Vulvar Lichen Sclerosus and Neoplastic Transformation: A Retrospective Study of 976 Cases

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Objective: The aim of the study was to estimate the neoplastic potential of vulvar lichen sclerosus (VLS).

Materials and Methods: This was a retrospective study of 976 women with VLS. We recorded age at diagnosis of VLS, length of follow-up, and type of neoplasia, categorized as the following: (1) vulvar intraepithelial neoplasia (VIN), further subdivided in differentiated VIN (dVIN) and high-grade squamous intraepithelial lesion; (2) superficially invasive squamous cell carcinoma; and (3) frankly invasive squamous cell carcinoma. Neoplasia incidence risk, neoplasia incidence rate, and cumulative probability of progression to neoplasia according to the Kaplan-Meier method were estimated. Log-rank test was used to compare the progression-free survival curves by age at diagnosis of VLS.

Results: The mean age at diagnosis of VLS was 60 (median = 60; range = 8–91) years. The mean length of follow-up was 52 (median = 21; range = 1–331) months. The following 34 patients developed a neoplasia: 8 VIN (4 dVIN, 4 high-grade squamous intraepithelial lesions), 6 keratinizing superficially invasive squamous cell carcinoma (5 with adjacent dVIN), and 20 keratinizing invasive squamous cell carcinoma (1 with adjacent dVIN). The neoplasia incidence risk was 3.5%. The neoplasia incidence rate was 8.1 per 1,000 person-years. The cumulative probability of progression to neoplasia increased from 1.2% at 24 months to 36.8% at 300 months. The median progression-free survival was significantly shorter in older women (≥70 years) when compared with that in younger women (p = .003).

Conclusions: Vulvar lichen sclerosus has a nonnegligible risk of neoplastic transformation and requires a careful and lifelong follow-up in all patients, particularly in elderly women. Early clinical and histological detection of preinvasive lesions is essential to reduce the risk of vulvar cancer.

Key Words: vulvar lichen sclerosus, lichen sclerosus, vulvar neoplasms, squamous cell carcinoma, retrospective study

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According to the current International Society for the Study of Vulvovaginal Disease (ISSVD) terminology, vulvar lichen sclerosus (VLS) is included in the vulvar dermatoses, which are considered nonneoplastic, noninfectious, dermatologic disorders.[1] In spite of this, the literature suggests that VLS has the potential for neoplastic transformation. Specifically, differentiated vulvar intraepithelial neoplasia (dVIN) and subsequently keratinizing squamous cell carcinoma (keratinizing SCC) can develop within VLS.[2]

The evaluation of the neoplastic potential of VLS has been carried out in 2 different ways, firstly, through histopathological studies of the lesions adjacent to neoplasms. These studies show that VLS, dVIN, and keratinizing SCC are frequently associated with each other.[3] However, in these studies, there is no evidence of temporality, because coexistence of VLS and neoplasia does not imply that VLS preceded the neoplasia. Therefore, they do not provide information about the progression from VLS to neoplasia.

The second approach has been carried out in the form of follow-up studies, in which patients with VLS are followed over time until a neoplasia develops. These studies establish temporality, and thus, they provide information about progression from VLS to neoplasia. However, nearly all of the studies published before the 1975 ISSVD classification of vulvar distrophies[4] contain data that are unusable, because they use poorly defined terminology (such as leukoplakia, kraurosis, dystrophy) and lack uniform diagnostic criteria for lichen sclerosus.[5–10] The 1975 ISSVD classification of vulvar distrophies introduced VLS as a separate entity with clearly defined clinical and histological features.[4] In the studies after 1975, the mean incidence risk of developing neoplasia in women with VLS is 2.8%.[11–20] However, there is a high variability in incidence risk reported, ranging from 0%[17] to 31.3%,[14] and therefore, the exact risk of neoplastic transformation of VLS is uncertain.

The aim of the study was to estimate the neoplastic potential of VLS retrospectively in a large series of women diagnosed with VLS.

