VULVAR LICHEN SCLEROSUS DIAGNOSIS CHALLENGES

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KEYWORDS

Vulvar lichen sclerosus, ulcerative, diagnosis.

ABSTRACT

Background: Vulvar lichen sclerosus (LSV) is a chronic inflammatory dermatosis that affects the vulva and anus. Vulvar lichen sclerosus is a multifactorial disease. Establishing a diagnosis of LSV requires challenges, because the course of the disease is very heterogeneous and the signs and symptoms of LSV are very diverse and non-specific, making diagnosis quite difficult.

Case: A 48-year-old woman presented with anogenital ulceration for 1 month. The complaint began with an itching feeling in the genital area. The wound was getting wider and accompanied by dysuria. The histopathological examination findings were consistent with vulvar lichen sclerosus. The immunohistochemistry examination revealed negative staining of p16 expression in the epidermal cell nuclei and cytoplasm and positive staining of p53 expression in the nuclei of some epidermal cells. The diagnosis was ulcerative vulvar lichen sclerosus. The patient was treated with NaCl 0.9% compress for 10 - 15 minutes, and mupirocin 2% cream, applied on the skin lesion area twice a day. After three months of therapy, the patient's lesions improved and the patient was given cetirisin 1 x 10 mg orally, zinc 1 x 1 tablet and vaseline album moisturizer to protect the skin.

Discussion: Vulvar ulcers are a non-specific finding with various etiologies, they can be caused by sexually and non-sexually transmitted infections, dermatoses, trauma, neoplasms, hormone-induced ulcers, and drug reactions. Several vulvovaginal conditions are more common in menopausal women, such as lichen sclerosis of the vulva, vulvar intraepithelial neoplasia (VIN), and squamous cell carcinoma. Confirming the diagnosis of LSV is still a challenge for clinicians because the signs and symptoms are non-specific so a biopsy needs to be performed especially if the patient has suspicious wounds (erosion or ulceration, pigmented areas or ecchymoses, popular or wart-like lesions). Typical histopathological examination of LSV is severe hyperkeratosis, basal cell vacuoles, fibrosis and inflammatory cells. Immunohistochemical examination was carried out to rule out the differential diagnosis of VIN and squamous cell carcinoma, namely p16 positive and p53 negative, whereas in the patient p16 was found negative and p53 was slightly stained positive in the nuclei of some of the basal cells of the epidermis.

I. INTRODUCTION

Lichen sclerosus (LS) is a chronic inflammatory dermatitis with predilection in the anogenital area. Lichen sclerosus in some cases can damage the surrounding tissue to cause atrophy of the labia minor, *phimosis*, introitus stenosis and others.[1] Lichen sclerosus vulva (LSV) is a chronic skin condition affecting the vulva (skin around the vagina) and anus accompanied by itching and pain.[2]

The prevalence of LS is unknown due to the lack of extensive epidemiological studies in this field and 15 - 40% of cases are asymptomatic.[1] Lichen sclerosis in general hospitals is a rare disease with a prevalence of 0.1 - 0.3%.[3] The etiology of LSV is currently unknown.[4] However, lichen sclerosis has several risk factors including family history of LS, trauma, chronic irritation,

hormones, infection and medication. Local vulvar factors such as urine, sweat, friction and microbiome are also thought to be among the risk factors for LSV.[5,6] Lichen sclerosus has clinicopathologic subtypes of erosive and ulcerative which are often used as markers of disease severity. Ulcerative lichen sclerosus occurs in patients with uncontrolled or untreated LS.[7] Early clinical manifestations in women are generally atypical, even asymptomatic until more severe symptoms and disease severity appear.[1] Lichen sclerosus will become brittle, appearing atrophic lesions, fissures and erosions. These symptoms can interfere with the patient's quality of life.[5,8,9]

Lichen sclerosis of the vulva has several differential diagnoses, such as *vulvar intraepithelial neoplasia* (VIN) and squamous cell carcinoma. The diagnosis of LSV is based on history and physical examination, and biopsy may be performed if the patient's clinical picture is atypical to rule out differential diagnosis or suspicion of malignancy and treatment failure.[5,6,8] Although there is no specific therapy to cure LS, there are many treatment options that have been studied and are able to achieve remission and prevent disease worsening ranging from ultrapotent topical corticosteroids, topical *calcineurin inhibitors, platelet-rich plasma*, ultraonosgraphy, laser, and forodinnamic therapy. Ultrapotent topical corticosteroids are the gold standard therapy for LS.[8] Early diagnosis, appropriate management and long-term monitoring have an impact on the prognosis of LSV.[5,6] Establishing the diagnosis of LSV is still a challenge for clinicians due to non-specific signs and symptoms so biopsy is necessary especially if the patient has suspicious lesions (erosion or ulceration, pigmented areas or ecchymosis, popular or wart-like lesions) especially if resistant to first-line treatment to rule out differential diagnosis such as *vulvar intraepithelial neoplasia* (VIN) and cancer.[(1,8)] This case report was prepared to explain the challenges in establishing the diagnosis of LSV

II. CASE

A 48-year-old woman came to the Dermatology and Venereology Department of Dr. Moewardi Regional General Hospital (RSUD) because of pubic wounds since 1 month ago. The patient initially complained that her genitals itched so much that scratching could not be restrained. The itching felt very disturbing to the patient and a wound appeared on the scratching area in the vaginal lip area. The patient had been treated by an Internal Medicine Specialist (Sp.PD) and was given medicine that was inserted into the vagina for 7 days and itching medicine, but the patient did not remember the name of the medicine. Itching complaints had improved.

