use and monitoring, disease control can be achieved in 3 to 4 months in most patients, but treatment regimens should be tailored for individual patients. Even when vulvar disease is well-controlled on maintenance regimens, patients should be seen in follow-up every 6 to 12 months to monitor disease activity and potential complications (atrophy, scarring, dysplasia). Patients who fail to improve despite correct medication use should be re-evaluated to ensure that the initial diagnosis was indeed correct and that there is no additional superimposed pathologic process (allergic/irritant contact dermatitis, infection, malignant transformation). Areas of persistent erythema, erosion, or hyperkeratosis may represent malignant change; there should be a low threshold for biopsying these lesions especially if the patient is not responding appropriately to treatment. A multidisciplinary approach is imperative to reduce morbidity and optimize patient outcomes.

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