MATERIALS AND METHODS

This was a noncomparative observational retrospective case series study.[21] The study was approved by the institutional review board of the Sant'Anna Hospital, University of Torino, in Italy and the research was carried out in accordance with the Declaration of Helsinki (2013) of the World Medical Association. All patients signed a written informed consent to participate in potential future clinical research at their first clinical visit.

Clinical charts and pathology reports (but not original slides) of 1,511 women with clinical alone (n = 799) or both clinical and histological (n = 712) diagnosis of VLS who were seen at the vulvar clinic of the Department of Gynecology and Obstetrics of the University of Torino between November 1981 and July 2014 were reviewed retrospectively. From the 1,511 cases screened, 976 women diagnosed with having VLS on the basis of clinical examination alone (n = 546) or on the basis of both clinical and histological features (n = 430) remained under our care, with at least 1-month follow-up, and were therefore included in the study. Diagnosis of VLS was made at the first visit. Cases with clinical diagnosis of VLS along with cases with histological diagnosis were included in the study population, because the diagnosis of VLS is based on the typical clinical appearance of VLS, and biopsy should only be performed in clinically dubious cases.[22] None of the patients included in the study had a history of vulvar neoplasms before or at the time of diagnosis. Follow-up was performed at

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This study was approved by the institutional review board of the Sant'Anna Hospital, University of Torino, in Italy.

TABLE 1. Neoplasia Incidence Risk and Neoplasia Incidence Rate

Neoplasia (no.)	Incidence risk, %	Incidence rate (no. per 1,000 person-years)
dVIN (4)	0.4	1.0
HSIL (4)	0.4	1.0
SISCC (6)	0.6	1.4
ISCC (20)	2.1	4.7
Total (34)	3.5	8.1

dVIN indicates differentiated vulvar intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesion; SISCC, superficially invasive squamous cell carcinoma; ISCC, frankly invasive squamous cell carcinoma.

1 month, 4 months, and then at least yearly, according to patients' need.

The following data were obtained from archive files: age at diagnosis of VLS, length of follow-up, and type of neoplasia, categorized as: (1) VIN, further subdivided into dVIN and high-grade squamous intraepithelial lesion (HSIL); (2) superficially invasive squamous cell carcinoma (SISCC), with 1 mm or less of invasion; (3) frankly invasive squamous cell carcinoma (ISCC), with greater than 1 mm of invasion. Regarding SISCC and ISCC, the histologic type (keratinizing, basaloid, or warty) and the adjacent lesions were recorded. All cases of neoplasia were confirmed histologically.

We estimated neoplasia incidence risk, defined as the proportion of VLS women initially free of neoplasia who developed a neoplasia within the follow-up period, and neoplasia incidence rate, defined as a measure of the frequency with which a neoplasia occurs in a population for a period (i.e., yearly). We estimated cumulative probability of progression to neoplasia at 24, 60, 120, 160, 240, and 300 months according to the Kaplan-Meier method. Progression-free survival was defined as the time from the VLS diagnosis to the diagnosis of neoplasia (VIN, SISCC, or ISCC).

Women without progression to neoplasia at their last follow-up visit were defined as censored. To analyze the effect of age at diagnosis of VLS as a prognostic factor for neoplastic transformation, we classified women into the following 3 groups on the basis of a previous follow-up study:[16] younger than 50 years (n = 183), 50–69 years (n = 568), and 70 years or older (n = 225). Log-rank test was employed to compare the progression-free survival curves by age at diagnosis of VLS. All tests were 2 sided and considered statistically significant at a p value of less than.05. All analyses were performed using SAS 9.3 (SAS Institute Inc, Cary, NC).

RESULTS

The mean age at diagnosis of VLS was 60 (median = 60; range = 8–91) years. The mean length of follow-up was 52 (median = 21; range = 1–331) months. The following 34 patients developed a neoplasia: 8 VIN (4 dVIN, 4 HSIL), 6 SISCC, and 20 ISCC. All SISCC and ISCC were of the keratinizing type. Vulvar lichen sclerosus was reported as an adjacent lesion in all keratinizing SISCC and in 8 keratinizing ISCC (40%). Vulvar lichen sclerosus associated with dVIN was reported in 5 keratinizing SISCC (83.3%) and in 1 keratinizing ISCC (5%).