Two weeks prior to hospitalization, the patient complained of a widened pubic wound, accompanied by severe itching and pain when urinating, but the patient did not go to the doctor to treat the wound, the patient only cleaned the wound with warm water. Three days prior to admission, the patient went to the Emergency Department (ED) of Dr. Moewardi Hospital because the wound was widening and bothering her. The patient was diagnosed with genital ulcer suspected mole ulcer with differential diagnosis of squamous cell carcinoma and vaginal intraepithelial neoplasia. The patient received azithromycin 1 x 500 mg, NaCl 0.9% compress for 10 minutes and mupirocin 2% cream applied twice a day. The patient was advised to do a biopsy. Other complaints such as the appearance of water-filled plums, vaginal discharge, fever and weight loss were denied by the patient.

The patient had never experienced similar complaints before. History of drug allergy, food allergy, diabetes mellitus, hypertension and genital warts were denied by the patient. Family history of similar illness, drug allergy and food allergy were also denied by the patient. The patient *had menarche* at the age of 13 years. The patient has not menstruated since the last 2 years. The patient first had sexual intercourse when she was 21 years old with her husband and last had sexual intercourse three months ago with her husband. The patient has one sexual partner (her husband). The patient's sexual orientation is genital-genital. Complaints of sexually transmitted infections in sexual partners and changing sexual partners were denied by the patient.

Physical examination of the patient's general condition revealed moderate pain. Vital signs examination was within normal limits. Venereological examination of the genitalia region revealed multiple ulcers with the largest size of 7 x 0.5 x 0.5 cm with irregular edges, *slough* (+), blood (+), granulation tissue (+), pus (-) and necrotic tissue (-) **(Figure 1)**. Based on history and physical examination, the differential diagnosis of the patient was genital ulcer suspected mole ulcer with differential diagnosis of squamous cell carcinoma and vaginal intraepithelial neoplasia.

Gram examination found *polymorphonuclear* (PMN) 2-3 / field of view (LPB), gram-negative rods >100 / LPB **(Figure 2)**. *Treponema Pallidum Hemagglutination Assay* (TPHA) showed non-reactive results, *Venereal Disease Research Laboratory* (VDRL) showed negative results, and anti *Human Immunodeficiency Virus-1* (HIV-1) showed non-reactive results.

Figure 1. Venereological examination. The genitalia region showed multiple ulcers with the largest size of 7 x 0.5 x 0.5 cm with irregular edges, *slough* (+), blood (+), granulation tissue (+), pus (-), and necrotic tissue (-).

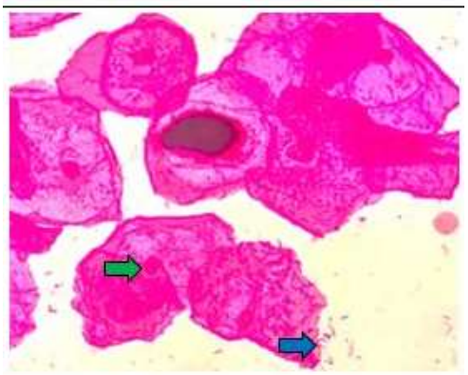


Figure 2. Gram examination. *Polymorphonuclear* (PMN) 2-3/field of view (LPB) (green arrow), gram-negative rods >100/LPB (blue arrow).

The patient was biopsied and received post-biopsy therapy of cefixime 2x100 mg, mefenamic acid 3 x 500 mg *orally*, as well as NaCl 0.9% compress for 10 - 15 minutes, and mupirocin 2% cream applied to the wound twice a day. The patient was educated not to have sexual intercourse for a while and to keep the pubic area clean. On biopsy examination, it was found that in the epidermis layer, hyperkeratosis and horn pearls were found, in the dermis layer, granulation was found and no signs of malignancy were found. The diagnosis was concluded to be *vaginal intraepithelial neoplasm* (VIN) grade I. From the results of the history, physical examination and supporting examination, the differential diagnosis of mole ulcer and squamous cell carcinoma can be excluded.

The patient was consulted to the Obstetrics and Gynecology Sub. Oncology and advised to observe for 3 months with appropriate therapy from Dermatology and Venereology. If the lesion does not improve, a *Human Papilloma Virus Deoxyribonucleic Acid* (HPV DNA) test will be planned and a wide incision will be performed if the lesion worsens.

Three months later, the patient returned for follow-up. The patient's complaints had improved and a venereological examination of the genitalia revealed whitish/ivory *patches* **(Figure 3).**

Figure 3: Genitalia region showing whitish/ivory *patches*.

