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A Retrospective Analysis of 32 Women With Erosive Vulval Lichen Planus and Assessment of Cervical Cancer Screening Results

Eroziv Vulval Liken Planus Tanılı 32 Hastanın Retrospektif Olarak İncelenmesi ve Serviks Kanseri Tarama Sonuçlarının Değerlendirilmesi

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ABSTRACT

Introduction: The aim of this study was to analyze the clinical features of erosive vulval lichen planus (LP) and their coexistence with human papilloma virus (HPV) infection via cervical HPV test results.
Material and Method: The clinical data and results of HPV tests in the medical records of 32 erosive vulval LP patients at Bakırköy Dr. Sadi Konuk Teaching and Research hospital from January 2017 to August 2019 were analyzed retrospectively.
Results: The mean age of vulval LP patients was 57.5± 6.3 years. On examination, the sites of mucosal involvement in vulval LP were the vulva only (56%; 18 patients); vulva, vagina and oral cavity (18%; 6 patients); the vulva and vagina (12%; 4 patients); and vulva and oral cavity (12%; 4 patients). Two patients had only the HPV 16 genotype, one patient had the HPV 11 and 40 genotypes and one patient had the HPV 58 genotype.
Conclusion: Gynecological evaluation was required for all vulval LP patients. Although only four patients had positive HPV test results in our study, we emphasize that the treatment process of vulval LP may have an effect on HPV infection. Nevertheless, further community-based studies are needed.

Key Words: Cervical Cancer Screening, Human Papilloma Virus, Lichen Planus, Vulval

ÖZET

Amaç: Çalışmanın amacı eroziv vulval liken planus (LP) tanılı hastaların klinik özelliklerini ve servikal insan papilloma virüsü (HPV) enfeksiyonu ile birlikteliğini servikal HPV test sonuçları ile analiz etmektir.
Gereç ve Yöntem: 32 eroziv vulval LP tanılı hastanın klinik dataları ve sonuçları Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesinde, Ocak 2017 ve Ağustos 2019 tarihleri arasında retrospektif olarak analiz edildi.
Bulgular: Vulval LP hastalarında ortalama yaş 57.5± 6.3 oalarak saptandı. Yapılan hasta muayenelerinde mukozal tutulum sadece vulvada 12%; 4 hasta); vulva, vajen ve oaral kavitede (18%; 6 hasta); vulva ve vajende (12%; 4 hasta); vulva ve oral kavitede (12%; 4 hasta) olarak değerlendirildi. 2 hastada sadece HPV 16 genotipi, 1 hastada HPV 11 ve 40 genotipi, ve 1 hastada HPV 58 genotipi saptandı.
Sonuç: Jinekolojik değerlendirme tüm vulval LP hastaları için gerekmektedir. Çalışmamızda sadece 4 hastada HPV test pozitifliği saptanmış olmasına rağmen, vulval LP hastalarında uygulanan steroid tedavisinin HPV enfeksiyonunun üzerinde etkileri olabileceğini vurgulamaktayız. Bununla birlikte, toplum temelli daha ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Servikal kanser taraması, İnsan papilloma virüsü, Liken Planus, Vulval

Introduction

Lichen planus (LP) is an uncommon chronic inflammatory disease with histological subtypes that can disturb the skin, oral mucosa, scalp, vagina and vulva (1). Vulval LP is a subtype of LP that is represented by erosive, papular, or hypertrophic lesions on the vulval tissue. The most common type of vulval LP is the erosive subtype (also known as mucosal LP), which can result in serious tissue destruction with vulval pain (2).

The incidence and prevalence of erosive vulval LP has not been definitely established, but vulval