Incidence risk and incidence rate according to neoplasm type are shown in Table 1. Overall neoplasia incidence risk was 3.5%, and neoplasia incidence rate was 8.1 per 1,000 person-years. The cumulative probability of progression to neoplasia increased from 1.2% at 24 months to 36.8% at 300 months (see Table 2). Progression-free survival curve is plotted in Figure 1. The comparison of the progression-free survival curves by age at diagnosis of VLS is illustrated in Figure 2. The median neoplasia-free survival was significantly shorter in patients aged 70 years or older when compared with younger women: 196 months (95% CI = 143.0–249.6) in elderly women compared with not reached median survival in younger women (log-rank test, p = .003). The sample size for dVIN, HSIL, and SISCC cases was insufficient to obtain separate progression-free survival curves.

DISCUSSION

Neoplasia incidence risk in this study was 3.5%, which is comparable with the mean incidence risk reported in previous follow-up studies published since 1975,[11–20] when ISSVD introduced clear clinical and histological criteria for diagnosis of VLS.[4] The smallest of these studies, with only 32 patients, reports the highest neoplasia incidence risk (31.3%) in the literature.[14] This study was performed by a pathology laboratory service, where patients presumably underwent biopsy by their clinicians because of some clinical concern. This selection bias would be expected to increase the incidence risk of neoplasia.

Our results suggest that nearly 1% of patients diagnosed with VLS can develop a neoplasia every year. The Kaplan-Meyer survival curve showed that the cumulative probability of progression to neoplasia increases from approximately 1% at 2-year follow-up to nearly 37% at 25-year follow-up. Lifelong follow-up is therefore necessary.

Furthermore, the comparison of the progression-free survival curves by age at diagnosis showed a higher probability of neoplasia occurrence in women older than 70 years. Because the duration of lesions or symptoms were not always recorded in the medical archives at the first visit, it was not possible to determine whether the higher probability of neoplasia occurrence observed in elderly women was a consequence of age-related risk factors, such as immune dysregulation,[23] or because of longer-standing lesions at diagnosis of VLS. However, a previous retrospective case-control study showed that in VLS, advanced age is independent risk factor for developing SCC.[24]

TABLE 2. Cumulative Probability of Progression to Neoplasia

Months of follow-up	No. (%) of patients still in follow-up	Cumulative probability of progression to neoplasia, %[a]
24	479 (49.1)	1.2 ± 0.01
60	276 (28.3)	3.0 ± 0.01
120	141 (14.4)	7.1 ± 0.02
180	69 (7.1)	11.0 ± 0.03
240	25 (2.6)	21.6 ± 0.05
300	3 (0.3)	36.8 ± 0.09

[a]Data are presented as percent ± standard error.

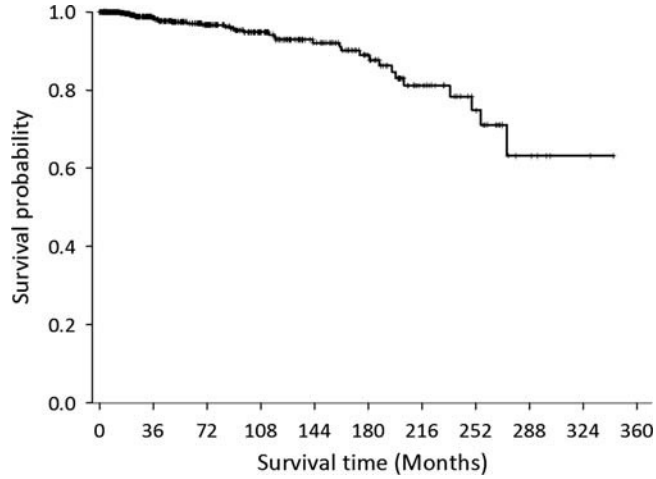

FIGURE 1. Curve of progression-free survival of women with VLS.