Clinically, we suspected lichen sclerosus of the vulva, and we performed histopathologic re-reading, which showed connective tissue covered with squamous epithelium that was hyperkeratosis, hypergranulosis, and acanthosis. Some *rete ridges* were elongated, basal cells were proliferated, and the basement membrane was intact. Basal cell vacuole degeneration was observed. In the connective tissue, there were inflammatory cells consisting of lymphocytes, histiocytes, and a few *polymorphonuclear* leukocytes (PMN). There was also no squamous epithelial dysplasia and no malignant signs. All histopathologic findings were consistent with *vulvar lichen sclerosus* **(Figure 4)**.

From the first and second histopathology readings, we found different diagnosis results, then we performed immunohistochemical examination of P16 expression and P53 expression to confirm the exact diagnosis. P16 expression examination was performed as a marker of HPV infection, because VIN can be associated with HPV infection. P53 *wild* expression examination was performed as a marker of one of the tumor suppressor genes. In the patient, p16 expression was found to be negative in the nucleus and cytoplasm of epidermal cells, this may indicate the absence of HPV infection, *wild* p53 expression which is slightly positive in the nucleus of some epidermal basal cells plays a role in preventing the onset of tumors **(Figure 5)**. Based on history, physical examination, histopathologic examination and immunohistochemistry, the patient's diagnosis was vulvar lichen sclerosus. The patient was given cetirisin 1 x 10 mg orally, zinc 1 x 1 tablet and vaseline album moisturizer to protect her skin. The patient was also educated not to have sexual intercourse beforehand and to keep the pubic area clean.

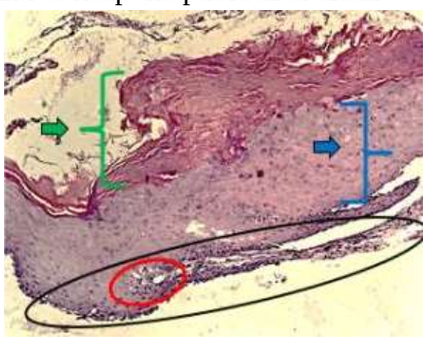


Figure 4: Histopathologic examination results. The epidermal layer shows hyperkeratinocytes (green arrow). The dermis layer shows acanthosis (blue arrow), basal cell vacuoles (red circles), inflammatory cells (black circles) (H&E 40x).

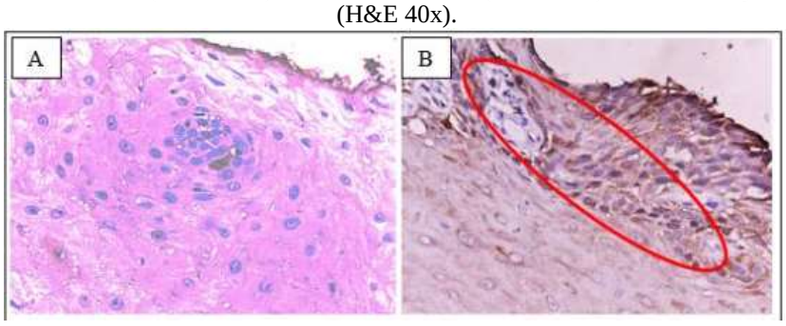


Figure 5. Immunohistochemical examination results. **A.** Negative expression of p16 in the nucleus and cytoplasm of epidermal cells. **B.** Positive p53 expression in the nucleus of some epidermal basal cells (red circle) (IHC 400x).

III. DISCUSSION

Vulvar ulcers cause pain, anxiety and emotional distress for patients as they can interfere with daily life. Vulvar ulcers are non-specific findings with various etiologies, which can be caused by sexually and non-sexually transmitted infectious diseases, dermatoses, trauma, neoplasms, hormone-induced ulcers, and drug reactions. Women go through menopause as they age and there are several vulvovaginal conditions that are more common in menopausal women such as *vulvar* lichen sclerosus, *vulvar intraepithelial neoplasia* and squamous cell carcinoma. Diagnosis of vulvar ulcers is difficult due to the variety of clinical features and often the primary features of vulvar ulcers are difficult to assess due to secondary changes and the possibility of more than one condition. Lichen sclerosus is most common in women over 50 years of age. Biopsy is required for accurate diagnosis as in practice distinguishing LS from other conditions in the vulvar area is not easy even though malignant lesions in the vulva have an irregular shape, structure, color and distribution.[10,11]

Lichen sclerosus (LS), also known as *lichen sclerosus et atrophicus, balanitis xerotica obliterans, kraurosis vulvae,* or *hypoplastic dystrophy.* Lichen sclerosus is a chronic, immune-mediated mucocutaneous disease that commonly occurs on the genital skin. Lichen sclerosus is a lymphocyte-mediated inflammatory condition that can lead to changes in genital anatomical structures if it persists. The term was first proposed by Hallopeau in 1987. The term LS was first accepted by the *International Society of the Study of Vulvovaginal Disease* in 1976.[5,12] Vulvar lichen sclerosis is a chronic inflammatory dermatosis that can lead to scarring of the vulva and sexual dysfunction.[8]

Lichen sclerosus can occur at any age in both men and women and about 85 - 98% of cases occur in the anogenital skin with the highest onset in pre-pubertal children and *post-menopausal* women.[3,5,13] Lichen sclerosus is more common in women with a female : male ratio ranging from 3:1 to 10:1.[5] Lichen sclerosus in men generally occurs in the age group of 30 - 50 years.[3] The prevalence of LS in women is higher during adulthood while LS in men is higher during childhood.[3,13] The case in this patient was a 48-year-old woman which is generally a *post-menopausal* age.