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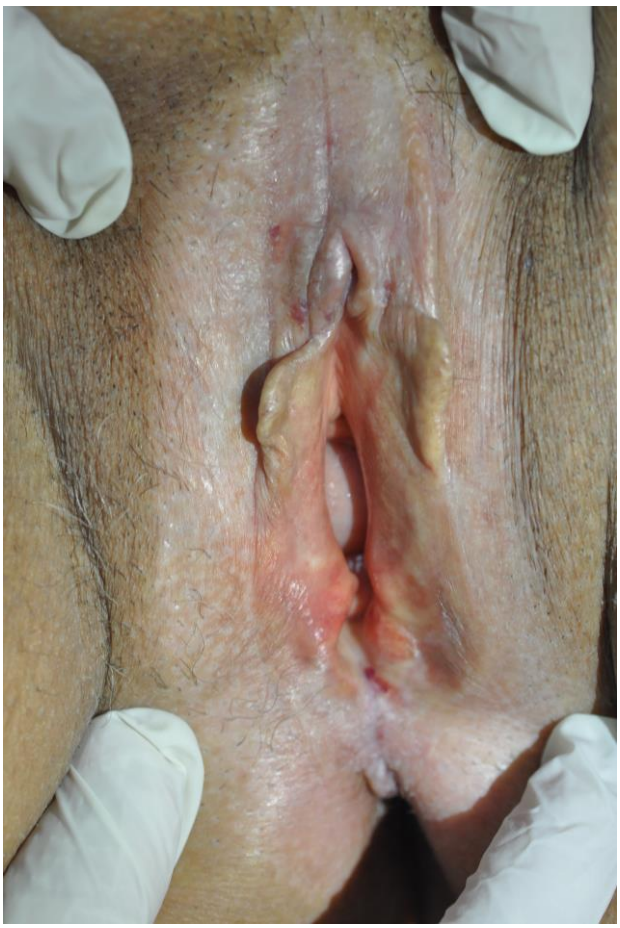

Fig. 1. Characteristic findings in erosive vulval lichen planus. Discoloration and inflammatuar response are seen

disease may be a prevalent manifestation of LP in women. In a series of 37 women diagnosed with LP, vulval lesions were present in 51% of the women (2). Additionally, the etiology of vulval LP is unknown. The features of vulval LP lesions are thought to derive from a T-cell-mediated autoimmune response against keratinocytes (3).

Vulval LP generally develops in women 50 to 60 years of age, though younger and older women can be affected (4,5). Women with vulval LP frequently present with complaints of vulval pain, burning, pruritus, soreness or dyspareunia (6,7). Symptoms of vulval LP can be continual or periodic. A few women are asymptomatic or have isolated minimal symptoms. Studies have shown that over 50% of patients with gingival or mucocutaneous LP also have symptoms of vulval LP (8,9). Periodic aggravations, desquamation on all mucosa membranes and scarring features are prevalent in vulval LP patients. Scarring can lead to significant tissue resorption including atherosis of the vagina and anatomic disruption with a violaceous border (Figure 1).

The erosive, desquamative lesions may involve the vagina. Vaginal involvement has been reported in up to 70% of patients with erosive LP; in contrast, vaginal involvement is rare in lichen sclerosus (10). In addition, vulvo-vagino-gingival syndrome is a subtype of erosive LP in which the disease affects the vulva, vagina and gingival margins (11).

The variability in clinical presentation, lack of other cutaneous signs, unreliability and inconsistent use of histopathology may result in significant diagnostic difficulties (7). Biopsy is commonly recommended for vulval LP, especially in the erosive form of LP. Additionally, clinicopathological diagnostic criteria have been suggested following an electronic Delphi consensus exercise involving experts in the diagnosis and management of vulval disease (7). General agreement was reached on nine diagnostic criteria (Table 1). It was recommended that at least three supportive features be presented to diagnose erosive vulval LP.

A woman with vulvo-vagino-gingival syndrome is at increased risk for vulval squamous cell carcinoma, although the exact rates are unknown (12,13). Additionally, oral LP is considered a premalignant lesion with a prevalence of malignant transformation between 0% and 10% (14). However, the risk of associated cervical precancerous or cancerous lesions with vulval LP and the etiology of disease remain unclear. Due to the natural association between human papillomavirus (HPV) effects and cervical cancer, HPV tests have been qualified, and their efficacy as a procedure for evaluating the cervix has been commonly examined (15). With cumulative data, it is seen that HPV is associated with many diseases such as vulval cancer or cervical precancerous-cancerous lesions.

This is the first retrospective study to evaluate the coexistence between erosive vulval LP and cervical HPV infection. In this study, we aimed to analyze the clinical features and cervical cancer screening results of erosive vulval LP patients.

Materials and Methods

From January 2017 to August 2019, we evaluated the data of 32 women with vulval LP presenting at the tertiary referral vulval specialty clinic of the Department of Obstetrics and Gynecology. Ethical approval was obtained from our hospital's local ethics committee (approval number: 2018/238). Informed consent forms were obtained from each patient participating in the study regarding the use of their photographic and clinical data.