In most (83%) of keratinizing SISCC of this study, both VLS and dVIN lesions were reported in peritumoral areas. This finding is in agreement with the previously described carcinogenic pathway, which proposes a progression from VLS to keratinizing SCC through dVIN.[2] In contrast, dVIN along with VLS was rarely reported (5%) as adjacent lesion to ISCC. A possible explanation is that the ISCC replaced or obliterated the precursor lesion or that dVIN was not diagnosed or reported in pathological report.

In our study, women with VLS developed less dVIN than keratinizing SCC. Two possible explanations for the low incidence of dVINs are (1) that it is a transient intraepithelial lesion that rapidly progresses to invasive carcinoma or (2) that it is an underdiagnosed lesion because of its difficult clinical and histological recognition.[25] The latter is further supported by a recent study on the basis of a careful review of previously reported histological specimens, where dVIN was found in 42% of lesions previously diagnosed with VLS, which progressed to vulvar SCC.[26] Rapid progression to neoplasia or its underdiagnosis could also explain why dVIN accounts for only 2% to 10% of all reported VIN in the literature.[2] Our study showed that dVIN was frequently found adjacent to SISCC lesions, which implies that careful clinical surveillance could allow for the early identification of dVIN lesions before invasive carcinoma has supervened.

Vulvar HSIL refers to vulvar HSIL related to human papillomavirus (HPV) and it is the precursor lesion of basaloid or warty type vulvar SCC.[2,27–29] A patient with VLS can be infected with HPV, so she can develop not only dVIN, but also HSIL and subsequently basaloid or warty vulvar SCC. It is possible that VLS could also act as cofactor in the HPV-dependent carcinogenic pathway. This observation may account for the 4 cases of HSIL arising within VLS background reported in our study. These 4 women with HSIL and VLS underwent surgical excision of HSIL, without recurrence of HSIL or progression to invasive cancer by their last follow-up visit.

Our study aims to clarify the extent of the risk of neoplastic transformation from VLS; however, it cannot establish a direct link between VLS and vulvar neoplasms, because it is a noncomparative observational retrospective study,[21] and therefore lacks a healthy control group. Nonetheless, causality is supported by a previous cohort study, reporting that the risk of developing cancer in women with VLS is more than 300-fold when compared with unaffected women of similar age.[13]

This study did not explore the role of VLS treatment in the prevention of the malignant transformation of VLS, mainly due to the variability of the treatment regimens used over time (i.e., changes in products used, vehicles, duration, and frequency of application). However, a recent prospective cohort study indicates that long-term topical corticosteroid treatment could prevent the progression of VLS and the development of vulvar cancer, and thus, long-term treatment for VLS should be the norm.[20]

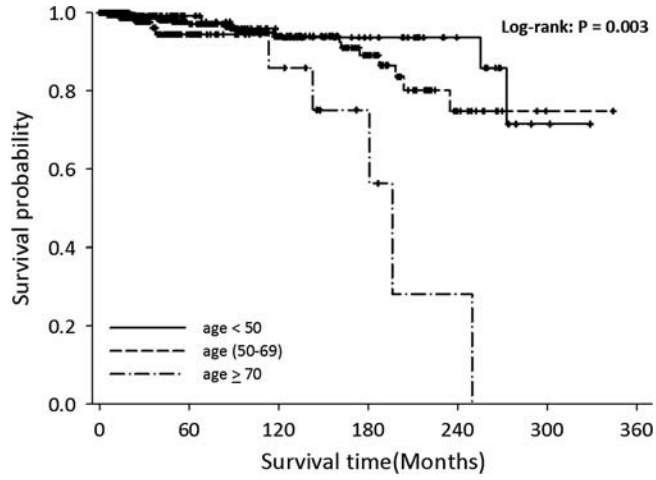

FIGURE 2. Curves of progression-free survival of women with VLS divided by range of age at diagnosis.

CONCLUSIONS

Vulvar lichen sclerosus has a nonnegligible risk of neoplastic transformation and requires a careful and lifelong follow-up in all patients, particularly in elderly women. Early clinical and histological detection of preinvasive lesions are therefore essential to reduce the risk of vulvar cancer.

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