The pathogenesis of LS is not well known, but some hypotheses suggest autoimmune, isotraumatic, and infectious agents.[13] However, about 22% of LS cases can be inherited.[14] As previously described, LS is an immune-mediated disease. A history of LS in a sister in the nuclear family was found in 12% of LS patients. *Human Leukocyte Antigen-DR Isotype* (HLA-DR) and *Human Leukocyte Antigen-DR Isotype* (HLA-DQ) are thought to be involved in susceptibility and protection against LS. About 66% of children with LSV have HLA-DQ7. In both male and female adult patients, HLA-DQ7 is more common in LS patients. Lichen sclerosus also has epigenetic changes that can potentially trigger malignant transformation. Vulvar lichen sclerosus *is* associated with changes in *isocitrate dehydrogenase,* an enzyme that plays a role in the *deoxyribonucleic acid* (DNA) 5-hydroxymethylation *pattern* so that the methylation level in the epidermis decreases in LSV. Genetic predisposition to LSV reflects the cumulative effect of variations in the expression of multiple loci that lead to disease susceptibility. The disease susceptibility requires interaction with exogenous factors to cause LSV.[5,6]

Lichen sclerosus also has T cell infiltration in the dermis, especially CD8+ and Treg cells. Immunologic dysreactivity and autoimmune response seem to be relevant pathophysiology. The cells express *Chemokine Receptor Type* 3 (CXCR3) and *Chemokine Receptor* (CCR5) receptors and lack CCR3 and CCR4 reflecting a Th1 profile. The Th1 response is enhanced through the production of *interferon-γ* (IFN-γ). Th1-type pro-inflammatory cytokines and immune mediators such as *interleukin-1* (IL-1), IL-6, IL-15, *tissue necrosis factor-α* (TNF-α), IL-12 receptor, *caspase* 1, *intracellular adhesion molecule-1* (ICAM-1), and CD11a *ligand* are also increased in LSV. In contrast to Th-1, the expression of Foxp3, a transcription factor of Treg cells, was decreased, resulting in impaired immune tolerance and autoreactive CD4+ effector T cells triggering an

immune response to *self-antigens.* Genital lichen sclerosus is also found to have autoantibodies to *extracellular matrix protein* 1 (EMC1) which is a molecular binding glycoprotein in the basement membrane zone and dermis and reduced expression of CD44 which plays a role in cell adhesion and migration as well as a hyaluronate receptor.[5,6]

Increased fibroblast activity and growth and abnormal collagen synthesis are important events in the pathogenesis of LSV and the formation of sclerotic dermal tissue with hyaline. Overexpression of miR-155 suppresses the expression of *Forkhead Box* O3 (FOXO3) and *Cyclin dependent kinase inhibitor* 1B (CDKN1B) resulting in fibroblast proliferation. The presence of *extracellular matrix protein* 1 (ECM1) autoantibodies also increases collagenase activity, disrupting the basement membrane zone. In addition to the increase in collagen I and III, there is abnormal deposition of collagen V. Just like other inflammatory diseases, oxidative stress also plays a role in the pathogenesis of LS. Oxidative stress also plays an important role in the worsening of LS as well as causing DNA damage resulting in malignant transformation.[5,6,15]

The etiology of LS is unknown, but infectious agents such as *Borrella burgdorferi, human papilloma virus* (HPV), hepatitis C virus and *Epstein-Barr* virus have been studied as etiologic agents of LS.[1,4] Lichen sclerosus has several risk factors such as parity history where women who have given birth are more at risk than nulliparous women for LS but the higher the number of parities, the lower the risk of LS. Autoimmune diseases of the skin and urinary incontinence are also risk factors for LS.[8]

Chronic irritation and trauma play an important role in the occurrence of LS. Habitual scratching, friction and surgical procedures contribute to the *Koebner* phenomenon resulting in LS. High body mass index (BMI) is also associated with LSV in elderly women. The role of hormones in LS is still controversial, in the past hypoestrogen was considered a risk factor for LSV because LSV cases were more common in the pre-pubertal and *postmenopausal* period. Hormonal changes play a role in LS due to decreased levels of *dihydrotestosterone* and *androstenedione,* and decreased *5α-reductase* activity. Some cases of LS are associated with certain drug treatments. A study reported that genital LS occurred in adult patients with malignancies treated *with pembrolizumab, nivolizumab*, or *iplimumab,* while angiotensin *converting enzyme* (ACE) *inhibitors* and *beta-blockers* reduced inflammatory cell infiltrates and triggered keratinocyte proliferation and lymphocyte motility.[1,5,16]