Table 1. Diagnostic criteria for vulval lichen planus.*

Well- demarcated erosions or erythematous areas at the vaginal introitus
Presence of a hyperkeratotic border to lesions
Symptoms
Scarring or loss of normal architecture
Presence of vaginal inflammation
Involvement of other mucosal surfaces
Presence of inflammatory band involving the dermoepidermal junction
Presence of inflammatory band consisting predominantly of lymphocytes
Signs of basal layer degeneration

**At least three of the features in the table should be in the diagnosis of vulval lichen planus*

Anthropometric Evaluation: All patients were examined by the same physician (S.Y.). A complete inspection of the vulval skin, vaginal mucosa and oral mucosa was performed. Physical examination, medical history and cervical HPV test screening (as a routine part of gynecological evaluation) results in all women with a histological diagnosis of vulval LP were analyzed. The patients were diagnosed clinically with the criterias that we mentioned in Table 1. After that, the diagnosis of all patients was confirmed by biopsy. A sample for the histopathological examination of lesions was obtained by a 5 mm punch biopsy. Characteristics of the histopathological findings consisted of hypergranulosis, irregular acanthosis, vacuolar alteration of the basal layer, orthokeratosis and a bandlike lymphocytic infiltrate in the dermis. Necrotic keratinocytes, also referred to as colloid, hyaline, cytoid, or Civatte bodies, are frequently seen in the lower epidermis and especially in the papillary dermis (16). The body mass index (BMI) was calculated as the weight (kg) divided by the square of the height (m^2).

Cervical Cancer Screening and Management: According to the national cervical screening program, the first cervical screening test is recommended at the age of 21 years, and women <30 years old are screened only with the Papanicolaou (PAP) test every three years. Women >30 years old are screened with both HPV testing and liquid-based cervical cytology every five years (17). Two cervical swab specimens were obtained from the women. The first specimen was assembled and spread onto a thin plate for cytological evaluation. The second specimen was obtained with a different swab, and the end of the swab was separated. Then, the specimen was inserted into Standard Transport Medium (STM) for HPV-DNA examination. Nationwide specimens are delivered to two national laboratories for cervical cancer prevention plans. After that, the Hybrid Capture 2 assay (Qiagen, Germany) order was utilized for HPV-DNA examination. This method identifies 13 varied high-risk HPV genotypes (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) and describes the analysis results as positive or negative. The results of the analysis of HPV status, HPV genotype, and cytology (when HPV-positive) are registered into a national screening software system, and the patient's family physician/nurse at primary healthcare centers is informed of the results (18). Additionally, the results of HPV tests are printed and delivered to the patient. These test results are recorded when the patient is evaluated at our vulval outpatient clinic.

Statistical analysis: The medical data of HPV tests and clinical outcomes were analyzed. Data examination was completed with SPSS (version 20.0; SPSS Inc., Chicago, IL, USA). Descriptive statistics are presented as frequencies in the text and tables.

Results

The study consisted of 32 patients with a mean age of 57 years (range 32-72). The characteristics of women with vulval LP are shown in Table 2. The mean parity number was 3.01±1.95. Additionally, the mean BMI score was 28.0±4.22. Four- patients had autoimmune thyroid disease and one- patient had celiac disease. One- patient had a family history of LP. The symptoms of vulval LP were vulval pruritus (68%; 22 patients), dyspareunia (62%; 20 patients), vulval burning (56%; 18 patients), gums that bleed easily (12%; 4 patients), vaginal discharge (6%; 2 patients) and dysuria (6%; 2 patients). Thirty-one patients could determine the lenght of time they had experienced symptoms of vulval LP. Two- patients reported that they had experienced symptoms of disease for up to ten years. On examination, the sites of

Table 2. Characteristics of 32 women presenting with vulval lichen planus

Characteristic	Value*
Age at diagnosis, y	
Mean±(SD)	57.5± (6.3)
Range	32.0-72.0
Parity	
Mean±(SD)	3.01±1.95
BMI (kg/m2)	
Mean±(SD)	28.0±4.22
Autoimmun Diseases	5 (15%)
Thyroid disease	4 (12%)
Celiac disease	1 (3%)
Family history of lichen planus	1 (3%)
Duration of complaints (categorical,y)	
0-1	8 (25%)
1-2	8 (25%)
2-5	9 (28%)
5-10	4 (12%)
>10	2 (6%)
unknown	1 (3%)
Complaints at first examination	
Vulval pruritus	22 (68%)
Dysparenuia	20 (62%)
Vulval burning	18 (56%)
Easily bleeding gums	4 (12%)
Vaginal discharge	2 (6%)
Dysuria	2 (6%)
Mucosal tissue involvement	
Only vulva	18 (56%)
Vulva, vagina, oral cavity	6 (18%)
Vulva, vagina	4 (12%)
Vulva, oral cavity	4 (12%)

BMI body mass index*, SD* standart deviation. *Values are designed as a number and percantage of patient unless specified otherwise

mucosal involvement with vulval LP were the vulva only (56%; 18 patients); vulva- vagina- and oral cavity (18%; 6 patients); vulva- and vagina (12%; 4 patients) and the vulva- and oral cavity (12%; 4 patients).

