Vulvar cancers in women with vulvar lichen planus: A clinicopathological study

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Background: Vulvar squamous cell carcinomas (SCCs) arising in association with vulvar lichen planus (LP) are poorly documented.

Objectives: We sought to present clinicopathological features of 38 patients (median age 61 years, range 39-90 years) with LP-associated vulvar SCCs.

Methods: Evaluated were location of vulvar SCC and metastases at presentation, recurrences, survival, precursor lesions, presence of human papillomavirus DNA, $p16^{ink4a}$, and p53 expression.

Results: In all, 32 solitary (5 pT1a, 20 pT1b, 7 pT2) and 6 multifocal SCCs, located in the vestibulum (n = 20) and in nonhair-bearing modified and glycogenated mucosa (n = 18), arose in erosive (n = 13) and nonerosive (n = 25) LP. All SCCs were human papillomavirus DNA and $p16^{ink4a}$ negative. Sixteen of 38 (42%) women had inguinal metastases at presentation. Treatment was surgery with clear margins (36/38) and chemoradiation (2/38). Fourteen of 36 (39%) surgically treated patients developed between 1 and 5 new SCCs in the residual diseased mucosa. Of all recurrences, 68% developed within 12 months via precursors revealing various histologic features including elongated, but also flat rete ridges, basaloid and hypertrophic differentiation with inconsistent p53 expression. Fourteen of 38 (37%) patients died of SCCs.

Limitations: Retrospective study and lack of a standardized treatment protocols are limitations.

Conclusion: LP-associated SCCs were located in nonhair-bearing vulvar mucosa. Patients had a high rate of inguinal metastases, recurrent vulvar cancers in diseased mucosa, and disease-related death. (J Am Acad Dermatol 2014;71:698-707.)

Key words: differentiated vulvar intraepithelial neoplasia; human papillomavirus–negative vulvar carcinoma; precursor lesions; vulvar dermatosis; vulvar squamous cell carcinoma.

Lichen planus (LP) is a chronic inflammatory autoimmune dermatosis with a prevalence of 1% to 2% in the general population. LP may involve extragenital and genital skin along with mucosal surfaces. In the vulva, presentation of LP depends on site of involvement. In vulvar hair-bearing skin of mons pubis and labia majora, and modified mucosa of interlabial sulci, labia minora, clitoris, and perineum, LP is characterized by individual white or skin-colored papules or plaques. The erosive variant of LP with typical Wickham striae is seen in the glycogenated squamous mucosa of vestibule, introitus vaginae

Abbreviations used:

d-VIN:	differentiated vulvar intraepithelial neoplasia
HPV:	human papillomavirus
LP:	lichen planus
SCC:	squamous cell carcinoma

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and vagina, often referred to as "lichen ruber planus."[1,2] The risk of a patient developing a squamous cell carcinoma (SCC) depends on the site of involvement of LP. Although LP in extragenital skin has no cancer risk, a 5% risk has been described in oral and esophageal mucosa.[3] Recently, LP has been recognized as an associated condition in human papillomavirus (HPV)-negative penile SCCs.[4,5] In contrast, although the association of vulvar LP and SCC was reported as early as 1989,[6] the association of vulvar SCC with LP is poorly documented with either case reports only or brief mention in larger series dealing with diagnoses and treatment of vulvar LP.[1,7-12] Only 1 larger series reported the association of LP in 5 of 23 anogenital SCCs.[13] The risk for cancer in vulvar LP is unknown, as are the typical sites of involvement, the type of precursor lesions, and clinical characteristics of LP-associated SCC.

CAPSULE SUMMARY

- Lichen planus (LP) in oral and esophageal mucosa has a cancer risk of up to 5%, and LP is recognized as a risk factor for penile human papillomavirus–negative cancer. The association of vulvar LP and cancer, however, is poorly documented.
- Vulvar LP-associated human papillomavirus–negative squamous cell carcinomas are located in nonhairy vulvar mucosa, particularly in the vestibulum, have a high percentage of inguinal metastases at presentation, and have a high rate of recurrent cancer in residual diseased mucosa.
- The high risk for squamous cell carcinoma in vulvar mucosal LP suggests the need for regular and close monitoring.

Vulvar SCCs can be divided according to cause into cancers induced by HPV and those arising independently of HPV[14] through precursor lesions called "differentiated vulvar intraepithelial neoplasia" (d-VIN),[14,15] originally described as "differentiated simplex in situ SCC."[16] The origin of HPV-negative SCCs is unclear, although mutations in the p53 gene have been suggested[17,18] and the association of HPV-negative SCC with lichen sclerosus, a common vulvar dermatosis with a prevalence of up to 8% in gynecologic practices,[19] is well accepted. The aim of this article is to document clinical and histologic features of a large series of vulvar SCCs arising in the background of LP to elucidate possible LP-specific characteristics.

METHODS

In all, 38 patients with a primary LP-associated vulvar SCC were treated at the Department of Gynecology at the Medical University Graz, Austria, during the past 12 years. All cancers were classified according to the seventh edition of TNM classification of malignant tumors[20]: pT1a SCCs are tumors 2 cm or less in greatest diameter and with stromal invasion no greater than 1.0 mm; pT1b SCC are tumors greater 2 cm in greatest diameter or with stromal invasion greater than 1.0 mm; pT2 SCCs are tumors of any size with extension to adjacent structures (lower third urethra, lower third vagina, anus); and pT3 SCCs are tumors of any size with extension to the following structures: upper two thirds of urethra, upper two thirds of vagina, bladder mucosa, rectal mucosa, or fixed to pubic bone. Entry criteria were an unequivocal (clinical and histologic) diagnosis of LP and a minimum follow-up of 12 months, unless the end point death or recurrence occurred earlier. LP was divided into erosive and nonerosive forms, and extent of vulvar scarring was reported.[1] LP was diagnosed clinically and confirmed histologically, following published criteria.[21] Formalin-fixed and paraffin-embedded archival tissues from the Institute of Pathology at the Medical University Graz, Austria, were evaluated for HPV DNA (INNO-LiPA HPV Genotyping Extra, Innogenetics Diagnostic, Heiden, Germany). All primary and recurrent invasive SCCs and precursors were evaluated by immunohistochemistry with monoclonal antibody to p53 (clone DO-7; DAKO, Corp, Capinteria, CA) and $p16^{ink4a}$ (Roche Diagnostics, Indianapolis, IN, formerly MTM Laboratories, Heidelberg, Germany), an indirect marker for a transforming infection with HPV high-risk genotypes. Institutional ethics committee approval and research study approval for this study was obtained (Medical University, EK number 20-255ex 08/09). All patients gave consent to photographic documentation.

RESULTS

I Clinical characteristics of primary LP-associated SCC

See Table I. In all, 38 women (median age 61 years at diagnosis; range 39-90 years; 9 premenopausal and 29 postmenopausal) with a primary vulvar SCC arising in nonerosive vulvar LP (n = 25) (Fig 1, *A* to *H*) and erosive LP (n = 13) were evaluated. The nonerosive form of LP presented either as skin-colored or white, individual or multiple papules (n = 13) (Fig 1, *A* and *C* to *F*) or larger, partly

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