The disease course of LSV is very heterogeneous, making diagnosis quite difficult. Signs and symptoms of LSV vary widely and may be nonspecific.[17,18] Most LS occurs in the genital and perianal areas (83 - 98% of cases). The most common symptoms are itching and pain in the affected area. The itching may be accompanied by burning, which is usually worse at night. In 15 - 20% of anal-genital LS cases, extragenital lesions may be found.[13] Other symptoms include *dyspareunia, dysuria,* pain, urinary dysfunction, and bleeding.[1,8,15]

A thorough history and physical examination should be performed. Lesions should be documented to monitor therapeutic efficacy or disease worsening. The LSV clinical scoring system is a validated tool to facilitate diagnosis as well as evaluate associated symptoms and therapeutic response **(Table 1)**.[5] The patient's case obtained a clinical score of 5, namely macroscopically visible erosions and/or more than 2 or confluent lesions = 2, generalized vulvar fissures = 2, atrophy of the labia minor and clitoris = 1. The patient's total score was 5, indicating vulvar lichen sclerosus.

Although some patients with LS are asymptomatic, most patients have a history of itching, *dyspareunia* or pain at the vulva. In fact, LS patients tend to have less sexual intercourse. About 79% of LS women experience chronic vulvar pain. Lichen sclerosus commonly occurs on areas of the vulva that do not have hair such as the inside of the labia major, labia minor, vestibulum, *clitoral hood,* and may reach the *genitocrural* folds. In 30% of cases, lesions may appear in the perianal area. If the vulva and perianal area are involved, the lesion will give a typical "*figure of 8*" or *"key hole sign*" that encircles the vulva, perineum, and perianal area. Physical examination may also

reveal *purpura*, petechiae, ecchymosis, erosion, fissures, hypertrophic plaques, ulceration, and hyper- or hypopigmentation indicating that LS has been present for a long time.[1,8,9(,19]

Table 1. Clinical scoring system in LSV.[5]

Clinical Signs	***Grade* 1 (moderate change)**	***Grade* 2 (severe changes)**
Erosion	1 - 2 small erosions, barely visible markoscopically.	Macroscopically visible and/or more than 2 or confluent lesions.
Hyperkeratosis	Occurs on the vulva and perineum (up to 10%).	Occurs on the vulva and perineum (>10%).
Fissures	A fissure occurs at the posterior introitus.	Generalized vulvar fissure.
Agglutination	Some occur on the clitoral prepuce and labia minor.	Agglutination was complete in both.
Stenosis	Narrowing of the introitus that can still be passed by 2 fingers.	Two fingers cannot pass through.
Atrophy	Labia minor and clitoris shrink	The clitoris and labia minor are not visible.

Vulvar agglutination: complete or partial adhesion of the labia minor or major
The scoring system assesses 6 clinical signs, each of which has a score of 1 or 2.
Grade 0 describes normal anatomy. If the score is >4 there is a 90% chance of LSV

Physical examination may reveal brightly colored papules or whitish or *ivory patches* accompanied by erosions, fissures, purpura, ecchymosis, and sometimes hyperkeratosis. The lesions are accompanied by a waxy texture or epidermal wrinkling (*cigarette paper*). Even in severe LSV, there may be loss of labia minora, introitus stenosis, and *vulvar kraurosis* **(Figure 6**).[1,15] Lichen sclerosis of the vulva may also present as shiny white atrophic plaques with a *"figure of 8"* pattern encircling the vulva, perineum and *perianal* area, *and* lesions may also be found in the surrounding areas. Severe scarring may be found in sustained vulvar LS. Other findings include *ecchymosis*, erosions, fissures, hypertrophic plaques, and hyperpigmentation **(Figure 7)**.[9] Based on the history and physical examination, the patient's symptoms are consistent with those of LS, namely itching and pain during micturition. . Itching is the most common symptom of LS. Venereological examination of the genital area showed multiple ulcers with the largest size of 7 x 0.5 x 0.5 cm with irregular edges, *slough* (+), blood (+), granulation tissue (+), pus (-), and necrotic tissue (-). The patient had been experiencing these complaints since 3 months ago, the presence of ulceration indicates a long-standing LS, as in this case.