Four- patients (12%) in the vulval LP cohort had positive cervical HPV test screening results. Two- patients had only the HPV 16 genotype, one patient had the HPV 11 and 40 genotypes, and one- patient had the HPV 58 genotype. All HPV-positive patients with vulval LP had normal cytological results (Table 3). Additionally, four cases with HPV positive cervical test results were evaluated with colposcopy and no clinical or pathological findings were detected.

In this study, four women (12%) were initially managed with a medium-potency topical steroid (mometasone furoate 0.1% lotion), and twenty patients (62%) were initially managed with high potency topical steroid (clobetasol propionate 0.05% ointment). Twelve patients (37%) were treated with topical calcineurin inhibitors: four patients (12%) with tacrolimus 0.1% oinment and eight patients (25%) with pimecrolimus 1% cream. Four patients (12%) were managed with a combination of topical steroids and calcineurin inhibitor therapy. Twenty of the patients were treated with systemic therapy, such as oral corticosteroid (50%; 16 patients) and methotrexate (%12; 4 patients) (Table 4).

Table 3. Summary of positive HPV test results with vulval lichen planus

Age at diagnosis of HPV infection	Duration of vulval LP	Complaints at first visit	Mucosal lesion	HPV Genotypes	Cytologic result
Patient 1, 42 y	3 y	Pruritus, dysparenuia	Only vulva	HPV 16	normal
Patient 2, 50 y	>10 y	Pruritus, pain	Only vulva	HPV 11,40	normal
Patient 3, 54 y	8 y	Pruritus, vaginal discharge	Only vulva	HPV 58	normal
Patient 4, 52 y	8 y	Pruritus, burning	Only vulva	HPV 16	normal

HPV human papillomavirus, *LP* lichen planus

Table 4. Treatment of vulval lichen planus patients

Management	Patients n (%)*
Topical steroid therapy	24 (75%)
Moderate steroids	4 (12%)
Superpotent steroids	20 (62%)
Topical calcineurin inhibitors	12 (37%)
Tacrolimus	4 (12%)
Pimecrolimus	8 (25%)
Combination of topical therapy	4 (12%)
Tacrolimus and superpotent steroid	1 (3%)
Pimecrolimus and superpotent steroid	3 (9%)
Systemic therapy	20 (62%)
Oral corticosteroids	16 (50%)
Methotrexate	4 (12%)

*Values are designed as a number and percantage

Discussion

Our study was a retrospective analysis of patients with a rare disease, vulval LP, at a tertiary referral vulval speciality clinic. Additionally, this study is the first in the literature to consider the coexistence of vulval LP and HPV infection via cervical cancer screening results.

LP is a disease that is relatively difficult to diagnose and manage. This disease generally occurs in the 60s, with an average age of the initiation of symptoms between 48 and 58 years (16,19). In our study the mean age was 57.5 years. A few retrospective studies are available in the literature (2,20,21). In our study, vulval pruritus (68%) was the most commonly recorded symptom. Lindy et al. (20) suggested that the most common presented symptoms were dyspareunia (54%), vulval burning (50%) and vulval pruritus (48%). In addition, the mucosal sites involved in women with vulval LP in our study were the vulva only (56%); the vulva-, vagina-, and oral cavity (18%); the vulva- and vagina (12%); and the vulva- and oral cavity (12%). Moreover, oral mucosal involvement with vulval LP was reported in several studies (11). We reported 10 women (31%) with oral LP lesions. The inspection of the oral cavity mucosa should be performed carefully on vulval LP patients. This careful inspection can be used to differentiate the diagnosis of LP from that of lichen sclerosis.

The mucosal immune system is associated with genetic status, environmental effects and aging. LP may develop in patients that are predisposed by these effects. Fahy et al. (21) suggest that the percentage of association of autoimmune disease with vulval LP is 22%. In our study five patients (15%) with autoimmune disease developed vulval LP.