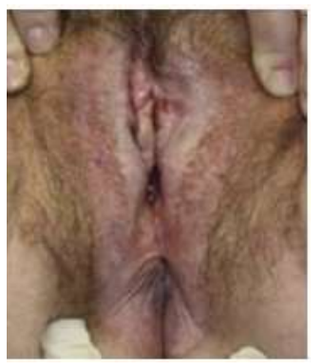


Figure 6. Whitened vulva to perianal skin, fusion and resorption of the labia minor and anal and vaginal stenosis.[14]

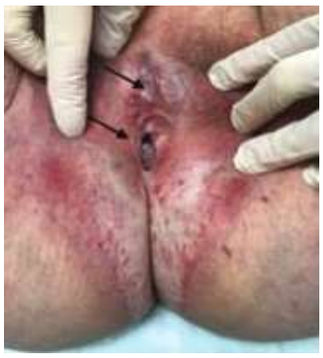


Figure 7. Vulva with large, shiny atrophic white plaques accompanied by *petechiae* on the *vulva, perineum* and *perianal* area with a "*figure of eight*" distribution. There is severe scarring and bilateral loss of *clitoral hood* and *labia minor* (black arrows) with narrowing *of the introitus.*[11]

Histopathologic examination is generally not necessary if the clinical picture is clear. However, there are certain conditions where histological examination is necessary such as atypical clinical features, the presence of pigmented areas (to rule out abnormal melanocytic proliferation), therapy failure, extragenital LS resembling *morphea,* young adult female patients suspected of LS before therapy is given and suspected neoplastic changes (hyperkeratosis, erosion, erythema, and papules).[5] Histopathological examination of LS will give a picture according to the stage. However, typical changes in LS are severe hyperkeratosis, thin (atrophic) epidermis, loss of *rete ridges*, thin epidermis (atrophic epidermis), basal cell degeneration, loss of *rete ridges*, homogeneous bands of fibrosis in the papilla of the dermis, edema of the upper dermis, lymphatic infiltrates in the dermis, and often chronic inflammation such as bands around blood vessels (mainly eosinophils) **(Figure 8).**[19,20,21] Histopathologic changes in the early stages are generally less obvious and are often more pronounced in the adnexal structures compared to the interfollicular skin. Adnexal structures show acanthosis, luminar hyperkeratosis, and hypergranulosis with/without hair dystrophy and basement membrane thickening. Early dermis changes are homogeneous collagen and dilated capillary vessels of dermis papillae located beneath the basement membrane. The number of lymphocytic infiltrates found can be large or small. The minimal histological criteria of LSV is vascuolization along with dermal sclerosis (homogeneous, hyalinized eosinophilic collagen *bundles*) between the inflammatory infiltrate and the epithelium or vessel wall but a study showed that one-third of LSV cases do not have typical histopathological findings.[8,17] Immunohistochemistry is a very important examination to exclude differential diagnosis. Biopsy with *hematoxylin eosin* (HE) staining and immunohistochemistry should be performed for better understanding. [22]

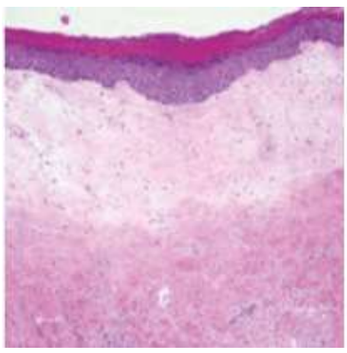


Figure 8: Histopathology of LSV. Vulva showing thin epidermis, severe keratosis, basal cell degeneration, loss of *rete ridges*, homogeneous bands of fibrosis in papilla dermis, edema of upper dermis. [22]

The differential diagnosis of LSV is *vulvar intraepithelial neoplasia* (VIN) and vulvar squamous cell carcinoma.[5] Symptoms of VIN are itching, vulvar pain, burning and easy bleeding. Histopathologic examination is necessary to diagnose VIN, which is the presence of atypical basal cell proliferation. Five atypical criteria are basal layer involvement, enlarged nuclei, hyperchromasia, pleomorphic cells and increased mitotic features.[23,24]

Vulvar intraepithelial neoplasia is divided into two namely *well-differentiated vulvar intra-epithelial neoplasia* (dVIN) and *usual vulvar intra-epithelial neoplasia* (uVIN). *Well-differentiated vulvar intra-epithelial neoplasia* is a premalignant lesion that occurs in a pre-existing vulvar lesion e.g. LS while uVIN is associated with HPV infection. Based on history taking, patients with VIN have non-specific *warning signs* such as itching, vulvar pain, burning, and provoked bleeding and discharge (indicating invasion) especially in the *perianal* area. The intensity of symptoms is related to the severity of the lesion. Chronic symptoms are more suggestive of lesions not caused by *human papilloma virus* (HPV). Physical examination of uVIN reveals lesions around the *introitus* in the form of macules or pigmented erythemal plaques with well-defined borders or irregular plaques that merge with each other **(Figure 9a)**. In dVIN, there are extensive maculopapular plaques with a slightly wart-like appearance or indistinctly demarcated leukoplaia-erythematous plaques (**Figure 9b**).[23] A biopsy of dVIN will show abnormal atypical keratinocytes, thickened epidermis with parakeratotic surface reaction. **(Figure 10).** In uVIN, undifferentiated cells resembling basal cells will be seen and replace the entire thick, non-papillomatous epidermis in flat lesions (basaloid uVIN) **(Figure 11a)** while in *wart-like* lesions (*warty* VIN), a wide and long *rete ridge* can be found and gives a typical condyloma-like appearance. **(Figure 11b)**.[25]

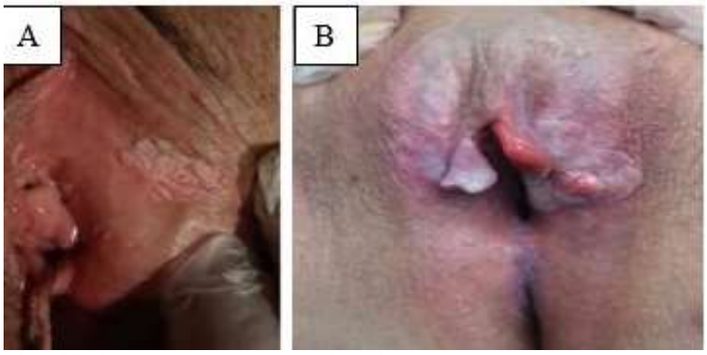
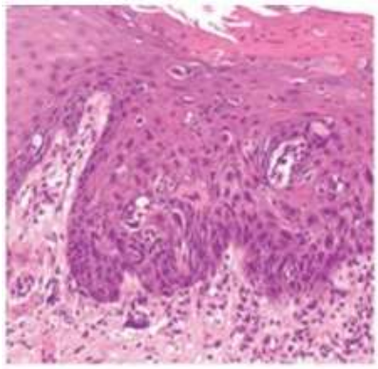
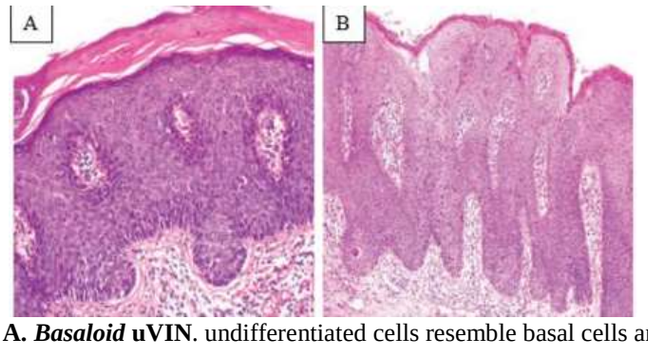


Figure 9. VIN lesions (A. uVIN. Lesions around the *introitus* in the form of macules or pigmented erythematous plaques with well-defined **borders** or irregular plaques merging with each other **B. dVIN.** Extensive maculopapular plaques with a slightly wart-like appearance or indistinctly demarcated leukoplaia-erythemic plaques).[(2)(5)]

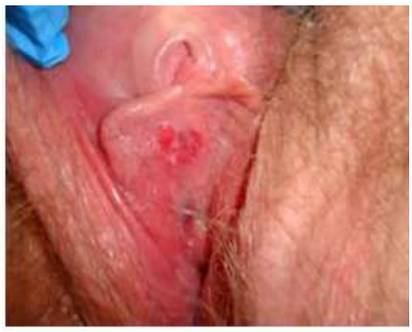


Histopathology of dVIN. Abnormal atypical keratinocytes, thickened epidermis with parakeratotic surface reaction.[25]



Histopathology of uVIN. A. *Basaloid* uVIN. undifferentiated cells resemble basal cells and replace the entire thick, non-papillomatous epidermis in flat lesions **B. *Warty* uVIN.** A wide and long *rete ridge* is seen and gives a typical condyloma-like appearance.[25]

Vulvar carcinoma is a rare disease but the majority of vulvar cancer cases are squamous cell carcinoma. *Vulvar* squamous cell carcinoma is a female disease in elderly and *post-menopausal* women with a history of LS or vulvar skin epithelial conditions related to *well-differentiated vulvar intra-epithelial neoplasia* (dVIN).[26-28] Most patients are asymptomatic at diagnosis, but some patients experience *pruritus*, burning, or bleeding especially if the cancer is invasive to other tissues.[29] Vulvar carcinoma patients on physical examination show an elevated, flat plaque-like mass accompanied by ulcerated, *polypoid* or wart-like masses on the vulva **(Figure 12).**[30] Based on biopsy results, vulvar squamous cell carcinoma will show typical epithelial cells accompanied by keratinized pearls (horn pearl or *corneal* pearl) (**Figure 13).**[31]**.**



Invasive Squamous Cell Carcinoma. an elevated, flat plaque-like mass accompanied by ulcerated, *polypoid,* or wart-like masses on the vulva. [30]

Figure 13. Histopathology of Squamous Cell Carcinoma. typical epithelial cells accompanied by keratinized pearls (*corneal* pearl).[31]

Immunohistochemical examination of VIN that binds to HPV (*basal* uVIN or *warty* uVIN) found p16 positive and p53 negative while in dVIN generally p53 positive and p16 negative and most vulvar squamous cell carcinomas originate from VIN that binds to HPV.[28,31] The patient's case found negative P16 expression and slightly positive P53 expression. This suggests the patient's case did not bind to HPV. This confirms the findings from histopathology leading to the diagnosis of vulvar lichen sclerosus, as dVIN binds to vulvar lichen sclerosus.