One hypothesis is that hypersensitivity to an antigen may play a role in disease etiology (3). This hypersensitivity is thought to be associated

with a viral- specific T-cell response such as in hepatitis C (22). However, Cooper et al. (22) found no evidence for a relationship between hepatitis B or C viruses and genital LP. Additionally, Boyd and Leonardi (23) investigated vulval biopsies with cutaneous LP, searching for HPV: no HPV-DNA was demonstrated. Additionally, only four patients (12%) had positive cervical HPV-DNA test results in our study. We detected two positive results for high-risk HPV genotypes (HPV-16-positive, normal cervical cytology) and two positive results for low risk HPV types (HPV-11-40-positive, normal cervical cytology; HPV-58-positive, normal cervical cytology). According to these results, it is unlikely that cervical HPV types act in the etiology of mucosal vulval LP. In more descriptive terms, we did not found a definitive association between vulval LP and cervical HPV infection. Additionally, more comprehensive studies are needed on this subject.

Multiple treatment options are feasible for vulval LP such as local and systemic steroids, oral methotrexate and topical calcineurin inhibitors (24). Nevertheless, often high-potent topical steroids are used for the initial treatment. In addition, tacrolimus and pimecrolimus agents were used in the case of steroid treatment failure. As in classical vulvar LP management, our department also uses high-potent topical steroids as an initial treatment for vulvar LP patients. According to each patient's specific evaluation, systemic steroids, oral methotrexate or topical calcineurin inhibitors are included in treatment of vulval LP patients in case of local steroid failure or inadequate clinical response to treatment. Additionally, in our study the most commonly used treatment was superpotent topical steroids and a remarkable number of patients were managed with calcineurin topical steroids.

High-risk HPVs is the most significant etiological agent for cervical cancerous lesions. However, the relationship with vulval cancerous lesions is less significant, as high-risk HPV has been observed in less than 50% of patients; in addition, a prolonged immune reaction may act as in a significant and very likely interdependent and pathophysiological role (25). In light of these suggestions, we think it is significant to discuss the possible reactivation or activation of HPV infection after or during extended steroid treatment. Classically, high-potent steroid therapy is used as an initial treatment in vulval LP patients. Additionally, we propose that patients should be monitored for cervical cancer screening before or during steroid or other treatment options of vulval LP. In addition, we suggest that patients with the high-risk HPV-DNA genotype and vulval LP must be followed at frequent intervals due to the possibility of being affected negatively by prolonged steroid treatment. The cervical inspection should be performed carefully with speculum examination at all outpatient visits. The intraepithelial cervical examination of patients should be performed by colposcopy.

Additionally, vulval LP patients are often challenged with anatomical, sexological and urogynecological problems. Moreover, due to the postmenopausal nature of this disease, the importance of urogynecological evaluation is increased. Further studies are needed on the sexological and urogynecological aspects of vulval LP disease. Therefore, our study also emphasizes the significance of the involvement of urogynecological specialty clinics in the management of vulval LP that requires special attention.

The main limitation of this study is that it is a retrospective patient analysis of a relatively small cohort. Selection bias was prevented by the inclusion of only patients who had a confirmed pathological diagnosis. The long-term outcomes of vulval LP could not be analyzed because patient follow-up was performed for a relatively short time.

In conclusion, the diagnosis, management and cervical cancer screening of vulval LP is important. Vulval LP patients should be evaluated in detail and attention should also be paid to oral LP lesions. Additionally, in patients with vulval LP, it is necessary to examine the cervical mucosa carefully. Gynecological assessment and urogynecological evaluation are required for all vulval LP patients. Furthermore, in addition to dermatological monitoring, a gynecological multidisciplinary approach should also be followed. Additionally, further clinical research is warranted on the molecular association of HPV with vulval LP, which may provide new management approaches for vulval LP and HPV-positive patients.

References

1. Eisen D. The evaluation of cutaneous, genital, scalp, nail, and ocular involvement in patients with oral lichen planus. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 88 1999; 88: 431.
2. Lewis FM, Shah M, Harrington CI. Vulval involvement in lichen planus: a study of 37

women. Br J D ermatol 1996; 135: 89.