The histopathologic findings in this case were consistent with LSV, with severe hyperkeratosis, basal cell vacuoles, fibrosis and inflammatory cells. Histopathologic and immunohistochemical examinations were performed to exclude the differential diagnosis of VIN and vulvar squamous cell carcinoma. The diagnosis of vulvar squamous cell carcinoma was considered in this case as squamous cell carcinoma is associated with LSV. The differential diagnosis of VIN was also considered in this case because VIN has similar symptoms to this case, namely itching and pain. The supporting examinations performed in this case, namely immunohistochemistry and biopsy, were in accordance with the literature.

The management of LSV can be given in two phases: ultrapotent topical corticosteroid ointment (e.g., clobetasol propionate 0.05%) to induce remission and long-term maintenance therapy with medium potency topical corticosteroids (e.g., betamethasone valerate 0.1%) daily or ultrapotent corticosteroid ointment twice a week. LSV therapy is essential to control symptoms and reduce the risk of squamous cell carcinoma.[9] The gold standard therapy for LS is ultrapotent topical

corticosteroids. According to the *British Association of Dermatologists* (BAD) guidelines for the management of LS, clobetasol propionate ointment 0.5% should be given. Other treatments include calcineurin inhibitors (tacrolimus 0.1% ointment or pimecrolimus 1% cream once or twice daily for 1-2 months) if clobetasol propionate fails or is not tolerated. Systemic therapy may be given for LS that are severe or unresponsive to topical therapy. Systemic therapy should be given after the diagnosis is confirmed by biopsy. Systemic therapies that can be given are systemic retinoids (*etherinate* and *acitrecin)*.[1,5,8] Other systemic therapies such as *hydroxyzine* or *doxepin* can also be given to relieve itching at night. However, guidelines for systemic therapy in LSV are limited.[32,33] Topical corticosteroids have some side effects that are influenced by the extent of the skin area and the potency of the topical corticosteroid. The larger the skin area treated with topical corticosteroids and the higher the potency of the corticosteroid used, the risk of side effects will increase. One of the side effects of topical corticosteroids is ulceration. In LSK, the recommended corticosteroid is clobetasol propionate 0.05% which is classified as class I potency (very high) so the risk of side effects will increase. In addition, the genital area is an area with thin skin so the risk of side effects is also higher. [34] The case in this patient had ulceration so that the condition was one of the reasons why the patient did not get topical corticosteroids.

Emollients or moisturizers are important as LSV therapy to soften and protect LSV skin. Application of moisturizers and paraffin can prevent skin contact with urine so as to relieve symptoms as well as to maintain the effect of topical corticosteroids.[34] Vitamin E can also be given to relieve symptoms after topical corticosteroid administration. Surgery in LSV is only indicated in certain cases such as urethral stenosis, clitoral phimosis, introitus stenosis, and labia adhesia. Energy-based therapies such as photodynamic therapy, *high-intensity focused ultrasound* (HIFU), and *fractional CO2 lasers* (FxCO2) can be performed for LS but further studies are needed. Corticosteroid administration needs to be monitored especially after three months as most side effects appear after 3 months. Antibiotic therapy can be given if there are signs of secondary infection.[1,5,8] A study showed that *penicillin* or *cephalosporin* can relieve symptoms of pain, itching and burning in LSV patients. Phototherapy with UVA1 light is also effective in patients with LSV. After therapy, three months of monitoring is needed to evaluate the patient's condition.[32,33,35]

LSV patients have a low risk of malignancy if diagnosed and treated appropriately. Several studies have shown that patients with controlled LS have a low risk of scarring and carcinoma. Patients with uncomplicated LSV who improve with topical therapy need to *follow-up* twice after the first visit, the first visit after 3 months to assess the response to therapy and assess whether the patient is using topical corticosteroids appropriately and the second visit 6 months later to confirm the patient's condition and discuss whether the patient still has residual symptoms or not. Emollients should be continued and if the patient needs to use topical corticosteroids regularly, the patient should be seen annually by the primary care physician. Long-term monitoring with a specialist should be done if the patient has persistent symptoms, has a history of cancer or suspicion of intraepithelial neoplasia. Biopsy should be performed on persistent lesions to exclude neoplasia or invasive squamous cell carcinoma.[33,35]

This patient was treated with 0.9% NaCl compress for 10-15 minutes, and mupirocin 2% cream applied to the wound twice a day. After three months of , the patient's lesions improved and the patient was given cetirisin 1 x 10 mg orally, zinc 1 x 1 tablet and vaseline album moisturizer to protect her skin.

IV. SUMMARY

Establishing the diagnosis of LSV remains a challenge for the clinician due to non-specific signs and symptoms so biopsy is necessary especially if the patient has suspicious wounds (erosion or ulceration, pigmented areas or ecchymosis, popular or wart-like lesions). The typical histopathologic examination of LSV is severe hyperkeratosis, basal cell vacuoles, fibrosis and inflammatory cells. Immunohistochemical examination was performed to exclude the differential

diagnosis of VIN and squamous cell carcinoma, namely p16 positive and p53 negative, while the patient was found p16 negative and p53 slightly positive in the nuclei of some epidermal basal cells so that the diagnosis of VIN and squamous cell carcinoma could be excluded.

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