3. Sugerman PB, Satterwhite K, Bigby M. Autocytotoxic T-cell clones in lichen planus. Br J Dermatol 2000; 142: 449-456.
4. Kennedy CM, Galaks RP. Erosive vulvar lichen planus: retrospective review and outcomes in 113 patients seen in a vulvar specialty clinic. J Reprod Med 2007; 52: 43.
5. Cooper SM, Wojnarowska F. Influence of treatment of erosive lichen planus of the vulva on its prognosis. Arch Dermatol 2006; 142: 289.
6. Cooper SM, Hafner HK, Abrahams-Gessel S, Margesson LJ. Vulvovaginal lichen planus treatment: a survey of current practices. Arch Dermatol 2008; 144: 1520.
7. Simpson RC, Thomas KS, Leighton P, Murphy R. Diagnostic criteria for erosive lichen planus affecting the vulva: an international electronic-Delphi consensus exercise. Br J Dermatol2013; 169: 337.
8. Moyal-Barracco M, Wending J. Vulvar dermatosis Best Pract Res Clin Obstet Gynaecol 2014; 28(7): 946-958.
9. Bhattacharya M, Kaur I, Kumar B. Lichen planus: a clinical and epidemiological study. J Dermatol 2000; 27(9): 576-582.
10. Zendell K, Edwards L. Lichen sclerosus with vaginal involvement: report of 2 cases and review of the literature. JAMA Dermatol 2013; 149: 1199.
11. Belfiore P, Di Fede O, Cabibi D, Campisi G, Amaru GS, De Cantis S et al. Prevalence of vulval lichen planus in a cohort of women with oral lichen planus: an interdisciplinary study. Br J Dermatol 2006; 155(5): 994-998.
12. Regauer S, Reich O, Eberz B. Vulvar cancers in women with vulvar lichen planus: a clinicopathological study. J Am Acad Dermatol 2014; 71(4): 698-707.
13. Kennedy CM, Peterson LB, Galaks RP. Erosive vulvar lichen planus: a cohort at risk for cancer? J Reprod Med 2008; 53(10): (2008) 781-784.
14. Irani S, Esfahani AM, Ghorbani A. Dysplastic change rate in cases of oral lichen planus: a retrospective study of 112 cases in an Iranian population. J Oral Maxillofac Pathol 2016; 20(3): 395-399.
15. Arbyn M, Anttila A, Jordan J, Ronco G, Schenck U, Segnan N et al. European guidelines for quality assurance in cervical cancer screening, Second edition–summary document. Ann Oncol 2010; 21(3): 448–458.
16. Kirtschig G, Wakelin S, Wojnarowska F. Mucosal vulval lichen planus: outcome, clinical and laboratory features. J Eur Acad Dermatol Venerol 2005; 19: 301-307.
17. https://hsgm.saglik.gov.tr/tr/kanser-tarama-standartlari/listesi/483-serviks- kanseri-tarama-program%C4%B1-ulusal-standartlar%C4%B1.html. Accessed date; January 27, (2019).
18. Gultekin M, Karaca MZ, Kucukyildiz I, Dundar S, Keskinkilic B, Turkyilmaz M. Mega Hpv laboratories for cervical cancer control: Challenges and recommendations from a case study of Turkey. Papillomavirus Res 2019; 7: 118-122.
19. Lotery HE, Galaks RP, Erosive lichen planus of the vulva and vagina. Obstet Gynecol 2003; 101: 1121-1125.
20. Santegoest LA, Helmerhost TJ, van der Meijden WI. A retrospective study of 95 women with a clinical diagnosis of genital lichen planus. J Low Genit Tract Dis 2010; 14(4): 323-328.
21. Fahy CMR, Torgerson RR, Davis MDP. Lichen planus affecting the femal genitalia: A retrospective review of patients at Mayo Clinic. L Amad Dermatol 2017; 77(6): 1053-1059.
22. Cooper SM, Kirtschig G, Jeffery KJM, Wojnarowska F. No association between hepatitis B or C viruses and vulval lichen planus in a UK population. BJOG 2204; 111: 271-273.
23. Boyd AS, Leonardi CL. Absence of human papillomavirus infection in cutaneous lichen planus. J Am Acad Dermatol 1997; 36: 267-268.
24. Scardina GA, Messina P, Carini G, Maresi E. A randomized trial assessing the effectiveness of different concentrations of isotretionin in the management of lichen planus. Int J Oral Maxillofac Surg 2006; 35: 67-71.
25. Von Krogh G, Horenblas S. Diagnosis and clinical presentation of premalignant lesions of the penis. Scand J Urol Neprol 2000: 205: 201-214.